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Extracts and Essential Oils from Medicinal Plants and Their Neuroprotective Effect

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Abstract

Current therapies for neurodegenerative diseases offer only limited benefits to their clinical symptoms and do not prevent the degeneration of neuronal cells. Neurological diseases affect millions of people around the world, and the economic impact of treatment is high, given that health care resources are scarce. Thus, many therapeutic strategies to delay or prevent neurodegeneration have been the subject of research for treatment. One strategy for this is the use of herbal and essential oils of different species of medicinal plants because they have several bioactive compounds and phytochemicals with neuroprotective capacity. In addition, they respond positively to neurological disorders, such as dementia, oxidative stress, anxiety, cerebral ischemia, and oxidative toxicity, suggesting their use as complementary treatment agents in the treatment of neurological disorders.

Keywords: neuroprotection, herbal medicines, neurological disorders, oxidative stress

1. Introduction

A number of complementary treatment are currently being investigated to provide neuroprotection or to treat neurodegenerative diseases. Some therapies are known to provide limited benefits because, despite their treating the clinical symptoms, they are not effective in preventing neuronal cell degeneration.

The economic impact of treating neurodegenerative disorders is also high with disproportionately scarce neurological services and resources that patient survival may depend on. Studies have shown that over 80% of natural deaths in low- and

middle-income countries may be attributed to stroke [1]. In the United States alone, the combined annual costs of neurological diseases total nearly \$ 800 billion, expected to increase in the coming years due to an aging population, resulting in a severe economic burden to the health system [2].

Recent advances in understanding the pathophysiological mechanisms of neurological disorders have led to new strategies in drug development. Animal models have contributed considerably to these advances, as they play an important role in evaluating potential drugs that can alleviate these conditions and also delay their processes [3].

Interest in natural products has increased significantly, resulting in the increasing use of herbal medicines [4]. In a recent review, Izzo et al. report a 6.8% increase in US herbal and food supplement sales in 2014, with an estimated over \$ 6.4 billion in total sales [5].

The clinical and social repercussions of neuropathologies reveal an important theme of study and commitment to structure strategies that can contribute to the quality of life of society. Scientific research has explored which stimuli and substances can contribute to neural cell plasticity, resulting in improved quality of life for people with depression, Alzheimer's Disease (AD), Parkinson's Disease (PD), among other nervous system-related disorders [6].

Increased neurogenesis and the facilitating effects of plasticity can be produced by a variety of treatments, including enriched environment, physical activity or drug action [7]. A complementary treatment proposed is the use of herbal medicines, which have scientific relevance in the treatment of neurological diseases because they contain multiple compounds and phytochemicals that can have neuroprotective effect, with a consequent beneficial action for health in different neuropsychiatric and neurodegenerative disorders [8].

2. Neuroprotective effect of extracts

Studies have investigated therapies that can alleviate the symptoms of neurodegenerative disorders and also avoid the multiple pathogenic factors involved in these diseases. One promising approach is the use of herbal extracts and their isolated bioactive compounds for the treatment of conditions such as Parkinson's, Alzheimer's, cerebral ischemia. Behavioral analysis has shown them to have neurochemical activity and symptom reduction [9].

Recent advances in understanding the pathophysiological mechanisms related to neurodegenerative diseases point to new strategies in drug development [10]. Animal models have contributed considerably to these advances and play an even greater role in evaluating possible drugs with therapeutic potential, not only to alleviate these pathologies, but also to modify the disease process [3]. Rodents are suitable models for these studies because of their well-characterized brain organization and the magnitude of information focused on altered states of the nervous system [11, 12].

Phytotherapies have scientific relevance in the treatment of neurological diseases, as they contain multiple compounds and phytochemicals that can have neuroprotective effects, with consequent beneficial health action between different neuropsychiatric and neurodegenerative disorders [8–10]. Several extracts that have shown beneficial action in these disorders as will be addressed in this paper.

2.1 Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative pathology that results in progressive loss of cell function, structure and number, leading to widespread brain

atrophy and profound cognitive and behavioral deficit [13]. Histopathologically, it is characterized by accumulation of beta-amyloid peptide (β A), which can initiate a cascade of oxidative events and chronic inflammation leading to neuronal death [14].

Several studies have investigated the action of *Piper methysticum* in experimental models of neurodegenerative diseases, specifically in AD, demonstrating the neuroprotective effect of this herbal medicine [15–17].

