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Avaliação da atividade neuroprotetora de palntas medicinais chinesas

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Evaluation of the neuroprotective activity of Chinese medicinal plants

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Resumo

As doenças neurodegenerativas, como a Doença de Alzheimer e a Doença de Parkinson, assim como distúrbios emocionais, como a depressão, englobam um conjunto de condições incuráveis que perturbam a qualidade de vida dos indivíduos afetados. Esta condição tem como características o declínio da capacidade cognitiva e motora que se agrava com o passar dos anos. Apesar destas doenças serem incuráveis, estudos têm vindo a ser realizados de modo a compreender of mecanismos por detrás do agravamento destas condições, de tal modo a suprimir ao máximo a sua propagação. Até hoje, as hipóteses e teorias mais discutidas revolvem a volta de processos enzimáticos, do agonismo e antagonismo de recetores neuronais, de stress oxidativo, e da citotoxicidade de complexos proteicos, portanto, terapias eficazes têm vindo a ser desenvolvidas de modo a suprimir a progressão destas doenças. As terapias já existentes centram-se na administração de fármacos que atuam nos mecanismos inerentes de cada condição neurodegenerativa. Neste aspeto, as plantas medicinais surgem como fortes candidatos a integrarem estas terapias, uma vez que, no passado, eram administradas para tratar diferentes doenças inflamatórias, por exemplo. Cada planta apresenta uma panóplia de compostos bioativos que, em alguns casos, compõe alguns fármacos especificados para este tipo de doenças. De todas as terapias existentes, a Medicina Tradicional Chinesa surge como uma das mais antigas, praticadas, e mais bem documentadas do mundo. Esta dissertação tem como principal objetivo averiguar o potencial de algumas das mais utilizadas plantas medicinais (e um fungo) na Medicina Tradicional Chinesa, na intervenção benéfica dos mecanismos inerentes de cada doença neurodegenerativa.

Palavras-chave: Medicina Tradicional Chinesa; Neurónio; Doenças neurodegenerativas; Doença de Alzheimer; Doença de Parkinson; Depressão; plantas medicinais; toxicologia.

Abstract

Neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, and disorders, like depression, belong to a group of incurable conditions that affect the quality of life of those that are affected by them. The most characteristic clinic features include cognitive and motor symptoms, in which, a significant loss of memory and reduction of motor ability is observed, respectively. Despite these kinds of diseases are considered incurable, numerous studies have suggested that symptoms can be controlled, and disease's progression can be delayed. The most discussed theories and hypotheses show that neurodegenerative conditions involve enzymatic processes, receptor agonist and antagonist interactions, oxidative stress, and protein cytotoxicity, therefore, therapies have been designed to act at these specific mechanisms. The available therapies require the administration of different pharmaceuticals that act at the inherent mechanisms of each neurodegenerative condition. Medicinal plants appear as strong candidates to integrate therapies, as they have been utilized as medication for treating all kinds of ailments for over 4000 years. Each plant presents a wide variety of bioactive compounds, which have already been integrated into pharmaceuticals designed to treat said neurodegenerative conditions. Out of all known natural therapies, Traditional Chinese Medicine is at the forefront of the medicinal plant industry as one of the oldest practiced therapies in the world, as well as being one of the most well-documented. The primary objective of this dissertation aims is to evaluate the potential of some of the most predominant medicinal plants (and one fungus) used in Traditional Chinese Medicine to positively intervene in the most known mechanisms that contribute towards neurodegenerative disease progression.

Keywords: Chinese Traditional Medicine; Neuron; Neurodegenerative disease; Alzheimer's Disease; Parkinson's Disease; Depression; Medicinal plants; Toxicology.

Index

Figure index

Table index

List of abbreviations

2-AG- 2-Arachidonoylglycerol

5-HIAL- 5-Hydroxy-indol acetaldehyde

5-HT- 5-Hydroxytryptamine

5-HTF- 5-Hydroxytryptophan

A_1AR- A_1 Adenosine receptor

A_{2A}AR- A_{2A} Adenosine receptor

A_{2B}AR- A_{2B} Adenosine receptor

A_3AR- A_3 Adenosine receptor

AAAD- Aromatic L-amino acid decarboxylase

ACh- Acetylcholine

Acetyl-Co A- Acetyl coenzyme A

AChE- Acetylcholinesterase

AD- Alzheimer's disease

AICD- APP intracellular domain

ALDH- Aldehyde dehydrogenase

ALP- Autophagy lysosomal pathway

AMPA- α-Amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid

APP- Amyloid precursor protein

APoE4- Apolipoprotein E4

ATP- Adenosine triphosphate

BGT_1- Betaine GABA transporter

BuChE- Butyrylcholinesterase

cAMP- Cyclic adenosine monophosphate

CB_1- Cannabinoid receptor 1

CB_2- Cannabinoid receptor 2

CBD- Cannabidiol

cDNA- Complementary DNA

ChAT- Choline acetyltransferase

CMA- Chaperone-mediated autophagy

CNS- Central Nervous System

CNT- Concentrative nucleoside transport

COMT- catechol-*O*-methyltransferases

CSP-α- cysteine string protein-α

DR- Dopamine receptor

D_1DR- D_1 dopamine receptor

D_2DR- D_2 dopamine receptor

D_4DR- D_4 dopamine receptor

DAGL- Diacylglycerol lipase

E1- Ubiquitin-activating enzyme

E2- Ubiquitin-conjugating enzyme

E3- Ubiquitin-polymerizing enzyme

$EAAT_1$- Excitatory amino acid transporter 1

$EAAT_2$- Excitatory amino acid transporter 2

$EAAT_3$- Excitatory amino acid transporter 3

ECS- Endocannabinoid system

ENT- Equilibrative nucleoside transporter

FAAH- fatty acid amine hydroxylase

GABA- Gamma-aminobutyric acid

$GABA_A$- $GABA_A$ receptor

$GABA_{B1}$- $GABA_{B1}$ receptor

$GABA_{B2}$- $GABA_{B2}$ receptor

$GABA_C$- $GABA_C$ receptor

GSK3β- Glycogen synthase kinase 3-β

HACT- High affinity choline transporter

HSC70- Heat shock cognate protein 70

iRNA- RNA interference technology

KERFQ- Lysine-phenylalanine-glutamate-arginine-glutamine peptide

LACT- Low affinity choline trasporter

LAMP2- Lysosome-associated membrane protein 2

L-DOPA- Levodopa

MAGL- Monoacylglycerol lipase

MAO- Monoamine oxidase

MAO-A- Monoamine oxidase A

MAO-B- Monoamine oxidase B

MT_1- Melatonin receptor 1

MT_2- Melatonin receptor 2

NAC- Non β-amyloid component

NAPE- Arachidonoyl-phosphatidylethanolamine

NAPE-PLD- N-acyl-phosphatidylethanolamine phospholipase D

NMDA- N-methyl D-aspartate

NS- Nervous System

PD- Parkinson's disease

PNS- Peripheral Nervous System

PKA- protein kinase A

ROS- Reactive oxygen species

RNS- Reactive nitrogen species

sAPPα- α-Secretase cleaved soluble protein

sAPPβ- β- Secretase cleaved soluble protein

SNAP-25- Synaptosome-associated protein-25

SNARE- Soluble N-ethylmaleimide-sensitive factor attachment protein receptor

siRNA- Small interference RNA

TCM- Traditional Chinese Medicine

THC- Tetrahydrocannabinol

UPS- Ubiquitin-proteasome system

VAMP-2- vesicular protein synaptobrevin-2

VDAC-1- Voltage-dependent anion channel-1

1. Introduction

Neurodegenerative diseases belong to a group of pathologies of incurable and debilitating nature that affect people of all ages, mostly the elderly. Generally, these diseases are responsible for the progressive and irreversible degradation of the neurons that compose the human brain, which can lead to the death of these cells and the reduction of synapses. According to the World Health Organization (WHO), the increase of the average life expectancy of the world population is one of the main factors of the prevalence of chronic and progressive conditions in which neurodegenerative diseases are included (Duthey, 2013).

With aging, the human body loses some of its ability to carry out certain body functions properly. Neuron production decreases over time (Duthey, 2013). Since birth, the size of the human brain increases due to an increase of neuron production, and at a certain point in life, the overall production ceases, even though recent studies evidence that neuron regeneration can occur in the *substantia nigra* of adult mice (Zhao *et al*., 2003). Most of the available literature on the human brain is based on studies applied to mice's brains since both show similarities in gene expression (Miller *et al*., 2010). When the growth stagnation point of the brain is reached, a disproportion between neuron production and neuron death occurs, where the latter prevails. Although not desirable, this condition is considered a normal symptom of aging and not a disease. However, in the case of disease, the rate of neuron death sharpens and causes severe effects on the patient, such as loss of memory and motor performance, which are the main neurodegenerative effects of Alzheimer's Disease (AD) and Parkinson's Disease (PD), respectively. Common comorbidity of these kinds of pathologies is depression, which is normally detected in elderly patients, as some may demonstrate signs of social isolation, agitation, and slow behavior and motor response. Depression during the early stages to mid-stages of life has been pointed out to increase the risk of both AD and PD in the long run, as behavioral alterations affect important neuronal processes (Ownby *et al*., 2006). So, as the probability of neurodegenerative disease progression increases with life expectancy, so too does research increases to develop viable and successful treatment methods. Depression is also seen as a target point, as more young adults succumb to this psychological condition.

Traditional medicine, more specifically Chinese Traditional Medicine (TCM), has gained traction over the years as a viable treatment alternative to pharmaceuticals, as it is seen by the population as a safer, less costly, and more effective option, although this last argument is debatable among specialists. The typical application of medicinal plants come in the form of teas and are usually associated with antioxidative and anti-inflammatory effects. In this sense, the main objective of this thesis is to evaluate the different effects of used plants in TCM on the overarching neurodegenerative effects of AD, PD, and depression.

2. Nervous System

The nervous system (NS) is responsible for the everyday actions that the human body performs. From a generic point of view, the NS is involved in the following functions: collection, assimilation, and interpretation of sensorial information. The collected information is transmitted from several parts of the body directly to the brain through neurons, synapses, and glial cells,

through electric impulses (Rea, 2016). After processing the information collected from the exterior of the body, the brain transmits its impulses to the spinal cord and muscles, which will produce the most adequate response to the phenomenon. The NS can be divided into two components: the Central Nervous System (CNS), composed of the spinal cord and the brain, and the Peripheral Nervous System (PNS), which aggregates all nerves and ganglia throughout the body that connect to the spinal cord. (Rea, 2016). This thesis will focus on conditions that affect the CNS.

2.1. Central Nervous System (CNS)

The CNS is the processing center of the NS. Its main function is to gather and to integrate inputs from different parts of the body and to induce several types of impulses in the body. The CNS consists of the brain and the spinal cord, which in turn can also be divided into various other components. The cerebral cortex, the cerebellum, and the brain stem are the main components that form the brain (Duthey, 2013).

2.1.1. Neurons

Neurons are the cells that form most of the NS. They have three distinct structures:

- Dendrites: Small ramifications near the cellular body responsible for the reception of electric impulses from neighboring neurons and subsequent transmission towards the other extreme of the cell. (Moreira, 2013). The dendrites connect to the axonic terminal of other nerve cells, forming synapses, which are the active locals where the impulse is transmitted.
- Cell body: The cell body resembles that of other mammalian cells, possessing the same kind of membrane and organelles, such as mitochondria, ribosomes, Golgi apparatus, etc. Like any other cell, the nerve cell body is responsible for its support, both structurally and functionally (Palay & Palay, 2011);
- Axon: The axon is a stretched component connected to the cell body responsible for transmitting the nervous impulse towards its neighboring nerve cells. This section is responsible for the accumulation of choline from the bloodstream, the production, and storage of cholinesterase (Moreira, 2013);

Neurons are responsible for transmitting an electric stimulus, also called nerve impulse. The dendrites receive the impulse transmitted by the terminal axons of other neighboring nerve cell terminal axons, which form the synapses (Rea, 2016). The impulse propagates through the cellular body, which triggers the cell to produce its very own impulse and immediately transmits it to other cells, through the terminal axons, as shown in Figure 2.1.

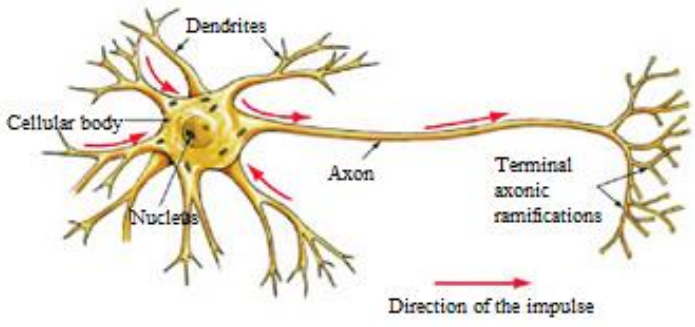

Figure 2.1. The general structure of the neuron (Ferreira et al., 2013) [Adapted].

The impulse transmission occurs by cell membrane depolarization (Silva *et al*., 2019). The membrane of the neuron holds a positive electrical charge in its exterior, meaning that the electrical charge in the interior of the cell is negative. This means that the membrane is correctly polarized. In this state, the neuron is considered to be in a "resting state". Under these conditions, the potential difference of the membrane is defined as a resting potential (-70mV) (Silva *et al*., 2019); this potential is maintained by the cell's natural active transporting system run by protein pumps that actively transport Na^+ ions to the exterior and K^+ ions to the interior of the cell, with ATP degradation (Krueger-Beck *et al*., 2011). To maintain this potential, the Na^+ ion concentration must exceed that of K^+ in the exterior of the membrane, and vice-versa. Because of the existing concentration gradient, following the principle laws of diffusion in this particular case, the Na^+ ions permeate the membrane towards the interior of the cell, and the K^+ ions follow the opposite flow, towards the exterior of the membrane, to balance out the concentrations of both species. So that the cell's metabolism can properly function, it must maintain the resting potential. Therefore, the cell must maintain low concentrations of Na^+ ions in the exterior of the cellular membrane.

This system, commonly known as a Na^+/ K^+ pump system, is responsible for regulating the pumping of Na^+ ions towards the exterior of the neuron, with subsequent transport of K^+ ions into the cell's interior with regular ATP consumption, in simultaneous (Krueger-Beck *et al*., 2011). The transporting system of the cells is responsible for its membrane's charge: for every 2 K^+ ions that enter the cell, 3 Na^+ ions leave the cell. The unbalance of charged ions that are transferred at the same time provide the interior membrane a negative charge. (Pivovarov *et al*., 2019).

When a stimulus is induced in a neuron, the membrane is depolarized, inverting the electric potential throughout the cell membrane. The depolarization momentarily increases the permeability of sodium ions towards the interior of the cell. This is because of the existing concentration gradient. Passive transport through membrane channels is responsible for ion diffusion, and in this particular case, the Na^+ ions permeate the membrane towards the interior of the cell, and the K^+ ions follow the opposite flow, towards the exterior of the membrane. This causes a change in membrane potential from -70mV to -35mV – the depolarization potential. (Moreira, 2013). The phenomenon also induces the influx of calcium ions through specific channels of entry. While the depolarization continues throughout the rest of the axon membrane, the affected area suffers repolarization to balance out the resting potential, with the help of the Na^+/ K^+ system. If the impulse's intensity hits a certain threshold action potential, then the transmission continues to the remaining neuron structure, also reaching neighboring neurons. Therefore, the general intensity of an impulse depends on the number of depolarized neurons (Moreira, 2013).

2.1.2. Glial Cells

Glial cells, or neuroglia, are non-neuronal cells responsible for the support and compaction of the CNS and nutrition support to all neurons. (Rea, 2016). Glial cells act as an intermediate phase between blood capillaries and the cellular body of neurons and allow ion and other molecule exchange between each other. (Gomes *et al*., 2013). In this sense, glial cells are vital to regulating the transport of precursor molecules that are at the base of neurotransmission. Over the years, numerous discoveries regarding the functions of these cells have been made, like its significant role in synapse modulation, neurotransmitter absorption and displacement, and the release of neurotrophic factors present in nerve cell's development (Gomes *et al*., 2013). Glial cells are divided into two types: microglia and macroglia. Microglia are the immune cells involved in the protection of the CNS from strange species to the medium, fighting against infections, injuries, and neurodegenerative conditions, such as Alzheimer's disease (Hemonnot *et al*., 2019).

Macroglia, on the other hand, comprise the following cell types:

- Astrocytes: These are the most common type of glial cells in the CNS. The morphology may vary from star-shaped cells (located in the grey matter) or elongated cells, like Müller cells (located in the retina) and Bergmann cells (present in the cerebellum). Their main functions are to provide structural support to the brain, for regulating the transmission of neurotransmitters, and for maintaining cerebral homeostasis (Silva *et al*., 2019).
- Oligodendrocytes: These cells are responsible for the formation of myelin, the lipidic outer layer protecting the axons, and for the stabilization of pH in the extracellular medium to ensure nerve cell survival (Silva *et al*., 2019).
- Schwann cells: Similar to oligodendrocytes, these cells produce myelin in the PNS (Rea, 2016);
- Ependymal cells: These cells form the epithelial lining of the brain ventricles and the central canal of the spinal cord (Gomes *et al*., 2013).

2.1.3. The brain

The brain occupies the majority of the encephalon. This organ is sectioned into two hemispheres (left and right), surrounded by the superficial cerebral cortex, composed of grey matter. The inner region of either section is composed of white matter (Marieb & Hoehn, 2012). One of the most common characteristics associated with the cerebral cortex is the nervous tissue's folds, which form various elevations and sulcus, defined as *gyri* and *sulci*, respectively (Hines, 2018). These folds result from the superior white matter growth rate over the growth rate of grey matter, which implies a constrain of the cerebral cortex. (Gholipour, 2014). The brain is composed of a huge number of neurons and neuroglia. The cerebral cortex is responsible for the performance of many ordinary tasks in human lives, playing a key role in memory, language, conscience, among other activities (Hines, 2018). The folding of the cortical tissue naturally allows for the superficial area of the cortex to increase, allowing for more nerve and non-nerve cell aggregation and a better transmission process between them.

As mentioned earlier, the brain possesses two hemispheres, separated by a longitudinal fissure. Both sections are structurally identical and are made up of four superficial lobes (frontal,

temporal, parietal, and occipital), and by one subcortical lobe (limbic). Figure 3 shows the structure of the cerebral cortex, along with the location of the four superficial lobes.

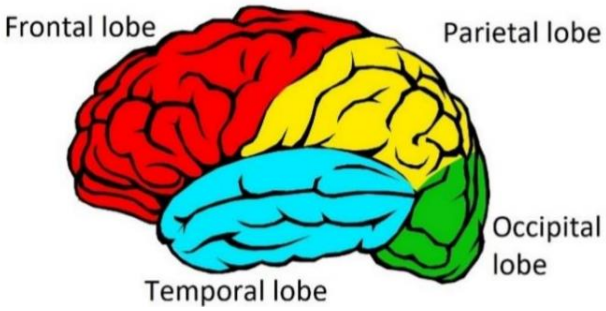

Figure 2.2. The cerebral cortex (Shah, 2019).

Among all lobes, the frontal lobe occupies the major area of the cerebral cortex and positions itself in the frontal section of the brain, behind the forehead bone. This lobe performs ordinary functions, like the elaboration of objectives, strategic planning required to fulfill those objectives, the proper selection of cognitive and motor abilities to perform the plan, and the coordination of the abilities (Seruca, 2013). The frontal lobe is arranged by the following sections: the primary motor cortex, the premotor cortex, the frontal eye field, the supplementary motor area, and the prefrontal cortex (Standring, 2016).

The parietal lobe is placed behind the frontal lobe and regulates sensory and perceptual processes integrated into everyday life activities, such as knowledge, speech, writing, reading, among others. (Brownsett & Wise, 2010). The parietal lobe comprises three main functional areas: the primary somatosensory cortex the upper parietal lobe and the lower parietal lobe (Huang, 2017).

The temporal lobe lies in the lower lateral area, below the side fissure of the hemispheres. This section of the cerebral cortex only resides in the primate's encephalon, which accounts for about 17% of the human's superficial cortical area on both sides of the brain. The temporal lobe grants some important abilities such as visual memory, emotion, language comprehension, and hearing ability (Huang, 2017).

The occipital lobe lies in the most posterior area of the brain and is typically associated with the processing of visual information. The regions which compose this lobe are responsible, for instance, for the identification of movement, color, the sense of location, and the shape of objects, among others (Rehman & Khalili, 2019).

The limbic lobe or limbic system is a subcortical lobe located beyond the superficial lobes. This system is located between the frontal and temporal lobes and includes structures that collect nerve impulses from various regions of the brain, and plays a significant role in information, memory, and emotion storage, as it is shown in Figure 4. The limbic system is composed of four primary areas, being the amygdala, hippocampus, thalamus, and hypothalamus (Hines, 2018).

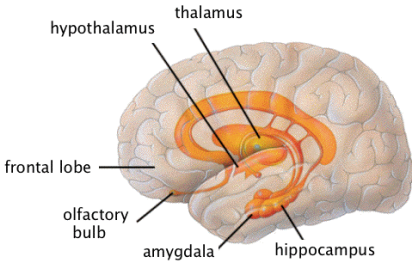

Figure 2.3. The limbic lobe (Boeree, 2011).

2.1.4. The cerebellum

The cerebellum is the structure lying in the most inferior and posterior section of the cerebral cortex. The cerebellum has the capability of performing both cognitive and motor functions, but the latter represents most of its performances. It regulates the body's movements and plays a role in acquiring motor memories essential for everyday practice, to minimize possible motor-related errors. This encephalic component comprises two hemispheres, like the brain, and three lobes: the anterior, posterior, and flocculonodular lobes, as seen in Figure 5 (Damiani *et al*., 2016).

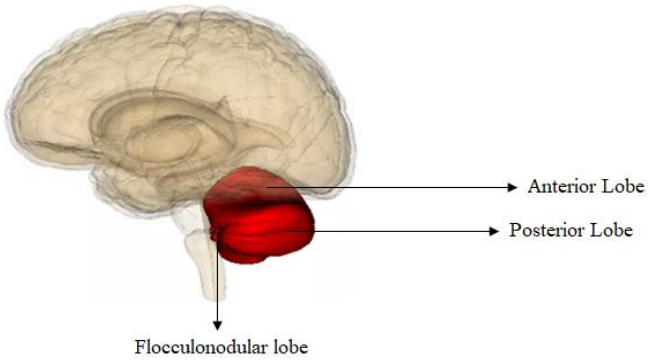

Figure 2.4. Human cerebellum (Cherry, 2019) [Adapted].

2.1.5. The brain stem

The brain stem acts as an intermediate section of the encephalon, which conducts ascending and descending nerve impulses between the PNS and the encephalon. This suggests that the brain stem in the center of the information and command transmission processes (White & Cant, 2012).

The neurotransmitter dopamine is produced in this section. The brain stem receives an impulse from the cerebellum and, afterward, induces a motor response on the body by liberating the dopamine (White & Cant, 2012). The brain stem is composed of the bulb and bridge, directly connected to the spinal cord and encephalon, and by the mesencephalic nucleus, made up of brain peduncles, and by the substantia nigra, the latter being the portion where dopamine production occurs (Hurley *et al*., 2010). This zone of the brain stem is composed of dopaminergic neurons and neuromelanin, a pigment accumulated in the mesencephalic nucleus, which confers its dark coloration. This portion's primary function is to protect the whole encephalon from chelating metals capable of causing oxidative stress, even though it can turn into a source of free radicals by reacting with H_2O_2 (Zecca *et al*., 2003).

3. Diseases of the Central Nervous System

Neurodegenerative diseases are multifactorial conditions, meaning that their causes can vary from individual to individual. Furthermore, there are no similar patients since they have different metabolic systems and biochemical processes. Symptoms may manifest more aggressively in one patient than in another, meaning that the required treatment may differ between them. Regarding neurodegenerative diseases, several patients may develop comorbidities like depression and anxiety. The way AD and PD appear in a patient can also differ. Spontaneous development accounts for most of the neurodegenerative disease progression cases, commonly described as late-stage/onset diseases. Familial neurodegenerative diseases are rare occurrences, however, the genetic modification of certain brain genes are known to negatively influence certain mechanisms that contribute towards AD, like tau-protein and β-amyloid (Raghavan & Shah, 2014). Other ways of increasing the progression risk of neurodegenerative diseases come in the form of environmental issues, such as exposure to toxic metals that disrupt metabolic pathways in the body (Yadav, 2018), or accidents, such as lesions in the brain (Ramos-Cejudo *et al*., 2018).

3.1. Alzheimer's Disease

Alzheimer's disease (AD) is known as the most common form of dementia in the world today. This pathology's exacerbation is associated with the patient's age (OCED, 2017). According to a report published by the Organization for Economic Co-operation and Development (OECD), around 18.7 million people were suffering from AD in 2017 (OECD, 2017). Like in any other neurodegenerative disease, early-stage detection proves itself to be impossible, which results from slow alterations in the organism of natural biochemical, metabolic, and neuropathologic processes. Its main symptoms are linked to progressive loss of intellectual and cognitive abilities. The patients develop limitations in their daily tasks, such as lack of attention and concentration, the incapacity of recognizing visual space and verbal fluency, and inability to interact with familiar objects. Another characteristic of AD patients consists of sporadic mood swings. (Alzheimer's Association, 2018). In the most severe cases, the patient shows muscular weakness, resulting in limitations to the individual's motor abilities.

The functionality of many systems in the organism decreases with aging, even in healthy persons, which is considered a natural process; for instance, memory lapses are very common in the elderly. There is also a reduction of the brain's volume which can be traced back to the neuron loss due to the disproportion between neuron production and neuron death. However, the number of nerve cells lost is not enough to evidence injuries like that of AD patients (Duthey, 2013). A patient is reported to carry AD when the tendencies of normal aging are intensified, leading to a faster decline of functional neurons and respective synapses. When the vital processes that ensure nerve cell survival and neurotransmitter-based communication are compromised, then the neurons involved lose functionality and die.

The hippocampus is the section of the brain responsible for the creation of memories, and one of the most important to be affected first. According to the *Alzheimer's Society*, an injured hippocampus does not necessarily translate to a total loss of memory if the individual possesses a healthy temporal cortex (Simons & Collerton, 2014).

3.2. Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disease that affects the CNS, mainly all encephalic areas meant to regulate the organism's motor capacity. Although less predominant, other manifestations of PD are that of cognitive, psychiatric, and autonomous character; such disturbances include sleep deprivation, mild memory loss, depression, among others (Cabrita, 2017). This condition affects people of all ages, however, much like AD, it is in older communities that symptoms are shown to be more exacerbated, due to age-related malfunctions of the human body. According to a report by Global Health Metrics, between 1990 and 2015, PD carriers were estimated at around 6.2 million (Dorsey *et al*., 2018), however, the data recollected by Parkinson's Foundation estimated that number exceeded 10 million patients in 2018. (Marras *et al*., 2018).

DP is characterized by the continuous and incremental loss of neurons found in the substantia nigra, in the mesencephalic nucleus, in the brain stem. The most affected neurons are those which are responsible for the production of dopamine, an essential neurotransmitter involved in the induction processes of muscle movement (Cabrita, 2017). Recent clinical and pathological studies point to defects in the function of the PNS and autonomic nervous system as well (Comi *et al*., 2014).

3.3. Major depressive disorder

Depression is a psychological condition in which an individual shows a negative attitude and signs of demotivation. The primary indications of a depressed person involve mood induced alterations, such as in humor. The patient is more prompted to demonstrate negative thoughts, like sadness, emotional anguish, worry, and in severe cases, suicide. Minor symptoms like sleep and hunger deprivation can also manifest in some cases. (Carvalho, 2018).

Depression is also a multifactorial condition with multiple causes. In most circumstances, depression appears after the patient suffers an extreme shift in its ordinary life (Carvalho, 2018). Even though everyone is susceptible to these drastic changes, everyone's reaction may differ. The causes can be traced back to financial, domestic, or social problems. In some cases, the depressive state may accentuate at sporadic intervals. In the case of bipolar depression, the individual shows volatile mood swings, ranging from euphoric states, immediately followed by inexplicable depressive states (Parikh & Health, 2015). Even though depressive states in an individual might develop when suffering from the situations, they are also comorbidities of neurodegenerative diseases, such as in the case of AD and PD patients. Despite these conditions holding distinct characteristics, like the affected area of the brain, some of the neurodegenerative mechanisms displayed are overlapped. In this case, depressive states might develop as a symptom of other conditions (Galts *et al*., 2019).

A report disclosed by the OECD shows that around 7.9% of all the European population experience any kind of depressive state, with a duration of around 12 months. Alongside Iceland, Portugal exhibits one of the most significant rates of depression in all of Europe, especially when analyzing data regarding depression in women (OECD, 2017).

4. The causes of neurodegenerative diseases

4.1. Cholinergic hypothesis

In the 1970s, a breakthrough in research leads to the discovery of the relation between the brain's cholinergic system and AD (Falco *et al*., 2016). Some of the common features observed in patients with AD included a deficiency of acetylcholine (ACh) levels, reduced reactive capability of choline acetyltransferase (ChAT) in the cerebral cortex and hippocampus, and a reduction of functional neurons involved in cholinergic processes in the nucleus basalis of Meynert (Paul *et al*., 1999). ACh was the first-ever discovered neurotransmitter. The molecules are produced in the neurons and reside in the terminal axons of the neurons. When stimulated, they are released to the synapses, to trigger new impulses in neighboring nerve cells (Falco *et al*., 2016). Figure 4.1 displays the simplified processes involved in the cholinergic neurotransmission.

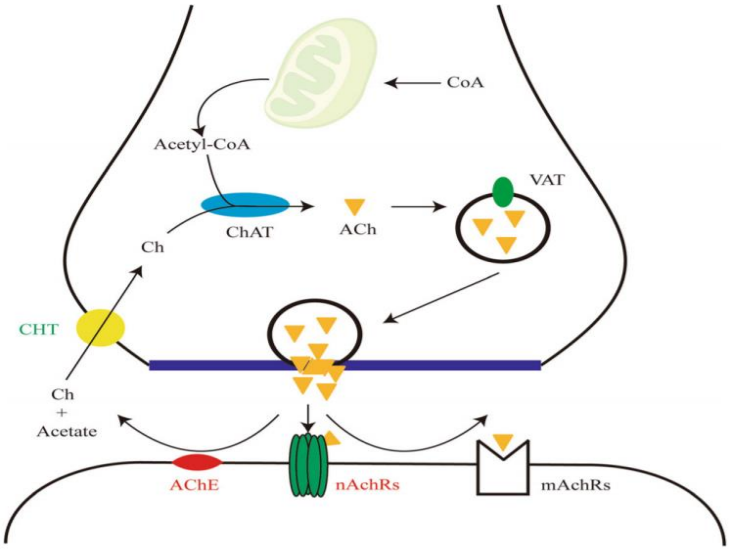

Figure 4.1. The cholinergic system (Wang et al., 2019).

ACh synthesis requires two precursor molecules: choline and acetyl coenzyme A (Acetyl-CoA). Choline is provided from the regular dietary intake of more complex structures, like glycerophosphocholine, phosphocholine, and phosphorylcholine. A fraction of the ingested choline species is absorbed in the small intestine by enterocyte transporter proteins and subsequently relocated to the liver, whereas the other parcel is metabolized by gut bacteria to form betaine. From the liver, the choline molecules enter the bloodstream, where they cross the blood-brain barrier through a specific transport mechanism. The absorption of choline is accomplished by low and high-affinity choline transporters (LACT and HATC, respectively)(Lockman & Allen, 2002). HATC are found across the presynaptic membrane to facilitate choline uptake after ACh degradation and are considered to be the limiting step of ACh synthesis (Lockman & Allen, 2002). LATC provides choline for metabolic purposes to the non-neuronal cells in the brain (Inazu, 2019). Other regions of the body may hold a role in either choline secretion (pancreas) or accumulation (kidney) (Institute of Medicine, 1998). Another effective method of the cholinergic neurons to obtain this precursor involves the absorption of choline from the synapses after the breakdown of ACh by acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). The precursor Acetyl-CoA is obtained from neuronal

mitochondria from the axonic terminals. The production of ACh involves the acetylation of the choline molecules catalyzed by choline acetyltransferase (Petronilhoa *et al*, 2011), as seen in Figure 4.2.

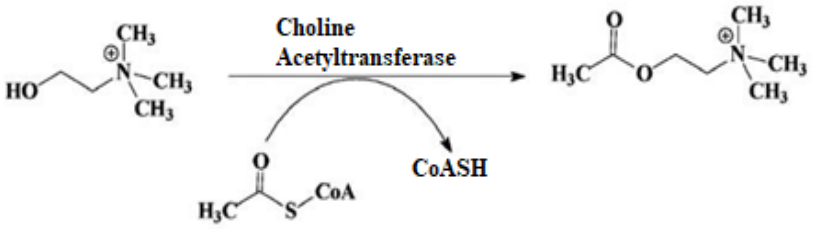

Figure 4.2. Acetylcholine production (Viegas et al, 2004) [Adapted].

After ACh synthesis, the neurotransmitter molecules are stored in presynaptic vesicles in the axon terminal (Ventura *et al*., 2010). When the native cell is stimulated, ACh is released to the synapse. The ion influx allows for the vesicles to fuse with the presynaptic membrane, to allow ACh release to the synaptic cleft. In the synapse, the neurotransmitters interact with postsynaptic receptors to induce a new impulse in the neighboring neurons (Petronilhoa *et al*., 2011).

After the impulse is generated, it is fundamental for the neurotransmitter-receptor interaction to instantly cease since post-synaptic cell overstimulation can cause stress to the cells and may eventually lead to neuronal cell death. Figure 4.3 shows the degradation reaction of acetylcholine observed in the synapse. The reaction is catalyzed by AChE, an enzyme belonging to the cholinesterase family located in both the CNS and PNS. Its primary function consists of converting ACh into its simplified molecular bases, choline, and acetate. (Xu *et al*., 2008).

