INTERNATIONAL ACADEMIC STUDIES IN THE FIELD OF PHARMACY

MEDICINAL PLANTS EXTRACTION AS NEUROPROTECTIVE AGENTS

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ASSOC. PROF. DR. DILEK BILGIC ALKAYA
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Chapter 1

EXTRACTION METHODS

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1. INTRODUCTION

The whole set of processes involving the separation of bioactive components from inert or inactive parts of plant or animal tissues using selective solvents is defined as extraction (Handa et al, 2008). In chemistry, extraction is the separation of inorganic or organic matter in a solution or suspension with the help of another organic solvent that dissolves but does not mix with the solvent in the solution or suspension. The differences in extraction methods are generally the length of extraction time, solvent used, pH, temperature, particle size of plant tissues and solvent-sample ratio. The basic principle is to grind the plant material (dry or wet) finer, which increases the surface area for extraction, thus increasing the ratio, which increases the yield (İlbay, 2016). Herbal extracts can be defined as active components or a mixture of components obtained by applying an extraction method from leaves, flowers, seeds, roots or bark parts of plants (Chemat et al, 2011). Bioactive components obtained by extraction method should be obtained without loss and degradation and without additional purification (Demir et al, 2015). Medicinal plants are prepared for experimental purposes. This is followed by extraction and determination of quantity and quality of bioactive compounds

2. COMMONLY USED EXTRACTION METHODS

A) **Liquid-Liquid Extraction**

Liquid-liquid extraction method, as an isolation and purification method, is the phenomenon of drawing substances dissolved and dispersed in a liquid phase into a second liquid phase that does not mix with this liquid but has the ability to dissolve the ingredients. In practical studies, liquid-liquid extractions are applied by using the separation funnel in liquid-liquid extractions, utilising the density difference between the two liquids. When the mixture is placed in the separation funnel, the liquid with a small density is collected at the top and the liquid with a large density is collected at the bottom. Substances with close densities are not easily separated. In such a case, it is necessary to increase the density of the water phase by saturating it with a salt such as NaCl or separation is achieved by shaking the separation funnel.

B) **Solid-Liquid Extraction**

Efforts to overcome problems encountered in classical extraction such as long extraction time, high cost, need for high purity solvent, necessity and difficulty of evaporating large amounts of solvent, low extraction selectivity and thermal degradation of temperature-sensitive components have led to the development of this technology (Chemat, 2017; Azmir et al, 2013). In solid-liquid extraction, one or more compounds in the solid phase are selectively dissolved by a liquid solvent and passed to the solvent phase. Solid-liquid extractions are applied in the preparation of various extracts used as drugs from various substances or fresh biological material, isolation and purification of analytical substances or substance mixtures.

Maceration

It is a word derived from the Latin word "to shake". Dried or wet, fresh plant parts are ground in a grinding machine and shaken vigorously with a certain amount of solvent for 5 - 10 minutes or left for 24 hours, after which the extract is filtered. The resulting filtrate is then dried under reduced pressure and redissolved.

Digestion

Digestion is a method of extracting bioactive components from plants using hot solvents between 40-60 °C. Water or alcohol can be used as solvent. Powdered plant materials are mixed extraction solvent and placed over water bath or in an oven.

Infusion

Infusion is the extraction process performed by adding boiling water to the substance divided into small pieces, heating on a boiling water bath for a while with frequent stirring, and filtering after cooling. The condition of sensitive substances affected by heat should be taken into account.

Decoction

It is the process of adding cold water to the disintegrated substance and filtering it while hot after boiling in a water bath at 90-100°C with a heating time of 30 minutes. The decoction of substances containing the active substance mucilage in plants such as flaxseed, marshmallow, hibiscus is done in the cold.

Percolation

It is the extraction process in which the solvent used is slowly passed through the substance separated into small pieces at a certain speed. Percolation is carried out in containers called "percolators". It can be in very small capacities (~ 50-100 g) as well as in very large capacities (several tonnes). The percolation process can be carried out at room temperature or at different temperatures by heating the percolator from outside with the help of a jacket.

C. Solid Sample Extraction Techniques

Soxhlet extraction method, pressurised liquid extraction method, superheated water extraction method, supercritical fluid extraction method, microwave extraction method, ultrasonic extraction method and solid phase extraction method (SPE).

Soxhlet Extraction Method (Continuous Extraction)

Soxhlet extraction is the process of continuously extracting phytochemicals using solvent in a hot environment. Plant materials, usually dried and powdered, are placed in an extraction tube and placed in the chamber of the

Soxhlet device in the Soxhlet extractor. The extractor consists of a glass bottle containing a condenser and solvent, which is cooled and heated. Extraction solutions such as ethanol or methanol are placed in the lower bottle. The solvent is evaporated by heating, and condensed in the condenser located at the top of the device. Phytochemicals are extracted with a reflux condenser. The main advantage of this method is that the extraction It is the process of evaporating and concentrating only the pure solvent to extract the solid material. Higher yields are obtained compared to extraction techniques based on maceration. (Patel, et al, 2019).

Super Critical Liquid Extraction Method

Supercritical Liquid Extraction, liquids used in the extraction process should have solubilisation, low viscosity, high diffusion and minimal surface tension properties in relation to density. These properties enable the extraction of compounds with higher efficiency (Sihvonen et al, 1999).

While the density of the liquid expands and decreases due to the heat effect, the density of the gas increases due to the increase in pressure. As the densities of the two phases approach each other, the differences between gas and liquid disappear. When approaching the critical point; while the density of the liquid decreases due to thermal expansions The density of the gas increases due to the increase in pressure. The densities of the two phases approach each other. Thus, the differences between gas and liquid disappear. Supercritical fluids have properties between liquid and gas. They have liquid-like densities and behave like a liquid solvent. They have good diffusion properties that give low viscosity and mass transfer properties. Their high relative density makes them a good solvent. The density of supercritical fluid depends on temperature and pressure. The energy requirement of the system is low. Surface tension coefficients and viscosities are low and therefore pumping costs are low. One of the most important properties of supercritical fluids is the absence of surface tension. The penetration of these gases into a substance is like a gas at high pressure. However, their dissolving properties are similar to liquid solvents. The dissolving power varies depending on temperature and pressure. The dissolving power of supercritical fluids is usually provided by increasing their density.

Critical temperature and pressure should not be too high, non-toxic. Should not leave undesirable residues, should not be explosive, should be cheap, should be easily separated. Carbon dioxide, nitrogen, methane, ethane, propane, ethylene, propylene, acetone, toluene, methanol, ethanol, ammonia, hexane and water are the supercritical fluids used. Among these, carbon dioxide is the ideal solvent that is increasingly being used because it has all the properties sought in a supercritical fluid.

It is used in isolation and purification of new products, molecular structure, phase behaviour, co-solvent effects, food technology (decaffeinated

coffee, decaffeinated tea, nicotine extraction), pharmaceutical technology, active substance quantification, obtaining monomers and residual solvents from polymers, microparticle formation. In supercritical flow extraction, fewer samples can be worked with compared to classical extraction methods. Recovery of supercritical fluid is possible (Lang and Wai, 2001).

Accelerated Solvent Extraction (ASE) Method

"Accelerated solvent extraction", called ASE in short, has gained importance in recent years due to the less use of solvents, high yield and short time. This method is a more reliable extraction method compared to Soxhlet extraction and maceration extraction performed with suitable solvents. In this method, an extraction cell made of stainless steel, first filled with the sample, is then filled with solvent and placed between layers of inert silica separated by cellulosic filter papers. The system is heated at increasing temperature and pressure for a predetermined period of time.

Pressurised Solvent (liquid) Extraction (PSE) Method

"Pressurised solvent extraction", called PSE in short, is a method used to obtain the desired components in solid samples using different solvents under high temperature and pressure. PSE is a method in which high pressure is applied to keep the solvent used in the method well above its boiling point. (Azmir et al, 2013). Since the substance is continuously treated with fresh solvent, there is an increase in mass transfer and as a result, the extraction rate increases and the time is shortened (Bautz et al, 1998).

Under high temperature conditions, the viscosity of solvents decreases and the capacity to wet the medium increases, thus increasing the solubility of the target components. BSE technique is a more advantageous solid-liquid extraction technique compared to other extraction methods in terms of solvent consumption, extraction efficiency and reproducibility in a shorter time (Kaufmann, et al, 2002).

Compounds that cannot be extracted with water under normal conditions can be extracted by changing the character of water with this technique. The advantages of extraction with water are that it is not harmful compared to organic solvents, water is an environmentally friendly and cheap solvent (Ibañez et al, 2012).

Before the sample to be subjected to the extraction process is placed in the extraction cell, the diffusion of the analyte from the sample to the solvent is generally increased by grinding and grinding into small pieces. In the grinding process, since the moisture in the sample may adversely affect the extraction process, drying the sample positively affects the extraction process. Especially when apolar solvents are to be used, moisture retaining agents such as Na_2SO_4, cellulose are placed in the extraction cell. (Gamiz - Gracia, L et al, 2000;

Kubatova, A, et al. 2001; Özel, M.Z et al, 2003; Deng, C.H et al, 2004; Deng, C.H, et al, 2005).

Microwave assisted extraction (MAE) Method

Microwave-assisted extraction (MAE) is a method in which microwave energy is used for heating the sample in contact with the solvent to take the analytes in the sample to the solvent. This process is a new method in which microwave energy is used in the extraction of natural products containing solvents. The frequency of the beams providing microwave energy is between 300 MHz and 300 GHz. During the extraction process, the temperature of the microwave energy increases the kinetics of the extraction by heating the solvent and the plant tissue in it. The advantages of the system are rapid heating, increased extraction efficiency and the scarcity of equipment used in the extraction of bioactive components from plant material (Cravottoa et al., 2008). The low viscosity of the solvent facilitates the distribution of ions and thus their dissolution. The extraction process involves the diffusion of solvents into the sample, followed by the separation of the solute and the release of solutes into the solvents. MAE is usually performed in a closed vessel, in which case the pressure increases and the solvent is heated to temperatures higher than the boiling point. For many solvents (such as acetone, acetone-hexane, dichlormethane-acetone) the temperature inside the vessel is 2-3 times the boiling point of the solvent (Camel et al, 2000).

Ultrasonic Extraction Method

Ultrasound-assisted extraction is a technique that uses ultrasonic waves to disrupt the plant cell wall and accelerate mass transfer to obtain bioactive ingredients in a shorter time and with higher efficiency. It is also an environmentally friendly technology with less energy consumption and less solvent usage(Vilkhu et al, 2008; Jadhav et al, 2009).

In ultrasound extraction method, acoustic vibrations are applied to the sample with frequencies above 20 kHz. When these vibrations pass through the liquid, cavity formation occurs. This void, caused by the ultrasonic energy, creates numerous small bubbles in the liquid medium and causes the solids to be mechanically shaken and causes the particles to break off. Sound waves are used in both solid and liquid sample preparation and favour the extraction, digestion and slurry formation of solid samples (Tadeo et al, 2007). The extraction of analytes from solid samples is performed by applying ultrasonic radiation to a water bath or by using devices such as a probe (Santos et al, 2007; Huertas-Perez et al, 2006).

In order to increase the extraction yield, it is necessary to optimise different factors such as solvent type, temperature and sonication amplitude conditions, other parameters are sonication time, sample particle size, sample

quantity and the devices used. Ultrasound-assisted extraction systems can also be static or dynamic. The use of dynamic extraction and the continuous exposure of the sample to fresh solvent in a dynamic system is advantageous, as analytes are removed as soon as they are transferred from the solid to the solvent. This increases the transfer of analytes from the sample matrix to the solvent. Extraction typically requires 20-200 mL of solvent and extraction time is in the range of 2 to 20 minutes.

Solid Phase Extraction Method (SPE)

In the mid-1970s, a new technique, solid phase extraction (SPE), was introduced. The solid phase extraction method is an economical sample preparation technique that is faster, uses less solvent and has no emulsion formation problem, since a small amount of sample is processed compared to classical liquid-liquid extraction. In the solid phase extraction method (SPE), samples of the desired density can be obtained with cleaner extract and high recovery rate. Samples to be analysed chemically contain many components other than the substance sought. For this reason, sample preparation is a very important step that should be applied before analyses to be performed with the help of devices such as high pressure liquid chromatography (HPLC), gas chromatography (GC), gas chromatography-mass spectrophotometry (GC-MS).

SPE is based on the principle of filling small, disposable extraction columns or disks with various retaining substances and passing liquid samples through the prepared columns and disks to concentrate the sample, exchange it and separate the liquid. In the solid phase extraction method (SPE), during the passage of the substance to be analysed through the column, a chemical interaction occurs between the molecules of the substance to be analysed and the trapping agent. The molecules of the sample to be analysed are bound to the active groups in the scavenger substances by ionic, hydrogen, dipole-dipole, dipole-induced dipole and induced dipole-induced dipole (Van der Waals) bonds. Thus, the sought substance, unwanted compounds in the matrix and solvents are separated from each other. Since the SPE method requires minimal evaporation (evaporation of the solvent in a solution), the formation of unstable samples is very rare. It allows a large number of samples to be processed simultaneously and reproducibly.

3. CONCLUSION

Today, extraction methods that are widely used in various industries and especially in the acquisition of bioactive compounds found in plants are very important. The active ingredients found in plants are also used in drug production, as food supplements, and in complementary medicine, and in obtaining them, it is necessary to select appropriate extraction conditions, for example, when type, time, conditions, cost and efficiency are considered.

For example, the environmentally friendly ultrasonic-assisted extraction method, which ensures that the desired bioactive components are obtained in a shorter time, with less solvent use and higher efficiency compared to classical techniques by ensuring the degradation of the cell wall in plants, is a widely used extraction method. In recent years, in addition to ultrasound-assisted extraction; effective methods such as microwave-assisted extraction, pressurized liquid extraction and supercritical flow extraction methods have been developed, and in addition to these methods, the above-mentioned extraction methods combined with classical extraction methods are also used. As a result, thanks to the restrictions and regulations imposed within the scope of minimum use and minimum environmental pollution in order to increase environmental pollution and the harm caused by the chemicals used, 'green extraction techniques' have been developed; It should be taken into account that new extraction techniques with less energy, less cost, less chemicals and less time have been described above and can be developed further.

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Chapter 2

MEDICINAL PLANTS EXTRACTS AND ALZHEIMER'S DISEASE

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1. INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease characterized by cognitive impairments and memory problems. Although the etiology of AD is not clearly known, environmental effects such as genetic factors, mental stress, nutritional habits and lifestyle are thought to be effective in the disease (Di Stefano et al, 2011). However, it is not only caused by these factors; accumulation of beta-amyloid (Aβ) plaques outside neurons (amyloid cascade hypothesis), neurofibrillary tangles formed by hyperphosphorylated tau proteins (tau hypothesis), cholinergic transmission (cholinergic hypothesis). In addition, it has been revealed that there are multifactorial disorders as a result of neuropathological manifestations such as oxidative stress, causing neurodegeneration (Schneider et al, 2009).

Amyloid castade hypothesis): Extracellular compartment of Aβ plaques and intracellular neurofibrillary. It is the formation of neurofibrillary tangles. During aging, excess Aβ decrease in production occurs, resulting in plaque formation.

Tau hypothesis: Neurofibrillary tangles, which are the neuropathological feature of AD, are produced by the hyperphosphorylation of a protein called Tau protein along with microtubules in the cell structure. While tau proteins can stabilize microtubules in pathways, hyperphosphorylation of tau proteins in Alzheimer's patients leads to the formation of neurofibrillary tangle filaments.

Oxidative stress: A common feature of neurodegenerative diseases is mitochondrial dysfunction and the overproduction of reactive oxygen species (ROS), which lead to oxidative stress. This stress results in damage to DNA, proteins, and other macromolecules, triggering neurotoxic events. The excessive production of oxidative agents, including ROS and free radicals, causes mitochondrial dysfunction and impairs the autophagic processes of mitochondria in AD patients.

Cholinergic hypothesis: The cholinergic system is effective in the progression of AD. Acetylcholine is abundant in brain synapses and is essential for memory formation. Acetylcholin levels have been shown to decrease in areas of the brain involved in cognition and memory. With the discovery that the cholinergic system is effective in the progression of AD, drugs that affect the acetylcholine enzyme began to be used in the treatment of Alzheimer's, and the most successful of these drugs were drugs called acetylcholinesterase inhibitors. Three FDA-approved acetylcholinesterase enzyme inhibitors (donepezil, rivastigmine and galatamine) and one N-methyl-D-aspartate receptor antagonist (memantine) are used in the treatment of AD. These drugs slow down cognitive and functional loss in AD by preventing the destruction of the acetylcholine enzyme released into the environment and increasing its amount (Kurban et al, 2024)

Studies on herbal active ingredients have gained momentum with the idea that modern medicine and complementary and alternative medicine methods that will improve the treatment of the disease and the dementia process can also contribute to the treatment. However, in drug efficacy studies of plants for treatment, extraction conditions such as the effectiveness of the material, temperature, time and method used are extremely important in obtaining bioactive components. Therefore, this chapter aims to present extraction techniques from medicinal plants used to obtain rich bioactive compounds that apply an important strategy in the treatment of neurological disorders.

2. SCREENING OF SOME PROMISING MEDICINAL PLANTS FOR ALZHEIMER TREATMENT

With increasing concerns about the side effects of synthetic drugs, there is an increasing trend towards the use of neuroprotective natural compounds that act through different metabolic mechanisms in order to prevent the progression of neurodegenerative diseases and improve the patient's quality of life. Because the drugs available for the treatment of AD are based on neurotransmitter or enzyme modulation. These drugs have side effects on patients, causing them to discontinue treatment. Due to the short lifespan of tacrin, it must be applied every day. Similarly, rivastigmine and galantamine need to be administered twice daily. Memantine, another medication that helps manage AD, can cause problems such as vomiting, constipation, confusion, and dizziness (Chin et al, 2022).

Medicinal plants and natural compounds; It slows down the developmental course and effects of AD by reducing β-amyloid level, inhibiting acetylcholinesterase, promoting neurogenesis, and also increasing neuroprotective, anti-inflammatory and antioxidant effects. Major classes of phytochemicals include polyphenols (flavonoids, tannins), lignins, lignans terpenoids, steroids and alkaloids. Curcumin, apigenin, genistein, ginkgolides, luteolin, melatonin, naringenin, piperine, quercetin, resveratrol, thymoquinone, S-allyl cysteine, eucalyptol, silibinin, epigallocatechin gallate, routine, hesperidin, celastrol, protopanaxatriol, viniferin, baikalein, ligustilide, sinomenin and honokiol are important bioactive compounds used in AD due to their anticholinesterase and anti-amyloidogenic activities (Gezici & Sekeroglu 2022).

For this reason, in order to present the protective and therapeutic effects of various herbal medicines on Alzheimer's, studies are being carried out to evaluate the role of some existing and routinely used medicinal plants in new drug modeling based on their extractions (Soheili et al, 2021). In this context, the extraction conditions and methods obtained from the roots, stems and leaves of some plant species known to have neuroprotective and anticholinesterase activity are presented below. Accordingly, considering the

effect of these plants in treatment, it is aimed to contribute by evaluating different extraction conditions. Extraction conditions of plants with AH mechanism of action in treatment are presented in Table 1.

***Lavandula angustifolia* L.**

Lavandula angustifolia L. commonly known as lavender, is an aromatic shrub belonging to the Lamiaceae family. The main components of lavender essential oil are linalool and linalyl acetate, while the aqueous extract of lavender mainly contains caffeic acid and luteolin. It has been stated in studies that lavender extracts show antioxidant and acetylcholinesterase activities. Accordingly, 250 g of dried lavender flowers were concentrated in 1000 mL of water at 100 ^{0}C by stirring, filtering and evaporating for 4 hours (Kashani et al, 2011). Considering the effect of *Lavandula angustifolia* flowers in treatment, studies on different extraction conditions were also examined by ultrasound-assisted extraction, rapid pressure extraction and subcritical liquid extraction. The solvents used were water and alcohol, glycerin and propylene glycol mixtures, and the phenolic components in the extracts were examined. These extracts were analyzed by high-performance thin-layer chromatography, attenuated total reflection. analyzed by infrared spectroscopy and Raman spectroscopy (Radulescu et al, 2017).

***Crocus sativus* L.**

Crocus sativus, a species of the *Iridaceae* family, also called saffron, is widely used in traditional medicine. Antioxidant activity of saffron, which is attributed to its neuroprotective effect, are phenolic and carotenoid compounds. Aqueous methanolic saffron extract may protect against AD by regulating acetylcholinesterase activity, thus improving cholinergic transmission and inhibiting Aβ aggregation. Since cholinergic changes are associated with cognitive deficits, it has been reported to be therapeutic approach for the treatment of AD (Hatziagapiou et al, 2019). In the study for extraction, the combined solvent ratios (v/v), total bioactive component and antioxidant activity values in different solvent systems and extraction time systems were determined through preliminary trial studies to maximize the total bioactive component and antioxidant activity values (Zarinkamar et al, 2017). Accordingly, A/E: (Acetone/Ethanol) (v/v, 50/50); A/S/M/E: (Acetone/Water/Methanol/Ethanol) (v/v/v/v, 25/25/ 25/25); A/M: (Acetone/Methanol) (v/v, 50/50);A/M/E: (Acetone/Methanol/Ethanol) (v/v/v, 30/40/30); A/ S: (Acetone/Water) (v/v, 50/50); (Water/Ethanol) (v/v, 50/50); E/M: (Ethanol/Methanol) (v/v, 50/50); S/E/M: (Water/Ethanol/Methanol) 30/30/40); S/M: (Water/Methanol) (v/v, 50/50) solvent mixtures were used. After grinding 2 g of saffron spice for each different solvent system, it was extracted in the dark for 2 hours in a shaking mixer set at 100 rpm (Chobdar et al, 2021).

Panax ginseng

Panax ginseng, from the Araliaceae family, is an important medicinal plant. One of the significant areas of research on *Panax ginseng* is its potential in combating neurodegenerative diseases such as AD. The inhibition of Aβ-induced neurotoxicity and the improvement of memory functions in experimental models highlight its potential as a therapeutic agent for AD and other neurodegenerative conditions. The root extract of ginseng has shown promising results in inhibiting the neurotoxicity induced by amyloid-beta (Aβ) peptides, which are a hallmark of AD (Razgonova et al, 2019). In the study where the aqueous extract of polyphenol-containing ginseng exhibited antioxidant activity, the dried materials were extracted from the solvents (water, methanol, ethanol, ethylene acetate and acetone) for 24 hours (Malathy et al, 2021).

Salvia miltiorrhiza

Salvia miltiorrhiza, is a perennial plant in the Lamiaceae family. It has been widely used in traditional Chinese medicine for centuries. The plant is native to China and Japan, where it has been used to treat various health conditions. *Salvia miltiorrhiza,* with its main active ingredient cryptotanshinone, offers significant pharmacological benefits, particularly in neuroprotection. Its anti-acetylcholinesterase, anti-neurotoxicity, and antioxidant properties make it a promising candidate for the treatment of AD and other neurodegenerative conditions. Therefore, in the study on its extraction from the plant, its roots were extracted using 50% ethanol (24 hours) at room temperature (22 ± 1 °C). The extract was then frozen at −55 °C and lyophilized. Phytochemical profile of ethanol extract of *Salvia miltiorrhiza* roots determined by HPLC and spectrophotometrically. The effect of standardized 50% Ethanol extract of *S. miltiorrhiza* (200 mg/kg) on the impairment of short-term and long-term memory was demonstrated (Ozarowski et al, 2017).

Magnolia officinalis

Magnolia officinalis which belongs to the *Magnoliaceae* family, shows anti-inflammatory, anti-oxidative and neuroprotective activities. The air-dried bark of *M. officinalis* (3 kg) was extracted twice with 95% (v/v) ethanol (four times as much as the weight, it showed an inhibitory effect on Aβ accumulation in the mouse brain (Lee et al. 2010). In another study, researchers reported that aqueous and methanol extracts of *Magnolia officinalis* reduced intracellular ROS formation (Lopez et al, 2009). Additionally, in another study, it was supported that *M. officinalis* has antioxidant properties. It has also been reported to play a powerful antioxidant role in mediators of oxidative stress (Safaeian et al, 2016).

Lawsonia Inermis L.

Lawsonia inermis (henna), which belongs to the *Lythraceae* family, grows in dry climates and hot weather in North and East Africa, the Arabian

Peninsula, the southern regions of the Middle East and South Asia, and has strong antioxidant, antiviral, antibacterial, hepatoprotective and antiparasitic properties. It is also used in traditional medicine as a memory enhancing substance. The antioxidant properties of *Lawsonia inermis* extracts have been supported by studies indicating their ability to reduce memory loss due to neurodegeneration and their mechanisms to modulate AD (Anwar et al, 2019). In this context, Dhouafli et al., a new compound with anti-Aβ42 aggregation properties was purified with 50% methanol, ethyl acetate and petroleum ether fractions using *Lawsonia inermis* leaves. They reported that it showed strong antioxidant activity when characterized by spectroscopic methods. In the study, the leaves of *Lawsonia inermis* are dried and then ground into a fine powder. To remove oily materials, powders were extracted in a Soxhlet extractor with hexane for 6h at 55°C. The powders were then re-extracted with methanol (99 %) at 65°C for 6h. The collected extract was evaporated to dryness under vacuum at 45°C (Dhouafli et al, 2019). Moreover, Amat-ur-Rasool et al reported that methanolic extracts of *Lawsonia inermis* extracted by soxhlet extraction method extracted the most potent cholinesterase inhibitor (Amat-ur-Rasool et al, 2020).

Nymphaea micrantha

Nymphaea micrantha, a newly discovered member of the Boraginaceae family. Molecules such as phytol, neophytadiene, decamethylene dibromide, crodacid, stigma-5-en-3-ol have been reported to have various pharmacological potentials. Phytol has been reported to have anti-inflammatory and leukocyte recruitment potentials and cytokine and oxidative stress inhibition activities. In the studies, acetylcholinesterase inhibitor and antioxidant activities were investigated in order to find out its effectiveness in neurological disorders. Acetylcholinesterase (GC-MS analysis and antioxidant activities were determined in methanolic extraction from *Nymphaea micrantha.* Anticholinesterase and antioxidant activities of plant samples were determined by the effects of DPPH and ABTS on free radicals. Its promising feature in designated treatment using its scavenging potential has been highlighted. (Imran et al, 2017).

Eleutherococcus senticosus

Eleutherococcu, a woody shrub species belonging to the *Araliacea* family. Its stem and root are used as a fatigue reliever and tonic. It has been reported that triterpene saponins obtained from *Eleutherococcus senticosus* leaves reduce forgetfulness and the progression of AD (Załuski, & Kuźniewski, (2016). It was concluded that *Eleutherococcu senticosus* extract prepared with water and methanol extract protected against cell death (Tohda and et al, 2008).

Thunbergia grandiflora

Thunbergia grandiflora is a dicotyledonous plant belonging to the Acanthaceae family and widely distributed in tropical and subtropical regions. It has been confirmed to have important pharmacological effects in the treatment of many diseases such as cataracts, malaria, diabetes, gout, rheumatism, pink eye and stomach complaints. In addition, *thunbergia grandiflora* leaves, which have been found to have a very strong effect in reducing oxidative stress, have compounds that will be tested as drugs by extraction with methanol and show strong anticholinesterase activity (Uddin and et al, 2016).

Rosmarinus officinalis L

Rosmarinus officinalis, commonly known as rosemary, is a perennial medicinal plant belonging to the Lamiaceae family, generally grown in the Mediterranean region. *Rosmarinus officinalis* extract consists of alkaloids, oils, terpenoids and flavonoids that have important pharmacological properties. Therefore, studies have reported that the free radical scavenging potential of *Rosmarinus officinalis* extracts and the strong antioxidant potential of *Rosmarinus officinalis* can be attributed to the phenolic compounds of plants. Literature studies have shown that polyphenols can inhibit acetylcholinesterase (Roseiro and et al, 2012; Kamli and et al, 2022). It has been reported that rosmarinic acid and ursolic acid, two of the bioactive components of *Rosmarinus officinalis*, extracted with ethanol have prononeurogenic effects, and extraction with 3 different solvents (ethyl-acetate, ethanol, aqueous) was evaluated with Soxhlet extractor and ethyl acetate had the highest phenolic compound among all extracts (Mirza, et al, 2021; Kamli and et al, 2022; Ozarowski and et al, 2013; Khalid, A and et al, 2020; Diken & Yılmaz 2022).