Piper methysticum is popularly known as Kava or Kava-kava, a perennial shrub belonging to the Pacific Ocean pepper family (Piperaceae) with historical and cultural significance is described in the literature as a compound that has neuroprotective action and anxiolytic effects and is used in sedatives, and analgesics, being anti-inflammatory, anticonvulsant and anti-ischemic. Most of these pharmacological effects have been attributed to six kavalactones isolated from kava extracts, including yangonin, kawain and methysticin, dihydromethysticin, dihydrokawain and desmethoxyyangonin [18].

Recent studies, such as Fragoulis et al. have shown that one of the possible explanations for the action of piper mechanism in AD is associated with the activation of the erythroid2-related nuclear factor (Nrf2) [15].

Nrf2 is the major regulator of phase II detoxifying/antioxidant enzymes, including heme oxygenase 1 (HO-1). Transcription factor Nrf2 binds to ARE (antioxidant response element), transcribing a battery of genes involved in redox status, anti-inflammatory response and detoxification [19]. A study by Lobota et al. reports that Nrf2 activation and HO-1 induction are involved in the regulation of inflammation [20].

Another study developed to find agents that activate the Nrf2 factor was performed and three analytically pure kavalactones - Methysticin, Yangonin and Kavain - were researched. The effects of kavalactones on the protection of neural cells against beta-amyloid peptide (β A)-induced neurotoxicity were evaluated using the ARE-luciferase and Western blot assay. The results indicated that kavalactones Methysticin, Yangonin and Kavain activate time and dose-dependent Nrf2/ARE in astroglial PC-12 and C6 neural C6 cells and thus up-regulate cytoprotective genes. At the same time, viability and cytotoxicity assays have shown that Nrf2 activation is able to protect neuronal cells from neurotoxicity by attenuating neuronal cell death caused by β amyloid [14].

Taken together, it is understood that the Nrf2/ARE signaling pathway is an attractive therapeutic target for neurodegenerative diseases and that chemically modified kavalactones as well as naturally occurring kavalactones can attenuate neurological damage by reducing oxidative stress and neuroinflammation.

Some herbal medicines have shown neuroprotective effects, such as curcumin, which is the main polyphenol found in turmeric (*Curcuma longa*), belonging to the Zingiberaceae family, native to South Asia and cultivated in the tropics [21]. It has been reported that this compound has properties that can prevent or ameliorate pathological processes related to neurodegenerative diseases such as cognitive decline, dementia and mood disorders [22]. In addition, curcumin has been investigated for experimental models of treatment for Parkinson's disease and has shown hopeful results [9].

Saffron compounds have been linked to beneficial biological properties such as anti-inflammatory, pro-apoptotic, antiproliferative, anti-amyloidogenic, antioxidant, antiviral, and antidiabetic [23, 24]. Saffron's most bioactive constituents are curcuminoids, including curcumin and its derivatives such as demethoxycurcumin and bisdemethoxycurcumin [25, 26].

The features attributed to curcumin, such as inhibition of amyloid pathology, protection against inflammation and oxidative stress, inhibition of beta amyloid

plaque aggregation and tau protein hyperphosphorylation, suggest that this compound may prevent or improve pathological processes related to cognitive decline and dementia, as occur in the symptomatology of AD patients [27, 28].

A systematic review study showed that curcumin has a positive action on AD symptoms, both when assessing biochemical and behavioral symptoms. The proposed mechanisms of its action in AD show that it is able to act by preventing the formation and aggregation of β -amyloid protein and tau protein hyperphosphorylation [10], in addition curcumin has also been shown to prevent neural damage, mitochondrial disorders, cellular stress and glial hyperactivation, as shown in **Figure 1**.

Another compound that represents a promising approach is *astragaloside IV* (AS-IV), a triterpenoid saponin present in the root of *Astragalus membranaceus* (Fisch.) Bge. It is part of Chinese traditional culture [29], first described in the Chinese book Shen Nong Ben Cao Jing in 200 AD with a number of beneficial effects and no toxicity.

The biological and pharmacological properties of AS-IV include its protective effect on pathologies due to its wide range of beneficial actions, such as antioxidant, antibacterial, antiviral [30, 31], anti-inflammatory, anti-asthmatic, antidiabetic, antifibrotic, immunoregulatory and antimicrobial, and cardioprotective effects, preventing myocardial insufficiency in rats [29–32], able to improve the immune system, digestion and promote wound healing [33].

Astragalus action can be understood based on the regulation of the release of caspases and cytochrome c (both being inducers of apoptosis), since cytochrome binds to Apaf-1 and Procaspase-9c when released into cytosol, forming a functional apoptosome and subsequently triggering the sequential activation of caspase-3 and 9 [34]. Several stimuli that induce apoptosis, leading to the release of mitochondrial cytochrome c which plays a key role in a common pathway of caspase activation [34, 35]. In addition, caspase-3 activation has been shown to be a fundamental step in the apoptosis process and its inhibition may block cellular apoptosis.