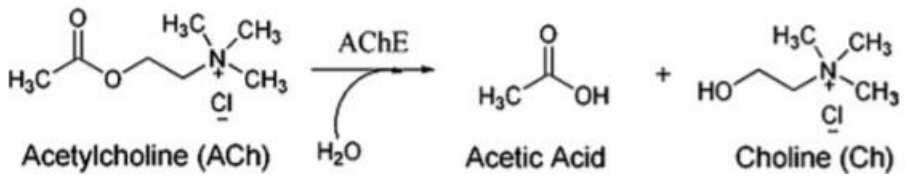

Figure 4.3. Enzymatic degradation of acetylcholine in the synapse (Xu et al., 2008).

When degraded, the native (presynaptic) neuron reabsorbs the choline from the synapse, so that the molecule can be converted back into ACh inside the cell. The transport to the interior of the axons is attributed to HACT, which are specific proteins spread out through the nerve cell's terminal membrane. The synthesis of ACh in the terminal axon depends mostly on the reuptake of choline from the synapse (Lockman & Allen, 2002).

Despite holding a significant role in the regulation of nervous stimulus, AChE is not the only enzyme capable of hydrolyzing ACh. Butyrylcholinesterase (BuChE) is also capable of the same function. BuChE is a native enzyme of the hippocampus and in some regions of the cerebral cortex (Mesulam *et al*., 2002). For many years BuChE was recognized as a pseudocholinesterase since it was thought that it was not involved in synaptic reactions. This belief was based on the enzyme's location, the neuroglia, which are not involved in nerve impulse transmission (Mesulam *et al*., 2002). However, studies now suggest a connection between BuChE and some types of neurons, mainly those of the regions related to behavioral and cognitive functions, like the hippocampus, amygdala, and thalamus (Jasiecki & Wasąg, 2019).

Cholinesterase inhibitors belong to a group of drugs administered to AD patients to attenuate their symptoms. Initially, the main focus of drug research consisted of the discovery of unknown AChE inhibitors, however, BuChE activity was shown to increase during the disease's progression in patients while AChE activity diminished (Lane *et al*, 2006). Now, several available drugs can attenuate the ACh breakdown by inhibiting cholinesterases. The repeated and excessive administration of the available medication might cause secondary effects to the patient, like vomit, nausea, and diarrhea (Onor *et al*, 2007). In the past, tacrine belonged to a list of authorized drugs to be administered to AD patients, however, it was discontinued, because of its severe side effects on the human liver (Alfirevic *et al*., 2007).

Rivastigmine is an AChE and BuChE inhibitor. The molecule belongs to the family of carbamates, and it is capable of performing a pseudo-irreversible inhibition (Lane *et al*., 2006), meaning that ACh degradation is temporarily limited in the synapses to ease nerve impulse transmission. Rivastigmine forms a covalent-bonded complex with cholinesterases to initiate the inhibition process (Müller, 2007). Of all available medication, rivastigmine lasts longer in the human body, which means that it inhibits cholinesterases the longest than any other drug (Onor *et al*, 2007).

Other drugs, like donepezil and galantamine, possess higher specificity for AChE than for BuChE (Lane *et al*., 2006). Donepezil is a piperidine derivative and is capable of reversible inhibition, which accounts for a brief duration of enzymatic inhibition (Cacabelos, 2007). This inhibitor performs a non-competitive inhibition, meaning that it can either bond to the enzyme or the enzyme-substrate complex. This type of inhibition is less effective than competitive inhibition. Galantamine is a natural tertiary alkaloid and, like rivastigmine, is capable of reversible competitive inhibition. Compared with donepezil's inhibitory ability, galantamine is a weaker inhibitor. (Lane *et al*., 2006).

4.2. β-amyloid deposit hypothesis

β-Amyloid is an insoluble peptide composed of around 39 to 42 amino acids found in a larger protein known as an amyloid precursor protein (APP). In 1906, Alois Alzheimer first described the effects of cognitive decline and neuropathology in a 51-year-old woman, with subsequent research identifying the presence of β-amyloid plaques and fibrils in the brain (Teich & Arancio, 2012), which occupy synapses and compromises the nerve impulse transmission process. Since then, the peptide has been one of the hallmarks of AD and the primary cause of the disease.

APP is a transmembrane protein expressed by the APP gene, located in chromosome 21. The protein belongs to the family of conserved type-1 proteins, such as APLP-1, APLP-2, with it being the only protein containing the β-amyloid peptide. APP is found in various tissues throughout the body; however, the protein is found in different isoforms. In the brain, APP appears in the APP-695 state, signifying that the protein is composed of 695 chained amino acids. The presence of APP stationed in the neuronic cellular membrane has been reported to positively influence the maintenance of the CNS. The exterior domain of the protein mostly promotes cell adhesion, structural growth of the dendrites and axons of developing neurons, or neurite outgrowth, synapse modulation, and cell surface receptors, which can bind to foreign molecules; the external domain of APP has been found to bind to β-amyloid, thus suppressing the neurotoxic effects of the peptide (Lorenzo *et al*., 2000).

Figure 4.4 shows the different steps that APP can undergo. While anchored in the cellular membrane, APP is initially cleaved by either α-secretase or β-secretase. Both enzymes cleave the protein in the extracellular domain at different locations. In the α-secretase pathway, the enzyme cuts through the β-amyloid peptide producing a soluble protein (sAPPα), which has been reported to improve neurogenesis and cell survival (Zhou *et al*., 2011). β-secretase also cleaves APP and produces a soluble protein (sAPPβ); however, the β-amyloid portion APP is unaffected. The succeeding step in both pathways involves the cleavage of the internal portion of APP by γ-secretase. This cleavage leads to the generation of the APP intracellular domain (AICD fragment), which is then translocated to the neuronal nucleus to regulate transcription (Jevtic & Provias, 2019).

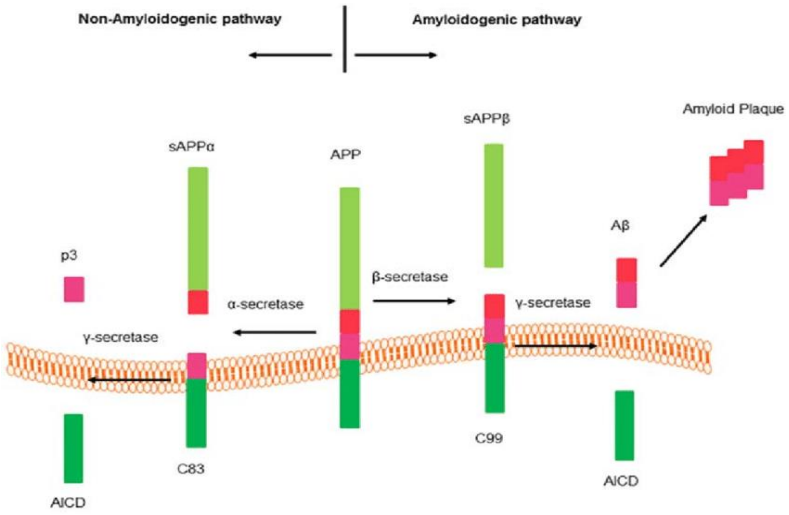

Figure 4.4. Cleavage pathways of APP (Zhao et al., 2016).

Through the β-secretase pathway, β-amyloid is generated at the tail-end of the process. Between both secretases, there is competition, evidenced by the presence of small β-amyloid plaques in healthy brains. α-Secretase possesses a higher activity rate than β-secretase in the brain: one of the most predominant theories for this phenomenon is based on the binding of the anchored APP protein to F-spondin, a secreted neuronal protein, a bond which prevents β-secretase cleavage of APP (Ho *et al*., 2004). Tyler *et al*. (2002) described the activity of both secretases in *postmortem* brain tissue. The authors reported that around 80% of the brain samples showed decreased activity of α-secretase, increased activity of β-secretase, or both. Although the specific mechanism is unknown, the primary hypothesis that explains the shift in enzymatic rates is the presence of a mutated gene that synthesizes apolipoprotein E4 (ApoE4). It has been documented that the presence of the ApoE4 genotype in AD patients diminishes α-secretase activity, which in turn allows β-secretase to cleave APP and produce β-amyloid fragments (Shackleton *et al*., 2017).

AD is often characterized by the extracellular accumulation of β-amyloid peptides, leading to the formation of different aggregates, from small, soluble oligomers composed of 3 to 50 β-amyloid units, to insoluble amyloid fibrils and plaques. Initially, the severity of AD in a patient was attributed to the accumulation of insoluble β-amyloid plaques and fibrils, however, it was proven that there existed no correlation between insoluble plaque density and age, brain tissue, thickness, or cell count (Terry *et al*., 1981). Instead, as seen in a report by McDonald *et al*. (2010), the levels of β-amyloid oligomers are substantially higher in AD patient's brain tissue than those observed in non-demented patients. The above information suggests a correlation between the size of the amyloid aggregates and their respective toxicity, whereas the more

complex the aggregate becomes, the lesser toxic effects it exerts. The higher toxicity levels of amyloid oligomers are a consequence of their structural arrangements. Compared to fibrils and plaques, oligomers are far more unstable and possess more free active groups to interact with cellular targets (Verma *et al*., 2015). Also, fibrils are more susceptible to hydrophobic stability, as most of the hydrophobic amino acid residues are allocated in the interior of the fibril, whereas the hydrophobic residues of amyloid oligomers are arranged in β-sheets, which increase the contact with the medium (Paravastu *et al*., 2008).

Both β-amyloid oligomers and fibrils display toxic effects on neurons that can deregulate downstream processes and cause death. Two primary toxic mechanisms are caused by β-amyloid: membrane disruption and Ca^{2+} flux deregulation. While interacting with the cellular membrane, β-amyloid bestows the outer lipid bilayer a negative charge, which facilitates the peptide's insertion within the lipid membrane (Ahyayauch *et al*., 2012). The presence of β-amyloid peptides in the cell membrane can lead to cytotoxicity, reduced levels of ACh uptake (Kar *et al*., 2004), β-amyloid fibrilization, and Ca^{2+} flux deregulation (Ahyayauch *et al*., 2012). The altered conductance of the cellular membrane affects calcium ion's permeation, which in turn destabilizes the downstream pathways dependent on the balanced ion flux. Deregulated absorption and release of Ca^{2+} through the cell can lead to transmembrane signaling processes, mitochondrial dysfunction, reactive oxygen and nitrogen species production, and apoptosis (Verma *et al*., 2015).

The increased levels of β-amyloid have been associated with higher concentrations of glycogen synthase kinase 3β (GSK3β). Though the specific mechanisms are yet unknown, one hypothesis suggests that GSK3β negatively interacts with voltage-dependent anion channel-1 (VDAC1), which is a transmembrane receptor. VDAC-1 is bonded to hexokinases, which interact favorably with mitochondria. GSK3β phosphorylates VDAC1 in the threonine residue, increasing the permeability of the membrane and detaching the bonded hexokinases, causing mitochondria dysfunction (Reddy, 2013).

One of the most prevalent abnormalities observed in β-amyloid-induced AD is the abnormal deposition of the peptide. The human body possesses enzymatic and mechanical systems capable of removing soluble forms of β-amyloid from the interstitial fluid. These include permeation through the blood-brain barrier (Mackic *et al*., 2002), proteolysis (Baranello *et al*., 2015), and perivascular drainage (Hawkes *et al*., 2014). However, insoluble oligomers of β-amyloid may deposit around perivascular spaces, more specifically in the medium where blood vessels reside. Accumulation β-amyloid occurs in the blood vessel walls of the perivascular pathway from which interstitial fluid drains from the brain. Solutes diffuse through the perivascular space and are drained by crossing basement membranes surrounded by smooth muscle cells (Hawkes *et al*., 2014). This condition is known as cerebral amyloid angiopathy.

In mid-to-late 2019, aducanumab entered phase 3 of clinical trials as an important anti-β-amyloid agent. Aducanumab is an antibody that binds selectively to β-amyloid oligomers and plaques and was proven to slow the rate of cognitive decline of patients with mild to advanced AD (Selkoe, 2019). In March 2019, the development of the antibody was halted due to a failed futility test, however, it was shown later that year that a higher dose of the therapeutic agent significantly improved the neurodegenerative effects of β-amyloid. Other treatment options involve the application of specific secretase inhibitors, such as NB-360, which has been proven to cross the blood-brain barrier and inhibit β-secretase and the accumulation of β-amyloid peptides in the brains of transgenic mice (Neumann *et al*., 2019), but as of today, no clinical trials on humans were reported. Another β-secretase inhibitor drug is CNP-520, which was found to

inhibit β-secretase activity in preclinical human trials, with an IC_{50} of 11 ± 0.4 nM (Neumann *et al*., 2018).

4.3. Tau protein hypothesis

Tau is a protein found in the CNS which stabilizes the microtubules that assemble the ramifications of the neurons. The protein is expressed by the MAPT gene, found in chromosome 17. In the human brain, the expression process generates six Tau isoforms, each one with a different molecular weight. The gene is composed of 16 exons, however, depending on the type of neurons, alternative RNA splicing occurs in exons 2, 3, and 10, thus producing different Tau isoforms (Mandelkow *et al*., 2016). The alternate splicing affects the length of the binding domain, as it can either express 3 or 4 repeats of a conserved tubulin-binding domain, each one composed of 18 amino acids (Kolarova *et al*., 2012). Tau protein is composed of four domains: an acidic N-terminal projection, a proline-rich domain, the microtubule-binding domain, and a C-terminal domain (Mandelkow *et al*., 2016). Figure 4.5 presents a representation of the largest Tau isoform, as a reference point to the basic structure of the protein.

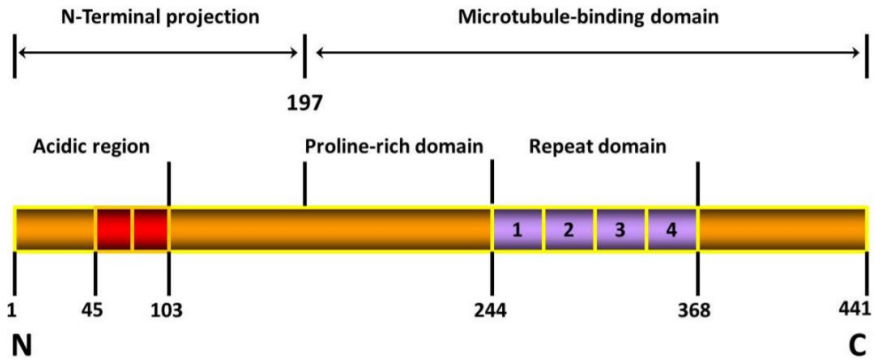

Figure 4.5. The four domains in Tau protein (Luna-Munoz et al., 2013).

The binding domain of tau protein is responsible for directly binding to microtubules, while the N-terminal projection interacts indirectly with the assembly process by regulating the spacing between microtubules (Chen *et al*., 1992), as well as playing a role in axonal transport, in which it facilitates the translocation of cellular content by electrostatically stirring motor proteins that attach to intracellular components from the soma to the axonic terminal, and vice-versa (Dixit *et al*., 2008). The actual functions displayed by the proline-rich domain are lesser-known. This Tau section has been found to neither exacerbate the assembly or stabilization process. It is thought that this domain stabilizes the microtubule-binding domain, maintaining the linear structure of the adjacent peptides (Goode *et al*., 1997). The proline-rich domain also is involved in the binding of actin and its bundling to generate filaments (He *et al*., 2009), which are vital for cell mobility and structural maintenance (Dominguez *et al*., 2011). The repeat domain is considered to exert both microtubule-binding and tubulin-assembly activity (Trinczek *et al*., 1995), however, the repeats have been described to establish weak bonds with microtubules. Microtubules are stabilized by bonding the proline-rich domain and the C-terminal domain (Chen *et al*., 1992). The C-terminal section of Tau protein stabilizes the microtubule-binding repeats in the same manner as the proline-rich domain. There are also indications that the C-terminal intervenes in the polymerization process by enhancing the polymerization process (Abraha *et al*., 2000). The C-terminal is acidic (positively charged) and can increase the nearby tubulin concentrations by electrostatic interactions (Barbier *et al*., 2019).

Across the length of Tau protein lie numerous phosphorylation sites in serine, tyrosine, and threonine residues. Phosphorylation of the Tau protein is an important factor in cell plasticity, as this process ruptures the protein-microtubule bonds. This process includes the transfer of phosphate groups from kinases to the residues, with a subsequent cleavage by phosphatases (Noble *et al*., 2013). In a healthy brain, Tau phosphorylation is a well-balanced process between kinases and phosphatases, however, in some pathologies, such as in AD, the phosphorylation process is disrupted. In some cases, tau protein-based pathologies have been linked with progressive states of AD, with β-amyloid intervening in the kinase release pathways from the neurons. The proline-rich domain possesses the most phosphorylation sites out of all protein sections and therefore is the most well-known (Iqbal *et al*., 2008). Some of the proline residues interact with GSK3β, whose high activity rate has been directly linked with increased concentrations of β-amyloid deposits (Wu *et al*., 2018). β-amyloid also has a foothold in the hyperphosphorylation process, as it can trigger the p38 pathway that generates mitogen-activated protein kinases (MAPK); these enzymes promote phosphorylation in serine and threonine residues (Zhu *et al*., 2002).

When hyperphosphorylation takes place, the microtubule-Tau bonds are disbanded, reducing microtubule stability, with a subsequent formation of neurofibrillary tangles of free Tau proteins (Noble *et al*., 2013). Neurofibrillary tangles act in the same manner as β-amyloid plaques, as the aggregation of hyperphosphorylated Tau stabilizes the deposit. The primary toxic effects of tau tangles involve the weakening of the microtubular structures, as well as the disruption of neuronal transport, as it played a pivotal role in the mobility of cellular content from the soma to the axonic terminal, which then leads to synapse loss and cell death (Kopeikina *et al*., 2012).

The most commonly available treatment options of tauopathies suggest the inhibition of GSK3β, as the enzyme is at the core of progressive states of AD. GSK3β has been proven to be inhibited by lithium salts, however, these salts have also been evidenced to promote hyperphosphorylation in certain serine residues in NIH-3T3 cells (Abdul *et al*., 2018). Other drugs have been postulated to reduce abnormal phosphorylation rates. Sodium valproate is an anticonvulsant that has also been evidenced to inhibit GSK3β in APP/PS1 double-transgenic mice, who were administered daily doses of sodium valproate of 50 mg per kg for 12 weeks (Hu *et al*., 2011). Clinical trials were conducted to assess the anti-dementia effects on human patients, however, sodium valproate was discouraged for safety reasons, since no treatment effects were registered, as well as the administration resulted in adverse behavioral and physiological effects (Tariot *et al*., 2011). Other GSK3β inhibitors include kenpaullone, which showed to suppress the kinase activity by around 10%, however, it shows itself as a promising drug, as it is thought to easily cross the blood-brain barrier due to its lipophilic properties, as it contains 2 benzene rings in its structure (Kitabayashi *et al*., 2019).

Pharmaceuticals such as statins have been thoroughly studied as possible treatment options for AD. Riekse *et al*. (2006) evaluated the effects of simvastatin, a pharmaceutical belonging to the family of statins, on the phosphorylated tau clearance from the cerebrospinal fluid. The clinical trial was performed on a group of 10 non-demented individuals, with ages ranging from 34 to 87 years. The patients were administered orally 20 mg/day of simvastatin for the first 2 weeks, with an increase to 40mg/day for the remaining 12 weeks. The results showed a reduction of phosphorylated tau protein content in the cerebrospinal fluid of all patients, from 48.1 pg/ml to 46.9 pg/ml. The postulated hypothesis relies on statins' potential to inhibit MAPK enzymes.

4.4 Glutamate excitotoxicity hypothesis

Glutamate is an amino acid that acts as the primary excitatory neurotransmitter in the brain, interacting with ionotropic and glutamate metabotropic receptors in synapses. Glutamate is produced from α-ketoglutarate, an intermediate product of the Krebs cycle, more specifically the tricarboxylic cycle that metabolizes citrate (Walls, 2016).

Glutamate is found in the blood; however, the blood-brain barrier blocks the amino acid's relocation to the brain. Instead, glutamine crosses the blood-brain barrier into astrocytes (Lee *et al*., 1998), with a subsequent transfer to the extracellular domain through excitatory amino acid transporter's 1 and 2 (EAAT1 and EAAT2), followed by neuronal absorption through EAAT3. As seen in Figure 4.6, glutamine is catalyzed to glutamate within the neuron by mitochondrial glutaminase (Stobart & Anderson, 2013). Like any other neurotransmitters, glutamate is encapsulated in vesicles to initiate synaptic release and post-synaptic receptor interaction. Glutamate can interact with three different ionotropic receptors: α-amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid (AMPA) receptors, kainate receptors, and N-methyl-D-aspartate receptors (NMDA) (Stobart & Anderson, 2013).

The glutamate metabotropic receptors are comprised of three groups: Group 1 includes mGlu1 and mGlu5 receptors, which are stimulatory groups that activate phospholipase C; Group 2 includes mGlu2 and mGlu3 receptors, while Group 3 aggregates mGlu4, mGlu6, mGlu7, and mGlu8 receptors. Groups 2 and 3 are inhibitory receptors, which suppress the formation of cAMP in the intracellular domain by inhibiting adenylyl cyclase activity (Crupi *et al*., 2019). After glutamate generates an action potential in the post-synaptic neurons, the neurotransmitter is either absorbed by neuronal EAAT (neuronal uptake), where it integrates the synaptic release process, or astrocyte EAAT (astrocyte uptake), in which it is catabolized by astrocyte glutamine synthetase, generating glutamine (Stobart & Anderson, 2013).

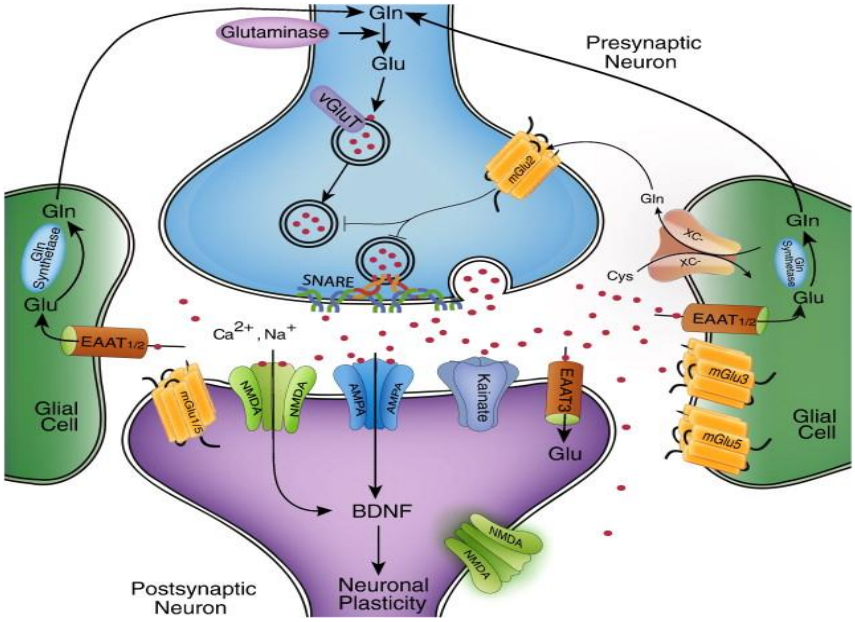

Figure 4.6. Production, neurotransmission, and recycling of glutamate in the glutamatergic system (Niciu et al., 2012).

NMDA receptors consist of two GLU_{N1} and two GLU_{N2} subunits, designed to recognize glycine and glutamate amino acids, respectively (Paoletti *et al*., 2013). The ionic entry point of

the NMDA receptor is blocked by Mg^{2+} ions (Zhang *et al*., 1996), which derive from the extracellular domain. Calcium permeation is dependent on the interaction between glutamate and the NMDA receptor, as well as a strong depolarization state of the post-synaptic membrane caused by an interaction between other ionotropic receptors (Mayer *et al*., 1984). Both effects induce a release of Mg^{2+} ions from the NMDA entry point, thus allowing for an increased calcium ion absorption.

The neuropathological effects associated with the glutamatergic system are derived from excessive glutamate interaction with ionotropic receptors. As seen with other cases of excessive neurotransmitter-receptor interaction, neurons are affected by excitotoxicity, in which the inward flow of calcium ions increases. According to with existing literature, NMDA receptors are described as the primary receptors involved in the neuropathological effects in neurons, since it is the only ionotropic receptor capable of permeating calcium ions, beyond sodium and potassium. During the neurotransmitter-receptor interaction, the inward flow of calcium ions induces either long-term potentiation or long-term depression (Müller *et al*., 2009). Long-term potentiation is achieved when strong polarization and glutamate interaction occurs, meaning that more calcium ions are permeated, whereas, in long-term depression, modest glutamate-NMDA receptor interactions take place. Depending on the observed effects, synapse plasticity can either increase or decrease. Chen *et al*. (2002) suggested that β-amyloid had a toxic effect in the glutamatergic system, by impairing NMDA receptors through ion channel blocking, thus suppressing long-term potentiation. However, the role of β-amyloid appears to be more elaborated, as it can also negatively enhance glutamate release. Kabogo *et al*. (2010) evidenced that β-amyloid and smaller amyloid peptides potentiated the presynaptic potassium ion dependent release of glutamate, although the underlying mechanisms remained unknown. β-Amyloid-induced glutamate release has been suggested as a cause of interactions with the nicotinic choline receptors and β-amyloid peptides (Mura *et al*., 2012).

Memantine is a low-affinity NMDA receptor antagonist. While cholinergic drugs are administered to patients in early to mild stages of AD, memantine demonstrates the most significant potential of application in more advanced and severe stages of the disease. Memantine's action in the glutamatergic system is similar to that of the Mg^{2+} ions, as a means to prevent or minimize the postsynaptic influx of Ca^{2+} ions, thus suppressing the effects of excitotoxicity in the neurons (Danysz & Parsons, 2003).

4.5. Endocannabinoid receptors

The endocannabinoid system (ECS) is a biological, modulatory system comprised of neurotransmitters, receptors, and enzymes found primarily in the CNS and in the immune system. Matsuda *et al*. (1990) were able to express and encode a cDNA sequence found in the cerebral cortex of mice, whose translated protein was identified as a G protein-coupled receptor and could interact with THC. However, the discovery of the ECS dates back to 1992, when Hanus *et al*. (1992) tested for cannabinoids in porcine brain extracts, resorting to a radiolabeled cannabinoid probe method. Researchers found the presence of a competitive ligand, later named anandamide, that inhibited the probes in a concentration-dependent manner, like psychotropic cannabinoids. Anandamide (arachidonoyl ethanolamide) and 2-arachidonyol glycerol, or 2-AG, are the most well documented cannabinoid neurotransmitters. These endocannabinoids are fatty acid neurotransmitters derived from arachidonic acid. Anandamide production involves the enzymatic conversion of arachidonic acid to arachidonoyl-phosphatidylethanolamine (NAPE) by N-

acetyltransferase, with subsequent NAPE catalysis by N-acyl-phosphatidylethanolamine phospholipase D (NAPE-PLD) (Maccarrone, 2017). 2-AG production also involves two steps. Phosphatidylinositol is firstly transformed into 1,2-diacylglycerol by phospholipase C, followed by the intermediate's conversion into 2-AG by diacylglycerol lipase (DAGL) (Stella *et al*., 1997). Both endocannabinoids are produced in the postsynaptic terminal. Endocannabinoids interact primarily with cannabinoid receptors 1 and 2 (CB_1 AND CB_2). Both receptors are G protein-coupled receptors, specifically G_0 and G_i proteins. As discussed throughout this chapter, this coupling results in adenylyl cyclase inhibition, which in turn suppresses calcium ion influx, thus suppressing neurotransmitter release (Lu *et al*., 2017). CB_1 is one of the more predominant receptors in the CNS. CB_1 has gained traction as a potential therapeutic point of action in neurophysiological disorders, such as chronic pain, ticks, and in the sense of this report, PD, and AD (Consroe, 1998). On the other hand, CB_2 is found primarily in the peripheral nervous system, immune system, and in the brain, although not in the same proportions as CB_1 (Munro *et al*., 1993). In the immune system, CB_2 receptors are expressed in leukocytes and its activation is suggested to treat inflammation and pain (Turcotte *et al*., 2016).

The endocannabinoid system is different from other neurotransmitter-signaling systems. Both anandamide and 2-AG are produced "on-demand", meaning that production only occurs when the neurotransmitters are needed, therefore, vesicle storage is not required. This implies that anandamide and 2-AG production is activated under specific stimuli, like calcium ion influx. Cannabinoid receptors are anchored in the presynaptic membrane, meaning that anandamide and 2-AG are retrograde messengers. To reach the CB_1 receptors, endocannabinoids are directed to the specific interaction area employing putative extracellular transporter proteins (Di Marzo *et al*., 2004). After interacting with the presynaptic receptors, the endocannabinoids enter through the axonic membrane, either by passive diffusion or via facilitated membrane transport. Within the cells, the endocannabinoids are then directed by intracellular transporter proteins to initiate their degradation process (Maccarrone, 2017). Anandamide degradation is carried out by fatty acid amine hydroxylase (FAAH), localized in the endoplasmic reticulum (Maccarrone *et al*., 2010) and the mitochondria (Morozov *et al*., 2004), generating ethanolamine and arachidonic acid (Deutsch & Chin, 1993), while 2-AG is hydrolyzed by monoacylglycerol lipase (MAGL), located in both neurons and astrocytes (Viader *et al*., 2015), which produces arachidonic acid and glycerol (Rademacher *et al*., 2005).

The endocannabinoid system has emerged as a potential treatment target for numerous neurodegenerative diseases. For example, the connection between the endocannabinoid system and AD can be traced to the cognitive effects of THC, which result primarily in memory impairment, as CB_1 receptors are localized in the axonic GABAergic and glutamatergic terminals (Puighermanal *et al*., 2009). Cannabinoid interaction with its receptors can trigger different neuroprotective mechanisms against multiple neurodegenerative diseases. As CB_1 receptor interaction can inhibit the influx of calcium ions in the presynaptic membrane, so to can it regulate glutamate release to the synapse, thus suppressing excitotoxicity (Marsicano *et al*., 2003). The generation of β-amyloid has been evidenced to negatively affect the endocannabinoid system. β-Amyloid is known to activate microglial immune cells, which triggers the formation of pro-inflammatory cytokines, as it is common in AD (Strohmeyer & Rogers, 2001). CB_2 receptors are mainly expressed in microglia, where they are known to inhibit microglial neurotoxicity. As a result of β-amyloid surrounding microglial cells, CB_2 receptors are overexpressed, as a means to compensate for the excessive neuroinflammation (Benito *et al*., 2003).

On the other hand, studies regarding CB_1 receptor expression under surrounding β-amyloid did not generate concordant results. Ramírez *et al*. (2005) conducted an immunolabeling assay to identify the presence of CB_1 receptors in the presence of senile plaques in control and AD *postmortem* brain tissue samples. The results showed that four AD tissue samples had lesser CB_1 receptor density, however, the remaining two tissue samples did not show any significant receptor loss. There has also been evidence that the enzymes belonging to the endocannabinoid system are also affected. In glial cells, the activities of FAAH (Benito *et al*., 2003), MAGL, and DAGL (Farooqui *et al*., 1990) have been evidenced to increase. In the case of MAGL and DAGL, as they partake in the synthesis and degradation progress of 2-AG, there is a case to be made that the neurotransmitter levels in the brain can increase in AD pathologies, however, no studies on 2-AG levels in AD were found. The endocannabinoid system is also related to the dopaminergic system. CB_1 receptors and D_1/D_2 receptors are localized in striatum neurons, with each other having a direct effect on the other. It has been reported that anandamide interaction with CB_1 receptor-induced a decreased dopamine release to the striatum synapse, while this effect was inverted in the *nucleus accumbens*, which is situated in the hypothalamus. D_2 receptors, on the other hand, have been evidenced to increase the levels of anandamide in the basal ganglia (Scotter *et al*., 2010). Also,

Despite the discussed effects on the endocannabinoid system, treatment options are available in the form of cannabinoid receptor agonists and antagonists. In the cases where β-amyloid strikes, the administration of CB_1 and CB_2 agonists have been proven to protect the brain from several AD pathologies. The administration of CB_1 receptor agonists has been identified in inhibiting $^{\bullet}NO$ production (Cabral *et al*., 2001), and inhibiting GSK3β (Libro *et al*., 2017), which prevents tau protein hyperphosphorylation, while the administration of CB_2 receptor agonists reduces the production of pro-inflammatory cytokines (Parlar *et al*., 2018), and facilitation of β-amyloid clearance from the brain (Aso *et al*., 2016). No noteworthy and commercial agonists are available. The primary agonist is THC; however, it is associated with psychoactive effects. Cannabinoid receptor antagonists can be administered to patients with short-term memory loss. One of the most popular cannabinoid receptor antagonists is cannabidiol, a neuroprotective component extracted from cannabis without exerting psychoactive effects on the patient (Peres *et al*., 2018).

4.7. Monoamine theory (Monoamine oxidase A and B)

Dopamine is one of the most necessary monoamine neurotransmitters in the CNS (Klein *et al*., 2019). Production and neurotransmission of dopamine in Parkinson's disease are altered. Dopamine is generated in the organism by the daily ingestion of the nonessential amino acid tyrosine, the most common dopamine precursor in regular dietary intake (Thorne Research INC, 2007). Tyrosine holds a structure like that of dopamine.

The metabolic pathway for neurotransmitter generation from tyrosine is composed of two steps: the production of the precursor levodopa (L-DOPA) and its subsequent conversion to dopamine. When the human body is nourished with tyrosine-rich products, the amino acid is stored and then transported to the brain, namely to the dopaminergic neurons, through the blood flow (Klein *et al*., 2019). Tyrosine-hydroxylases catalyze the precursor's hydroxylation, promoting the junction of a hydroxyl group in the molecule's aromatic ring. Figure 4.7 shows the reaction steps in L-DOPA production.

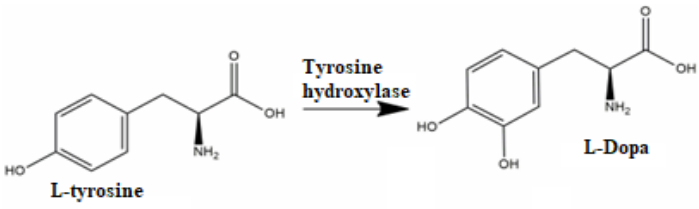

Figure 4.7. L-DOPA biosynthesis (Silva, 2015) [Adapted].