Pistacia terebinthus L

It is from the *Anacardiaceae* family and is more common in the southern and western regions of Turkey and is popularly called "menengic". In a study investigating the effect of *Pistacia terebinthus* (terebinthus) on Alzheimer's, researchers determined the antioxidant and enzyme inhibitory effects of hexane, acetone and ethanol extracts from different parts (bark, nuts and fruits) against acetylcholineesterase. For this, the samples were dried at room temperature and extracted with n-hexane by maceration at room temperature for 24 hours. (Akyuz and et al, 2022). Methanolic extraction was repeated twice, and then the fatty acid composition and antioxidant activities were examined by gas chromatography system and flame ionization detector (FID) (Durmaz& Gökmen, 2011); Ozcan and et al, 2020).

Syagrus romanzoffiana

Palm trees are common in subtropical and tropical regions of Latin America. The fruit of Jerivá (*Syagrus romanzoffiana*), a member of the Aracaceae family,

is approximately 3 cm long, fibrous, sweet and fleshy, orange-yellow in color, and has a high nutritional value due to its high lipid content. In the study, there are various chemical classes (phenolic acid) containing high fatty acids in both fruits and leaves. 39 metabolites (e.g. stilbenoids, flavones and lignans) were discovered. Its neuroprotective effects and inhibition of acidocholinesterase activity have shown comparable results to Aricept, a standard drug used by Alzheimer's patients (El-Hawary and et al, 2021; Andrade, A. and et al, 2020).

Curcuma longa L. (Zingiberaceae)

Turmeric, whose active ingredient is curcumin, is a yellow pigment obtained from the roots of the plant called *Curcuma longa*. Various studies have shown that curcumin, derived from the rhizome or roots of the turmeric plant, has anti-inflammatory, antioxidant and cholesterol-lowering properties. Dried plant material was solved of 45% ethanol. The solution was extracted 2 times by refluxing, at 75–85°C for 3 h. The extract was concentrated under reduced pressure at ~60°C and then dried in a vacuum dryer at ~60°C for 18 h. (Kim and et al, (2019). The extract has also been reported to improve the cognitive functions of Alzheimer's patients with its anti-inflammatory and anti-inflammatory properties as an antioxidant. In the literature, *Curcuma longa* has antioxidant, antimicrobial, anti-inflammatory properties. It has been reported that it has many pharmacological activities, including antidementia and antidiabetic activities, and can reduce β-amyloid plaques and delay the deterioration of neurons in patients (da Costa and et al, 2019).

Cassia obtusifolia

Assiae semen is the seed of *Cassia obtusifolia* L., an annual plant of the family Leguminosae. It has been used in traditional Eastern medicine to treat headaches and benefit the eyes by stabilizing and nourishing the liver, and has been reported to have neuroprotective effects in brain disease models. Regarding the extraction of the plant, it was extracted with 85% ethanol for 2 hours by ultrasonic extraction technique, then the resulting solution was filtered, concentrated under vacuum in a water bath, frozen and lyophilized. (Kim and et al, 2007). Extraction conditions. dried *Cassia obtusifolia* seeds were degreased with 95% ethanol for 2 days with stirring (500 rpm) at room temperature. The residue was mixed with 2 L ultrapure water (1:10, 1:10, 100 g) with stirring (500 rpm) for 6 hours at 80 °C. (Feng and et al, 2016).

Moringa oleifera

Moringa oleifera, commonly known as the drumstick tree, is a versatile and nutrient-rich plant from the Moringaceae family. It is widely cultivated in Africa and Asia, where it is valued for its various edible and medicinal parts, including bark, leaves, and flowers. MO has gained significant attention due to its potential health benefits and diverse applications. (Olorunfemı & Adewolu

2020). In the study on the effect of *Moringa oleifera* extract on Alzheimer's, it was obtained from its leaves. The obtained powder sample is boiled with 500 mL of boiling water for 5 minutes and filtered (Finbarrs-Bello and et al, 2022). *Moringa oleifera* seed kernels powder is extracted separately with 100 mL of methanol, acetone and water at room temperature for 48 hours. After 48 hours, it was filtered and the extract was concentrated, dried at low temperature under vacuum, and antioxidant activity was determined (Jahan et al, 2018).

Ginkgo Biloba

Ginkgo biloba is widely used in the treatment of early-stage AD, (Sierpina et al, 2003); Luo, 2001). Four extraction methods (maceration, reflux, shaker and soxhlet) were used in the study to obtain the relevant extracts. In the reflux method, extraction was carried out with 3 ml of concentrated HCl 5 mL of H_2O for 2.5 hours. Soxhlet extraction was performed in a soxhlet device at 60 °C for 6 h. Shaker extraction was performed at 200 rpm at 25°C. Extractions were performed with the same solid/solvent ratio between 5 g of ground leaf sample and 50 mL EtOH (99.7%, v/v). For maceration extraction, the extract was prepared at room temperature overnight. Concentrated extracts were dissolved in Methanol and sonicated at 40°C for 15 min (Sati et al, 2019).

Melissa officinalis

Melissa officinalis (lemon balm), is a perennial plant belonging to the Lamiaceae family. Native to the Mediterranean regions and Southern Europe, *Melissa officinalis* is a versatile medicinal plant with a wide range of therapeutic applications, especially for nervous and gastrointestinal disorders. Its anti-inflammatory, antioxidant, and neuroprotective properties make it a valuable component in phytotherapy. Ongoing research continues to explore and validate its efficacy and potential uses in modern medicine. It has anti-inflammatory, antioxidant, neuroprotective, cholinergic receptor binding capacity and anticholinesterase activity and has the potential to provide a natural treatment for AD (Olorunfemı and Adewolu,2020*).*

In studies on the extraction of the plant, the powder of the dried aerial parts (5 g) was extracted three times consecutively with 200 ml of dichloromethane, ethyl acetate, methanol and water after maceration at 4°C for 24 hours. Solvents were removed under vacuum to dryness on a rotary evaporator and aqueous extracts were lyophilized (López et al, 2009).

Corydalis ternata

Corydalis ternata, commonly known as three-leaved corydalis, is a medicinal plant belonging to the *Papaveraceae* family. It is native to East Asia, including regions such as Korea and China. This plant has been recognized for its various biological activities attributed to its major phytochemicals. Research has reported several significant biological activities of the phytochemicals

found in *Corydalis ternata*, including: Anti-memory, anti-cancer, anti-neuroinflammation, anti-hyperlocomotion.

In the study of *Corydalis ternata,* two primary standard components, coptisine and berberine, were quantitatively analyzed for their potential therapeutic effects, particularly in the context of AD (Kim et al, 2017). They also found that the methanolic extract of *Corydalis ternata*, extracted with water or methanol, significantly inhibited acetylcholineesterase. The combined effects of acetylcholinesterase inhibition, free radical scavenging, and neuroprotection suggest that *Corydalis ternata*, particularly its components coptisine and berberine, has significant potential as a candidate for AD treatment (Kim et al, 1999).

Garcinia hanburyi

The *Garcinia* genus belongs to the *Clusiaceae* family and is widely grown in tropical Asia, Australia, Polynesia and South Africa. Phytochemical studies of the extract showed the presence of phenols, alkaloids, steroids, resins and saponins. In the study showed that the extract from *Garcinia hanburyi* could inhibit acetylcholinesterase and butyrylcholinesterase activity (Chitra & Narayanan 2018). Butyrylcholinesterase inhibition of acetylcholinesterase was observed. Methanol extract prepared from the leaves of plant showed neuroprotective effects, including superoxide scavenging effects (70.65% inhibition at 100 g/ml concentration), protection against DNA damage (Supasuteekul et al, 2016).

***Leucojum aestivum* L**

The ability of the plant alkaloid Galantamine to reduce the action of acetylcholinesterase has led to its clinical use in the treatment of choline deficiency conditions in the brain. In the literature, the isolation of alkaloid components in *L. aestivum* is carried out using an acidic solvent extraction system and is used to isolate galantamine from the extract in pure form (Halpin et al, 2010). In the study conducted by Demir et al. regarding the extraction, the bulbs and leaves of the plant were freeze-dried at -65°C in a water bath at 40°C for 18 hours, and then the extract was concentrated using a rotary evaporator to obtain the crude extract. (Demir et al, 2022).

Narcissus

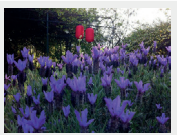
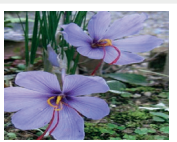
Narcissus is a genus belonging to the Amaryllidaceae family, comprising 80-100 wild species. The alkaloids present in these species have been recognized for their various pharmacological properties, including antiviral, antitumoral, and acetylcholinesterase inhibitory activities (Lisa-Molina and et al, 2023; de Andrade et al, 2012). A study investigated the acetylcholinesterase inhibitory activities of twenty-six methanolic extracts of *Narcissus* plant species. The evaluation was conducted using a microplate assay, which is a standard

method for screening enzymatic activity. Additionally, *narcissus* extracts were analyzed by HPLC for the content of four alkaloids that were found to exhibit the highest acetylcholinesterase inhibitory activity. Triturated tissues (50 mg) were extracted with methanol for 24 h by sonication for 30 min every 8 h during this 24-h ultrasonic bath at room temperature (Ingkaninan and et al, (2000; Rhee and et al, 2001; Bores and et al, 1996; López and et al, 2002). The study revealed that several methanolic extracts from *narcissus* species showed significant acetylcholinesterase inhibitory activity. This suggests that these extracts, and potentially the individual alkaloids within them, could be useful in the development of treatments for neurodegenerative diseases such as AD.

Camellia japonica

Camellia japonica, belonging to the Theaceae family, is a plant commonly cultivated in the southern coastal areas of Korea and frequently found in Korean gardens. This plant has a rich history of use in traditional folk medicine in both Korea and Japan, where it is valued for its tonic properties and its ability to treat various ailments such as inflammation and stomatic problems. A study by Jeong and colleagues investigated the potential health benefits of *Camellia japonica,* particularly its antioxidant activity and its implications for neurodegenerative diseases such as AD. The study involved suspending 100 grams of powdered camellia leaves and extracting them with water at 100°C (Jeong and et al, 2000).

Table 1. Extraction Conditions of Plants with AD Mechanism of Action in Treatment

Medicinal plants (Family)	Bioactive constituents	Extraction	Mechanism of Effect	References
 *Lavandula angustifolia (Lamiaceae)*	Linalool, tannins, linalyl acetate, camphor, coumarins, triterpenes, flavonoid	Material:300 g of dried leaves and flowers Solvent: Water Time: 4h Heat: 100 °C Method: Water bath.	Acetylcholinesterase	Kashani and et al, 2011; Radulescu and et al, 2017; Soheili & Salami 2019); Akbar, S. (2020).
 *Crocus sativus L (Iridaceae)*	Crocin, crocetin, picrocrocin, and safranin	Material: 2 g saffron Solvent: Ethanol, methanol water (0-100)% Time:2 h Heat: At room temperature Method: Shaker exraction	Acetylcholinesterase, preventing the accumulation of beta-amyloid (Aβ) plaques	(Chobdar Rahım and et al, 2021). Akbar, S. (2020).
 *Panax ginsengi (Araliaceae)*	Ginsenosides, gintonin	Material: Root(100 g) Solvent: Water, methanol, ethanol, ethylene acetate and acetone) Time: 24 h Heat: At room temperature Method: Maceration	Oxidative stress	(Malathy and et al, 2021) Wikipedia contributors. (2024, April 29). Panax ginseng. In *Wikipedia, The Free Encyclopedia*. Retrieved 11:06, June 6, 2024, from https://en.wikipedia.org/w/index.php?title=Panax_ginseng&oldid=1221438997

 *Manolya officinalis (Magnoliaceae)*		Material: Air dried bark Solvent:%95 (h/h) ethanol) Time: 72 h Heat: at room temperature Method: Maceration	preventing the accumulation of beta-amyloid (Aβ) plaques Oxidative stress	(Lee and et al, 2010); Akbar, S. (2020). Wikipedia contributors. (2022, October 29). Magnolia officinalis. In *Wikipedia, The Free Encyclopedia*. Retrieved 11:06, June 6, 2024, from https://en.wikipedia.org/w/index.php?title=Magnolia_officinalis&oldid=1118930706
 *Lawsonia Inermis (Lythraceae)*	Phytol, pseudoephedrine, aspidofractinine-3-methanol, phenol, 2,6-bis (1,1-dimethyl ethyl)-4-methyl, methylcarbamate	Material: 300g plant Solvent: %99 methanol Time: 6 h Heat: 55-65°C Method: Soxhlet	Acetylcholinesterase Oxidative stress	(Dhouafli and et al, 2019; Mir and et al, 2019) ;Akbar, S. (2020).
 *Thunbergia grandiflora (Acanthaceae)*	ridoid glycosides, isounedoside, and grandifloric acid	Material: Air-dried leaves and flowers (700g) Solvent: MeOH Time: 1 week Heat: 25 °C Method: Maceration	Acetylcholinesterase Oxidative stress	(Uddin et al, 2016. Wikipedia contributors. (2024, April 2). Thunbergia grandiflora. In *Wikipedia, The Free Encyclopedia*. Retrieved 11:05, June 6, 2024, from https://en.wikipedia.org/w/index.php?title=Thunbergia_grandiflora&oldid=1216867656
 *Rosmarinus officinalis (Lamiaceae)*	alkaloids, oils, terpenoids and flavonoids	Material: 1000 g plant Solvent: Water, ethyl-acetate, ethanol Time:24 h, 48 h Heat: 25 °C'de Method: Soxhlet extraction	Acetylcholinesterase Oxidative stress	(Mirza and et al,2021) (Kamli and et al, 2022; Ozarowskiet al, 2013) Wikipedia contributors. (2024, June 1). Rosemary. In *Wikipedia, The Free Encyclopedia*. Retrieved 11:04, June 6, 2024, from https://en.wikipedia.org/w/index.php?title=Rosemary&oldid=1226725587

 *Pistacia terebinthus (Anacardiaceae)*	quercetin and α-tocopherol such as phenolics and flavonoids	Material: Fruit peels, nuts and whole fruits) 500 g Solvent: Hexane, acetone and ethanol Time: 24h Heat: At room temperature Method: Maceration	Oxidative stress		(Akyuz and et al, 2022). Wikipedia contributors. (2024, May 18). Pistacia terebinthus. In *Wikipedia, The Free Encyclopedia*. Retrieved 11:03, June 6, 2024, from https://en.wikipedia.org/w/index.php?title=Pistacia_terebinthus&oldid=1224462547
 *Curcuma longa (Zingiberaceae)*	Curcumins, flavonoids, phenols	Material: 500 g of turmeric rhizome powder Solvent: 45% ethanol Time: 3 h Heat: 75-85 C Method: Maceration	Preventing tau protein aggregation		(Kim et al, *2019*; Akbar, S. (2020).
 *Moringa oleifera* ***Moringacea***	carotenoids, polyphenols, phenolic acids, flavonoids, alkaloids, glucosinolates, isothiocyanates, tannins and saponins	Material: Oleifera seed, Leaf Solvent: Water Time: 5 min Heat: 100°C Method: Maceration	Acetylcholinesterase Oxidative stress		(Hossain and et al, 2018) Wikipedia contributors. (2024, May 6). Moringa oleifera. In *Wikipedia, The Free Encyclopedia*. Retrieved 11:02, June 6, 2024, from https://en.wikipedia.org/w/index.php?title=Moringa_oleifera&oldid=12224799

 *Ginkgo Biloba* Ginkgoaceae	the flavone glycosides and the terpene lactones. flavonoid	Material: 5 g grounded leaf sample 5 g Solvent: EtOH (99.7%, h/h) Time: 6 h Heat: 25°C Method: Shaker extraction, Soxhlet extraction maceration	Oxidative stress	(Sati and et al, 2019; Drieu, 1988). Wikipedia contributors. (2024, May 14). Ginkgo biloba. In *Wikipedia, The Free Encyclopedia.* Retrieved 11:02, June 6, 2024, from https://en.wikipedia.org/w/index.php?title=Ginkgo_biloba&oldid=1223849312
 *Melissa officinalis* , Lamiaceae	flavonoids (luteolin, apigenin, quercetin, kaempferol glycosides), monoterpene glycosides, polyphenols (rosmarinic acid, chlorogenic acid, caffeic acid, hydroxyl cinnamic derivatives) and triterpenes	Material: (5 g) Solvent: Dichloromethane, ethyl acetate, methanol and water Time 24 h. Heat:4°C Method: Maceration	Acetylcholinesterase Oxidative stress	(López and et al, 2009). Akbar, S. (2020)..
 *Narcissus (Amaryllidaceae)*	Alkoloids galantamine	Material: (50 mg) plant Solvent: Methanol Time: 30 min every 8 hours during this 24-hour period Heat: At room temperature Method: Ultrasonic bath	Acetylcholinesterase Oxidative stress	López and et al, 2002; Ingkaninan , A. Hazekamp , CM de Best , H. Irth , UR Tjaden , R. van der Heijden , J. van der Greef , R. Verpoorte Wikipedia contributors. (2024, May 26). Narcissus (plant). In Wikipedia, The Free Encyclopedia. Retrieved 11:00, June 6, 2024, from https://en.wikipedia.org/w/index.php?title=Narcissus_(plant)&oldid=1225740192
 *Camellia japonica*	polyphenolic compounds containing catechins	Material: Powdered leaves (100 g) Heat: 100° C Solvent: Water Method: Suspension	Oxidative stress	(Jeong and et al, 2010). Wikipedia contributors. (2024, June 4). Camellia japonica. In *Wikipedia, The Free Encyclopedia.* Retrieved 10:59, June 6, 2024, from https://en.wikipedia.org/w/index.php?title=Camellia_japonica&oldid=1227191886

3. CONCLUSION

The role of plants in the treatment of diseases has been extremely important from past to present. In order to minimize the use of chemical drugs in treatment or to increase the synergistic effect of the drug, the tendency to obtain drugs naturally from chemicals has been increasing in recent years. As plant therapeutic agents, flavonoids, phenolic compounds, alkaloids, flavanols, flavanols, terpenes, steroids and various other secondary plant metabolites obtained from root leaves and stems have shown effective results in treatment. For this purpose, it is important to completely exceed the extraction conditions used and obtain high yields. This leads to increased effectiveness and decreased toxicity. In order to reduce the side effects of drugs currently used to treat AD and to investigate alternative treatments, plant extracts and their bioactive components have been extensively studied for their protective effects against this debilitating condition. It is promising that plant extracts show protection against various pathological events and markers associated with AD, such as amyloid-beta (Aβ) plaques and tau protein tangles. Therefore, the extraction conditions of plant bioactive components are crucial for optimizing their effectiveness in treatment. Therefore, in this chapter, the effectiveness of some plants used in AD treatments under different extraction conditions is presented.

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Chapter 3

MEDICINAL PLANTS USED IN THE TREATMENT OF PARKINSON'S DISEASE AND EXTRACTION METHODS

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1. INTRODUCTION

Parkinson's disease, which is included in the category of neurodegenerative diseases and whose most common and visible symptoms are tremors and slowness, is a movement disease that occurs due to the loss of cells that produce dopamine in the brain.

Parkinson's disease is named after the English doctor James Parkinson, who first described the disease in 1817. It is a disease that is more common in older ages (between 40-70 years of age) and can also be seen at younger ages (between 20-40 years of age). Parkinson's disease is not a contagious disease; genetic and environmental factors may play a combined role in the emergence of the disease. Subtypes in which genetics play a dominant role are generally present in cases where the disease begins at a young age. Parkinson's, which is diagnosed in approximately 7 million people today and is the second most common neurological disease after Alzheimer's, is thought to affect the lives of 18 million people in 2040 with the increasing elderly population. Its incidence in men is 50% higher than in women.

Dopamine is a substance that facilitates electrical communication between brain cells. The area of the brain that works with dopamine is a region that allows people to adjust their movements as they wish. The cause of Parkinson's disease is dopamine deficiency as a result of cell loss or damage to the cells that produce dopamine in the brain. Symptoms of Parkinson's disease vary among patients, especially in the early period of the disease.

The symptoms of the disease cause the person's quality of life to decrease significantly.

Due to the slowly progressive nature of the disease, Parkinson's patients can live for many years with correct diagnosis and treatment. Parkinson's is known not for its sudden onset, but for its symptoms to manifest themselves over time. The first symptoms usually encountered in people experiencing Parkinson's symptoms are as follows:

Slowness in walking, tendency to shuffle on one side when walking,

Unilateral decrease in arm swinging movement that accompanies walking,

Acceleration forward with the feeling of being pushed from behind while walking,

It is difficult to stand up from low places,

Dullness in facial expression,

One hand moves slower than the other,

Letters getting smaller and smaller while writing,

Unexplained shoulder pain.

Parkinson's is examined in two ways: movement-related and non-movement-related symptoms. Movement-related symptoms of this disease include tremors, slow movements, contractions in muscles and limbs, forward bending, and gait disorders. Non-movement-related symptoms can be listed as loss of sense of smell, anxiety, depression, constipation, sleep and sexual dysfunction.

Although various medications are used in the treatment of Parkinson's disease, there is no permanent cure today. The drugs used in treatment have side effects. In research conducted either in a laboratory environment or with treated patients; phytotherapy, apitherapy and aromatherapy have been shown to be effective in the treatment of Parkinson's disease. It has been determined that the active ingredients of plants in terms of phytotherapy, products obtained from beehives in terms of apitherapy, and some plants used in aromatherapy are useful in the treatment of Parkinson's disease. (Yunusoğlu et al., 2022).

2. MEDICINAL PLANTS USED IN THE TREATMENT OF PARKINSON'S DISEASE

Medicinal plants were discovered thousands of years ago by different nations around the world. These plants have been used by people for centuries because they are effective in treating diseases and have relatively fewer side effects compared to pharmaceutical formulations. Studies have shown that the antioxidant activity of phenolic compounds found in medicinal plants has benefits for human health. Scientists continue to work to identify undiscovered plants and their active ingredients. It is now better understood that plants, along with the drugs used in the treatment of diseases, are also effective in these treatments.

In this review, the effects of medicinal plants and their antioxidant activities in the treatment of Parkinson's disease were investigated (Chan et al., 2009; Gao et al., 2009; Noelker et al., 2005).

It has been reported by researchers in their articles that the active substances obtained as a result of the extraction of the medicinal plants we investigated in our study prevent and treat Parkinson's disease. Most of the studies we reviewed focused on the antioxidant, anti-inflammatory and antiapoptotic properties of these plants (Rabiei et al., 2019).

The most commonly used medicinal plants in the treatment of Parkinson's disease, their extraction methods, and the methods used by scientists to detect the neuroprotective effects of plants are summarized as follows:

Carthamus tinctorius L.

Carthamus tinctorius L. is from the Asteraceae family and is also known as field saffron, parrot seed, dyer's safflower, and haspir. Its homeland is the Arabian Peninsula and it has spread to countries such as Iran, India and Pakistan.

Carthamus tinctorius L. contains flavonoids that have been reported to be effective in neurodegenerative disease models. It has been reported that flavonoids in the aqueous extract of this plant exhibit strong biological activities. It has been shown that kaempferol derivatives obtained from *Carthamus tinctorius* L. can bind DJ-1, a protein associated with Parkinson's disease, and a flavonoid extract obtained from this plant stimulates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. It was reported in the studies of Ablat et al. that it showed neuroprotective effects in mice with Parkinson's disease (Ablat et al., 2016).

Table 1. Methods used for the extraction of *Carthamus tinctorius L.*

Common name	**Extraction method**	**Extraction conditions**	**Methods**	**References**
Carthamus tinctorius L.	Aqueous extraction	Dried flowers of *C.tinctorius* were extracted by refluxing with water at 60 °C for 45 minutes.	HPLC-DAD	(Fan et al., 2009)
Carthamus tinctorius L.	Ethanol extraction	*C.tinctorius* was soaked in ethanol for 2-3 hours and extracted with heat under reflux twice.	HPLC and LC/MS	(Ablat et al., 2016)
Carthamus tinctorius L.	Ethanol extraction	Dried flowers of *C.tinctorius* were extracted twice with ethanol.	HPLC	(Ablat et al., 2022)

Tinospora cordifolia

It is a genetically diverse, large, deciduous, climbing shrub with typical greenish-yellow flowers, belonging to the Menispermaceae family, found at high altitudes.

As a result of extractions using various parts of plants such as roots, stems, leaves and flowers, alkaloids, steroids, diterpenoid lactones, aliphatics and glycosides can be separated from the plant. *Tinospora cordifolia* plant has attracted great attention from researchers worldwide due to its medicinal properties, as it shows a wide range of activities, including antioxidant activity. The study by Kosaraju et al. demonstrated the neuroprotective role of *Tinospora cordifolia* ethanolic extract prepared from the aerial parts of the plant in the 6-hydroxy dopamine-induced Parkinson's disease rat model (Kosaraju et al, 2014).

The benefits of *Tinospora cordifolia* extracts against various diseases, including neurodegenerative diseases, have been reported in articles. To examine the effect of *Tinospora cordifolia* extracts, scientists studied aqueous,

butanol, ethanol and alcoholic extracts prepared from different parts of the plant on various neurodegenerative in vitro models. Because oxidative stress is directly associated with neurodegenerative diseases such as Alzheimer's and Parkinson's disease, alleviating oxidative stress may prevent the progression of these diseases. Ethanol extract prepared from the stems of *Tinospora cordifolia* and n-butanol fraction, 1,1-Diphenyl-2-picrylhydrazyl (DPPH), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS), and has been reported to have antioxidant activity that effectively reduces nitric oxide (NO) free radical production (Polu et al., 2017).

Table 2. Methods used for the extraction of *Tinospora cordifolia*

Common name	Extraction method	Extraction conditions	Methods	References
Tinospora cordifolia	Ethanol extraction	Dried plant material was extracted by filtration with 70% ethanol.	HPTLC	(Kosaraju et al., 2014)
Tinospora cordifolia	Maceration Aqueous extraction	Dried plant material was extracted by filtration with 70% ethanol. The stem of the plant was pulverized by the maceration method, avoiding exposure to sunlight to prevent loss of active ingredients. It was dissolved in distilled water and extracted.	Test kits	(Birla et al., 2019)
Tinospora cordifolia	Soxhlet extraction	Shade-dried and coarsely powdered *T.cordifolia* stems were extracted with absolute ethanol via conventional soxhlet extraction at 60°C.	MTT and SRB assay	(Polu et al., 2017)
Tinospora cordifolia	Soxhlet extraction	The stem of *T.cordifolia* was separated from the leaves, dried in the shade and ground into a coarse powder. This powder was extracted with methanol in a soxhlet extractor.	Spectrophotometry	(Pushp et al., 2013)
Tinospora cordifolia	Soxhlet extraction	The powdered plant was extracted with ethanol and methanol in a soxhlet device for approximately 48 hours. The solvent was then evaporated in a rotary evaporator.	Spectrophotometry	(Upadhyay et al., 2013)
Tinospora cordifolia	Hydroalcoholic and Aqueous extraction	Hydroalcoholic extract and water extract of dry leaves were prepared by suspending dry leaf powder in ethanol and double distilled water, respectively.	LC-MS/MS	(Reddi & Tetali, 2019)

Chaenomeles speciosa

Chaenomeles speciosa, a member of the Rosaceae family, is a thorny, deciduous or semi-evergreen shrub native to East Asia.

Zhao et al. proved the antiparkinsonian effects of *Chaenomeles speciosa* with in vivo and in vitro analyses. In neurobehavioral studies, the extract attenuated 6-hydroxydopamine-induced hemi-parkinsonian rotation in rats

time-dependently and dose-dependently attenuated 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine-induced deficits in mice during endurance performance (Zhao et al., 2008).

Table 3. Methods used for the extraction of *Chaenomeles speciosa*

Common name	Extraction method	Extraction conditions	Methods	References
Chaenomeles speciosa	Aqueous extraction	The plant sample was washed, crushed and homogenized. The crushed aggregate was diluted with distilled water and heated at 100 °C for 1 hour and an aqueous extract was obtained.	Cell culture	(Zhao et al., 2008)
Chaenomeles speciosa	Methanol extraction	The twigs of *C.speciosa* were extracted with 80% methanol under reflux, filtered, and the methanol extract was suspended in distilled water.	HPLC	(Suh et al., 2017)

***Portulaca oleracea* L.**

Portulaca oleracea L. is a plant from the Portulacaceae family and is a vegetable whose leaves are used as salad or cooked like spinach. Although its origin is the Middle East and India, it is found in many parts of the world.