In addition, Chang et al. evaluated the action of AS-IV on the cerebral cortex after A β infusion, showing that i.p. Administration of 40 mg/kg/day of the herbal compound once daily for 14 days reduced the levels of mitochondrial dysfunction apoptosis in cortical cells blocked by inhibition of phosphoinositol 3-kinase (PI3K) protein kinase, known as AKT [36].

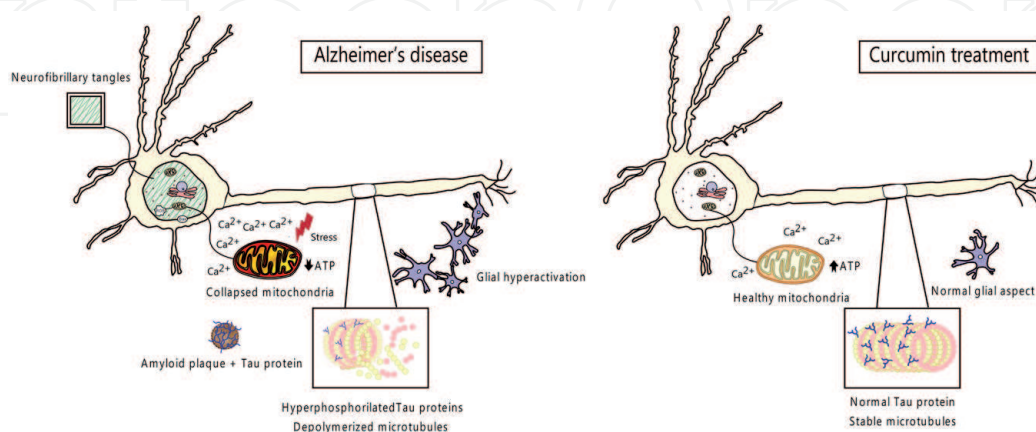


Figure 1.

Active curcumin mechanisms after experimental treatment in AD models. Curcumin acts by preventing the formation and aggregation of β -amyloid protein and hyperphosphorylation of tau protein, stabilizing microtubules and preventing the formation of neurofibrillary tangles that occur due to deposition of this protein. It has also been shown to prevent mitochondrial damage favoring the increase of cellular ATP and the healthy maintenance of mitochondria, avoiding excessive Ca^{2+} intake. Curcumin is also able to counteract cellular stress and glial overactivation.

The beneficial effects of AS-IV administration in experimental models of neurodegenerative diseases proved to be effective in both in vivo and in vitro models, such as PD and AD, cerebral ischemia and encephalomyelitis by characterizing the antioxidant, antiapoptotic and anti-inflammatory action of this bioactive compound on the various neurochemical substances and behavioral mechanisms. This suggests that the mechanisms presented by AS-IV offer a possible future complementary treatment for the potential treatment of these pathologies [10].

2.2 Parkinson's disease

Parkinson's disease (PD) is a condition that causes progressive neurodegeneration of dopaminergic neurons with the consequent reduction of dopamine content in the substantia nigra. The 6-hydroxydopamine neurotoxin (6-OHDA) is widely used to mimic the neuropathology of PD [37].

There are reports in the literature analyzing the effect of supplementation, including Chinese herbs and herbal extracts that have shown clinical potential to attenuate the progression of PD in humans. In addition, plant extracts act on the neurochemical or motor profile in isolation [38]. It is known, however, that this pathology involves symptomatology related to both characteristics.

A recently published systematic review study discussed studies showing neuroprotective properties of medicinal plants and their bioactive compounds. These included *Amburana cearenses* (Amburoside A), *Camellia sinensis* (Catechins and Polyphenols), *Gynostemma pentaphyllum* (Saponin Extract), *Pueraria lobata* (Puerarin), *Alpinia oxyphylla* (Protocatechuic Acid), *Cistanches salsa* (Glycosides or Phenylethanoids), *Spirulina platensis* (Polysaccharide), and *Astragalus Membranaceus* - AS IV Tetracillic Saponin Triterpenoid [9].