After L-DOPA is synthesized, the enzymatic-catalyzed decarboxylation step takes place. As seen in Figure 4.8, a terminal carboxyl group is removed, in a reaction catalyzed by aromatic amino acid decarboxylases (AAAD) (Klein *et al*., 2019). Like the cholinergic system, after the neurotransmitter production, the molecules are stored in presynaptic vesicles in the dopaminergic neuron's terminal axons.

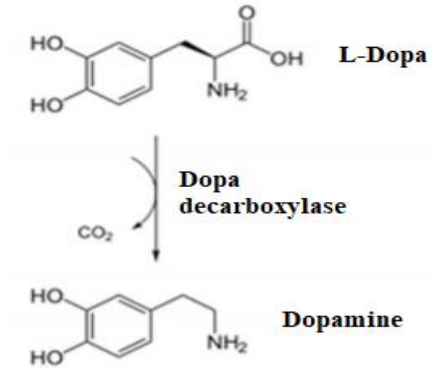

Figure 4.8. Dopamine production from the L-DOPA precursor (Jami et al., 2014) [Adapted].

The control of movements of the body limbs is dependent on the dopamine systems located in the substantia nigra in the brain stem (Köhl *et al*, 2009). The type of interaction between the dopamine and postsynaptic receptors resemble that examined in cholinergic processes. Consequently, dopamine is released from the vesicles to the synapse, followed by the propagation of the nerve impulse. After the necessary interaction, the neurotransmitter is absorbed into its native cell and then stored. These biochemical interactions are then responsible for inducing a motor response in the body.

Like in cholinergic systems, the degradation step of the neurotransmitter is carried out by specific enzymes in the dopaminergic synapses that catalyze the oxidative deamination of dopamine deamination. These enzymes belong to the family of monoamine oxidases (MAO). There are two isoenzymes in the synapses, MAO-A and MAO-B. The key difference between them resides in their specificity to substrates. MAO-B has more affinity to dopamine than MAO-A, the latter being more specific for serotonin and noradrenaline (Fowler & Benedetti, 1983).

After the neurotransmission takes place, dopamine molecules are re-uptaken to the axon terminals. While inside the cell, MAO degradation proceeds, to alleviate the neurotransmitter's concentration inside the axons (Klein *et al*., 2019). This step forces the neurons to synthesize new molecules of dopamine only when needed to regulate the necessary concentration levels and to control the propagation of the nerve impulse to prevent overstimulation of post-synaptic neurons. Dopamine is decomposed into homovanillic acid, which is then excreted of the body by urine (Thorne Research INC, 2007). MAO-B inhibitors, such as selegiline and rasagiline are available as antiparkinsonian drugs for PD treatment. Other enzymes are also involved in catecholamine

degradation, such as catechol-*O*-methyltransferases (COMT). Indeed, COMT inhibitors are commonly used as an adjunct to levodopa in patients with PD (Müller, 2015).

Even though MAO-A enzymes assume a lesser role in dopamine decomposition, they take part in other metabolic processes more emphatically, such as is the case of serotonin degradation. This neurotransmitter, known as 5-hydroxytryptamine (5-HT), is present in the brain stem's regions, in serotoninergic systems perform. Serotonin is synthesized in the brain from the precursor L-tryptophan. This amino acid is introduced in the body from food sources and transported through the bloodstream to the brain (Gray & Roth, 2007). The serotonin synthesis pathway is shown in Figure 4.9.

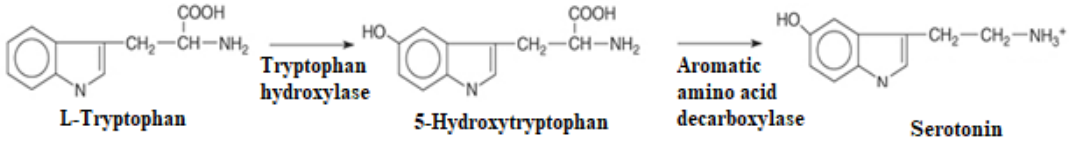

Figure 4.9. Serotonin production from tryptophan (Gray & Roth, 2007) [Adapted].

The metabolic reaction of serotonin production comprises of two steps. Initially, L-tryptophan suffers a hydroxylation by tryptophan hydroxylase, a native enzyme in serotoninergic neurons, and 5-hydroxytryptophan is produced as a result. The final step involves the molecule's decarboxylation in the presence of AAAD (Gray & Roth, 2007). The degradation reaction of serotonin is demonstrated in Figure 4.10.

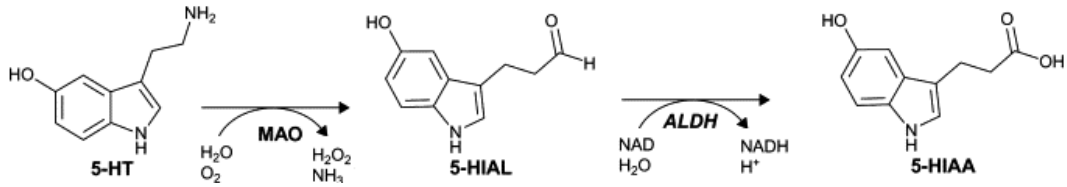

Figure 4.10. Serotonin degradation process [Adapted] (Bortolato et al, 2010).

The breakdown process of this neurotransmitter involves two steps. Firstly, MAO-A oxidizes 5-HT to 5-hydroxy-indol acetaldehyde (5-HIAL). As a result of this oxidation, hydrogen peroxide (H_2O_2) is produced as a secondary product, which is regarded as one of the primary reactive oxygen species (ROS) responsible for oxidative stress that incapacitates neurons. (Youdim *et al*., 2006). In the second stage, the enzyme aldehyde hydrogenase converts the aldehyde 5-HIAL into 5-hydroxy-indol acetic acid (5-HIAA), by converting the terminal aldehyde group into a carboxylic group (Gray *et al*., 2007).

MAO-A inhibitors are responsible for inactivating the enzyme, and to increase neurotransmitter levels and postsynaptic receptors interaction. The available drugs in the market, such as phenelzine, isocarboxazid, and tranylcypromine, act as antidepressant drugs. All of the mentioned MAO-A inhibitors are irreversible and nonselective (Soares *et al*., 1999).

4.8. GABAergic release theory

Gamma-aminobutyric acid, or GABA, is a low molecular weight amino acid produced in the cytoplasm of GABAergic neurons that functions in the CNS as its primary inhibitor neurotransmitter. GABAergic neurons are interneurons that connect two brain regions that

perform different body activities, as seen with motor and sensory neurons. GABAergic neurons are scattered throughout the CNS (Vargas, 2018). GABA is produced is a derivative product of glutamate, which may be an indicator of the consociation between the glutamatergic and GABAergic systems. The Krebs cycle's α-ketoglutarate intermediate is enzymatically converted to glutamate by GABA-transaminase. After glutamate is produced, it takes part in the GABAergic shunt cycle, which encompasses all conversion steps from the production of α-ketoglutarate to the final conversion to succinate, which then reenters the tricarboxylic acid cycle. The middle step of the shunt cycle involves the enzymatic conversion of glutamate to GABA by glutamate decarboxylase. From this point, GABA can be converted to succinic semialdehyde by GABA-transaminase. Lastly, this intermediate product is converted to succinate by succinate-semialdehyde dehydrogenase (Walls, 2016). Like any other neurotransmitter, GABA is encapsulated by vesicles in the axonic terminal, awaiting outside stimulation to enter the synapse.

When GABA is released to the synapse, it can interact with three GABA receptors: $GABA_A$, $GABA_B$, and $GABA_C$. $GABA_A$ and $GABA_C$ are ionotropic receptors. When GABA binds to any of these two receptors, it increases the inner permeability of chloride ions, which cross the postsynaptic membrane and hyperpolarize it. The inward flux of chloride ions causes the actual membrane potential to decrease, making it less likely to achieve the action potential for excitation to occur (McNamara *et al*., 2004). This manifestation only occurs under low concentrations of chloride in the synapse. When the postsynaptic neuron has high chloride levels, the ionic equilibrium potential increases. When this value is more positive than that of the membrane's resting potential, GABA receptors translocate chloride back to the synapse, thus inducing depolarization (Rahmati *et al*., 2018). GABA was found to exert excitatory effects in developing brains, where synapses are yet to be formed. Neurons in developing brains release GABA to the extracellular domain in an attempt to stimulate itself, as these cells are absent of pre and post-synaptic receptors (Ben-Ari, 2014; Braun *et al*., 2010). $GABA_C$ is usually associated as being part of the $GABA_A$ receptor family, however, it is important to note that $GABA_C$ receptors are insensitive to $GABA_A$-activating drugs, such as benzodiazepine (Bormann & Feigenspan., 1995).

$GABA_B$ are metabotropic receptors, similar to those of glutamate, coupled with G proteins that mediate the inhibition of the postsynaptic membrane, by inhibiting adenylyl cyclase, as seen with glutamate, which in turn activates the inward flow of potassium ions and simultaneously blocks the voltage-dependent calcium channels. $GABA_B$ receptors can be divided into two groups defined as $GABA_{B1}$ and $GABA_{B2}$. These receptors form heterodimers with each other, with the $GABA_{B1}$ receptor as the only one that can interact with extracellular molecules, be it, agonist or antagonist. However, $GABA_{B1}$ cannot induce GABAergic signaling, as the receptor's internal C-terminal is bonded to the endoplasmic reticulum, which impedes the receptor from reaching the plasma membrane. The heteromer conformation forms a coil between each receptor's C-terminal domain, which allows for $GABA_{B2}$ to initiate membrane signaling. $GABA_{B2}$ is also coupled to G proteins that initiate adenylyl cyclase inhibition (Xu *et al*., 2014). $GABA_B$ receptors are found both in the pre and postsynaptic membranes. In the presynaptic membrane, GABA receptors can either be autoreceptors or heteroreceptors. Autoreceptors are responsible for inhibiting calcium flow in the presynaptic membrane, only suppressing GABA release from the axonic terminal, whereas heteroreceptors decrease neurotransmitter release, apart from GABA. Calcium influx is also blocked in the postsynaptic membrane, where it suppresses long term potentiation and NMDA receptor excitation as a result (Pinard *et al*., 2010).

To maintain the balance of the GABA system, it is fundamental that the neurotransmitter gets cleared from the synapse, to cease interactions with its receptors. Both neighboring neurons

and astrocytes possess transporter proteins capable of up-taking GABA, which help regulate GABA levels in the synapse, translocating the neurotransmitter to the intracellular domain of the cells to initiate mitochondrial degradation. GABA transporters belong to the family of sodium symporters. The human brain possesses 4 subtypes of GABA transporters: GABA Transporter 1 (GAT_1), GAT_2, GAT_3, and betaine GABA transporter (BGT_1). Out of all types of GABA transporters, GAT_1 and GAT_3 are considered the most important transporter subtypes, as they are more abundant in astrocyte membranes, where uptake is more common (Govindpani *et al*., 2017).

As the brain's primary inhibitor neurotransmitter, GABA is necessary to assure that the brain can cease activity so that the body can relax, without compromising the well-being of the body. Brain homeostasis, however, is only achievable when the GABAergic and glutamatergic systems form a steady balance between them. The coordination between both excitatory and inhibitory actions leads to a well-defined rhythmic activity of the body, thus preventing any kind of neuronal disorders. Such disorders take place when a disruption of the neurotransmitter activities occurs. A stronger tendency of the imbalance towards the glutamatergic system has been evidenced to induce anxiety and autism in an individual, whereas the overexpression of GABA leads to overrelaxation and sedation (Hampe *et al*., 2018). Although the exact mechanisms are unknown as of yet, studies suggest that the GABAergic system-induced imbalance derives from the overexpression of GABA in astrocytes, more specifically the abnormal activation of glutamate decarboxylase, possibly as a result of fibrillar β-amyloid accumulation (Mitew *et al*., 2013). In association with this information, Wu *et al*. (2014) evidenced that human GAT_3 is responsible for releasing into the synapse high concentrations of GABA from astrocytes localized in the dentate gyrus (located in the hippocampus) when surrounded by β-amyloid plaques. This excessive release of GABA leads to abnormal $GABA_A$ receptor modulation, which suppresses important signaling processes and leads to cell death.

GABA transporters are also important factors to account in GABAergic neurodegeneration; GABA transporters allow for regulated neurotransmitter interaction without exposing the receptor to abnormal levels of synaptic GABA, meaning that a negative alteration in the uptake system can lead to a significant disruption of the GABAergic system. Simpson *et al*. (1988) evidenced that AD patients showed fewer amounts of GABAergic neurons in the temporal cortex. The author and his coworkers reached this notion by evaluating the binding affinity of nipecotic acid, a GABA uptake inhibitor, to GABA transporters in samples of postmortem brain tissue. However, these results seem as dependent on the brain region. For example, Nägga *et al*. (1999) conducted a similar assay to assess the binding affinity of tiagabine to GAT_1 on postmortem brain tissue from the temporal lobe, cortical, and subcortical areas. In this case, the results showed that, compared to control brain tissue, no significant differences of GAT_1 were registered, which suggests that GABAergic neuron loss may depend on the location in the brain.

The GABAergic system holds different points of action in which pharmaceutical drugs can suppress disruption effects and improve the well-being of the patient. The conventional treatment involves the administration of GABA receptor agonists that mimic the effects of the neurotransmitter in the synapse. Administration of agonists is best advised for when cortical GABA levels are low. Some of the most documented GABA agonists include benzodiazepines and barbiturates for $GABA_A$ receptors and baclofen for $GABA_B$ receptors. GABA antagonists are prescribed to counteract the sedative effects of the neurotransmitter. GABA antagonists include bicuculine, which selectively interacts with $GABA_A$ receptors, and salophen for $GABA_B$ receptors (Jembrek & Vlainic., 2015). Another strategic treatment option, when faced with low GABA

levels on the brain, is the inhibition of GABA transporters, so that the neurotransmitter can induce its sedative effects. Tiagabine is an anticonvulsant which binds selectively inhibits GAT_1 (Gaitatzis *et al*., 2002). Lastly, GABA-transaminase inhibition is also viewed as a potential treatment option for patients with low GABA levels in the brain. Even though GABA-transaminase mediates both production and degradation of GABA, extrasynaptic GABA is recycled through neurons and astrocytes. Inhibiting GABA-transaminase is seen as a crucial step in preventing further neurotransmitter degradation when its levels in the brain are low. Valproate has been documented to stabilize the mood of patients by inhibiting GABA-transaminase (Johannessen, 2000).

4.8. α-Synuclein protein hypothesis

α-Synuclein is a presynaptic protein composed of 140 amino acids encoded by the SNAC gene. α-Synuclein is found in axonic terminals of dopaminergic neurons, primarily either as monomers or α-helically folded tetramers. Though not fully proven, α-synuclein appears to be involved in regulating neuronal physiological processes by interacting with the lipid membrane or its anchored proteins, contributing towards vesicle trafficking, vesicle fusion with the lipidic membrane, and neurotransmitter release (Butler *et al*., 2017; Snead & Eliezer, 2014).

α-Synuclein is thought to mediate vesicle fusion with the phospholipid membrane by binding to the vesicular protein synaptobrevin-2, or VAMP-2, which, with further interactions with membrane-integrated, synaptosome-associated protein-25 (SNAP-25) and syntaxin-1, assembles a temporary SNARE-complex (soluble N-ethylmaleimide-sensitive factor attachment protein receptor), as seen in Figure 4.11. α-Synuclein mimics the function of cysteine string protein-α (CSP-α), which is a chaperone involved in the assembly of the SNARE-complex. The effects of absent CSP-α in the neuronal terminals have been evaluated in transgenic mice, where the lack of chaperone in this mechanism significantly decreased the SNARE-complex and SNAP-25 levels in the axonic terminals, as well as promoted nerve cell degeneration, cell death, and motor impairment (Burré *et al*., 2010). α-Synuclein was evidenced to imitate CSP-α by increasing the levels of SNARE-complex, however, no direct effects on SNAP-25 recuperation were reported (Cooper *et al*., 2006).

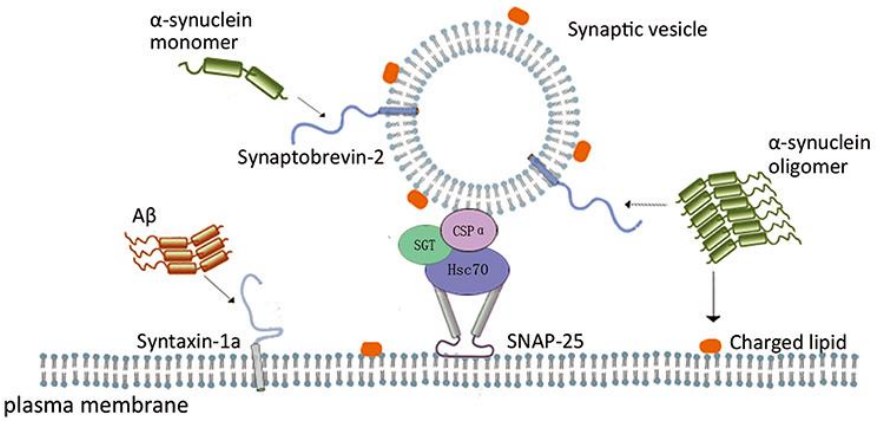

Figure 4.11. α-Synuclein-mediated SNARE-complex fusion with the cellular membrane (Hou et al., 2017).

α-Synuclein has been linked with dopaminergic neuron loss and the progression of PD; like the hypothesis regarding β-amyloid plaques and tau protein neurofibrillary tangles, the general pathogenic properties of α-synuclein revolve around the abnormal oligomerization of

protein monomers to one another, resulting in the disruption of several important processes. Certain mutations of the SNAC gene have been linked with the prevalence and progression of sporadic and familial PD. Sporadic PD is associated with the substitution of nucleotides in the SNAC gene, while familial PD is attributed to duplication or triplication of SNAC locus, in which one or two more alleles are inserted in the chromosome, respectively. The addition of SNAC alleles increases the production of α-synuclein (50% for one additional allele) (Nishioka & Hattori, 2011).

α-Synuclein is comprised of three domains: A N-terminal domain containing 65 amino acids, a non-β-amyloid component (NAC) containing 30 amino acids, and a C-terminal domain containing 45 amino acids (Stefanis, 2012). The N-terminal domain has been linked with the pathological dysfunction of α-synuclein since all known mutations affect the section at hand. Seven different mutations in the SNAC gene have been found to contribute to the progression of familial PD. The mutations in the SNAC gene result in the expression of different α-synuclein with substituted amino acids in specific positions of the N-terminal. These substitutions include Ala53Thr, Ala30Pro, Glu46Lys, His50Gln, Gly51Asp, Ala53Glu, and Ala53Val. Out of all mutations, Ala53Thr (Polymeropoulos *et al*., 1997), Glu46Gln (Choi *et al*., 2004), and His50Gln (Ghosh *et al*., 2013) are mostly involved in the prevalence of familial PD, as these mutations are autosomal dominant, or hereditary, causing abnormal genetic α-synuclein oligomerization and misfolding of α-synuclein. After protein-encoding, the N-terminal domain is subjected to acetylation by an enzymatic process involving N-α-acetyltransferase. This process is suggested to stabilize the helical structure of the N-terminal, which prevents α-synuclein aggregation and slightly increases the binding affinity towards physiological membranes (Dikiy & Elizier, 2014).

The NAC domain has been identified as a component of Lewy bodies in the brain. Lewy bodies are formed from aggregated α-synuclein, as the protein fragment possesses a stretch of 12 hydrophobic amino acids from position 71 to 82 essential for the polymerization process of α-synuclein monomers (Giasson *et al*., 2001). The NAC domain has also been evidenced to promote β-amyloid oligomerization, as it assists the formation of a single and double-layered β-sheet structure with β-amyloid oligomers, resulting in the stabilization of β-amyloid and the formation of plaques (Atsmon-Raz & Miller, 2016).

The C-terminal domain is an important fragment that increases the solubility of α-synuclein in the cerebral fluid; this feature prevents synucleinopathy effects, as solubility directly inhibits the aggregation of α-synuclein monomers (Sang *et al*., 2002). The C-terminal domain also influences the fusion between the synaptic vesicles and the cellular membrane, as the fragment has a binding affinity towards lipids, even increasing when bonded with calcium ions (Lautenschläger *et al*., 2018). However, the domain was found to amplify the aggregation of α-synuclein when truncated. The most common protein truncation process takes place when the cells form inflammasomes as a signaling molecule of pathogens in the medium. Caspase-1 cleaves inflammasomes, producing pro-inflammatory cytokines designed to activate an immune response. The same enzyme was shown to cleave α-synuclein in between the Asp121 and Asn122 amino acids, in the C-terminal domain (Wang *et al*., 2016). Some studies have compared the effects of truncated α-synuclein with the already documented effects of normal α-synuclein, evidencing that the truncated protein loses its hydrophilic component located in the C-terminal domain. The cleavage of the hydrophilic component diminishes the chaperone-like activity of α-synuclein, as well as its solubility, which is a fundamental necessity to prevent oligomerization (Sang *et al*., 2002; Wateren *et al*., 2018).

The abnormal aggregation of unfolded α-synuclein oligomers can lead to the formation of larger, toxic, agglomerates, such as protofibrils and fibrils. As discussed previously, fibrils are much more stable than oligomers (and protofibrils), suggesting that the former species are more neurotoxic, as some studies evidence a poor correlation between the size of Lewy bodies with the severeness of PD effects (Colosimo *et al*., 2003; Parkkinen *et al*., 2011). α-Synuclein is subjected to phosphorylation in the C-terminal domain, more specifically at the Ser129 amino acid, a modification suggested for increasing the neurotoxic effects of the protein, by potentiating agglomeration (Wang *et al*., 2012). Neurons have specific pathways capable of controlling certain protein levels in the cytoplasm. The most important and studied degradation mechanisms of α-synuclein are the ubiquitin-proteasome system (UPS) and the autophagy lysosomal pathway (ALP).

UPS degradation occurs as ubiquitin chains are formed and bind to specific protein substrates, followed by proteasomal degradation. The polymerization of ubiquitin is carried by three enzymes: E1, E2, and E3. Firstly, E1 (ubiquitin-activating enzyme) bind to wild ubiquitin to integrate the polymerization process; E2 (ubiquitin-conjugating enzyme) then binds to activated ubiquitin to prepare conjugation. E3 is a protein-ligase that forms a complex with E2 to remove ubiquitin and liberating the conjugation enzyme. This step repeats until a ubiquitin chain is formed and E3 binds to a protein substrate, like α-synuclein, and catalyzes the formation of a ubiquitin- α-synuclein complex. The degradation of α-synuclein is conducted by the 26S proteasome, composed of a cylindrical 20S core and two 19S particles that regulate degradation. Polymerized ubiquitin binds to either 19S domains, releasing it from the complex, as α-synuclein enters the cylindrical domain to begin degradation into smaller peptides and building blocks. Ubiquitin chains are then depolymerized by deubiquiting enzymes (Lecker *et al*., 2006).

ALP is composed of three primary pathways: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). CMA is the primary degradation pathway of α-synuclein monomers and takes place in the neuron's lysosomes. CMA is composed of two stages: a chaperone-induced unfolding of α-synuclein, with subsequent translocation to the neuron's lysosomes, where degradation occurs. Misfolded α-synuclein in the cytoplasm are selectively targeted by heat shock cognate protein 70 (HSC70), which is a cytosolic chaperone that binds to proteins containing a lysine-phenylalanine-glutamate-arginine-glutamine (KERFQ) domain (Kenney *et al*., 2015). HSC70 plays an important role in minimizing synucleinopathy effects, as this step alters the conformation of toxic α-synuclein aggregates by unfolding it (Salvador *et al*., 2000). Once the chaperone-protein complex is formed, the substrate is targeted and translocated to the lysosomal membrane, where the protein substrate binds to a lysosome-associated membrane protein 2, or LAMP2 receptor. The interaction between the protein substrate and LAMP2 initiates a multimerization of the receptor, generating a translocation complex that facilitates the relocation of α-synuclein to the lysosomal lumen, where proteolysis occurs (Cuervo *et al*., 2014).

One of the mechanisms involving α-synuclein oligomers that contribute to the progression of PD is thought to be transmembrane seeding, in which several oligomers are deposited in the extracellular domain, with subsequent aggregation into Lewy bodies (Li *et al*., 2008), in a process defined as transmembrane seeding. α-Synuclein oligomers disrupt the maintenance of neuronal mitochondria, by interacting with its membrane, promoting calcium ion overflow, which in turn leads to ROS overproduction, membrane depolarization, and death (Luth *et al*., 2014). The presence of oligomers in the endogenous cellular domain also affects the release of neurotransmitters to the synapse. α-Synuclein oligomers have been evidenced to bind to

VAMP-2, as their monomeric counterparts, however, the formation of the SNARE-complex is inhibited (Choi *et al*., 2013). The mutated Ala53Thr α-synuclein was also found to impair UPS, by reducing the degradation of the protein substrate. Fluorescence assays were conducted on adult female Sprague-Dawley rats induced with HEK293 cells expressing Ala53Thr mutant α-synuclein to evaluate the effects on UPS impairment. The results showed that accumulated Ub^{G76V}-GFP, a protein complex formed with either free or chained ubiquitin, which suggests that the available levels of ubiquitin are reduced for α-synuclein degradation (McKinnon *et al*., 2020). In the same manner, CMA activity is reduced by mutant Ala53Thr and Ala30Pro α-synuclein, as it was evidenced to possess a higher affinity to the LAMP2 receptor, which reduces lysosomal uptake and proteolytic degradation (Cuervo & Wong, 2014). Other studies suggest ALP is negatively affected by reduced LAMP2 receptor expression, which deregulates lysosomal uptake (Alvarez-Erviti *et al*., 2010).

Available synucleinopathy treatment involves either increasing the degradation rate of α-synuclein or decreasing α-synuclein expression. Today, prescription drugs can be administered to attenuate PD progression, with some immunotherapy technologies showing promise, although not yet clinically available. RNA interference (iRNA) technology is an emerging therapy method, which has been utilized to prevent the translation of a specific gene or more. Lewis *et al*. (2008) conducted an intravenous administration of SNCA RNA small interferent (siRNA) 2mM at a rate of 0.25 µl/hour over 15 days to C57BL/6 female mice. The results showed an α-synuclein level reduction of 71% in the mice *substantia nigra*. Nilotinib is a drug utilized in the treatment of chronic myelogenous leukemia which has also shown promise in reducing α-synuclein levels in the brain. Nilotinib has been evidenced to inhibit Abl-tyrosine kinase, which is a cytosolic enzyme involved in several functions in the cell, as apoptosis (Hebron *et al*., 2013). When Abl-tyrosine kinase is activated, it increases the phosphorylation of α-synuclein, thus generating neurotoxic oligomers. The inhibition of this enzyme allows for the regulation of α-synuclein degradation pathways, such as CMA.

4.9. Adenosine receptor theory

Adenosine is an endogenous nucleoside composed of a β-N9-glycosidic bond between adenine and ribose molecules. Adenosine is found across the human body, with it playing a crucial role in the homeostasis of the heart and the brain. Adenosine modulates extracellular signaling in cells, by interacting with adenosine receptors in presynaptic, postsynaptic, and non-synaptic membranes, depending on the receptor's location in the brain. Intracellular adenosine is produced from its direct precursor AMP, derived from the gradual cellular metabolism of ATP and ADP. In the extracellular domain, adenosine mostly arrives from active nucleoside transport proteins of intracellular adenosine, as well as from the enzymatic degradation of exogenous ATP and cyclic-AMP (cAMP), an ATP derivative catalyzed by endogenous adenylyl cyclase (Layland *et al*., 2014). The adenosine transport receptors can be classified as either equilibrative (ENT) or concentrative (CNT). ENTs are passive transporters regulated by adenosine concentration gradients in the extracellular and intracellular domain (Pickard *et al*, 1972), whereas CNTs activity is mediated by sodium ions, in which adenosine diffusion occurs against the gradient (Gray *et al*., 2004).

While on the synapse, adenosine interacts with adenosine receptors found in the presynaptic and postsynaptic membranes. Presynaptic adenosine-receptor interactions have been evidenced to modulate vesicle release of different neurotransmitters, such as acetylcholine,

dopamine, glutamate, and GABA, while the postsynaptic interactions usually modulate the excitatory activity of said neurotransmitters (Sperlagh & Vizi, 2011). The adenosine system has been shown to impact sleep and wakefulness states. The documented effects of adenosine variate depending on which receptors it is interacting with. These receptors are coupled to G proteins that initiate secondary messaging generation and are divided into four subclasses: A_1AR, A_{2A}AR, A_{2B}AR, and A_3AR. In literature, A_1AR and A_{2A}AR have been documented the most due to their distribution in synapses and for their high affinity for adenosine, while A_{2B}AR and A_3AR have low affinity for the nucleoside (Cieślak *et al*., 2008). Depending on the subtype of G protein, the adenosine receptors can induce different responses. Adenosine-receptor interactions target adenylyl cyclase, favoring the transformation of intracellular ATP molecules to cAMP. The production of cAMP induces a concentration-dependent activation of protein kinase A (PKA), which phosphorylates neighboring ion channels (Pedarzani *et al*., 1995). When phosphorylated by PKA, calcium ion influx increases, while potassium efflux decreases (Ismailov & Benos, 1995). A_1AR and A_3AR are coupled to G_s proteins, which induce inhibition on adenylyl cyclase, while A_{2A}AR and A_{2B}AR are coupled to G_i proteins, boosting the enzyme's activity (Jacobson, 2009).

In mice brains, the A_1 adenosine receptor is found in the cerebellum, the cortex, and the hippocampus (Fredholm *et al*., 2011). A_1AR is linked with the inhibitory effects in neurotransmitter release in the presynaptic membrane and anti-excitatory effects in the postsynaptic membrane. The interactions demonstrate inhibition of the calcium channels in the membrane, which in turn reduces synaptic neurotransmission. The activation of A_1AR by adenosine has been evidenced to inhibit adenylyl cyclase, which activates potassium ion channels. The conductance of potassium ions minimizes calcium ionic flux (Linden, 1991). A_{2A}AR, on the other hand, is found in striatum cells, in the subcortical basal ganglia, and in the hippocampus of mice (Fredholm *et al*., 2011). Around 70% of all A_{2A}AR are found in the postsynaptic membrane, with 23% of the total receptors localized in the presynaptic membrane. A_{2A}AR is considered an excitatory adenosine receptor since the interaction with adenosine results in increased neurotransmitter release to the synapse, which induces increased activation of the postsynaptic receptors. Adenosine interaction with A_{2A}AR has been documented to activate calcium channels, thus facilitating calcium influx (Gonçalves *et al*., 1997). As opposed to its A_{2A} counterpart, A_{2B}AR is more distributed in the brain, specifically in the hippocampus and cerebral cortex, as antagonist-receptor interactions were identified in these areas (Sebastião *et al*., 1996). A_{2B}AR also activates adenylyl cyclase, however, its lower affinity for adenosine results in a weaker response. A_3AR is scarcely found in the brain, predominantly in the hippocampus and cerebral cortex, however, this receptor is mostly found in the heart, where it has shown to exert potential cardioprotective effects while assessing A_3AR knockout FVB/N and C57BL/6 mice (Ge *et al*., 2006).

While on the synapse, adenosine indirectly affects the dopaminergic signaling process. In the synaptic membranes, dopamine and adenosine receptors form heteromeric complexes, where one's interaction with their respective agonist and antagonist molecules initiates an intracellular pathway of the other receptor. A_1AR forms a heteromer with the D_1 dopamine receptor (DR), while A_{2A}AR is colocalized with D_2DR (Fredholm *et al*., 2011). When one receptor in a heteromer interacts with its agonist, the observed effects on its counterpart resemble those observed from its interaction with an antagonist. When A_1AR interacts with an agonist, as described previously, the production of cAMP in the neuron decreases, all the while reducing the binding affinity of synaptic dopamine for the D_1DR, impeding the neurotransmitter to mediate necessary pathways, like signaling propagation. In the same manner, A_1AR antagonists maintain cAMP production, all the while activating A_1AR's induced cAMP production (Ferré *et al*., 1998). In the presynaptic

membrane, the adenosine-A_1AR interactions lead to the reduction of calcium influx, which is a necessary step for dopamine release, as observed in the release of glutamate (Ambrósio *et al*., 1996).

The A_{2A}AR-D_2DR complex is one of the most studied heteromers, as both receptors are documented as strategic points of treatment of neurologic disorders, such as PD and schizophrenia. Much like the A_1AR-D_1DR heteromer, agonist interaction with A_{2A}AR has been evidenced to lower the binding affinity of dopamine to D_2DR, while the antagonist interaction balanced the D_2DR agonist effects (Ferre *et al*., 1991). The same effects were observed for D_2DR, in which the agonist-D_2DR interaction reduced the binding affinity of A_{2A}AR for adenosine, reducing the production of cAMP as well. The interactions of the dopaminergic neuron with its antagonist molecules revert the antagonistic effects on A_{2A}AR (Watts *et al*., 2004).

With the progression of PD, some therapy methods that were considered essential in preventing neurologic disorder render useless. Levodopa supplements administration is one of the most popular treatment drugs on the market, however, prolonged intake of the dopamine precursor worsens the physical conditions of patients, such as motor fluctuations and dyskinesias. One of the suggested mechanisms involved relates to the sensitivity of the postsynaptic dopaminergic neurons, as more doses are required in the long run to maintain the prescribed effects of levodopa administration. In the wake of this, several studies are conducted to discover new and overarching treatment options (Stoker *et al*., 2018). As a result of these investigations, the A_{2A}AR-D_2DR complex was found to play a role in improving the PD suffering patient's motor abilities, as both receptors were co-localized in the regions identified for inducing motor behavior (Fink *et al*., 1992). Also, A_{2A} receptors located in the glutamatergic neuron terminals have been evidenced to interact with CB_1 receptors.