Portulaca oleracea L. is a species with antioxidant and neuroprotective activities. The effects of *Portulaca oleracea* L. extracts were investigated in the 6-hydroxydopamine rat model of Parkinson's disease. In conclusion, it has been shown that aqueous and ethanolic extracts of *Portulaca oleracea* L. can reverse 6-hydroxy dopamine-induced behavioral motor deficits and neuronal loss, and these effects may be related to their antioxidant activities and bioactive compounds. Therefore, *Portulaca oleracea* L. has been reported to be an important plant with therapeutic potential for the treatment of neurodegenerative diseases (Martins et al., 2016).

Table 4. Methods used for the extraction of *Portulaca oleracea L.*

Common name	Extraction method	Extraction conditions	Methods	References
Portulaca oleracea L.	Aqueous extraction	The plant material was boiled in distilled water at 80 °C for 60 minutes, crushed with a blender apparatus and lyophilized under vacuum.	HPLC	(Hozayen et al., 2011)

Portulaca oleracea L.	Ethanol extraction	The plant material was extracted with 100% ethanol at room temperature in a dark, closed container for one week, concentrated using a rotary evaporator, and then lyophilized.	HPLC	(Wanyin et al., 2012)
Portulaca oleracea L.	İnfusion	The juice of *P.oleracea* was prepared by crushing, kept in the refrigerator for 24 hours, and crude extract was obtained after crushing and infusion.	Spectrophotometry	(Abdel Moneim, 2013)

***Mucuna pruriens* L.**

Mucuna pruriens L. is a widely naturalized and cultivated tropical legume in the family Fabaceae, native to Africa and tropical Asia.

Various parts of *Mucuna pruriens* L., such as seeds, leaves, and stems, exhibit potent neuroprotective properties. Among the different parts, the seeds are widely used for anti-parkinson's due to its higher percentage of Levodopa. Besides its anti-parkinsonian activity, the neuroprotective potential of *Mucuna pruriens* L. has also been investigated in an ischemic stroke model. Rai et al., have conducted several clinical studies on the anti-parkinsonian activity of *Mucuna pruriens* L. on patients with Parkinson's disease, which showed convincing results (Rai et al., 2020).

Medications such as levodopa cause involuntary movements in many patients with Parkinson's. Used in Ayurveda to treat Parkinson's disease, *Mucuna pruriens* is known to provide benefits that treat Parkinson's without triggering involuntary muscle movements. Lieu et al. investigated the effects of aqueous extract of *Mucuna pruriens* seed powder. As a result of their studies, they reported that the effects of aqueous extract of *Mucuna pruriens* seed powder were promising for patients with Parkinson's disease

In their study, Cassani et al. analyzed 25 samples from Africa, Latin America and Asia of the *Mucuna pruriens* plant, which grows in all tropical regions and is a source of Levodopa, for patients who cannot afford this drug even though the drug called Levodopa is used for treatment purposes in Parkinson's disease. In their study, they measured the Levodopa content in dried, roasted and boiled *Mucuna pruriens* L. plant preparations (Cassani et al., 2016).

Table 5. Methods used for the extraction of *Mucuna pruriens L.*

Common name	Extraction method	Extraction conditions	Methods	References
Mucuna pruriens L.	Aqueous extraction	*M.pruriens* endocarp powder was prepared by mixing in sterile water for 30 minutes.	HPLC	(Lieu et al., 2010)
Mucuna pruriens L.	Aqueous extraction	Drying: Raw seed samples were prepared by grinding in a mortar. The final powder was suspended in acidic water and extracted with the help of ultrasound for 24 hours. Boiling: The seeds were extracted by soaking in water for 15 hours and boiling for 90 minutes. Roasting: Roasting on the stove at 150° for 15 minutes, then decorticated.	HPLC-MS	(Cassani et al., 2016)
Mucuna pruriens L.	Aqueous extraction	Seed powders were soaked in autoclaved distilled water, mixed and left overnight. The extract was dried in a rotary vacuum evaporator.	RP-HPLC	(Rai et al., 2017)
Mucuna pruriens L.	Maceration (with ethanol)	*M.pruriens* seeds were dried in the sun for three days and crushed into powder. The extract was obtained by softening in ethanol:water for 3 days.	HPLC-UV	(Sardjono et al., 2024)
Mucuna pruriens L.	Soxhlet extraction	Roasted *M.pruriens* seeds were extracted by continuous extraction with a Soxhlet apparatus using 80% ethanol as the solvent.	HPLC-UV/VIS	(Rachsee et al., 2021)
Mucuna pruriens L.	Ethanol extraction	Dried seed powder was heated under reflux with ethanol/water mixture for 1 hour, evaporated under vacuum and lyophilized.	LC-MS/MS	(Denne et al., 2023)

***Hyoscyamus niger* L.**

Hyoscyamus niger L., from the Solanaceae family, is used in Ayurveda, the traditional Indian medicine system, and in nervous system disorders in the Chinese medicine system. The neuroprotective potential of methanol extract of *Hyoscymus niger* seeds was evaluated in mice (Khatri & Juvekar, 2015).

Table 6. Methods used for the extraction of *Hyoscyamus niger L.*

Common name	Extraction method	Extraction conditions	Methods	References
Hyoscyamus niger L.	Methanol extraction	Dried *H.niger* seeds were pulverized into fine powder and extracted with methanol for 72 h, and the solvent was evaporated in a vacuum rotary evaporator.	LC-MS HPLC-UV	(Khatri & Juvekar, 2015)
Hyoscyamus niger L.	Petroleum ether and aqueous methanol extraction	*H.niger* seeds were dried in the shade for three days and then turned into powder. After waiting in petroleum ether for 72 hours, the petroleum ether was evaporated in a vacuum rotary evaporator and then kept in aqueous methanol for 72 hours and the solvent was evaporated in the same way.	LC-MS and HPLC-electrochemical	(Sengupta et al., 2010)
Hyoscyamus niger L.	Percolation (with methanol)	100 g of sliced, air-dried H.niger L. seeds were ground into powder. The powder was extracted with 80% aqueous methanol for 72 hours by percolation method, and the methanolic extract was concentrated to dryness under reduced pressure in a rotary evaporator.	Test kits	(Reza et al., 2009)

Hibiscus asper

Hibiscus asper is a traditional plant from the Malvaceae family, grown in tropical regions of Africa and also used as an antidepressive medicine. There is little scientific data on the effectiveness of this herb (Foyet et al., 2011).

Table 7. Methods used for the extraction of *Hibiscus asper*

Common name	Extraction method	Extraction conditions	Methods	References
Hibiscus asper	Maceration	Leaves of *H.asper* were dried in the shade, turned into powder, and softened in 90% methanol at 25 °C for 5 days.	Spectrophotometry	(Foyet et al., 2011)

Gynostemma pentaphyllum

Gynostemma pentaphyllum belongs to the genus Gynostemma in the family Cucurbitaceae, which is also widespread in Southern and Eastern Asia.

It is used as an herbal tea and is believed to have healing properties for disorders such as depression and anxiety. The main components of *Gynostemma pentaphyllum* have been isolated and numerous gypenosides, but their in vivo functions for medical applications, especially antioxidant activity, have not been fully elucidated (Choi et al., 2010).

Table 8. Methods used for the extraction of *Gynostemma pentaphyllum*

Common name	Extraction method	Extraction conditions	Methods	References
*Gynostemma pentaphyllu*m	Ethanol extraction	Air-dried leaves of *G.pentaphyllum* were extracted with ethanol (70%).	HPLC	(Choi et al., 2010)
Gynostemma pentaphyllum	Ethanol extraction	Air-dried leaves of *G.pentaphyllum* were extracted with water and ethanol (80%), respectively, and then the water and ethanol extracts were evaporated to dryness.	HPLC	(Shin et al., 2014)
Gynostemma pentaphyllum	Soxhlet (kloroform), Maceration (ethanol) and lyophilization	Powdered *G.pentaphyllum* was extracted with chloroform using a Soxhlet apparatus and macerated in ethanol overnight. The residue was extracted twice with distilled water for 2 h at 80 °C and then lyophilized to obtain crude polysaccharides.	Cell culture, detection kits, Elisa test	(Deng & Yang, 2014)

Alpinia oxyphylla fructus

Alpinia oxyphylla, sharp-leaved galangal, is a species of ginger from the Zingiberaceae family, native to East Asia. It was first identified by Friedrich Anton Wilhelm Miquel. *Alpinia oxyphylla fructus* is the dry ripe fruit of *Alpinia oxyphylla* Miq. It is a plant that has important therapeutic effects in Alzheimer's disease, Parkinson's disease, depression, learning and memory disorders and other nervous system diseases.

Table 9. Methods used for the extraction of *Alpinia oxyphylla fructus*

Common name	Extraction method	Extraction conditions	Methods	References
Alpinia oxyphylla fructus	CCl_4 and Ethanol extraction	Dried *A.oxyphylla fructus* was ground into powder, the powders were degreased with carbon tetrachloride for 24 hours, filtered and the degreased dry powder was extracted with 70% ethanol solution.	Cell culture, detection kits, Elisa test	(Zhou et al., 2023)
Alpinia oxyphylla fructus	Ethanol extraction	Dried plant material was pulverized in an electric blender, 80% aqueous ethanol was added, and sonicated in an ultrasonic bath at 50°C for 30 min. The residue was extracted two more times with 80% aqueous ethanol.	HPLC-UV LC-MS	(Zhang et al., 2012)

Bacopa monnieri L.

Bacopa monnieri L. is a perennial, creeping plant from the Plantaginaceae family, native to the wetlands of southern and eastern India, Australia, Europe, Africa, Asia and North and South America. *Bacopa monnieri* L. is a nerve tonic widely used in the traditional Indian medical system Ayurveda. *Bacopa monnieri* L., a medicinal herb in Ayurveda, is widely known for its ability to enhance memory and improve brain functions.

Table 10. Methods used for the extraction of *Bacopa monnieri L.*

Common name	Extraction method	Extraction conditions	Methods	References
Bacopa monnieri L.	Ethanol extraction	Powdered plant material was cold extracted with 90% ethanol.	Spectrophotometry	(Shobana et al., 2012)
Bacopa monnieri L.	Ethanol extraction	The plant was dried in the shade until it turned into powder and extracted with 95% ethanol three times. The extract was filtered and concentrated under reduced pressure in a Buchi rotavapor.	test kits	(Swathi et al., 2013)
Bacopa monnieri L.	Aqueous and Ethanol extraction	After the extraction with water, the water in the aqueous extracts was removed, the extract was extracted with ethanol three times, and after the solvent was evaporated, the residue was softened with acetone.	Spectrophotometry	(Jyoti & Sharma, 2006)
Bacopa monnieri L.	Used in powder form	Fresh leaves of *B.monnieri* were dried in the shade and turned into powder. Leaf powder has been used in this manner for inclusion in the commercial powdered diet. The powder was then subjected to physical and chemical analysis.	HPLC	(Shinomol, 2011)

Althaea officinalis L.

Althaea officinalis L. belongs to the Malvaceae family and grows in Asia, Europe and the United States. *Althaea officinalis* L. contains various antioxidants and polyphenols with antioxidant and anti-inflammatory activity. *Althaea officinalis* L. is rich in phenolics with strong neuroprotective and antineurodegenerative activity that protects neuronal cells. In the study by Rezaei et al., the neuroprotective effects of *Althaea officinalis* L. aqueous extract were investigated in a rat model (Rezaei & Alirezaei, 2014).

Table 11. Methods used for the extraction of *Althaea officinalis L.*

Common name	Extraction method	Extraction conditions	Methods	References
Althaea officinalis L.	Aqueous extraction	Boiling water was poured onto the plant leaves in a beaker and infused at room temperature for 2 hours. Then the solution was kept in a bain-marie.	method of Lowry, colorimetry, biochemical analysis	(Rezaei & Alirezaei, 2014)
Althaea officinalis L.	Aqueous and methanolic extraction	Plant parts were air dried in the dark at 25°C. It was pulverized and extracted with absolute methanol by shaking for 48 hours. The extracts were then filtered and evaporated below 40°C using a rotary evaporator.	Spectrophotometry	(Arab et al., 2017)

Albizia adianthifolia

Albizia adianthifolia is a tree from the Fabaceae family. It grows in places from eastern South Africa to Tropical Africa.

In the study of Beppe et al., it was reported that the aqueous extract of *Albizia adianthifolia* leaves has antioxidant activity and may help in the treatment of Parkinson's disease. In HPLC analysis, apigenin was shown to be the main compound among flavones, hence its cognitive enhancing effects in the 6-OHDA lesion rodent model of Parkinson's disease (Beppe et al. 2014).

Table 12. Methods used for the extraction of *Albizia adianthifolia*

Common name	Extraction method	Extraction conditions	Methods	References
Albizia adianthifolia	Aqueous extraction	The leaves of the plant were air dried and ground into powder. It was softened in distilled water at room temperature for 48 hours, and the aqueous extract was then lyophilized.	HPLC-DAD	(Beppe et al., 2014 and 2015)
Albizia adianthifolia	Ethanol extraction	Air-dried leaves were ground into powder and kept in 50% ethanol for 72 hours. The filtrate was concentrated by rotary evaporator.	convulsions assays	(Aderibigbe, 2016)

Valeriana officinalis

Valeriana officinalis is a perennial flowering plant from the Caprifoliaceae family that blooms with fragrant pink or white flowers in summer. Extracts of the *Valeriana officinalis* flower were used as perfume in the 16th century. There are 25 known species of *Valeriana officinalis* in the United Kingdom and over 400 in Germany.

Several studies suggest that flavonoids may be useful for protecting cells from rotenone toxicity. *Valeriana officinalis* contains many chemical components with antioxidative and vaso-relaxant activities of flavonoids on the central nervous system, and the neuroprotective effects of *Valeriana officinalis* extracts on mice were described in the studies of de Oliveria et al. (de Oliveria et al, 2009).

Table 13. Methods used for the extraction of *Valeriana officinalis*

Common name	Extraction method	Extraction conditions	Methods	References
Valeriana officinalis	Aqueous extraction	The powdered thick, horizontal stem of the plant was diluted with water, heated to 100°C for 10 minutes, and centrifuged for the same minute.	Cell Culture, MTT assay	(de Oliveria et al., 2009)
Valeriana officinalis	Ethanol extraction	The plant was extracted with ethanol.	HPLC	(Sudati et al., 2009)
Valeriana officinalis	Aqueous extraction	*V.officinalis* root powder was diluted with water, heated to 100°C for 10 minutes, and centrifuged for the same minute.	Cell Culture	(Amaral de Brito et al., 2020)

Black tea

Black tea, or plain tea, is a type of tea that is more oxidized than oolong, green and white teas. Black tea, like these three teas, is prepared from the leaves of the *Camellia sinensis* branch. Black tea is more dominant in taste than less oxidized teas.

Caruna & Vassallo reported in their study that tea consumption can provide protection against Parkinson's disease and that this protective effect can be seen more clearly in the Chinese population, which consumes the most tea in the world (Caruana & Vassallo, 2015).

A study has shown that the polyphenols in black tea have protective effects against brain damage in different animal models of Parkinson's disease. A combination of epigallocatechin compound or black tea extract was used in the study. Long-term administration of individual epigallocatechin and black tea polyphenol extracts to animals receiving parkinsonism-inducing 1,2,3,6-tetrahydropyridine neurotoxins, such as 6-hydroxydopamine and 1-methyl-4-phenyl, caused striatal dopamine depletion and substantia nigra (black substance) has been observed to reduce dopaminergic neuron loss (Chaturvedi et al, 2006).

Table 14. Methods used for the extraction of *Black tea*

Common name	Extraction method	Extraction conditions	Methods	References
Black tea	Aqueous extraction	Tea is brewed fresh every day to obtain black tea extract. To prepare 1.5% black tea extract, it was suspended in hot water (85°C), infused for 5 minutes, cooled to room temperature and filtered.	Spectrophotometry, colorimetry	(Chaturvedi et al, 2006)

***Hypericum perforatum* L.**

Hypericum perforatum L. is also known as Sword grass, Mayasıl grass and Koyunkıran. It is a flowering plant species of the genus *Hypericum* of family Hypericaceae. It is a plant found in many places around the world. The plant, which grows naturally on fields, roads and forest edges in Europe, has also adapted to North America and started to grow naturally in the countryside.

Hypericum perforatum L. plant extract is used in the treatment of depression. Some studies have shown the anxiolytic and anti-inflammatory effects of the plant *Hypericum perforatum* L. It has been shown that this plant can alleviate toxicity through its antioxidant defense system in limiting oxidative stress. Meanwhile, it has been demonstrated that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine of *Hypericum perforatum* L. can alleviate striatal astrogliosis, restore monoamine oxidase-B activity (Kiasalari et al, 2016).

Table 15. Methods used for the extraction of *Hypericum perforatum L.*

Common name	Extraction method	Extraction conditions	Methods	References
Hypericum perforatum L.	Ethanol extraction (Maceration)	The aerial parts of the plant were dried in the shade for a week and then ground into powder in an electric grinder. Extraction was performed using the maceration method with 70% ethanol for 72 hours at room temperature and in the dark. The solution was then filtered three times and the ethanol was removed in a rotary evaporator at 40°C.	HPLC	(Kiasalari et al., 2016)
Hypericum perforatum L.	Methanol extraction (Soxhlet)	The leaves of *H.perforatum* L. plant were dried in the shade and ground into powder in a mechanical grinder. It was extracted with 100% methanol in a Soxhlet apparatus and the filtrate was vacuum dried at 40°C.	method of Lowry, Spectrophotometry, colorimetry	(Mohanasundari & Sabesan, 2007)
Hypericum perforatum L.	Methanol extraction	*H.perforatum* L. plants were dried in the shade, powdered and extracted with methanol. The extracts were evaporated under low pressure using a Buchi type rotary evaporator.	method of Lowry, Spectrophotometry, colorimetry	(Mohanasundari et al., 2006)

***Oxalis corniculata* L.**

Oxalis corniculata L., creeping tree sorrel, lying yellow sorrel, or sleeping beauty, is a somewhat delicate-looking, low-growing herbaceous plant from the family Oxalidaceae.

Oxalis corniculata L. exhibits wound healing, cardio relaxant, nematocidal, anticancer, antimicrobial, antifungal, antiamoebic, antiimplantation, allelopathic, antioxidant and steroidogenic activity. Recently, Aruna et al. reported that *Oxalis corniculata* L. exhibits strong anxiolytic potential, nephroprotective, anti-stress and memory enhancing properties. In their study, they evaluated the anxiolytic effect of ethanolic extract of *Oxalis corniculata* L. on male mice using various anxiety paradigms (Aruna et al, 2016).

Table 16. Methods used for the extraction of *Oxalis corniculata L.*

Common name	Extraction method	Extraction conditions	Methods	References
Oxalis corniculata L.	Ethanol extraction (Soxhlet)	Samples were dried in the shade at room temperature for 3-8 weeks. It was completely powdered and the powder was subjected to continuous hot filtration with ethanol at 65-70°C in a soxhlet device. The extracts were evaporated under reduced pressure using a rotary flash evaporator until all the solvent was removed.	Actophotometry	(Aruna et al., 2016)

3. CONCLUSION

Recently, the focus of Parkinson's disease treatment has shifted towards medicinal plants and therefore herbal medicine. The purpose of this research is to examine articles evaluating the neuroprotective effect of extracts of medicinal plants used in the treatment of this disease using various solvents (aqueous, ethanol, methanol, etc.) using different extraction methods (maceration, percolation, infusion, soxhlet, etc.). As a result of our research in search engines, among the medicinal plants used for the treatment of Parkinson's disease; *Carthamus tinctorius* L., *Tinospora cordifolia, Chaenomeles speciosa, Portulaca oleracea* L., *Mucuna pruriens* L., *Hyoscyamus niger* L., *Hibiscus asper, Gynostemma pentaphyllum, Alpinia oxyphylla fructus, Bacopa monnieri* L., *Althaea officinalis* L., *Albizia adianthifolia, Valeriana officinalis,* Black tea, *Hypericum perforatum* L., and *Oxalis corniculata* L. it has been observed that studies are concentrated on the plants.

Many of the herbs and active ingredients described in this article increase the levels of glutathione, superoxide dismutase and catalase in the brain and thus exert neuroprotective effects. Studies on Parkinson's disease report a role for oxidative stress as well as neuroinflammation in neurodegeneration. As a result of the experimental studies conducted by researchers with these plants, it has been proven through in vivo and in vitro studies that the phenolic compounds in the plant extracts treat Parkinson's disease, a neurodegenerative central nervous system disorder, by showing antioxidant activity.

This research includes a compilation of extraction methods used for plants in experimental studies on the activities of medicinal plants' active ingredients against Parkinson's disease. When articles on this subject were examined, it was observed that plant extracts had various anti-Parkinson activities. In order to decide the effectiveness of medicinal plant extracts and active substances obtained from plants in Parkinson's disease, there is a need to adequately explain the mechanisms of action of the active substances and more experimental studies.

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Chapter 4

MEDICINAL PLANTS USED IN THE TREATMENT OF HUNTINGTON'S DISEASE AND EXTRACTION METHODS

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1. INTRODUCTION

"Traditional Medicine", which has been based on experiences and beliefs since ancient times, continues to be used for many different procedures and attracts people's attention due to its therapeutic effect against various ailments, low cost, easy access and fewer side effects. In traditional medicine, herbal mixtures prepared by healers have attracted the attention of experts working on these issues and have led to an increase in studies on these plants (Dey et al., 2015). According to the World Health Organization (WHO), almost 80% of the population in some African and Asian countries rely on traditional medicine for basic health services.

Phytochemicals found in medicinal plants have an effect on cellular and molecular mechanisms associated with the development of neurodegenerative diseases and contribute greatly to slowing down the prognosis of the disease. It has been observed that various central nervous system receptors provide pharmacological effects as a result of their interactions with components in plant extracts, thus playing a role in the treatment of neurodegenerative diseases. When recent studies are examined, it is seen that the use of herbal medicines has increased in the treatment of neurodegenerative diseases due to their effects on HD and neurotoxicity. (Dey et al., 2015).

The 4 horsemen of the apocalypse, Alzheimer's, Parkinson's, Huntington's and Amyotrophic lateral sclerosis, stand out in neurodegenerative diseases (Tomruk et al., 2018).

Although there is no definitive treatment method for these diseases today, there are some drugs that slow down the progression process and improve the patient's quality of life. The emergence of serious side effects in the regular use of these drugs used today is a very important and undesirable situation for the patient. Therefore, treatment with medicinal plants, or alternative treatment methods, can be used as treatment methods with low side effects in the treatment of neurodegenerative diseases.

In this section, a compilation was created by investigating the neurodegenerative disease "Huntington disesase", neuroprotective medicinal plants that have the potential to be used as therapeutic agents in the treatment of the disease, the extraction conditions of these plants and the methods used. The study, which was conducted as a systematic compilation, was created by scanning Turkish and English databases Web of Science, Pubmed and Science Direct with the given keywords.

2. HUNTINGTON'S DISEASE

Medicinal plants have been used in the treatment of diseases throughout history in India and continue to be used. Herbs have been used in Ayurveda, the Indian system of traditional medicine, as the pharmacopoeia of nearly 70 000

formulations was improved over a long period of time, stretching from 1500 BC to the 18th century AD. This method used in India is the oldest and first known treatment method with medicinal plants in the world and this method is called "Ayurveda". In fact, it is a well-known and widespread method used as alternative medicine today. It is known that the plants called Ayurveda are medicinal plants and that the products containing them do not cause side effects and provide relief to patients when used for a long time. When we look at Ayurvedic texts, it is explained that many plants have healing properties in Huntington's disease (HD), one of the neurodegenerative diseases. (Nataraj et al. 2018)

Huntington's disease (HD) is a very uncommon disease, and in its later stages, nerve cells in the brain gradually disappear. The people with HD usually experiences cognitive, mobility, and psychological impairments that importantly impact the functional abilities. George Summer Huntington was the first to describe this disorder as a fatal neurodegenerative disease in 1872, and the disease was named after him. In the early 20. century, an autosomal dominant inheritance pattern was found due to a 50% probability of occurrence of the disease. HD is related with an inhibitory effect on the cerebral nervous system and degeneration of the basal ganglia, the control center of the extra-pyramidal motor system. This will filter out unwanted motor movements and, as a result, contribute to the improvement of motor movements. Only those who inherit the mutation can pass it on to the next generation (Venkatramaniah & Praba, 2015).

In Huntington's disease, an autosomal fatal genetic disease, commonly used therapeutics include monoamine-depleting agents, antidepressants, tranquilizers, and antipsychotics. However, these medications cannot prevent the behavioral dysfunctions, cognitive and psychotic, related with HD. Additionally, their chronic use is limited due to their long-term side effects. Herbal medicines propose a reasonable another to this and have shown significant therapeutic effects against HD. Moreover, their safety profile is better in terms of side effects. However, herbal medicines have not reached the clinical research stage due to limited drug solubility and permeability to reach the target site. Lately, the research pattern has moved for the development of herbal medicine-form nanoformulations that can increase its permeability bioavailability and blood-brain barrier bioavailability. (Vishwas et al., 2021)

A damaging grows in the number of guanine-adenine-cytosine trinucleotide substitutions in exon 1 of huntingtin quality is associated with HD, a distinctive, autosomal dominant neurodegenerative disease. The age at which HD begins to appear is usually between 30 and 50 years of age (average 15-20 years). Disease that begins before the age of 21 is defined as Juvenile HD, while disease that begins after the age of 60 is defined as "late-onset" HD, the disease lasts an average of 17 to 20 years. According to statistics, the number of people with HD disease is around 2.7 per 100 000 people in the

world; Western populations have the highest Asian groups have the lowest incidence. However, the worldwide prevalence of HD remains unknown, as clinical reviews and case studies are now only available from populations in Asia and Africa. In spite of ordinary genetic causes of HD can be identified, an individual's mutation rates and criteria will likely affect how quickly the disease progresses. The harmful effects of HD can occasionally be decreased with symptomatic treatments. For that reason, to address the pathophysiology of HD, analysts have begun to implement various treatment pathways, concentrating on the mHtt formation pathway. Nutraceuticals such as phytochemicals can prevent side effects in HD and similar diseases, as well as assist in HD treatment methods. (Islam et al., 2023).

HD is a devastating, hereditary and familial disease with developing muscle function and loss of brain. HD is a monogenic disease in which programmed neuronal deterioration occurs in different regions of the brain. In the wild-type gene, there are 6-35 CAG repeats in exon 1 of the Huntingtin (Htt) gene on chromosome number 4, while in affected individuals, these repeats increase to over 36. As a result, Huntington protein accumulation occurs in the neuron and causes the death of the neuron. About 95% of GABAergic medium spiny neurons (MSNs) reflecting to the globus pallidus and substantia nigra are extinct, causes atrophy in the hypothalamic nuclei, cortex, and thalamus. Indications include concentration problems, absence of focus, snatchy memory, tripping, depression, awkwardness, difficulty speaking, nutrition problems, weight loss, itching, out of controlled facial acts etc. takes place. In short, HD is associated with decreased independent living skills, impaired motor senses and cognitive functions, and the emergence of psychiatric symptoms. People suffering from HD is visible characteristic and specific cognitive difficulties. Typically, this cognitive change is called dementia. Behavioral changes are a hallmark of HD, which is the maximum stressful strand of the condition for individuals and families coping with it. Another fewer prominent but debilitating features of HD include unexpected sleep, weight loss, autonomic nervous system (ANS) dysfunction, and circadian rhythm problems. Much research is ongoing in the field of prevention and treatment of HD. To date, no cure has been found for the disease, and current medications appear to provide only symptomatic relief. From past to present, natural compounds have always been used in the treatment of various diseases, and many of them have shown promising positive responses to treatment in pre-clinical studies. (Khan et al., 2020; Kshirsagar et al., 2021).