As previously mentioned, Astragaloside showed a neuroprotective effect on several AD models. In addition, studies have shown the positive action of AS-IV in PD models. One of the studies induced Parkinson by the action of 6-OHDA, where AS IV attenuated the loss of dopaminergic neurons and the treated group presented intact germination, neurite growth and increased immunoreactive TH and NOS. In addition, when the pathology was induced in SH-SY5Y cell culture by MPP + (DP inducing drug) action, it also significantly reversed cell loss, nuclear condensation, intracellular generation of reactive oxygen species and pathway inhibition as mediated by Bax; these effects, however, were related only to neurochemical analysis. Behavioral findings were not reported [39].

One legume that has become the target of scientific research for its neuroprotective properties is *Mucuna pruriens*. Behavioral analysis studies have been carried out with *Mucuna pruriens* (Alkaloids, coumarins, flavonoids, triterpenes, saponins, carotenoids) and Baicalein (Flavonoids) for PD, but no neurochemical evaluation has been performed. There are also publications demonstrating in vivo behavioral effects and in vitro neurochemical analyses, such as a recent publication showing the effect of *Ligusticum officinale* (Makino) on MPTP (1-methyl-4-phenyl-1,2,3,6)-induced with an animal model and tetrahydropyridine, a neurotoxin capable of permanently causing symptoms of Parkinson's disease by destroying the dopaminergic neurons of the substantia nigra. This drug has been used to study the disease in experiments with animals; the treatment restored behavior when compared to the control group. In this study, *Withania somnifera* (Ashwagandha) extract also showed improvement in all these physiological anomalies [9, 40–43].

Another study investigated the ability of guanosine to protect neuronal PC12 cells from toxicity induced by 1-methyl-4-phenylpyridinium (MPP), the active metabolite of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), which mediates selective damage to dopaminergic neurons and causes irreversible

Parkinson-like symptoms in humans and primates. The results demonstrated that MPP-induced apoptosis of PC12 cells (cell line derived from a rat adrenal membrane pheochromocytoma) was significantly prevented by guanosine pretreatment for 3 h. In addition, guanosine attenuated the collapse of the MPP-induced mitochondrial transmembrane potential and prevented subsequent activation of caspase-3, thus protecting dopaminergic neurons against mitochondrial stress-induced damage [44].

Other studies have shown plants with neuroprotective properties capable of protecting from PD damage. These include plants such as *Amburana Cearenses* (Amburoside A) [5], *Myracrodruon urundeuva* (tannins and chalcones) [45], *Camellia sinensis* (catechins and polyphenols) [46], *Gynostemma pentaphyllum* (saponin extract) [47], *Pueraria lobata* (Puerarin) [48], *Alpinia oxyphylla* (protocatecholic citric acid) [49], parsley *Cistanches salsa* (phenylethane glycosides) [50, 51], *Spirulina platensis* (polysaccharide) [22] and *Astragalus membranaceus* (triterpenoid saponin), as mentioned in a review study [9, 39].

Current PD medications treat symptoms; none prevent or retard the degeneration of dopaminergic neurons. It is understood that the above-mentioned herbal medicines have neuroprotective properties.

2.3 Neurological disorders/cerebrovascular diseases/brain dysfunctions

Stroke is the second leading cause of death in industrialized countries and the leading medical cause of acquired adult disability [52].

Piper methysticum is cited as a multi-potent phytopharmaceutical due to its numerous pharmacological effects including anxiolytic, sedative, anticonvulsant, anti-ischemic, local anesthetic, anti-inflammatory and analgesic activities. The use of Kava in brain dysfunctions has clinical and financial advantages, acting as an adjunct or complementary treatment to existing medications [53].

Chang et al. [9] have shown that the use of combined glucose and oxygen administration of guanosine (100 μ M) significantly reduced the proportion of apoptosis. To determine whether guanosine was also neuroprotective in vivo, middle cerebral artery occlusion (CoA) was performed in male Wistar rats and guanosine (8 mg/kg) intraperitoneally or saline (control vehicle) was administered daily for 7 days. Guanosine prolongs survival and decreased neurological deficits and tissue damage resulting from CoA. These data are the first to demonstrate that guanosine is neuroprotective in stroke.

Through an experimental study developed by Backhauss and Krieglstein [55] that induced focal cerebral ischemia in rodents, through left middle cerebral artery (MCA) microbipolar coagulation, with the objective of evaluating whether kava extract and its constituents, kawain, dihydrokawain, Methysticin, dihydromethysticin and yangonin, are capable of reducing the size of a heart attack zone in rats and mice, providing protection against ischemic brain damage. Compounds were administered ip, except kava extract, which was administered orally. The results demonstrated that Kava extract decreased the infarct area in mouse brains and the infarct volume in rat brains. Methysticin and dihydromethysticin significantly reduced the infarct area in mouse brain, thus evidencing neuroprotective activity of the mice. Kava extract works by the action of its constituent's methysticin and dihydromethysticin. The other Kavapyronas could not produce a beneficial effect on the infarct area.