Agonism and antagonism of A_{2A}AR have been proven to suppress neurodegenerative effects caused in PD. A_{2A}AR has been evidenced as a necessary component in the mediation of dyskinesia effects. Fredduzzi *et al*. (2002) experimented with the effects of daily intake of L-DOPA on the behavioral sensitization of wild-type and A_{2A}AR knockout mice. The mice models were subjected to 6-hydroxydopamine lesioning for seven days. The results evidenced that the knockout mice had not displayed any kind of dyskinesia effect, suggesting the need for the A_{2A}AR in the process. Dyskinesia causes visible effects in the human body, as it mediates the involuntary and spontaneous movement of the body parts, which is a common effect of PD. The A_{2A}AR agonist CGS-21680 has been evidenced to suppress the progression of dyskinesia induced by L-DOPA in 6-hydroxydopamine lesioned mice, suggesting that the simultaneous administration of A_{2A}AR agonists and L-DOPA has the potential to enhance patients motor ability, all the while minimizing the effects of chronic L-DOPA intake (Agnati *et al*., 2004). One of the primary concerns involving the administration of A_{2A}AR agonists, despite their potential, to integrate PD therapy, is the reduction of dopamine-induced signal transmission, which disrupts the dopaminergic system, thus contributing to the progression of PD. As a result, A_{2A}AR antagonists have been administered to maintain the balance of the dopaminergic system. One common example is caffeine, which is a non-selective antagonist that has been evidenced to boost motor behavior, but increasing dopamine-D_2DR activity in the postsynaptic membrane (Fredholm *et al*., 1999). Regarding the interactions with the endocannabinoid system receptors, it was reported that the antagonism of A_{2A} receptors has been evidenced to suppress both the motor-depressant and addictive effects of THC in mice (Carriba *et al*., 2007), while antagonism of CB_1 receptors was found to reduce the A_{2A}AR positive effects on glutamate release (Castillo *et al*., 2010).

4.10. Melatonin receptor theory

Melatonin is a neuronal hormone produced in the brain, predominantly in the pineal gland, as well as in the retina, gastrointestinal tract, and gut, to name a few. Melatonin is involved in maintaining the body's chronobiotic system, commonly described as the body's "biological clock", by inducing periodic effects through melatonin receptor interaction. Melatonin is produced when serotonin is catalyzed by N-acetyltransferase, however, this conversion step's rate exhibits a strong circadian rhythm, in which it maximizes during the nighttime and is minimized during the day time (De Berardis *et al*., 2013). The night-time production of melatonin is stimulated by a neuronal structure, named the suprachiasmatic nucleus, which acts as the primary circadian clock in mammalian bodies (Abrahamson & Moore, 2001). Daytime production is hypothesized to be inhibited by natural or artificial light (Haimov *et al*., 1994).

The synchronizing effects of melatonin are best described in its regulation of sleep and wakefulness cycles. Melatonin is part of the group of inhibitory neurotransmitters, which help attenuate the excitatory transmission of other neurotransmitters, such as glutamate. Melatonin has been evidenced to directly inhibit presynaptic neurotransmitter release, such as dopamine (Dubocovich, 1983), glutamate (Escames *et al*., 2001), and acetylcholine (Redburn, 1991), with all case studies evidencing the blocking effects of melatonin on the calcium ions influx. Redburn (1991) also suggested that the inhibitory effects of melatonin on acetylcholine release extended to other pathways, specifically the GABAergic pathway. Rosenstein & Cardinali (1986), indeed, evidenced that the administration of melatonin to Wistar mice enhanced the levels of GABA in the hypothalamus, cerebellum, cerebral cortex, and pineal gland, three hours after intake. GABA is also involved in the release of melatonin from the suprachiasmatic nucleus, in the hypothalamus, where it is thought to act as a mediator of light-induced inhibition of melatonin release to the bloodstream (Kalsbeek *et al*., 1999).

Besides presynaptic interactions with other neurological systems, melatonin induces several neuroprotective effects in the brain on its own, as it has been linked with reducing proinflammatory cytokines (Hardeland, 2010), or by generating defined sleep-wake cycles by interacting with two receptors, known as melatonin receptors 1 and 2 (MT_1 and MT_2) as receptor activation triggers the intracellular expression of free radical enzymes, such as superoxide dismutase and glutathione peroxidase (Mack *et al*., 2016). Melatonin receptors are coupled with G proteins, in the same manner as adenosine receptors. Both MT_1 and MT_2 receptors are expressed in the hippocampus, the thalamus, cerebellum, and suprachiasmatic nucleus (Liu *et al*., 2016). The presence of MT_1 in dopaminergic regions of the brain leads to the belief that this receptor is associated with the dopaminergic system and can have a direct effect on it. Both MT_1 and MT_2 are coupled to the G_i protein, which as seen in the adenosine chapter, melatonin-receptor interactions leads to the inhibition of adenylyl cyclase in the intracellular domain, subsequently reducing cAMP and PKA activity (Legros *et al*., 2020). The presence of melatonin receptors in the retina is a determining factor in the human body's natural adaptation to the day-night cycle. Dubocovich (1983) evidenced that melatonin present in the retina of rabbits could inhibit the release of dopamine when exposed to light and facilitate light adaptation. Later on, the same author elaborated on the receptor's actual function in the retina, as MT_2 was more intrinsically involved in the body's adaptation to the day-night cycle than MT_1, with the latter having a more direct effect on inhibiting the release of excitatory neurotransmitters, as a means to sedate and relax the body, as sleep was induced (Dubocovich *et al*., 2003).

The melatoninergic system provides several neuroprotective effects to the brain, however, it is also be subjected to impairment by different AD and PD effects. The primary impairment method observed is the reduced expression of melatonin: β-amyloid was evidenced to inhibit melatonin production by activating the NF-κB pathway (Mack *et al*., 2016), which is a pro-inflammatory process that blocks the pineal gland from excreting melatonin (Machado *et al*., 2010). β-amyloid can also interact with both melatonin receptors, thus reducing the binding sites for neurotransmitter interaction. PD suffering patients are also subjected to melatonin receptor impairment, as it was evidenced that the available number of melatonin receptors in the suprachiasmatic nucleus is reduced (Mack *et al*., 2016). The dopaminergic system has also been involved in reductive melatonin secretion. The pineal gland is home to high levels of dopamine 4 receptors (D_4R), which have been implicated as important receptors in the synchronization of the day-night cycle in the retina. D_4R form heteromers with adrenergic receptors, which directly control the release of melatonin by interacting with norepinephrine. So, when D_4R is agonized, the adrenergic receptor signal propagation is disrupted, thus reducing melatonin production. This stimulation affects calcium-dependent melatonin release (González *et al*., 2012).

The melatoninergic system is essential for suppressing the neurodegenerative effects of conditions like AD and PD. As described above, β-amyloid can inhibit the production of melatonin in the penial gland. As a result, melatonin levels in the brain decrease with age, as β-amyloidogenic effects progress. However, oral administration of melatonin in transgenic mice with APP and PS1 mutation showed to reduce the aggregation process of β-amyloid to small oligomers and monomers (Olcese *et al*., 2009). PD was also found to disrupt the biological phase shift that occurs during day-night cycles as a consequence of decreased melatonin protection, inducing sleep disorders in PD patients. Dowling *et al*., (2005) evaluated the effects of oral administration of two doses (5 mg and 50 mg) of melatonin in 40 PD patients with ages ranging from 43 to 76 years, 30 minutes before bedtime, for 2 weeks. The overall sleep time was recorded with the assistance of an actigraphy method, which monitors the relaxation and activity cycles in the brain. The results showed that the PD patients exhibited lesser sleep disturbance when administered melatonin, with no significant difference between doses. The aggregation of these results suggests that the intake of melatonin and agonists of MT_1 and MT_2 receptors have the potential to suppress neurodegenerative effects in the brain. Besides melatonin, other agonists are commercially available. For instance, ramelteon is a selective agonist of MT_1 and MT_2 receptors prescribed towards insomnia treatment (Pandi-Perumal *et al*., 2009).

4.11. Tyrosinase hypothesis

Tyrosinase is a key enzyme in skin melanin production. Despite being its leading role, it is also associated with neuromelanin production. Structurally, neuromelanin is equivalent to melanin and confers color to the substantia nigra in the mesencephalic nucleus. According to a report directed by Greggio *et al*. (2005) tyrosinase sustains a key role in oxidizing dopamine into dopaquinone. The molecules deteriorate and kill nerve cells, contributing to the incremental severity of PD.

As aforementioned in the dopamine synthesis, tyrosine prevails as the substrate of choice. This amino acid is unexclusive to the dopamine pathway production, as it is equally involved in neuromelanin production. The pigment's accumulation progresses with aging and at the age of 3 years old is already possible to detect neuromelanin in the mesencephalic nucleus. This phenomenon results from the body's inability to decompose neuromelanin (Carballo-Carbajal *et*

al., 2019). The metabolic pathway of neuromelanin production includes tyrosinases. Both tyrosinase and tyrosine hydroxylase equally compete for tyrosine. Despite belonging to the same family, the enzymes have unique functions. Tyrosinase is responsible for oxidizing tyrosine (Pawelek *et al*., 1998), while tyrosine hydroxylase, as its name suggests, hydrolyzes the amino acid.

Figure 4.12 represents the competition of tyrosinase and tyrosine hydroxylase for tyrosine, with a more substantial focus on the neuromelanin pathway. As aforementioned in the dopaminergic process, tyrosine hydroxylase converts the substrate in L-DOPA. The precursor can subsequently be converted into dopamine, or it can be oxidized by tyrosinase and produce dopaquinone. The remaining step in neuromelanin synthesis includes dopaquinone self-oxidation, which is a spontaneous process unable to be regulated. Dopaquinones are extremely unstable molecules, which produce other hazardous chemical compounds, as described in Figure 13. Excessive concentrations of these new molecules can induce several problems in the organism, like oxidative stress. Their synthesis can be attributed to the oxidation of the catechol ring in the dopamine structure, either by tyrosinase or by the dopamine's self-oxidation (Carballo-Carbajal *et al*., 2019). The dopamine degradation process leads to the increased concentration of toxic intermediate products, and an undesirable inhibition of tyrosine hydroxylase. The enzymatic inactivation interrupts dopamine production, which constitutes a self-damaging process.

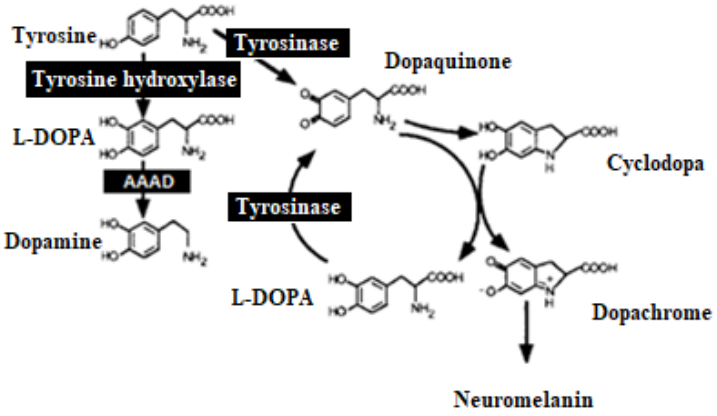

Figure 4.12. Neuromelanin biosynthesis (Eisenhofer et al., 2003) [Adapted].

Due to the impact of tyrosinase in both the production of neuromelanin and dopaquinone, the clinical administration of enzyme inhibitors has been investigated to prevent PD's progression.

4.12. Oxidative Stress

A healthy organism can maintain a balance between ROS and its antioxidant systems. When the balance is disturbed, ROS predominate and induce a condition called oxidative stress. This is a biological condition observed in most patients that suffer from neurodegenerative diseases. Even though it is associated with AD and PD, it is equally accepted as one of the primary causes of depression. Oxidative stress is responsible for nerve cell death and the reduction of the hippocampus and prefrontal cortex's volume (Michel *et al*, 2012).

There are radical and nonradical ROS. Oxygen based free radicals possess an unpaired electron in the oxygen atom and are extremely unstable. Radical ROS possesses the ability to acquire electrons from other key cell molecules When this situation takes place, affected molecules become reactive species themselves, which promotes ROS propagation (Michel *et al*.,

2012). Although nonradical species do not possess unpaired electrons, they are also capable of reacting with other molecules. Free radicals are involved in the oxidative stress of various cells, which is characterized by the unbalancing observed between the cell's oxidative system and antioxidant compounds capable of suppressing the excessive oxidation. Between all ROS, superoxide ($O_2^{\bullet-}$) and hydroxyl ($^{\bullet}HO$) stand out, while the most predominant nonradical molecule is hydrogen peroxide (H_2O_2). Other produced reactive species are that of nitrogen-based, such as nitric oxide ($^{\bullet}NO$) (Gülçin, 2012). Under certain circumstances, the reaction between $O_2^{\bullet-}$ and nitric oxide leads to the formation of peroxynitrite ($ONOO^-$), which is extremely reactive. Free radicals originate from mitochondrial respiration, as subproducts from the Krebs Cycle (Zhang *et al*., 2016) This process is also present in the cellular body of neurons. Therefore, oxidative stress is caused by the cell's metabolic systems (Dias *et al*., 2013).

Despite the negative aspects, free radicals can also be beneficial when in limited quantities. The generation of ROS implies that the neurons possess a well-balanced physiological system. The presence of ROS implies that the cells are capable of performing the required mechanisms, like the aforementioned Krebs Cycle and the subsequent elimination of these subproducts (Dias *et al*., 2013). Some free radical species, such as $^{\bullet}NO$, are considered as second messengers involved in cell signaling: these molecules are produced as a direct response to the interaction between the native cell's receptors and foreign molecules (first messengers), which trigger different responses (Newton *et al*., 2016). Free radicals are also produced by other biochemical pathways as a direct defense response when strange and pathogenic entities are present in the organism, like bacterial infections (Zhang *et al*., 2016). Therefore, the free radical absence does not represent a desirable circumstance since they are essential for the maintenance of the brain's homeostasis.

It is common for patients with neurodegenerative diseases to have an abnormal quantity of ROS in the brain. Some of the most well-known consequences of oxidative stress include lipidic peroxidation, the oxidation of proteins, and DNA degeneration, which can result in nerve cell death (Caruso *et al*., 2019). One of the most successful defense mechanisms used by neurons to combat these ROS includes the consumption of antioxidant compounds from the diet. Cells can also use endogenous antioxidant systems to decompose ROS, like the enzymes superoxide dismutase, catalase, peroxidase, ascorbate peroxidase, guaiacol peroxidase, and glutathione reductase (Haida & Hakiman, 2019).

5. Medicinal plants

Medicinal plants are species producing valuable bioactive compounds, contained in different parts of the plant, that, for a long time, have been cultivated for the prevention or treatment of several diseases and conditions. Medicinal plants are distributed all around the world, with most of them being native to tropical, humid, and dry environments, like the Amazonian forest and, as this thesis is mostly centered, in Southern Asian forests. It has been reported for a while that around 350 000 different plant species are distributed around the world (Joppa *et al*., 2011), with around a tenth of them with reported medicinal properties (Allkin, 2017). In the last few years, consumers' concern towards the harmful effects of processed foods and synthetic pharmaceuticals has increased, which in turn raised the interest in more natural and healthy alternatives. As a result, the need for medicinal plants rose. The global market size of medicinal

plants has registered a steady increase throughout the years. From 2003 to 2012, the WHO estimated the herbal medicine market value at 60 billion and 83 billion US dollars, respectively (Allkin, 2017). In 2019, the Polaris Market Research institution reported a market value of 84.5 billion US dollars.

As the global demand for natural medicinal alternatives increases each year, in 2019, the WHO released a report entitled "WHO Global Report on Traditional and Complementary Medicine 2019", intending to successfully integrate qualified and effective medicinal services into the member state's health systems, by developing norms, standards, and technical documents based on reliable information. According to the report, currently, 170 out of 194 countries have acknowledged the use of traditional and complementary medicine, meaning that those member states have either implemented regulation, programs, laws or national policies on the integration of medicinal and conventional herbs in medical treatment methods. Of those, 98 member states have national policies on the matter, meaning that the respective governments issue specific guidelines to further develop, and/or integrate the use of traditional medicine in health systems. 79 member states have included traditional medicine program on their long-term health plans or national strategic health plans, while the remaining countries have a stand-alone program (World Health Organization, 2019).

As the study and commercialization of medicinal plants gain traction, so did the risk factors normally associated with plantations increase. In this particular case, faster growth of the market size implies an increase in the extinction risk through overharvesting (World Health Organization, 2015). In 1995, experts estimated that the extinction rate at the time allowed for the loss of one plant species every year (Pimm *et al*., 1995). The lack of mutualisms is also a risk factor that may lead to the extinction of plantations, as the reproduction of some plant species is dependent on the mutual benefits of two entities, such as plants and pollinators. The lack of understanding between two entities that control each segment can lead to a weakened habitat, or, in severe cases, to the possible extinction of a plant species with great treatment potential (Subsidiary Body on Scientific Technical and Technological Advice, 2018). Another important risk factor is climate change. In this virtue, the United Nations issued a report on sustainable development goals to be achieved by 2030. One of those goals specifies the need to promote and implement sustainable ecosystems, protect forests, combat desertification, and most importantly, prevent the loss of biodiversity (Nations, 2016). With the counseling of both the United Nations and the World Health Organization, herbal medicine has the potential to grow and to integrate treatment methods for several ailments.

The available treatments for neurodegenerative diseases, such as AD, PD, and depression, involves the administration of enzymatic inhibitors capable of regulating the neurotransmitter levels in the synapses. Today, the commercialization of drugs to attenuate neurodegenerative disease effects remain a viable means of attenuate the symptoms, still, research continues to find more efficient and safer inhibitors for the same targets or to find other drugs affecting other targets not explored yet. Many drug discovery programs use natural products or natural products scaffolds to produce new leads. In the literature, several studies were already conducted to assess the neuroprotective effect of medicinal plants and isolated compounds against neurodegeneration.

6. The neuroprotective role of plant bioactive compounds

For thousands of years, plant extracts have been administered to prevent or treat several diseases. Each plant possesses diverse effects on the body, mostly due to the variety and quantity

of bioactive metabolites, such as phenolic compounds. These are recognized antioxidants. Many plant phytochemicals are best known for their ability demonstrated to alleviate oxidative stress in neurodegenerative disease patients. Furthermore, they also demonstrate potential in neurodegenerative disease treatment. Even though the plants maintain the same metabolic pathways that generate diverse phytochemicals, their synthesis is affected by some environmental factors, like the season, temperature, hydric and nutrient availability, exposure to UV radiation, and external pressure (Gobbo-Neto & Lopes, 2007). The various combinations of factors affecting the plant can produce unique mixtures of phytochemicals. The diverse classes of these plant compounds depend on the core carbon structure of the molecules (Cai *et al*., 2006). The molecule's antioxidant performance depends on molecular moieties, such as the number and location of hydroxyl groups in the structure and the degree of the molecule's alkylation and glycosylation (Rice-Evans *et al*., 1996).

Neurodegenerative disease treatment is available through the administration of several commercial drugs. Commercial drugs are prescribed to act at possible therapeutic points of action in several pathologies. As is the case in the enzymatic theories described earlier, the employment of specific medication can allow a steady increase of neurotransmitter levels by forming a reversible and temporary bond with the degradation enzymes. Besides drugs, many plants and isolated phytochemicals have been assessed more specifically in preventing the progression of neurodegenerative conditions. In this report, flavonoids, phenolic acids, alkaloids, terpenoids, fatty acids, cannabinoids, saponins, iridoids, polysaccharides, and steroids are discussed.

Flavonoids represent a class of phenolic compounds characterized by molecules that possess a carbonic structure similar to that of phenylbenzopyranone molecules (C6-C3-C6), in which two phenyl rings are attached oppositely to a carbon bridge, which itself forms a pyrene ring with oxygen. Flavonoids can be distinguished by the number and arrangement of hydroxyl groups attached to the molecule's core structure. The main subclasses of flavonoids found in the examined plants range from flavones, isoflavones, flavonols, anthocyanidins, flavan-3-ols, and flavanones, and procyanidins (Corradini *et al*., 2011). Table 1 shows the classification of the major flavonoids found in nature.

Table 1. Classification of the flavonoid molecular species present in the studied Chinese teas (Huang et al., 2010; Klósek et al., 2017).

Flavonoid Classes	**Compounds**
Flavones	Luteolin, apigenin, vitexin, chrysin
Isoflavones	Daidzein, daidzin
Flavonols	Quercetin, isoquercetin, rutin, kaempferol, myricetin, orientin
Anthocyanidins	Cyanidin, delphinidin, peonidin, malvidin
Flavanones	Naringenin
Flavanols	Catechin, Epicatechin and derivatives (Epicatechin gallate, Epigallocatechin, Epigallocatechin gallate)
Procyanidins	Oligomeric compounds, formed from catechin and epicatechin
Chalcones	4,2′,4′,6′-Tetrahydroxychalcone, licocalchone A, licocalchone B

Plant flavonoids are known for their role in the protection of cells from oxidative stress, as for their ability to absorb UV radiation. Regarding the fact that flavonoids possess a role in the prevention of neurodegenerative disease aggravation (oxidative stress being the primary evidence), some studies were conducted in recent years to broaden the knowledge of their role against enzymes involved in neurodegenerative processes. Flavonoids are mostly found in their glycosylated form in nature.

Phenolic acids are the second most common phenolic compounds found in nature, after flavonoids. The general structure of these molecules is composed of a benzylic ring, a carboxylic group, and an assortment of hydroxyl and ester groups randomly distributed (Soares, 2002). The term "phenolic acid" is attributed to two classes of acids, hydroxybenzoic (C6-C1) and hydroxycinnamic (C6-C3) (de Oliveira & Bastos, 2011). Both molecular structures differ; the former exhibits a carboxylic group attached to the benzylic ring, while the latter is a propanoic acid. Hydroxycinnamic acids are frequently found in food sources and plants, unlike hydroxybenzoic acids. Examples of hydroxycinnamic acids vary from ferulic, *p*-coumaric, caffeic, and chlorogenic acid. On the other hand, hydroxybenzoic acids range from gallic, protocatechuic, and p-hydroxybenzoic acid (Manach *et al*., 2004). Despite lesser available literature regarding their neuroprotection activity when compared to flavonoids, phenolic compounds also possess high potential regarding this subject. According to Grosso *et al*. (2016), phenolic acids, such as caffeic acid and chlorogenic acid, hold the potential to diminish the risk of depression.

Alkaloids are produced as secondary metabolites and possess a role in the plant's defense mechanisms against bacteria, insects, and other microorganisms (Jogaiah & Abdelrahman, 2019). Usually, these molecules are responsible for awarding the plants their distinct bitter flavor (Main, 2017). Alkaloids belong to a group of alkaline molecules possessing numerous and diverse heterocyclic rings, as well as one or more nitrogen atoms. Alkaloids include several classes depending on each molecule's carbon structure, such as xanthines, indoles, quinolines, pyrrolidines, pyridines, terpenoids, among others (Kurek, 2019). These organic compounds show tremendous potential in therapeutic methods due to their immense structural diversity. Some of the most common applications of alkaloids in neurodegenerative disease treatment relate to galantamine and rivastigmine, both of which are involved in AChE inhibition. Caffeine is also an important alkaloid, implied in preventing memory impairment. Alkaloids have also been documented as potential candidates to integrate other pathological treatment methods, most of which have been described in the course of this report, such as β-amyloid, α-synuclein, the dopaminergic system, among others (Girdhar *et al*., 2015).

Terpenes represent the largest class of secondary metabolites. The basic core structure of terpenes consists of one or more sequences of isoprene units, each composed of 5 carbons. By itself, the isoprene structure does not potentiate any noteworthy effects on the human body, as it is just a hydrocarbon; however, altered forms of terpenes containing hydroxyl and methyl groups can boost the molecule's their therapeutic effects, such as terpenoids. Depending on the repeated isoprene structures, terpenoids can manifest in nature as mono-, sesqui-, di-, ses-, tri-, and tetraterpenes, composed of 2, 3, 4, 5, 6, and 8 isoprene units, respectively (Perveen, 2018). Terpenoids arrange a wide variety of compounds, similarly to alkaloids. Their involvement in the treatment of neurodegenerative pathologies has been evidenced. For example, β-carotenoids (tetraterpenes), such as fucoxanthin, lutein, and lycopene, have been evidenced to inhibit β-amyloid aggregation (Lakey-Beitia *et al*., 2019). Squalene (triterpene) has also been evidenced to possess antioxidant activities, such as preventing lipid peroxidation and quenching singlet

oxygen, as well as preventing PD neurotoxicity (Kabuto *et al*., 2013). Several monoterpenes, including fenchone, S-carvone, and linalool produced AChE inhibition (López & Pascual-Villalobos, 2010).

Phytosterols are natural steroid compounds similar in structure to cholesterol and regarded as a viable replacement to it. Sterols are mainly composed of two major structures: a gonane portion, made up of 3 continuous cyclohexane rings, followed by a cyclopentane, and an adjacent methyl chain. This phytochemical classification encompasses both sterols and stanols: the primary difference between both sterol subtypes is based solely on a double bond in the second cyclohexane ring. Sterols possess a double bond in this region, making them unsaturated molecules, while stanols don't (Ogbe *et al*., 2015). Although phytosterols are mostly associated with treating cardiovascular diseases, it has been proven that stigmasterol is able of inhibiting the activity of β-secretase, which triggers the formation of β-amyloid peptides in AD (Burg *et al*., 2013). Other sterols, like statins, have been proven to contribute towards inhibiting MAPK, which promotes tau protein hyperphosphorylation (Riekse *et al*., 2006).

Fatty acids are essential lipids in the human diet. They are composed of a carboxylic acid moiety in one end and an aliphatic hydrocarbon chain in the other which can range from two hydrocarbons, up to 26, and are the main component of cellular membranes (Watkins, 2012). In nature, the most common fatty acids contain 16 or 18 hydrocarbons in the aliphatic chain. These include palmitic acid, stearic acid, linoleic acid, and oleic acid, among others (Rustan & Drevon, 2005). Fatty acids can be either saturated or unsaturated, which classify which fatty acids contain double bonds in the aliphatic chain; unsaturated fats, which contain at least one double bond, are considered the healthier option between the two subtypes, as the molecule can display a *cis* conformation. Cell conformation is essential in regulating protein flow between the lipid bilayer. A *trans* conformation straightens the molecule, while the *cis* conformation allows for more membrane flexibility and fluidity (Rustan & Drevon, 2005). Besides this, fatty acids are important compounds that serve as building blocks for other essential molecules produced in the body, as is the case with eicosanoids (Watkins, 2012). In the endocannabinoid system, the neurotransmitter precursor arachidonic acid is generated in the body from linoleic acid (Salem *et al*., 1999). This notion suggests that fatty acid intake can promote the response and balance of the endocannabinoid system, in moderate doses, as its excessive intake can lead to negative health effects.

Cannabinoids are natural lipids with psychoactive effects on the human body. This classification englobes endocannabinoids, which as discussed above, are substances produced in the body by consumption of fatty acids, and phytocannabinoids, which are substances that occur naturally in all plant components of cannabis. Natural phytocannabinoids have a complex structure, composed of a cyclohexane ring, a tetrahydropyran, and a benzene ring. The most known natural cannabinoids are tetrahydrocannabinol (Δ^9 and the Δ^8 isomer), cannabinol, and cannabidiol. Both tetrahydrocannabinol isoforms and cannabinol have been described as having potent and mild psychoactive activity respectively (Sharma *et al*., 2012), which makes them illegible to integrate therapeutic methods. In this sense, cannabidiol emerges as a potential therapeutic agent, as it is devoid of psychoactive effects on the body. For example, cannabidiol has been evidenced as a potent antioxidative capable of scavenging $O_2^{\bullet-}$ and hydroxyl radicals (Atalay *et al*., 2020), as well as to suppress the neurodegenerative effects of AD, as it can inhibit tau hyperphosphorylation by suppressing the activity of GSK-3β (Esposito *et al*., 2006).

Saponins are glycoside molecules with foaming properties. These secondary metabolites are produced in various plants and are composed of two moieties: glycone, predominantly a sugar

molecule, like glucose, and an aglycone, which can consist of either a triterpenoid or steroid (sterol) (Desai *et al*., 2009). The presence of a hydrophilic moiety (glycone), in association with the fat-soluble moiety (glycone), enhances the foaming ability of saponins. Saponins are also termed as phytoanticipins, which means that saponins are involved in the defense mechanisms of the plant in which they reside, even before pathogenic attacks. These metabolites have been documented as being natural pesticides and fungicides, implying that human consumption of saponins can lead to adverse effects in the body (Faizal & Geelen, 2013). However, some saponins have also been associated with antioxidant, cardiovascular, anticholesterolemic (steroid glycosides), immunomodulatory, and anticarcinogenic effects (Shi *et al*., 2004). Saponins have also been implied in a wide variety of neurodegenerative conditions related to one another. Some of these saponins include ginsenosides (*Panax ginseng*), astragalosides (*Astralagus membranaceous*), gypenosides (*Ginostemma pentaphyllum*), among others (Sun *et al*., 2015).

Polysaccharides are polymeric molecules comprised of monomeric carbohydrates (monosaccharides) linked by glycosidic bonds. This class of natural compounds is the most abundant in nature. Depending on the location and type of plant, polysaccharides display different structures. Polysaccharides appear as homoglycans, composed of one monosaccharide, or heteroglycans, composed of two or more monosaccharides, linear or branched (ramification), and cationic or anionic. From a function standpoint, polysaccharides can still be differentiated as either granting structural conformation or as energy storage, as is the case with polysaccharides composed of sugars (Donato *et al*., 2014). In terms of therapeutic effects, some polysaccharides are capable of exerting antioxidant, $O_2^{\bullet -}$, and hydroxyl radical scavenging, and anti-inflammatory effects, such as the case of the extracted polysaccharides from the brown algae *Lobophora variegate* (Paiva *et al*., 2011).

Iridoids are derivatives of monoterpenoids composed of a core cyclopentanepyran skeleton. The term "iridoids" comprises four different molecule classes: iridoid glycosides, secoiridoid glycosides, non-glycosidic iridoids, and bis-iridoids. In nature, iridoids are mostly found in their glycosylated form, normally coupling with a glucose moiety (Wang *et al*., 2020) Similar to saponins and alkaloids, iridoids have been documented as intervening in the defense mechanisms of plants against pathogens and insects (Yamane *et al*., 2010). In general, plant iridoid has been evidenced as possessing anti-inflammatory, hypoglycemic, anti-tumor, hepatoprotective, and neuroprotective effects (Wang *et al*., 2020).

Traditional medicine has been pushed as a viable candidate to integrate several treatment methods, however, there is skepticism in the actual health benefits of the consumption, mostly deriving from the toxic effects some plant species are associated with. Toxicity is often associated with an excessive intake of a certain substance. Numerous reports suggest these claims, evidencing that plant toxicity is influenced by the composition and levels of certain phytochemical compounds. For example, flavonoids (Birt *et al*., 2013) and phenolic acids (Sreekrishnan *et al*., 2008) have been associated with low toxicity when consumed moderately, however, alkaloids have been labeled as toxic molecules to be avoided (Diaz, 2015); depending on the plant, the present alkaloids provide a characteristic bitter taste, which is usually associated with a certain degree of toxicity (Bassoli *et al*., 2007).

7. Chemical and biological activity of Chinese medicinal plants

7.1. Plant neuroprotective effects

To understand how each plant mixture can influence the human organism's neuroprotective defense, it is of the utmost importance to understand how and which plant compounds can properly interact with the targeted enzymes. In the early stages of this thesis, it was proposed that the intended results would be achieved by identifying the primary phenolic compounds present in the mixtures, by HPLC-DAD, and by evaluating both the enzymatic inhibition and ROS and RNS scavenging activities of aqueous extracts of the five Chinese multicomponent mixtures, through spectrophotometric methods. The comparison of both the detection and the inhibitory effect/ scavenging activity results would allow establishing a correlation between chemical composition and bioactivities observed. However, due to the precautionary health measures related to the SARS-CoV-2 outbreak, a new approach was adopted. Instead, it was proposed a compilation of the available literature regarding the chemical characterization of bioactive compounds of each plant, mainly phenolic acids, flavonoids, alkaloids, terpenes, terpenoids, coumarins, and lignans. Since the influence of the exact quantity of these compounds cannot be determined in real samples, the main goal of this thesis is to achieve an overall idea of which plants are more promising in terms of neuroprotection, based on the available literature describing the neurodegenerative suppressing effects described from each plant, from the scavenging potential of ROS and RNS, enzymatic inhibition, and toxic deposit clearance.

7.1.1. Green, *oolong*, and black tea

From all the species addressed in this thesis, *Camellia sinensis* (L.) Kuntze (Theaceae family) leaves are the only ones that can are subjected to a fermentation process. Depending on the fermentation rate, the leaves can have different designations: green tea (unfermented), oolong tea (semi-fermented), and black tea (fully fermented) (Singh *et al*., 2019). The fermentation process affects the composition of phenolics in the plant. There is evidence that the concentration of catechins ((-)-epicatechin, (-)-epicatechin gallate, (-)-epigallocatechin, and (-)-epigallocatechin gallate) originally found in the leaves decreases with increasing degree of fermentation. In contrast, the leaves that are subjected to longer fermentation periods are richer in theaflavins and thearubigins, two types of flavonoids derived from the oxidation and condensation of catechins (Chen *et al*., 2018). Table A.1 in Attachment A shows the primary compounds found in *C. sinensis* that contribute to its neuroprotective effects.

Ray *et al*. (2012) carried out a study in which infusions and decoctions of different black tea aqueous extracts, prepared from 20g of leaves and 170 ml of distilled water, were mixed with sodium phosphate buffer containing AChE extracted from the brains of 3-4 week old, unidentified mice models, and incubated for 20 minutes. The results noted that all aqueous extracts exerted anti-AChE activity, with one black tea decoction sample having an IC_{50} value of 30.49 ± 0.86 µg/ml. The results also evidenced that the decoction samples had a lower IC_{50} value than infusions, which is a factor seen in several tea extracts.