3. MEDICINAL PLANTS USED IN THE TREATMENT OF HUNTINGTON'S DISEASE

3.1.Acorus calamus L. (Family, *Araceae*)

Acorus calamus (AC) L. (Apiaceae) is semi-aquatic, aromatic and annual plant found in Europe, Asia and North America. Its rhizomes are often used by

Americans, Chinese, and Native Americans as well as other cultures. Natural products and plants contain naturally occurring secondary metabolites with safe, potential neuroprotective properties. Its secondary metabolites, α- and β-asarone, can be found at high levels in the rhizomes of *Acorus calamus* (L.). Saponins, α- and β-asarone, exhibit many pharmacological properties, anti-inflammatory, including antioxidant, anticancer, anti-apoptotic, and neuroprotective effects (Balakrishnan et al., 2022). Herbs such as *Acorus calamus* L., *Centella asiatica* (L.) Urban, Boswellia serrata Roxb. ex Colebr. is used in Unani medicine to improve memory by clearing Acetylcholinesterase and β-amyloid plaques, antioxidation and anti-inflammatory activity (Umar et al.,2023). Ethnobotanical studies and documentation have shown their use in the treatment of various diseases such as diabetes, insomnia, epilepsy, asthma, diarrhoea, inflammation and neuropathic pain for their potential to lower blood lipid levels and in neuropharmacology for epilepsy, amnesia, hallucinogenic, neuropathic disorders and sedative. However, special attention should be paid to β-asaron, which is known to be a good natural pesticide from *A. calamus*. Therefore, *A. calamus* is classified as a poisonous plant (Agil et al., 2023).

3.2.Anemarhenae asphodeloides (Family, *Asparagaceae*)

Anemarrhena asphodeloides root extract has been used in traditional medicines for thousands of years in China, Japan and Korea. The traditional corrective elements of Anemarrhena asphodeloides are to treat febrile diseases, fever, disease and diabetes, etc. is to treat. In the light of phytochemical and pharmacological investigations since the 1930s, *Anemarrhena asphodeloides* extract has been shown to be effective against Parkinson's disease, Alzheimer's disease, and Schizophrenia, etc. can treat. The mixtures isolated so far from *Anemarrhena asphodeloides* mainly contain steroidal saponins, flavonoids, norlignanes and polysaccharides, etc. Contains. Current pharmacological research has confirmed that unrefined concentrates and unadulterated mixtures of hydrogenated polyisobutene *Anemarrhena asphodeloides* root extract have beneficial results for the focal sensory system and can control the state of mind (Piwowar et al., 2020; Lum et al., 2021).

3.3.Bacopa monnieri L. (Family, *Plantaginaceae*)

Bacopa monnieri, also known as Aindri (Sanskrit) and Brahmi, is a member of the Scrophulariaceae family and grows in moist soil and humid environments in India. It grows around the world, including Sri Lanka, India, Taiwan, Vietnam, China, Florida and other southern parts of the USA. These plants, which are also seen in the United States, are perceived as weeds in rice fields and are a succulent plant that is abundant in wetlands and swamps in hot regions and grows abundantly in places at an altitude of 1500 meters in subtropical countries. Traditionally known as "medhya rasayana" meaning

nootropic or brain tonic or from the Sanskrit word for improving the cognitive properties of the brain, Ayurvedic use of Brahmin is popular and used as a brain tonic it is known to strengthen memory, promote longevity, cognitive functions, and supply relaxation to patients together fever, epilepsy or anxiety , and is used in the treatment of asthma. Besides, the existence of other phytoactives like jujubogenin and dammarane-type triterpenoid saponins aglycones, bacosides, jujubogenin bacopa saponins have been notified in the alcoholic extract of BM. The biological effects of *Bacopa monnieri* are reviewed periodically. Recently, the protective effect of BM on brain cells and tissue against oxidative damage that may occur with free radicals, with its antioxidant properties, has been reported in an animal model of ischemia-induced brain injury (Shinomol et al., 2012; Jyoti, & Sharma 2006).

3.4.Boerhaavia diffusa L. (Family, *Nyctaginaceae*)

The Sanskrit name of this plant is punarnava*; Boerhaavia diffusa* L. (Nyctaginaceae) is a perennial herbaceous plant that grows in tropical regions, particularly in the Antilles, Africa, South America, and India, with a long history of utilize by tribal and Indigenous peoples. In Asian medicine practiced in Britain, its roots are used as stomachic preparations, laxative, diuretic, and expectorant while its leaves are used like an appetizing and alexiotic preparation, used to treat stress, indigestion, abdominal pain, inflammation, jaundice, etc. It is widely used in treatment for. Ayurvedic preparations have anti-aging properties that prevent psychotic diseases as well as influence life-enhancing activities. Its seeds are used as carminative preparations and tonic. Ethanol extracts of the root and the isolated alkaloid punarnavin have been reported to show antidepressant activity in experimental animals. It has been tested against brain oxidative stress, which causes various neurodegenerative complications, and has been found to have high antioxidant potential (Hiruma et al., 2000).

3.5.Calendula officinalis L. (Family, *Asteraceae*)

Usually known as marigold (Asteraceae), it is a plant of medicinal importance known in traditional medicine and homeopathic since ancient times. Natural marigold localizations are in the Mediterranean region, the Middle East and Europe. Today, it is a common and valuable plant grown for ornamental and medicinal purposes in other parts of Europe (Eastern Europe, Germany and Balkans) and North America. In addition to its antiviral, antibacterial, antimutagenic, antifungal, anti-inflammatory, renoprotective, hepatoprotective and free radical scavenging properties, it is also known to be estrogenic and effective on the central nervous system. In a recent study, *C. officinalis* flowers were found to be effective against excitotoxic brain damage and monosodium glutamate-induced oxidative stress (OS) in rats. Compounds with inflammatory properties and

antioxidant have been reported to have a useful effect in animal models of HD and another neurodegenerative diseases (Dey et al., 2020; Shisvaran et al., 2013; Szopa et al., 2020).

3.6.Cassia occidentalis L. (Family, *Caesalpiniaceae*)

Cassia occidentalis Linn. (COL) family Caesalpiniaceae is a widespread weed distributed from the foothills of the Himalayas to West Bengal, Burma and South India and Sri Lanka. Several parts of this plant have antiplasmodial, anti-inflammatory, antibacterial and antihepatotoxic activities. It has been reported in the Unani literature that it is especially useful as an expectorant, carminative, blood purifier, diuretic, digestive aid, reducer of joint pain, diaphoretic, and in hemorrhoids, fever, epilepsy, tonic, jaundice, laxative, liver and skin dyscrasia. The plant is also used to treat eye pain, hematuria, diabetes, rheumatism, typhoid, asthma, leprosy, and hemoglobin disorders. There are a wide variety of chemical components isolated from *C. occidentalis,* including anthraquinone glycoside, sennoside, fatty oils, glycosides, flavonoids, alkaloids, polysaccharides, tannins and galactomannan (Silva et al., 2023; Mahanthesh et al., 2019).

3.7.Celastrus paniculatus Willd. (Family, *Celastraceae*)

Jyotishmati (*Celastrus paniculatus Willd.)* is a well-known woody climbing plant belonging to the Celastraceae family, distributed in subtropical and tropical regions of India, and is a nootropic. It is an Ayurvedic medicinal plant and has strong pharmacological effects against diseases such as cough, inflammation, vomiting, nephropathy, heart failure, memory enhancer, skin disease, asthma and leprosy. Its seed oil and seeds are used for their neuroprotective properties and memory enhancing. When crushed seeds are boiled or the oil obtained from the seeds is taken internally, it is used to relieve paralysis, muscle and joint pain, and to reduce fever due to its sweating properties. In Ayurveda, it is also categorized as Medhaya Rasayana, i.e. nerve medicine. The plant contains numerous phyto-constituents such as celapanigin, paniculatin, celastrin and selapanin. Several sesquiterpenoid polyalcohols and esters (malkanguniol, malkangunine, polyalcohol A-D, celapnin) from CP seeds and seed oil; alkaloids (paniculatin, celastrin); fatty acids (linoleic, oleic, linolenic, palmitic, lignoceric acid and stearic); phenolic triterpenoids (paniculatadiol, celastrol) There are also agarofuran derivatives isolated (Malik et al., 2017; Godkar et al., 2004).

3.8.Centella asiatica (Family, *Apiaceae*)

It is widely called Gotu kola, Indian Pennywort, Jal Brahmi, Wild violet, Asiatic pennywort, Indian water navelwort, and tiger grass" and is a little, frost-resistant, herbaceous, perennial plant from the Umbelliferae family. It is categoried as Rasayana in Ayurveda for its quality of improving

memory and age-connected brain problems. It is a tropical medicinal plant belonging to the Apiaceae family and native to Sri Lanka, Southeast Asia and India. It is a tropics plant grown successfully in some countries due to its medicinal importance. It has a lasting history of use in Ayurvedic and Chinese traditional medicines, including Turkey, for centuries. It is a managing brain tonic that has long been used in Ayurveda. In the Indian system of medicine, Ayurveda, *Centella asiatica* (Umbelliferae) Hydrocotyl asiatica is used in several parts of India for various illness such as body pain, headache, insanity, leprosy, asthma, ulcers, and wound healing eczema. It is traditional medicine used to increase intelligence, reanimate the body and cure cognitive problems like Alzheimer's disease. *Triterpenoid saponins* like madecassoside, madecassic acid, asiaticoside and asiatic acid (AA) found in this Plant are the basic contituents of *C. asiatica*. Their ability to protect mental functioning is assigned to their antioxidant properties. Monographs describing the plant's principally wound-healing and memory- enhancing effects are available in the German Ministry of Health Commission E, European Pharmacopoeia, and the World Health Organization (WHO). In addition to the neuroprotective effect of C. *asiatica,* it has wound healing, antipsoriatic, anti-inflammatory, antiulcer, anticonvulsant, immunostimulant, hepatoprotective, sedative, cytotoxic, cardioprotective, antidiabetic, antibacterial, antiviral, antitumor, insecticidal, antifungal, antioxidant, for leprosy and antifungal. It has activities such as venous insufficiency treatments. (Kumar and Gupta, 2002; Orhan, 2012)

3.9.Convolvulus pluricaulis Choisy (Family, *Convolvulaceae*)

Commonly known as shankhpushpi (Convolvulaceae), it is an indigenous perineal herb from the best Medhya Rasayana (nerve medicine) in Ayurveda, used since ancient times and considered as a memory glory. It is used for its memory enhancing, antianxiety, sedative and anticonvulsant properties. As the components it contains, kaempferol, convolamine, convolin, convolvin, convosin, convolidin, b-sitosterol, confoline, scopoletin and seril alcohols are some of the phytoconstituents in the treatment of various disorders in medical applications. Shankhpushpi has pharmacological effects in the treatment of diseases such as depression, stress, amnesia, bacterial infection, cardiovascular and neurological disorders. It has therapeutic value in the treatment of oxidative stress disorders and neuronal dysfunctions (Malik et al., 2015; Dhuna et al., 2012)

3.10.Coriandrum sativum L. (Family, *Apiaceae*)

Coriandrum sativum L. is a species belonging to the Apiaceae family of the Apiales order, which includes more than 3000 species and approximately 300 genera. Coriander is a native annual plant of West Asia and North Africa, but it is also a medicinal plant that is common in the Mediterranean region

and used in the kitchen, and is now widely grown all over the world. It is used both as food and medicine. It is one of the oldest spices in the world and is produced in India, the Netherlands, the Russian Federation and Morocco. The essential fatty acids found in *Coriandrum sativum* fruits were determined as oleic acid, stearic acid, palmitic acid and linoleic acid. Since the Middle Ages, extracts prepared with the plant have been widely used in cosmetic and medical applications as virucides, antibacterials, fungicides, insecticides and parasiticides. Various parts of the plant (leaves, fruit, flowers) have antimicrobial, antioxidant, antidiabetic, antidepressant, anticonvulsant, anxiolytic, antidyslipidemic, antihypertensive, antimutagenic, anti-inflammatory and diuretic properties. Meanwhile, the leaves of coriander are an important herb for their carminative, spasmolytic, digestive and galactagogue effects. In the European Pharmacopoeia, coriander is also used in the treatment of rheumatism, against intestinal worms and as a digestive. In addition, it is also used in the food, beverage, cosmetics and fragrance industries (Wishvas et al.; 2021).

3.11.Dalbergia sissoo DC. (Family, *Fabaceae*)

Dalbergia sissoo Roxb. ex DC., commonly known as Shinshapa (Fabaceae), Indian rosewood, and Sheesham is a long-lived tree native Southern Iran and to the Indian subcontinent The bark and leaves of *D. sissoo* are used in traditional medicine for skin problems and various stomach including dysentery, leucoderma and sore throat, bronchitis, headaches, inflammations, hernias, skin diseases and infections, gonorrhea and in the treatment of syphilis, as a blood purifier. The juice of its leaves is an anthelmintic and is useful for eye and nose diseases. It is also widely used in scabies. The juice of *D. sissoo* leaves is used to treat old age and stimulate brain functions. *D. sissoo* is known to have various phytoconstituents, including, tectorigenin, biochanin A, mesoinisitol, tectorigenin, isocaviumin, dalberginone, dalbergin, tannins, essential oils and fixed oils. A number of studies have shown that it has anti- inflammatory, antioxidant, antiemetic, antispermatogenic, memory, enhancer, cardioprotective, gastroprotective activities, neuroprotective effects and antioxidant (Raheja et al., *2021;* Mannan et al., 2017)

3.12.Ficus religiosa L. (Family, *Moraceae*)

Ficus religiosa Linn (Moraceae), of chemical constituents isolated from C. occidentalis a broad- leafed deciduous tree with heart-shaped, spreading branches and gray bark. *Ficus benghalensis* (Indian banyan) and *Ficus religiosa* (Bo tree or sacred fig) have tremendous therapeutic significance and sacred. *Ficus religiosa* is used in traditional medicine for a broad variety of ilness. Its fruits, bark, leaves, latex, seeds and roots, are used medicinally in several forms, occasinally in combination with other plants. All parts of the plant

are used for gonorrhea, dysentery, diarrhea, hemorrhoids, anti-inflammatory, gastrohelosis, burns, anticancer, antidiabetic, antimicrobial, anticonvulsant, antioxidant, anthelmintic, antiulcer, antiamnesic, antiasthmatic, etc. It exhibits a wide range of activities such as. The bark of the plant has been used as an aphrodisiac, astringent, antibacterial against and cooling, Escherichia coli and Staphylococcus aureus. The leaves are used in hemoptysis, hematuria, nosebleeds, menorrhagia, skin diseases and blood dysentery. Leaf's juice is used to cough, treat asthma, sexual disorders, diarrhea, toothache, hematuria, migraine, eye disorders, stomach problems, scabies and eye disorders. The fruits have been used to treat asthma, as a digestive and laxative.

F. religiosa has traditionally been used to treat neurodegenerative disorders (including HD) and is also known to have antioxidant activity. Its structure contains compounds with a extensive range of biological properties such as flavonoids, phenols, carotenoids, anthocyanins, sterols, alkaloids, saponins, tannins, vitamins and terpenoids (Bhangale & Acharya, 2016; Shim et al., 2022).

3.13.Garcinia kola Heckel (Family, *Clusiaceae*)

Garcinia kola is a type of flowering plant commonly known as Bitter kola, which grows widely in the tropical rainforest region of West and Central Africa. All parts of the plant, its stems, seeds and leaves, are parts of the plant that have medicinal value for folkloric medicine. Its seeds are edible and consumed for medicinal purposes and as a supplement to real kola (Cola nitida). In ethnomedicine, *Garcinia kola* has been used as an antimicrobial agent and antiparasitic, laxative, throat infection, bronchitis, diarrhea, and aphrodisiac. The pharmacological effects of its seeds include anti-inflammatory, antidiabetic, antipyretic, antiatherogenic, immunomodulatory, antimicrobial, anticancer, analgesic, antidiabetic, antimicrobial, antimalarial, liver disorders, neuroprotective and hepatoprotective effects. Various organic groups from *G. kola,* such as benzopyran, benzophenones, biflavonoids, benzofurans, vitamin E, phytosterols and xanthones (many of these, such as garcinianine, kolanone, garcinoic acid, gakolanone, garcinal, garsipiran, garcifuran A and B, appear to be found only in this species) isolated. (Akinmaludin et al., 2015).

3.14.Gastrodia elata Blume. (Family, *Orchidaceae*)

In East Asia, especially Chinese speakers in Korea, India, China and Japan *Gastrodia elata* (Blume (Orchidaceae)) is a perennial parasitic plant commonly referred to as Tian ma. *Gastrodia elata* Blume *(G. elata)* is a traditional herb that has been used in East Asian countries for centuries. The dried rhizome tuber of this plant (tianma) is formally booked in the Chinese Pharmacopoeia and has been used as an analgesic, sedative and anticonvulsant product. In Shennong's Materia Medica Classic (Shennongbencaojing) throughout history, it has been considered the primary herbal medicine that can enter the

liver meridian and is used. So far, more than 81 compounds have been isolated and identified from the plant, including polysaccharides, phenolics, organic acids and sterols. In traditional Chinese medicine (TCM),

G. elata is thought to stop endogenous wind, stop tetany, and suppress hyperactive liver. In traditional Chinese medicine (TCM), G. elata is thought to stop endogenous wind, stop tetany, and suppress hyperactive liver. Since ancient times, *Gastrodia elata* has been used as a Chinese medicine for the treatment of different situations, with the inclusion of its antiepileptic, analgesic, anticonvulsant, a neuroprotective, and sedative effects against vertigo, tetanus and general paralysis. In terms of clinical application, *G.elata* is mostly applied for insomnia, neurasthenia, convulsions, hypertensive, Alzheimer's disease, and others. Modern pharmacological investigation show that active compounds of *G. elata* or its extracts have vast- ranging biological activities, including antitumor, memory enhancing, anti-virus, anti-aging and antioxidation effects. It is thoroughly used as a aphrodisiac and tonic in traditional medicine another Asian countries and in China, and is also used as a practical food by putting it to porridge or alcoholic beverages to enhance sexual power and vision and to prevent abortion. (Matias et al., 2016).

3.15.Glycyrrhiza glabra (Family, *Fabaceae*)

Licorice plant, known as *Glycyrrhiza glabra,* is a herbaceous perennial plant grown in Southern Europe and parts of Asia. *Glycyrrhiza glabra* is probably the most famous medicinal plant belonging to the Fabaceae family (called Leguminosae), and this family of plants is currently used for consumption purposes. The term glycyrrhiza is a derivative of the Greek words 'glycos' (sweet) and 'rhiza' (root). It is also called Liquorice, glycyrrhiza, sweet tree. Traditionally, licorice has been used for medicinal purposes in ancient times in many regions, including the Middle East, China, India, and Japan. Commercial products commonly known as licorice are derived from the stoloniferous root of this plant and are used in tobacco flavoring, the food industry, and herbal medicine. It contains flavonoids, isoflavonoids and triterpenes. It is indicated for use in a variety of medical conditions such as viral diseases, peptic ulcer disease, and psychiatric disorders. Recent studies have scientifically proven various therapeutic properties for licorice root. Various studies have confirmed that licorice root and its dynamic components are indicated in various medical conditions, including their antimicrobial, antispasmodic, antifungal, antiallergic, antiviral, anticarcinogenic, antineoplastic and antioxidant cytotoxic activities, as well as their neuroprotective role in chronic or acute neurodegenerative cycles (Sarkar et al., 2023); Mallavadhani et al., 2019; Ravanfar et al., 2018).

3.16.Luehea divaricata March. (Family, *Malvaceae*)

Luehea divaricata March, from the Malvaceae family, known by the people in South America as "açoita-cavalo". It contains many polyphenols and is a tree from the Brazilian Cerrado known for its medicinal use. People living on the coasts of the Pantanal region in Brazil use the stems of the plant as anti-inflammatory, the leaves as a diuretic, the barks as a remedy for vaginal discharge, and for healing acne and skin wounds. The plant has traditionally been used in folk medicine to treat leukorrhea, dysentery, blennorrhea, rheumatism, tumors, skin lesions, and bronchitis, among others. In the phytochemical screening conducted with *L. divaricata* leaves, tannins, saponins, mucilage and flavonoids were found in the leaves; It was determined that the crude extracts contained fixed oils, alkaloids, anthocyanidins, polysaccharides and carotenoids. *L. divaricata* is prepared by infusion and syrup. In a recent study, it was determined that the aqueous extract prepared with the leaves of the plant has high antioxidant activity and has genotoxicity properties, the methanolic extract of the leaves has a cytostatic effect and the aqueous extract of the bark has antimutagenic activity. (Kroth et al., 2021; Courtes et al., 2015).

3.17.Momordica charantia L. (Family, *Cucurbitaceae*)

Momordica charantia (MC), known as bitter melon and bitter gourd or, is widely grown in Africa, South America, Asia and Central Asia and various regions and is often consumed as an important medicinal plant. MC originates from East Asia, possibly Southern China or East India. As part of the Indo-Aryan culture, Ayurvedic books date back to the small-fruited or wild cultivars of the MC, dating back to B.C. It is mentioned between 2000 and 200 BC, the earliest inscribed reference in China was made in 1370 AD *Momordica* grows in tropical, humid and hot regions during the rainy summer and spring seasons, and in subtropical climates for winter cultivation. MC contains various bioactive components such as saponin, polysaccharide, vicin, polyphenols, vitamin C and flavonoids. It has antioxidant, hypolipidemic and antidiabetic properties. MC is known to have antibacterial, anticancer, antidiabetic, antioxidant, antifungal, anti-inflammatory, antiviral, anti-HIV, antihelminthic, antimycobacterial, hypotensive, antihelminthic, anti-obesity, immunomodulatory, antihyperlipidemic, immunomodulatory, neuroprotective and hepatoprotective functions in its different extracts. (Kim et al., 2018; Venugopal & Dhanasekaran, 2020).

3.18.Olea europaea Linn. (Family, *Oleaceae*)

Olea europaea Linn., is a tree that grows naturally in the Mediterranean region and has been cultivated for thousands of years. It is one of the oldest known cultivated trees in the world, commonly known as olive, with tremendous medicinal values. Olives and related products have been widely

used as folk medicine for centuries in Turkey, Spain, France, Italy, Greece, Morocco, Israel, Tunisia and the Mediterranean islands. The olive plant is known all over the world for its fruit and the oil produced from the fruit. All parts of this ancient plant, whose fruit and oil are used as food, are included in every aspect of daily life. Olive seeds and olive leaves, which are considered waste, have been used in folk medicine for many years. Olive, known for its health benefits, has been used to reduce the incidence of heart diseases as one of the most important nutrients for heart health. In experimental studies conducted with the fruit and leaf extracts of the olive tree, it has been determined that olives are used as diuretic, antipyretic, antihypertensive, antidiabetic, anti-constipation and appetite stimulant, as well as anti-cancer, anti-thrombotic, hypoglycemic, anti-microbial, anti-inflammatory and anti-atherogenic properties. The main active ingredients in olives and their oil are phenolic compounds such as oleuropein, tyrosol, hydroxytyrosol, protocatechuic acid, 4-hydroxyphenyl acetic acid, p- coumaric acid and caffeic acid. In addition, it contains other biologically active ingredients. (Kim et al., 2013; https://tibuad.istanbul.edu.tr/tr/content/blog/olea-europaea-l.-folium-(zeytin- yapragi).

3.19.Panax ginseng (Family, *Araliaceae*)

The root of *Panax Ginseng* belongs to the Araliaceae family, which has a medical history dating back thousands of years, was discovered by C.A. Meyer (Araliaceae) is one of the herbal medicines that started to be used in Asian countries and spread all over the world in the treatment of many diseases, including aging disorders and neuro-degenerative diseases. The word Panax means "heals all" in Greek, and this is based on the sight that ginseng is strong enough to cure all kinds of diseases. Ginseng is derived from the Chinese word "Jen Sheng", meaning "man-herb", due to the shape of the plant root resembling a humanoid form. The best extensively researched ginsengs are *Panax ginseng* (Korean ginseng), *Panax notoginseng* (Chinese ginseng) and *Panax quinquefolius* L. (American ginseng). In terms of pharmacological effects, Ginseng and its components have been proven to have a wide range of beneficial pharmacological effects. Components of the ginseng plant have been shown to produce restorative, adaptogenic, vasodilator, anti-inflammatory, immunomodulatory, antioxidant, anticancer, antiaging, antifatigue, antistress, antidiabetic, antidepressive effects in humans and animals. Ginseng has beneficial effects on the brain and nervous system; In addition, Ginsenoid and ginseng are known to increase memory and cognitive performance and exhibit neuroprotective properties, thanks to the other active ingredients they contain. The hemajoractive compounds contained in ginseng are triterpenoid glycosides known as ginsenosides, found in leaves, roots, stems, fruits and flower buds. Ginsenosides contained in ginseng plants are part of the defense mechanism. (Rokot et al., 2016; Wu et al., 2009).

3.20.Phoenix dactylifera L. (Family, *Palmaceae*)

Date tree (*Phoenix dactylifera* L.), also known as an ancient product, is an important fruit with high nutritional value, as it is one of the plant species cultivated in the early periods of agricultural culture on earth. For this reason, it is also referred to as an antique product. It is also the fruit that has importance in Islam, Judaism, Judaism and Christianity. Date cultivation is believed to have originated in the ancient Mesopotamia region or western India. Today, it grows in all warm regions, including North Africa, the Middle East and Central America, Asia, Europe and Australia. Dates provide energy due to the high amount of carbohydrates they contain. It also contains proteins, fats, minerals, vitamins, phenolic compounds and flavonoids in its structure. It has been found that date seed extract has a significant antioxidant capacity because it contains flavonoids, total phenolics, epicatechin and catechin. Phenol content is higher in palm kernel oil than olive oil and it is a very rich herbal source of phenolic compounds (Majid et al., 2008; Yıldız & Sohrabi, 2019).

3.21.Psoralea corylifolia or Cullen corylifolium (Family, *Fabacea*)

Psoralea corylifolia is a known widely conventional medicinal plant used in the cure of varied ailments since ancient times. *Psoralea* comes from the Greek word psoraleos, meaning "affected by itching or leprosy". *Psoralea* species are native to the Americas and are commonly found as a weed in the cold weather of the Himalayas in the South and India. The plants are extensively spreaded in Pakistan and the Himalayan regions of China, and there are reports of sightings in South Africa. It is widely distributed in Ayurvedic and Chinese medicines and is an important part of therapeutics, recently proven to have an antidepressant effect. As a therapeutic herb, PCS has been used empirically to prevent brain aging and treat dementia. It has cardiotonic, vasodilator, pigmentor, antitumor, antibacterial, cytotoxic and anti-helmintic properties and is used locally in alopecia, inflammation, leucoderma, leprosy, psoriasis and eczema. Until now, nearly a hundred bioactive compounds have been isolated from the fruits and seeds of the plant, the most important of which are flavonoids, coumarins, phenols and terpenoids. *Psoraleae* fruits are considered to have the effect of "warming and invigorating the Kidney-Yang, relieving chronic morning diarrhea, restoring the spirit, enriching the bone marrow" in the Compendium of Materia Medica. According to traditional Chinese medicine, psoraleae fruits have an anti-aging function (Alam et al., 2018; Im et al., 2014; Zhou et al., 2020).

3.22.Punica granatum (Family, *Punicaceae*)

Pomegranate (Punica granatum), often referred to as the "Fruit of Heaven," belongs to the Punicaceae family, originates from Western Asia,

and is native to Iran and the northwestern Himalayas. It is one of the oldest edible fruits, grown for centuries in variable climatic conditions in America, Asia, the Mediterranean, Europe and Africa. *Pomegranate* is mentioned in various religious manuscripts. Traditionally, *Punica granatum* has been used to urinary tract infection and treat kidney disorders and. It is used to cure diabetes in Indian Unani medicine. It is a food and medicinal plant containing, fatty acids, anthocyanins, flavonols, tannins, rich in polyphenols. The most abundant polyphenols in *pomegranate* are Ellagitannins (ETS). Nearly 50% of the total weight of the fruit corresponds to its peel, which is an significant source of phenolic compounds, minerals and complex polysaccharides. The edible piece of the pomegranate fruit consists of water, sugar, seeds (10%) and pectin-rich grains (40%). It has broad pharmacological activities, antioxidant, osteoporosis, anti-inflammatory, including anticancer, antiobesity, lipid metabolism and antiulcer. It has been observed in numerous studies that pomegranate polyphenols have a direct effect on both glial and neuronal cells, and also affect the blood-brain barrier function, restoring the redox balance there and increasing blood flow to the cells. (Guerra-Vázquez et al., 2022; Hussain et al., 2021; Lum et al., 2021).