The study by Deng et al. examined whether late administration of GUO (guanosine) improved long-term functional recovery after stroke. Late administration of GUO improved functional recovery from day 14 after stroke when compared with the vehicle group [56].

Gerbatin et al. evaluated the effect of guanosine on TBI-induced neurological damage. The findings showed that a single dose of guanosine (7.5 mg/kg), intraperitoneally (i.p) injected 40 min after fluid percussion injury (IPF) in rats protected them from locomotor and exploratory impairment, observed 8 h after injury, guanosine protected against neuronal death and activation of caspase 3 (protein responsible for cleaving genetic material.) This study suggests that guanosine plays a neuroprotective role in TBI and can be explored as a new pharmacological strategy [57].

Experimental models of ischemic stroke help our understanding of the events that occur in the ischemic and reperfused brain. One of the main developments in the treatment of acute ischemic stroke is neuroprotection.

2.4 Psychological disorders/anxiety/depression

Depression and stress-related disorders affect approximately 17% of the population, resulting in enormous personal suffering as well as social and economic burdens [58].

Guanosine is a nucleoside that has a neuroprotective effect. Current studies have analyzed the action of guanosine as an antidepressant. One study investigated the effects of guanosine on the tail suspension test (TT), open field test and adult hippocampal neurogenesis. The results suggest that the antidepressant effect of chronic guanosine use causes an increase in neuronal differentiation, suggesting that this nucleoside may be an endogenous mood modulator [59].

The ability of this nucleoside to nullify acute stress-induced behavioral and biochemical changes has not been evaluated in female mice, given that depression has a greater impact on women. A study aimed at investigating the protective effect of this nucleoside against oxidative damage and stress response evaluated this using the FST (forced swimming test). The Acute Containment Stress Protocol (ARS) has been proposed as a model that triggers biochemical changes in the rat brain that may be detrimental to CNS (central nervous system) function, implicated in several psychiatric disorders, including major depression [60].

Considering that the hippocampus plays a key role in mood regulation, numerous studies have evaluated whether adult hippocampal neurogenesis is altered in psychiatric disorders. Stress is a risk factor for depression that can manifest itself years after the stressful event [54].

Behavioral studies have shown that guanosine produces anxiolytic substances and amnesic effects. Other analyses have shown that reductions induced by hippocampal stress, cell proliferation and/or neuronal differentiation cause depressive symptoms. Deng et al. explain that hippocampal neurogenesis in humans is affected by various neurological disorders, including depression [56].

According to Duman et al. chronic administration of an antidepressant regulates neurogenesis in the hippocampus of adult rodents. Overregulation of neurogenesis could block or reverse the effects of stress on hippocampal neurons, which include downregulation of neurogenesis as well as atrophy. The possibility that the cAMP signal transduction cascade contributes to antidepressant regulation of neurogenesis is supported by previous studies and recent work [61].

Disturbances in hippocampal neurogenesis may be involved in the pathophysiology of depression. It has been argued that an increase in the generation of new hippocampal nerve cells is involved in the mechanism of action of antidepressants. This study, using adult Wistar rats given fluoxetine, showed that a significant behavioral effect occurred. It also pointed out that chronic antidepressant treatment increases cell proliferation as well as neurogenesis in the dentate gyrus.

Neurogenesis may serve as an important parameter for examining the efficacy and mechanism of action of new drugs [61].

Anxiety is a diffuse mental condition manifested through unpleasant feelings of fear and apprehension without specific cause [62].

Currently, the psychotherapeutic complementary treatment chosen to treat patients is through antidepressant drugs such as selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs), tricyclic antidepressants and benzodiazepines [63]. Due to the undesirable and destructive side effects of these drugs, including drowsiness, cognitive impairment, and symptoms of dependence and withdrawal, many patients prefer herbal remedies. Several plants with anxiolytic activity have been studied in clinical trials, and Kava (*Piper methysticum*) has been shown to be effective and is mentioned as a nonadditive, nonhypnotic anxiolytic with phytotherapeutic potential to act as an adjuvant or complementary treatment to anxiolytic drugs [64, 65].

A meta-analysis review by Pittler et al. evaluated the efficacy and safety of kava extract versus placebo for treating anxiety. Seven randomized controlled trials using *Piper methysticum* indicated that kava extract is superior to placebo and relatively safe as a treatment option for anxiety [66].

