

Pharmacotherapeutic potential of walnut (*Juglans* spp.) in age-related neurological disorders

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ABSTRACT

Global and regional trends of population aging spotlight major public health concerns. As one of the most common adverse prognostic factors, advanced age is associated with a remarkable incidence risk of many non-communicable diseases, affecting major organ systems of the human body. Age-dependent factors and molecular processes can change the nervous system's normal function and lead to neurodegenerative disorders. Oxidative stress results from a shift toward reactive oxygen species (ROS) production in the equilibrium between ROS generation and the antioxidant defense system. Oxidative stress and neuroinflammation caused by Amyloid- β protein deposition in the human brain are the most likely pathogenesis of Alzheimer's disease (AD). Walnut extracts could reduce Amyloid- β fibrillation and aggregation, indicating their beneficial effects on memory and cognition. Walnut can also improve movement disabilities in Parkinson's disease due to their antioxidant and neuroprotective effect by reducing ROS and nitric oxide (NO) generation and suppressing oxidative stress. It is noteworthy that Walnut compounds have potential antiproliferative effects on Glioblastoma (the most aggressive primary cerebral neoplasm). This effective therapeutic agent can stimulate apoptosis of glioma cells in response to oxidative stress, concurrent with preventing angiogenesis and migration of tumor cells, improving the quality of life and life expectancy of patients with glioblastoma. Antioxidant Phenolic compounds of the Walnut kernel could explain the significant anti-convulsion ability of Walnut to provide good prevention and treatment for epileptic seizures. Moreover, the anti-inflammatory effect of Walnut oil could be beneficial in treating multiple sclerosis. In this study, we review the pharmaceutical properties of Walnut in age-related neurological disorders.

1. Introduction

Among the wide range of noncontagious diseases, diseases caused by neurological disorders account for a large share of mortality and morbidity (Feigin et al., 2020; Anon, 2022). We know that subclinical changes that occur at the molecular level can affect the aging process.

These subclinical changes involve telomere attrition, accumulation of mutations, and epigenetic alterations, which result in genomic instability. These changes, like the snowball effect, increase over time and lead to adverse changes in the central nervous system (CNS) such as degeneration of brain function, progressive neuronal loss, decreased level of neurotransmitters, and impaired vascular integrity which leads

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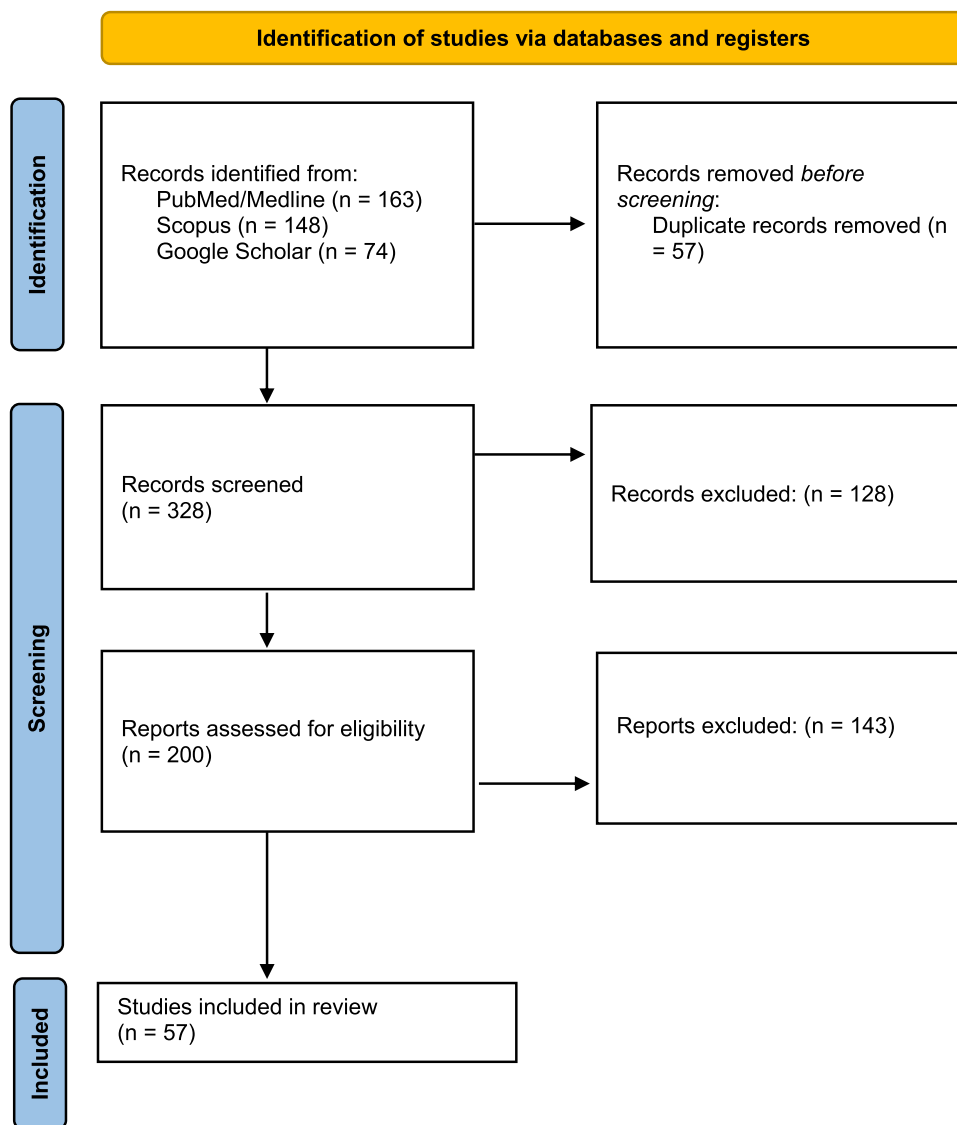


Fig. 1. The PRISMA flow diagram of study.

to infarction and microbleeds. In addition, impaired performance of the deoxyribonucleic acid (DNA) repair process can increase the likelihood of spontaneous mutagenesis, eventuating in age-related neoplasia. Besides, many elderly suffer from malnutrition, leading to vitamin B12 and folic acid deficiencies. The lack of these two essential elements leads to homocysteine metabolic disorders that ultimately cause damage to the vascular system. All the factors mentioned above can lead to multiplying the risk of getting conditions related to the CNS in older people, such as Alzheimer's disease (AD), epilepsy, stroke, and Parkinson's disease (PD) (Kowalska et al., 2017). We should consider that not only is there no pharmaceutical product to prevent age-related neurological disorders (ANDs), but also there are not many drugs available to treat this disease (Bhullar and Rupasinghe, 2013), and these available AND drugs have only a symptomatic effect (Berg et al., 2013).

For the reasons mentioned above, we can also consider herbal medicines and natural products. Herbal medicines and natural products contain various chemical elements, which have evolved to fortify the survival of organisms (Brahmachari, 2013). So, it is better to consider natural products to prevent ANDs. English Walnut is one of these natural products rich in alpha-linolenic acid, polyphenolics, linoleic acid, and micronutrients. The results of laboratory research have shown us that a Walnut diet can play a role in improving memory and cognitive level

(Willis et al., 2009, 2008). This study aims to gather all available information about the pharmacotherapeutic potential of Walnuts in ANDs.

2. Walnut and its active constituents

Walnut is the name called for the seed of the *Juglans* plant. Interestingly, it has 21 species which are distinguished by some chemical makers such as tetralones, naphthoquinones, and diarylheptanoids. The Walnut's fruit has four principal parts: kernel, skin, shell, and green husk. According to Jahanban-Esfahlan et al. study, the green husk part is a rich source of some bioactive chemicals such as antioxidants, antimicrobial compounds, and other constituents like chlorogenic acid, caffeic acid, ferulic acid, sinapic acid, gallic acid, ellagic acid, protocatechuic acid, syringic acid, vanillic acid, and Catechin (Jahanban-Esfahlan et al., 2019; Habibie et al., 2019; Chatrabnous et al., 2018a).

The kernel part contains high levels of unsaturated fatty acids, digestible proteins, phenolic compounds, and dietary fiber. Additionally, this part is found in both fresh and dried manner, but fresh ones have a higher quality than dried ones (Pakrah et al., 2022). One of the active substances of Walnut, which is found in various parts is Juglone (the chemical formula: 5-hydroxy-1,4-naphthoquinone). It can inhibit the key enzymes of metabolic reactions and has anti-cancer properties.

Here is a list of chemical constituents of Walnut (especially the husk part's contents):

Hydrolyzable Tannins, Naphthoquinones, Naphthoquinone Glycosides, Naphthalenes, α -Tetralones, α -Tetralones Glycosides, and α -Tetralone Dimers, Hydroxybenzoic Acids, Hydroxycinnamic Acids, Flavonoids, Diarylheptanoids, Ceramides, Alkanes, Steroids, Triterpenoids, Sesquiterpenes, Neolignans and other compounds such as minerals (Jahanban-Esfahlan et al., 2019; Chatrabnous et al., 2018b; Pakrah et al., 2021). These chemicals cause antioxidant, antimicrobial, antifungal, anti-cancer, and antiplatelet properties in Walnut (Jahanban-Esfahlan et al., 2019; Jahanbani et al., 2016).

Walnut is an excellent option for a healthy diet because it is a rich source of vitamins (folic acid, vitamin B5, vitamin B6, tocopherols), minerals (phosphorus, manganese, magnesium, zinc, potassium), omega-3 fatty acids, and phytochemicals (Vu et al., 2020).

Concerning Vu DC et al. study, the antioxidant activity of Walnut is significantly related to phenolic compounds which exist in the Walnut. These phenolic compounds are a group of phenolic acids, flavonoids, stilbenes, coumarins, and tannins. In addition, this group causes antibacterial properties in Walnut. For example, gallic acid, ellagic acid, ferulic acid, and naringin can inhibit bacteria from growing. This process is done by destroying their plasma membrane or inhibiting their DNA from being duplicated (Vu et al., 2020). In addition, some phenolic compounds such as gallic acid, quercetin, quercetin glycosides, 3-methylquercetin, and ellagitannins are linked to causing anti-inflammatory activities. It is suggested that these compounds can suppress some inflammatory cytokines (Vu et al., 2020).

Antidiabetic activity of Walnut is due to the significant amount of linoleic acid, which is an unsaturated fat that affects insulin sensitivity, that can impact glycemic control. Another positive feature of Walnut is its anti-cancer activity which is related to the γ -tocopherol compound (Vu et al., 2020). About 400 compounds are found in various parts of Walnut, but the most available compounds are quinones, phenolics, triterpenoids, and diarylheptanoids. These constituents cause pharmacological activities, such as anti-tumor, immunoregulatory, anti-inflammatory, neuroprotective, antidiabetic, anti-viral, antimicrobial, and anti-melanogenesis activities (Luan et al., 2021).

Due to Junaidh et al. study, Walnut has anti-histaminic, bronchodilator, anti-fertility, analgesic, immunomodulatory, hepatoprotective, anti-ulcer, lipolytic, anti-hypertensive, neuroprotective, and insecticidal properties (Mohammed Junaidh et al., 2022). Furthermore, it has been proved that some protein compounds of Walnut have inhibitory effects on angiotensin-converting enzyme (ACE). This enzyme converts angiotensin I to angiotensin II. Angiotensin II causes contraction in blood vessels which increases the blood pressure. Therefore, inhibition of ACE can help with the treatment of high blood pressure (Jahanbani et al., 2018).

More and more studies indicate the relation between the existence of Walnut in diet and disease prevention and treatment. According to Zhi-Jing Ni et al. study (Ni et al., 2021) polyphenols in Walnut can decrease the risk of cardiovascular diseases due to their effect on the amount of low-density lipoprotein cholesterol. It's because of polyunsaturated fatty acids (PUFA) and linoleic acid in Walnut. In addition, previous studies have shown the effect of Walnut (as a rich source of PUFAs) on boosting brain's health and function. They have also demonstrated the inhibitory effects of Walnut compounds such as ellagic acid on cancer development and inflammation. Some surveys have reported that the long-term consumption of Walnut effectively prevents type 2 diabetes. A tremendous amount of Walnut's therapeutic effects are due to its antioxidant activity. Walnuts contain many unique and potent antioxidants such as quinone, tannin, neuraminic acid, and flavonol. Overall, Walnut is recommended as an excellent snack due to their contents. Its compounds can forbid inflammation and oxidative stress, which leads to the prevention of many diseases. From the information mentioned above, Walnut consumption can reduce the probability of cardiovascular diseases, depression, dementia, and type 2 diabetes. However,

Table 1

Search strategies for Google Scholar, PubMed, and Scopus Databases.