3.23.Sesamum indicum L. (Family, *Pedaliaceae*)

Sesamum indicum L. belongs to the Pedaliaceae family and is native to Africa, India and China. It is also grown in Asia mostly for its edible seeds and oil. Traditionally, it has been called the "queen of oilseeds" due to its big degree of resistance to oxidation and rancidity. The plant is used as a nutritional supplement and is also popular worldwide due to its antioxidant value against neurological disorders, which is effective in preventing pain, skin lesions, aging, oxidative stress, atherosclerosis, cataracts, hyperlipidemia, hypertension and atherosclerosis, and has properties such as antiaging and anticancer. It has been widely used as a dietary supplement. The plant contains many active ingredients such as acteoside, pedalin, luteolin, cistanoside, sesamoside and sesamol. Sesamol, one of the main components of sesame oil, is responsible for its antioxidant activity. (Choudhary et al., 2013; Kumar et al., 2010; Lum et al., 2021).

3.24.Sida cordifolia L. (Family, *Malvaceae*)

Sida cordifolia is a shrub native to India and now grown worldwide. It is a commonly used ingredient in herbal preparations in many traditional systems of medicine. In Ayurveda, a pharmacopoeia of approximately 70,000 formulations and medicinal herbs were developed and used during the period from 1500 BC to the 18th century AD. *Sida cordifolia* (Flannel Weed, Bala) (SC) is a perennial growing shrub of the Malvacea mallow family native to India. SC is widely used in Ayurveda to treat diseases of the nervous system.

Sida cordifolia (Malvaceae) is a extremely looked on medicinal herb in Ayurveda and other traditional systems of medicine in India and many other countries. Leaves, stems are roots traditional medicine for chronic diseases. In the Ayurvedic medical system, it has antiasthmatic, analgesic, antirheumatic, antipyretic, antiviral, nasal anticongestant, laxative, aphrodisiac, diuretic, hepatoprotective properties hypoglycemic. The chemical composition of this plant consists of fatty acids, flavonoids, phytoecdysteroids, alkaloids, sterols. (Galal et al., 2015; Simha et al., 2023)

3.25.Tinospora cordifolia (Family, *Menispermaceae*)

Tinospora cordifolia Miers (Menispermaceae), usually known as "Amrita" or "Guduchi", is an important medicine of Indian Systems of Medicine (ISM) and has been used in medicine since ancient times. It is found in tropical regions of India and another Asian countries such as China, Bangladesh, Myanmar and Sri Lanka. *T. cordifolia* has been specially mentioned in Ayurveda as well as in Chinese and another traditional systems of medicine. It is also known as the 'Heavenly elixir' for its rejuvenating potential and great medicinal values. There are reviews in the literature about its ethnopharmacology, phytochemistry and medicinal properties, especially focusing on its immunomodulatory potential. It is an ancient, famous medicinal plant with numerous medicinal properties such as antihyperlipidemia, antihyperglycemic, antioxidant, antineoplastic, antipyretic, antistress, antispasmodic, antileprotic, anti-inflammatory, chemo- and radioprotective, antianxiety and neuroprotective properties. The medicine is the well-known Indian bitter and the therapeutic values of *T. cordifolia* extracts have long been used in varied health problems such as fever, jaundice, skin diseases, gastrointestinal problems, disorders of semen morphology and spermatogenesis, diabetes, indigestion, urinary problems, as well as heart diseases, It has also been shown to be useful in the treatment of rheumatoid arthritis, leprosy, and helminthiasis. In addition, it has been reported to have other beneficial effects in the treatment of neurodegenerative diseases (Sharma et al., 2020; Singh et al., 2023; Polu et al., 2017).

3.26.Tripterygium wiilfordi (Family, *Celastraceae*)

Tripterygium wiilfordii Hook F. (TWHF), a traditional Chinese medicine, is extensively used in China to treat inflammatory and autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and dermatomyositis. From recent studies, the bioactive components of TWHF appear to have effective therapeutic potential on neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease and Multiple Sclerosis. TWHF is poisonous and only the root pulp contains therapeutic compounds including alkaloids, terpenoids and steroids. *Tripterygium wilfordii* Hook (Celastraceae) is a type of ivy-like vine that has been used for many years in traditional Chinese medicine to treat fever and joint pain. Root bark extract contains

celastrol, which has neuropharmacological effects against neurotoxicity. It reduces the oxidative effect by preventing the formation of reactive oxygen species (ROS). Celastrol, the bioactive compound obtained in abundance from the root of this plant, also called tripterin, is a promising compound. It has many therapeutic effects against nervous disorders, infection, cancer, inflammatory conditions, hearing loss, atherosclerosis, diabetes and obesity. (Li and Hao 2019; Lum et al., 2021; Pinna et al., 2004).

3.27.Valeriana officinalis (Family, *Caprifoliaceae*)

Valeriana officinalis (*Caprifoliaceae*) has been used as an herb in traditional medicine since ancient Greek and Roman times. It was Hippocrates who determined the properties of the plant, and Galen who later prescribed it as an insomnia reliever. It is said that in Sweden it was sometimes placed inside the groom's wedding clothes to ward off the "jealousy" of medieval elves. *Valeriana officinalis*, which blooms with fragrant white or pink flowers in summer, is a perennial flowering plant that is native to Asia and Europe and spread to North America. Extracts of its flowers were used as perfume in the 16th century. It is used in various traditional herbal medicines as a mild tranquilizer, anticonvulsant, hypnotic, sedative, sedative and sleep enhancer, antioxidant, anti-neurotoxic and anti-epileptic agent. The three main chemicals considered to be active components of plant essential oils include valenol, valerenic acid, valepotriates, and several alkaloids. Since the compounds contained in this herb are involved in the formation of central nervous system depression, it should not be used with other depressants such as ethanol, barbiturates, benzodiazepines, kava, opiates and antihistamine drugs. (Ortiz et al., 1999; Das et al., 2021; Malva et al., 2012).

3.28.Withania somnifera (Family, *Solanaceae*)

Withania somnifera is a perennial plant belonging to the *Solanaceae* family that has been used in traditional Indian, Arabic and Chinese traditional medicines for over 100 years. The biologically active components in WS are alkaloids (topine, cuscohygrine, ashwagandhin, anahygrine, etc.), steroidal compounds, including ergostane type. Steroidalactones, withanolides A-Y, withaferin A, withasomniferin A, withasomnierose A-C, withasomnidienone, withanone, etc. Other additional components include an acid group including withasomniferin, saponins, withanolides, hanolide A-Y, tannic acid, gallic acid, and chologenic acid. WS is classified as Rasayana in Ayurveda, known to increase defense against diseases, arrest aging, revitalize weakened body and increase mobility. *Withania somnifera* extracts (root, leaf or fruit) have been found to have antitumor, anti-inflammatory, anti-stress, immunomodulatory, antioxidant, hemopoietic and rejuvenating properties. Besides extracts, Withaferin A, a steroidal lactone found in extracts of the plant, has also been extensively researched as an anti-cancer drug. They reported

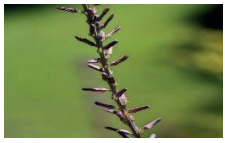
the neuroprotective effects of WS root extract. Perhaps the neuroprotective act of WS may be concerned to its antioxidant effect and ability to inhibit lipid peroxidation both in vitro and in vivo. Glycowithanolides found in WS provide protection against lipid peroxidation due to their antioxidant effect. *Withania somnifera* extracts have been reported to be broadly neuroprotective in neurodegenerative disease models such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and traumatic brain injury and cerebral ischemia. (Bhatnagar et al., 2009; Dutta et al., 2018; Gupta et al., 2022).

3.29.Zingiber officinale Roscoe (Family, Zingiberaceae)

Zingiber officinale Roscoe (Ginger) is one of the most widely used dietary seasonings in the world. Members of Zingiberaceae are distributed mainly in tropical and subtropical regions, including the Indo-Malayan region, which is the center of distribution and extends from tropical Africa to central and south. India is the largest producer and has been producing it as a tonic root for over 5000 years to treat many ailments as an anti-inflammatory agent, antioxidant, anti-cancer agent and anti-nausea compound. The *Zingiberaceae* family contains varied phenolic compounds that have important systemic bioactivities on the brain, bearing age- connected neurodegenerative diseases. Phenolic compounds out of the Zingiberaceae family are used in complementary and traditional medicine (TCM) to develope cognitive functions. Its

rhizomes are a origine of phytochemicals useful for bioactivities and are used in dietary intake, and many are used as spices or condiments. *Zingiber officinale* is rich in antioxidants. As a result of the extraction of zingiber rhizomes, it was found to contain, beta-carotene, ascorbic acid, phenolic acids, diarylheptanoids, polyphenols, sesquiterpene hydrocarbons, gingerols, terpenoids, paradols, and terpenes. Some of them have been found to contain oils such as Eugenol, Limonin, Geranioland Pinene (Adekoya et al., Akila et al., 2021; Razak et al., 2023).

4. MEDICINAL PLANTS AND EXTRACTION METHODS

Medicinal plants and Family	Extraction and Analytical Methods	Experimental Methods
 ***Acorus calamus L.*** **(Acoraceae)**	Methanol soaking Extraction Soxhlet extraction HPLC	*Dried AC rhizome plant powder is kept in Methanol (100%) and methanol:water mixture (50%:50%) at room temperature for 3 days. The processed solvents are collected together, changed with new solvent every day. Then concentrated using rotary evaporator. Soxhlet extraction is done and then concentrated by evaporating the solvents in rotary evaporator. Dried AC extracts are stored in airtight container in refrigerator at 4˚C (Yousuf et al, 2020). *AC is ground into powder. The plant rhizome powder is applied for methanol extraction (1:10 (w/v) root powder:methanol) using soxhlet apparatus for 7-8 hours. The extract is concentrated and the solvent is evaporated using rotary evaporator and stored at -20°C for further use (Vohora et al., 1990). *The coarsely powdered plant material is extracted with an ethanol:water mixture (1:1, 50%) at room temperature. After the extraction is complete, the solvent is completely removed by vacuum drying at low temperature (<50°C). (Muthuraman & Singh, 2011) https://en.wikipedia.org/wiki/Acorus_calamus
 ***Anemarhenae asphodeloides*** **(Asparagaceae)**	Maceration Extraction TLC, HPLC UV spectrophotometer	*The powdered plant material is degreased by maceration in n-hexane in a flask for 2 hours on an orbital shaker at 100°C. The hexane is then filtered off and the rhizome powder is thoroughly dried under a fume hood. It is mixed with 80% aqueous ethanol and sonicated for 2 hours. The extract is then filtered through filter paper. The crude extract is passed through octadecyl-silyl ODS silica gel in a 500 mL glass Büchner funnel, washed with purified (HPLC grade) water (eluate discarded), then 40% ethanol is added and evaporated at 40°C in a rotary vacuum evaporator until a yellow-orange, dry, crystalline powder is obtained (Piwowar et al, 2020). *The aerial parts of the plant were ground after drying in the shade. Then, the ground powdered plant was extracted with n-hexane and then with acetone to remove oils and chlorophyll type pigments. The powdered plant was then extracted with methanol in a soxhelet apparatus. The methanolic fraction of the plant was used during the experiments (Rauf et al, 2014) *The whole plant (B. monniera) was dried in the shade and powdered and extracted with distilled water. The aqueous extract was discarded and the remaining plant material was extracted three times with 90% ethanol. The resulting residue was dried in vacuum after the solvent was evaporated. The powdered sample was dissolved in acetone again and prepared for the experimental part (Deepak et al., 2003). https://en.wikipedia.org/wiki/Anemarrhena

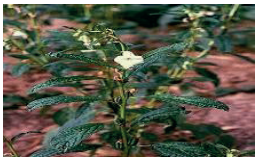
 ***Bacopa monnieri*** **(Plantaginaceae)**	Extraction HPLC UV spectrophotometer	*The above ground part of the plant dried in the shade is ground. The plant powders are extracted with n-hexane and then with acetone to remove oils and chlorophyll type pigments. Then, it is extracted with methanol in the soxhelet apparatus and the methanolic extract is used in the experiments (Rauf et al., 2014). *The all plant dried in the shade is turned into powder. The plant powders are first extracted with distilled water and the watery part is discarded. Then the remaining plant extract is extracted 3 times with 90% ethanol. The ethanol is evaporated and the drying process is done in vacuum. The dry powder is used by dissolving in acetone for the experiment Deepak Rai et al., 2003). https://en.wikipedia.org/wiki/Bacopa_monnieri
 ***Boerhaavia diffusa*** **L. (Nyctaginaceae)**	Soxhlet extraction	*The dried roots are ground to a coarse powder. The powdered plant is extracted with ethanol (95%) in a Soxhlet apparatus at 70°C until the siphoning solution becomes colourless. The solvent is distilled off and the extract is dried using a water bath at 50-60°C. The dried brown ethanol extract is stored in an airtight container in the refrigerator (4- 8°C) (Dhingra & Valecha, 2014). https://en.wikipedia.org/wiki/Boerhavia_diffusa
 ***Calendula officinalis*** **L. (Apiaceae)**	Maceration Extraction HPLC	*The shade dried flowers were extensively extracted using 70% methanol by cold maceration method for 14 days. The extract was concentrated to obtain a dark brown semi-solid paste (yield, 18.66%) (Shivasharan et al, 2013). https://en.wikipedia.org/wiki/Asteraceae
 ***Cassia occidentalis*** **L.** ***Caesalpiniaceae)***	Extraction Lyophilization	*The dried plant powders are macerated in 70% ethanol at room temperature for 7 days and shaken occasionally. After filtration of the ethanolic extract, the extract is evaporated to dryness under reduced pressure and then lyophilized. The dry residue obtained is stored at 4°C. It is resuspended in distilled water for use (Silva et al., 2023). https://en.wikipedia.org/wiki/Senna_occidentalis

 ***Celastrus paniculatus Willd.*** **(Celastraceae)**	Maceration Extraction Electrophysiological studies HPTLC UV spectrophotometer	* Finely powdered CP seeds are vortexed in deionized water for four hours and then centrifuged. The seed powder remaining in the water is removed by vacuum drying. The pellet obtained from the extract at room temperature is vortexed again in hot water (70◦C) for 4 hours. Again the hydrated sotum powders are dried in vacuum. For the acid fraction, the pellet remaining from the hot water extraction is resuspended in hydrochloric acid solution pH=4, vortexed for 4 hours, then centrifuged and finally vacuum dried. (Godkar et al., 2004). *Coarsely powdered Celastrus paniculatus Willd seeds were extracted by maceration using ethanol for 3 days and fresh ethanol was used every day. Shaking was done occasionally during the extraction period. Ethanol extract of seeds (CPEE) was filtered and concentrated under vacuum using rotary evaporator. The extracts thus obtained were prepared by suspension using different solvents (petroleum ether, ethyl acetate and n-butanol) (Malik et al., 2017). https://en.wikipedia.org/wiki/Celastrus_paniculatus
 ***Centella asiatica*** **(Apiaceae)**	Extraction UV spectrophotometer	* After the plant is dried, it is ground coarsely. For the aqueous extract, the plant powders are boiled in water for 5 hours and then filtered. The extract is concentrated and turned into powder. For the methanol and chloroform extract, the plant powders are extracted with methanol at 60-65 °C for 5 hours and filtered to obtain the extract. Then, the extract is concentrated in vacuum and the solvent is completely removed until a viscous liquid is obtained. (Kumar &Gupta, 2002). https://en.wikipedia.org/wiki/Centella_asiatica
 ***Convolvulus pluricaulis*** **(Convolvulaceae)**	Extraction Soxhlet extraction Lyophilization HPTLC UV spectrophotometer	*The dried and powdered plant is suspended separately in methanol/ethanol/distilled water and stirred for 48 hours at 30 ± 5°C, then filtered under sterile conditions. The filtrates thus obtained are concentrated with a vacuum rotary evaporator at 35°C and 280, 170 and 60 mbar pressure for methanolic, ethanolic and water extracts, respectively. The concentrated extracts thus obtained are air dried to be powdered. They are further diluted in different solvents to give each final concentration (Dhuna et al., 2012). * The shade dried plant is roughly ground to powder. The plant powders are extracted with petroleum ether (60-80 oC) in Soxhlet for 6 hours to remove the oil. The obtained extract is air dried. Then, it is extracted in 80% aqueous methanol with Soxhlet for 8 hours. A portion of the extract obtained is concentrated under vacuum and subjected to lyophilization for 48 hours. The main portion here is suspended in pure water and divided into 3 parts with petroleum ether, ethyl acetate and n-butanol, respectively. The fractionated fractions are desolvated in a rotary evaporator. The dried fractions are further lyophilized (Malik et al., 2015). https://en.wikipedia.org/wiki/Convolvulus_prostratus

 ***Coriandrum sativum*** **(Apiaceae)**	Maceration Extraction UV spectrophotometer	*The plant seeds are crushed and then macerated using ethanol. After waiting for 24 hours, the solution is filtered and evaporated to obtain the ethanol extract. This extract is subjected to a freeze-drying process, which gives it a more concentrated, water-soluble and stable form. The extraction process is repeated six times and the final extract is stored in a refrigerator at 4 °C (Hardiany et al., 2024). https://en.wikipedia.org/wiki/Coriandrum
 ***Dalbergia sissoo DC.*** **(Fabaceae)**	Extraction UV spectrophotometer	*The leaves dried in the dark are ground to a fine powder. The powdered dried leaves are extracted with methanol in a beaker for 3 days at 25 ± 2 °C with occasional stirring. The extract is then filtered using Whatman No. 1 filter paper and sterilized cotton filter. The filtered solvent is placed in the rotary evaporator and completely removed. (Mannan et al., 2017). *The leaves are dried in shade for two weeks and then ground to a fine powder. In continuous hot extraction method, the powder of plant leaves is extracted in ethanol at 78-80°C for 3 daysThe mixture is then filtered and concentrated at 40°C in a rotary evaporator under reduced pressure. The extract obtained is stored in a desiccator for experiments. For the preparation of Dalbergia sissooleaf extract suspension, weighed amount of ethanolic leaf extract is suspended in distilled water using 0.5% v/v Dimethyl sulfoxide and administered orally to mice. The extract is prepared fresh every day (Thonda et al., 2014). https://en.wikipedia.org/wiki/Dalbergia_latifolia
 ***Ficus religiosa L.*** **(Moraceae)**	Soxhlet extraction	* The leaves dried in the shade are dried and turned into coarse powder. The plant powders are subjected to sequential extraction with petroleum ether (60-80 °C), ethanol and ethyl acetate solvents in a soxhlet apparatus for 72 hours. After each extraction, the solvents are distilled and the concentrated extracts obtained are taken into petri dishes. To obtain dry extracts, the extracts are evaporated at room temperature (45-50 °C) (Bhangale et al., 2016; Gupta et al., 2022). https://en.wikipedia.org/wiki/Ficus_religiosa

 ***Garcinia kola Heckel* (Clusiaceae)**	Soxhlet extraction TLC UV spectrophotometer	*The powdered seeds are extracted with petroleum ether in the light and then with methanol in a Soxhlet apparatus at 40-60°C. The petroleum extract, which does not show antihepatotoxic activity, is discarded. The methanolic extract is extracted with benzene under reduced pressure and concentrated. The defatted alcoholic extract is partitioned between chloroform and water. On evaporation of the solvent, the chloroform extract contains a golden yellow powder, kolaviron (Akinmoladun et al., 2015). https://en.wikipedia.org/wiki/Garcinia_kola
 ***Gastrodia elata Blume* (Orchidaceae)**	Extraction ELISA	*The plant extract is prepared by extracting G. glabra powder with chloroform-water (0.1%) in a 1:8 ratio by double maceration (24 hours each maceration). The aqueous extract is then filtered through muslin cloth. The filtrate is boiled for 5 minutes. The extract is then set aside and filtered again using filter paper. The extract is concentrated to a density of 1.169 g/ml. The glycyrrhizin content is standardized to 4.22% (w/w). For use, the extract is diluted with distilled water (Huang et al., 2011). * Fresh plant roots were chopped and extracted in methanol at 60°C for 8 h, 3 times the volume of the roots. The concentrated plant extracts were resuspended in distilled water and diethyl ether was added to the volume and extracted. This ether fraction was collected in a separating funnel and concentrated at low temperature and pressure. The collected dry fractions were resuspended using 1% carboxymethyl cellulose (CMC). (Ha et al., 2000). https://en.wikipedia.org/wiki/Gastrodia_elata
 ***Glycyrrhiza glabra* (Fabaceae)**	Maceration Extraction HPLC	*The plant extract is prepared by extracting G. glabra powder with chloroform-water (0.1%) in a 1:8 ratio by double maceration (24 hours each maceration). The aqueous extract is then filtered through muslin cloth. The filtrate is boiled for 5 minutes. The extract is after that set aside and filtered once more using filter paper. The extract is concentrated to a density of 1.169 g/ml. The glycyrrhizin content is standardized to 4.22% (w/w). For use, the extract is diluted with distilled water (Michel et al., 2013). https://en.wikipedia.org/wiki/Glycyrrhiza
 ***Luehea divaricata Mart* (Tiliaceae-Malvaceae)**	Extraction IR NMR MALDI-TOF/TOF	*Powdered plant samples are extracted in ethanol for 7 hours in a Soxhlet apparatus. These extracts are freeze-dried. Each extract is dissolved in 10 mL volumetric flasks using different solvents (Mallavadhani et al., 2019). https://en.wikipedia.org/wiki/Luehea_divaricata

 ***Momordica charantia L. (Cucurbitaceae)***	Maceration Sonication Incubation HPLC-DAD ELISA Comet assay UV spectrophotometer Flow cytometry	*The fruits and seeds are ground and macerated in a hydroalcoholic solution at 25°C every day for one week by shaking. This maceration process is repeated for another three weeks so that the plant is completely transferred to the solution. At the end of the period, the crude extract is filtered and evaporated to dryness with a rotary evaporator to remove ethanol and water. Thus, the dry extract of Momordica charantia L. (MCE) is obtained. Fischer et al., 2022). * Dried fruit powders are sonicated in 70% ethanol for 10 minutes. After the primary incubation is done at 37 ◦C and 150 rpm for 6 hours, the supernatant is removed and new 70% ethanol is added again and a second incubation is done at 37 ◦C and 150 rpm for 18 hours. Then, the primary and secondary incubations The obtained solutions are combined and centrifuged at 3000 rpm for 3 minutes. The liquid remaining in the upper part is filtered through a 0.22 µm PVDF syringe filter (Millipore, Bedford, MA, USA). This solution is evaporated with the nitrogen generator used. Finally, the obtained The extract is dissolved in dimethyl sulfoxide and stored in the freezer at -30◦C until use. (Baldemir et al., 2018); Kim et al., 2018). https://en.wikipedia.org/wiki/Momordica_charantia
 ***Olea europaea* L. (Oleaceae)**	Extraction UVspectrophotometer ELISA	* To obtain green olive fruit extract, the fruits are ground in a blender and extracted three times with 80% ethanol to extract the oil. The fruit pulps are extracted with absolute ethanol (EtOH) at a ratio of 1:10 (w/v) in a heated mantle at 70-80 °C for 2 hours. The supernatant is filtered and concentrated in a rotary evaporator at 50 °C. From the fruit pulp The resulting ethanol extract was resuspended in a mixture of water:EtOH (9:1, v/v) and partitioned sequentially with n-hexane, ethyl acetate and n-butanol to obtain the final solution. The extract was dissolved in sterile distilled water and diluted with 0.22 It is filtered through µm filters. (Kim et al., 2013). https://en.wikipedia.org/wiki/Olive
 ***Panax ginseng* (C.A. Mey.) (Araliaceae)**	Extraction Electrophoresis LC-ELSD	*Fresh 6-year-old P. ginseng roots were steamed at 90–100◦C for 3 h and then dried at 50–80◦C. Prepared from water extract extracted by three 8-h cycles of circulating hot water (85–90◦C) (Jang et al., 2013). *Raw and steamed fresh ginseng were refluxed with methanol for 6 hours. After removing the methanol with an evaporator, the aqueous residue was extracted with butanol by dissolving it in water. The organic solvent was removed, then the remaining residue was dissolved in water and extracted using dichloromethane. The aqueous layer was extracted with n-butanol saturated with water for three more times (Kwon et al., 2001). https://en.wikipedia.org/wiki/Panax_ginseng

 ***Phoenix dactylifera* L. or *Date palm*** **(Arecaceae)**	Extraction Lyophilization	*The pulp of freshly ripened date fruits collected from date palm trees was extracted by grinding them three times with distilled water in a mechanical grinder. It was centrifuged at 4000 rpm for 20 min at 4°C and the supernatant was collected, and then lyophilized and stored at -20°C until use (Majid et al., 2008). https://en.wikipedia.org/wiki/Date_pal
 ***Psoralea corylifolia or Cullen corylifolium*** **(Fabacea)**	Incubation Extraction Fluorescence Spectroscopy HPLC ELISA	*Aqueous extracts of seeds are prepared by mixing powdered plant material with distilled water in a bottle and sonicating for 2 hours. The process is repeated three times. The suspension is lyophilized from the water extract. An 80% ethanol extract is prepared by sonication of the ground powder suspended in 80% ethanol solvent (v/v% in water) and dissolving it, the same method is used for the aqueous extract. (Im et al., 2014) *The dried seeds are extracted twice with 70% ethanol by reflux for 2 hours. The extracted solution is filtered through a filter paper and evaporated in a rotary evaporator. It is heated in the evaporator under vacuum until dryness. The 70% ethanol extract of the seeds is dissolved in methanol and filtered (Kim et al., 2016). https://en.wikipedia.org/wiki/Cullen_corylifolium
 ***Punica granatum* L.** **(Punicaceae)**	Squeezing method UV spectrophotometer	*Fresh pomegranate seeds are separated and crushed to obtain juice separately for all varieties. The juices are air-dried at 40∘C and concentrated under reduced pressure to get the extract (Braidy et al., 2013). *Punica granatum L. juice or aqueous extract is prepared (Sharma et al., 2020). https://en.wikipedia.org/wiki/Punica
 ***Sesamum indicum* L.** **(Pedaliaceae)**	Squeeze method Colorimeter UV spectrophotometer	*Sesame oil was squeezed and used directly as oil. (Kumar et al., 2009). https://en.wikipedia.org/wiki/Sesame

 ***Sida cordifolia* L.** **(Malvaceae)**	Maceration Incubation	*The plant roots are washed, dried and ground. The ground plant powders are macerated with ethanol in cold water. Then, the roots were incubated in a conical flask (1:10, w/v) in a shaking incubator for 72 hours at 37°C. This mixture is filtered using Whatman filter paper. The solvent is evaporated in a rotary evaporator to obtain methanol-free extracts that are stored at -20°C for later use (Simha et al., 2023). https://en.wikipedia.org/wiki/Sida_cordifolia
 ***Tinaspora cordifolia*** **(Menispermaceae)**	Maceration Incubation Soxhlet extraction Infusion Extraction Lyophilization UV spectrophotometer HPLC HPTLC ELISA UPLC/MS	*The plant roots are washed, dried and ground. The ground plant powders are macerated with ethanol in cold water. Then, the roots were incubated in a conical flask (1:10 ratio, w/v) at 37°C for 72 hours in a shaking incubator. This mixture is filtered using Whatman filter paper. The solvent is evaporated in a rotary evaporator to obtain methanol-free extracts that are stored at -20°C for later use (Singh et al., 2023; Polu et al., 2017). The plant stems are dried in the shade and turned into powder. It is extracted by soxhlet extraction at 60°C using absolute ethanol. Then, the extract is concentrated under reduced pressure and constant temperature, and stored in a desiccator for later use. After extraction with ethanol (TCE), the residues are extracted sequentially with petroleum ether (TCP), then with Dichloromethane (TCD), then with n-butanol (TCB) and finally with water. All fractions obtained are evaporated to dryness in a rotary evaporator at low pressure and controlled temperature and stored for use. (Agarwal et al., 2002). After drying, the coarsely powdered raw plant is taken into a bottle and 2 liters of distilled water is added to it and left for 2 hours. Then, after boiling for 4 hours, the obtained extract is poured into the beaker. Then, it is concentrated in the water bath so that 1/6 of the total volume remains. In order to preserve, a few drops of chloroform are added to the extract and it is stored in the refrigerator in cold conditions (Sharma & Kaur, 2018). *Dry stem powders are prepared by extracting 4 times in a 50% ethanol-water mixture and filtering. The collected extract is evaporated at 45 °C using a rotary evaporator and lyophilizer and further separated into fractions with n-Hexane, Chloroform, Ethyl acetate and n-Butanol (level). Each fraction is collected and evaporated to dryness using a rotary evaporator; this, Hexane extract, Chloroform, ethyl acetate extract and Butanol extracts are obtained. Stock solutions are prepared in DMSO for use in culture (Lange et al., 2017). https://en.wikipedia.org/wiki/Tinospora_cordifolia

Tripterygium wiilfordi **(Celastraceae)**

Homogenization
Extraction

*The root, leaf or stem parts of the plant are collected in liquid nitrogen. The tissue samples frozen in this way are taken into a teflon container and shaken with stainless steel balls for 45 seconds at 20(1/s) speed and liquid nitrogen Homogenized in a mixer mill under. The finely powdered root homogenate is taken into glass tubes and metabolites are extracted with acetone in an ultrasonic bath for 30 minutes. The tubes are then centrifuged at 3000 rpm for 5 minutes and the upper liquid is transferred to another glass tube. The solvent is evaporated in vacuum and the remaining part is dissolved in acetone for the second extraction according to the above method. In this way, the tissues are extracted a total of four times and the resulting residue (after removing the solvent) is dissolved in a mixture of acetonitrile:water (80:20, v/v). The extracts are 20 mm It is filtered through a filter (polytetrafluoroethylene). After preparation, it can be stored at -20°C for 5 days to be used in analyses. (Lange et al., 2017).

https://en.wikipedia.org/wiki/Tripterygium

Valeriana officinalis **L. (Caprifoliacea)**

Extraction
Incubation
Fluorescence spectroscopy

*For the preparation of petroleum ether extract, Valeriana officinalis root is pulverized and macerated with petroleum ether three times (3x48 hours). Following filtration and extraction, the solvent is removed using a rotary evaporator at 40-40 ° C. In order to the preparation of the aqueous extract, the powdered roots were added to 90 ◦ C distilled water for 60 minutes. The aqueous extract is then filtered, lyophilized and stored in closed bottles (Ortiz et al., 1999).