Another recent meta-analysis, conducted by Ooi et al., revealed similar results, mentioning that there is promising evidence from well-designed clinical studies suggesting Kava, particularly aqueous extracts, as an effective treatment for generalized anxiety disorder (GAD) [67]. The authors add that the effect of Kava is comparable to commonly prescribed pharmacological drugs (buspirone and opipramol), but with fewer adverse consequences.

It is suggested that the progression of new treatments for psychological disorders is described in the identification of neural substrates and mechanisms underlying their etiology and pathophysiology. Adult hippocampal neurogenesis is a candidate mechanism for the etiology of depression and may be used as a substrate for antidepressant action, as it may also be important for some of the behavioral effects of antidepressants [68].

The therapeutic properties of kava are supported by the six major kavalactones (dihydromethysticin, kavain, dihydrokavain, methysticin, yangonin and desmethoxyyangonin), of which kavain and dihydrokavain have more intense anxiolytic activity [69].

3. Neuroprotective effect of essential oils

In recent years, growing interest in research on medicinal plants and the effects of essential oils (EOs), especially for the treatment of neuropathologies, has emerged [70]. EOs (also called volatile or ethereal oils) are odorous and volatile compounds found only in 10% of the plant kingdom [71–76].

Secondary metabolites present in SOs have been widely used as antibacterial, antifungal and insecticidal agents. Their chemical and biological properties, especially antioxidants, have been considered important tools for the management of various neurological disorders [76].

Natural antioxidants derived from herbaceous plants have demonstrated in vitro cytoprotective properties and have a long history of providing benefits to human health [70]. Evidence of oxidative stress in neuronal damage and the benefits of antioxidant therapy have elucidated the importance of eliminating free radicals as a fundamental principle for the prevention and treatment of neurological disorders [77]. In addition, OEs derived antioxidants have been considered as a complementary treatment against neuronal loss as they have the ability to counteract the

activity of free radicals responsible for neurodegeneration [78], protecting against cellular stress, as outlined in **Figure 2**.

Neural cells suffer functional or sensory loss due to neurological disorders and, in addition to other environmental or genetic factors that contribute to this loss, oxidative stress is a major contributor to neurodegeneration. Therefore, excess reactive