The catechins found in *C. sinensis* (L.) Kuntze have been reported to inhibit toxic β-amyloid aggregation. Rho *et al*. (2019) conducted a thioflavin-T fluorescence assay, accompanied by a transmission electron microscopy test, to determine the inhibitory rates of the isolated compounds, dissolved in a 50% aqueous/ethanol solution. The results showed that (-)-epigallocatechin 3-O-gallate, (-)-epicatechin 3-O-gallate, and (-)-catechin 3-O-gallate exerted the lowest fluorescence values (78.0 ± 4.6%, 62.8 ± 10.3%, and 46.4 ± 8.9%, respectively), meaning that these catechins had the highest inhibitory rate on β-amyloid aggregation.

Chesser *et al*. (2016) evaluated the effects of epigallocatechin-3-O-gallate extracted from *C. sinensis* (L.) Kuntze on the potential amelioration of neurodegenerative conditions mediated by tau protein. For this, three tauopathy epitope (p-S396/404, p-S262, and p-T231) samples of cortical Sprague-Dawley mice embryo neurons were isolated, cultured, and treated with 25 µM and 50 µM of stock epigallocatechin-3-O-gallate, followed by 24h incubation and subsequent tau level measurement with a Western blot procedure and an ANOVA statistical assay. The blot results evidenced weaker dotting in the lanes treated with 50 µM stock epigallocatechin-3-O-gallate solution; the ANOVA assay revealed that the epitope samples treated with the catechin exhibited reduced levels of phosphorylated tau of around 60% (p-S396/404 and p-S262 epitopes and 80% (p-T231 epitope). The authors also revealed that epigallocatechin-3-O-gallate increased the expression of two adaptor proteins necessary for tau protein autophagy.

The catechins found in *C. sinensis* (L.) Kuntze have been found to modulate neurotransmitter transporters involved in both inhibitory and excitatory stimulation. Wang *et al*. (2016) evaluated the stimulating potential of green tea extracts by conducting an assay where *Xenopus* cells were treated to four samples of (-)-epicatechin and (-)-epigallocatechin gallate, at a concentration of 40 µM and 50 µM each, to determine the inhibitory effects of the tea catechins on GAT_1 (GABA transporter) and $EAAT_1$ (glutamate transporter). The cells were previously injected with the respective cDNA which expresses GAT_1 and $EAAT_1$ and incubated between 24-48 hours. The results obtained results were then utilized to determine the needed concentration to achieve an inhibition rate of 50%. The obtained results indicated that the (-)-epicatechin samples did not register significant inhibition for GAT_1, while (-)-epigallocatechin gallate revealed a 50% inhibition rate at around 100 µM. For $EAAT_1$, (-)-epicatechin showed an IC_{50} of around 5 µM, while (-)-epigallocatechin gallate did not register any effects. These results suggest that *C. sinensis* (L.) Kuntze extracts intake might successfully modulate excitability.

C. sinensis (L.) Kuntze catechins have been associated with the endocannabinoid system. (-)-Epigallocatechin gallate, for example, has been shown to suppress the increase in appetite levels (Auvichayapat *et al*. 2008), which is normally associated with the activation of the endocannabinoid system. Korte *et al*. (2010) evidenced that green tea catechins exerted a modest endocannabinoid system modulatory activity. A radioligand assay was conducted with recombinant human cells containing CB_1 and CB_2 receptors were treated to 10 µl of (-)-epigallocatechin gallate, (-)-epigallocatechin, and (-)-epicatechin gallate, with subsequent incubation in a 96-well plate. To determine the inhibition constant values of each catechin, a nonlinear regression equation was utilized. The obtained results indicated that the inhibition constant for CB_1 was overall inferior to that registered for CB_2 receptors. This suggests that *C. sinensis* (L.) Kuntze catechins have a more predominant effect on the CNS cannabinoid system than in the PNS.

C. sinensis (L.) Kuntze has been evidenced to inhibit MAO-B. The main compounds responsible for this neuroprotective effect are catechins (Mazzio *et al*., 2013), meaning that, of

the two, black tea possesses a weaker inhibitory activity than that of oolong tea. Of all the catechins, (-)-epigallocatechin3-O-gallate is the most important phenolic compound found in *C. sinensis* (L.) Kuntze since it simultaneously inhibits MAO-B and boasts antioxidant activity. Regarding MAO-A, there is no available evidence of inhibition by theaflavins and thearubigins, whereas catechins have been proven incapable of inhibiting the enzyme by Bandaruk *et al*. (2012), unlike other flavonoids, like quercetin. Further investigation is needed on whether the fermentation process affects the inhibition rate of MAO enzymes, as well as if the remaining compounds exert inhibitory activity.

L-Theanine is an important amino acid found in *C. sinensis* (L.) Kuntze and has been involved in the glutamatergic system. Kakuda *et al*. (2002) evaluated the possible effects of L-theanine on glutamate receptors AMPA, kainate, and NMDA. To achieve this, cortical membrane samples of Wistar mice were prepared with buffer solution and treated separately with 1 µM of L-theanine and L-glutamic acid. The IC_{50} values for each receptor were determined by utilizing the Hill equation. The administration of L-theanine exhibited IC_{50} values of 24.6 ± 0.9 µM, 41.5 ± 7.6 µM, and 347 ± 47 µM, for AMPA, kainate, and NMDA receptors, respectively. However, the binding affinity for L-glutamic acid was 30-to-50 fold that of AMPA and kainate receptors, and 30,000-fold for NMDA receptors.

Grelle *et al*. (2011) evidenced the effects of *C. sinensis* (L.) Kuntze theaflavins against the neurotoxic effects of α-synuclein. First, monomeric α-synuclein was dissolved in water until a concentration of 50 µM was reached. Separate stock solutions of theaflavin, theaflavin 3-monogallate, theaflavin 3′-monogallate, theaflavin 3,3′-digallate were also prepared by dissolving the compound in distilled water at a concentration of 5mM. The α-synuclein solution was then spread through 96-well plates with different theaflavin solutions and as a control and subsequently incubated at 37ºC for three days. The aggregation effects were then determined by an atomic force microscopy method. After incubation, the control formed α-synuclein fibrils, whereas, in the analyzed wells, fibrilization was suppressed.

C. sinensis (L.) Kuntze is known to regulate the activity of brain tyrosinase, especially those that are subjected to fermentation. Black tea has been reported to possess a strong inhibitory effect in tyrosinases, mostly due to the presence of theaflavins. Kim *et al*. (2015) conducted an assay to evaluate the anti-tyrosinase activity of 12.5 µg/mL white, green, and black tea water extracts. In this study, samples containing 49µL of the supernatant of centrifuged Melan-A cells, 50 µL phosphate buffer, 1 µL of tea water extracts, and lastly, 50 µL of L-DOPA solution were prepared, with a subsequent absorbance measurement. The results indicated that, of the three tea samples, black tea reduced the activity of tyrosinase in the cells by 45%. Another factor that influences the enzymatic binding is the available hydroxyl groups of all the extract's phenolic compounds, such as gallic acid and chlorogenic acid (Korkmaz *et al*., 2019). Black tea also affects the accumulation of neuromelanin (Kim *et al*., 2015).

C. sinensis (L.) Kuntze has its free radical scavenging potential mediated by fermentation state. Theaflavins have been associated with a superior $O_2^{\bullet-}$ scavenging activity than that of catechins, as seen in a report by Chen *et al*. (1995), in which the isolated catechins and theaflavins of green tea were isolated and subsequently dissolved in a 95% ethanol solvent and a 35% acetone solvent, respectively. The results were obtained by spectrophotometry, in which 50 µM theaflavin 3,3′-digallate and 50 µM epigallocatechin-gallate exerted the highest $O_2^{\bullet-}$ scavenging activity at around 70%. Also, equal doses of theaflavin and theaflavin monogallate (50 µM) exerted scavenging activity at around 65%, while other major catechins had lower scavenging potential. Xu *et al*. (2011) evidenced that *C. sinensis* (L.) Kuntze was able to scavenge nitric oxide radicals.

At a concentration of 1000µg of leaves per ml of phosphate buffer solution, green tea and black tea extracts exerted a scavenging activity of 40.19% and 33.25%, respectively. In this case study, the presence of catechins is more favorable. Lastly, Ruch *et al*. (1989) evidenced the effects of green tea to scavenge H_2O_2 radicals. Lyophilized green tea extracts were dissolved in DMSO at a concentration of 50µg/ml and were added to a 4mM H_2O_2 solution, with a subsequent spectrophotometry measurement. The results showed that green tea extracts were able to scavenge H_2O_2 at a rate of around 0.07µmol of H_2O_2 per µg of green tea extract.

The administration of caffeine-containing beverages has been linked with increased levels of serotonin in mice brains (Yokogoshi *et al*., 1987), mostly induced the formation of spherical α-synuclein, while theaflavin and theaflavin 3-monogallate induced spherical and chained structures. These results suggest that black tea has the potential to suppress fibrilization. *C. sinensis* (L.) Kuntze leaf extracts are classified as caffeine-containing beverages. Besides flavan-3-ols, caffeine also shows neuroprotective potential in all of the aforementioned targets, as it was shown to improve the motor deficit of PD patients (Tan *et al*., 2009). The basal ganglia are home to several adenosine receptors, which operate alongside the dopaminergic receptors in the regulation of the CNS (Cieślak *et al*., 2008). Under low levels of dopamine, the human body shows signs of fatigue, which restricts movement. The common knowledge of caffeine promoting a sense of wakefulness stems from the binding of the molecule to the adenosine receptors (Lazarus *et al*., 2011). Other neuroprotective activities of caffeine include its ability to inhibit AChE (Pohanka *et al*., 2013) and tyrosinase at a low concentration (Lee *et al*., 2019), as well as to selectively scavenge $^{\bullet}HO$ radicals (Varma *et al*., 2010).

7.1.2. Ginseng

Out of all the plants identified in the commercial tea mixtures, *Panax ginseng* C.A. Meyer (*Araliaceae* family) is thought to be one of the first plants to ever be administered as a remedy thousands of years ago. Its popularity in traditional Chinese medicine allowed it to bespread into eastern medicine as well (Cho, 2012), being implemented in several pharmaceutical preparations. The phytotherapeutic effects of ginseng are attributed to its content and a wide variety of saponins, designated as ginsenosides. The therapeutic effects of each ginsenoside are dependent on the arrangement and complexity of the sugar moiety present in its molecular structure (Tzen *et al*., 2009). Depending on the complexity of the ginsenosides, ginseng can exhibit neuroprotective, immune-protective, cardiovascular, anti-inflammatory, antioxidant, vasodilation, memory enhancement, and cognitive performance enhancement properties (Sun *et al*., 2019). Table A.2 of Attachment A shows the primary compounds found in *P. ginseng* that contribute to its neuroprotective effects.

Regarding the inhibition of AChE and BuChE, Lee *et al*. (2011) conducted a fluorescence assay to determine the cholinesterase inhibition rate of red, black, and white ginseng extracts. Three mixtures were made, containing 40 µL of different ginseng extracts at different concentrations (2. 4. 6, and 8 mg/ml), and 460 µL of either AChE or BuChE (0.22 U/ML). The results showed that, for AChE, black ginseng extract exerted the highest inhibition rates, at 25.67±0.71%, 64.98±3.56%, 84.28±2.18%, and 95.47±1.20% for the concentrations of 2, 4, 6, and 8 mg/ml, respectively. As for BuChE, white, red, and black ginseng extracts were found to inhibit 50% activity (IC_{50}) at a respective concentration of 2.56 mg/ml, 1.84 mg/ml, and 1.88 mg/ml.

Ginsenoside Re has been evidenced to prevent β-amyloid peptide production by inhibiting β-secretase. Cao *et al*. (2016) conducted an β-amyloid ELISA assay, where N2a/APP695 mutant human cells were treated to ginsenoside Re DMSO solutions with concentrations ranging from 0 to 200 µM, and incubated them for 24h, in order the effects of the ginsenoside on the levels of the β-amyloid peptide. The obtained results indicated that the ginsenoside Re inhibited β-amyloid production in a dose-dependent manner, with the 200 µM dose registering an inhibition rate of 26.82%

The anti-AD effects of *P. ginseng* also expand to the neurodegenerative impact of tau protein, specifically to the toxic effects of its aggregation. Red ginseng, a processed variation of the rhizome, has been evidenced to both inhibit recombinant K_{18} tau fragment aggregation and exacerbate aggregate dissociation; Shin *et al*. (2020) evaluated the effects on incubated K_{18} tau fragment aggregates treated with aqueous red ginseng extracts with concentrations of 10, 50, 100, 250, and 500 µg/ml, through a thioflavin T fluorescence assay. A similar assay was conducted, where tau fragment aggregation was induced and solely incubated, with red ginseng extract treatment occurring after. The obtained results for each ginseng concentration allowed for the determination of the IC_{50} value for tau aggregation and DC_{50} value for its dissociation, respectively being 545.0 ± 124.4 µg/ml and 713.5 ± 158.3 µg/ml.

The extracted ginsenosides from *P. ginseng* have been evidenced to exert relaxing effects on the body. This phenomenon occurs due to the compounds' interaction with postsynaptic receptors, which regulate the ion channel currents. These compounds have been found to play a role in both the glutamatergic and GABAergic systems, in which they act with the involved receptors as antagonists and agonists, respectively. For the glutamate system, Radad *et al*. (2004) conducted an assay where the dopaminergic neurons of pregnant OF1/SPF mice were cultured with excess glutamate, to cause excitotoxicity, and to different concentrations of ginsenosides Rb1 and Rg1 (0.1, 1, 2, 10, and 20 µM) for 4 days, to determine the survival effects of the ginsenosides. The singular exposition to glutamate decreased the dopaminergic cells by around 58% and reduced the total neurite length by 24%. Of note, the 10 µM Rb1 sample improved the cell count by 17%, when compared with the untreated control, as well as an attenuation of the neurite lengths of about 27% for Rb1 and 9% for Rg1. These results suggest that ginsenosides Rb1 and Rg1 act as NMDA receptor antagonists, thus suppressing glutamate-induced excitotoxicity.

As for these compounds' involvement in the GABAergic system, Yin *et al*. (2011) evaluated the effects of aqueous extracts of Korean red ginseng with $GABA_A$ receptors found in the *substantia gelatinosa* found in mice brain. For this, the authors cultured mice brain slices with growth nutrients, artificial cerebrospinal fluid, different concentrations of the ginseng extract (0.3, 1, 3, and 10 µM), and tetrodotoxin, which is a sodium-channel blocker. To determine the effects of the ginseng extracts, the samples were introduced in a patch-clamp chamber, which is a technique used to study excitation in cells. The obtained results evidenced ion inward flow on the extracts on the brain cells, suggesting that the ginsenosides in the extracts target the GABA receptors.

Ginseng extracts have shown some neuroprotective effects that attenuate the symptoms of PD. The administration of specific ginsenosides, such as ginsenosides Rg1, Re, and Rd, has shown to prevent dopaminergic and tyrosine-hydroxylase cell death, boosting the expression of tyrosine-hydroxylase, which in turn augments dopamine production and limits locomotor dysfunction (Kampen *et al*., 2003), and suppressing free radical generation and the related injuries in the brain (Hu *et al*., 2011). Hao *et al*. (2011) reported that ginsenoside Rb1 was capable of

inhibiting both isoforms of MAO in mice brains, increasing dopamine and serotonin levels. This was evidenced by the better performance of the mice regarding proper object identification and reduced immobility time during the forced swimming test, which allows the behavioral evaluation of mice when they are drowning. Other assays, like the measurement of tryptophan hydroxylase and AAAD, were conducted. Hao *et al*. (2011) also evidenced that the activity of both enzymes rose, meaning that the production rates of dopamine and serotonin increased.

Recent studies indicate that ginsenosides play a central role in suppressing other pathologies, not related to MAO, that leads to the progression of PD, such as the case with the inhibition of α-synuclein aggregation. Similar to the effects described earlier about tau protein, the extracted ginsenosides have been evidenced to decrease α-synuclein aggregation, as well as enhancing its dissociation. Ardah *et al*. (2015) conducted a thioflavin T fluorescence assay to determine the effects of different DMSO ginsenoside solutions of Rb1, Rg1, and Rg3 on α-synuclein fibrilization. Samples of 25μM α-synuclein were treated with different concentrations of Rb1, Rg1, and Rg3 (25 μM, 50 μM, and 100 μM) and incubated at 37ºC for 5 days. After the incubation period, the 100 μM Rb1 solution exerted the most significant aggregation inhibition, at around 80%, Rg3 inhibited around 25% of total aggregation, and Rg1 did not produce significant inhibition. The dissociation assay was conducted with help of western blotting. α-Synuclein fibrils were treated solely to Rb1, with the same concentrations as in the previous assay, with an incubation period of 2 days. The results evidenced that the fibrils dissociated in the presence of the ginsenoside, in a dose-dependent manner.

Shin *et al*. (2009) reported that the administration of ginsenosides could regulate the excitotoxic activation of adenosine receptors by kainate. In Sprague-Dawley mice, daily kainate administration lead to the development of seizures, oxidative stress, and neuron loss (Liang *et al*., 2007). The evaluation of the ginsenoside effects on the adenosine receptors was conducted in Sprague-Dawley mice, where the test subjects were orally administered two ginsenoside extracts (50 and 100 mg/kg) and 10 mg/kg kainate. For 4 hours, the seizure activity was recorded. The recorded results evidenced that the mice that were solely administered kainate exhibited robust seizures during the 4-hour timeframe, while the mice treated to the 100 mg/kg ginsenoside extract developed lesser seizure activity. Two days after documenting these results, the hippocampus of the test subjects was dissected and analyzed through micrographs. The obtained micrographs evidenced well-preserved cells in the hippocampus sample of the ginsenoside-treated mice. The authors suggested that ginsenosides interact with adenosine A_{2A} receptors as antagonists.

Different phenolic components found in ginseng have been reported to interact in the production of neuromelanin. *p*-Coumaric acid is a hydroxycinnamic acid that can successfully inhibit tyrosinase at different stages of the melanogenesis process. Found mostly in the leaves of *P. ginseng*, *p*-coumaric acid has a high affinity for the copper ion in the catalytic site of tyrosinase. Lim *et al*. (1999) evidenced that methanolic extracts of p-coumaric acid from ginseng were able to inhibit mushroom tyrosinase by 50% at a concentration of about 3.65 mM. The authors also evidenced that the phenolic acid possessed a higher affinity for the enzyme during the oxidation step of L-tyrosine than the L-DOPA oxidation step. This knowledge suggests that p-coumaric acid has more specificity to bind with the copper ions in the *oxy* form, while also having a lower affinity for the *met* form, in the case of L-DOPA oxidation. Other components of ginseng extracts, such as ginsenosides, are potent tyrosinase inhibitors, as well as preventing the oxidative stress induced by exposure to UV lights from the sun (Saba *et al*. 2020).

P. ginseng extracts have also been indicated as possessing modest antioxidant activity. Kim *et al*. (2002) conducted numerous assays to determine the potential of aqueous *P. ginseng*

extracts. The main practice of this report was to determine the effects on different concentrations of *P. ginseng* aqueous extracts in scavenging $O_2^{\bullet-}$, $^{\bullet}OH$, $^{\bullet}NO$, DPPH, and carbon radicals, through measurement in an electron spin resonance spectrometer. The results showed that: at a concentration of 2 mg/mL, DPPH was completely scavenged; at a concentration of about 0.5 mg/mL, around 80% of all carbon-free radicals were quenched; at 0.1 mg/mL, around 40% of the total $^{\bullet}OH$ radicals were scavenged; at 2 mg/ml, s $O_2^{\bullet-}$ was completely scavenged; in regards to $^{\bullet}NO$ scavenging, it was documented that ginseng extracts exhibited no scavenging activity.

7.1.3. Chrysanthemum

The flowers of chrysanthemum (Asteraceae family) are one of the most used plant components in traditional Chinese medicine. In nature, numerous chrysanthemum subspecies are found, with *Chrysanthemum indicum* and *Chrysanthemum morifolium* as the predominant species cultivated in gardens. Chrysanthemum has been involved in the treatment of various ailments since the 15th century B.C. (Shahrajabian *et al*., 2019). The primary health benefits of the flower range from anti-inflammatory, immunomodulatory, antibacterial, anti-tumor, and antioxidant properties (Cheng *et al*., 2005; Yuan *et al*., 2015). Other benefits include the mitigation of anxiety and stress, the detoxification of the liver, the improvement of eyesight, cooling of pathogen-induced fever, and the improvement of neurotransmitter activity, among others (Shahrajabian *et al*., 2019). Table A.3 of Attachment A shows the primary compounds found in the *Chrysanthemum* species that contribute to its neuroprotective effects.

The study of the neuroprotective effects of *C. indicum* Linne petal tea has been growing in recent years, mostly due to the number of different flavonoids in its composition. To assess its potential in AD treatment, Sun *et al*. (2008) conducted an assay where mice were administered with 1mg/kg of scopolamine, a cognitive diminishing drug, and aqueous extracts of chrysanthemum petals, to evaluate the mice's performance in a passive avoidance test, to determine the latency period of a mouse located in an illuminated box to enter a dark section, and a Morris water maze test, to assess the time taken by mice to reach successive times a hidden platform in a water maze. The results concluded that the extracts prevented a deficit in the cognitive ability of the mice, as well as improving the memory of mice with amnesia. It was reported that the main phenolics responsible for these results were luteolin and acacetin. Further investigation of the effects of acetylcholinesterase was conducted. The scopolamine-induced mice and scopolamine-chrysanthemum-induced mice were sacrificed after the cognitive tests, and their brains were prepared for a colorimetric method with acetylcholine iodide. The obtained results evidenced that the mice treated with aqueous *C. indicum* Linne extract registered a lower AChE activity than that registered on scopolamine-induced mice, of around 20%.

The administration of chrysanthemum aqueous extracts has been evidenced in folklore medicine to reduce anxiety levels. These inherent anxiolytic effects are also associated with the GABAergic system. To further understand the link between chrysanthemum extract intake and the GABAergic system, Hong *et al*. (2012) investigated the effects of *C. indicum* extracts on $GABA_A$ receptors. Male ICR mice were separated into groups and administered bicuculline (0, 0.3, and 1 mg/kg) 30 minutes before administration of 0.1 ml of *C. indicum* aqueous extracts (125, 350, and 500 mg/kg) per 10 grams of weight. Bicuculline is a $GABA_A$ receptor antagonist. The anxiety levels in the mice were then measured with an elevated plus maze, which consists of an elevated structure with barriers in some sections. The authors then measured the time spent by the mice in the open arms section, which is supposed to induce anxiety in the test subjects. The group

which was only administered the chrysanthemum extracts registered increased time spent in the open arms section of the maze in a dose-dependent manner. Contrary to this, the group which was administered both bicuculline and the chrysanthemum extracts spent less time in the open arms section. Since bicuculline is a selective $GABA_A$ receptor antagonist, these findings suggest that chrysanthemum can suppress the anxiety-induced effects of bicuculline.

The chrysanthemum species has been evidenced to exert inhibitory activity towards MAO. Han *et al*. (1987) isolated six flavonoids from *C. indicum*, which were identified as acacetin, diosmetin, luteolin, 5,7-dihydroxychromone, apigenin, and eriodictyol. The extraction was conducted with methanol and ether solvent and was subsequently subjected to chromatographic separation. Each flavonoid was then isolated with an ethanolic solvent. The enzymatic inhibition assay was conducted with cultured mice liver MAO-B, which was treated with the isolated flavonoids, and benzylamine as the enzyme's substrate. The results showed that, out of all isolated compounds, 5,7-dihydroxychromone, acacetin, and diosmetin were revealed to exert potent MAO-B inhibition, with IC_{50} values of 0.19 mM, 2.11 mM, and 2.46 mM, respectively. Han *et al*. (1988) also furthered the study of *C. indicum* to inhibit MAO-A. For this, mice brain MAO-A was cultured similarly to the previous essay on MAO-B and was treated with methanol plant extracts, including chrysanthemum flowers, fractioned with hexane, ether, and butanol, and serotonin as a substrate. Some isolated compounds of *C. indicum* were also evaluated. The results showed that the ether fraction of *C. indicum* exerted an inhibition rate of 94%, while apigenin and luteolin were founds as the most influential compounds in the plant, registering an inhibitory activity (IC_{50}) of 10 µM and 100 µM for apigenin and luteolin, respectively.

C. indicum has been shown to exert anti-melanogenic properties. Choi *et al*. (2016) evaluated the effects of *C. indicum* flower methanolic extracts on the activity of mushroom tyrosinase resorting to a spectrophotometry assay. Two mother-solutions were prepared by extracting 100 g of dried *C. indicum* flowers with 10 L of both methanol and distilled water. 100 µL of the solutions were separately added to a cuvette with 100 µL of 150 U/ml stock mushroom tyrosinase, 200 µL of L-DOPA as a substrate for the enzymes, and 50 µL of phosphate buffer. The inhibitory activity of the plant extract was determined by evaluating the absorbance of dopachrome, which is a product of catalyzed L-DOPA and compared with a positive control containing kojic acid. The obtained results showed that the methanol extract more potent inhibitory effects compared with the aqueous extract. At a concentration of 100 µg/ml, the methanol extract inhibited mushroom tyrosinase activity by 60%, while the water extract exhibited an inhibition rate of about 50%.

Chrysanthemum has been proven to induce sleep. According to Oh *et al*. (2011), the sleep-inducing effects of chrysanthemum flowers have been linked with GABA receptor interactions between the plant compounds. As the inducing of sleep is also a trait of the melatonin receptor system, studies were conducted to link the administration of chrysanthemum extracts to this neurological system. Hattori *et al*. (1995) evaluated the melatonin contents of fruits and plants, including *C. coronarum*. The extraction revealed contents of about 416.2 ± 54.6 µg per gram of flower.

The antioxidant properties of chrysanthemum are due to the plant's vast phytochemical composition, which ranges from caffeoylquinic acids, flavonoids, and terpenes (Lin *et al*. 2010; Yoshikawa *et al*., 2000). These properties result from the phenolics containing one or more hydroxyl groups in the molecule's aromatic rings (Liu *et al*., 2012). According to the available literature: Kim *et al*. (2005) evidenced that 3,5-dicaffeyol-epi-quinic acid and 1,3-dicaffeyol-epi-

quinic acid, fractioned from a methanol extract of *C. morifolium*, scavenged $O_2^{\bullet-}$ radicals with an associated IC_{50} of 2.9 ± 0.1 µg/ml and 2.6 ± 0.4 µg/ml, respectively; Zeng *et al*. (2014) evidenced ˙HO free radical scavenging activity at a rate of 54.450 ± 1.539 % and 33.513 ± 0.844 %, and DPPH radical scavenging activity, at a rate of 14.125 ± 0.313 % and 11.970 ± 0.296 %, of 0.1 ml samples of 0.4g/ml *C. indicum* and *C. morifolium* aqueous extracts.

7.1.4. Dandelion

Dandelion or *Taraxacum officinale* (Asteraceae family) is a widely used remedy in both Asia and Europe throughout the years. Both the roots and leaves are used in clinical treatment, although they are usually mixed with other plants since, by itself, dandelions are applied in very specific conditions. They are usually administrated to patients suffering from diuretic and gastrointestinal conditions, while other properties have been suggested, but not fully agreed upon (Yarnell & Abascal, 2009). Table A.4 in Attachment A shows the primary compounds found in *T. officinale* that contribute to the plant's neuroprotective effects.

T. officinale leaves have been reported to reduce the effects of AD through its involvement in the cholinergic system. This plant component contains lecithin (González-Castejón *et al*., 2012), a fatty acid substance rich in choline found in eggs. The dietary intake of lecithin is viewed as a preferable source of choline compared to the approved pharmaceuticals containing choline, like choline chloride. Pharmaceutical doses are administered to temporarily increase the choline levels in the blood, which subsequently reach the brain, while the regular consumption of lecithin helps to maintain the levels of choline constant in the body (Magil *et al*., 1981).

The analysis of extracts of *T. officinale* leaves has been reported that the main flavonoids consisted predominantly of luteolin and other luteolin derivatives (Fatima *et al*., 2018), molecules which were previously proven to inhibit AChE, however, *T. officinale* has been found to not influence the activity of the enzyme. Jukic *et al*. (2012) screened different plants for possible acetylcholinesterase inhibition and antioxidant activity, including *T. officinale*. For this, methanol, ethyl acetate, and chloroform extracts were produced, with subsequent measurement of the enzymatic activity in a microplate reader. While all samples of *T. officinale* possessed different phenolic content, AChE inhibitory activity was not affected. One report also evidenced that *T. officinale* leaves extracts could induce anticholinergic effects, as an acetylcholine receptor antagonist in the human trachea (Awortwe *et al*., 2011).

Mazzio *et al*. (2013) screened the MAO-B inhibition activity of several plants, including the roots of *T. officinale*. To achieve this, the plants were macerated and extracted with enough 100% ethanol to achieve a 50 mg/ml sample, while recombinant human MAO-B was cultured and distributed in a 96-well plate, along with the samples, benzylamine as a substrate, and a chromogen agent, with a subsequent incubation period of 18-24 hours. The measured MAO-B IC_{50} value for the roots of *T. officinale* was about 7mg/ml, which was labeled as a weak inhibition.

Chicoric acid is typically found in the leaves of dandelions and is considered to be one of the prevalent polyphenols when discussing the antioxidant activity of the plant's extracts (Ivanov, 2014). Kour & Bani (2011) conducted an assay in the effects of chicoric acid, where stressed induced mice were subjected to the forced swimming test and a "helplessness test", or passive avoidance test, a trauma-inducing foot shock method used as a model for depression, designed to raise the levels of behavioral despair or to evaluate subject cognition. The results showed that the levels of despair induced stress were diminished in the test subjects.

Xie *et al*. (2018) investigated different *T. mongolicum* extracts on their potential to inhibit mushroom tyrosinase. To achieve this, leaf and stem extracts were isolated with water, ethanol, and a 50% ethanol solution, at a liquid to solid ratio of 30:1, with the samples being subjected to either evaporation of ethanol, lyophilization, or both. 100 µL of 125U/ml mushroom tyrosinase were added to a 96-well plate, with buffer solution, L-DOPA as a substrate, and the powder extracts dissolved in 5% DMSO aqueous solution. The results were obtained using a colorimetrical measurement method. The obtained IC_{50} values for the leaf extracts were similar, with the aqueous extract possessing a more potent tyrosinase inhibitory rate at about 1.00 ± 0.02 mg/ml, while for the stem extracts, the water/ethanol extract exerted a higher inhibitory rate, at about 0.48 ± 0.04 mg/ml.

Dandelion leave extracts have been reported to successfully scavenge various ROS and RNS, as well as scavenging chelating metals. Kitts & Hu (2005) conducted different assays to determine the *T. officinale* flower extract's $O_2^{\bullet-}$, hydroxyl, and nitric oxide scavenging activity. For the superoxide assay, 0.1 ml of a 0.5U/ml solution of xanthine-xanthine oxidase was used to produce the $O_2^{\bullet-}$ free radical, which was then treated with different concentration of *T. officinale* flower extract (25, 50, 100, and 200 µg/ml), followed by absorbance measurement using a control without the xanthine-xanthine oxidase solution. The results evidenced a dose-dependent scavenging ability of the free radical, with the most concentrated plant extract scavenging around 71.0 ± 0.6 %. For the hydroxyl assay, 3.6 mM deoxyribose was treated with the T. *officinale* flower extracts. The results also evidenced a dose-dependent scavenging activity, although to a lesser extent, with the most concentrated extract quenching around 54.6 ± 1.7 % of total $^{\bullet}HO$ free radicals. As for the nitric oxide assay, murine macrophage RAW264.7 cells were cultured 10% bovine serum and antibiotics and incubated. The cells were then distributed in a 96-well plate and treated with the T. *officinale* flower extract samples. The extracts were able of suppressing the production of nitric oxide in the cells, with an associated IC_{50} value of around 130 µg/ml of extract needed.

7.1.5. Licorice

Licorice, or *Glycyrrhiza glabra* L. (Fabaceae Family), is a notorious plant used in TCM, only surpassed by ginseng in terms of prevalence, importance, and benefits. The roots and rhizome of this plant are commonly known for their mellow flavor and is typically used in western cultures as a confection product. Licorice roots are also utilized in various remedies due to the plant's flavor-enhancing properties. Meanwhile, in some Asian cultures, licorice has been used as a tonic throughout history. The plant has been documented to demonstrate anti-inflammatory, antitussive, expectorant, anti-hepatic, anti-asthma, anti-ulcerative, and antimicrobial properties (Abouelnour, 2016). The main active compound found in licorice is glycyrrhizin, a triterpenoid saponin mostly responsible for the mellow taste of the plant (Abouelnour, 2016), and for the antiviral effects evidenced in hepatitis B carriers, such as preventing liver cell apoptosis (Muriel & Tovar, 2019). Table A.5 of Attachment A shows the primary compounds found in *G. glabra L.* that contribute to its neuroprotective effects.

The extracts of licorice roots have been reported to ameliorate the cognitive ability of scopolamine-induced mice, by inhibiting AChE. This was evidenced by Dhingra *et al*. (2006), when the authors evaluated the effects of root aqueous extract administration on the brain tissue of Swiss male albino mice, through the Ellman method, a common method that measures acetylcholinesterase activity indirectly by quantifying the concentration of 5-thio-2-nitrobenzoic

acid (TNB) formed in the reaction between the thiol reagent 5,5′-dithiobis-2-nitrobenzoic acid (DTNB) and thiocholine iodide, which acts as a substrate (Šinko *et al*., 2007). The results of this assay revealed that consecutive administration of 150mg/kg licorice root aqueous extract for 7 days decreased the overall acetylcholinesterase activity by 25.4%. Despite this notion, glycyrrhizin is known to dose-dependently enhance the activity of AChE, as reported by Zhou *et al*. (2012). The inhibitory activity of cholinesterases by licorice roots is attributed to glycyrrhizin aglycones, such as glycyrrhetinic acid and its derivatives. As for the root's BuChE inhibitory activity, no studies were yet conducted.