*The plant roots are ground in a blender. They are extracted with 95% ethanol (1:40 w/v) at low speed for five minutes. The mixture is left for 48 hours. The mixture is filtered through a filter. It is dried using a paper rotary evaporator. Aliquots of the dried 95% ethanol plant extract mixture are stored at 0° C (Bhatnagar et al., 2009).

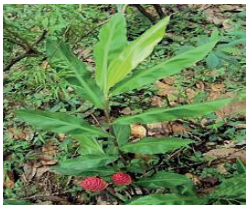
https://en.wikipedia.org/wiki/Valerian_(herb)

Withania somnifera **L. (Dunal) (Solanaceae)**

Extraction
Incubation
ELISA
UV spectrophotometer

*The plant roots are dried and powdered, thoroughly extracted with aqueous alcohol (1:1) at 55±5°C. The ethanol is removed under pressure and the aqueous concentrate is extracted with chloroform to remove oily material and free withanolides. The chloroform-insoluble (water-soluble) fraction is spray-dried to give a free-flowing, colorless powder. In use, dissolve in 0.9% saline. The powdered WS roots are extracted with Chloroform-methanol and dried to remove solvents (Bhatnagar et al., 2009).

Extracted in ethanol (Venkatramaniah & Praba, 2015) https://en.wikipedia.org/wiki/Withania_somnifera



Extraction
Colorimetry
ELISA
NMR

* Plant rhizomes are extracted using absolute ethanol and distilled water. A: Absolute ethanol: Rhizomes are thinly sliced, dry weight is determined for stabilization and 2 dried for 1 week. Dried rhizomes are ground into powder and left in 1.5 L of absolute ethanol at room temperature (25-30 °C) for 3 days. B. Aqueous extraction: Before cooling to room temperature, the powdered rhizome is refluxed in 1 L of distilled water. (100 °C) for 60 minutes. At the end of each extraction, the mixture is filtered through gauze. The solutions filtered from each solvent are then filtered through Whatman no. 1 filter paper using a vacuum pump. These solutions leave a dark brown, viscous, crude extract. It is concentrated using a rotary vacuum evaporator to obtain Extracts are stored in brown bottles at 4 °C. Dilutions and stock solutions of crude extracts are prepared by dissolving each crude extract in DMSO. (Inthanon et al., 2018).

***Zingiber officinale Roscoe;* (Zingiberaceae)**	Chemiluminescence method UV spectrophotometer	*Extraction of dried plant roots is done by filtration. Roots are crushed with a blender and then kept in 70% methyl alcohol for 3 days. After filtering the homogenized mixture using Whatman filter paper No. 40, the filtrate is kept in vacuum at 50°C to evaporate methanol. Crystallized extract is obtained (Azizidoost et al., 2019). *Freshly taken samples are washed with clean water, cut into smaller pieces and dried in an oven at 70°C until they reach constant weight. Samples are then ground into powder with a mortar and stored in an airtight container at 20°C in a refrigerator. Samples are weighed into a bottle for use. 25 mL of distilled water is added and the mixtures are stirred at 60°C. Then the mixture is filtered through Whatman No. 1 filter paper and stored in a brown bottle in a -20°C refrigerator (Adekoya et al., 2016). https://en.wikipedia.org/wiki/Zingiber_zerumbet

5. CONCLUSION

Many studies have been conducted and continue to be conducted on the effectiveness of plant-based compounds obtained from plant roots, leaves and fruits in in vitro and in vivo neurodegenerative studies. It is known that oxidative pressure plays an important role in the pathophysiology of HD. In the compilation, it is seen that plants with neuroprotective activity are beneficial against the negative effects of HD. In the future, more and more in-depth studies are needed to evaluate the existence and therapeutic properties of phytochemicals contained in herbal supplements with neuroprotective properties against HD effectively and safely and to identify new phytochemical components. Although there is no definitive treatment method for neurodegenerative diseases today, there are some drugs that slow down the progression process and improve the patient's quality of life.

In recent years, studies with plants used in applications called alternative or complementary treatment methods used in the treatment of some diseases have accelerated with developments in medicine. The purification of the rich bioactive active ingredients contained in these plants and the transformation of these active ingredients into products in different forms have created and continue to create a large market as herbal food supplements in pharmacies, markets and the internet. People use these products to strengthen the immune system, increase energy levels and support general health. When used regularly, these drugs can cause serious side effects and irreversible problems for the patient. For this reason, the best extraction conditions for obtaining the phytochemicals contained in these drugs, the appropriate solvents and methods used to obtain each phytochemical, high efficiency and the results of animal experiments conducted with them should not be ignored. In addition, the most important point to remember in the use of herbal products should not be forgotten that they should be taken under the supervision of a doctor. The second important point should be considered that if the person has a significant illness and uses medications regularly, these food supplements may interact with the medications

they use and cause undesirable results.

As a result, the extraction conditions and activities of neuroprotective medicinal plants used in the treatment of Huntington's disease, which contribute to the recovery of brain damage in neurodegeneration and have the potential to increase learning and memory functions, have been examined. It has been determined that more in vivo studies are required with these plants under appropriate extraction conditions.

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Chapter 5

EFFECT OF PLANT EXTRACTS ON MULTIPLE SCLEROSIS

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INTRODUCTION

The central nervous system (CNS) plays a crucial role in carrying out the human body's basic functions. Neurodegenerative disorders occur when there are anatomical problems with brain or spinal cord function. The increase in life expectancy has increased the prevalence of common neurodegenerative disorders and therefore neuroprotection strategies are widely sought. A recent publication by the World Health Organization (WHO) estimates that almost one billion people currently suffer from neurodegenerative disorders, with about 6.8 million succumbing to them each year, with such disorders being more common in developing countries than in developed countries (Upadhyay, 2014; Kundap et al., 2017). Multiple sclerosis (MS) is a chronic autoimmune condition where the immune system targets the central nervous system, leading to demyelination and neurodegeneration (Piehl, 2021).

Multiple sclerosis (MS) affects neurons in the brain and spinal cord, which are crucial for cognitive, emotional, motor, sensory, and visual functions. These neurons are protected by a fatty layer called the myelin sheath, which facilitates signal transmission. MS leads to the gradual destruction of this myelin (demyelination), resulting in the impairment of axons in the brain and spinal cord, potentially causing paralysis (Namjooyan et al., 2014). MS symptoms appear when the myelin sheath around nerve cells in the central nervous system (brain and spinal cord) begins to be destroyed and so impaired. The mechanism responsible for the onset of MS can be summarized in two reasons: (1) the immune system destroys the myelin sheath and (2) myelin-producing cells fail to produce new sheaths (Koriem, 2016).

MS initially presents with sensory disturbances, optic neuritis, diplopia, Lhermitte's signs, limb weakness, ataxia, and bladder and bowel issues, alongside various neurological symptoms. Recurrent stereotypic phenomena are common in MS. Cognitive impairment in MS patients often prolongs task completion times (Namjooyan et al., 2014).

MS can present in several ways: clinically isolated syndrome (CIS): describes a constellation of neurological symptoms that is the first clinical manifestation of possible MS; Relapsing-remitting (RRMS): The most common form of MS, characterized by intermittent episodes of symptoms (relapses) followed by a short or prolonged absence of clinical attacks (remissions); Secondary progressive (SPMS): After living with RRMS for a long time, relapses decrease and symptoms gradually persist without relapse or improvement; and Primary Progressive (PPMS): Starting from the first symptoms, the disease gradually progresses and worsens, with no apparent relapse or remission (Theodosis-Nobelos and Rekka, 2022; Namjooyan et. al., 2014). Although several treatments for relapsing-remitting MS are now available and many patients are already treated with these drugs, most patients eventually become

secondary progressive without treatment against this phase. Unfortunately, there is no effective treatment for the secondary progressive stage. This makes the identification and characterization of neuroprotective compounds in MS an important scientific challenge.

MS is pathologically detected by the appearance of demyelinating areas in the white matter of MS and perivascular T cell inflammation (Namjooyan et. al., 2014; Koriem, 2016). Experimental autoimmune encephalomyelitis (EAE) has been used worldwide as an animal model of MS and has helped to identify autoantigens associated with its pathology and progression. It is now well documented that inflammatory responses may play a role in the pathogenesis of EAE. (Vazirinejad et. al., 2014).

Smoking, infections, low vitamin D levels, vaccination, gut microbiota, stress, obesity, exposure to heavy metals and pesticides have been recognized as risk factors for the development of MS (Costantini et. al., 2022). However, the pathophysiology of MS is not fully understood, which makes the treatment strategy very difficult and complex. Furthermore, no definitive cure for MS has been found so far, so the search for a completely effective and safe treatment is still ongoing (Mojaverrostami et. al., 2018).

The global MS population has grown from 2.3 million in 2013 to 2.8 million in 2020 and 2.9 million in 2023 (Figure 1). (www.atlasofms.org)

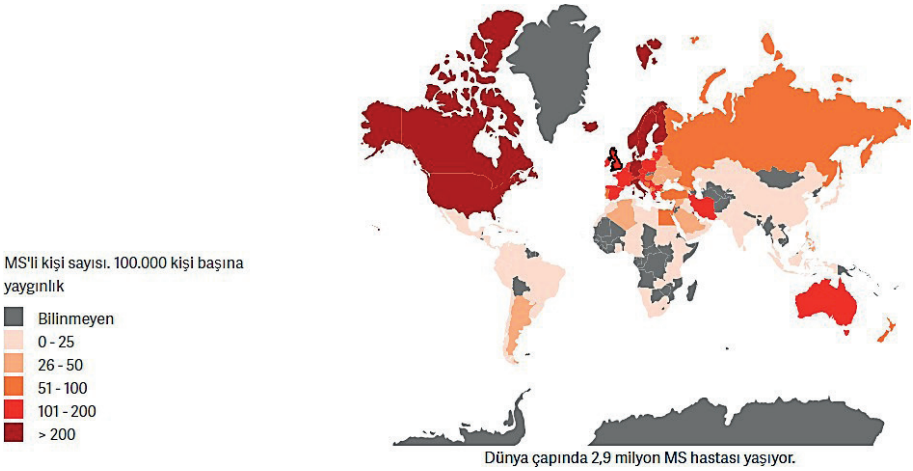


Figure1. *Number of people with MS worldwide (www.atlasofms.org; 20.05.2024)*

Moreover, data from multiple large-scale cohort registries have corroborated the finding that life expectancy in the MS population is reduced by a range of 7 to 14 years in comparison to the general population without the disease. A minimum of 50% of patients die as a direct consequence of MS (Scalfari et al., 2013). So far, there is no cure for MS. All MS treatments try to

improve neuronal function and stop the progression of the disease after MS has occurred (Koriem, 2016).

Interferon beta (IFN-beta) was confirmed for the first time in 1993 as an effective drug for the treatment of MS. Subsequently, other drugs for the treatment of MS have been launched, including fingolimod, natalizumab, glatiramer acetate and alemtuzumab (Mojaverrostami et. al., 2018). But all traditional pharmacological drugs have potentially unpleasant side effects. (Farzaei et. al., 2017). Several studies have shown adverse effects of taking IFN-beta, including stroke, headache, migraine and depression (Mojaverrostami et. al., 2018). Unfortunately, therapeutic failure is widespread among individuals in the chronic or severe stages of the disease (Farzaei et al., 2017). As a result, the use of complementary and alternative medicine (CAM) in MS patients has expanded significantly, with 33 to 80% of patients using various types of CAM, the most prevalent of which is herbal therapy. Yadav et al. (2014); Petersen et al. (2021); Amiri et al. (2023); Bahrami et al. (2020).

Medicinal herbs have a long history of clinical usage, are well tolerated, and have sparked significant interest in treating neuropsychiatric/neurodegenerative illnesses due to their therapeutic potential (Moreira et al., 2023). Furthermore, numerous studies have demonstrated the antioxidant and anti-inflammatory effects of medicinal plants and other useful substances that create natural, reliable, and safe treatments in the treatment of neurodegenerative diseases (Mohaverostami et al., 2018).

An increasing body of research is being undertaken on the effectiveness of medicinal herbs in MS. A growing body of evidence indicates that certain herbal compounds may facilitate myelin repair and contribute to the suppression of inflammation. (Namjooyan et al., 2014; Olsen, 2009; Kaplan et al., 2007). Therefore, the demand for medicinal plants that may have beneficial effects on MS patients is constantly increasing (Costantini et. al., 2022). Numerous plants contain many active ingredients with pharmacological activity that are promising for the treatment of neurological diseases. However, the current challenge in the use of herbal medicines is the lack of documented, precise information on plant species, their extraction, and safety profiles. In this chapter, medicinal plants with neuroprotective, anti- inflammatory, and immunomodulatory properties, which are vital in addressing the complex pathology of disease, are investigated in terms of extraction conditions.

1. THE EFFECTIVENESS OF MEDICINAL PLANTS IN MS

A plethora of molecular structures are present in nature, and they are instrumental in the creation of new drugs that are effective against a range of diseases. Medicinal plants have a long history of clinical use, are better tolerated and, given their therapeutic potential, attract considerable interest in treating neurodegenerative and neuropsychiatric diseases (Moreira et al.,

2023). Plants produce various organic chemicals consisting of primary and secondary metabolites. Primary metabolites include protein, sugar, lipids, and nucleotides. Secondary metabolites, also called phytochemicals, are abundant in fruits and vegetables and exhibit excellent antitumor properties as well as antioxidant, antimetastatic, antiproliferative, anti- inflammatory, and antiangiogenic activities. Secondary metabolites or phytochemicals are classified according to their structure as polyphenols, triterpenoids, flavonoids, alkaloids, and glucosinolates (Gautam et al., 2023).

Most of the active or natural components extracted from various plant parts, including leaves, flowers, roots, stems, and fruits, are predominantly secondary metabolites (Abdin et al., 2007; Sharif-Rad et al., 2020). These compounds have a long history of use in traditional medicine systems, where they have been employed for their antioxidant properties, which confer therapeutic benefits. Secondary metabolites may include alkaloids, flavonoids, phenolic acids and terpenes (Teng et al., 2023). Flavonoids (flavones, flavonols, isoflavones, isoflavones, anthocyanins, flavanones) constitute an important part of phenolic antioxidants. (Karak, 2019). It has cyclooxygenase (COX) and lipoxygenase (LOX) inhibitory effects, leading to anti-inflammatory potential, including radical scavenging, solvent chelation, antioxidant enzyme promotion, and prooxidant enzyme silencing activity. In addition, flavonoids can reduce the expression of pro-inflammatory mediators (Theodosis-Nobelos and Rekka, 2022).

Vegetable oils have shown promise in treating MS and its symptoms by reducing inflammation, promoting remyelination, immune modulation, and inhibiting oxidative stress (Al-Naqeb et al., 2023). Studies from East Asia have consistently demonstrated the beneficial effects of various plants and their compounds on MS (Costantini et al., 2022).

Fingolimod (FTY720) exemplifies an anti-MS drug developed through the chemical modification of mirocin, a natural product isolated from Cordyceps sinensis, a mushroom used in traditional Chinese medicine. It was approved in 2010 (Bayat, et al., 2021). There is great interest in the medicinal applications of Cannabis sativa L. In several countries, products derived from Cannabis sativa L. have been licensed as medicines for the treatment of MS symptoms. Tetrahydrocannabinol (THC) and cannabidiol (CBD) are two compounds of great interest. THC, known for its psychotropic effects, has shown efficacy in reducing MS-related tremors by acting as an agonist at the CB1 receptor and also exhibits analgesic properties. CBD, on the other hand, has anti-inflammatory effects and provides some pain relief. An oral spray (Sativex®) containing cannabidiol (CBD) and tetrahydrocannabinol (THC) has recently been approved in Canada for the treatment of neuropathic pain associated with MS (Ikan, 2008).

Andrographolide, ginkgo flavone glycosides, boswellic acid, epigallocatechin-3-gallate, ginsenosides, cannabinoids (cannabidiol and delta-9-tetrahydrocannabinol), and proanthocyanidins are key bioactive components of medicinal plants with therapeutic potential in MS (Farzaei et. al., 2017). Flavonoids are identified as potential therapeutic agents that target immune inflammation pathways, thereby potentially inhibiting the inflammatory processes implicated in neurodegenerative disorders (Bayat et al., 2021).

2. MEDICINAL PLANT TREATMENTS FOR COMPLICATIONS OF MULTIPLE SCLEROSIS (MS)

MS is an autoimmune disease affecting the nervous system. Recently, there has been growing interest in exploring plants and natural compounds as potential complementary or alternative therapies for MS (Costantini et al., 2022). Existing MS treatments often exhibit limited efficacy or pose safety concerns, prompting the exploration of novel drugs to address inflammatory conditions in MS (Bayat et al., 2021).

Reducing the severity of MS is one of the beneficial effects of medicinal plants in MS. They promote the differentiation of local stem cells into myelin-producing cells and have antioxidant, anti-apoptotic, and anti-inflammatory properties. Medicinal plants play an important role in the treatment of MS and its associated symptoms (Mojaverrostami et. al., 2018). Our knowledge of the effects of medicinal plants, or the compounds they contain, in treating this disease has increased significantly over the last decade with the use of animal models of MS (experimental autoimmune encephalomyelitis; EAE) (Watson and Killgore, 2016).

Table 1 describes the medicinal plants effective in multiple sclerosis, the phytochemicals they contain, their extraction conditions and mechanisms of action. Many researchers have reported the efficacy of medicinal plants and their extracts against multiple sclerosis. Plants containing different types of phytochemicals have revealed a potential mechanism against MS.

Achillea millefolium L. (Yarrow)

Achillea millefolium L. (yarrow) belongs to the Asteraceae family. It is known worldwide as a powerful medicinal plant (Ayoobi et al., 2019). In traditional medicine, *A. millefolium* has long been used to treat various ailments such as infectious diseases, pain, wounds and gastrointestinal complaints. It is also reported to have anxiolytic-like and anti- inflammatory properties in the nervous system. (Watson and Killgore, 2016). *A. millefolium* contains a wide range of bioactive constituents including succinic acid, caffeic acid, ascorbic acid, fatty acids, amino acids, folic acid, salicylic acid and flavonoids. Most of the antioxidant and anti-inflammatory properties of

this plant are due to the flavonoids kaempferol, luteolin and apigenin. (Ayoobi et al, 2017). It has been shown to protect against learning deficits in MS (Liu et. al., 2014; Daily et. al., 2021). Studies have shown that apigenin is effective in insomnia and various neurological disorders (Patil et. al., 2022). Apigenin has also been reported to reduce disease severity and progression in an animal model (EAE) of MS. (Ginwala ve ark., 2016).

In a recent study, the flowers and stems of *A. millefolium* were extracted by maceration in distilled water for 24 hours and the dried extracts were administered in 250 and 500 mg doses. The amount of luteolin (0.28 mg/g) and apigenin (1.58 mg/g) in the extract was determined by the HPLC method. In this study, the aqueous extract of *A. millefoliumu* was found to significantly reduce the relapse rate in MS patients and prevent the progression of MS associated with the alleviation of inflammation (Ayoobi et al., 2019).

Vazirinejad et al. (2014) extracted the aerial parts of the plant with water in a Soxhlet apparatus followed by evaporation at 40°C to obtain the dried extract. In the EAE model of MS in male C57BL/6 mice, oral administration of aqueous extract of *A. millefolium* attenuated disease severity as well as inflammatory responses and demyelinating lesions.

There are some reports that *A. millefolium* and its flavonoid components have sedative effects; for example, intraperitoneal injection of *A. millefolium* leaf extract extracted with petroleum ether in a Soxhlet apparatus into Wistar rats was found to have a greater sedative and anxiolytic effect than diazepam (Rezaie and Ahmadizadeh, 2013).

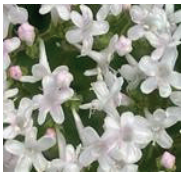
Furthermore, aqueous extract of *A. millefolium* obtained by maceration using 90% ethanol, administered by chronic gavage (Baretta et al., 2012) or aqueous *A. millefolium* extract injected intraperitoneally as such showed anti-anxiety effects in albino Swiss male mice (Molina-Hernandez et al., 2004). Therefore, *A. millefolium* can be an effective additional treatment for MS patients.

***Andrographis paniculata* (Burm. f.) Nees.**

A. paniculata is an Asian plant, known since ancient times as "King of Sorrows". It has attracted particular attention for its main constituent Andrographolide, a diterpene lactone. *A. paniculata* is known for its anti-inflammatory, antibacterial, antiviral, antineoplastic, hepatoprotective, hypolipidemic, and hypoglycemic properties (Bosco et al., 2023). Andrographolide treatment reportedly reduced behavioral disturbances in mice with EAE by inhibiting T cell and antibody responses to myelin (Watson and Killgore, 2016).

Aqueous and ethanolic leaf extracts have significant analgesic, anti-inflammatory and antioxidant properties. It has been reported that methanol and ethanol leaf extracts have the strongest antioxidant activity (Akbar, 2020). In the study conducted by Sani et al. (2019), the leaves of *A. paniculata* were extracted in distilled water at 60°C for 4-5 hours and dried as dry powder. The extract was then standardized by HPLC for neoandrographolide (NAG), 12- didehydroandrographolide (DDAG), and 14-deoxy-11, andrographolide (AGP) contents. The potential of a standardized aqueous extract of *A. paniculata* to reverse lipopolysaccharide (LPS)-induced neuroinflammation and cognitive impairment was examined in vivo. This study demonstrated that the aqueous extract of *A. paniculata* protects against LPS-induced cognitive impairment and neuroinflammation. Pharmacokinetic analyses in Wistar rats treated with *A. paniculata* and Andro extract revealed its ability to cross the blood-brain barrier and exert neuronal effects due to its significant brain distribution. *A. paniculata* also reduced LPS- induced cholinesterase activity, indicating anti-inflammatory properties and enhancing spatial learning in cognitive tests (Sani et al., 2019; Bosco et al., 2023). Methanol extract of leaves of *A. paniculata* and andrographolide were found to exhibit adaptogenic properties and significantly ameliorate stress-induced pathological changes (Akbar, 2020).

Table 1. *Medicinal plants effective in multiple sclerosis, extraction conditions and mechanisms of action*

Plants	Active Constituents	Extraction	Effect in MS	References
 *Hypericum perforatum* L.	Hypericin	The above-ground parts of *H. perforatum* were extracted in ethanol- water (70/30, v/v) for 72 h in the dark on a shaker	Attenuated EAE autoimmune responses by inhibiting immune cell infiltration and T reg cell expansion Anti-depression activity	Nosratabadi et al., 2016; https://www.nccih.nih.gov/health/st-johns-wort
 *Valeriana officinalis* L.	Isovalporate, valeric acid, valernal, valeron, isovaleric acid, valproate, α- and β- pinene, and didovalporate	Root parts of *Valeriana officinalis* were extracted with soxhlet using ethanol-water (70:30)	Decrease in pain score in acute and chronic phase; neuroprotective effect	Zare et al., 2018; Das et al., 2021; Duke, 2002 https://identify.plantnet.org/tr/k-world- flora/species/Valeriana%20officinalis%20L./data
 *Ginkgo biloba L.*	Kaempferol, quercetin, myricetin, apigenin, luteolin, tamarixetin, ginkgolides	*G. biloba* leaf extract, long-term extraction with ethanol at 30°C	The anti-inflammatory properties and the inhibition of the platelet activating factor (PAF)	Mojaverrostami et al., 2018; Duke, 2002 https://identify.plantnet.org/tr/k-world- flora/species/Ginkgo%20biloba%20L./data

 *Oenothera biennis* L.	γ-linoleic acid	The oils are extracted from flowers and seeds. The method of cold pressing.	Anti-inflammatory and immune-modulating effects	Mojaverrostami et al., 2018 https://identify.plantnet.org/tr/k-world- flora/species/Oenothera%20biennis%20L./data
 *Panax ginseng* CA Mayer	Ginsenosoides	Extracted from *panax ginseng* roots in hot water (85-90°C) with three 8- hour extraction cycles.	Downregulates the p38 MAPK/NF-κB signaling pathway and protects against spinal demyelination in an acute EAE model	Lee et al., 2018; Duke, 2002 https://identify.plantnet.org/tr/k-world-flora/species/Panax%20ginseng%20C.A.Mey./data
 *Cannabis sativa L.*	Cannabinoides	*Cannabis sativa* flowers or leaves extract. Cannabinoid extraction with different solvents. After extraction with the non-polar solvent, the application of a second liquid-liquid extraction (LLE) with the addition of 0.1 M NaOH makes it possible to	Improves some symptoms associated with MS. These include spasticity, pain, tremor and depression.	Novak and Blüthner, 2020; Farzaei et al., 2017; Mojaverrostami et al., 2018 ; Akbar, 2020
 *Curcuma longa* L.	Curcumin	*C. longa* rhizomes extracted by fermenting with 50% ethanol solution at 80oC for 4 hours and then lyophilized. C. longa rhizomes were extracted with 80% methanol solution at 26°C for three days with shaking.	Anti-neuroinflammatory effects, neuroprotective activity	Kim et al., 2022; Hassan et al., 2021; Akbar, 2020
 *Cinnamomum zeylanicum* Nees	Cinnamaldehyde, sodium benzoate	*C. zeylanicum* bark extracted with 50% ethanol in orbital incubator shaker at 20°C at 60 rpm.	Antiinflammatory activity	Joshi et al., 2010; Akbar, 2020

 *Crocus sativus* L.	Lycopene, safranal, zeaxanthin, carotenoids, terpenes, crocin, crocetin, picrocrocin	*C. sativus* stigma extracted with ethanol (80%) by percolation procedure.	Reduces clinical symptoms, delays disease onset, and reduces depression in the EAE mouse model	Akbar, 2020; Akhondzadeh et al., 2005; Ghazavi, et al., 2009; Akbar, 2020
 *Nigella sativa* L.	Thymoquinone	*N. sativa* seeds were grinded and suspended in distilled water	Improves clinical signs of EAE, suppresses inflammation, increases remyelination, increases remyelination in the cerebellum, and reduces TGF β1 expression	Noor et al., 2015; Fahmy et al., 2014; Akbar, 2020
 *Punica granatum* L.	Ellagic acid, punicalagin and punicalin	*Punica granatum* peel was extracted with 50% ethanol in an ultrasonic bath at 60 °C for 40 min (solid/ solvent ratio 1:10)	Inhibits the production of Th17	Rabiei, 2019; https://identify.plantnet.org/tr/k-world- flora/species/Punica%20granatum%20L./data
 *Artemisia dracunculus* L.	Essential oils, Flavonoids, coumarins, tannins and phenylpropanoids	the above-ground parts of *A. dracunculus* were extracted by maceration method for 24 hours in water at 50°C and then lyophilized.	EAE was found to modulate immune responses, increase antioxidant serum levels, increase levels of inflammatory cytokines including IL-17 and IL-23, and reduce immune cell infiltration and demyelination in the brain of EAE mice	Safari et al., 2021; Ekiert et al., 2021; https://identify.plantnet.org/tr/k-world- flora/species/Artemisia%20dracunculus%20L./data
 *Nepeta hindostana* Haines	Cadina-1,4-diene, α- humulene, (E)- caryophyllene, β-sesquiphellandrene, α- cadinene and β-bisabolene.	*N. hindostana* leaves were extracted by maceration method for 72 hours in ethanol	Exhibited significant effects on remyelination and neuroprotection	Rasool et al., 2022; Siddique et al., 2019; https://www.gbif.org/occurrence/2423139525

 *Vitex negundo* L	Protocatechuic acid, oleanolic acid, flavonoids, Salviaplebeiaside, γ- tocopherol,	*V. negundo* leaves were extracted by maceration method for 72 hours in ethanol	Antiinflammatory activity	Rasool et al., 2022; Gill et al., 2018 https://identify.plantnet.org/tr/k-world- flora/species/Vitex%20negundo%20L./data
 *Pterodon emarginatus* Vogel	sesquiterpenes from volatile aromatic terpenes and phenyl propanoids, mainly β- elemine and β-caryophyllene	*P. emarginatus* seeds were extracted by ethanol extraction and maceration crushing method at room temperature for 48 hours.	It reduced neurological symptoms and the development of EAE. It inhibits both microglial activation and iNOS expression, associated with the inhibition of axonal demyelination and neuron death.	Alberti et al., 2014; https://identify.plantnet.org/tr/k-world- flora/species/Pterodon%20emarginatus%20Vogel/data
 *Capparis ovata* Desf	Kaempferol, quercetin, rutin, phenylpropanoic acids	The aqueous extract of *Capparis ovata*; butanol fraction of the hydroalcoholic extract	Anti-neuroinflammatory effects in SH-SY5Y cells in vitro	Sen et al., 2014 https://www.gbif.org/occurrence/3427836535

Another study investigated *A. paniculata*'s effect on relapse rate and fatigue in interferon beta-treated relapsing-remitting MS (RRMS) patients. The leaves and above-ground parts of *A. paniculata* were extracted with 75% ethanol and made into tablets. The amount of andrographolide, 14-deoxyandrographolide, and neoandrographolide in the tablets was determined by HPLC method. This study demonstrated that the ethanol extract of *A. paniculata* alleviated fatigue in patients with RRMS who were treated with interferon beta, both in comparison to a placebo and to interferon beta treatment alone, after one year (Bertoglio et al., 2016).