Search engine	Search Strategy	Additional filters
PubMed/ MEDLINE	(("Neurodegenerative Diseases"[Mesh]) OR ("Nervous System Diseases"[Mesh]) OR ("Oxidative Stress"[Mesh]) OR ("Neuroinflammatory Diseases"[Mesh]) OR ("Glioblastoma"[Mesh]) OR ("Glioma"[Mesh]) OR ("Epilepsy"[Mesh]) OR (Seizure) OR ("Alzheimer Disease"[Mesh]) OR (Alzheimer's disease) OR ("Parkinson Disease"[Mesh]) OR (Parkinson's disease) OR ("Multiple Sclerosis"[Mesh]) OR (MS) OR (Neuroinflammation)) AND ("Juglans"[Mesh]) AND ((Walnuts [Title/Abstract]) OR (Walnut [Title/Abstract])))	English, August 31, 2022
Scopus	TITLE-ABS (((("Neurodegenerative Diseases") OR ("Nervous System Diseases") OR ("Oxidative Stress") OR ("Neuroinflammatory Diseases") OR ("Glioblastoma") OR ("Glioma") OR ("Epilepsy") OR ("Seizure") OR ("Alzheimer Disease") OR ("Alzheimer's disease") OR ("Parkinson Disease") OR ("Parkinson's disease") OR ("Multiple Sclerosis") OR ("MS") OR ("Neuroinflammation")) AND ("Juglans") OR ("Walnuts") OR ("Walnut")))) AND (LIMIT-TO (SUBJAREA,"MEDI")) AND (LIMIT-TO (LANGUAGE, "English"))	English, Medicine Subject area, August 31, 2022
Google Scholar	#1: "neurodegenerative diseases" OR "Nervous System Diseases" OR "Oxidative Stress" OR "Neuroinflammatory Diseases" OR "Glioblastoma" OR "Glioma" OR "Epilepsy" OR "Seizure" #2: "Alzheimer Disease" OR "Alzheimer's disease" OR "Parkinson Disease" OR "Parkinson's disease" OR "Multiple Sclerosis" OR "MS" OR "Neuroinflammation" #3: "Juglans" #4: "Walnuts" #5: "Walnut" #6: #1 AND #3 #7: #1 AND #4 #8: #1 AND #5 #9: #2 AND #3 #10: #2 AND #4 #11: #2 AND #5 #12: #6 OR #7 OR #8 OR #9 OR #10 OR #11	English, August 31, 2022

additional research is strongly recommended (Ni et al., 2021).

3. Methods

The data supporting this review article was collected by applying an advanced search strategy in google scholar, PubMed/Medline, and Scopus electronic databases. Filtering the search results to English Publications, we searched the following Keywords and MeSH terms filtered on title or abstract: ("Neurodegenerative Diseases"[Mesh]), ("Nervous System Diseases"[Mesh]), ("Glioblastoma"[Mesh]), ("Glioma"[Mesh]), ("Epilepsy"[Mesh]), ("Alzheimer Disease"[Mesh]), ("Parkinson Disease"[Mesh]), ("Multiple Sclerosis"[Mesh]), ("Neuroinflammatory Diseases"[Mesh]), ("Oxidative Stress"[Mesh]), ("Juglans"[Mesh]) and (Walnuts). After screening the titles and abstracts of the articles provided by our search strategy, 57 original articles were considered to review in this study (Fig. 1). This method was applied to retrieve documents published until August 2022. The search strategy of Google scholar, PubMed and Scopus are summarized in Table 1.

4. Investigated disorders

In this section, we examined the neurological diseases that Walnuts can play a role in improving.

4.1. Glioblastoma

Glioblastoma (GBM), comprised of astrocytes of the brain or spinal cord as the most malignant primary cerebral neoplasm, tends to rapid proliferation and progression (Chen et al., 2016). As the most aggressive type of astrocytoma, it makes up 50% of all gliomas and accounts for 2.5% of neoplasm-associated death in 2018 worldwide (Hanif et al., 2017; Rock et al., 2012). The rapid progression of GBM as one of the malignant primary brain neoplasms with a mean diagnosis age of 68–70 years could be significant (Ostrom et al., 2020). Recent studies indicate the effects of age-dependent factors influencing GBM (Kim et al., 2021). The poor prognosis of this type of astrocytoma concerning the current therapeutic approach in glioma eliminating tumor stem-like cells (TSCs) cannot be accomplished even by combined-modality therapy, indicating the principal reason for relapse and chemotherapy resistance of GBM (Qiang et al., 2009). Resistance of GBM to chemotherapy is considered one of the critical barriers to achieving effective anti-cancer treatment, showing the importance of investigating effective chemotherapeutic agents targeting GBM to improve quality of life and life expectancy for patients who have GBM (De Matteis et al., 2019; Naletova et al., 2019). Accumulated knowledge reveals that Pin1 protein, which has a critical role in malignant neoplasm formation, is overexpressed in GBM specimens, suggesting that Pin1 inhibitors should be scrutinized as novel therapeutic agents to improve clinical management of GBM (Atkinson et al., 2009; Yang et al., 2013).

Juglone (5-hydroxy-1,4-naphthoquinone) is a natural element extracted from *Juglans nigra* and its potential antiproliferative effects on GBM by suppressing the Pin1-mediated signaling pathway are significant (Wang et al., 2017). The processes of redox cycling and reactivity to nucleophiles have contributed to the cytotoxicity effect of naphthoquinones associated with apoptosis of glioma cells in response to oxidative stress. According to the study conducted by Pavan et al. (2017), to evaluate the antiproliferative effect of 2-(2,4-dihydroxyphenyl)-8-hydroxy-1,4-naphthoquinone (DiNAF), a synthetic derivation of Juglone, on rat glioma cells. This substance and its properties are compared with the element of natural resources and a series of naphthoquinones. According to biological results and NMR experiments, DiNAF has the lowest tendency to undergo reduction; thus, compared to juglones and other derivatives, DiNAF reduced glioma cell viability due to its efficient proapoptotic effect. In addition, compared with Juglone, temozolomide, and paclitaxel (PTX), DiNAF represented a remarkably increased apoptosis induction in vitro and diminished cell viability in rat glioma. These observations suggest the potential therapeutic effects of DiNAF and its cytotoxic activity in the treatment process in the glioma (Pavan et al., 2017). In another research, Wang et al. (2017) evaluated the anti-cancer effects of Juglone on the U251 human glioma cell line and explored its prospective basic molecular processes. Apoptosis, angiogenesis, migration, cell survival, and molecular targets were examined. The results revealed that juglone significantly suppresses tumor cell viability and triggers apoptosis of cultured U251 cells, gradually attenuating glioma cell viability in a way that depends on concentration and time. Angiogenesis, as a prerequisite for migration of glioma, is inhibited by juglone, indicating that juglone manages the proliferation and migration of tumor cells. According to the findings of this study, juglone may prevent neoplasm formation by stimulating apoptosis, restricting migration of U251 glioma cells, and deranging angiogenesis.

Former studies revealed that reactive oxygen species (ROS) could activate the p38-MAPK pathway involved in apoptosis. In another study, Wu et al. (2017) assessed the cytotoxicity effect of juglones on TSCs. TSCs (in glioma) are composed of U87 and two primary cells (SHG62

and SHG66). According to the findings, juglone can dramatically prevent glioma (stem-like cells) growth by reducing cell viability, inducing apoptosis, and cell shrinkage, along with increasing caspase-9 cleavage in a dose-dependent manner. Meanwhile, juglone may be involved in ROS production and increased p38 phosphorylation (leading to activation of the p38-MAPK pathway in TSCs). Additionally, the cytotoxicity induced by juglone can get eliminated by ROS scavengers. Most notably, juglone as an effective anti-glioma therapeutic agent could markedly inhibit tumor proliferation in vivo and enhance the survival rate of glioma-carrying mice compared to controls. However, temozolomide showed a better cytotoxic result.

The standard therapy, based on temozolomide, induces several side effects, in particular, lymphocytopenia and neutropenia, which commonly triggers opportunistic infections. Genovese et al. (2020) studied the impact of Walnut septum extract on GBM cell survival and its anti-bacterial properties. The cytostatic task of the function of Walnut septum extract against the human GBM cell line (A172) was carefully studied, and from the results of these studies can be assumed that Walnut extract can reduce the proliferation and migration of GBM. The possible cytotoxic effects of Walnut on A172 cells and a non-cancerous cell line (HFF-1) are evaluated using a mean transit time assay. A considerable reduction in HFF-1 cell viability is detected in response to the highest concentration of Walnut extracts. Although, a dose-dependent decrease in cancer cell viability is identified when GBM cells are exposed to higher doses of the Walnut septum extract. The caspase-3 assay and cytofluorimetric analyses are performed to investigate the proapoptotic properties of the Walnut extract against GBM. The results showed that therapy with Walnut extract could increase early and late apoptosis of A172 cells. Examination of the anti-bacterial effects indicated the ability of Walnut extract to decrease Gram-negative and Gram-positive bacterial growth. Most of them are resistant to the antibiotic ciprofloxacin. More importantly, prediction of the activity spectrum for high-performance liquid chromatography detected compounds analysis suggested a range of activities for each substance involving antimutagenic, anti-infective, antineoplastic, antiseptic, and cytostatic effects.

4.2. Epilepsy

Epilepsy is one of the leading neurological diseases of the CNS, affecting nearly 4% of individuals during their lifetime (Browne and Holmes, 2001; Thurman et al., 2018). The current therapeutic approach is based on pharmacological agents, effects on ion channels, and neurotransmitter receptors of nervous systems (Oyler et al., 2018). Conventional antiepileptic drugs only suppress seizures and provide symptomatic treatment but cannot completely cure the disease (Macleod and Appleton, 2007). Despite the common antiepileptic drugs, approximately 30% of epileptic patients proceed to present seizures that are refractory to all therapeutic plans (Löscher, 2011; Shorvon, 2009). Given the current situation, research is needed in the field of novel and effective anti-convulsion therapeutic approaches to provide good prevention and treatment for epileptic seizures. Phenolic compounds in the Walnut kernel have antioxidant functions and can play an essential role in maintaining human health. Walnut kernel also has a neuroprotective function, which can be due to the elements they contain, such as melatonin, vitamin E, and folate. According to Shekaari et al. (Asadi-Shekaari et al., 2012a), study, Walnut kernel extract administration considerably increased the Pentylentetrazole (PTZ) dose for threshold seizure induction and reduced the severity of attacks to an acceptable amount. Flumazenil did not significantly reduce the anticonvulsant effect of Walnuts. On the other hand, a combination of diazepam and Walnut showed a synergistic anticonvulsant effect. Based on available data, it is said that Walnut kernel can protect neurons against oxidative stress caused by seizures. Their study confirmed that Walnut has anticonvulsant effects and suggested that this effect may be mediated through mechanisms other than the Benzodiazepines pathway.

In another study, the walnut peptide extracts' anti-seizure property was evaluated in three different mouse seizure models including PTZ-induced clonic seizure, chemical kindling, and maximal electroshock. Walnut peptides (20 mg/Kg) were administered by intraperitoneal injection of mice 60 min before seizure induction in the three models. To delineate the mechanisms of walnut peptides' anti-seizure activity, they evaluated the impact of diazepam, flumazenil, and a nitric oxide synthase (NOS) inhibitor on this activity. Intraperitoneal administration of walnut peptides significantly increased the seizure threshold. Their results also demonstrated that walnut peptides exert their anti-seizure properties through the modulation of benzodiazepine receptors. Thus, walnut peptides may be considered a new anti-convulsion agent, which can reduce seizure occurrence and slow down seizure progression (Jahanbani et al., 2021).

Oxidative stress is associated with the appearance of epilepsy and seizure development. Accordingly, antioxidants that could decrease oxidative stress are considered in epilepsy treatment approaches (Delanty and MAJAon, 2000; Shekh-Ahmad et al., 2019). According to research, natural protein sources that have oxidant effects are abundant. among these, trees have a significant place. Many are used in traditional medicine because of their anti-convulsion effects (Yaro et al., 2018). Many herbal antioxidant products have anticonvulsant activity (Hsieh et al., 1999; Lian et al., 2005). Walnut kernels phenolic compounds have beneficial properties for human health, including antioxidant, neuroprotective, and anti-atherogenic effects. Moreover, it is confirmed that extreme generation of free radicals has been associated with the pathogenesis of epilepsy and some neurological disease, suggesting that antioxidants coupled with antiepileptic medicines can be effective for improving the management of seizures (Devi et al., 2008). Walnut is one of the substances that has the freest and the most fiber-bound antioxidants. Walnut kernel contains high oil levels which have polyunsaturated fatty acids. Walnuts have many valuable nutrients that are important for maintaining human health (such as omega 3, 6, and 9). Some studies revealed that increasing the use of Walnut kernels can delay the kindling process and reduce seizures caused by the amygdala (Harandi et al., 2013a, 2013b).