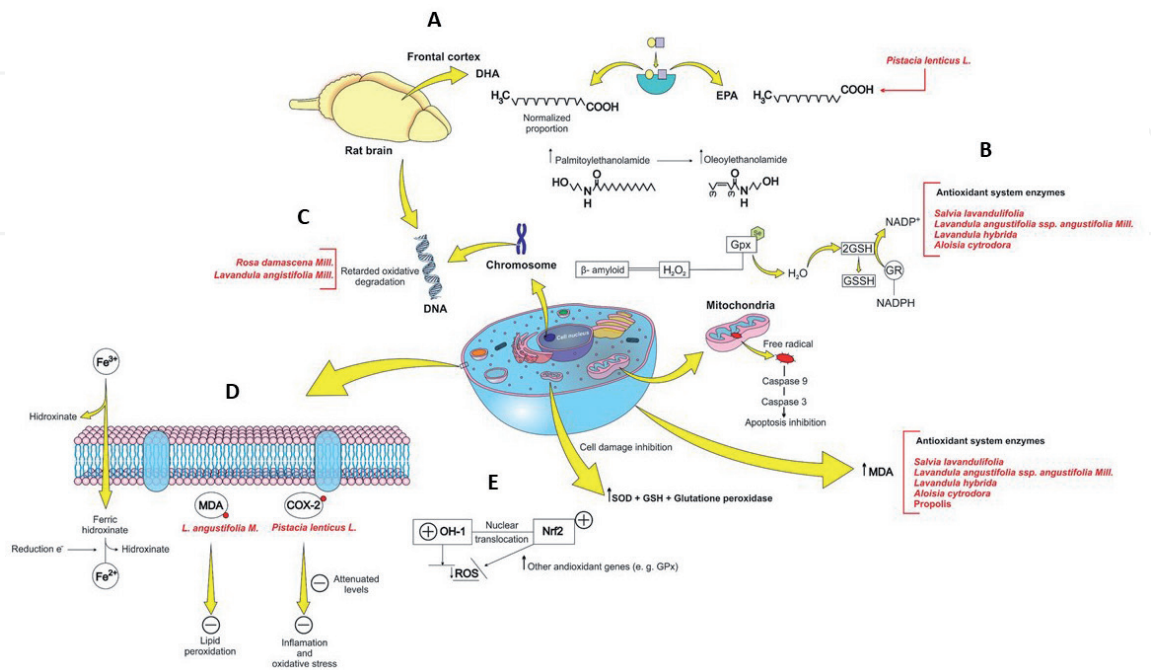


Figure 2. Main identified mechanisms for the action of medicinal plant essential oils in experimental models of neurological disorders. In step A: In an experimental model of cerebral ischemia after occlusion of the common carotid artery followed by reperfusion (BCCAO/R), it was observed that occlusion in the frontal cortex caused a decrease in docosahexaenoic acid (DHA). with *Pistacia lentiscus* L. showing positive plasma levels in the proportion of DHA-for its precursor, eicosapentaenoic acid (EPA) and levels of palmitoylethanolamide (PEA) and oleoylethanolamine (OAS), reversing its reduction, consequently decreasing the susceptibility to oxidation. In step B: essential oils from different medicinal plants demonstrated positive effect on the cellular antioxidant system. *Salvia lavandulifolia* Vahl, *Lavandula angustifolia* SSP. mill and *Lavandula hybrida* acted by increasing the multiple enzyme system (Cat, SOD, GPX, GSH and GSSG), *Salvia l.* (GR) and propolis (SOD) after induction of oxidative stress induced by different oxidants. *Salvia* essential oil reduced the expression of malondialdehyde (MDA), a marker of lipid peroxidation, thus inhibiting effector caspase-3 by preventing cellular apoptosis and preventing mitochondrial damage. The essential oil of *Lavandula angustifolia* ssp. *angustifolia* Mill also potentiated the described antioxidant enzyme system, reversing the scopolamine-induced damage (simulating a dementia model) as well as decreasing MDA levels. *Aloysia citrodora* acted upon damage in an experimental model of H_2O_2 and B-amyloid induced AD and its ability to act on the antioxidant system was observed due to the ability of its compounds to act as free radical scavengers or hydrogen donors. Increasing the antioxidant defense system through the action of these essential oils assists in reducing hydrogen peroxide (H_2O_2) to H_2O and O_2 . Essential oils from other medicinal plants also regulated MDA (*Lavandula hybrida*, *Aloysia citrodora* and Propolis) levels. In step C: *Lavandula A. Mill.* and *Lavandula hybrida* demonstrated effects on DNA fragmentation (cleavage patterns were absent in the treated groups suggesting their antiapoptotic activity), similar effects were also observed in *Rosa damascena* mill treatment. Which also slowed the oxidative degradation of DNA, lipids and proteins due to the presence of phenols in their composition. In step D: *Aloysia citrodora* essential oils acted on the cell membrane, helping to increase iron chelation in vitro through Fe_3^+ to Fe_2^+ + hydroximation, an important mechanism because the transition metal ions contribute to the oxidative damage in Neurodegenerative disorders, thus the chelation of transition metals, prevent catalysis of hydrogen peroxide decomposition via Fenton-type reaction. *L. angustifolia* Mill, acting on MDA levels and in the formation of reactive oxygen species (ROS), which are oxidative markers, consequently also prevents lipid peroxidation (determined by MDA level) in rat temporal lobe homogenates. *Pistacia lentiscus* also acts by attenuating the levels of the enzyme Cox-2 cyclooxygenase 2, consequently decreasing the inflammation and oxidative stress observed in untreated groups. In step E: The essential oils of *S. lavandulifolia* are capable of activating the transcription factor Nrf2 - Nuclear factor (erythroid-derived 2) -like 2, a regulator of antioxidant genes, since protein expression and enzyme activity CAT, SOD, GR, GPx and HO-1 is markedly reduced, correlating with a decrease in nuclear Nrf2 protein. After treatment with *S. lavandulifolia*, regulation of Nrf2 was identified with a concomitant increase in antioxidant enzymes and HO-1, avoiding the formation of ROS, oxidation and decreased cell viability.

oxygen species and an unbalanced metabolism lead to a number of neurological disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD) [78].

3.1 Alzheimer's disease

Alzheimer's disease (AD) is an age related neurodegenerative disease of the brain and this disease is characterized by a progressive deterioration of cognitive functions [79]. Oxidative stress, a detrimental factor during aging and pathologies, is involved in various neurodegenerative disorders [80, 81].

Studies suggest that caspase activation and apoptosis play important roles in AD neuropathogenesis [82]. Thus, SOs have been considered multi-potent agents against neurological disorders, being able to improve cognitive performance [83].

Lavender EO has several protective properties for the nervous system, as evidenced by its effectiveness in controlling depression, anxiety, stress, and cerebral ischemia [84, 85]. Some experimental models of AD have confirmed the neuroprotective effect and cognitive improvement of lavender OS, whose properties have been attributed to its antioxidant activity [86, 87].