***Artemisia dracunculus* L. (Tarragon)**

A. dracunculus belongs to the Asteraceae (chamomile) family, widespread in America, Asia and Europe, and contains flavonoids (quercetin, kaempferol, luteolin, isorhamnetin, naringenin), phenylpropanoids, coumarins (scopoletin, scoparone, artemidin, esculetin, capillarin), tannins and essential oils (elemicin, sabinine, estragole, methyl eugenol) (Ekiert et al., 2021; Safari et al., 2021). This species has a long history of use in traditional medicine for treating gastrointestinal disorders, serving as an anesthetic, and addressing conditions such as dermatitis, insomnia, and epilepsy (Ekiert et al., 2021; Safari et al., 2021).

Extracts from the aerial part, leaves, and essential oil have been shown to have antifungal, antioxidant, antiprotozoal, immunomodulatory, antibacterial, antineoplastic, anti- inflammatory, antidepressant, and analgesic properties (Ekiert et al., 2021). Both above-ground parts and leaves of *A. dracunculus* were extracted by ultrasonic, soxhlet, accelerated solvent, maceration, supercritical, or microwave extraction methods using polar or non-polar solvents such as methanol, hexane, water, acetone, ethanol (Can Gerçek et al., 2023). Phenolics and flavonoids, the major *A. dracunculus* compounds, play key antioxidant roles (Costantini et al., 2022).

In the study by Safari et al. (2021), the above-ground parts of *A. dracunculus* were extracted by maceration method for 24 hours in water at 50°C and then lyophilized. Oral administration of the obtained aqueous extract of *A. dracunculus* to animal models of MS such as EAE was found to modulate immune responses, increase antioxidant serum levels, increase levels of inflammatory cytokines including IL-23 and IL-17, and reduce immune cell infiltration and demyelination in the brain of EAE mice (Safari et al., 2021). The beneficial effects of the aqueous extract of *A. dracunculus* are likely due to its compounds, including alkaloids, tannins, terpenes, and particularly flavonoids. These compounds may be useful in treating MS.

Cannabis sativa L. (Bang, Marijuana ve Hachis)

Cannabis sativa L. (Marijuana) belongs to the Cannabidaceae family and is widely cultivated worldwide. Since ancient times, its medicinal uses have included diarrhea, pain and inflammation, autoimmune diseases and as a psychoactive drug (Kumar et al., 2021; Akbar, 2020).

Many known chemical compounds are present in *C. sativa*, of which about 100 are classified as cannabinoids, which are aryl-substituted meroterpenes. Over 500 metabolites have been identified, including sugars, terpenes, steroids, hydrocarbons, nitrogenous compounds, amino acids, non-cannabinoid phenolics, and flavonoids (Novak and Blüthner, 2020; Kopustinskiene et al., 2022). The biological effects of the cannabinoids in *C. sativa* have been extensively researched. These chemicals bind to proteins in the central nervous system (CNS) that reduce nerve cell activity (Bowling, 2007). The most important active compounds are Δ-9- tetrahydrocannabinol (THC) and cannabidiol (CBD) due to their lipophilic structure which allows it to pass through the blood-brain barrier. (Kopustinskiene et al., 2022).

Various methods have been developed for the determination of cannabinoids in plant material. Cannabinoid extraction can be performed with different solvents depending on the analytical technique used. After non-polar solvent extraction, a second liquid-liquid extraction (LLE) with 0.1 M NaOH separates the acidic cannabinoids in the aqueous phase. These methods are effective for analyzing flowers or leave with high cannabinoid content.

(Novak and Blüthner, 2020). Clinical evidence confirms the therapeutic potential of cannabinoids in treating MS symptoms (Rabiei, 2019).

Numerous studies have shown that cannabinoid consumption in MS patients reduces muscle stiffness, spasms, bladder discomfort, sleep disturbances, and neuropathic pain (Mojaverrostami et al., 2018). Some studies have shown that cannabinoid administration for the improvement of spasticity in MS has shown that cannabinoid consumption leads to significant improvement in patient-reported spasticity (Mojaverrostami et al., 2018). The study evaluated the therapeutic efficacy of cannabinoids in MS. 667 patients with stable MS and muscle spasticity were given *C. sativa* extract, THC, or placebo for 15 weeks. It was found that both extract and THC showed significant improvement in spasticity and pain compared to placebo controls, and also improved muscle spasm, sleep, and pain perception (Farzaei et al, 2017).

Nabiximols (trade name Sativex) is a mucosal mouth spray composed of two cannabinoids, THC and CBD, extracted from *C. sativa*. It is used to alleviate neuropathic pain, spasticity, sleep issues, bladder discomfort, and other symptoms related to MS. In 2011, Nabiximols, an alcohol-based Cannabis extract with a 1:1 ratio of THC to CBD, received regulatory approval. Administered via a sublingual dose pump, Nabiximols remains the only cannabinoid-based drug approved in Germany for treating MS-related spasticity (Havlíček and Spížek, 2014; Mojaverrostami et al., 2018).

***Crocus sativus* L. (Saffron)**

Saffron, obtained from the dried red tops of the flower of *Crocus sativus* L., is a legendary plant that is one of the most expensive products among medicinal plants in the world and is therefore called "red gold" (El Midaoui et al., 2022). It has been known for more than 4,000 years. In traditional medicine, it is mainly used as a tonic and antidepressant (Cardone et al., 2020).

Saffron stigmas are rich in over 150 compounds. The aqueous and ethanol extracts of saffron stigmas contain alkaloids and saponins. Key bioactive volatile compounds are terpenes, terpene alcohols and their esters, picrocrocin, crocetin, crocin and safranal (Akbar, 2020). *C. sativus* and its active components (crocin, safranal, crocetin) have powerful antioxidant and anti-inflammatory effects on brain cells (Yang et al., 2023). An abundance of evidence suggests that *C. sativus* supplementation may provide antidepressant, cardioprotective, neuroprotective anxiolytic, and neurocognitive effects. Concerning MS in particular, given the properties mentioned above of *C. sativus*, it may prove to be a valuable complementary therapy in the management of various symptoms of the disease (Grammatikopoulou et al., 20-22).

C. sativus plays a role in the prevention of multiple sclerosis thanks to its active component crocin (a water-soluble carotenoid), which helps prevent the construction of myelin brain cells; Crocin and crocetin plays an important role in the efficiency of electrical transmission of nerve impulses in the central nervous system and peripheral nervous system (El Khoudrı et al., 2021). Crocin exerts its anti-inflammatory effects by inhibiting the cytotoxicity of astrocytes and oligodendrocytes induced by syncytin-1 and nitric oxide (NO), thereby reducing neurological damage in experimental autoimmune encephalomyelitis (EAE) (Mojaverrostami et al., 2018).

The effect of an 80% ethanol extract of *C. sativus* on EAE in mice was assessed, revealing that saffron had a protective effect, delayed disease onset, and lowered the maximum clinical scores in C57BL/6 mice. Treated mice had a significantly lower mean cumulative disease index and a reduced overall disease course compared to controls (Ghazavi et al., 2009). These findings suggest that saffron may be beneficial in treating MS (El Khoudrı et al., 2021).

***Curcuma longa* L. (Turmeric)**

Curcuma longa, commonly known as turmeric, is a perennial, herbaceous plant belonging to the family Zingiberaceae. It has been used in traditional medicine for the treatment and prevention of various diseases (Fuloria et al., 2022). *C. longa* is used in traditional medicine and contains more than 300 biologically active compounds (Iweala et al., 2023).

In several studies using different identification methods, phytochemical analysis of various parts of *C. longa* has revealed many bioactive phenolic compounds. Diethyl ether and methanol extracts of *C. longa* rhizome possess phenolic compounds such as dimethoxy curcumin, dihydro curcumin, and tetrahydrobisdemethoxy curcumin. The ethanol extract of *C. longa* rhizomes contains caffeic acid, coumaric, sinapic acid, casuarin isohammetin, and quercetin-3-D-galactoside (Sabir et al., 2020; Chumroenphat eta al., 2021).

C. longa has received considerable attention in the scientific community for its potential therapeutic applications in various health conditions, including MS, a debilitating autoimmune disorder (Zeng et al., 2022). The most bioactive chemical constituents of *C. longa* are the curcuminoids, a group of polyphenols that mainly include curcumin, demethoxy curcumin, and bisdemethoxy curcumin (Iriti et al., 2010). Curcumin, the primary bioactive compound in *C. longa*, has been extensively studied for its anti-inflammatory, neuroprotective, and immunomodulatory properties. Recent studies have suggested that curcumin may be promising as a complementary or alternative treatment for multiple sclerosis and may offer potential benefits in managing symptoms and progression of the disease (Moreira et al., 2023; Zeng et al., 2022; Iriti et al., 2010).

Petracca et al. (2021) combined curcumin with IFN β-1a therapy to treat MS patients. They discovered that curcumin improved the efficacy of IFN β-1a on inflammatory radiologic symptoms of MS without increasing the risk of adverse reactions.

Kim et al. (2022), extracted *C. longa* rhizomes by fermenting with 50% ethanol solution at 80°C for 4 hours and then lyophilized. The anti-neuroinflammatory effects of the obtained *C. longa* extract on lipopolysaccharide (LPS)-induced BV2 microglial cells were investigated. He found that pretreatment with *C. longa* extract inhibited the overproduction and overexpression of proinflammatory mediators including nitric oxide (NO), prostaglandin E2 (PGE2), nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and proinflammatory cytokines.

In another study, *C. longa* rhizomes were extracted with 80% methanol solution at 26°C for three days with shaking. The obtained *C. longa* extract was found to show in vitro neuroprotective activity in SH-SY5Y cell model (Hassan et al., 2021).

***Ginkgo biloba* L.**

Ginkgo biloba is the oldest living tree in the world. It is the most studied plant and has been evaluated in many clinical studies on humans. The extract from the leaves of the *Ginkgo biloba* tree is usually referred to as ginkgo biloba. *Ginkgo biloba* has been associated with several biological effects (Bowling, 2007).

The phytochemicals of *Ginkgo biloba* are quercetin, kaempferol, myricetin, isorhamnetin, apigenin, luteolin, terpene thiclatones (ginkgolides), tamarixetin, proanthocyanidins and bilobalide (Dziwenka and Coppock; 2021). Ginkgolides, the active compounds in *Ginkgo biloba*, possess antioxidant properties and inhibit platelet-activating factor (PAF), which is involved in both inflammation and thrombosis (Bowling et al., 2000).

In the treatment of various neurological disorders, *G. biloba* is widely used. It has been found that *G. biloba* has a promising function in modulating cognitive and neurological disorders in people (Farzaeibet al., 2017).

In animal models of MS (EAE), PAF exacerbated the disease, whereas *G. biloba* showed beneficial effects in some studies. A small clinical trial involving *G. biloba* treatment reported recovery in eight out of ten participants experiencing MS attacks (Bowling, 2007). Given PAF's role in inflammation and *G. biloba*'s PAF antagonistic properties, there is growing interest in

G. biloba as a potential treatment for MS (Bowling et al., 2000).

This natural remedy has been approved by the German Commission E for the symptomatic treatment of concentration and memory deficits as well

as depression (Farzaeibet al., 2017). Studies show the anti-inflammatory and PAF-inhibitory properties of *G. biloba* extract. (EGB761; obtained by long-term extraction with ethanol at 30°C) are effective in MS. The role of PAF in the inflammatory process has been demonstrated, so *G. biloba* may inhibit this process. Ginkgo also reverses cognitive impairment and reduces fatigue in MS patients (Mojaverrostami et al, 2018).

***Hypericum perforatum* (St. John's wort)**

St. John's wort or *Hypericum perforatum* L. is a herbaceous perennial plant and belongs to the family Hypericaceae. *Hypericum perforatum* L. contains bioactive components such as hypericin, phenols, flavonoids and xanthones (Afsharzadeh et al., 2021). Its efficacy in managing psychiatric and neurological disorders has been well-documented (Nosratabadi et al., 2016).

The use of *H. perforatum* in MS is related to its antidepressant effects and inhibition of ROS production (Watson and Killgore, 2016; Mojaverrostami et al., 2018). Naziroglu et al. (2014) demonstrated that treating MS patients with ethanol extract of *H. perforatum* reduced lipid peroxidation, apoptosis, and Ca^{2+} concentrations, bringing them closer to normal levels (Naziroglu et al., 2014). In another study, the above-ground parts of *H. perforatum* were extracted in ethanol-water (70/30, v/v) for 72 h in the dark on a shaker. The final solution was filtered and the eluate was transferred to a rotary evaporator and processed under vacuum at 40°C. HPLC was used to determine the hyperforin content of the extract. It was shown that the incidence and severity of EAE were reduced by hyperforin and *H. perforatum extract*. Hyperforin also induced increased levels of T-reg cells in the spleen in this study. These results suggest that hyperforin and *H. perforatum* extract may attenuate the autoimmune response in EAE by inhibiting immune cell infiltration and T reg cell expansion, and could ultimately be considered as a potential candidate for use in treating MS (Nosratabadi et al., 2016).

***Panax ginseng* CA Mayer**

Panax ginseng, belonging to the Araliaceae family, has been a traditional herbal medicine in Asia. Ginseng root is traditionally used in powder form to regenerate the mind and body, prevent aging, and increase physical strength. *P. ginseng* is one of the most useful medicinal plants in the treatment of different neuroinflammatory diseases (Mojaverrostami et al., 2018).

Ginsenosides are recognized as the primary active phytochemicals in *P. ginseng*, known for their anti-inflammatory, antioxidant, and anti-apoptotic properties. The plant also contains flavonoids, triterpenoids, and polysaccharides among its active compounds. Modern pharmacological studies have highlighted *P. ginseng*'s beneficial effects on cardiovascular, reproductive, and CNS systems, as well as its roles in antidepressant, antihyperglycemic

antiobesity, anti-fatigue, and antioxidant activities (Farzaei et al., 2017). Some evidence has shown that ginseng can reduce inflammation and fatigue, which may be beneficial in people with MS (Mojaverrostami et al, 2018).

Numerous studies utilizing the EAE model have demonstrated that *P. ginseng* can slow EAE progression by promoting the generation of immunosuppressive Treg cells and suppressing Th1 and Th17 cells (Costantini et al., 2022).

Lee et al. (2018) found that Korean Red Ginseng extract (KRGE) protects against spinal demyelination in an acute EAE model by down-regulating the p38 MAPK/NF-κB signaling pathway. In another study, the aqueous extract of North American ginseng reduced clinical manifestations of EAE by inhibiting circulating TNF-α and CNS immunoreactive inducible nitric oxide (iNOS) (Costantini et al., 2022).

CONCLUSION

Research on the effects of plant extracts against Multiple Sclerosis (MS) underlines their potential as valuable therapeutic agents. Medicinal plants have demonstrated effectiveness in treating MS and its symptoms by reducing demyelination, promoting remyelination, and suppressing CNS inflammation. It shows that medicinal plant compounds have neuroprotective and anti-inflammatory properties that can alleviate symptoms and potentially alter the progression of MS. The primary therapeutic effect of medicinal plants in MS is attributed to their anti-inflammatory properties, which improve disease severity and reduce neuropathological changes. While many studies have focused on animal models, clinical trials are needed to validate these findings before recommending herbs for MS patients. As interest in natural and complementary therapies grows, herbs could increasingly contribute to holistic and patient-centered care for individuals with multiple sclerosis.

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Chapter 6

EXTRACTION METHODS OF PHYTOCHEMICAL COMPONENTS FROM MEDICINAL PLANTS AND EPILEPSY DISEASE

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1. INTRODUCTION

Epilepsy is a chronic neurological nerve disease characterized by recurrent seizures that is extensive worldwide. It is defined by symptoms of an autonomic, sensory, and motor nature. Emotional disturbances such as depression, sleep deprivation, and psychosis can trigger this. The prevalence of epilepsy is increasing worldwide. Epilepsy is among the most widespread neurological diseases in the world. Causes of epilepsy include prolonged febrile seizure, brain tumor, lead poisoning, electrolyte abnormalities, increased intracranial pressure, congenital malformation of the brain, and severe anoxic encephalopathy.

For a long time, the treatment of epilepsy consisted mainly of cures such as medication, surgery, diet, and acupuncture (Zheng et al., 2022; Abramov et al., 2022). Among these, drug therapy is utilized as the most preferred remedy method. There are nearly 50 different antiepileptic drugs. Nowadays, lamotrigine, carbamazepine, oxcarbazepine, gabapentin, topiramate, lacosamide, pregabalin sodium valproate, levetiracetam, etc. in the world pharmaceutical market. Although most patients profit from antiepileptic drugs with different effectiveness, various side actions and convulsion resistance are encountered. In particular, 30-40% of patients can often experience side efficacy when using standard antiepileptic drugs (AEDs). In conclusion, there is still an unmet need for the treatment of epilepsy (Khan et al., 2020; Hayatdavoudi et al., 2022). Moreover, long-term utilization of some antiepileptic drugs (AEDs) has caused adverse effects and also led to the risk of drug-drug interactions and the formation of drug resistance (Wu et al., 2023). In recent years, drug-resistant epilepsy has become more prevalent in patients using AEDs (Kandeda et al., 2021).

Therefore, there is an urgent requirement to improve new AEDs that relieve multiple symptoms and have fewer side impacts. With these increasing side effects problems, many scientists aim to cultivate new plant-based drug agents with antiepileptic and anticonvulsant effects in the treatment of epilepsy, based on clinical studies and research that herbal medicines have less toxic impressions and have a powerful therapeutic effect. It can be said that many medicinal plants utilized in traditional medicine are potential drug candidates in the treatment of refractory epilepsy. Medicinal plants for epilepsy are often considered a mild and safe alternative to chemical antiepileptic drugs (He et al., 2018, He et al., 2023a, He et al., 2023b; Nkamguie Nkantchoua et al., 2018; Kaur et al., 2021).

Antiepileptic efficiency of plant extracts; can be classified as modulating GABAergic and glutamatergic systems, acting as an antioxidant, obtainment neuroprotection, and having antineuroinflammatory efficacy. Many of the herbal preparations recorded in the background are still available. For

instance, more than 20 Chinese patented medicines consisting of medicinal plants turn to account nowadays are ready for clinical use (National Pharmacopoeia Committee, 2020). The leaves, roots, and bark of medicinal plants prescribed by traditional medicine healers are taken orally (Gwedela et al., 2022). Additionally, herbal treatments for epileptic patients are widely put into account in traditional medicine in the form of infusions or decoctions. It alleviates tonic-clonic seizures and convulsions in epilepsy patients. Most of the prescriptions in traditional medicines are polyherbal. The most considerable reason for combining herbs is that they have a synergistic action. Bioavailability and bioefficacy are recognized to maintain a more effective remedy for epilepsy patients by adding low doses of herbs.

This book chapter has been prepared in our department with terms such as 'anticonvulsant', 'antiepileptic activity', 'extraction methods', and compilations taken from databases and scientific investigations such as Pubmed, Research Gate, and Springer Link. In many articles, many medicinal plants such as *Albizia adianthifolia* var., *Cannabis sativa* L, *Anacyclus pyrethrum*, *Grewia asiatica*, *Solanum torvumu*, *Paeonia officinalis* L., *Imperata cylindrica* L., *Solanum torvumu* Sw., *Zingiber officinale* Rosc., *Berberis* L., *Curcuma Longa* L., *Acorus calamus* var. have been discovered to treat epilepsy, and comprehensive analysis on them have been reviewed. The chemical components, extraction methods used, and mechanisms of action of drug molecules that have the potential to become new drugs from these medicinal plants were evaluated. These investigations supported by scientists and doctors, and even herbal medicines prescribed to patients, are aimed at becoming drug candidates for the treatment of epilepsy patients, with further inquiry and research. Nevertheless, there is limited information on the pharmacological screening of medicinal plants and phytoconstituents related to their application method, and dosage. For the utilization of medicinal plant extracts, there is a need to investigate their potential in patients in the clinic to develop effective drugs and conduct more studies.

2. MEDICINAL PLANTS AND BIOACTIVE COMPONENTS USED IN EPILEPSY TREATMENT

Considering the handling of medicinal plants in the recovery of epilepsy around the world, it is seen that many approved anti-epileptic / anticonvulsant plant species are prescribed. However, the magnitude and value of the active principles and the mode of action of their antiepileptic effects have not yet been fully defined. Hence, new treatment strategies should be developed for epilepsy patients and antiepileptic components should be comprehensively investigated. The reason for this is that epilepsy treatment is not possible at present. it has been reported that epilepsy patients are resistant to existing anticonvulsants and antiepileptic drugs and adverse reactions begin to occur (Asmat Ullah Han et al., 2019). As a result, many plant families and species in

the literature have to continue increasing experimental research to obtain new potential active substances for the cure of epilepsy. The reason for this is that there is not enough convincing data to assist the usage of plant extracts before and after clinical tests. These evaluations on alternative healing methods are aimed at eliminating various drug-related side effects, and their use is intended to be increasingly widespread.

Many plants researched in alternative and traditional medicine are known to have strong antiepileptic/anticonvulsant effects. In addition, many academic works are promoted by animal models, and data regarding clinical research are verified through various electronic databases. For the plant species we will talk about in this section, chemical components were extracted from different parts of the plants using assorted extraction methods (distillation, boiling, heat reflux, maceration, soxhlet extractor, microwave-assisted, ultrasound-assisted) established in the literature. Diverse in vivo and in vitro analyses have been carried out for these chemical components obtained from various parts of plants such as roots, stems, leaves, and rhizomes, and it has been determined that they have an anticonvulsant effect.

Phytochemicals isolated in plant extracts have anticonvulsant/anti-epileptic components with secondary metabolites such as phenylpropanoids (Pieretti et al., 1992), flavonoids (Łuszczki et al., 2010), furanocoumarins (Łuszczki et al, 2010) and terpenoids (Kubacka et al., 2006). There is a significant relationship between the activities. The following medicinal plants have been scientifically confirmed as powerful anticonvulsant / anti-epileptic plants by reviewing the literature: *Albizia adianthifolia* L. (Nkwingwa et al., 2023), *Cannabis sativa* L. (Agarwal et al., 2018), *Anacyclus pyrethrum* L. (Manouze et al., 2019), *Grewia asiatica* L. (Kaur et al., 2022), *Paeonia officinalis* L. (Mirmoosavi et al., 2021), *Imperata cylindrica* L. (Ssempijja et al., 2023), *Solanum torvumu* Sw. (Zapata et al., 2022), *Zingiber officinale* Roscoe (Poorrostami et al., 2014), *Berberis Sibirica* L. (Gawel et al., 2020), *Berberis integerrima* L. (Hosseinzadeh et al., 2013), *Berberis vulgaris* L. (Fatehi et al., 2005), *Curcuma Longa* L. (Orellana-Paucar et al., 2012), *Acorus tatarinowii* Schott (Chen et al., 2020). Various complex plant extracts and secondary metabolites of phytochemicals form the basis of these explorations for the discovery and development of targeted anti-epileptic drugs. Accordingly, phytochemicals constitute the basis for the detection and improvement of targeted anti-epileptic drugs.

Albizia adianthifolia* var. *(Mimosoidea)

The leaves, roots, and bark of *A. adianthifolia* have been used in herbal medicine for centuries to remedy epilepsy and memory disorders in Africa. Significant breakthroughs have been made in revealing the pharmacological and phytochemical properties of this medicinal plant species. When the literature was examined, it was revealed that it was utilized as herbal

medicine for hemorrhoids, headaches, respiratory problems, eye problems, and neurodegenerative disorders. There are chalcones, ellipsoids, flavonoids, steroids, triterpenoids, apocarotenoids, dipeptide, imidazolyl carboxylic acid, and prosapogenins identified from the plant species. Pharmacological works have revealed that *A. adianthifolia* compounds and extracts have various properties such as antibacterial, antimycobacterial, against sexually transmitted infections, antifungal, and acetylcholinesterase enzyme inhibitors.

To identify the active compounds in the extract, Nkwingwa et al., 2023 in this scientific research, the aqueous extract was extracted by boiling and utilizing distilled water as the solvent. The phytochemical components identified in the literature were examined for identification in this extract. The purity of the obtained compounds was assessed by Nuclear magnetic resonance (NMR) and Ultra Performance Liquid Chromatography-Mass Spectrometry analysis (U-HPLC/MS). Three fractions collected from the aqueous extract were identified to be phytochemical compounds of murrayanine (alkaloid), safranal (apocarotenoid), and apigenin (flavonoid). In the experiment conducted on sick mice, the activation of GABAergic neurotransmission may also explain its significant anti-amnesic and anticonvulsant effects. It has been observed that neuroinflammation and oxidative stress status diminish in the prefrontal and hippocampal cortex.

In the research conducted by Tamokou et al., 2012, an extraction mechanism was established by utilizing the *A. adianthifolia* plant and ethyl acetate as the solvent, by maceration from the root bark of the plant. Column chromatography (CC) was utilized to fractionate the extraction. It has yielded two known compounds: aurantiamide acetate and lupeol, as well as phytochemical compounds such as n-hexadecanoic acid, oleic acid, and docosanoic acid in fatty acids. The antioxidant and antimicrobial activities of the isolated compounds were elucidated with spectroscopic data. Looking at this information, aurantiamide acetate was determined to be the most active phytochemical compound. It provides basic information regarding their potential use in the healer of infections associated with the studied microorganisms, as well as in the treatment of antimicrobial, antioxidant, and oxidative damage.