NO can participate in the mechanisms involved in seizure progression and PTZ-induced seizure threshold (Bahramnejad et al., 2018; Bahremand et al., 2010). Elevated Levels of secondary products originating from lipid peroxidation have also been found to be significant in the cerebral cortex of rats with these types of seizures (Bashkatova et al., 2003). NOS inhibitors are capable of postponing or suppressing the occurrence of PTZ-induced clonic seizures (Osonoe et al., 1994). It is validated that Walnuts could diminish the generation of NO, tumor necrosis factor- α , and the expression of inducible NO synthase in BV-2 microglial cells stimulated by lipopolysaccharides. Asadi-Shekaari et al. (2012b) evaluated the efficacy of the anticonvulsant and neuroprotective effects of Walnut kernel on rat brain cortex. Adult male rats were divided into three groups: an experimental group (PTZ injection, fed with Walnut kernel), a control group (PTZ injection, fed with ordinary food), and a sham group (without PTZ injection, only for histological studies). The results revealed that Pretreatment with Walnut kernel is associated with an increased threshold of PTZ-induced seizure and decreased mortality rate in the experimental group compared with controls. Moreover, after PTZ administration, the architecture of cortical neurons in the Walnut kernel-treated group was almost intact. However, in the control group majority of the cortical neurons underwent significant changes involving cytoplasm darkening, mitochondrial swelling, and shrinkage of nuclei. Accordingly, Walnut pretreatment is associated with remarkable neuroprotective and anticonvulsant activities in PTZ-induced seizures, this indicates that Walnut kernel supplementation may be effective in PTZ-induced seizure prevention and its relevant neurodegeneration in male rats. In another study, Asadi-Shekaari et al. (2014) assessed the potential antiepileptic properties of Walnut kernel extract on PTZ-induced seizures in rats. They evaluated the effects of benzodiazepines and ethosuximide on these pathways. They divided

male Wistar rats into eight groups. Seizures were induced by PTZ intravenous injection. Applying PTZ, animals were treated with Walnut kernel extract, with or without cotreatment with diazepam, or flumazenil. they observed that Walnut kernel extract administration could remarkably increase the PTZ dose needed to provoke the first myoclonic motion, decrease seizure grades' severity, and reduce the mortality rate of rats to 0%. The application of flumazenil had no significant effects in lowering the anticonvulsant properties of Walnut kernel extract. The combination of Walnut kernel extract and diazepam exhibited a synergic antiepileptic activity; conversely, ethosuximide had no considerable impact on Walnut anti-seizure effects. Considering the low influence of flumazenil on Walnut kernel extract effects as an antagonist of benzodiazepine receptors and the synergistic effect of Walnuts and diazepam, it can also be said that the antiepileptic effects of Walnut is exerted through pathways other than benzodiazepine receptors. different ways could contribute to the antiepileptic effects of Walnuts. Various studies have been performed on the role of NO in the pathophysiology of disorders such as trauma, stroke, and seizures (Bashkatova et al., 2000; Wiesinger, 2001)., which could explain the mechanisms underlying the anticonvulsant effect of Walnuts. In a nutshell, the findings of this study indicated that Walnut kernel extract was effective at increasing the needed dose to the first myoclonic jerk, at reducing the severity of seizures, and the high efficacy of the extracts at preventing mortality was considerable, 100% of animals were protected (Asadi-Shekaari et al., 2014). The results are also supported by the study by Poulouse et al. (2014).

4.3. Parkinson's disease

Monoamine oxidase (MAO) is a catalytic enzyme that catalyzes the oxidative deamination of monoamines like dopamine. In Parkinson's disease (PD), MAO is highly expressed. MAO activity rises with age, which may lead to neuronal degeneration within brain as a result of oxidative stress. The gradual decline of dopaminergic neurons within the substantia nigra pars compacta (SNpc) is followed by a decrease in striatal dopamine as well as its metabolites in such a procedure. ROS produced by MAO-B can harm cells in the environment as well as in neurons (Tatton et al., 2003). Neurons are primarily liable to oxidative stress (Mallajosyula et al., 2008). Through PD model types, MAO-B levels doubled in the SNpc, which corresponds well with the proportion of selective dopaminergic cell death in the SNpc (Mallajosyula et al., 2008; Damier et al., 1996). MAO-B inhibitors have been shown to reduce dopamine breakdown and limit the generation of neurotoxic dopamine metabolites and ROS. As a result of its protective role, this type of drug is now employed in the symptomatic therapy of PD (Nagatsu and Sawada, 2006; Schapira, 2011; Weinreb et al., 2010). Choi et al. found that juglandis semen extract, a water-soluble extract of juglandis semen, has superior antioxidant properties and MAO-B has an inhibitory activity in vitro compared to extract of a ginkgo leaf, which is a common natural MAO-B inhibitor. In comparison to the control group, juglandis semen extract therapy decreased the MAO-B fluorescence intensity generated by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) poisoning. The in vivo capacity of juglandis semen extract to inhibit parkinsonian neurodegeneration was investigated in this study. Juglandis semen extract therapy reduced mesencephalic neuronal death in vitro by inhibiting oxidative and nitrosative stresses induced by 1-methyl-4-phenylpyridinium (MPP+). In mice susceptible to the neurotoxic action of MPTP, juglandis semen extract protected dopaminergic neurons and avoided the decrease of striatal dopamine and its metabolites (Choi et al., 2016).

Complex I, which is located in the mitochondrial electron transport chain, also named nicotinamide adenine dinucleotide-ubiquinone oxidoreductase, is an integrated complex that facilitates electron flow from nicotinamide adenine dinucleotide to ubiquinone. These enzymes cause a speed-limiting phase for the mitochondrial respiratory chain. As a result, it is vital in regulating oxidative phosphorylation, which is

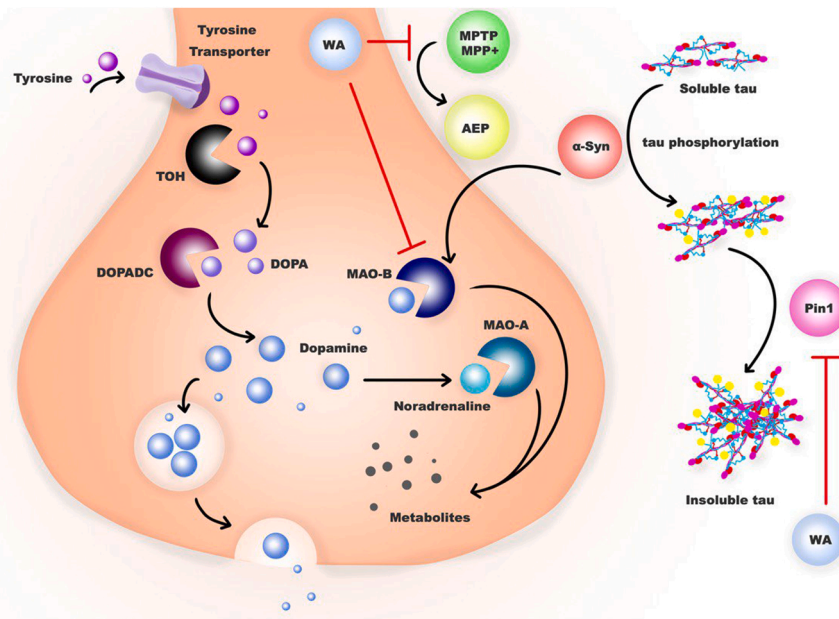


Fig. 2. Walnut function as a MAO-B inhibitor in Parkinson's disease. Alpha-synuclein (α -Syn) aid tau protein phosphorylation, leading to formation of insoluble tau. Pin1 has also been found in Lewy bodies in Parkinson's disease and has been demonstrated to aid in the production of α -Syn aggregation. Monoamine oxidase (MAO)-A converts noradrenaline and MAO-B converts dopamine into its metabolites, resulting in neuronal disruptions. Walnut can inhibit MAO-B and Pin1 activity.

linked to the synthesis of adenosine triphosphate (Petrosillo et al., 2008). Complex I function is reduced in the substantia nigra of PD, yet stays normal in other neuronal areas (Schapira et al., 1990), which is consistent with Essa et al. (2015). research. When compared with control mice, MPTP dramatically increased MAO-B activity and decreased mitochondrial complex I performance in substantia nigra. Since passing the blood-brain barrier, accumulating MPTP is processed by MAO-B to MPP+ and absorbed by the dopamine transporter, which suppresses complex I of the mitochondrial respiratory chain. In addition, the current study found that Walnut may have mitochondrial protective properties through recovering complex-I function. Inside the substantia nigra of PD patients, post - mortem investigation showed higher rates of lipid peroxidation, Superoxide dismutase (SOD), and catalase (CAT) activity, as well as enhanced free iron amounts (Sian et al., 1994). The actions of glutathione (GSH) and its dependent enzyme, GSH peroxidase (GSH-Px), were reduced in the MPTP-induced group. Walnut treatment results in a significant increase in GSH content and GSH-Px activity. Because of its antioxidant effect, Walnut intake decreased the lipid peroxidation reactions, the actions of SOD, and CAT generated by MPTP in Essa et al. study (Essa et al., 2015).

Proline-directed protein kinases and phosphatases control bidirectional phosphorylation on Ser/Thr-Pro motifs (a crucial molecular shift in managing numerous cellular activities). For controlling cellular signaling, proline-directed kinases, as well as several Ser/Thr phosphatases, phosphorylate and dephosphorylate these patterns. Pin1 is one of the few peptidyl-prolyl isomerases that detect phosphorylated serine or threonine sites directly before proline (Ser(P)/Thr-Pro) in a set of proteins and catalyzes the isomerization of the peptide bond's cis/trans conformation (Joseph et al., 2003). Conformational regulation intervened by Pin-1 has been demonstrated in various studies to include a significant influence on cell proliferation, stress feedback, immunological function, germ cell formation, neuronal specialization, and survival. Pin 1 signaling imbalance is associated with a variety of diseases. Pin1 is highly expressed in differentiated cells and post-mitotic neurons, suggesting that this might have a function in the nervous system. Pin1 has been found in Lewy bodies in PD and has been demonstrated to aid in producing alpha-synuclein aggregates in a cellular model of alpha-synuclein clusters (Becker and Bonni, 2006; Ryo et al., 2006).

Pin1 is substantially increased in cell culture, animal models of PD, and in human PD brains. According to Ghosh et al. (2013), Pin1 operates as a proapoptotic mediator in dopaminergic neuron atrophy, suggesting that knocking it out reduces apoptotic processes in PD cell culture models. MPP-induced Pin1 production was decreased in a PD cellular model when Pin1 activity was inhibited with the pharmacological antagonist juglone. In an experimental mouse model of PD, juglone therapy reduced Pin1 levels and preserved the nigrostriatal axis. To test the neuroprotective potential of juglone, a recognized suppressor of Pin1, they used a validated MPTP model of PD. Pin1 inhibitors include juglone (5-hydroxy-1,4-naphthalenedione (C₁₀H₆O₃)), the naphthoquinone discovered mainly in the roots, leaves, and bark of black Walnut trees. By modifying the thiol groups of molecules, juglone disables human Pin1's reaction rate irreversibly. We discovered that micromolar doses (1 M) of juglone inhibited Pin1 production which is generated by MPP, in their research. Juglone also preserved mesencephalic and striatal primary neurons and their neurites against MPP+ poisoning and greatly improved dopamine uptake in principle mesencephalic neurons. In the striatum of mice medicated with MPTP, juglone recovered behavioral activity and also dopamine and its metabolites concentrations. Numerous lines of the research reported in the study by Gosh et al. distinctly reveal up-regulation of Pin1 production in dopaminergic cell culture models, an animal model of PD, and the midbrain of PD patients. They further show that a pharmacological suppressor of Pin1 which prevents Pin1 production from being induced preserves dopaminergic neurons from neurotoxic stimuli (Ghosh et al., 2013).

Extraction of Walnut in aqueous form has a neuroprotective role. Utilizing a mouse model of PD, Walnut juice decreased ROS and NO generation, and limited the reduction of striatal dopamine and its metabolites, leading to a significant enhancement in PD motion abnormalities (Choi et al., 2016). Walnut has neuroprotective properties due to its capacity to suppress the MAO-B enzyme which raises oxidative stress in PD patients, as well as antioxidant and mitochondrial defensive properties (Essa et al., 2015).

Gallic acid, according to Sameri et al., helps reduce motor dysfunctions and enhances gamma wave power in rats with 6-hydroxydopamine-induced dopaminergic neurodegeneration and PD. They discovered that GA's positive impact is due to its antioxidant and free

radical neutralizing properties (Sameri et al., 2011).

"Hormesis" is a modifying stress reaction in which a cell or organism develops tolerance to a harmful chemical after being exposed to a low dosage, and "neurohormesis" is hormesis inside the nervous system. Several neurohormetic phytochemicals interfere with the hormetic pathways, which is fascinating. Hormetic phytochemicals are valuable assets for the production of new neuroprotectants. Hormetic phytochemicals can trigger several transcription elements and regulate the adaptive stress reaction to various stressors. The stimulation of antioxidants and detoxifying enzymes implicated in the control of oxidative stress and cellular calcium homeostasis occurs often when the hormetic path is activated. Naphthoquinones, including juglone, are some of the known hormetic phytochemicals with strong hormetic stress reactions. The study conducted by Choi et al. (2012), showed that naphthazarin, a naphthoquinone derivative, has a protective effect on neurons in a PD model produced by MPTP and MPP1. Fig. 2 summarizes the impact of Walnut on PD.

4.4. Multiple sclerosis

Multiple sclerosis (MS) is a long-term disease in which demyelination of the CNS and inflammation occurs. Women are affected twice more often as men by this disease beginning generally from the age of 20–40 years (Tullman, 2013). The exact cause of MS is not known yet. This disorder is known as a multi-factorial disease in which environmental and genetic components have an effect on susceptibility to disease. The immune system in patients with MS and its animal figure, determined as experimental autoimmune encephalomyelitis, attacks the myelin cover that encircles neurons' axons in the central nervous system. Since there is no cure for some inflammatory disorders, such as MS, investigators and physicians have concentrated on the benefits of fruits, vegetables, and seeds for the reduction of manifestation. In that wise, Walnut is an anti-inflammatory nut. Walnut oil carries unsaturated fatty acids. Walnut oil is also exceedingly enhanced in omega-3 and omega-6 fatty acids, proteins, sterols, potassium, tocopherols, aliphatic alcohol, fiber, vitamin E, magnesium, triterpenes, and copper, each of which has anti-inflammatory and antioxidant properties (Leray et al., 2016; Polman et al., 2011).