EO (100 mg/kg) presented significant protection in the cognitive deficits evaluated, where the mechanism involved seems to be by a protection against decrease in the cellular antioxidant defense system, thus avoiding the reduction of the activity of superoxide dismutase, glutathione peroxidase and protection of the increase acetylcholinesterase malondialdehyde activity. The authors also demonstrated that lavender EO and its active component linalool protect against oxidative stress, cholinergic function and Nrf2/HO-1 pathway protein expression and synaptic plasticity. Therefore, it is suggested that linalool extracted from lavender OS may be a potential agent for improving cognitive impairment, especially in AD [88].

3.2 Oxidative stress

Oxidative stress occurs when the balance between antioxidants and reactive oxygen species (ROS) occurs negatively due to the depletion of antioxidants or the accumulation of ROS (Reactive Oxygen Species) [89]. Hydrogen peroxide (H_2O_2) is a major ROS and is involved in most cellular oxidative stresses [90, 91]. Several plants are considered a rich source of antioxidants because they inhibit or retard ROS-induced oxidative degradation [92–94].

Porres-Martínez et al. demonstrated that *Salvia lavandulifolia* E.O has neuroprotective activity against H_2O_2 -induced oxidative stress in PC12 cells [93]. These effects appear to be related to *Salvia lavandulifolia* EO's ability to activate the transcription factor Nrf2. Therefore, pretreatments with *S. lavandulifolia* EO resulted in decreased lipid peroxidation, ROS levels and caspase-3 activity, showing cell viability and morphological recovery.

Natural antioxidants present in some herbal plants are responsible for inhibiting or preventing oxidative stress, one of the agents that acts in AD, due to their ability to eliminate free radicals. The neuroprotective effect of *A. citrodora* has been attributed to its chelating activity. As described in the literature, an important mechanism of antioxidant effect is the chelation of transition metals, thus avoiding the catalysis of hydrogen peroxide decomposition via the Fenton type reaction [95]. The main proposed mechanisms regarding the action of *A. citrodora* and *Salvia lavandulifolia* OE in vitro models of neurological disorders.

A pioneering study by Abuhamdah et al. showed that *Aloysia citrodora* EO provides complete and partial protection from oxidative stress in an experimental model with H_2O_2 -induced Alzheimer's disease and β -amyloid-induced neurotoxicity

using neuroblastoma cells. This study showed that 250 μm H_2O_2 could not trigger its neurotoxic effect when in the presence of 0.01 and 0.001 mg/mL *O. citrodora* EO, exhibiting neuroprotective activity at both concentrations [70].

Chelating agents have been reported to be effective as secondary antioxidants because they reduce the redox potential of transition metals, thereby stabilizing the oxidized form of the metal ion [96]. This seems to be one of the mechanisms involved in the antioxidant activity of some essential oils, as some of them were able to effectively chelate iron (II).

3.3 Brain ischemia

Cerebral ischemia consists in decreased blood flow in specific areas of the brain, causing hypoxia, which leads to an insufficient supply of glucose and oxygen, the magnitude of which disturbs the development of normal brain functions [97].

Currently, treatments that minimize neuronal damage after cerebral ischemia are limited, thus leading to the search for new complementary treatment therapies [98]. Terpenoids present in some essential oils constitute the largest group of secondary metabolites with neurological properties, including sedative, antidepressant and antinociceptive activities [99].

Another metabolite with neuroprotective function is linalool, a monoterpene present in volatile lavender oil, responsible for important therapeutic properties [100]; its activity on nerve disorders is well documented [101, 102]. Vakili et al. demonstrated that *Lavandula angustifolia* had a protective effect on focal cerebral ischemia in Wistar rats, especially when the treatment was performed with *Lavandula angustifolia* EO at 200 and 400 mg/kg. The results of the administration of this EO were an avoidance of a total antioxidant defense, reduced cerebral edema, and reduced infarct size. In addition, it improved functional performance after cerebral ischemia [103].

4. Concluding remarks

Neurodegenerative and neuropsychiatric diseases have multiple etiology. Multiple studies have been developed to clarify which approaches might be promising in prevention and treatment. We have targeted studies that present a neuroprotective perspective, herbal medicines and essential oils from different species of medicinal plants. These have various bioactive and phytochemical compounds with neuroprotective capacity, and also have given positive responses in studies on neurological disorders such as dementia, oxidative stress, anxiety, cerebral ischemia and oxidative toxicity. We suggest that these present a potential as agents in the treatment of neurological disorders.

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