The extracts of *G. glabra* have been found to suppress β-amyloid production. Zhu *et al*. (2010) conducted an assay where APP-PS1 Tg mice were divided into three groups, with two groups subjected to daily intake 2,2´,4-trihydroxychalcone, a compound found in *G. glabra* at doses of 3 and 9 mg/kg/day, for 106 days, while the other was treated with a control vehicle. All sample administration was conducted by intraperitoneal injection. After the administration period, the mice were subjected to a Morris water maze. The group which was administered 9 mg/kg/day registered the shortest periods in the maze. After the test, the mice were sacrificed, and the brain tissue was cultured to assess β-amyloid content and β-secretase activity. The results showed that 2,2´,4-trihydroxychalcone inhibited 50% of β-secretase at a concentration of 4.75 μM, which correlated with the reduced β-amyloid contents in the brain tissue.

The phenolic compounds found in licorice roots have been described as to have antidepressant properties. Dhingra *et al*. (2006) evaluated the effects of consecutive oral administration aqueous licorice root extract for 7 days in Swiss male mice by analyzing the test subject's performance in both forced swimming and tail suspension test (utilized to measure the total immobility time when the mice tail is suspended). Alongside this, other mice groups were administered a control sample, fluoxetine, and imipramine by intravenous injection. The results after 7 days evidenced that 150mg/kg licorice aqueous extracts exerted the most significant anti-depressant effects in the mice, suggested by the registered immobility times of 157.2 ± 6.8 seconds in the forced swimming test and 109.8 ± 9.6 seconds in the tail suspension test, however, the effects were less potent than those observed for fluoxetine. The authors suggested that the phytochemical components of the licorice extracts interact with dopamine receptors as agonists.

18β-Glycyrrhetinic acid is a triterpenoid saponin found in the roots of *G. glabra* and has been associated with the plant's potential to interact with the cannabinoid receptors. Park *et al*. (2014) examined the inhibitory activity of licorice root and isolated 18β-Glycyrrhetinic acid in 30% ethanol extracts with different concentrations (0.1, 1, 3, 10, 30, and 100 μg/ml) on human CB_1-expressing Chem-1 cells. Separate cells were also treated with 3 μM anandamide to produce a control sample. As expected, the control sample activated the influx of calcium ions, with an EC_{50} of 0.91 ± 0.08 μM; the 30 μg/ml licorice extract exerted inhibitory activity towards the CB_1 receptor, with an associated IC_{50} of 9.17 ± 1.62 μg/ml. At a concentration of 30μM, 18*β*-glycyrrhetinic acid showed an inhibition rate above 90%, with an associated IC_{50} of 1.96 ± 0.05 μM.

Glabridin is one of the most well-studied flavonoids found in *G. glabra*. Glabridin was found to stimulate $GABA_A$ receptors, thus inhibiting the neurotransmission, which was evidenced by Hoffmann *et al*. (2016). The authors utilized a voltage-clamp technique on *Xenophus laevis* oocytes with different GABA receptor subunits, which were treated with a 30 μM glabridin extract with ethanol. Glabridin was found to strongly potentiate the $GABA_A$, α1β2γ2 receptor subtype, which registered an EC_{50} of 6.30 ± 1.70 μM.

Although glycyrrhizin is the primary compound in licorice, other components have been found in the plant, that, by themselves, expand the overall beneficial effects of licorice consumption. An example of this occurrence regards isoliquiritigenin and liquiritin, which have been evidenced by Liao *et al*. (2016) to inhibit α-synuclein aggregation. The authors isolated 3.0 µg of isoliquiritigenin, and 19.7 µg liquiritin from a lyophilized 70% ethanol solvent extract of *G. uralensis*. Human α-synuclein was expressed from recombinant *E. coli* bacteria and was treated to the different extracts of the isolated compounds, as well as the lyophilized powder. The inhibition activity was measured with a THT fluorescence assay. The results showed that, at a concentration of 250 µM, isoliquiritigenin and liquiritin inhibited α-synuclein aggregation by 36.9 ± 1.7% and 62.5 ± 1.5%, while 1mg/ml of the lyophilized *G. uralensis* extract inhibited aggregation by 66 ± 5.5 %. At a concentration of 100 µM, the inhibitory effect of isoliquiritigenin increased to 60.4 ±1.9%, while liquiritin and lyophilized *G. uralensis* extract (500 µg/ml) showed little to no effects. In this study, glycyrrhizin was also extracted and evaluated, however, the compound did interact with α-synuclein.

Licorice roots also have a decisive role in melanogenesis. For instance, the isoflavone glabridin is the main flavonoid of the plant that significantly inhibits the melanogenesis process (Yokota *et al*. 1998). Khanom *et al*. (2000) conducted an assay where various medicinal plants, including *G. glabra*, were studied on their potential to inhibit tyrosinase. A 5g dried sample of *G. glabra* trunk was extracted with 150 ml of ethanol, lyophilized, and dissolved in three different solvents: 50% methanol, 60% acetone, and 10%DMSO aqueous solutions. The results showed that the tyrosinase inhibition rate of the DMSO extract exhibited an inhibition rate of 48.6%. while the methanol (50%) and acetone (60%) extracts of the same sample showed an inhibition rate of around 92.1% and 94.1%, respectively.

The flavonoids present in licorice roots stand out for their inherent antioxidant activity. This property is normally attributed to the positioning of free hydroxyl groups throughout the molecular structure of the flavonoids. An example of this is featured in glabridin, where the placement of its two hydroxyl groups in the aromatic ring has been shown to exacerbate the molecule's activity (Yokota *et al*., 1998). While the proper scavenging mechanisms of licorice phenolics are uncertain, Tohma & Gulçin (2010) extracted four samples of both 25 g macerated *G. glabra* root and aerial components, with 400 ml of distilled water and 500 ml of ethanol, and lyophilized both, to determine the inherent $O_2^{\bullet-}$, H_2O_2, DPPH scavenging activity, and Fe^{2+} chelating activity, and Fe^{3+} and Cu^{2+} reduction activity of the extracts. The results regarding ROS scavenging activity evidenced that the aqueous root extracts exhibited the most potent $O_2^{\bullet-}$ and H_2O_2 scavenging activities, at rates of 41.0 ± 4.8% and 51.2 ± 8.6%, respectively. All samples exerted similar DPPH radical scavenging activity, ranging from 50-60% total quenching, apart from the aqueous extract of *G. glabra* aerial components, which was lesser. The authors also concluded that all extracts had exhibited strong metal reducing activity and electron-donor properties. According to Jong *et al*. (2005), *G. glabra* extracts also can suppress nitric oxide synthase, thus suppressing nitric oxide radical formation.

7.1.6. Bamboo

Bamboo is one of the most common plants spread throughout Asian countries, and the fastest growing plant known to date. This plant can adapt to numerous kinds of weather conditions, from tropical to dry regions, henceforth its global distribution, except for Europe. Bamboo is a woody grass that was used in ancient civilizations for decorative and day-to-day

tasks, due to its durability and sturdiness, such as construction. The bamboo grass/leaves/shoots, still to this day, are implemented in the dietary intake of several communities with assess to it and have been a common component in TCM. (Wróblewska *et al*., 2019). Bamboo leaves are rich in flavonoids, such as luteolin, vitexin, and orientin, as well as some phenolic acids, like caffeic, ferulic, and cholinergic acid, among other important compounds, as shown in Table A.6 of Attachment A. The administration of the leaves, either by infusion or direct consumption, have exerted anti-inflammatory, antioxidant, diuretic, expectorant (Shukla *et al*., 2012), and anticarcinogenic properties (Seki *et al*., 2010).

The extracts of bamboo leaves have been associated with AD and PD as a potential treatment method, though the available information is limited. The upper section of bamboo shoots has been proven to possess unusually high levels of acetylcholine (Horiuchi *et al*., 2003). No further studies were conducted yet to verify the existence of ACh in the leaves, although there is the belief that the leaves near the shoot may possess low amounts of this neurotransmitter.

Liu *et al*. (2015) evaluated both the behavioral and biochemical effects of dementia-induced mice through intraperitoneal injection of D-galactose. The behavioral assay was determined by subjecting three groups of mice (one control, one with senile demented mice, and one group with senile demented mice, treated with bamboo leaf extract) to a daily Morris water navigation test, recording the path length and escape latency. The obtained results showed that, by the second day of testing, the treated mice had completed the test in less time than the untreated group. Complementary assays on ACh content and AChE activity indicated that the levels of the neurotransmitter in the hippocampus and the cortex of the mice group treated with bamboo extract was the highest, as a result of the diminished enzyme activity. The neurotransmitter production rate did not suffer alteration. The authors also evaluated the effects of the administration of bamboo leaf extracts on the brain levels of glutamate and GABA. Compared with the control group, no significant changes were evidenced, however, glutamate and GABA levels were higher than those observed in the senile mice group. These results suggest that the leaf extracts of bamboo possess a role in the regulation of spatial memory, by inhibiting AChE in the cortex and hippocampus.

In the same study, the author also evaluated the levels of dopamine, as well as the activity of MAO-B. Much like the ACh and AChE inhibition assays, the levels of dopamine in the hippocampus and cortex rose in the treated mice brain, as MAO-B activity lowered. Regarding MAO-A, there is limited evidence that bamboo leaf extracts possess any sort of inhibition on the enzyme. Liu *et al*. (2015) evaluated the effects of administering bamboo leaf extracts on the levels of serotonin in the brain of mice, with no significant alteration.

Bamboo leaves are known to contain several phenolic compounds capable of preventing neuromelanin accumulation in the *substantia nigra*. The extracts of bamboo stems, which are equivalent in terms of phenolic composition to the leaves, have been reported to both inhibit tyrosinase and reduce neuromelanin production (Song *et al*., 2007). Choi *et al*. (2018) examined the inhibitory activity of an ethyl acetate fraction of 80% ethanol bamboo leaf extract on mushroom tyrosinase, with melanin as a substrate. The assay was conducted with a cell-free system, an *in vitro* technique that allows for the evaluation of a cell activity without the involvement of extracellular interactions. The obtained results report that the bamboo leaf extract has an associated IC_{50} value of 243.7 µg/ml. The anti-melanogenic effects of this extract have been evidenced to depend on the presence of important phenolic compounds, such as *p*-coumaric acid, caffeic acid, chlorogenic acid, luteolin, rutin, and catechin.

The positive effects of bamboo leaf extracts on the body are usually associated with the plant's antioxidant activity. Choi *et al*. (2018) also attested to the antioxidant capability of bamboo leaves in different mechanisms, such as inhibiting superoxide dismutase. The authors also reported a scavenging potential of DPPH and ˙HO radicals with associated IC_{50} values of 565.63 ± 17.75 µg/ml and 509.17 ± 33.76 µg/ml, respectively. Khatun *et al*. (2013) evidenced that a 0.1g/ml 80% methanol bamboo leaf solution extracted for 1 hour had an $O_2^{\bullet-}$ scavenging activity of about 10%. Other studies have attested to other antioxidant and scavenging activity effects. Macwan *et al*. (2010) evaluated the nitric oxide scavenging potential of three bamboo leaf extracts: 10.8% (w/w) water extract, 13.7% methanol extract, and 3.09% butanol extract, with associated IC_{50} values of 644 µg/ml, 433 µg/ml, and 664 µg/ml, respectively.

7.1.7. Hemp

Cannabis sativa L. (*Cannabaceae* family) is a plant most known for its psychoactive effects and its use as a recreational drug throughout the world, with some suggestions that it's one of the most consumed substances in the world. The whole plant has been documented in several old Chinese medicinal texts to treat various ailments for over 2000 years, with other day-to-day applications dating even further in history (Brand & Zhao, 2017). Cannabinoids are the predominant phytochemical components found in *C. sativa* and they hold a significant role in our daily lives. These types of phytochemicals can be synthesized in the body (endocannabinoids) or administered (plant cannabinoids), which can then bind to cannabinoid receptors spread throughout the cells in the NS. The interaction between both can alleviate inflammation, chronic pain, as well as preventing cancer growth (Kumar & Zou 2018). Other compounds found in hemp are shown in Table A.7 of Attachment A.

The social stigma around this plant revolves around the presence of THC, a psychoactive cannabinoid Today, many countries have slowly increased the restrictions surrounding this plant, which allowed only for the legal medicinal use in cancer patients, as well as an extensive investigation of the plant. Several sources throughout the years attested for the medicinal properties of *C. sativa* and attributed these effects to cannabidiol (CBD) (Brand *et al*., 2017). When compared with THC, CBD shows no psychoactive effects in the body, while maintaining other properties attributed to cannabinoids. CBD has been reported as being a nonselective compound to both CB_1 and CB_2 receptors (Zou *et al*., 2018).

Hemp-based products have gain popularity in some parts of the world since this section of *C. sativa* registers low contents of THC. Hemp seed oil is the most common product available in many countries. While the seeds contain neither THC nor cannabinoids naturally, they are usually processed with a resin coating, rich in cannabinoids (Leizer *et al*., 2015). Numerous studies have reported the presence of cannabinoids in hemp seed samples (Yan *et al*., 2015). In some cases, commercial hemp seed oils are enriched with CBD to boost the product's healing properties.

CBD has been reported to enhance the cognitive ability of mice. Murillo-Rodríguez *et al*. (2018) conducted an assay where the Wistar mice forebrain was collected and treated to different doses of CBD (5, 10, and 30 mg/kg) and a vehicle control sample free of CBD 6 times across 6 hours. All forebrain samples treated with CBD were reported to increase acetylcholine levels. Compared with the control sample, the 5 mg/kg dose increased ACh levels by 25%, while the 10

mg/kg and 30mg/kg dose increased ACh levels around 100% and 167%, respectively. The authors suggested that CBD interacts with CB_1 receptors in the forebrain as an antagonist. Hemp seeds extracts have also been evidenced to inhibit AChE. Yan *et al*. (2015) isolated several compounds from *C. sativa* and evaluated each compound's inhibition activity on *Torpedo californica* AChE. Then, 100 µg/ml isolate compound extracts dissolved with 0.1 M Tris-HCl buffer containing 85% MeOH were prepared and added to AChE samples. The results reported overall modest AChE inhibitory rates, with the undisclosed compounds 13, 7, and 3,3′-dimethyl-heliotropamide exhibiting a 50% inhibitory rate at 38.7 µM, 216 µM, and 46.2 µM. No assays were conducted to evaluate the inhibition rate of BuChE with hemp seed extracts.

Iuvone *et al*. (2004) evidenced the neuroprotective effects of cannabidiol against β-amyloid toxicity. The authors prepared a culture medium to supplement PC12 cells. Thereafter, these cells were treated with 1 mg/ml β-amyloid peptide fragment solution and served as a control sample. The effects of cannabidiol were measured by treating the PC12 cells/β-amyloid sample with different concentrations of the cannabinoid (10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4} M). These samples were then incubated for 24h at 37ºC. Cell death was measured by optical density spectrophotometry. In the control sample, β-amyloid was responsible for reducing viable cell density by 38.8 ± 2.2%. With the increase in cannabidiol concentration, the total cell death decreased even further, with the 10^{-4} M dose registering cell death just above 10%.

As a continuation of the overlapping effects of β-amyloid, Esposito *et al*. (2006) then studied the possible effects of cannabidiol in inhibiting tau protein hyperphosphorylation. The cell preparation was like that used to evaluate the neurotoxic effects of β-amyloid, as mentioned above, with the same cannabidiol concentrations. In this instance, the cells were washed after incubation, and were equal amounts of sample cells were extracted from the produced hyperphosphorylated tau protein by polyacrylamide gel electrophoresis. The protein samples were then transferred to a nitrocellulose membrane and were prepared for an immunoblotting assay, with the resource of a tau protein antibody for detection purposes. As expected, the control sample detected the heightened amount of hyperphosphorylated tau protein. Cannabidiol was also found to suppress the levels of hyperphosphorylated tau protein in a dose-dependent manner.

Although the relaxing effects of CBD consumption are primarily related to the compound's interaction with the CB_1 receptors, however, other non-cannabinoid related systems have been evidenced in the past to exert similar behavioral properties, like the GABAergic system. Lile *et al*. (2012) evidenced that THC augmented the interaction between GABA and its receptors by specifically inhibiting transporter proteins involved in cellular uptake. On the other hand, Pretzsch *et al*. (2019) evaluated the possible effects of a single 600 mg dose of CBD of GABA and glutamate levels in 34 male patients, as a means to further understand excitatory/inhibitory mediation of CBD in both normal and autistic patients. The neurotransmitter levels were measured by magnetic resonance spectroscopy, two hours after administration. The obtained results evidenced that glutamate levels in both groups of patients were increased in the basal ganglia and reduced in the dorsomedial prefrontal cortex. As for GABA, the results evidenced an increase in the neurotransmitter's levels in the basal ganglia and dorsomedial prefrontal cortex in the autism-free patients, while autistic patients had their levels of GABA reduced in both regions. These results show that, for neurotypical patients, CBD helps regulate both glutamatergic and GABAergic systems, while further studies are needed to comprehend the cannabinoid's effects on autistic patients.

Cannabinoids, like CBD, have shown to inhibit both MAO isoforms, at different rates. Despite not showing high specificity to either enzyme, (Schurr & Rigor 1984) reported that the

phytochemicals inhibited MAO-B at a higher rate, although the inhibition is dose-dependent. The authors testes the MAO-A inhibitory activity of different extracts, including a petroleum ether *C. sativa* extract, CBD, THC, and 11 other isolated compound fractions. MAO-A samples were treated with 100 µg of extract per 1 mg of the enzyme. The results showed that the *C. sativa* extract inhibited MAO-A activity by around 60%, while the CBD extract did not exert any significant inhibitory activity. Other fractions, like the undisclosed F_4, F_5, and F_6, were reported to strongly inhibit MAO-A at a rate of around 85%, 70%, and 50%, respectively. Cannabinoids can also boost the release of neurotransmitters like dopamine and serotonin (Fišar, 2012), as well as modulating the desensitization of monoaminergic neurons, by regulating spontaneous action potential boosts (Pidoplichko *et al*., 1997).

Castillo *et al*. (2010) reported that CBD exerts anti-excitatory effects on cannabinoid receptors, which in turn affect adenosine receptor-induced glutamate release to the synapse. The brains of newborn C57BL6 mice were sliced and incubated in a culture medium. The slices were then treated to 1000 µM dimethyl sulfoxide CBD solution and a vehicle sample (control). Cell death was measured by spectrophotometric determination of lactate dehydrogenase efflux, which is a marker for necrotic tissue damage. To quantify released glutamate from the damaged cells, ELISA kits were utilized for neurotransmitter quantification. The obtained results reported that the administration of CBD to the brain samples decreased cell death, as seen by the lesser amounts of extracellular lactate dehydrogenase, as well as reducing extracellular glutamate levels in the extracellular domain.

The effects of *C. sativa* extracts of different plant organs have shown similar results regarding the melanogenic process, with different pathways. Manosroi *et al*., (2019) performed an absorbance assay where both hemp leaves and seeds were evaluated in different procedures, including tyrosinase activity. 50 µL of 5 hemp DMSO solutions with different concentrations, from 0.001 to 10 mg/ml were incorporated in 50 µL of a 1mg/ml mushroom tyrosinase solution. A solution replacing the hemp extract with phosphate buffer was used as a control sample. The results allowed for the determination of the IC_{50} of the leaf and seed hemp extracts, which was 0.049 ± 0.002 mg/ml and 0.07 ± 0.06 mg/ml, respectively. The results showed that the hemp seed extracts were able to inhibit tyrosinase at a lower rate than the leaf extracts, which may indicate that other phytochemicals in the extracts can positively influence the inhibition process, although the specific compound interactions are not entirely comprehended.

Manosroi *et al*. (2019) also evaluated the antioxidant and scavenging activities of both extracts. As seen in the tyrosinase inhibition assay, the leaf extract also possessed higher DPPH scavenging activity, with an associate SC_{50} value of 2.73 ± 0.42 mg/ml, compared to the seed extract's 14.39 ± 2.27 mg/ml, almost seven times higher, as well as a metal chelating activity, with an associated 0.93 ± 0.20 mg/ml CC_{50}, compared to the seed extract's 1.92 ± 1.05 mg/ml. Regarding scavenging ability, Ojezele *et al*. (2019) reported an EC_{50} value of 95.07 ± 0.01 µg/ml of a 0.2 mg/ml methanol extract of *C. sativa* leaves, as well as a DPPH scavenging activity EC_{50} of 78.75±0.08 µg/mL for an n-hexane fraction of the original extract solution and an iron-chelating activity of (EC50=100.00±0.03µg/mL for a chloroform fraction. Hemp seed extracts have also been proven to increase the activity of superoxide dismutase and catalase (Girgih *et al*., 2014).

7.1.8. Adlay

Adlay (*Coix lacrima-jobi* L., Poaceae family) is a tall grass that contains important nutrients and proteins that, to this day, serves as a source of food in some Asian countries, like China and Japan. Out of all the plant's parts, the seeds are the most consumed. Adlay seeds are a well-established botanical medicine in TCM, with its application dating back to thousands of years ago to treat patients of various ailments, mostly cancer (Yu *et al*., 2017). Adlay seeds exert many properties, such as anti-inflammatory, antimutagenic, anti-tumor, anti-allergic, anti-glycemic, anti-microbial, anti-cancer, hormone modulating, diuretic, among others (Kuo *et al*., 2012). Table A.8 of Attachment A shows the primary compounds found in adlay seeds that contribute to its neuroprotective effects.

Adlay seeds extracts have been proven to display anti-AD properties, mostly regarding AChE inhibition and β-amyloid. Seo *et al*. (2009) evaluated the anti-cholinesterase effects of an undisclosed compound, referenced as AChE inhibitor, extracted from a methanol extract of adlay seed hull. The extract was prepared to achieve a 1:15 weight/volume ratio between the hull powder and the solvent and was later lyophilized. The extract was then fractioned with different solvents, including n-hexane, chloroform, ethyl acetate, butanol, and water, and was applied to thin-layer chromatography where for each fraction the AChE inhibitor was then isolated, dissolved in 100% methanol, and finally lyophilized. The inhibitory assay samples were prepared with 30µL of stock solution (0.8 U/ml) and 30µL of acetylcholine chloride as a substrate and 10µL of each fractioned AChE inhibitor. The results indicated that the n-hexane fraction showed the highest inhibitory activity at around 75.5%, which according to the authors, translates to an IC_{50} value of 176 µg.

No reports were yet conducted to assess the β-amyloid inhibitory activity of adlay seed extracts in the brain. However, during an investigation on the adlay extracts anti-diabetic effects on ICR mice, Chen *et al*. (2019) found that these extracts significantly reduced β-amyloid levels in the blood.

No anti-MAO effects of adlay seed extracts were reported, however, the case can be made that these extracts can inhibit the isoenzymes of both species, since adlay seeds are rich in polyphenols that have proven to reduce the activity of MAO-A and B, like quercetin and luteolin (Dhiman *et al*., 2019). Instead, the properties of the seed extracts are usually related to their potent antioxidant and free radical scavenging activities, which prevents inflammation-induced AD and PD.

The phytochemical components found in adlay seeds have been suggested as a valid treatment option to suppress melanogenesis in the brain. Huang *et al*. (2014) evaluated the effects of adlay seed extracts on mushroom tyrosinase. A 75 g sample of adlay seeds powder was subjected to supercritical fluid extraction with CO_2. Then, tyrosinase inhibition assays were conducted, where 10 µL containing 200 U of mushroom tyrosinase were treated with L-DOPA (substrate), phosphate buffer, and different concentrations of adlay extract dissolved in DMSO (25, 50, 100, and 250 mg/ml) were incubated at 37ºC for 30 minutes. The inhibitory activity was measured spectrophotometrically by determining dopachrome formation and was compared with a kojic acid-containing positive control. The results showed that mushroom tyrosinase activity was reduced in a dose-dependent manner, with the 100 and 250 mg/ml samples exhibiting similar results with that of kojic acid; these two samples reduced tyrosinase activity to 46.68% ± 3.52% and 38.85% ± 3.31%, respectively.

Adlay seed extracts are capable of inhibiting inflammation-inducing enzymes, such as nitric oxide synthase, preventing the production of $NO^{\bullet}$ and $ONOO^{-}$ (Chung *et al*., 2009). Kuo *et*

al. (2001) evaluated the scavenging properties of different components of adlay seeds, like the hull, seed, testa, bran, and polished adlay. 100g of each seed component was extracted with 1 L of methanol, dried, and finally dissolved in methanol again in various concentrations. Then, superoxide, hydroxyl, and hydrogen peroxide scavenging assays were conducted, with the application of 1 ml of different extract solutions. At doses of 250µg/ml, hull and testa extract scavenged: 50% and 25% total $O_2^{\bullet-}$ radicals, respectively; 19% and 21% of total H_2O_2 radicals; all extracts were reported to accelerate the oxidative damage of deoxyribose, a compound whose degradation generates hydroxyl radicals, apart from the hull extract at 1000 µg/ml, which scavenged around 20% of total $^{\bullet}HO$ free radicals.

7.1.9. Purslane

Portucala oleracea L. (Portulacaceae Family), or purslane, is a fast-growing weed used around the world for medicinal and food purposes. Its global distribution and fast growth in both arable and arid soils make it one of the most common plants, with some estimates pointing it as the eighth-most distributed plant in nature. It is believed that purslane has originated from Asian regions. Even though its use as a medicinal plant has been documented, the interest in this plant was renewed when it was determined to contain high levels of fatty acids and antioxidants (Simopoulos, 2004).

Table A.9 of Attachment A shows the primary compounds found in *P. oleracea L.* that contribute to its neuroprotective effects. From the addressed plants in this thesis, purslane is one of the most unique species, as it contains important molecules that are involved in excitatory and inhibitory receptor interactions, such as the case of adenosine and melatonin. However, melatonin shows great potential in various treatment procedures, since it performs important functions discussed in this report, such as scavenging free radicals, regulating enzymes that catalyze free radicals, and interacting synergistically with other components in the plant, therefore boosting their medicinal effects (Simopoulos *et al*., 2005). One of the most important uses of melatonin, however, derives from its interaction with the melatonin receptors in the brain, which have been evidenced to cement the human circadian clock (Khanom *et al*., 2000). Purslane extracts intake has been documented to exert antimicrobial, neuroprotective, anti-inflammatory, anti-diabetic, hepatoprotective, immune-modulatory, antiarthritic, among others (Simopoulos *et al*., 2005).

Agrawal *et al*. (2008) evaluated the cognitive effects of melatonin in adult male Swiss albino mice with scopolamine-induced amnesia. The authors subjected the mice to a passive avoidance test: in the first trial, the mice that entered the dark chamber were locked and punished with a light foot shock; in the second trial, the passage to the dark chamber is opened, but mice are free from foot shock. The second trial acts as a memory retention test. Different mice groups were treated to 10mg/kg and 20mg/kg melatonin doses, 5mg/kg donepezil, and 0.5mg/kg insulin, 1 hour before the first trial, with the intake of 3mg/kg scopolamine 5 minutes before the first trial. The observed effects in the mice groups revealed that donepezil and melatonin increased transfer latency time to cross from the initial section to the dark chamber. Afterward, the mice were sacrificed to assess AChE activity in each group's brain sample, resorting to detergent soluble and salt soluble fractions, according to the Ellman method. In the detergent soluble fraction, all studied drugs inhibited AChE activity in the hippocampus and hypothalamus, when compared to the control group. These results suggest that melatonin can help suppress amnesiac effects in patients by inhibiting AChE.

According to Cheng *et al*. (2006), melatonin was evidenced to possess a deeper role in AD suppression, by also intervening in β-amyloid and hyperphosphorylated tau protein neurotoxicity. Although the authors did not reveal the inhibition rates, they reported that PC12 cells were treated with β-amyloid fragments, as well as different concentrations of melatonin (10^{-5}, 10^{-6}, and 10^{-7}), which significantly attenuated β-amyloid-induced apoptosis. Lahiri (1999) evidenced the effects of melatonin as well on β-amyloid. The author treated SK-N-SH cells to different 95% ethanol solutions of melatonin with different concentrations (0.4, 1.7, and 3.4 mM), as well as a vehicle containing only the ethanol solvent, with subsequent incubation. Then, the secreted levels of β-amyloid were measured by an ELISA assay. The results indicated that melatonin could suppress β-amyloid secretion in a dose-dependent manner. Compared with the vehicle sample, which was attributed as having 100% of β-amyloid content, the 3.4 mM melatonin sample was able of suppressing the secretion of the peptide to 44.4% of total content.

Das *et al*. (2020) evidenced that melatonin is capable of inhibiting tau protein aggregation. The authors conducted an assay, where tau protein was expressed in recombinant E. coli bacteria and purified. Samples for tau aggregation measurement were prepared with a buffer solution, and heparin as a filament inducer, to which a 1000 µg/ml melatonin solution dissolved in 10% DMSO, were administrated to the samples and incubated for 24 hours. The samples were then subjected to size-exclusion chromatography, right before and after incubation, to evaluate the effects of melatonin in inhibiting tau protein oligomerization. The obtained fractions of tau protein aggregated were then measured with THT fluorescence assay. The obtained results evidenced reduced tau-protein aggregates in the samples treated with melatonin.

Purslane extracts are often reported as possessing anxiolytic effects in patients, which is normally derived from the activation of the GABAergic system. Lee *et al*. (2009) investigated the effects of 70% ethanol extracts of purslane in ICR mice. For this assay, the mice were separated into groups and were orally administered purslane extracts dissolved in a 10% aqueous solution of Tween-80, with different concentrations (50, 100, 200, and 400 mg/kg). The control group was administered a vehicle solvent. The mice were then subjected to an elevated maze test, a horizontal wire test, which is designed to record the mice's ability to grasp a horizontal wire, when faced with a falling scenario, to evaluate induced relaxation on the subjects, and an open field test, set in a closed box to determine the locomotor activity levels of mice by the subjects' position in the field, as mice typically avoid open areas to avoid predators. The results evidenced that: the 200 mg/kg dose had the best effects in the elevated maze test, as this group of mice spent more time in the open areas; all samples of purslane did not harm the mice's ability to grasp the horizontal wire; no significant changes were registered in the locomotor activity levels of mice, as the measured distance traveled by the mice groups were similar. In a separate group, mice were administered to 400 mg/mg purslane extract and 10 mg/kg doses of flumazenil, a GABA receptor antagonist, to evaluate the compound's effects on the elevated maze test. As expected, flumazenil administration induced shorter periods spent by the mice in the open arms section. This suggests that the purslane extracts induced its anxiolytic effects by interacting with the GABA receptors in the brain.

Melatonin has been reported to increase serotonin levels in the hypothalamus. Miguez *et al*. (1994) further investigated the involvement of melatonin on the serotoninergic metabolism and reported that the phytochemical could dose-dependently boost serotonin production rate for about one hour. Similarly, this compound was also reported to enhance the production rate of dopamine at lower rates. Purslane extracts have also been found to inhibit both MAO-B. Mazzio *et al*. (2013) evaluated the anti-MAO-B activity of a wide arrange of plants, including purslane.

The plants were extracted in a 95% ethanol solution until a concentration of 50mg/ml was reached and were incorporated in an MAO-B activity assay, alongside the enzyme and benzylamine, which acts as a substrate. The results reported that the IC_{50} value associated with the purslane extract was around 7mg/ml, which was defined by the authors as a weak inhibition. Urry *et al*. (1975) evidenced that melatonin was also capable of inhibiting MAO-A. The author reported that a 95% ethanol extract containing melatonin at a concentration of 10^{-4} was able to reduce hypothalamus' MAO-A activity from the control's 81.32 ± 1.20% to 58.53 ± 0.83%.

Purslane also contains other important phytochemical compounds that have been proven to inhibit tyrosinase, such as quercetin, kaempferol, gallic acid, among others (Şöhretoğlu *et al*., 2018; Sun *et al*., 2017). However, purslane also contains betalains, which are nitrogen-containing pigments that confer purslane flowers their characteristic color. Betalain molecules can appear in the glycosylated form, which normally includes a cyclo-DOPA group. Gandía-Herrero *et al*. (2009) evaluated the interaction between these glycosylates and tyrosinase through fluorescence assays and reported that the molecules were catalyzed by the enzyme. Further studies are needed to determine the actual effects of purslane on tyrosinase activity.

Purslane, in general, demonstrates significant antioxidant activity, hence it has a strong basis of the diet for several populations. Its growing consumption throughout the world has triggered a need in investigating its effects on the body. Purslane extracts have been evidenced to possess scavenging activity. Kashef *et al*. (2018) extracted 5 g of purslane leaves with 100 ml of (80% ethanol, 80% methanol, cold water, and boiling water). The authors then conducted DPPH, nitric oxide, and hydroxyl radical scavenging assays. The results were as follows: for the DPPH scavenging assay, the methanol and boiling water extracts exerted the most potent scavenging ability (78.25 ± 0.23 % and 75.89 ± 0.38%, respectively), at a concentration of 25000 ppm; for the nitric oxide assay, the ethanol extract exhibited the highest scavenging rate (75.69 ± 0.13 %) at a concentration of 7500 ppm; for the hydroxyl radical assay, the methanol extract exhibited the highest scavenging rate (57.95 ± 0.19 %) at a concentration of 980.39 ppm. Melatonin was also shown to protect dopaminergic neurons in mice brain, by inhibiting the production of 6-hydroxydopamine in the brain, which is a cytotoxic molecule that gets absorbed by the neurons. 6-hydroxydopamine is thought to be responsible for the reduction of dopamine production and release to the synapse (Borah & Mohanakumar, 2009).

7.1.10. Chinese Hawthorn

Crataegus sp. (Rosaceae family), also known as hawthorn, is a flowering tree whose berries have been utilized in the production of pre-historic fermented beverages since 7000 B.C.. Hawthorn berries have a characteristic sweet and sour taste, due to the high levels of sugar and tartaric acid, which amounts to four times that found in grapes (McGovern *et al*., 2004). The denomination "Chinese hawthorn" comprises 18 different species, including *Crataegus pinnatifida* Bunge and *Crataegus cuneate* Siebold & Zucc.. Hawthorn berries are known for their high phenolic content, which comprises primarily of flavonoids (epicatechin and rutin, mostly) and chlorogenic acid (Jurikova *et al*, 2012). Berry extract administration has been reported as a viable treatment method for cardiovascular diseases, as its consumption increases the blood flow in the arteries. The fruit has been attributed to other significant properties, such as digestive, antibacterial, antiviral, anti-inflammatory, anti-tumor, immunoregulative, and antioxidant properties, among others (Wu *et al*., 2014). Table A.10 of Attachment A shows the primary compounds found in *C. pinnatifida* that contribute to its neuroprotective effects.