Ganji et al. studied the result of using Walnut oil on encephalomyelitis. After Walnut oil therapy the severity of mice's experimental autoimmune encephalomyelitis disorder was reduced, and the immune response shifted from destructive to regulatory. These discoveries recommend that Walnut oil is an effective treatment for MS. Walnut oil decreases the mean maximum seriousness of the sickness by lessening T-helper 1 activity. There is evidence that pro-inflammatory cytokines, like interferon-gamma (IFN- γ), released by T-helper 1 cells, participate in the pathogenesis of MS. Walnut oil also diminishes the usual maximum seriousness of the illness by boosting T-helper 2 cell responses. It has appeared that T-helper 2 cells can restrain T-helper 1 cell reactions through cytokine generation containing interleukin (IL)-4, IL-5, IL-10, and tumor growth factor- β . There was a notable reduction in disorder severity, a hindrance to plaque formation, and modified cytokine production (Ganji et al., 2019).

4.5. Neurotoxicity

Neurotoxicity is caused by the direct or indirect effects of chemicals on the nervous system, nerve cells, or metabolic processes vital to the nervous system that impair the function of the human nervous system, harm growth, or damage the adult nervous system. Numerous studies have shown that the aging process can have an undeniable effect on neurotoxicity. It is also shown that diet and using a range of specific nutrients can slow or even stop the progression of this process. One nutrient that cannot be overlooked because of its unique effect on neurotoxicity is Walnut (Spencer and Lein, 2014). In a study conducted by Liu et al. (2019a), the antioxidant and anti-apoptotic effects of the

Walnut kernel and Walnut seed coats on the diet of aging mice with learning and memory impairments treated with D-galactose were investigated. It is noteworthy that D-galactose impairs memory and cognition, causes signs of aging in mice with brain and liver damage, and moderates levels of hepatocyte apoptosis, necrosis, and inflammatory cell infiltration. It can also increase malondialdehyde (MDA) concentration and decrease total antioxidant (AOC) functions, total SOD, and GSH-Px activities. Adding Walnut kernels and Walnut seed coats to these mice's feeding program causes extensive changes. Chemical analysis of these nutrients has shown that Walnut kernels contain a variety of substances with antioxidant properties (such as flavonoids, melatonin, and vitamin E), antioxidant unsaturated fatty acids, and polyphenols. Also, Walnut seed coats are rich in polyphenols. The result of research has shown that these nutrients reduce oxidative damage and inflammation, improve learning and memory, reduce the weight of mice, and return antioxidant enzyme concentration to normal levels. They also prevent damage to the hippocampus and liver in D-galactose-induced aging mice. Walnut seed coats reduced pathological changes in the liver and brain tissue and increased the number of round-shaped neurons and well-organized fibers in the hippocampus of experimental mice. The mechanism of action of Walnut seed coats may include the regulation of acetylcholinesterase action, the reform of histopathological changes, and the providing adenosine triphosphate energy to brain tissue. In the final results of the experiment, an increase in lots of hairs in mice and a decrease in the number of errors and jumping time of mice with the mentioned diet from the platform were also observed, the second said item is due to the increase in cognitive abilities of this group. Walnuts are generally considered as an anti-cancer, anti-inflammatory, blood purifier, and antioxidant nutrient and also as a treatment for a wide range of diseases in traditional medicine. In research conducted by Shabani et al. (2012), the ability of Walnut to protect against cisplatin-induced neurotoxicity was evaluated by observing behaviors related to the hippocampus and cerebellum of these mice. The purpose of this was to investigate the effect of Walnuts on pain. Extensive tissue damage and negative impact on cerebellar cortical neurons (especially Purkinje cells which have a significant impact on the control of motor activity) resulted in complications such as renal toxicity, neurotoxicity, ear toxicity, movement, balance problems, muscle weakness, and vomiting. It increased pain response delay and decreased exploratory behaviors and memory function. One of the ways to overcome the side effects of this drug in cancer patients is to intervene in their diet with a variety of nutrients as a moderator of toxicity of anti-cancer agents. Walnuts are also rich in omega-3 and alpha-linolenic acid, which boost cognitive function. It also has anti-inflammatory and antioxidant properties and a defensive role against cisplatin-induced neurotoxicity due to its various substances such as vitamin E, folate, melatonin, flavonoids, and polyphenols. Also, Walnut peel extract, with its antioxidant properties, is effective in modulating the effects of cisplatin on the liver and kidneys of male mice. Also, the final results of the research show that the movement balance and coordination of the muscles of mice treated with a diet containing Walnuts are different due to the richness of this nutrient from linoleic acid and α -Linolenic acid, the prevention of cisplatin-induced memory changes in them due to other diets. The inclusion of Walnuts in the diet of these mice modulates cisplatin-induced CNS changes.

Investigate the preventive and therapeutic effects of Walnut leaf extract on diabetic neuropathy. Intraperitoneal injection of STZ into diabetic rats showed sciatic nerve degeneration, more expression of caspase 3, cyclooxygenase-2 (COX-2), and inducible NOS (iNOS) were present in these rats after STZ injection. These effects are moderated after the administration of Juglans regia L. (GRL) leaf extract. Administration of this nutrient extract also reduced lipid peroxidation and pain response, besides improving the antioxidant status of the sciatic nerve in these rats. In conclusion, GRL leaf extract can improve the behavioral and structural parameters of diabetic neuropathy, fasting blood sugar, and hemoglobin A1c and increases glucose uptake by inhibiting protein

tyrosine phosphatase 1B. STZ injection also caused thin, loose, irregular myelinated nerve fibers with the infiltration of several inflammatory cells into the isolated nerve fibers. Administration of GRL leaf extract improved this effect, after which only the focal loss of myelin sheath and several scattered inflammatory cells were observed around nerve fibers.

Neurotoxicity can occur because of exposure to toxic substances or heavy metals like cadmium. A small amount of cadmium can have harmful effects on nerve cells and the brain. It can affect memory, and speed of learning, and lowers intelligence quotient levels. Further conditions may also develop (Batool et al., 2017). Batool et al. (2019) studied the protective effect of nuts such as Walnuts and almonds on the neurotoxicity of cadmium - a metal without physiological function in humans and a potent neurotoxin that is toxic to body tissues due to long half-life and accumulation even in shallow doses on mice. Cadmium causes depression, anxiety, and decreased memory function by reducing the concentration of noradrenaline, dopamine, and serotonin in the brain and by significantly increasing the concentration of metabolites. Cadmium can also cause neurotoxicity by reducing neurotransmitters at synapses by blocking Ca^{2+} -dependent intracellular signal pathways and inhibiting the integration of storage vesicles. Walnuts and almonds reduced the toxicity of this metal, increased the synthesis of neurotransmitters, and overcame nutritional deficiencies. Also, these nutrients reduced the degree of anxiety and depression in mice. According to the Batool et al. research, rats with the administration of cadmium escape slower than rats with a diet of Walnut and almond. Open field test checks the effect of cadmium besides Walnut and almond on memory functionality. It demonstrated that substances in Walnut and almonds can reduce the impact of cadmium on memory functionality.

Walnut as a nutrient has a wide range of different benefits. One of the compounds in this nutrient is ellagic acid, a polyphenolic and organic heterotricyclic compound. In a study by Ceci et al., strategies for providing ellagic acid as a nutrient with comprehensive therapeutic and pharmacological benefits were examined. The results illustrated the broad effects of ellagic acid on the recovery of chronic diseases associated with oxidative damage (such as cancers, cardiovascular, neurodegenerative disorders, etc.). In addition, it has anti-cancer, anti-inflammatory, anti-bacterial, and anti-viral properties. Also, ellagic acid is effective in wound healing by increasing blood coagulation, via activating the intrinsic cascade factor, XII. The compound has low water solubility, limited absorption, and low plasma half-life while increasing its solubility can increase the absorption of this nutrient. It is also effective in neutralizing active species by increasing the expression and activity of SOD, GSH-Px, GSH reductase, and CAT enzymes. Ellagic acid has an anti-tumor effect in organs such as the prostate, colon, pancreas, and ovary with different mechanisms such as inhibition of cell proliferation, angiogenesis, and invasion of the extracellular matrix. So, it can be considered as a chemopreventive or chemotherapeutic compound. Finally, this substance with anti-inflammatory traits can be effective in the treatment of chronic inflammatory diseases (such as contact dermatitis and pancreatitis).

The study of Ren et al. (2018) illustrated that the Manchurian Walnut hydrolyzed peptide is an antioxidative protein and can decrease oxidative stress and apoptosis and control neurotransmitter action. Manchurian Walnut hydrolyzed peptide can boost the functionality of memory and speed up learning and lessen the effects of oxidative stress. Oxidative stress can damage nerve cells and make some problems with memory and the brain's functionality. Manchurian Walnut hydrolyzed peptide, as an antioxidative substance, can reduce the damage and help to improve. In this study, the mice taking some dose of Manchurian Walnut hydrolyzed peptide did the water maze test better and escaped faster. According to the high susceptibility of the brain to the degenerative changes caused by some species of free radicals and oxidative products, the effect of Walnut on these impairments is searchable. All of the examined mice were separated into two groups: saline and scopolamine-treated groups. The results showed that scopolamine-treated mice were confronted with cholinergic dysfunction

and oxidative stress which were entirely eliminated by the usage of Walnut.

Feng et al. (2018) did some research about the dose-related effects of Walnut on memory. These investigations show that a high-Walnut-dose regimen will induce an increase in memory functions and recognition index and a decrease in transfer latency and escape latency. In another part of the research, the effect of Walnut on memory functions and the level of acetylcholine was investigated. Generally, the level of acetylcholine shows the rate of memory function. But, as the research results conducted, there is a more significant increase in the level of acetylcholine via using Walnut in saline and scopolamine-treated mice. In another part of the study, it was observed that Walnut is also effective in the relation between MDA level and memory retention. Any correlation between MDA level and memory retention was observed in saline and scopolamine-treated mice. Also, there was a negative correlation between MDA level with SOD, GSH-Px, and CAT activities in these mice.

Oxidative stress is one of the causes of cell death and is involved in neurodegenerative disorders such as AD, PD, or cerebral ischemia-reperfusion after stroke (González-Sarrías et al., 2017). Neurons consume large amounts of oxygen and produce hydrogen peroxide through their mitochondria. Since the central nervous system contains a high amount of neurons, its sensitivity to reactive oxygen species is also increased (Shichiri, 2014). Walnut hydrolysis protein has various peptides. One of these peptides, which has an EVSGPGLSPN sequence, has an antioxidant function and can play a role in protecting neurons by reducing ROS generation (Liu et al., 2019b). A study written by González-Sarrías et al. (2017) showed that dietary polyphenols can have health benefits. The results of experiments performed by this research group include the role of 3,4-dihydroxy phenyl propionic acid, 3, 4-hydroxyphenyl acetic acid, gallic acid, gallic acid, and urolithins in reducing the amount of ROS and subsequently preventing apoptosis. Nutrients that contain polyphenols precursors of the molecules mentioned above can play a role in reducing oxidative stress and later cell death and preventing neurological disorders (examples of these nutrients are cocoa, tea, strawberries, Walnuts, and pomegranates) (González-Sarrías et al., 2017). Amelioration of oxidative stress was the main approach to boost neurodegenerative disorder. In the Liu et al. (2019b) study, one of the effective peptides in Walnuts was identified as EVSGPGLSPN by sequencing. This peptide has a unique property in reducing ROS and has an antioxidant effect. As a result, treatment with this peptide can play a role in reducing the amount of ROS and increasing cell viability. According to research, scopolamine can play a role in memory loss. Peptides in Manchurian Walnuts can prevent or reduce this memory impairment. Their data indicated the EVSGPGLSPN was qualified to protect PC12 cells from H₂O₂-induced damage. EVSGPGLSPN considerably inhibited ROS levels compared to the H₂O₂ injured group. As a result of this experiment, it can be said that peptide EVSGPGLSPN plays an essential role in cell defense against oxidative damage caused by H₂O₂. SOD, CAT, and GSH-Px are some of the most important antioxidant enzymes that work in the brain. Among the enzymes mentioned, SOD and CAT are involved in cell protection against damage caused by ROS. After exposure of PC12 cells to H₂O₂, the activities of SOD, CAT, and GSH-Px in the cells were greatly reduced (in comparison with control group). Although, treatment of these PC12 cells with EVSGPGLSPN peptide can significantly improve SOD's action. Moreover, pretreatment with this peptide dramatically boosted the activity of CAT.

Enhanced accumulation of p-CREB in hippocampal CA1 neurons was shown previously to be along with increased neuroprotection in a mice model of vascular dementia (Hu et al., 2017). Macromolecules in cells and tissues (such as carbohydrates, lipids, proteins, and nucleic acids) can be disrupted by oxidative stress damage and ultimately interrupt tissue and organ function. Urolithins are a subset of dibenzo [b, d] pyran-6-ones (Djedjibegovic et al., 2020). Based on the results of experimental data (OARC test) it can be said that Urolithin A has a higher antioxidant activity than ellagitannins, and this result tells us that

Urolithin can be an essential mediator to protect ellagitannins. It has been proven that oxidative stress can cause inflammatory activities. Since antioxidants play a role in eliminating ROS, they can also play a role in preventing provocative activities (Ishimoto et al., 2011). Due to the position of pomegranate, Walnuts, and berries in protecting the cardiovascular system, these nutrients are called “superfoods.”