***Cannabis sativa* L. (Cannabaceae)**

Cannabis sativa (marijuana), which is a perennial herbaceous plant grown in countries such as China, Kazakhstan, Pakistan, and Uzbekistan, which is considered to belong to Central and South Asia, is a potential species known especially for its medicinal and recreational activities. The cannabis plant has the potential to be grown in many regions because it is suitable for various climatic conditions. Considering the therapeutic impacts or medical activities of cannabis and its derivatives in various neurological diseases; It

has a considerable role in relieving symptoms and treating many diseases such as alzheimer, parkinson, tumors, depression, anxiety, epilepsy, post-traumatic stress disorder (PTSD), cancer and skin diseases. *C. sativa* played a considerable role in the therapy of many acute and chronic diseases in the past. It is of great interest due to the presence of secondary metabolites such as anthocyanins, flavonoids, terpenoids, cannabinoids, alkaloids, lignans, and quinones in the leaves and female flowers of cannabis plants. Cannabis-derived terpenes and cannabinoids have promising therapeutic activities in the cure of epilepsy and seizures. In this section of the article, bioactive compounds are separated by using different solvents (supercritical fluids, butane, propane, methanol, ethanol) and different extraction methods (microwave, ultrasound-assisted solvent extraction, heating, soxhlet extraction, heat reflux extraction) to recover bioactive compounds in current healer applications. It is aimed to obtain more information about their physicochemical structures (Gonçalves et al., 2019).

Ultrasonication methods used to extract bioactive compounds such as cannabinoids, flavonoids, and polyphenols in Agarwal et al., 2018 and Hazekamp et al., 2004 have demonstrated that the properties significantly boost the extraction efficiency of cannabinoids; this was proven true by both high-performance liquid chromatography (HPLC) and gas chromatography (GC). This method is a more efficient and green extraction compared to the traditional method, and it also supplies significant savings in terms of time, cost, and energy. In Rovetto et al., 2017 and Aizpurua-Olaizola et al., 2014 the extracts obtained by supercritical fluid extraction by HPLC-MS/MS and ultra-high performance liquid chromatography with quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF-MS) methods were successfully obtained and measured. Nearly 30 types of cannabinoids (cannabidiol, cannabigerol, tetrahydrocannabinol, tetrahydrocannabinolic acid), optimized by quantitative isolation, were obtained and measured from this plant extract. In Chang et al. 2017, the lowest solvent consumption and the highest extraction efficiency of total cannabinoids in the shortest time were obtained in the microwave-assisted extraction (MAE) method. The MAE method is an environmentally friendly, fast, and economical extraction method that is both practical and effective for industrial applications, as it achieves significant cell separation in the microstructure.

Table 1. *Methods used for the extraction of Cannabis sativa L. species*

Common name	Extraction method	Extraction conditions	Methods	References
Cannabis sativa L.	Ultrasound-assisted methanol extraction	Extraction time: 15 min, Power: 130 Watts; Methanol: 80%	Spectrophotometer (UV-VIS) HPLC-MS/MS	Agarwal et al. (2018)
C. sativa L.	Ultrasonic-assisted solvent extraction	Solvent(methanol: chloroform) = 9:1 vol/vol Reaction time:10min, Ultrasonication time: 2 min	1H-NMR GC	Hazekamp et al. (2004)
Poppy (C. sativa: C. indica = 50:50)	Ethanol-assisted supercritical CO_2 extraction	Temperature:5°C Ethanol: 10% by weight Pressure:34 MPa	HPLC	Rovetto et al. (2017)
Creme Caramel (CC), Amnesia (A), New York Diesel (NYCD) Cannabis Types	Ethanol-assisted supercritical CO_2 extraction	Ethanol: 20% vol/wt; Extraction time: 10 min; Flow rate: 1mL/min; Pressure: 10 MPa; Temperature: 35 °C	HPLC HPLC-MS/MS UPLC-Q_TOF-MS	Aizpurua-Olaizola et al. (2014)
Hemp nut	Microwave-Assisted Extraction	Solvent: Methanol microwave power; (375 W) at 109 C; Filtering process: filter paper; Stored at 20°C	High-performance liquid chromatography and electrochemical detection (HPLC-EC)	Chang et al. (2017)
	Heat Reflux Extraction	Boiled in methanol. Filtration process		
	Soxhlet Extraction	Methanol - 90°C - 8 hours extraction The extract was filtered		
	Ultrasound-Assisted Extraction	Methanol in a tube. 30 minutes - sonication at 47 kHz		

Anacyclus pyrethrum (L.) (Asteraceae)

This medicinal plant belongs to the Asteraceae family; It is found in many countries such as North Africa, the Mediterranean Region, and India. *A. pyrethrum* has been utilized as a brain tonic in Ayurveda. It has been exploited in many diseases such as epilepsy, facial paralysis, and rheumatic diseases. It is reported to have been traditionally used to treat, manage, and control various types of epilepsy due to its antirheumatic, antiepileptic, and antirheumatic properties. Pharmacological exploratory have been conducted with extracts from *A. pyrethrum* root. The results indicated that the extract had anti-tumor, anti-inflammatory, aphrodisiac, and antiepileptic activities.

The research conducted by Manouze et al. (2019), it was aimed to compare the efficiencies of 2 different extraction methods using the root of the *A. pyrethrum*. It aimed to evaluate the neuroprotective and anticonvulsive impacts on status epilepticus (SE) by using the soxhlet device with methanol and aqueous phase as solvents. Based on the findings, furthered its understanding of the efficacy of methanol extract of *A. pyrethrum* root (MEAPR) and aqueous extract of *A. pyrethrum* root (AEAPR) in the brain and found that this natural compound may be convenient in providing neuronal protection in epilepsy, neuroinflammation, and other brain injuries associated with excitotoxicity. Nevertheless, no significant difference was found between the two extracts in terms of total phenolic, tannin, and flavonoid amounts. Total phenolic, flavonoid, and tannin contents were determined by phytochemical evaluation by HPLC and spectrophotometric analysis (UV-visible) method (Manouze et al., 2019)

In the disquisition by Chen et al. (2024), the molecular structures of 12 identified various anacycloline alkaloids obtained from the methanol extract of *A. pyrethrum* root were analyzed by spectroscopic analyses (UV, IR, NMR) in epilepsy patients. The identification of 12 different unidentified alkaloids isolated through this explorative was achieved. It has been successfully announced that it will benefit the treatment. (Chen et al., 2024)

In this scientific research by Pahuja et al. (2012), the result of HPLC analysis performed with the hydroalcoholic root extract of *A. pyrethrum* exhibits its phytochemical effects. In experimental seizure models, it was observed that it alleviated its efficacy against cognitive impairment, and seizure-induced oxidative stress, and its protective impact against seizures significantly affected dose-dependently. (Pahuja et al., 2012)

Grewia asiatica* L. *(Malvanaceae)

Phalsa (*Grewia asiatica* L.) is a therapeutic and nutritious plant that grows in the Southeast Asia region. The plant is a shrub plant that grows mostly in the Indian subcontinent and is identified for its fresh and ripe fruits. It is widely available commercially in Pakistan, Bangladesh, India, and other tropical regions. The leaves, fruits, and bark of *G. asiatica* are considered to be of significant value in the treatment of many diseases. *G. asiatica* plant continues to be widely utilized in many diseases due to its antioxidant, analgesic, antibacterial, antipyretic, and anti-diabetic properties. Many researchers are investigating its tonic and stimulant efficacy in the treatment of epileptic seizures. These investigations conducted with extracts obtained by different methods have shown that they have significant antiepileptic and anxiolytic impacts. In particular, disquisitions have reported that methanol extract from the leaves of *G. asiatica* has sedative, neuroprotective, antidepressant, and hypnotic effects.

When looking at the literature, Kaur et al. (2022) made a comparison according to increasing polarity using different solvents and extracted the leaves of the *G. asiatica* plant at an average temperature of 60-80°C. This scientific explorative was then investigated using mice in animal models. Soxhlet extraction was carried out using petroleum ether, chloroform, and methanol solvents, respectively, according to polarity. According to the findings, the extraction compound, especially extracted utilizing methanol, was found to have promising anxiolytic and antiepileptic effects. As a result, in the experiment conducted with mice, it was concluded that it can protect people experiencing electroshock-induced seizures. The presence of kaempferol flavonoids and quercetin components, which have antiepileptic and neurotoxicity properties, was explored in the extract isolated by column chromatography. Its anti-anxiety effects have been proven by subjecting it to NMR spectroscopy.

In the disquisition by Khatune et al. (2016), *G. asiatica* dried stem bark was fermented with 96% ethanol solvent and kept for 1 week. In this way, it was aimed to explore the antioxidant, antidiabetic, and antihyperlipidemic activities of the ethanol extract. Looking at the phytochemical analysis results of asiatica, the presence of steroid, glycoside, tannin, triterpenoid, and flavonoid components from the root bark was detected. Moreover, a spectrophotometer (UV-visible) was used to determine the total flavonoids and total phenolic compounds in the ingredient.

Paeonia officinalis L. (Paeoniaceae)

Paeonia officinalis is a perennial native plant that has 35 species and grows especially in the Mediterranean region, Western Asia, and the South. There are 12 different varieties in Turkey, which is the most substantial gene center. This medicinal plant was recommended to be drunk as tea in the Anatolian region during the Ottoman period, for the treatment of various pains, internal diseases, and epilepsy. In particular, the roots of this plant are utilized to reduce the duration and frequency of seizures in intractable anticonvulsant epilepsy. A substantial reason for the efficacy of the *P. officinalis* root component in controlling the rate of epileptic seizures, many of which are refractory and untreatable, is the presence of flavonoids, and polyphenols. There are substantial components found in this medicinal plant: monoterpenes can be attributed to the presence of various bioactive components such as flavonoids, polyphenols, and monoterpenes. Hence, it is applied as an alternative approach in the treatment of severe epileptic seizures. It is a treatment option due to its low economic cost and few side effects. It has no serious side effects in terms of tolerability and safety in adults (Chang et al., 2020).

This scientific research by Mirmoosavi et al. (2021), was prepared from the root extract of *P. officinalis* (70%) using ethanol kept at room temperature

for 72 hours and then turned into syrup. Judging by the phytochemical analysis of the extract, its roots consist of saponins, tannins, flavonoids, glycosides, terpenes, and proteins. It is especially the main antioxidant substance of extracts of polyphenolic compounds (flavonoid and gallic acid derivatives). The ability of flavonoids to prevent brain damage has a potential role in controlling abnormal brain excitability and as an adjuvant treatment in epilepsy. The effects of this syrup, which was specially prepared for children with persistent epilepsy in childhood, were examined. It was observed that the syrup obtained by hydro-alcoholic extraction prepared from plant roots had fewer side effects in children and contributed to a significant improvement in the frequency of seizures. It was aimed to evaluate the tolerability and effectiveness of the drug. As a result of this work, it was observed that there were no serious side impacts in children with untreated epilepsy and that it contributed to their recovery. (Mirmoosavi et al., 2021)

In the disquisition conducted by Orhan et al. (2010), 14 root extracts prepared in ethanol solvent (75%) from 12 different plants belonging to the Paeonia taxon in Turkey were examined to compare the essential oil compositions and antioxidant potentials. For the isolation of essential oils, hydrodistillation was performed with the help of the Clevenger apparatus. The presence of components in the roots of Paeonia species and the antioxidant activities of essential oils were analyzed by gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS). The antioxidant activities of the main components extracted from the root tips of the species were determined as cis-mycorrhizal and salicylaldehyde, and it was concluded that they are promising for epilepsy patients. (Orhan et al., 2010)

***Imperata cylindrica L.* (Poaceae)**

I. cylindrica L. is a neuro-medicinal plant native to tropical and subtropical regions of Africa, southwestern Asia, and parts of the United States. As a result of its widespread use in the treatment of epilepsy, it may be a great resource for the improvement and discovery of alternative, complementary antiepileptic drugs worldwide. 5-Hydroxy-2-(2-phenylethyl) chromones and 2-(2-phenylethyl) bioactive compounds extracted from the plant were found to have neuroprotective potential on glutamate-induced neurotoxicity in rat cerebral cortical cells. It is not possible to find clear evidence regarding the safety and effectiveness of *I. cylindrica* as an antiepileptic. (Jung et al., 2021)

As a review, in the explorative conducted by Ssempijja et al. (2023), methanol extraction was performed with plant roots. The neuropathological effects of *I. cylindrica* root extract on convulsion, histological parameters, and cognitive changes in epilepsy were determined. Bioactive compounds extracted from plant roots, tannins, saponins, alkaloids, cardiac glycosides, flavonoids, and terpenoids, were isolated, and qualitative and quantitative analyses were

performed using spectrophotometric analytical methods (uv-visible and HPLC). When the resulting bioactive compounds were examined, it was stated that their antiepileptogenic and anticonvulsant values would be effective in patients. Its neuroprotective potential on neurotoxicity, receptor inhibition, and its effect on brain histopathology shows us that it is an antiepileptic plant, but there are not enough studies on its neuroprotective effectiveness. (Ssempijja et al., 2023)

***Solanum torvum* Sw. (Solanaceae)**

It belongs to the Solanaceae family and is widely found in Southern India, the Philippines, China, and Tropical America. Extracts prepared with the roots, leaves, and fruits of *S.torvum* have been proven to exhibit antioxidant, anti-inflammatory, analgesic, and antiviral activity (Balachandran et al., 2015). Findings from the seizure test of *S. torvum* extracts, which proved to be similar to the preparations in traditional herbal medicine used by epilepsy patients, confirm their use in treatment. For example, the effects of methanol, and ethylacetate extracted from the plant *S. torvum* on different extraction methods such as hexane extraction, soxhlet extraction, heat return flow extraction, maceration extraction, ultrasonic extraction, and microwave-assisted (MAE) were tested. (Knap et al. 2023)

In the scientific research conducted by Zapata et al., (2022) rich saponins were obtained from the fruit extract by Soxhlet and Ultrasound-assisted extraction. Nevertheless, in the disquisition conducted by Wójciak-Kosior et al. (2013), an aglycone formed as a result of acid hydrolysis of methanolic extract, indicated an anticonvulsant effect at high concentrations. MAE in the closed system was the most effective. Moreover, it is more advantageous and time-saving compared to other techniques. As demonstrated in their research, ultrasonic-assisted extraction has emerged as an alternative method attracting attention due to its simplicity, use of inexpensive equipment, and relatively high extraction efficiency.

Table 2. *Methods used for the extraction of Solanum torvum*

Common name	Extraction method	Extraction conditions	Methods	References
S. torvum	Soxhlet extraction Ultrasound-assisted extraction	Solvent/mass ratio; 1:7; Methanol; 80°C; 24 h	Fourier-transformed infrared spectrophotometry (FTIR) Thermogravimetric analysis (TGA)	Zapata et al. (2022)
S. torvum	Soxhlet extraction	Plant material dried with acetone in a Soxhlet device; 20h; Concentrated under vacuum;	HPLC	Wójciak-Kosior et al. (2013)
S. torvum	Heat Return Flow Extraction (HRE)	The dried plant material was added to acetone and heated in a water bath at 60 °C; 30 min; 3 times; Filtered concentrated.		
S. torvum	Maceration extraction (ME)	The dried plant was mixed with 100 ml acetone; 10 h; 3 times; Filtered and concentrated.		
S. torvum	Ultrasonic extraction (UE)	The dried plant was mixed with 50 ml of acetone; 15 minutes; 30 °C - 50 °C; 3 times; Filtered, and concentrated.		
S. torvum	Accelerated solvent extraction (ASE)	2 static cycles at two different temperatures 40 °C - 120 °C; 100 bar pressure; The extraction cell was then washed with N_2 for 90 seconds.		
S. torvum	Microwave-assisted extraction (MAE)	Extracted with 40 mL of acetone using various generator powers (30%, 65%, 100%); 10, 20, and 30 min.		

***Zingiber officinale* Rosc. (Zingiberaceae)**

The main components of this medicinal plant, which belongs to the Zingiberaceae family and is mostly found in Japan, South Asia, and China, consist mainly of phenolic acids and terpene compounds. Ginger, the rhizome of the plant *Z. officinale* Rosc, has been reported to contain more than 400 components. Ginger extracts have proven pharmacological effects such as anti-inflammatory, antioxidant, and antimicrobial (Kukula-Koch et al., 2018). Components isolated from its extracts have been reported in various diseases. The underground rhizomes of ginger contain medicinally substantial active compounds; shogaols, gingerols, essential oils, pungent phenol compounds, and zingerone These compounds are known to have antiseizure activity and anticonvulsant effects. (Sekiwa et al., 2000).

Gawel et al. (2021) in this scientific ascertainment, it was determined that the methanolic extract isolated from plant rhizomes and zebrafish larvae showed anti-seizure activity. 6-gingerol (6-GIN), a phytochemical component, was isolated from the rhizome of officinale. It has demonstrated potent and dose-dependent antiepileptic/anticonvulsant activity and has been confirmed electroencephalographically. It was developed to isolate 6-gingerol in high purity from total extract by HPLC. This investigation, which was isolated for the first time, will partially mediate future studies and further studies are needed.

In this scientific research by Poorrostami et al. (2014), it was observed that the hydroalcoholic extract of dried ginger rhizomes reduced the hepatotoxicity caused by lamotrigine used in epileptic rats. It was used for 2 days with the maceration method and ethanol was used as a solvent.

Simon et al. (2020) targeted in academic exploration in which different extraction methods were used, extraction with ethyl acetate in the soxhlet device at 80 °C for 6 hours was chosen as the most effective method compared to the others. For the analysis of shogaol and gingerol components isolated from ginger extract, they were isolated from ginger using the U-HPLC method. In addition to its positive effects on the central nervous system, it was found to have anti-epileptic/anticonvulsant activity in animal models of alzheimer's patients, parkinson's patients, and anxiety, and epilepsy patients.

***Berberis* L.**

The main component of these plant species, which belong to the Berberidaceae family, is one of the berberine alkaloids. Mostly berberine alkaloids are found in isoquinoline alkaloids found in the roots and stems of the plant. It is a shrub plant with yellow-brown bark, evergreen, woody roots, and red fruits. Found mainly in the temperate zone of the northern hemisphere, this species is used especially for liver disorders, neuroprotective, insomnia,

and lung disorders (Abdykerimova et al., 2020). They have also been found to have anti-inflammatory, antimicrobial, antinociceptive, and anticonvulsant properties (Knap et al., 2023). Berberine (BERB) and palmatine (PALM) are isoquinoline alkaloids commonly identified among representatives of the family Berberidaceae. The therapeutic effects of berberine include analgesic, antihypertensive, temperature-lowering, spasmolytic, and detoxification activity (Filli et al., 2020). Among the therapeutic effects of palmatin, it has been reported to be used in gastrointestinal and respiratory tract infections, jaundice and liver-related diseases, inflammation, hypertension, and dysentery (Tarabasz and Kukula-Koch et al., 2020). The antiepileptic activity of BERB has previously been demonstrated in experimental epilepsy models (Gawel et al., 2020).

In the disquisition by Gawel et al. (2020), both alkaloids shown were isolated from *B. sibirica* by the accelerated solvent extractor (ASE) method with methanolic root extract. Their quantitative structure-activities and ability to cross the blood-brain barrier were examined. Through electroencephalographic analysis, it was demonstrated that PALM and BERB exert antiseizure activity through different mechanisms of action and have anticonvulsant activity. It has been determined that their combinations give more effective results than their separate use. (Gawel et al., 2020).

A methanolic extract apparatus was established to evaluate the anticonvulsant activity of dried roots of *B. integerrima* by Hosseinzadeh et al. (2013) Considering the phytochemical screening during the extraction process carried out by the maceration method in methanol solvent, the presence of tannins and alkaloids was determined. According to the results of the anticonvulsant activity test conducted on mice, it was concluded that it may be beneficial in epilepsy patients and can be used as support in the discovery of new drug molecules (Hosseinzadeh et al. 2013).

In the research conducted by Fatehi et al. (2005), *B. vulgaris* fruits were extracted by boiling them in water. This prepared aqueous extract significantly reduced arterial blood pressure in rats in a dose-dependent manner and led to an increase in the magnitude of potassium current in brain cells. This action on potassium current explains how it has neuroprotective and sedative activities. As a result, it is thought to be promising in the treatment of some neurodegenerative disorders such as tachycardia, convulsions, and epilepsy.

***Curcuma Longa L.* (Zingiberaceae)**

Curcuma longa L., which belongs to the Zingiberacea family and grows mostly in South Asia, is used as a traditional medicine in the treatment of epilepsy thanks to its anticonvulsant activity (Orellana-Paucar et al., 2012). The main components of this powder (turmeric) obtained from the rhizomes of the plant are turmeric oil (2-7%) and curcuminoids (3-5%). Although its

antiepileptic properties have been proven in many works conducted with curcumin, its rapid metabolism and rapid absorption limit the application of its therapeutic potential to humans, and phase-I clinical studies reveal pharmacokinetic limitations. (Orellana-Paucar et al., 2021).

In Orellana-Paucar et al. (2012), it was revealed that the extraction processes with *C. longa* rhizome powders and turmeric oil (hydro distillation process) and curcuminoids (maceration process) reduced the convulsions that may occur in epilepsy and demonstrated anticonvulsant activity. In the study conducted on the methanolic extract of turmeric and the production of turmeric oil, its neuroprotective activity was reported (Dohare et al., 2008).

In Sabir et al. (2020), 15 phenolic compounds were identified in the HPLC of the ethanol extract from *C. longa* rhizomes. It was concluded that these compounds (curcuminol, curcumin-O-glucuronide, and demethoxycurcumin) indicated antidiabetic and antioxidant activity. In Hassan et al. (2021), methanol extract from *C. longa* rhizomes was made to evaluate its neuroprotective effects and antioxidant activities, proving that it displayed high activity. In Fernández-Marín et al. (2021), the oil extracts obtained by microwave-assisted extraction (MAE) and soxhlet technique in 2 different extraction types used are compared. Accordingly, it was revealed that better antioxidant yield was obtained from the oil extracted by MAE. (Fernández-Marín et al., 2021)

Table 3. *Methods used for the extraction of Curcuma Longa L.*

Common name	Extraction method	Extraction conditions	Methods	References
C. Longa	Maceration	Dried rhizome powder of *C. longa*; Solvent: methanol Concentrate with a rotary evaporator	NMR MS	Orellana-Paucar et al. (2012)
	Hydro distillation process	Dried rhizome powder of *C. longa*; 3h distillation; Clevenger type apparatus; Desiccant: Anhydrous Sodium Sulfate Storage Stored: + 4 °C		
C. Longa	Maceration	Ground powder rhizome; Solvent: ethanol; Extracted in a rotary evaporator	HPLC	Sabir et al. (2020)

C. Longa	Microwave Assisted Extraction	1:20 g/mL of *C. longa* L./EtOH; *3 times;* 160 W microwave power	Fourier Transform Infrared Radiation (ATR-FTIR) GC/MS	Fernández-Marín et al. (2021)
	Vacuum distillation	Dried Powder of *C. longa* ; Solvent: Ethanol; Soxhlet Extractor; Boiling for 6 hours		
C. longa	Maceration	*C. longa* rhizome powder; Solvent methanol; 26 °C; 3 days; Stored: + 4 °C	HPLC	Hassan et al. (2021)

***Acorus tatarinowii* (Araceae)**

It is recorded in Schott Materia Medica that *A. tatarinowii* has analgesic, diuretic, sedative, digestive, and antifungal effects in pharmacological studies from traditional Chinese medicine to the nowadays. Nevertheless, the most considerable one is that extracts obtained from *A. tatarinowi* rhizomes by various methods are proven to have sedative and anticonvulsant effects (Liao et al., 2005). *A. tatarinowii* rhizomes have been utilized clinically to treat central nervous system disorders. It has many coumarins, monoterpenes, lignins, eudesmins, diterpenes, and alkaloids that can be isolated from the plant (Liu et al., 2015).

The same process was repeated twice using the reflux method along with the dried rhizome petroleum ether extraction by Chen et al. (2020). Owing to this exploration, it is possible to operate information for the treatment of epilepsy patients. The pharmacological mechanism of action has been reached. Finding autophagy regulators is promising for targeted examinations and even for developing an alternative drug or treatment strategy for epilepsy. (Chen et al, 2020).

In the research conducted by He et al. (2023), the 2 plant pairs utilized [*Gastrodia elata* - *A. tatarinowii* (GEAT)], they were extracted by first maceration and then boiling in distilled water. It can be put into account in mice with chronic epilepsy as it obstructs oxidative damage and neuroinflammation. Liu et al. (2015) in this scientific ascertainment process prepared from the rhizomes of A. tatironowii, maceration was performed with the help of ethanol. The mechanisms of eudesmia were investigated with ethyl acetate fraction. As a result, it was concluded that eudesmin has remarkable sedative and anticonvulsant effects. In the scientific research conducted by Liao et al. (2005), supercritical CO_2 was extracted from ATS rhizomes by liquid extraction and boiling methods. Both types of extraction have anticonvulsive effects. The compound isolated by decoction is more influential for contractions.

Table 4. *Methods used for the extraction of Acorus tatarinowii*

Common name	Extraction method	Extraction conditions	Methods	References
A.tatarinowii	Solid-liquid extraction	Dried root (ground); Solvent: petroleum ether; 80°C; 2 times; Concentrated under reduced pressure.	HPLC	Chen et al. (2020)
A. tatarinowii	Maceration-Distillation	Before: Room temperature; Distilled water; Maceration; Filtering process After: Distilled water; 25 min; Stored at 4°C.	CC MS UHPLC-MS/MS	He et al. (2023)
A. tatarinowii	Maceration	Rhizome extract powder; 70% ethanol; Ethyl acetate fraction	CC Max Electroshock Test (MES) H-NMR	Liu et al. (2015)
A. tatarinowii	Decoction	ATS rhizome; Distilled water; Three times; Concentrated up to 2:1; Stored at 4°C.	Maximal electroshock (MES) model	Liao et al. (2005)
	Supercritical CO_2 fluid extraction	ATS rhizome powder; Respectively; 20 MPa - 40°C; 10 MPa - 55°C; 6 MPa - 45°C; 3 hours	Pentylenetetrazol (PTZ) seizure model	

3. CONCLUSION

Epilepsy is related to a chronic progressive neurological disease characterized by recurrent seizures. Many emotional state disorders can trigger this, including genetic conditions, depression, psychosis, and sleep deprivation. Drug therapy is utilized as the most preferred method to control seizure control and frequency in epilepsy patients. Nevertheless, the drugs

operated by epilepsy patients on the market cannot maintain sufficient therapeutic effects against seizures.

On the contrary, it has been observed that the drugs they use have developed resistance to the current drug and their side impacts have increased. As a result, there is a need to discover drug molecules that have the potential to be new drugs that can be obtained from plants, apart from existing drug molecules. With these increasing side effects problems, many scientists put faith in that herbal medicines have less toxic effects and are more effective in treating epilepsy, based on clinical studies and research. It is aimed at developing new plant-based drug agents with therapeutic, antiepileptic, and anticonvulsant effects. It can be said that many medicinal plants employed in traditional medicine are potential drug candidates in the treatment of refractory epilepsy. Many medicinal plants, whose effects have been proven all over the world, continue to be exploited for their therapeutic effects and anti-convulsant effects. In this review, it is clearly stated that the components of plant-derived extracts and phytochemicals discovered handling different extraction methods were comprehensively examined with analytical methods, and detailed clinical studies were conducted. From various preclinical studies, plant-derived compounds have been demonstrated to boost the tolerability of anti-epilepsy drugs for epilepsy patients. There is no doubt that it is on the right track in determining its safety and effectiveness.

On the other hand, the number of studies investigating the benefits and effectiveness of herbal medicines is extremely insufficient. Despite all this scholarly research, the lack of randomized clinical studies and the inadequate application of phytochemicals with antiepileptic effects as drugs can't ensure certain of with clear evidence-based information. Unless pharmaceutical industries supply marketing and manufacturing demands, herbal formulations are unlikely to become widely prescribed anti-epilepsy drugs. The effectiveness and safety of many medicinal plants have already been proven both in topical use and in studies on animal models. As a result, the antiepileptic properties of components isolated from medicinal plants need to be determined and made progress under different extraction conditions. More research is required to isolate various bioactive substances from plants and to cultivate new and effective drugs.

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