Numerous assays have proved that *Crataegus* berries possess neuroprotective abilities, with the potential to integrate therapy methods, such as AD. Lee *et al*. (2019) reported that the administration of berry extracts to β-amyloid-induced dementia mice helped in improving memory impairment. ICR mice were separated into groups, one being assigned as a control. The other groups were orally administered two doses of *C. pinnatifida* berry ethanol extracts (30 mg/kg and 300 mg/kg), as well as 30 mg/kg curcumin ethanol extract. Mice were anesthetized and were intracerebroventricularly injected with 5 µL of β-amyloid. This procedure was held to evaluate the mice's performance in the passive avoidance test and Y maze test, designed to evaluate mice's coordination and space alternation in a three-arm structure. After this, the mice's brains were isolated and cultured for a β-amyloid aggregation assay, resorting to a THT fluorescence assay. The fluorescence intensity was measured at the start, and regularly until 24 hours later. The behavioral tests reported that the *C. pinnatifida* berry extracts were able to prevent short-term β-amyloid-induced dementia, as the treated mice groups registered increased spontaneous alternation in the Y maze test and the step-through latency time in the passive avoidance test. The β-amyloid aggregation inhibition results also leaned towards the behavioral test results, as the berry extracts were able to suppress the formation of fibrils.

Other berry extract anti-AD properties consist of AChE and BuChE inhibitory activity. Tohtahon *et al*. (2017) performed an AChE inhibition assay on six extracted terpenoids from *Crataegus cuneata* berries. The authors also evaluated different extract factors that allowed for maximum extract quantity, including solvent proportion, ultrasound power, ultrasound time, and ultrasound temperature. Ursolic acid, maslinic acid, corosolic acid, pomolic acid, tormentic acid, and 2α,19α-dihydroxy-2-oxo-urs-12-en-28-oic acid were isolated with HPLC from an 80% methanol berry extract. The AChE inhibitory assay was conducted by preparing samples containing 25 µL enzyme solution (0.2U/ml), 50 µL of different concentrations of terpenoid extract, DTNB, and phosphate buffer. The samples were incubated and were administered acetylcholine iodide solution, as a substrate. The samples were then measured spectrophotometrically. The obtained results allowed for the determination of each triterpenoid's IC_{50} value. The obtained results indicate that ursolic acid, maslinic acid, pomolic acid, and tormentic acid exerted the highest inhibitory activities, with an associated IC_{50} of 0.62 ± 0.02 mM, 0.88 ± 0.03 mM, 0.56 ± 0.02 mM, and 0.91 ± 0.04 mM, respectively.

C. pinnatifida extracts have been reported to selectively inhibit MAO-B and the subsequent oxidative stress related to dopamine degradation. Lim *et al*. (2018) investigated the effects of administrating for 7 days lyophilized doses of *C. pinnatifida* berry ethanol extracts (300 mg/kg) and chlorogenic acid extracted from said berries (30 mg/kg) to ICR mice, to assess the induced behavioral effects in tail suspension, open field, passive avoidance, and forced swimming tests. As a complement to this procedure, an MAO inhibition assay was conducted in cultured C8-D1A cells treated with chlorogenic acid (1 and 10 µM) and *C. pinnatifida* berry (100 and 200 µg/kg). The results in the behavioral tests all showed that the administration of both chlorogenic acid and *C. pinnatifida* berry extract was able of reducing the immobility time of the mice in all tests, with the 30 mg/kg chlorogenic acid dose inducing more mobility. As for the MAO inhibition, the conducted assays did not report any significant changes in the activity of MAO-A, however, MAO-B was significantly inhibited by both chlorogenic acid and *C. pinnatifida* berry extract. When compared to the control sample, which was attributed a 100% MAO-B activity, 1 and 10 µM chlorogenic acid reduced the MAO-B activity to 23.36 ± 1.00 % and 22.13 ± 2.02 %, while 100 and 200 µg/kg *C. pinnatifida* berry extract inhibited MAO-B activity to 19.84 ± 0.73% and 20.02 ± 0.54 %, respectively. Doron *et al*. (2012) evidenced that the administration of a 15 µg/kg dose of 0.47 mg/ml 1% DMSO herbal mixture containing *Crataegus pinnatifida, Triticum*

aestivum, Lilium brownii, and Fructus zizyphi jujubae was hypothesized to increase the serotonin levels in the hippocampus of BALB mice, as the extract inhibited serotonin uptake.

The seeds of *C. pinnatifida* also have a role in neuroprotection, specifically because of its associated antioxidant activity and anti-tyrosinase activity. Huang *et al*. (2014) isolated four lignan glycosides (pinnatifidaninsides A-D) and two other compounds designated as 5 and 6, later identified as 7R,8S-dihydrodehydrodiconiferyl alcohol-9-O-β-D-glucoside, and 7R,8S-dihydrodehydrodiconiferyl alcohol-9′-O-β-D-glucoside, based on their retention time in HPLC column, from fractioned 70% ethanol *C. pinnatifida* seed extracts. The authors conducted assays on the isolate compound's ability to inhibit mushroom. For the anti-tyrosinase assay, the enzyme was treated to 500 µg/ml of each compound and L-tyrosine as a substrate. The control sample was treated with arbutin as a positive control. The results showed weak tyrosinase activity from pinnatifidaninsides A, B, C, and D (37.58%, 34.54%, 31.15%, and 32.97%, respectively), with compound's 5 and 6 exerting modest inhibition at rates of 46.00% and 58.15%, respectively, however, the arbutin control exhibited the highest inhibition rate.

The phenolic compounds present in *C. pinnatifida* berries possess antioxidant properties. The extracts of the fruit have been thoroughly investigated to assess different antioxidant-related properties. 100 µg/ml Aqueous *C. pinnatifida* berry extracts have been reported to possess an $O_2^{\bullet-}$ scavenging activity of 82% (Wang *et al*., 2011). Chang *et al*., (2013) reported that adding 12.5 µL *C. pinnatifida berry* methanol samples with concentrations ranging from 3.9 to 1000 µg/ml to 12.5µL of 0.15M H_2O_2 allowed for the determination of a 50% scavenging activity of total H_2O_2 radicals of 554.2 ± 21.8 µg/ml. Hwang *et al*. (2013) reported that a 1 mg/ml *C. pinnatifida berry* methanol sample was able to scavenge around 40% of total nitric oxide radicals. Other antioxidant properties of these extracts include the upregulation of superoxide dismutase and catalase, and the inhibition of lipid peroxidation (Wang *et al*., 2011).

7.1.11. Cape Jasmine

Cape jasmine, also known as *Gardenia jasminoides* J. Ellis (Rubiaceae family), is a fragrant shrub cultivated in Asian countries, like China, Taiwan, India, Japan, and distributed around the world, mostly for decorating and coloring purposes. However, the plant has been cultivated in China for, at least, a thousand years, for medicinal purposes (Soliman *et al*., 2013). The fruits of cape jasmine have been used in TCM to alleviate inflammation and to prevent thrombosis and arteriosclerosis. The main components found in *G. jasminoides* fruits are iridoid glycosides, like geniposide and genipin, crocin, and its derivatives, which are water-soluble pigments. These phytochemicals are responsible for providing the fruit's characteristic antioxidant activity, as well as antidepressant, antidiabetic, anti-insomnia, antihypertensive, anti-AD, and anti-PD properties (Xiao *et al*., 2017). Table A.11 of Attachment A shows the primary compounds found in *G. jasminoides* that contribute to its neuroprotective effects.

The extracts of *Gardenia* fruits have been documented to possess different anti-AD properties, regarding cholinesterase inhibitory activity and β-amyloid aggregation suppression. Li *et al*. (2017) conducted various neuroprotective assays to evaluate the potential effects of 26 plants used in TCM in inhibiting *in vitro* acetylcholinesterase and butyrylcholinesterase, β-amyloid aggregation suppression, antioxidant, and scavenging activities, one of those being *G. jasminoides* fruits. 20 g powder plant samples were extracted with 200 ml 95% ethanol in an ultrasonic bath at room temperature. The extracts were then lyophilized and were dissolved in a DMSO solution, to obtain 100 mg/ml and 200 mg/ml extract solution. For the cholinesterase

assays, 25 µL AChE (0.226 U/mL) and 25 µL horse serum BuChE (0.226 U/mL) stock solutions were treated to 10 µL of the plant extracts solution, along with their respective substrates, in a 96-well plate, incubated for 20 min in 4 °C. The absorbance tests revealed that 100 mg/ml and 200 mg/ml *G. jasminoides* fruit extracts were able of inhibiting AChE 34.50 ± 1.50 % and 43.74 ± 0.87 %, and BuChE by 14.66 ± 1.71 % and 23.50 ± 1.63 %, respectively. As for the β-amyloid aggregation suppression assay, 50 mM β-amyloid solution was treated to different concentrations of *G. jasminoides* fruit extracts (0, 100, and 200 mg/ml) and incubated for 48 hours. The test solution was then diluted from 80 µL to 600 µL with phosphate buffer containing 10 µM of thioflavin T, for a fluorescence test. The results were indicated by the inhibitory activity of the 100 mg/ml sample solution, which was 32.63 ± 2.58 %.

Geniposide, an iridoid glycoside found in *G. jasminoides* fruit, has also been evidenced as one of the primary suppressors of β-amyloid aggregation, tau protein hyperphosphorylation, and GSK3β activity. Gao *et al*. (2014) separated Sprague-Dawley male mice into 5 groups: a control treated to cerebral spinal fluid; a positive control treated with 50 µM geniposide; a negative control treated with 3mg/kg dose of streptozotocin: two test samples, treated with 50 µM geniposide, 3mg/kg dose of streptozotocin, in the absence or presence of 100 µM wortmannin). Streptozotocin is a natural agent that increases both GSK3β activity and hyperphosphorylated tau protein. Shortly after, the mice were sacrificed are cortex tissue samples were dissected, cultured, and incubated with rabbit antibodies against phosphorylated tau protein. Afterward, the samples were stained with 3,3′,4,4′-biphenyl tetraamine tetrahydrochloride for photomicrograph, and optical density analysis. Simultaneously, a Western blot assay was conducted, where cortex tissue was incubated with rabbit polyclonal GSK3β(pS-9), the primary antibody of GSK3β. Immunoreactive bands were analyzed and tau protein was quantified. The photomicrograph results reported that the geniposide-treated sample suppressed phosphorylated tau protein induced by spectrozotocin. The Western blot results corroborated with the hyperphosphorylation suppression, as the spectrozotocin-treated samples increased GSK3β activity, while the geniposide-treated samples suppressed GSK3β activity.

The anti-insomnia effects of *G. jasminoides* fruit are derived from the underlying mechanism of the GABAergic system. Choi *et al*. (2008) subjected ICR mice to different behavioral tests after orally administering 100 mg/kg and 200 mg/kg doses of *G. jasminoides* fruit, as well as intraperitoneally injecting both genipin and geniposide, at doses of 2 mg/kg, 10 mg/kg, and 20 mg/kg, for 1 week. The control group was administered saline, while the positive control group was administered diazepam. The mice were subjected to locomotor activity, horizontal wire, and elevated maze tests. Separately, human IMR-32 cells were treated to the *G. jasminoides* fruit extracts, as well as the isolate compounds, to measure intracellular chloride ion influx. In the behavioral tests, it was reported that the *G. jasminoides* fruit extracts decreased locomotor activity, decreased falling frequency in the horizontal wire test, and increased the total time spent on the open arms of the elevated maze test. As for the isolated compounds, geniposide only increased the time spent in the elevated maze test's open arms, while genipin did not influence any performance. As for the chloride influx assay, geniposide was reported to significantly increase the intracellular influx in a dose-dependent manner. The *G. jasminoides* fruit extracts also increased chloride influx, while genipin did not exert any significant effects. The authors concluded that *G. jasminoides* fruit extracts induce relaxation and calmness in the studied mice and suggest that the intracellular chloride influx effects were mediated by $GABA_A$ receptor interaction.

G. jasminoides fruit extracts have been reported to interact in various stages of dopaminergic and serotoninergic neurons. Kim *et al*. (2012) extracted 10 kg of *G. jasminoides* fruits with 30 L of 80% methanol. The solution was then suspended in water, extracted with sequential washing with n-hexane and ethyl acetate, with final evaporation. The ethyl acetate residue was then submitted silica-gel column, where protocatechuic acid, geniposide, 6'-O-trans-p-coumaroylgeniposide, 3,5-dihydroxy-1,7-bis(4-hydroxyphenyl) heptane, and ursolic acid were isolated. Each isolate was then dissolved in DMSO to form differently concentrated solutions, which were added to MAO-A and MAO-B samples, to assess each compound's inhibitory activity. The obtained results showed that all compounds were more potent MAO-B inhibitors than MAO-A. 3,5-Dihydroxy-1,7-bis(4-hydroxyphenyl) heptane was by far the most potent MAO-A inhibitor, with an associated IC_{50} of 400 µM; protocatechuic acid treatment, for example, revealed an IC_{50} of 2411 µM. As for MAO-B, some compounds were reported as displaying strong inhibition rates, with 6'-O-trans-p-coumaroylgeniposide having an IC_{50} of 127 µM, followed by 3,5-dihydroxy-1,7-bis(4-hydroxyphenyl) heptane (196 µM) and geniposide (223 µM). However, geniposide is more involved in the dopaminergic and serotoninergic neuron mechanisms. Liu *et al*. (2011) evaluated the effects of geniposide administration in the behavior of mice with forced swimming and tail suspension tests. The results showed that geniposide significantly reduced the recorded immobility time in both tests, with no abrupt changes to the locomotive action of the mice. Further investigation on the neuronal mechanisms showed that geniposide increased the levels of serotonin in the hippocampus and cortex, by inhibiting neuronal reuptake.

Geniposide has also been documented as displaying a role in preventing the progression of synucleinopathies. Uddin *et al*. (2014) divided C57BL/6N mice into five groups: a saline control, a geniposide positive control, a MPTP negative control, and two test groups. The test groups were intragastrically injected with 100 mg/kg doses of geniposide and intraperitoneally injected with 20 mg/kg doses of neurotoxin MPTP or intracerebroventricularly injected with miR-21, a micro RNA gene capable of reducing LAMP2A receptor expression in the brain, for 21 days. After administration, the mice were sacrificed and the brain tissue was dissected to perform Western blot assays, to determine the densities of both α-synuclein and LAMP2A receptors. According to the obtained blots, the mice group treated with MPTP revealed that the α-synuclein levels increased, compared to the saline control group, as well as having reduced LAMP2A receptors, however, when treated with geniposide, these effects were suppressed. As for the effects of miR-21, the groups treated with the RNA sample also showed higher α-synuclein levels in the brain samples, as well as reduced LAMP2A receptors. The targeting of miR-21 to LAMP2A receptors block the clearance mechanisms of α-synuclein, thus contributing to its agglomeration, however, when treated with the geniposide sample, these effects were also suppressed.

The extracts of *G. jasminoides* fruit have been reported as a viable treatment method in skin whitening. Lee *et al*. (1997) extracted various plants, including *G. jasminoides* fruit, with an 80% methanol solution, to evaluate each their potential for cosmetic use, regarding the anti-tyrosinase activity. After the extraction, the samples were evaporated. The solid extracts were then diluted in phosphate buffer to achieve concentrations of 3.3 µg/ml and 333 µg/ml. 0.5 mL of mushroom tyrosinase (70 U/ml) were treated to 0.5 mL of each extract and 0.5 ml of 0.1 mg/L L-tyrosine as a substrate. The results for the extracts of *G. jasminoides* fruit registered an inhibitory rate of 12 % and 40% from the 3.3 µg/ml and 333 µg/ml extracts, respectively. This activity can be attributed mostly to cocrin, which has been postulated as a specific tyrosinase inhibitor (Patil *et al*., 2014). However, some components, like geniposide, have been applied as treatment options

in patients with vitiligo, which is characterized by a lack of pigmentation in some areas of the body. This is due to the compound's ability to enhance the melanogenesis rate (Lan *et al*., 2008).

The folkloric use of *G. jasminoides* fruits in medicine is typically derived from the antioxidant activity that the fruits exert. Numerous studies have been conducted to extensively understand the specific effects that the phytochemicals of cape jasmine induce. Kang *et al*. (2003) reported the and hydroxyl free radical scavenging activities of G. *jasminoides* fruit methanol extracts fractioned with n-hexane, butanol, water, and ethyl acetate. In the superoxide scavenging assay, the aqueous extracts exerted the most significant scavenging activity out of any sample for either sample concentration (100 µg/ml and 200 µg/ml), at 54.6 ± 0.4 % and 68.8 ± 1.2 %, respectively. As for the hydroxyl scavenging assay, the 100 µg/ml and 200 µg/ml ethyl acetate solutions exerted the highest ˙HO scavenging activity for each concentration, at 32.1 ± 4.6 % and 46.7 ± 0.9 %, respectively. *G. jasminoides* fruits extracts have been reported to possess significant free radical scavenging *in vitro* DPPH assays by Uddin *et al*. (2014), which reported that 500 µg/ml *G. jasminoides* fruit extract was able to scavenge around 90% of total DPPH free radicals. Additionally, Gardenia fruit aqueous extracts have been reported to mimic the activity of both superoxide dismutase and catalase (Debnath *et al*. 2011).

7.1.12. *Poria cocos* fungus

Wolfiporia extensa, or *Poria cocos*, is a fungus that typically grows in the rotten bark of pine trees. The *P. cocos* sclerotium is an edible and medicinal component that has been cultivated and implemented in TCM for more than two thousand years. Out of all the addressed tea mixture components in this report, *P. cocos* stands out for its peculiar phytochemical composition. The fungus does not possess flavonoids or phenolic acids in its composition, with it being rich in terpenes and polysaccharides, however, the extracts of *P. cocos* have been reported to exert antioxidant, anti-tumor, anti-bacterial, anti-hyperglycemic, anti-inflammatory (Wang *et al*. 2013), anti-diabetic, immunomodulation, anti-hepatitis, and anti-hemorrhagic fever (Li *et al*. 2019) properties. Table A.12 of Attachment A shows the primary compounds found in *P. cocos* that contribute to the fungus' neuroprotective effects.

The consumption of *P. cocos* extracts has been linked to the improvement of memory. Lin *et al*. (2009) evaluated the cognitive effects of an herbal mixture containing *P. cocos* sclerotium, *Atractylodes macrocephala Koidz* rhizome, and *Angelica sinensis* root, as well as the effects of each standalone plant on ICR mice's cognitive performance and AChE and BuChE activity. The two tested mice groups were injected with 4 mg/kg scopolamine dose, along with 200 mg/kg and 600 mg/kg each of herbal mixture aqueous extract. The herbal mixture-treated groups reported less total swimming time compared to the negative control group (only 4mg/kg scopolamine dose), while the latency time in the passive avoidance test increased compared to the negative control group, with fewer errors committed in both tests. The herbal mixture was found to inhibit AChE and BuChE activity in the mice brain after the tests, however, the author reported that the anti-AChE activity of 200 µg/ml *P. cocos* aqueous extract exerted the lowest inhibition rate on the AChE assay, at 13.9%.

Park *et al*. (2009) reported the importance of *P. cocos* extracts in preventing β-amyloid-induced cell death. The authors extracted 1 kg of *P. cocos* sclerotium with 2 L of distilled water and lyophilized the sample. At the same time, PC12 cells were cultured with bovine serum and were incubated with 20µM β-amyloid fragments, in the absence (negative control) or presence of the *P. cocos* water extracts, ranging from 5 to 125 µg/ml. Cell death was evaluated with

microscopic analysis of isolated PC12 cell samples, β-amyloid samples, and β-amyloid samples with 5 µg/ml *P. cocos* water extracts. The observation of the samples indicated that the administration of *P. cocos* water extracts allowed for the mitigation of morphological alterations induced by β-amyloid in the cells. The cytotoxicity of β-amyloid was measured by determining the reduction of WST-1, a reagent utilized in cell viability assays. The administration of *P. cocos* water extracts was able to attenuate the cytotoxic effects of β-amyloid in a dose-dependent manner, with the 125 µg/ml enabling cell viability over 85%.

Until now, no MAO inhibition activity effects were reported from *P. cocos* extracts. However, the same extracts still hold great significance in the protection of the dopaminergic and serotoninergic system. Huang *et al*. (2020) evaluated the effects of *P. cocos* extracts on rats subjected to a forced swimming test and unpredicted chronic mild stress (UCMS), for 28 days and 5 weeks, respectively, with subsequent measurement of the dopamine and serotonin levels in the frontal cortex. The results of the forced swimming test showed that the immobility time of the test subjects significantly decreased. Further investigation showed that the UCMS-induced turnover of both dopamine and serotonin was significantly attenuated. This metabolic turnover can be interpreted as the ratio between a secondary metabolite, in this case, obtained from the catalysis of MAO, and the primary metabolite, being the neurotransmitters, implying that *P. cocos* extracts have reuptake inhibition properties.

The extracts of *P. cocos* have been documented as potent whitening agents. These extracts have been included in creams designated to reduce pigmentation in the skin. Hu *et al*. (2017) evaluated the influence of extracts containing some isolated compounds found in *P. cocos* on mushroom tyrosinase and mice B16 melanoma cells. One extract contained poricoic acid A, while the other contained total triterpenes. 60 µL of monophenolase mushroom tyrosinase (250 U/ml) samples were treated to each *P. cocos* sample with different concentrations ranging from 125 to 2000 µg/ml, and to L-tyrosine as a substrate. The samples were then incubated, and the inhibitory activity was measured spectrophotometrically. An arbutin-contained sample was used as a positive control. The anti-tyrosinase activity assay revealed that, at a concentration of 200 µg/ml, the poricoic acid A and total triterpene extracts exerted good inhibitory rates, approximately 40%, and 60%, respectively, with the latter exhibiting similar inhibition rates to the arbutin positive control. For the diphenolase mushroom tyrosinase assay, 60 µL of enzyme (250 U/ml) samples were treated to L-DOPA (substrate), and 50 µL of the *P. cocos* samples with the same concentrations as before. In this assay, the poricoic acid A extracts showed to exert a more potent inhibitory activity at higher concentrations than the arbutin control. At a concentration of 166.67 µg/ml, the extract inhibited tyrosinase by 45.24%. At lower doses, the triterpene extract had a higher inhibitory rate than poricoic acid A samples and was overall more potent than the arbutin control.

Pachymic acid has been described as a anxiolytic agent, which is an underlying effect mediated by the GABAergic system. Shah *et al*. (2014) administered stock pachymic acid at different doses (1,3, and 5 mg/kg) to ICR mice before partaking in a spontaneous locomotor activity test and an induced sleep test, where mice were injected with pentobarbital sodium, muscimol, and orally administered pachymic acid, to evaluate the sleep-inducing effects of the *P. cocos* compound, comparing it with other established sleep-inducing molecules. The administration of the 5 mg/kg dose of pachymic acid significantly reduced the locomotor activity and sleep latency of the test subjects. After these tests, the mice were sacrificed and their hypothalamus was cultured in bovine serum, to partake in intracellular chloride influx and $GABA_A$ receptor expression assays. The chloride influx was measured with a fluorescence test

on chloride. The treatment of the hypothalamic cells with 10 µM pachymic acid significantly increased the inward flow of chloride ions at a rate almost three times that observed in the control, while the treatment with 50 µM pachymic acid increased $GABA_A$ receptors. In conjunction, these results suggest that pachymic acid is an agonist of $GABA_A$ receptors.

The phytochemical composition of *P. cocos* has led to several studies regarding its antioxidant activity. The primary antioxidant mechanism of the extracts is free radical scavenging. Pachymaran is a polysaccharide found in *P. cocos* and was reported to successfully scavenge $O_2^{\bullet-}$, $^{\bullet}OH$, and H_2O_2 radicals, with a respective IC_{50} of 2.57 mg/ml, 7.66 mg/ml, and 4.56 mg/ml (Li *et al*., 2019). Cai *et al*. (2011) isolated eight triterpenes from the sclerotium of *P. cocos* and conducted a nitric oxide scavenging activity assay for each compound. The results indicated that 29- hydroxypolyporenic acid C and polyporenic acid C exerted the most significant nitric oxide free radical scavenging activities, with an associated IC_{50} of 16.8 ± 2.7 µM and 18.2 ± 3.3 µM, respectively, while 29-hydroxydehydrotumulosic acid, dehydrotumulosic acid, and tumulosic acid reported a higher IC_{50} value (39.8 ± 5.0 µM, 44.98 ± 4.1 µM, and 42.5 ± 5.3 µM, respectively). The remaining compounds (29-hydroxydehydropachymic acid, dehydropachymic acid, and pachymic acid) showing weak inhibitory rates.

7.1.13. *Citrus maxima* L.

Citrus maxima L., or pummelo (Rutaceae Family) is a citrus fruit cultivated mostly in South Asian countries, such as Malaysia and southern China. The fruit, like most citrus, is rich in vitamin C. In recent years, the commercialization of pummelo has gained attraction in several countries' domestic markets, either as beverages or sweets. In medicine, both the pulp and peel of the fruit have been administered to remove toxins and to treat indigestion (Sawant & Panhekar, 2017). All citrus fruits possess strong anti-inflammatory and antioxidant activity (Caengprasath *et al*., 2013), which makes them suitable treatment options to cure several ailments. The peel's composition differs from that of the pulp, exhibiting a higher alkaloid, phenolic acid, and flavonoid content (Ani *et al*., 2018). Most studies on pummelo peel extracts attest to their favorable antioxidant and free radical scavenging activity, which in the thematic of neurodegenerative diseases, shows great potential to take part in treatment methods. Table A.13 of Attachment A shows the primary compounds found in both pummelo peel and juice that contribute to the citrus' neuroprotective effects.

The pummelo peel contains naringin, which is a flavanone glycoside used as an artificial sweetener in the food industry. Its precursor naringin dihydrochalcone, also present in pummelo peel, has been reported to suppress β-amyloid aggregation and plaque formation. Yang *et al*. (2018) subjected APP/PS1 transgenic and wild type mice to a behavioral test (Morris Water Maze test). The transgenic group was orally administered of 200 µL of 100 mg/kg daily doses of naringin dihydrochalcone, or 200 µL vehicle solution per 20 g of mouse weight, for 3-4 to 6-7 months. The observed performances of the mice revealed that the vehicle-treated group took more time to locate the platform, as a result of cognitive decline, however, the naringin dihydrochalcone-treated group did not show any significant decreased cognitive impairment when compared to the wild type group. After the behavioral tests, the mice were sacrificed and brain tissue was removed for β-amyloid plaque and astrocyte, microglia, and neuron screening, resorting to an immunofluorescence test with thioflavin S staining. The analysis of the immunofluorescence assays revealed that β-amyloid plaque deposits were significantly reduced in the naringin dihydrochalcone-treated group when compared to the vehicle-treated group.

All citrus fruit peels display inhibitory activity towards AChE. Normally, the cognitive improvement of citric peel extracts is attributed to naringenin (Ademosun & Oboh, 2014). Heo *et al*. (2004) reported that the administration of 4.5 mg/kg doses of naringenin improved the short-term memory loss in ICR mice induced by injection of scopolamine, as the results from passive avoidance and Y maze tests showed increased latency time in the retention trial and increased alternation pathways, respectively. To further analyze these effects, an anti-AChE assay was conducted. PC12 cells were cultured, treated with acetylcholine iodide as a substrate, and to 10 µL of naringenin methanol extract fractions with different concentrations (70, 140, and 210 µg/ml), and incubated for 15 minutes. The results showed that the ethyl acetate fraction exerted the highest AChE inhibitory activity at around 60%. Out of all the citrus fruits, pummelo possesses the lower inhibitory effect of AChE. This is a direct result of the lower flavonoid content of the peel. However, pummelo peel extracts are potent BuChE inhibitors, displaying better inhibitory activity than that of *C. sinensis* extracts, although its activity lacks with that of other citrus fruit peels, like orange and grapefruit. Ademosun *et al*. (2014) reported that the treatment of 0-100 μL of different concentrations of pummelo juice (0-8 mg/ml) to 200 μL BuChE (0.415 U/mL) allowed for the determination of an EC_{50} value of 4.42 ± 0.07 mg/ml.

Ademosun & Oboh (2014)also evaluated the inhibitory effects of pummelo peel extracts on MAO-B, among other citrus fruits. The authors reported a 50% MAO-B inhibitory effect (EC_{50}) of 1.93 ± 0.06 mg/ml. The study showed that pummelo peel had the second-highest inhibitory activity on MAO-B out of all assessed citrus fruits, as well as that of green teas. The same author followed up on his study, by comparing the inhibitory effects of pummelo, tangerine, and, lime peels on MAO-B (Ademosun *et al*., 2019). The study concluded that the inhibitory activity displayed by pummelo was superior to that observed for the other citrus. In conjunction with the previous report, pummelo can be considered as one of the most favorable citrus species to prevent PD. No effects of pummelo on MAO-A activity were reported.

Pummelo Peel extracts might potentially exert significant anti-tyrosinase activity. Abirami *et al*. (2014) evaluated the tyrosinase inhibitory activity of pummelo juice. The assay involved the treatment of stock tyrosinase (1000 U/mL) to 100 µL pummelo juice sample and L-DOPA as a substrate. The samples were incubated at 25ºC for 5 minutes. The absorbance of the samples was measured with a spectrophotometer. The results evidenced strong inhibitory rates from all samples containing pummelo juice, with an associated inhibition rate ranging from 76.95% to 80.79%.

As a citrus fruit, pummelo shows great antioxidant activity. Pummelo extracts have been documented and reported to possess great free radical scavenging activity *in vitro*. Abirami *et al*. (2014) reported that 1 ml samples of juice from red and white pummelo were able to scavenge 20.50 ± 0.66 % and 18.70 ± 0.33 % of total $O_2^{\bullet-}$ radicals, respectively, and 46.43 ± 1.19 % and 48.09 ± 0.51 % of total $^{\bullet}HO$ radicals. Pummelo also exhibited favorable free radical scavenging activity on standardized *in vitro* assays. Jang *et al*. (2010) reported that water and methanol extracts of pummelo fruit pulp extracts were able to scavenge around 16.3 ± 0.6 % and 26.1 ± 1.2 %, respectively, of total DPPH free radicals.

7.1.14. *Ginkgo biloba*

Ginkgo biloba L. (Ginkgoaceae family) is regarded as being one of, if not the oldest tree in the world, with its existing uninterruptedly for over 270 million years. The tree height ranges from 20 to 40-meter-tall and is considered a "living fossil". *G. biloba* is found predominantly

found in Eastern China and has integrated traditional medicine in the country over 2000 years ago (Belwal *et al*., 2018). In TCM, the seeds are the most sought after component of the plant, as its consumption has been reported to cure lung-related ailments, like asthma and bronchitis, as well as treating kidney and bladder disorders, and exerting antibiotic effects against pathogens (Tredici, 2000), however, in the west, the leaves are the predominant component. *G. biloba* leaves have been documented as possessing skin nourishing and anti-aging effects (Wang *et al*., 2020), however, the predominant effects of the leaves are related to its numerous contributions towards neuroprotection. *G. biloba* leaves are mostly rich in flavonoids, such as kaempferol, quercetin, isorhamnetin, as their respective glycosides, and in triterpenoids, like bilobalide and ginkgolides A, B, C, and J (He *et al*., 2009). One of the most commercially available forms of the extract is EGB 761, a standardized *G. biloba* leaves extract, whose flavonoid and triterpenoid composition (24% and 6%) is regarded as a fundamental aspect that allows the extract to induce several effects in a given condition, like AD and PD. EGB 761 has been evidenced to promote free radical scavenging, neurotransmitter release, synaptic plasticity, as well as counteracting memory impairment (McKeage *et al*., 2018). Table A.14 of Attachment A shows the primary compounds found in G. biloba that attribute the plant's neuroprotective effects.

Ding *et al*, (2013) evaluated the acetylcholinesterase activities of 15 compounds isolated from the 80% methanol extracts of *G. biloba* leaves. The methanol extract was evaporated to produce a dry residue, which was portioned with water and ethyl acetate. Each extract was then subjected to chromatography in a silica gel column eluted with $CHCL_3$-MeOH, and each compound was purified. In total, fifteen compounds (13 flavonoids and 2 ginkgolides) were isolated. Both the isolated compounds and *G. biloba* leaves were then dissolved in methanol to achieve different concentrations (31.25, 62.5, 125, 250, and 500 μg/mL), which were then incorporated into samples containing AChE solution and substrate to determine each test solution's IC_{50}. The results showed that the *G. biloba* leaf extract has moderate inhibitory activity, with an IC_{50} of 252.1 μg/mL. As for the isolated compound's inhibitory activity, the ginkgolides did not influence AChE activity. Out of all compounds, quercetin-3-O- β-D-glucopyranoside exhibited the strongest inhibitory activity, with an associated IC_{50} of 57.8 μg/mL, while quercetin 3-O-α-D-glucopyranoside, quercetin 3-O-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside, and quercetin3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside had associated IC_{50} values of 79.4 μg/mL, 77.5 μg/mL, and 73.1 μg/mL, respectively.

The EGB 761 extract has been evidenced by Luo *et al*. (2002) to inhibit β-amyloid aggregation. For this, the authors' cultured mouse N2a neuroblastoma cells of wild type mice (control group) and APP/PS1 transgenic mice (test group) for an immunoblotting β-amyloid aggregation procedure. The cells were incubated in either the presence or absence of 100 µg/ml EGB 761 for 48 hours and immunoprecipitated with antibody 3D6. Separately, an *in vitro* assay was conducted to evaluate the β-amyloid fibrilization suppression effects of 100 µg/ml EGB 761, as well as 29 µg/ml solutions of bilobalide and ginkgolides A, B, C, and J. The immunoblotting results suggested that the transgenic cells expressed greater amounts of β-amyloid when compared with the control group, however, the EGB 761-treated cells were able to suppress the aggregation of the peptide. As for the *in vitro* assay, the authors reported that 100 µg/ml EGB 761 inhibited aggregation by 82 ± 6%, while bilobalide and ginkgolides A, B, C, and J inhibited β-amyloid aggregation by 73%, 35%, 20%, 42%, and 72%, respectively.