The general characteristic of these foods is the high compounds of ellagitannins and urolithins. In a review from Djedjibegovic et al. (2020), some studies showed that urolithin B increased mitogen-activated protein kinase (MAPK) phosphorylation which protects the oxidative stress attacks and declined some factors that indicated their function to enhance the oxidative stress levels, such as Akt, c-Jun N-terminal kinase (JNK), and extracellular signal-related kinases (ERK) phosphorylation without affecting phospho-p38. The expressed mechanisms exhibit anti-inflammatory activity. Urolithin B also has an antioxidant role due to its inhibiting ROS generation in lipopolysaccharides (LPS). It seems that the mechanism of the antioxidant effect is inhibiting NADPH oxidase subunits, along with the positive regulation of heme oxygenase-1 (HO-1). For the neuroprotective function of urolithin A, the condition of cytochrome c, cleaved caspase-9, cleaved caspase-3, and cleaved poly (ADP-ribose) polymerase (PARP) were repressed, which validates that urolithin A reduces cell death which exposed to H2O2.

In summary, urolithin A can reduce the amount of ROS in cells, prevent pathways leading to apoptosis and cell death, and modulate the MAPK p-38 pathway (Kim et al., 2020). The results obtained from studies prove that urolithins can be used as a treatment to counteract oxidative stress and reduce tissue injuries. Recent research shows that urolithin metabolism has a unique cell activity (cell-specific), which changes its activity in vitro. This evidence has not yet been proven and needs further investigation (Djedjibegovic et al., 2020). The results are consistent with Poulouse et al. (2014) and Fisher et al. (2017).

4.6. Neuroinflammation

Inflammation involves a set of local immune responses to trauma-induced injuries or infections caused by pathogens that can facilitate the destructive effects and angiogenesis in the affected area. On the other hand, inflammation in the brain, along with its necessity and positive impact, can destroy neurons. Inflammation of the brain affects all brain cells, including neurons, microglia, and macroglia. Inflammation is involved in many brain diseases such as AD, PD, and MS. High levels of inflammation and oxidative stress can lead to memory disorders. In cerebral inflammation, microglia in the CNS with excessive activity secretion of inflammatory mediators such as NO, prostaglandin E2, and IL-6 are involved, which ultimately leads to nerve damage. Walnut is one of the foods that, with its peptides, can modulate memory disorders and cognitive problems caused by inflammation (Wang et al., 2020). The results of previous research have shown us that a diet rich in nuts, vegetables, and fruits can affect a various range of diseases. Walnut has been proven to be a nutrient-rich in unsaturated and essential fatty acids such as alpha-linolenic and linoleic acid, which contribute to some cellular processes in the brain, such as activating microglia and thus producing cytotoxic mediators that are related to the development or progression of AND. Also, the effect of this nutrient on improving memory, cognition, and neurological outcomes associated with oxidative stress and inflammation has been proven (Shabab et al., 2017).

Willis et al. (2010) investigated the anti-inflammatory effects of Walnut, by generating methanolic extract of this nutrient and exposing microglia cells to it and studied its impact on activating these cells in contact with the bacterial cell wall (LPS). The result showed a reduction in the production of nitric oxide and nitric oxide synthase expression induction through desensitization of provocative actions of LPS as well as a drop rate production in tumor necrosis-alpha (TNF- α). In addition, they realized that Walnut extract makes internalization of the LPS receptor. The anti-inflammatory effects of Walnut depend on the activation of phospholipase D2 function. In the final results, they saw the

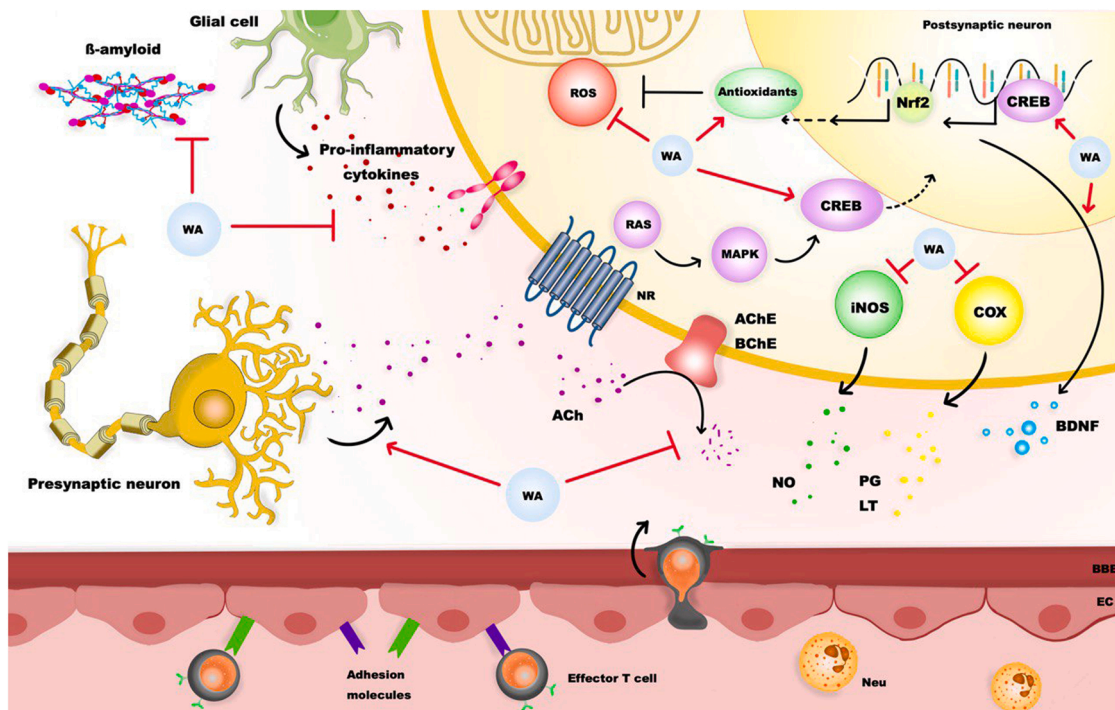


Fig. 3. Potential mechanisms of walnut in controlling the neuroinflammation. Neuroinflammation start with local immune responses, following recruitment of adaptive and innate immune cells to the brain. the anti-inflammatory effects of walnut (WA) on neurons include suppression of pro-inflammatory cytokines, β -amyloid aggregation, Reactive oxygen spice (ROS), Acetylcholine esterase (AChE) activation, and inducible nitrous oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) formation. Walnut can also induce Nrf2, brain-derived neurotrophic factor (BDNF) and cAMP response element binding protein (CREB) expression.

impact of Walnut on modulating the microglia cells' ability to respond to subsequent pro-inflammatory stimuli. Also, the fatty acids in this nutrient can have different impacts on molecular functions. For example, n-3 PUFA α -Linolenic acid suppresses nitric oxide production in macrophage cells, palmitic acid by stimulation of TLR4 signaling pathways, and oleic acid and linoleic acid fatty acids by inhibiting the stimulatory effects of LPS and saturated fatty acids in macrophages can affect molecular processes.

Findings from the research have shown that increasing the accumulation of misfolded/ damaged poly-ubiquitinated proteins has a significant effect on AND. In a different study, Poulouse et al. (2013) investigated the molecular effects of Walnut on the homeostasis of these proteins in the process of aging, the diet of laboratory mice with a food content of 6% or 9% Walnuts was adjusted, which was followed by autophagy activation through inhibition of mTOR phosphorylation, upregulation of ATG7, and Beclin 1 and circulating MAP1BLC3. Autophagy with protection against age-related oxidative stress and inflammation, degradation of amyloid- β ($A\beta$) precursor protein in the process of AD, α -Synuclein in PD, and Htt in Huntington's disease might reduce the accumulation of misfolded/ damaged poly-ubiquitinated proteins. In a study by Wang et al. (2020), the neuroprotective effects of Walnut peptides on memory-impaired mice fed a diet containing LPS and anti-inflammatory mechanisms against LPS 6-induced inflammation in BV-2 cells were investigated. The study showed the effect of Walnut protein hydrolysate and 18 peptides with anti-inflammatory activity in LDS-activated BV-2 cells in improving LPS-induced memory disorders by making the inflammatory response and oxidative stress in the brain seem normal. LPF, GVYY, and APTLW can reduce the concentration of cytokines by decreasing the expression of mRNA and the content of pro-inflammatory mediators by decreasing the expression of related enzymes, thereby modulating brain inflammation. The study of Xu et al. (2018) showed that Urolithins positively effect neuroinflammation. Urolithins are produced by the metabolism of ellagitannins of microbes in the gut. Walnuts, pomegranates, and strawberries are rich-ellagitannin food. Many of ellagitannins and ellagic acid in pomegranate can prevent inflammation in the brain of AD mice. Urolithin A, Urolithin B, and Urolithin C are different kinds of Urolithin and have other effects. Urolithins can cross the blood-brain barrier and affect inflammations in CNS. NO is an essential molecule in the cause of neuroinflammation. Urolithin A and B reduce the amount of nitric oxide and prevent inflammations. Urolithin A and B decrease the number of iNOS and COX-2 proteins. These two proteins have a significant role in the production of nitric oxide and cause neuroinflammation. The study showed that Urolithin A and B reduce the expression of inflammatory genes and help to accelerate the healing of inflammation in the CNS.

Neuroinflammation is related to cognitive decline and neurodegenerative disease. According to Fisher et al. (2021) study, Walnuts and blueberries have neuroprotective and anti-inflammatory effects. They tested the individual and potentially synergistic good symptoms of Walnut oil and blueberries on LPS-induced neuroinflammation in rat microglial cells by biomarkers measurement of inflammation: nitrite, iNOS, and COX-2. The tests showed that blueberry, Walnut oil, and Walnut oil/blueberry decreased LPS-induced nitrite, COX2, and iNOS relative to control. Blueberry was stronger in reducing nitrite generation than Walnut oil/blueberry, and both blueberries and Walnut oil/ blueberries were more substantial than Walnut oil. But, no notable differences between treatments for COX2 and iNOS expression were observed. All three treatments weakened LPS-induced nitrite, COX2, and iNOS in a concentration- and time-dependent manner. The reduction in neuroinflammation after all treatments indicates that adding blueberries and, or Walnuts to our diet can decrease the neurodegenerative effects of inflammation. However, the result suggests that blueberries and WO do not act synergistically to decline inflammation in microglia. Fig. 3 summarizes the impact of Walnut on Neuro inflammation.

4.7. Memory

Memory dysfunction is related to the whole gamut of neurologic issues that have an effect on brain functionality in disorders, some as low as epilepsy and some as dangerous as stroke. It has uprising clinical relevance as the people grow older and AD and other neurodegenerative diseases increase in prevalence (Matthews, 2015). The research of Lee et al. described urolithin B and its benefits. Urolithin B is the final product of ellagitannin metabolism. It prevents the production of nitric oxide and pro-inflammatory cytokines. Urolithin B is an antioxidative substance that reduces producing of reactive oxygen species.

On the other hand, Urolithin B increases the phosphorylation of adenosine monophosphate-activated protein kinase and stops the phosphorylation of JNK and ERK. Microglia is a defensive cell in CNS. It works in brain injury and inflammation and helps in apoptosis. Urolithin B forbids microglia activation after injection of LPS and prevents inflammation. Lipopolysaccharide cause memory deficiency and some other problems with memory function. The study of Kim et al. proved that proteins in Walnut could improve memory function and reduce the damage of inflammation in the blood-brain barrier and help to heal its cells faster. $A\beta$ can cause some structural defects in the blood-brain barrier, and cause Inflammatory reactions and damage, and cut the strong connection between cells in the blood-brain barrier. $A\beta$ can cause oxidative stress and destroy the central nervous system's cells. Walnuts have active antioxidative substances and polyunsaturated fatty acids. It prevents the aggregation of fat in the liver. The result of a few tests shows that Walnut improves the speed of learning and decreases ROS in mitochondria. Also, proteins in Walnut increase the synthesis of Acetylcholine and reduce the rate of its destruction.

Memory dysfunction has various causes, such as aging, injuries like brain tumors, stroke, etc. Unfortunately, sometimes even drugs have side effects and can affect memory. Scopolamine treatment can block the central muscarinic acetylcholine receptor, impairing cognitive and memory function. It has been proved that Walnut protein hydrolysates can decrease the memory shortage induced by scopolamine. Wang et al. have evaluated the neuroprotective effects of Walnut hydrolysis protein against defects of memory caused by scopolamine in mice and zebrafish. Their survey indicated that oral consumption of Walnut hydrolysis protein not only causes notable betterment in behavioral performance such as memory and learning but also moderates the disorders of the cholinergic system and oxidative stress in the brains of mice.

Moreover, it can boost the transcription of some genes associated with antioxidant defense-related proteins and neurotrophic-related proteins such as brain-derived neurotrophic factor and cyclic adenosine monophosphate response element-binding protein (CREB). In addition, it was understood that FY and SGFDAE could, respectively, inhibit acetylcholinesterase (AChE) and Keap1, which cause an improvement of memory deficits induced by scopolamine.

On the other hand, scopolamine can decrease GSH-Px, SOD, and CAT activities in the mice brains which weakens the antioxidant defense system. Although, piracetam and Walnut hydrolysis protein administration can normalize the activities of these antioxidative enzymes to some extent except for CAT activity. Injection of scopolamine showed MDA, the lipid peroxidation product in mice brains. Interestingly, it is validated that Walnut hydrolysis protein can reduce MDA contents.

Some kinds of Walnut-derived peptides such as YVLLSPK have had a significant neuroprotective result against scopolamine-induced cognitive deficits in mice. In this article, the main way in which YVLLSPK works is investigated. According to the researchers, YVLLSPK does not play any toxic role for mice and would not change any parts of their liver and kidney. According to Wu et al (Zhao et al., 2021), mice induced with scopolamine had a deficit in cognitive and memory abilities. These deficiencies were relieved by using Walnut products. Also, these mice showed a longer escape latency. Another investigation designed by Li et al. found that mice induced with scopolamine had longer escape latency and crossing and target times in

spatial probes. Also, Sheng et al. reported that having a defatted Walnut meal will decrease the escape latency in scopolamine-induced mice. According to all of these findings, YVLLPSPK, which has an essential role in Walnut antioxidant activity, has a significant correlation with escape latency and cognitive abilities in scopolamine-induced mice. Another part of YVLLPSPK is known to be used therapeutically to relieve escape latency and delayed neurological deficits in AD.

According to Maze et al (Liao et al., 2020), Walnut has some effects on memory impairment in mice, such as preventing cholinergic function damage, inhibiting oxidative stress, and preventing histological changes of neurons in hippocampal regions. On successive days, the behaviors of mice were measured, and there had been a noticeable improvement in them. All of the databases showed that Walnut usage would improve the spatial memory of mice, such as swimming distance and escape latency. Also, Walnut can affect the AChE and choline acetyltransferase (ChAT) activity caused by scopolamine administration. The results showed that Walnut will cause an increase in the activity of AChE and also a decrease in ChAT. The effects of this material were not restricted to these articles and it also has some significant influences on T-SOD, GSH, and MDA levels in brain tissues. The investigations showed an apparent increase in MDA levels, unlike the T-SOD and GSH levels. Another efficacy of Walnut is remarkable changes in the count of live neurons in hippocampal regions in mice's brains. It showed a noticeable increase in the count of the neurons (Liao et al., 2020).

Regarding the significant increase of neurodegenerative diseases in recent years, some products such as defatted Walnut meal protein hydrolysates have been used to treat these cases. In this article, the effect of defatted Walnut meal protein hydrolysates on neurotoxicity induced by D-galactose and aluminum chloride ($AlCl_3$) in mice is being investigated thoroughly. The results showed that defatted Walnut meal protein hydrolysates could reduce oxidative stress, reserve cholinergic dysfunctions, and decrease the effects of D-galactose and $AlCl_3$ in the brain of mice (Haider et al., 2018). According to one of the studies by Haider et al. (2018), mice treated with D-galactose and $AlCl_3$ had a decreased ability for memory and learning, their neurons were contracted, and their density was reduced in the cortex region. As the research showed, the amount of SOD and GSH-Px were decreased in the brain tissue of these mice; in contrast, the amount of MDA was increased. Also, their cholinergic system was confronted with some disorders, so, there was an increase in the amount of AChE but a decrease in the amount of ACh and ChAT. ACh is correlative with cognitive improvement, and its decrease has neurotic dysfunction. It was found in further research that the amount of TNF- α and IL-1 β was increased in the brain tissues of D-galactose and $AlCl_3$ treated mice which were eliminated by defatted Walnut meal protein hydrolysates. Also, the more microglia cells activated, the fewer TNF- α and IL-1 β remained in the tissue. Defatted Walnut meal protein hydrolysates is made structurally by amino acids. These are amino acids such as Lys and Asp that play a vital role as antioxidants. Also, because of its acidic amino structure, it is broken down by peptidase enzymes such as pepsin. It breaks defatted Walnut meal protein hydrolysates into small peptides, and then these molecules are again made into smaller portions, which can be absorbed quickly and be used for antioxidant activities (Haider et al., 2018).

In a 2-site randomized controlled trial on 708 free-living elders, Sala-Vila et al. discovered that compared to a control diet (abstention from Walnuts), nutritional supplementation with Walnuts at 15% of daily calories for two years did not affect cognitive function in cognitively healthy elderly. However, brain fMRI and post hoc analysis found that the intervention was successful in participants from the Barcelona location, who had poorer education and lower background status of dietary α -Linolenic acid (the -3 given by Walnuts) than the Loma Linda cohort (Sala-Vila et al., 2020a). Based on in vivo behavioral testing, Li et al. investigated the protective effects of Walnut protein hydrolysate on scopolamine-induced learning and memory impairments in mice. The biochemical results showed that the beneficial effects of Walnut hydrolysis protein on scopolamine-induced dementia mice might be

attributable to a dramatically increased number of acetylcholine receptors and up-regulation of choline acetyltransferase mRNA expression (Li et al., 2017). In a study by Bishop et al. on 3632 US adults, they attempted to evaluate the relationship between whole Walnut consumption and cognitive change. They found an association between Walnut consumption and cognitive function in elderly, but they did not discover that Walnut intake was preventative of age-related cognitive decline (Bishop and Zuniga, 2021).

4.8. Traumatic brain injury

Traumatic brain injury (TBI) can lead to brain edema due to blood-brain barrier (BBB) breakdown and increased endothelium permeability after TBI. Since brain edema increases intracranial pressure, it can cause nerve damage and higher mortality and morbidity rates in TBI patients (Ansari et al., 2016). Studies showed that Walnut kernel is rich in phenolic compounds with antioxidant and anti-inflammatory properties. Thus, Walnut kernel has positive effects on human health. Ansari et al. designed a study to investigate the impact of Walnut kernel feeding on brain edema and neuronal degeneration in male rats after TBI. The results showed brain water content, and intracranial pressure was lesser in the treatment group than in the control. According to these findings, Walnut kernel pretreatment can reduce pathological symptoms after TBI in male rats (Ansari et al., 2016).

Results showed that Walnut extract reduces TNF- α production in microglial cells, which are activated by LPS. Walnut extract and its component, ellagic acid, even showed anti-inflammatory results in human aorta endothelial cells and osteoblastic results in the cells. Moreover, a newer study showed that fatty acids have a role in inflammation response reduction in peritoneal macrophages (Papoutsis et al., 2008). In Ansari et al.'s study, the reduction of neuronal degeneration in the pretreatment group may be due to the anti-inflammatory constituents of Walnut kernel. Walnut kernel pretreatment reduced brain edema, improve neurological scores, and stopped increased neuronal degeneration post-TBI in male rats (Ansari et al., 2016).

Carbon tetrachloride (CCl_4) is extensively used to induce hepatotoxicity in experimental animals. High doses of CCl_4 lead to nonspecific toxicity, such as central nervous system depression and respiratory failure, with causes death. The free radicals generated from CCl_4 and CCl_4 harm the endoplasmic reticulum, which leads to the accumulation of lipids, reduced protein synthesis, and mixed-function oxidases activity (Weber et al., 2003; Recknagel et al., 1989; Ritesh et al., 2015). According to Aydin et al.'s (Aydin et al., 2015) study, Walnut is rich in nutrients with cholesterol-free contents, substitutes for animal proteins, and high concentrations of unsaturated fatty acids. It is rich in linoleic acid (18:3, n-3) and linolenic acid (18:2, n-6), polyunsaturated fatty acids that are essential for the body. It is metabolized to haloalkane free radicals (CCl_3 and CCl_3O_2) by a mixed-function cytochrome oxidase complex (NADPH)-cytochrome P450 electron transport chain in the hepatic smooth endoplasmic reticulum. These substances make hepatotoxic CCl_4 and initiate lipid peroxidation in the membranes. CCl_4 enters the body in various ways, such as air, water, food, and even skin. It goes through the whole body but has more concentration in the liver, kidneys, muscles, adipose tissue, and blood. The results showed the levels of fatty acids increase in the brain and kidney tissues after CCl_4 administration. In the groups given Walnut extract against CCl_4 , it was found that the GSH level increased and the MDA level reduced in all tissues. Given lipophilic vitamin levels, it was found that α -tocopherol levels increased in the brain and liver tissues in the group receiving additional Walnut in comparison with the controls, and cholesterol levels increased in the tissues, except the kidney, in all groups in comparison with the control group. Phenolic compounds, vitamins, and carotenoids existing in fruits such as Walnut possess antioxidant activity and are effective compounds to prevent diseases relating to oxidative stress.

4.9. Alzheimer's disease

AD is the common reason for dementia - a general term for memory loss and other cognitive abilities just as essential to alter with everyday life. Dementia should not be considered a normal part of growing up. Many people's memory fades a bit as they grow up, so the difference between usual age-related memory problems and early signs of AD is not that significant (Mucke, 2009). A β has 40–42 amino acids in length and is made by proteolytic cleavage of the more significant amyloid precursor protein, which is a transmembrane protein. Hyperphosphorylated tau, a protein in microtubule assembly and stabilization. Hyperphosphorylation of tau is very typical to find in diseases with tau filaments and might as well be required for toxicity (Goedert and Spillantini, 2006). Oxidative stress and neuroinflammation induced by A β in the brain are thought to be most likely the pathogenesis of AD (Zou et al., 2016). According to Zou et al. (2016) study, a highly concentrated Walnut peptides diet ameliorated the cognitive and memory disorders of mice. Their study also showed positive effects of restoration of levels of antioxidant enzymes and inflammatory mediators with consumption of Walnut peptides. The goal of the Morris Water Maze test was to check the results of Walnut peptides on the impairment of spatial learning and memory in A β 25–35-induced AD mice. The time that the mice needed to find the platform was lowered progressively during the test. The test showed considerable differences in the time of the animal between different test days and different dietary situations. The model group mice took longer to find the platform on the test days than those in the sham group, meaning that the hippocampus injection of A β 25–35 could induce many neurologic and cognitive disorders. The test also showed a big difference in spatial ability to learn, between the model group and the Walnut peptide treatment groups. However, the difference was not significant between the model group and the low-dose Walnut peptides group. The test also showed that injection of A β 25–35 efficiently impaired spatial learning and memory, which could be easily stopped via a Walnut peptides diet. In comparison to the sham animals, the step-down avoidance test showed a significant lowering of avoidance time and a highering of the error count in the A β 25–35-injected group, SOD and GSH activities were hugely lowered in the hippocampus of A β 25–35-treated mice, treatment could quickly force an increase of the AChE level in hippocampus and depressed the enhancement of AChE. Moreover, NO level in the hippocampus was more in the A β 25–35 group; just the treatment with A β 25–35 hugely increased the expressions of iNOS and activated NF- κ B p65.

Wang et al. (2019) examined the effect of Walnut on A β reduction. walnuts contain an active peptide called PW5(Pro-Pro-Lys-Asn-Trp), which has anti-A β 42 accumulation activity. The results of research on mice showed that PW5, with its anti-ab activities, could be effective in improving the patient's cognition. Serum levels of norepinephrine also increased significantly in response to PW5. As a result of experiments, it can be said that PW5 in Walnut protein can have a good effect on brain function and the prevention of AD. It is stated in another article written by Muthaiyah. et al., A β produces free radicals that eventually lead to oxidative stress and cell death.

Walnuts contain antioxidant compounds that could affect preventing oxidative stress. In a study conducted by wang et al. it was shown that walnut protein hydrolysates had antioxidant activity. Three out of 48 peptides identified, can act as an antioxidant inside and outside the cell. These peptides include QGRPWG, PSRADIY, and AYNIPVNIAR (Wang et al., 2022). The main focus of Wang et al. study (Wang et al., 2019) was whether walnuts can prevent cytotoxicity and oxidative damage caused by A β . One result of the article was that Walnut extract could reduce A β -induced cell death, DNA damage, and ROS production. As a result, eating a diet containing Walnut extract can effectively prevent memory loss and AD. In this article, Chauhan et al (Fotuhi and Do, 2010). Examined the role of Walnuts in improving learning ability in a transgenic mouse model of AD. There have been reports of the role of A β and oxidative stress in developing AD. Walnuts are rich in compounds that

contain melatonin and vitamin E, which are antioxidant compounds. Mice were grouped into two groups, the control, and experimental groups, and the difference between these two groups was in the Walnut diet. Decreased learning ability and anxiety-related behaviors were observed in control mice that did not have Walnuts in their diet. A significant improvement in memory and learning ability was observed in mice with diet Walnuts. Finally, the results showed that a Walnut diet could quickly stop and delay AD.

In conclusion, A β is a massive cause of amyloid plaques in AD patients. A β is involved in producing free radicals that ultimately lead to oxidative stress. As a result, researchers have recently been looking for antioxidant compounds to prevent oxidative stress, inflammation, and cell death. Walnut is one of these anti-oxidant and anti-inflammatory compounds. The positive effects of Walnuts on preventing AD are as follows: Walnuts can play a role in preventing beta-amyloid-dependent cytotoxicity by reducing the production of free radicals and reducing damage to cell membranes and DNA. As a result, a diet rich in Walnuts can prevent AD-related dementia by reducing A β fibrillation and oxidative stress (Chauhan and Chauhan, 2012).

Some laboratory research has indicated that Walnut extract can inhibit A β fibrillization and solubilize its fibrils and has a protective effect against AD-induced oxidative stress and cellular death, which leads to the inhibition of AD (Muthaiyah et al., 2014). According to Muthaiyah et al. (2014), the mice which consumed Walnut showed better improvements in their memory stage, the number of errors in the EPM assay (a test measuring anxiety in laboratory animals) in these mice was lower, and also their duration of staying information in mind was longer than controls (AD- Tg mice which no consuming Walnut). Their findings showed that long-term activity of a diet with 6% or 9% Walnuts in AD -Tg mice significantly lowered or even stopped deficits in memory and learning compared to AD-Tg mice on a diet that does not include Walnuts, and there was not a big difference in the activity of these mice (compared to wild-type control mice). For individuals with AD, diets with 6% or 9% Walnuts (equivalent to 1 oz. 1.5 oz. Walnuts per day in humans) ameliorated memory loss, improved learning, and motor skills, reduced anxiety-related behavior, and slowed the progression of AD.