Zeng *et al*. (2017) reported that EGB 761 also demonstrates neuroprotective effects against AD by attenuating the neurodegenerative effects induced by hyperphosphorylated tau protein. 24 out of 32 Sprague-Dawley mice were injected with 400 µg/kg/day doses of

homocysteine, to induce AD-like alterations in the subjects, while the other 8 were injected with saline as a control. From the homocysteine-treated mice, 8 were administered an equal dose of EGB 761 for the same amount of time. The mice were firstly subjected to open-field and Morris water maze tests then were sacrificed for Western blotting quantification of hyperphosphorylated tau protein and GSK3β activity. In the behavioral tests, treatment with EGB 761 did not significantly alter the traveled distance in the box, when compared with the saline and negative controls, however, EGB 761 treatment significantly reduced the escape latency time in the Morris water maze test. As for the Western blotting assay, it was reported that EGB 761 could suppress the induced hyperphosphorylation of tau protein by homocysteine. As for GSK3β, homocysteine was found to decrease inhibited GSK3β activity in the hippocampus and prefrontal cortex of the mice, whereas EGB 761 reverted these effects.

One of the more well discussed beneficial effects of *G. biloba* is relaxation. Plant extracts have been indicated to influence the glutamatergic and GABAergic systems in the brain. One report investigated the effects of treating Sprague-Dawley mice hippocampal slices to 0.1 mg/ml DMSO samples of nanometer and micrometer *G. biloba* leaf extracts (nanometer extract is more water-soluble than the micrometer extract), to evaluate the effects on the glutamatergic system, more specifically to study the type of interactions between the extract and NMDA receptors, by recording the NMDA-activated ionic currents. The results indicated that the 0.1 mg/ml *G. biloba* leaf extracts antagonized NMDA receptors since it was documented that the micrometer and nanometer extracts inhibited receptor activity by 40 ± 17% and 64 ± 15%, which amounts to an IC_{50} of 0.0210 ± 0.0055 and 0.0262 ± 0.0038 mg/mL, respectively (Li *et al*., 2011). As for the plant's involvement in the GABAergic system, Ivic *et al*. (2003) reported the *in vitro* treatment of test samples containing 30 µM of $GABA_A$ receptors with 50µM doses of ginkgolide B and bilobalide was able to inhibit receptor activity at a rate of 63.2 ± 0.3% and 46.8 ± 0.3%.

G. biloba leaves extracts have been evidenced to inhibit both isoforms of MAO. The plant is composed of several compounds that have already been documented as possessing BOTH MAO-A and MAO-B inhibitory activity. The first essay of this kind on *G. biloba* was conducted by White *et al*. (1996). In their report, two extract samples were prepared, by dissolving 2 g of dried *G. biloba* leaves with 20 ml of distilled water and 10 ml ethanol, and subsequently centrifuging the solutions. Then, MAO-A and MAO-B activity assays were conducted, by incubating test samples for 15 minutes at 37ºC, containing substrate (serotonin and phenethylamine, respectively), the respective enzyme, and different volumes of the *G. biloba* leaves extracts. As described by the authors, to determine the inhibition rate of each extract, the administered volumes to the assay were dried to determine the "mg equivalent", which is the amount of dried extract that inhibited the MAO enzymes. The obtained results suggested that, for an "mg equivalent" of 5 mg of aqueous and ethanol extract, the aqueous extract inhibited 54.6 ± 2.8% and 59.1± 1.4%, while the ethanol extract inhibited 69.1 ± 1.0% and 71.6 ± 0.7% of MAO-A and MAO-B, respectively.

Kuang *et al*. (2018) evaluated the effects of *G. biloba* leaves on A57T substituted α-synuclein mice. The authors separated the mice into five groups: one saline control, three test groups that were administered different doses of *G. biloba* leaves (20, 40, and 60 mg/kg), and a group treated with 75 mg/kg Madopa, for 21 days. After the administration period ended, the mice were subjected to a forced swimming test, horizontal wire test, and a pole test, designed to measure the time taken for the mice to descend from an elevated platform. Each performance has attributed a score to differentiate the effects of *G. biloba* leaves administration. After the behavioral tests, the mice were sacrificed and *susbtantia nigra* and striatum were dissected,

cultured, and incubated with rabbit DAT-antibody for an immunochemistry assay to detect tyrosine hydroxylase and dopamine transporters expressing neurons. The samples were also treated with immunoglobulin G and were counterstained with cresyl violet. As expected, the administration of the highest does of *G. biloba* leaves (60 mg/kg) exerted the best effects in the behavioral tests, as the respective group scored the highest score. As for the immunochemistry assay, the results evidenced increased expression of both tyrosine hydroxylase and dopamine transporters, in a dose-dependent manner.

One report evidenced that the administration of *G. biloba* to Swiss albino mice was able to suppress the THC effects on short-term memory loss and reduced motor coordination. Abdel-Salam *et al*. (2013) administered specific doses of different drugs, including 25 mg/kg *G. biloba*, to different mice groups, already treated with 5, 10, and 20 mg/kg doses of *C. sativa*, for one month. Then, the mice were subjected to a cognitive test that consisted of a water maze test, with an escape glass platform hidden from sight. After finding the platform for the first time, the mice would then relocate to the starting point. This essay aimed to analyze the time spent on the mice to rediscover the glass platform. As expected, the group solely treated to 20 mg/kg *C. sativa* showed higher escape latency than the other groups, however, the *C. sativa*-induced group treated with 25 mg/kg *G. biloba* was found to reduce the latency time for the mice to discover the glass platform. THC is responsible for the memory impairment evidenced in the test subjects. Since THC is a cannabinoid receptor agonist, this suggests that *G. biloba* might antagonize said receptors.

Shu *et al*. (2020) investigated the potential tyrosinase inhibitory activity of several compounds extracted from *G. biloba* leaves. The dried plant material was extracted with a 95% ethanol solution and evaporated under low pressure. The solid extract was then suspended in water and portioned with dichloromethane, ethyl acetate, and n-butanol. The n-butanol fractioned was then subjected to chromatography in a silica gel column and eluted by different solvents to ensure 8 fractions containing 12 compounds total. Each compound was dissolved in phosphate buffer to achieve a concentration of 25 µM. For the enzymatic inhibition assay, 20 µL of mushroom tyrosinase (1000 U/ml) were treated to 10 µL of the compounds' solution and L-tyrosine as a substrate. Out of all 12 compounds, only 5 inhibited tyrosinase at moderate levels. These compounds were identified as ginkgoside B, 2-(3,4-dihydroxyphenyl) ethyl 3-O-β-D-glucopyranosyl-β-D-glucopyranoside, methyl hesperidin, cytidine, and genistin, which inhibited tyrosinase at a respective rate of 19.12 ± 2.59%, 25.79 ± 1.83%, 16.07 ± 1.07%, 24.46 ± 1.10%, and 18.64 ± 3.62%.

Plant combinations in treatment therapies are normally associated with increased neuroprotective effects when compared with a single administration. In some cases, this increased therapeutic effect is nothing but a "stack up" of each plant's beneficial effects, however, some consociations allow for the increased effect of one plant, mediated by the other. *G. biloba* is widely incorporated in supplements containing *P. ginseng* (de Sousa *et al*. 2010). It was reported by Liang *et al*. (2020) that the extracts of *G. biloba* are able of increasing the brain's ability to uptake ginsenosides. Kunming and Sprague-Dawley mice were randomly administered either single 500 mg/kg doses of stock *P. ginseng* extract or 500 mg/kg doses of stock *P. ginseng* extract and 400 mg/kg of *G. biloba* extracts. Subsequently, the mice were sacrificed, and their brains were dissected. The brain samples were homogenized with methanol 50%, with the supernatant being injected in a chromatographer, to evaluate the presence of ginsenosides in the brain. The obtained results indicated that, compared to the control sample, *G. biloba* extracts increased the uptake of ginsenosides Rg1, Re, Rd, and Rb1 by 12, 6, 5, and 6.5-fold.

One of the main characteristics of *G. biloba* extracts is their antioxidant activity and scavenging activity. Pincemail *et al*. (1998) conducted an *in vitro* assay on the superoxide scavenging ability of *G. biloba* extracts, which at a concentration of 500 µg/ml, was able to almost scavenge all $O_2^{\bullet-}$ free radicals. Marcocci *et al*. (1994) evidenced that a 20 µg/ml EGB 761 solution inhibited nitric oxide activity by 40%, while, at a concentration of 40 µg/ml, the inhibition rate increased up to 70%. Köse *et al*. (1997) reported that a 250 µg/ml EGB 761 solution was able of inhibiting hydrogen peroxide-induced malondialdehyde production by 55.96% in blood samples of human patients.

7.2. Plant toxicological studies

The previous chapter highlighted the effects of some of the most predominant plants used in TCM. Overall, all the plant extracts either displayed some sort of anti-AD, anti-PD, or anti-depression properties or are rich in phytochemicals that exerted the same properties in other plants, with different rates. The visible effects of neurodegenerative diseases normally occur years after they first affect the human brain. Therefore, these plant extracts are expected to be consumed during vast periods. Normally, the studies that evaluate cognitive impairment on human patients document the effects on people that consume tea extracts chronically (Polito *et al*., 2018). For that reason, before discussing whether the examined plants can potentially integrate medicinal treatment plans, the toxicology and adverse effects need to be assessed. There is a need to clarify and validate the potential effects of the plants on the human body since there is both a lack of actual knowledge on the plant's beneficial properties, mostly covered by traditional use knowledge that mistakenly encompasses a variety of effects on a specific body part, and a misconception of the benefits and denial of adversities of a plant just because of it being a "natural product".

Since black tea is one of the most consumed beverages in the world, today, there have been several studies that assessed both the beneficial and toxic effects of excessive consumption. The adverse effects of *Camellia sinensis* are due to three main factors: the presence of caffeine, aluminum, and the effects on the iron bioavailability (Hayat *et al*., 2015). Black tea is wrongly associated with having a higher content of caffeine than other *Camellia sinensis* teas. As the leaves are fermented, they lose weight, while caffeine is preserved. To compensate, higher doses are usually administered, which in turn correlate to an increase in caffeine. The adverse effects of caffeine abuse include insomnias, nervousness, restlessness, motor agitation, cardiac arrhythmia, and gastrointestinal disturbance (Hughes *et al*., 1991). *Camellia sinensis* has been reported to be a viable option in soil treatment methods or phytoremediation. Karak *et al*. (2015) evidenced the plant's potential in the extraction of aluminum from municipal waste to the aerial parts. Aluminum can bind to proteins and ions, which can prolong the natural retention from the body, forcing patients to undergo dialysis. Aluminum overexposure has been linked with cognitive impairment effects, and in severe cases, to dementia and cancer (Klotz *et al*., 2017). The consumption of black tea has also been associated with reduced absorption of dietary iron. It has been suggested that both tannins and catechins found in *Camellia sinensis* absorb non-heme iron. This property suggests that patients suffering from anemia should avoid any sort of *Camellia sinensis*-based tea (Hayat *et al*., 2015).

Ginseng is a relatively safe plant to consume (Paik & Lee, 2015). When consumed moderately through vast periods, no significant toxicity or adverse effects were registered. Studies were conducted to evaluate some potential acute and chronic effects of daily ginseng

consumption. Both mice and dogs were administered with specific doses of ginseng, with one of those doses exceeding the recommended dietary intake of 7.5 mg/kg for humans by two-fold, with no physiological effects observed (Chan & Fu, 2007). The consumption of the plant is known for manifesting adverse effects in clinical trials, some of which can be considered life-threatening. However, these negative effects are mostly associated with the administration of high doses of ginseng, which is denominated as "ginseng abuse disorder". Siegel (1979) evaluated 133 patients that ingested high doses of ginseng for two years. Most of the subjects reported excitatory effects, such as sleeplessness, euphoria, and a feeling of well-being. However, other effects included diarrhea, nausea, skin eruptions, edema, and in some cases, hypertension, hypotension, appetite loss, and depression.

Chrysanthemum has been classified as a safe plant to ingest chronically. Li *et al*. (2010) conducted a case study, where the effects of chronic administering chrysanthemum extracts to mice were evaluated. For this, the mice consumed the extracts for 2 and 26 weeks, for short-term and long-term effect evaluation, respectively. The obtained results showed no toxic effects on the mice's weight, water, and food consumption, hematologic, and blood examination. The main side effect of chrysanthemum is derived from pyrethrin, which is a natural insecticide produced in the flower. This compound has been reported to exert allergy-related symptoms, such as skin irritation, as well as nausea, headaches, vomiting, among others. In some cases, it might negatively affect the nervous system (Shawkat *et al*., 2011).

Dandelion is a relatively safe plant to consume when it is incorporated into commercial products. Dandelion normally appears in these products as a lesser component of a mixture, as seen in herbal blends. However, at higher doses, dandelion can induce health issues, ranging from mild to severe. The plant is classified as an allergen, which usually includes symptoms as skin irritation and eczema (Rasmussen & Jacob, 2017). Posadzki *et al*. (2013) classified dandelion as a moderately severe plant, evidencing its reported effects, such as gastrointestinal upset, vomiting, lack of appetite, liver damage, and platelet aggregation. Another consideration regarding dandelion is the plant's phytoremediation properties. Bini *et al*. (2012) reported the ability of dandelion to absorb and translocate iron and zinc from the soil to the aerial parts of the plant.

When licorice is found in a confectionery product, it is considered safe to be consumed, However, regular and excessive consumption can lead to cardiovascular problems, such as hypertension, hypokalemia, and hypoglycemia. Hypertension and hypokalemia are adverse effects derived from the consumption of glycyrrhizin, one of the main components found in the roots of licorice. Glycyrrhizin is metabolized in the body to glycyrrhetinic acid, which increases the levels of cortisol in the kidneys. Cortisol activates renal mineralocorticoid receptors, which in turn deregulates sodium reabsorption and potassium release (Ross *et al*., 2017). Glycyrrhizin and its salts are potent sweeteners that have been reported to decrease glucose levels in the blood. The excessive intake of these components has been reported to cause hypoglycemia (Nazari *et al*., 2017).

Bamboo leaf extracts are safe to ingest in regular doses. Besides its numerous health benefits, some adverse effects were documented, however, they are usually derived from excessive intake. Lu *et al*. (2005) confirmed the overall safety of ingesting bamboo leaf extracts, by reporting no significant adverse effects on mice who were chronically administered bamboo leaf tea. Overconsumption of bamboo leaf extracts has been reported by Yakubu *et al*. (2009) to damage the kidneys and the liver, by increasing the activity of enzymes involved in the prevalence of chronic kidney and liver diseases. The same author reported the abortifacient properties of bamboo extracts. Bamboo leaf tea was found to decrease hormone levels in the ovaries of

pregnant rabbits, which increases the probability of a failed pregnancy occurring. No studies were conducted yet on the potential side effects of bamboo leaf tea on the thyroid, however, bamboo shoots have been evidenced to inhibit thyroid peroxidase, a crucial enzyme involved in the production of thyroid hormones (Jun, 2015).

From all the plant components of *Cannabis sativa*, the seeds are the safest for consumption, in moderate doses. Hemp seeds have been associated with some mild adverse effects, mostly related to gastrointestinal upset, bloating, and abdominal pain (Cheng *et al*., 2011). Hemp seed has been reported as a potential therapeutic agent to integrate hypertensive treatment methods (Girgih *et al*., 2014). This is mainly due to the seeds content of linoleic and α-linoleic acids, at a 2/1 ratio, which has been linked with preventing several chronic diseases, such as diabetes, coronary artery disease, inflammation, cancer, hypertension, among others. Although no reports are evidencing it, the overconsumption of hemp seed extracts can lead to hypoglycemia.

No major adverse effects on adlay seed extracts administration were reported. Adlay seeds have been evidenced to prevent cancer, metastasis, hypertension, arthritis, asthma (Chiang *et al*., 2020), reduce blood glucose levels (Yeh et al., 2006), and to prevent side effects derived from chemotherapy, like neurotoxicity, nausea, vomiting, diarrhea, oral mucositis, bone marrow suppression, and gastrointestinal symptoms (Zhan *et al*., 2012). Regarding the anti-diabetic properties of adlay seeds, even though no clinical studies were found to assess the effects of excessive consumption, the presumption can be made that a high intake of adlay seed extracts can lead to hypoglycemia.

The dietary intake of purslane has been recommended for its multiple health benefits since it is rich in vitamin C and fatty acids, aside from the effects against neurodegenerative diseases (Savage & Moreau, 2009). However, when consumed excessively, it can cause kidney problems. Purslane leaves contain significant levels of insoluble oxalates, which have been linked to health issues such as hypocalcemia and oxalate nephropathy. Oxalates normally absorb calcium present in the stomach and the bile and deposit in the kidneys. These deposits are commonly known as kidney stones. Kidney overexposure to oxalate-calcium deposits can lead to nephropathic effects, such as renal tubular atrophy and interstitial fibrosis (Nagaraju *et al*., 2013).

Chinese hawthorn berries have been documented as safe treatment agents in various cardiovascular diseases, such as cholesterol reduction, blood pressure reduction, chronic heart failure prevention, among others. The long-term effects of hawthorn berry consumption are unknown, however, it is suggested that the long-term intake requires regular stoppages, of around two to three days (Wang *et al*., 2013). Hawthorn berries have hypotension properties, more specifically on the diastolic pressure, which is the lowest pressure number registered in blood pressure meters. When patients have low bottom pressure, results in symptoms like fatigue, dizziness, blurred vision, and fainting. Hawthorn berries overconsumption has also been reported to inflict gastrointestinal upset, migraines, and palpitation.

Cape jasmine berries have been considered non-toxic to human patients, however, there have been no reports on the adverse effects of its overconsumption. *Gardenia* species, in general, have been reported to induce toxic effects on domesticated animals, such as diarrhea (Tang *et al*., (2020). This is expected, as small animals have a higher sensitivity to pharmaceutical agents. The main compound found in cape jasmine that exerts the berry's adverse effects is geniposide. To further evaluate the effects of *gardenia* berry overconsumption, Tian *et al*. (2018) conducted an assay, where four groups of mice were administered either a control sample or 3 geniposide

different concentrations,(25, 50, and 100 mg/kg/day) one of them exceeding the recommended human dose by ten-fold, for 26 weeks. The results showed that the group that consumed the 100 mg/kg sample had significant liver and kidney damage, as well as low iron levels. Cape jasmine berries have also been reported to alleviate hypertension (Chen *et al*., 2017). As with other plants, the overconsumption of the berries can lead to severely low levels of blood pressure, which can induce fatigue, and fainting, in some cases.

There is a lack of studies that thoroughly assess the adverse effects of *Poria cocos* intake. To date, only the potential benefits have been investigated. The polysaccharides of *Poria cocos* were reported as nontoxic (Sun, 2014). In TCM, *Poria cocos* is administered freely, with excessive doses, which can allude to its safety. Some postulated adverse effects include polyuria, which is a condition where a subject urinates more frequently, based on the fungus ability to remove oxalate-calcium deposits from the kidneys (Sun, 2014), as well as to treat chronic kidney disease (Zhao *et al*., 2013).

Various citrus peels, including pummelo, have been reported to be safe for consumption and nontoxic. Citrus peels are usually composed of the same phytochemicals of their respective fruit, at different levels of concentration, like flavonoids and vitamin C. Currently, no assays on the potentially toxic effects of pummelo peel were conducted. Some citrus peels have been linked to exert phototoxicity effects, usually skin irritation, however, further studies are needed to evaluate the same effects on other citrus peels. However, during the production of citrus fruits, several sorts of pesticides are spread in the peels to prevent microbial-induced degradation. Ortelli *et al*. (2005) evaluated the presence of 38 different fungicides, insecticides, and acaricides across 240 citrus fruits, including pummelo. The obtained results indicated that imazalil was found in 168 citrus peels. The authors also indicated that the regulated levels of metalaxyl found are lower in pummelo, which indicates that this is a recurrent fungicide applied in the fruit. The exposure to this kind of fungicides involves carcinogenic, mutagenic, reproductive, and organ failure effects.

Despite the numerous neuroprotective effects of *G. biloba*, several reports indicate that the plant is associated with a substantial amount of adverse effects, whether by itself or when consumed with certain pharmaceuticals when consumed exaggeratedly. A report by the Committee on Herbal Medicinal Products (HMPC), (2014) compiled the adverse effects of exaggerated consumption of *G. biloba* extracts. For example, some health risks include gastrointestinal problems, headaches, and hypersensitive reactions. The leaves also contain dangerous components, such as ginkgolic acids, whose excessive consumption has been linked with neuronal death by increasing phosphatase activity (Ahlemeyer *et al*., 2001), and 4'-O-methylpyridoxine, a neurotoxin found in the seeds and leaves of *G. biloba* that has been evidenced to inhibit $GABA_A$ receptor synthesis (Mei *et al*., 2017).

8. Conclusion

Neurodegenerative diseases are becoming one of society's most troublesome issues, as human life-expectancy increases due to the overall improvement of quality of life and technology. AD and PD are the most common neurodegenerative diseases in the world, and in most cases, it is difficult to identify the associated decline of cognitive and motor ability, respectively, in elderly people, the most affected age group, in the early stages of the disease, as one of the common implications of aging consists of some memory lapses and reduced motor ability. In a way, there exists a "blurred line" that prevents correct diagnosis. Depression is also an important condition to consider, as it is more frequent in younger individuals. Long and untreated periods of depression can lead to abnormal oxidative stress levels, which in turn leads to neuron death. Even though that it is unlikely for young individuals to show symptoms of either AD or PD, long-term depression in an early stage of life increases the probability of the individual "contracting" these diseases at a faster rate than other people. Therefore, it is important to design treatment methods, in this case, both pharmaceutical and psychological counseling therapies, to swiftly ameliorate and prolong the behavioral disposition of young individuals, to suppress the progression of mental illnesses in the future.

In the present dissertation, the mechanisms that contribute towards the progression of AD, PD, and depression were described as a means to understand each one's therapeutic point of action, and how each one interacts with another. These mechanisms revolve around enzymatic processes, neuron receptor interaction, protein-complex cytotoxicity, and oxidative stress. Then, medicinal plants (and one fungus) and their respective bioactive compounds were evaluated to better understand each one's role in disrupting each neurodegenerative mechanism. Overall, each plant was found to exert some type of anti-neurodegenerative activity. Out of all studied plants, *C. sinensis*, *P. ginseng*, *C. sativa*, *C. pinnatifida*, *G. jasminoides*, and *G. biloba* were found to be strong candidates to integrate medicinal therapies for either AD, PD, and depression. Overall, these plants were described as possessing great enzymatic inhibition, agonist/antagonist properties that allow for favorable neuron receptor interaction, and protein-complex aggregation and fibrilization inhibition properties.

In regards to plant consumption safety, toxicological studies on each plant all concluded that excessive intake of these plants or their extracts is regarded as safe, however, excessive intakes often result in health problems, such as hypersensitivity, inflammation, and in the case of *P. oleraceae*, kidney issues. One of the most discussed problems of the medicinal plant industry revolves around the lack of regulation and the recommended dosage.

In conclusion, the gravitation of society towards natural products has been increasing over the years, as the current knowledge on the bioactive compounds of medicinal plants increases and becomes more available. At the same time, global institutions are contributing to the sensibilization and regulation of medicinal plant integration in several therapies. Therefore, neurodegenerative disease treatment has the potential to grow and to aid people in need, thus suppressing its progression.

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10. Attachments

10.1. Attachment A- Phytochemical composition of medicinal plants

Table A.1. Phytochemical composition of *Camellia sinensis* (L.) Kuntze (Bhagwat et al., 2011; Chen et al., 2019; Kakuda et al., 2002).

Phytochemical class	Phytochemicals
Phenolic acids	Gallic acid, chlorogenic acid, theogallin
Flavonoids	Catechin, epicatechin, epicatechin-gallate, epigallocatechin, epigallocatechin-gallate, quercetin, theaflavin, theaflavin 3-monogallate, theaflavin 3′-monogallate, theaflavin 3,3′-digallate
Alkaloids	Caffeine
Amino acids	L-Theanine

Table A.2. Phytochemical composition of *Panax ginseng* rhizome. (Chung et al., 2016; Hong et al., 2014; Kim et al., 2018; Ratan et al., 2020).

Phytochemical class	Compounds
Phenolic acids	Chlorogenic acid, gentisic acid, *p*-coumaric acid, *m*-coumaric acid
Flavonoids	Kaempferol-3-O-b-D-glucopranoside, kaempferol-3-O-(2'',3''-di-*E*-*p*-coumaroyl)-α-L-rhamnoside), kaempferol-3-O-a-L-rhamnoside, rutin (quercetin-3-*O*-rutinoside)
Alkaloids	Ginsenine, 1-carbomethoxy-β-carboline, N9-formylharman, harman, norharman, perlolyrine, 4-methyl-5- 142 thiazoleethanol, and spinacine
Saponin glycosides	Ginsenosides Rb2, Rc, Rd, Re, Rg1

Table A.3. Phytochemical composition of *Chrysanthemum* species (Lin & Harnly, 2010; Mircea et al., 2015; Zhong et al., 2019).

Phytochemical class	Compounds
Phenolic acids	(1;3;4)-Caffeoylquinic acid, chlorogenic acid, caffeic acid, caffeic acid 4-glucoside, (1,3:1,4;1,5;3,5;4,5)-di-caffeoylquinic acids
Flavonoids	Luteolin, apigenin, acacetin, luteolin 7- O-rutinoside, quercetin 3-O-galactoside, quercetin 3-O-glucoside, eriodiocyol 7-O-glucoside, luteolin 7-O-glucoside, luteolin 7-O-glucuronide, apigenin 7-O-rutinoside, diosmetin 7-Orutinoside, apigenin 7-O-glucoside, diosmetin 7-O-glucoside, acacetin 7-O-rutinoside, diosmetin, eupatorin
Monoterpenes	eucalyptol, α-pinene, α-neoclovene, verbenone, chrysanthenone, camphor
Sesquiterpenes	Alantolactone

Table A.4. Phytochemical composition of *Taraxacum officinale* (Fatima et al., 2018).

Phytochemical class	Phytochemicals
Phenolic acids	Caffeic acid, chlorogenic acid, chicoric acid, monocaffeyltartaric acid, p-hydroxyphenylacetic acid
Flavonoids	Luteolin, luteolin-7-glucoside, luteolin 7-O-rutinoside, isorhamnetin 3-O-glucoside, quercetin 7-O-glucoside, apigenin 7-O-glucoside, luteolin-7-diglucoside
Sesquiterpenes	Taraxinic acid-D-glucopyranoside, 11β,13-dihydrotaraxinic-acid-D-glucopyranoside

Table A.5. Phytochemical composition of *Glycyrrhiza glabra L.* (Hatano et al., 2000; Hatano et al., 1998; Khalaf et al., 2012; Nakagawa et al., 2004).

Phytochemical class	Compounds
Phenolic acids	p-Coumaric acid, ferulic acid, sinapic acid, caffeic acid
Flavonoids	Luteolin, apigenin, quercetin, glabridin, daidzin, genistin, ononin, daidzein, glycitein, genistein, formononetin, naringenin, 18*β*-glycyrrhetinic acid
Saponins	Glycyrrhizin, liquiritic acid, glycyrretol, glabrolide, isoglabrolide
Chalcones	Licocalchone A and B, 2,2´,4-trihydroxychalcone

Table A.6. Phytochemical composition of common bamboo (J. Gong et al., 2015; Ma et al., 2020).

Phytochemical class	Compounds
Phenolic acids	Chlorogenic acid, caffeic acid, ferulic acid, p-coumaric acid
Flavonoids	Isorientin, orientin, homoorientin, isovitexin, apigenin, luteolin, cynaroside

Table A.7. Phytochemical composition of *Cannabis sativa L.* (Izzo et al., 2020; Manosroi et al., 2019; Pollastro et al., 2017; Y. Zhou et al., 2018).

Phytochemical class	Compounds
Phenolic acids	Caffeic acid, chlorogenic acid, p-coumaric acid, ferulic acid
Flavonoids	Kaempferol, catechin, epicatechin, Luteolin-7-O-glucoside, rutin, quercetin, 1uercetin-3-glucoside, Kaempferol-3-O-glucoside, apigenin-7-glucoside, luteolin, naringenin, apigenin, cannaflavin A,B
Lignandamides	Cannabisin A, B, C, D, E, F, M, isocannabisin N^{α}, N-trans-feruloyltyramine, N-trans-caffeoyltyramine
Monoterpenes	Myrcene
Sesquiterpenes	β-Caryophyllene

Table A.8. Phytochemical composition of *Coix lacrima-jobi* L. (Dhiman et al., 2019; Huang, et al., 2009; Matsuda et al., 2015; Wang et al., 2015).

Phytochemical class	Compounds
Phenolic acids	Gallic acid, vanillic acid, ferulic acid, p-hydroxybenzoic acid, caffeic acid, chlorogenic acid, p-coumaric acid, sinapinic acid, 2-hydroxyphenylacetic acid, dihydrocaffeic acid, 4-hydroxybenzoic acid
Flavonoids	Quercetin, apigenin, narigenin, genistein, luteolin

Table A.9. Phytochemical composition of *Portucala oleracea* L. (Aziz, 2016; Erkan, 2012; Carvalho, 2014; Zhou et al., 2015).

Phytochemical class	Compounds
Phenolic acids	Chlorogenic acid, caffeic acid, ferulic acid, p-coumaric acid, rosmarinic acid, gallic acid, benzoic acid, anisic acid, sinapic acid, oxalic acid
Flavonoids	Kaempferol, quercetin, catechin, epicatechin, anthocyanins (pelargonidin-3,5-glucoside, delphinidin-3-glucoside, cyanidin-3-glucoside, pelargonidin-3-glucoside), apigenin, luteolin, myricetin, portulacanones (A-D), genistein, genistin
Alkaloids	Adenosine, oleraceins (A-E;I, II), nandigerine, reticuline, (R)-3,4-dehydromagnocurarine, itingensine, (S)-Tembetarine, homolycorine, angustureine, cyclobullatine-A, 10-(5-p-coumaroyl-6-methylpiperidin-2-yl) dodecan-2- one, 10-(5-p-coumaroyl-6-methylpiperidin-2-yl)-tetradecan-2-one
Terpenes	Portuloside (A, B), portulene, lupeol
Sterols	Melatonin

Table A.10. Phytochemical composition of *Crataegus pinnatifida* (Jurikova et al., 2012; Tohtahon et al., 2017; Wen et al., 2015).

Phytochemical class	Compounds
Phenolic acids	Protocatechuic acid, chlorogenic acid
Flavonoids	Quercetin, (3-O-galactoside of quercetin), isoquercetin, rutin, kampferol, epicatechin, procyanidins (B2, B5, C1), apigenin, vitexin, vitexin-2"-*O*-rhamnoside, luteolin-7-glycoside
Tritepenes	Ursolic acid, corosolic acid, oleanolic acid, pomolic acid, euscaphic acid, maslinic acid

Table A.11. Phytochemical composition of *Gardenia jasminoides J.* Ellis (Kim et al., 2012; Uddin et al., 2014; Xiao et al., 2017)**.**

Phytochemical class	Compounds

Phenolic acids	Chlorogenic acid, 3,5-di-O-caffeoyl-4-O-(3-hydroxy-3-methyl)-glutaroylquinic acid, 3,5-di-O-caffeoylquinic acid, 4-O-sinapoyl-5-O-caffeoyl-quinic acid, gallic acid, protocatechuic acid
Flavonoids	Quercetin, rutin hydrate, (+)-catechin
Terpenes	Cocrin, crocetin, jasminoside B, C, E, G, H, I, K, J, M, N; iridoids, iridoid glycosides

Table A.12. Phytochemical composition of *Poria cocos* fungi (Fu et al., 2018; Hatip-Al-Khatib et al., 2004; Li et al., 2019; Ríos, 2011).

Phytochemical class	**Compounds**
Polysaccharides	Pachyman, pachymaran
Terpenes	Pachimic acid, dehydrotumulosic acid, polyporenic acid C, dehydrotrametenolic acid, dehydroeburicoic acid, poricoic acids, eburicoic acid
Sterols	Ergosterol

Table A.13. Phytochemical composition of pummelo (Lü et al., 2016; Vijaylakshmi & Radha, 2015; Xi et al., 2014).

Phytochemical class	**Compounds**
Phenolic acids	Gallic acid, chlorogenic acid, caffeic acid
Flavonoids	Naringin, hesperidin, eriocitrin, neohesperidin, naringenin, hesperetin, narirutin, acacetin, tangeritin, and didymin
Coumarins	5-Geranoxy-7-methoxy-coumarin, aurapte, auraptene, bergamottin
Carotenoids	β-Carotene, roseoside
Monoterpenes	α-Pinene, α-terpineol, anethole, β-pinene, camphene, camphor, citral, citronellal, citronellol, farnesol, geraniol, myrcene, neral, terpinene
Sesquiterpenes	α-Bisabolol, α-cadinene, α-copaene, elemol
Sterols	β-Sitosterol, campesterol, daucosterol, stigmasterol

Table A.14. Phytochemical composition of *Ginkgo biloba* (Ellnain-Wojtaszek, 1997; Strømgaard & Nakanishi, 2004; Yoshitama, 1997).

Phytochemical class	**Compounds**

Phenolic acid	Protocatechuic acid, vanillic acid, p-hydroxybenzoic acid, caffeic acid, ferulic acid, p-coumaric acid, chlorogenic acid
Flavonoids	Kaempferol, kaempferol 3-O-glucoside, kaempferoI 3-O-rhamnoside, kaempferol 3-O-rutinoside, kaempferoI 7-0-glucoside, quercetin, quercetin 3-O-glucoside, quercetin 3-O-rhamnoside, quercetin 3-O-rutinoside, isorhamnetin, isorhamnetin 3-O-glucoside, isorhamnetin 3-O-rhamnoside, sorhamnetin 3-O-rutinoside, myricetin, myricetin 3-O-rutinoside, apigenin, apigenin 7-O-glucoside, luteolin, luteolin 3'-O-glucoside, catechin , epicatechin, gallocatchin, epigallocatechin, dihydromyricetin
Terpenes	Bilobalide, ginkolide A, B, C, J