In another study, Joseph et al. (2009) showed that Walnut can affect aging and health span; the consumption of Walnut can slow the process of aging and, thus, the process of brain degeneration. Oxidative stress results from the shift toward ROS production in the equilibrium between ROS generation and the antioxidant defense system. In the brain, this is essential since, during periods of oxidative stress, Bcl-2 (a protein that participates in apoptosis) increases and accelerates cellular apoptosis and aging. In the process of aging, the expression of cyclooxygenase 2 appears to be related to α - β deposition in the hippocampus and inflammatory prostaglandins increase in the hippocampus and in other areas during aging. Since the prostaglandin synthesis pathway seems to be a significant cause of ROS in the brain and other organ systems. A high Walnut diet in the old rats had very positive results in cognitive function as those seen with berry fruit or Concord grape supplementation. Preliminary analyses of the stress signals that may be affected with Walnut supplementation suggest that the (n-3) PUFA, α -linolenic acid, was very effective in lowering stress signals such as cytokines and NF κ B.

Based on the fact that eating Walnuts can improve brain function, Sala-Vila et al. (2020b) conducted experiments. The tests were performed on a group of middle-aged people at risk for AD. In these experiments, the relationship between Walnut consumption and MRI-assessed brain phenotypes was investigated. One hundred eighty-seven people who consumed Walnuts more than once a week in this experiment showed lower WMH volume (WMH is a marker for diseases related to small cerebral arteries involved in AD). They also showed higher GMV levels (gray matter volume), indicating a healthy aging process. As a result of these experiments, it can be said that Walnut consumption has beneficial effects on brain phenotypes and regional GMV.

Honglin et al (Lv et al., 2021). examined the effect of Walnuts on

Table 2

A summary of the studies on the effect of walnut and its active constituents.

First author	Year	Type of study	Neurological disease	Name of walnut species	Type of extract or phytochemical	Dose	duration	Mechanistic pathway
Jifeng Wu (Wu et al., 2017)	2017	In vivo	Glioblastoma	–	Juglone	10, 20, and 40 μ M	48 h	<ul style="list-style-type: none"> Inhibition apoptosis of glioma stem cells with activation ROS-p38-MAPK pathway
Valeria Pavan (Pavan et al., 2017)	2016	In vivo	Glioblastoma	Juglans nigra	Juglone	–	–	<ul style="list-style-type: none"> Modification of DiNAF (Feigin et al., 2020) decrease of cytotoxicity Decrease of apoptosis
Jiang Wang (Wang et al., 2017)	2017	In vitro	Glioblastoma	Juglans mandshurica	Juglone (5-hydroxy-1,4-napthoquinone)	5, 10 and 20 μ M	24 h	<ul style="list-style-type: none"> Inhibition Pin1 expression blocking TGF-β1/Smad/ miR-21 signaling suppressing U251 glioma cell growth and migration disrupting angiogenesis
Carlo Genovese (Genovese et al., 2020)	2020	In vitro	Glioblastoma	Juglans regia L.	Juglone (from walnut septum in Trecastagni)	17,18–275 μ g/ml	24 h and 48 h	<ul style="list-style-type: none"> Revealing active compounds such as gallotannins, ellagic acid derivatives and flavanols reducing cell viability, proliferation and migration in human A172 glioblastoma
Raheleh Jahanbani (Jahanbani et al., 2021)	2021	In vivo	Epilepsy	–	Walnut kernel proteins	5, 10, 20, 50, and 100 mg/Kg	48 h	<ul style="list-style-type: none"> possession of neuro-protective effects(because of walnut peptides) against PTZ, MES and chemical kindling induced seizure threshold through benzodiazepine receptors, independent of the NO pathway
Majid Asadi-Shekaari (Asadi-Shekaari et al., 2014)	2014	In vivo	Epilepsy	Juglans regia	Walnut kernel extracts	50, 100, 200 and 500 mg/kg	–	<ul style="list-style-type: none"> Controlling seizure with activation of the ESM function pathway reduction in brain NO production activation of anti-inflammatory mechanisms reinforcement of the antioxidant system.
Majid Asadi-Shekaari (Asadi-Shekaari et al., 2012b)	2012	In vivo	Epilepsy	Juglans regia	Walnut kernel extracts	–	2 month(pre-treatment)	<ul style="list-style-type: none"> Prevention of PTZ-induced seizure and its further neurodegeneration
Musthafa Mohamed Essa (Essa et al., 2019)	2019	In vivo	Parkinson's disease	Juglans regia	Walnut kernel extracts lipids	20 mg/kg body weight day	28 days	<ul style="list-style-type: none"> Early intervention with walnut rich diet help in reducing the risk of developing PD or delaying its onset because of the cumulative antioxidant and mitochondrial protective effects of components in walnuts
Jin Gyu Choi (Choi et al., 2016)	2016	Both	Parkinson's disease	Juglans regia L.	Juglandis Semen(the polyphenol-rich aqueous walnut extract)	15–100 μ M	24 h	<ul style="list-style-type: none"> Protecting dopaminergic neurons against MPP+ or MPTP-induced neurotoxicity as an MAO inhibitor with antioxidant activity preventing depletion of striatal DA and its metabolites ameliorating motor symptoms in a mouse model of PD.
Seon Young Choi (Choi et al., 2012)	2012	In vivo	Parkinson's disease	–	Naphthazarin	0.1 or 1 mg/kg	5 days	<ul style="list-style-type: none"> modulating the astrocyte activation rather than by the direct protection of neurons inducing the nuclear translocation of Nrf2 in primary cultured astrocytes activating hormetic pathway particularly in astrocytes to defend neurons in response to MPP1- induced neuroinflammation
Anamitra Ghosh (Ghosh et al., 2013)	2013	In vivo	Parkinson's disease	Black walnut	Napthoquinone in leaves, roots, and bark of black walnut plants	(3 mg/kg) 24 h before the first MPTP injection	6 days	<ul style="list-style-type: none"> attenuation of Pin1 expression during dopaminergic neuronal degeneration in the nigrostriatal system. Improvement of behavioral deficits and neurochemical depletion by Pin1 inhibition

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Table 2 (continued)

First author	Year	Type of study	Neurological disease	Name of walnut species	Type of extract or phytochemical	Dose	duration	Mechanistic pathway
Sameri, Maryam Jafar (Sameri et al., 2011)	2011	In vivo	Parkinson's Disease	–	Gallic acid	8 micro gram	10 days	<ul style="list-style-type: none"> Reversal of movement disorders by strong antioxidant property and free radical scavenging of gallic acid
Ali Ganji (Ganji et al., (2019)	2019	In vivo	multiple sclerosis	<i>Juglans regia</i>	Walnut oil	5 ml/kg/day	21 days	<ul style="list-style-type: none"> Reducing pro-inflammatory cytokines such as IFN-γ amplifying Th2 cell responses to reduce the activity of TH1 by IL-4, IL-5, IL-10, and TGF-β moderating CNS changes induced by cisplatin increase of ALA and EPA to improves memory by enhancing the serotonergic pathways
Mohammad Shabani Shabani et al., (2012)	2012	In vivo	Neurotoxicity	<i>Juglans regia</i>	–	6%	5 weeks	<ul style="list-style-type: none"> increase of expression or activity of the antioxidant enzymes superoxide dismutase (SOD1), glutathione peroxidase (GPX1), glutathione reductase (GR) and catalase (CAT) reduction of pro-inflammatory cytokine IL-6 expression inhibition of expression of vascular cell adhesion molecule 1 (VCAM1) inhibition of cell proliferation, angiogenesis, and extracellular matrix invasion induction of caspase-dependent apoptosis
Claudia Ceci (Ceci et al., (2020)	2020	In vivo RCT	Neurotoxicity	<i>Juglans ailanthifolia</i> & <i>Juglans regia</i>	Ellagic acid (EA)	Rats: 50 mg/kg/day Humans: 45 g/day	Humans: 7 days	<ul style="list-style-type: none"> Increasing DA, and NA levels decreasing the level of DOPAC and HVA increasing the level of 5-HIAA oxidative stress alleviation cholinergic dysfunction was reversed release of proinflammatory cytokines in the brain of D-gal + AlCl₃-treated mice was suppressed
Zahra Batool (Batool et al., (2019)	2019	In vivo	Neurotoxicity	–	–	400 mg/kg/day	28 days	<ul style="list-style-type: none"> Walnut diet attenuated LPS-induced nitrite release Significant reduction in TNF-alpha, COX-2, and iNOS
Feng et al (Feng et al., 2018).	2018	In vivo	Neurotoxicity	–	Defatted walnut meal protein hydrolysates (DWMPH)	1 g/kg/day	90 days	<ul style="list-style-type: none"> Increase of the SOD activity Increase of the activity of CAT Upregulation of GSH-px Suppression of the increase of IKKβ Decrease of the p65, IL-1β and TNF-α expression Decrease of expression of cytochrome C, Caspase-9, Cleaved caspase-3 and Cleaved PARP-1 up-regulation of the expression of pCREB and synaptophysin
Fisher et al (Fisher et al., 2017).	2017	In vitro	Neurotoxicity	<i>Juglans regia</i>	Ground with skin	0% (control), 6%, and 9%	15 weeks	<ul style="list-style-type: none"> Suppression of the NF-κB Signaling Pathway in LPS-Induced BV Attenuated production of nitric oxide and expression of inducible nitric oxide synthase Reduced production of TNFα
Chunlei Liu (Liu et al., 2019a)	2019	In vitro	Neurotoxicity	<i>Juglans mandshurica Maxim.</i>	EVSGPGLSPN	12.5 μ M, 25 μ M, 50 μ M, and 100 μ M	24 h	<ul style="list-style-type: none"> Aggregate the clearance of polyubiquitinated protein including p62/SQSTM1 Reduced OS/ INF
Jialin Xu (Xu et al., (2018)	2018	In vivo	Neuroinflammation	–	Urolithin A and Urolithin B	3, 10, 30 μ M	24 h	
Willis et al (Willis et al., 2010).	2010	In vitro	anti-inflammatory effects of walnuts in microglia	<i>Juglans regia</i>	methanolic extract	ranged from 0.00001 to 10 mg of walnuts per milliliter of solution	overnight	
Poulose et al (Poulose et al., 2013).	2013	In vivo	maintain protein homeostasis	<i>Juglans regia</i>	ground walnuts	6% containing 60 g walnuts/kg and 9% containing 90 g walnuts/kg	15 weeks	

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Table 2 (continued)

First author	Year	Type of study	Neurological disease	Name of walnut species	Type of extract or phytochemical	Dose	duration	Mechanistic pathway
Fisher et al (Fisher et al., 2021).	2021	In vitro	Neuroinflammation	Juglans regia	Walnut oil	100 ng/ml	48 h, 1, 2 or 4 weeks	<ul style="list-style-type: none"> Reduced LPS-induced nitrite, COX2, and iNOS
Fanrui Zhao et al (Zhao et al., 2021).	2021	In vivo	Memory	<i>Juglans mandshurica Maxim.</i>	walnut-derived 99 peptide Tyr-Val-Leu-Leu-Pro-Ser-Pro-Lys (YVLLPSPK)	60 mg/kg/day	6 weeks	<ul style="list-style-type: none"> inactivating the expression of KEAP1 increasing 655 HO-1 in the NRF2/KEAP1/HO-1 pathway suppression of the increase of AChE higher activity of GSH
Jianqiao Liao et al (Liao et al., 2020).	2020	In vivo	Memory	–	Walnut oil	10 ml/kg walnut oil daily	8 weeks	<ul style="list-style-type: none"> suppression of the increase of AChE higher activity of GSH
Saida Haider et al (Haider et al., 2018).	2018	In vivo	Memory	<i>Juglans regia</i>	walnut suspension	400 mg/kg/day	4 weeks	<ul style="list-style-type: none"> Increase of levels of 5-HT and its metabolite, 5-hydroxyindoleacetic acid
Jong Min Kim (Kim et al., (2020)	2020	In vivo	Memory	<i>Juglans regia L.</i>	Leaf extract	20 mg/kg of body weight oral administration or 10 mg/kg by injection	Group A 41 days and group B 31 days	<ul style="list-style-type: none"> Reduction of MDA level Increase of SOD level Reduction of GSH level Increase of Ach level Amelioration of AChE activity increase of ChAT expression decrease of DCF production inhibition of the decreased expression of ZO-1 and occluding decrease of TNF-α, TNFR1, p-JNK, p-IκB, COX-2, and IL-1β level decrease of the expression level of capase-3 restoring of the expression of p-Akt and HO-1
Zahra Batool (Batool et al., (2017)	2017	In vivo	Memory	–	–	400 mg/kg/day	28 days	<ul style="list-style-type: none"> reduction the level of MDA non reduction of ACH level compared to cadmium treated group
Ansari, Javad Mohajer (Ansari et al., 2016)	2016	In vivo	Traumatic Brain Injury	<i>Juglans regia</i>	6% of daily food	Walnut kernel (WK)	60 days	<ul style="list-style-type: none"> reducing brain water content and ICP in the treatment group than in the control reducing WK pretreatment pathological symptoms after TBI in male rats increasing VCS amounts in the treatment group compared to the control increasing neurologic scores after TBI formation nodule in KS483 osteoblasts
Papoutsi, Z (Papoutsi et al., 2008)	2008	In vitro	Traumatic Brain Injury	<i>Juglans regia L.</i>	10–200 mg/ml	Walnut methanolic extract	24days	<ul style="list-style-type: none"> decreasing GSH concentration in the kidney and liver tissues of the groups added CCl₄ increasing MDA level in the brain, kidney and liver tissues augmenting lipid peroxidation increase of number of acetylcholine receptors up-regulation of mRNA expression of choline acetyltransferase
Aydn, Sevinç (Aydn et al., 2015)	2015	In vivo	Traumatic Brain Injury	<i>Juglans regia L.</i>	The fruit was frozen (50 g) and then prepared with a special method	Walnut fruits extract	45 days	<ul style="list-style-type: none"> decreasing GSH concentration in the kidney and liver tissues of the groups added CCl₄ increasing MDA level in the brain, kidney and liver tissues augmenting lipid peroxidation increase of number of acetylcholine receptors up-regulation of mRNA expression of choline acetyltransferase
Li et al (Li et al., 2017).	2017	In vivo	Alzheimer's disease	<i>Juglans regia L.</i>	walnut protein hydrolysate	Low dose (0.20 g/kg) medium dose (0.33 g/kg) high dose (0.66 g/kg)	5 days	<ul style="list-style-type: none"> reducing the risk of developing AD or delaying its onset because of the cumulative antioxidant and anti-inflammatory effects
Balu Muthaiyah (Muthaiyah et al., 2014)	2014	In vivo	Alzheimer's Disease	<i>Juglans regia L.</i>	English walnut kernels	6% or 9% walnut-enriched diet	9 – 10 months	<ul style="list-style-type: none"> reducing the risk of developing AD or delaying its onset because of the cumulative antioxidant and anti-inflammatory effects
Ilkay Eedoghan Orhan (Orhan et al., 2011)	2011	In vitro	Alzheimer's Disease	<i>Juglans regia L.</i>	leaves and fruits of <i>J. regia</i> (Dichloromethane- Acetone-Ethyl acetate-Methanol)	50, 100 and 200 mg /ml	–	<ul style="list-style-type: none"> Reduction of the risk of AD because of antioxidant activity Reduction of radicals such as NO and H₂O₂
Balu Muthaiyah (Muthaiyah et al., 2011)	2011	In vitro	Alzheimer's Disease	<i>Juglans regia L.</i>	Walnut extracts such as Phenolics, α -linolenic acid-flavonoids and gamma tocopherol	2 and 4 μ g GAE	12 and 24 h	<ul style="list-style-type: none"> Protection against $\alpha\beta$- mediated cell death by reducing the generation of free radicals inhibiting membrane damage attenuating DNA damage

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Table 2 (continued)

First author	Year	Type of study	Neurological disease	Name of walnut species	Type of extract or phytochemical	Dose	duration	Mechanistic pathway
Sujatha Rajaram (Rajaram et al., 2017)	2017	In vitro (single blind randomized clinical trial)	Alzheimer's Disease	<i>Juglans regia</i> L.	–	15% of daily energy intake as walnuts	2 years	<ul style="list-style-type: none"> delaying the onset of age-related degenerative diseases
Neha Chauhan (Chauhan et al., 2004)	2004	In vitro	Alzheimer's Disease	<i>Juglans regia</i> L.	(Methanolic Extract of Walnut) MEOW	(2.5, 5.0, 10.0 ml) of MEOW	1–2–3 days	<ul style="list-style-type: none"> Reducing the apoptosis by decreasing the reactive oxygen species Possession of antioxidative and free-radical scavenging property by Flavonoids and ellagic acid
Mirazkar D. Pandareesh (Pandareesh et al., 2018)	2018	In vivo	Alzheimer's Disease	<i>Juglans regia</i> L.	–	6%and 9% walnuts enriched diet	5, 10, or 15 months	<ul style="list-style-type: none"> Improving antioxidant status Decrease of ROS levels Decrease of lipid peroxidation Decrease of protein oxidation
Lv et al (Lv et al., 2021).	2021	Animal study	Alzheimer's disease	Walnut		800 and 1600 mg/kg/d	6 weeks	<ul style="list-style-type: none"> Improving memory and learning Elevating Acetylcholine level Decrease of oxidative stress and inflammation Improving neural stem cells 'expression restoring the shape and number of neurons Improving memory, learning ability, anxiety and motor development
Chauhan et al. (2010)	2010	Animal study	Alzheimer's disease	Walnut		custom-mix diets (pellets) containing 6% walnuts or 9% walnuts	4 months	<ul style="list-style-type: none"> Improving memory, learning ability, anxiety and motor development
Sala-Vila et al (Sala-Vila et al., 2020b).	2020	Cohort Study	Alzheimer's disease	Walnut		≥ 1 serving/week		<ul style="list-style-type: none"> Observation greater GMv in areas such as the anterior/middle cingulate cortex, which is relevant to cognition
Min Wang Wang et al., (2019)	2019	In vitro In vivo	Alzheimer	<i>Juglans regia</i>	PW5 WPH	80/ 400 pw5 mg/kg/day	12 weeks	<ul style="list-style-type: none"> Increasing level of NE decreasing level of Ache decreasing Proteobacteria and Verrucomicrobia increasing the abundance of the Firmicutes Decreasing SOD and GSH activities in the hippocampus depressing the enhancement of AChE in the hippocampus
Juan Zou Zou et al., (2016)	2016	In vivo	Alzheimer	<i>Juglans Sigilata</i> <i>Dode</i>	walnut peptides	200/ 400/ 800 mg/kg/ day	5 weeks	<ul style="list-style-type: none"> depressing the enhancement of AChE in the hippocampus
Bishop, Nicholas J (Bishop and Zuniga, 2021)	2021	Human study	Investigation of cognitive function in older adults	–	walnut	(none, low intake (0.01–0.08 1 oz. servings per day) and moderate intake (>0.08 1 oz. servings per day)	–	<ul style="list-style-type: none"> Those reporting any walnut consumption had greater cognitive scores at baseline than those not consuming walnuts walnut consumption was not associated with cognitive change. intake of nutrients had neuroprotective benefits. Increasing the AST and ALT levels
Ji Liu Liu et al., (2019a)	2019	In vivo	Oxidative stress	–	Walnut seed coat Walnut seed	100 (WSC) mg/kg/day 600 (WS) mg/kg/day	8 weeks	<ul style="list-style-type: none"> Increasing the AST and ALT levels
Shuguang Wang (Wang et al., 2021)	2021	In vivo	Oxidative stress	<i>Juglans regia</i>	WPH	333, 666 mg/ kg/ day	21 days	<ul style="list-style-type: none"> Increase of Level of ACH and ACHR Increase of many mRNA expression such as Nrf2, BDNF, and CREB
Shuguang Wang Wang et al., (2020)	2020	In vivo	Oxidative stress	<i>Juglans regia</i>	WPH	666 mg/kg and 400 mg/kg	21 days	<ul style="list-style-type: none"> Reduction of production of NO Normalization of overproduction of pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α Increase of the activity of SOD and CAT Decrease of lipid peroxidation in brain
Dayong Ren Ren et al., (2018)	2018	In vivo	Oxidative stress	<i>Juglans mandshurica Maxim.</i>	MWHP	200, 400, 800 mg/kg/day	30 days	<ul style="list-style-type: none"> Inhibiting the reduction of ACh content and ChAT activity caused by scopolamine inhibiting the H2O2-induced cell injury
Jahanbani, Raheleh (Jahanbani et al., 2021)	2021	In vivo	Anti-seizure effects	<i>Juglans regia</i> L.		5, 10, 20, 50, 100 mg/kg	A month	<ul style="list-style-type: none"> Modulation of benzodiazepine receptors

memory improvement in mice with AD. Since the Walnut kernel is a traditional Chinese medicine for improving brain function, experiments were performed to investigate its effect on brain function. The results are as follows: The first result was that eating Walnuts improves learning and memory. The second one was that eating Walnuts increases acetylcholine and reduces oxidative stress. The third result was that the consumption of Walnuts enhances the function of the nervous system and has a positive effect on neural stem cells. The results also showed that Walnut meal protein treatment could regulate genes. These results above show us that eating Walnuts can be helpful in improving memory and thus preventing AD.

Researchers found that Walnut extract could reduce oxidative stress and cytotoxicity caused by Ab in PC12 cell lines. The beneficial activity is achieved by reducing the formation of free radicals and impairing membrane and DNA damage. This beneficial impact might be attributed to the antioxidant polyphenols found in Walnut. A Walnut-rich diet may be a promising method for preventing and delaying the onset of AD (Essa et al., 2012).

In an article written by Orhan et al. (2011), the main focus was on evaluating the neuroprotective effects of the leaf and fruit extracts. Based on the results obtained in experiments, it can be said that anticholinesterase activity is in contrast to AChE and butyrylcholinesterase, which are essential enzymes in AD. The effect of antioxidants was also investigated in these experiments. Extracts were able to inhibit DPPH radicals, unlike H₂O₂. The sections were not able to inhibit butyrylcholinesterase and AChE. As a result, we can say that the common belief among locals about the positive effects of Walnuts consumption on brain health can be explained by its antioxidant and rich content of total phenol and flavonoids. Rajaram et al (Rajaram et al., 2017). designed experiments to investigate the effect of Walnuts on healthy aging. These experiments showed that Walnuts could have many benefits in delaying the onset of age-related diseases, including retinal pathology and cognitive impairment. These benefits of Walnuts are due to their effect on vascular health and heart protection, primarily because of the bioactive compounds (such as polyphenols and n-3 fatty acids). Mirazkar et al (Pandareesh et al., 2018). found that Walnuts can play an essential role in learning and memory. To better understand the function of Walnuts in reducing oxidative stress, they performed experiments on mice of different ages. The final findings showed that Walnuts could play a role in reducing oxidative stress and oxidative damage to proteins and lipids in AD by inhibiting free radicals and protecting the antioxidant status. As a result, a diet rich in Walnuts can help reduce the risk of AD and delay its onset.

Nowadays, some kinds of neurotoxicant materials, such as organophosphate, have gotten completely widespread in our environment. These chemicals used to be poisonous in warfare agents to threaten the military and civilian populations. But now, not only used on the battlefields and in the city regions. Bio terrorists are now using this chemical to inflict mass casualties. It can rapidly deactivate Acetylcholinesterase enzymes in synaptic areas and confront the body with cholinergic crisis, as acetylcholine plays a vital role at these points. To prevent these kinds of problems, some types of nutraceuticals, such as α -Linolenic acid, are being used. These materials are abundant in vegetable products like Walnut and flex. These products can be used to treat neurodegenerative diseases such as organophosphate and other ones. α -Linolenic acid has a vast safety margin which leads us to use it in widespread ways for strengthening the transcription and transplantation programs in our brains. Also, α -Linolenic acid has a very prominent ability to activate some vital and mechanical pathways, which can be helpful to restore brain function and treat neurodegenerative diseases.

Table 2 summarizes the studies on the effect of walnut and its active constituents on ANDs.

5. Conclusion

Walnut is a beneficial compound for health, especially the nervous

system. In this study effects of Walnut on ANDs such as AD, PD, GBM, epileptic seizures, MS, neurotoxicity, neuroinflammation, and traumatic brain injuries as well as their potential effects on memory and cognition were reviewed. Evidence suggests that Walnut can decrease the risk of oxidative stress and neuroinflammation caused by A β protein deposition in the human brain, preventing AD. Walnut and its compounds (such as vitamin E, melatonin, ellagitannins, and urolithins) prevent the formation of fibrillar A β -protein and defibrillate them. It contains antioxidant compounds that prevent oxidative stress and damage to lipids and proteins caused by A β fibrils and the MAO-B enzyme, which is involved in PD (Djedjibegovic et al., 2020; Pandareesh et al., 2018; Muthaiyah et al., 2011). As a result, it can play an important role in avoiding A β -dependent DNA damage, ROS production by MAO-B, and neuronal cell death (Tatton et al., 2003; Chauhan and Chauhan, 2012). In PD, dopaminergic neurons undergo cell death.

In neurodegenerative diseases, the activity of the MAO-B enzyme increases, causing oxidative stress and cell death. Compounds in Walnut work as antioxidant properties and MAO inhibitor factors. These products with anti-inflammatory compounds are effective in treating neuroinflammatory disorders like MS (Ceci et al., 2020). More importantly, Walnut extracts have potential antiproliferative effects on the most aggressive primary cerebral neoplasm, GBM. The potential therapeutic agent can trigger apoptosis in glioma tumor cells and limit tumor migration by restricting angiogenesis and improving the quality of life and life expectancy of patients with GBM. Oxidative stress is associated with the appearance of epilepsy and seizure development. Walnuts can protect neurons by increasing the seizure-induction threshold and reducing the severity of seizures to an acceptable amount.

Walnuts contain alpha-linolenic acid and omega-3, which can protect cells against cisplatin-induced neurotoxicity. Also, micronutrients can reduce the toxicity of metals like cadmium. The results show that Walnut can improve the speed of learning and, with the effect of its proteins, increase the synthesis of acetylcholine and decrease its destruction.

In this review, it has been shown that Walnut has beneficial effects on ANDs. Also, it can act as a preventive compound for these diseases with no significant side effects. We suggest that further in vivo and in vitro studies and clinical trials, should be carried out to consider the underlying mechanisms of Walnut in these disorders and gain a better understanding of this product's effects on human health.

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Conflict of Interest

None.

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