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Effect of Pomegranate Seed Oil and Punicic Acid on Alzheimer's Disease

Nar Çekirdeği Yağı ve Punisik Asidin Alzheimer Hastalığına Etkisi

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Abstract

Alzheimer's disease is a neurodegenerative disease and is one of the most common forms of senile dementia observed in the elderly population. It is estimated that the number of individuals affected by Alzheimer's disease will reach 115.4 million by 2050. It is imperative that novel and alternative methods be developed to prevent and slow the onset of Alzheimer's disease, as well as to alleviate the symptoms that manifest subsequent to its onset. Given the pivotal role of oxidative damage and inflammation in the pathogenesis of Alzheimer's disease, there is a growing interest in phytochemicals with high antioxidant and anti-inflammatory properties as potential therapeutic agents for halting disease progression. The anti-inflammatory, antioxidant and neuroprotective properties of pomegranate seeds and punisic acid (the omega-5 isomer of conjugated linoleic acid, the main component of pomegranate seeds) are hypothesised to be an effective method of reducing the occurrence and symptoms of Alzheimer's and neurodegenerative diseases. This review examines the impact of pomegranate seed oil and punisic acid on Alzheimer's disease.

Keywords: Alzheimer's disease, anti-inflammatory, neuroprotective, pomegranate seed oil, punicic acid

Özet

Alzheimer hastalığı nörodejeneratif bir hastalıktır ve yaşlı nüfus ile birlikte en sık görülen senil demans vakalarından biridir. Yapılan çalışmalar Alzheimer hastası olan bireylerin sayısının 2050 yılına kadar 115,4 milyon olacağını öngörmektedir. Alzheimer hastalığının oluşumunu önlemek, yavaşlatmak ve oluşumundan sonraki semptomları hafifletmek için yeni ve alternatif yöntemlere ihtiyaç vardır. Alzheimer hastalığı gelişiminde, oksidatif hasar ve inflamasyonun anahtar rolü olduğundan, yüksek anti-oksidatif ve anti-inflamatuar özelliklere sahip fitokimyasallar, hastalığın ilerlemesinin durdurulmasına yardımcı olmak için araştırılmaktadır. Nar çekirdeği ve içeriğindeki ana bileşen olan konjuge linoleik asidin omega-5 izomeri punisik asidin anti-inflamatuar, antioksidan ve nöroprotektif özellikleri Alzheimer ve nörodejeneratif hastalıkların oluşumunda ve semptomların azaltılmasında etkili bir yol olabileceği düşünülmektedir. Bu derlemede nar çekirdeği yağı ve punisik asidin Alzheimer hastalığı üzerine etkileri ele alınmaktadır.

Anahtar Kelimeler: Alzheimer hastalığı, anti-inflamatuar, nar çekirdeği yağı, nöroprotektif, punisik asit

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1. Introduction

The incidence of neurodegenerative disease appears to have increased in recent years, coinciding with a growth in the proportion of the population that is aged 60 or over. The term "neurodegenerative process" is used to describe the gradual decline in the functionality or demise of cells within the central nervous system, which ultimately results in an increasing prevalence of motor and cognitive impairments over time. The aetiology of neurodegeneration is characterised by oxidative damage and inflammation (Guerra-Vázquez et al., 2022).

Alzheimer's disease (AD) is one of the most common forms of dementia worldwide. Approximately 55 million people around the world are affected by Alzheimer's disease, and the number is doubling every 5 years (Dumurgier & Tzourio, 2020). It is expected that 65.7 million people will have dementia by 2030 and 115.4 million people by 2050 (Prince et al., 2013). Alzheimer's disease represents a significant cause of morbidity and mortality in ageing populations. Alzheimer's disease is a complex and multifactorial disease. The main neuropathological changes and hallmarks of AD involve extracellular plaques containing amyloid beta (Aβ) and intracellular neurofibrillary tangles (NFTs) containing hyperphosphorylated tau protein, as well as synaptic and neuronal loss (Ozben & Ozben, 2019). Alzheimer's disease is the most frequent form of advanced dementia and is characterised by memory loss, cognitive decline, personality and behavioural changes, aphasia, nutritional problems and infections. These symptoms cause a reduce in the quality of life of patients (Wong, 2020). It has been demonstrated that the passage of immune cells and molecules across the blood-brain barrier (BBB) is enhanced with age, which in turn contributes to degenerative processes in AD (Ozben & Ozben, 2019). Although some cases of AD are genetically linked, numerous disease and lifestyle factors have been identified as potential contributors to an elevated risk of developing AD. These include obesity, hypertension, diabetes, traumatic brain injury and other metabolic syndromes, as well as the natural aging process (Ozben and Ozben, 2019). The development of treatment and nutritional strategies to prevent these factors may prove an effective means of reducing the incidence of AD.

As the prevalence of AD is expected to increase with the ageing of the population, the development of novel treatments and management strategies is becoming increasingly urgent. Given that inflammation and oxidative damage are fundamental mechanisms in the progression of neurodegenerative disorders, phytochemicals with potent antioxidant and anti-inflammatory activities are being explored as potential neuroprotective agents to prevent neurodegeneration and halt disease progression (Guerra-Vázquez et al., 2022). A number of functional plants and foods, including pomegranate, date fruits, honey, black seeds and figs, have been demonstrated to possess beneficial nutritional properties that can help to alleviate AD. In vitro and in vivo studies have indicated that these functional foods can exert neuroprotective effects through their antioxidant and anti-inflammatory properties (Mohd Rosli et al., 2020).

The pomegranate (Punica granatum), throughout history a fruit that has been linked with a range of positive attributes, including vitality, wellbeing, longevity, fertility, erudition, morality, immortality and spirituality, is an ancient fruit of West Asian origin belonging to the Punicaceae family (Akbar et al., 2015;

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Okumuş et al., 2015). The peel constitutes roughly 50% of the total weight of the fruit. The pomegranate peel contains a number of important phenolic compounds, as well as a variety of mineral and complex polysaccharide sources. The composition of the pomegranate's edible portion is as follows: 40% pectin-rich grains, 10% seeds, and the remainder water (Jalal et al., 2018)

Seeds of pomegranate are a rich source of various components, including polyphenols and fatty acids. Approximately 12-20% of the weight of pomegranate seeds comprises oil content (Guerra-Vázquez et al., 2022). Pomegranate seed oil contains 14 distinct fatty acids, with punisic acid representing the most abundant constituent at concentrations of 50-80%. Additionally, notable amounts of other fatty acids are present, specifically linoleic acid (13–20%), oleic acid (8–9%), palmitic acid (6–9%), stearic acid (2–3%), linolenic acid (<0.06–0.08%), and arachidic acid (0.68–0.90%) (Kaseke et al., 2021).

Structurally very similar to conjugated linoleic acid (CLA), punisic acid is a conjugated alpha-linolenic acid's (CLnA) omega-5 isomer (Guerra-Vázquez et al., 2022). Punisic acid has been demonstrated to possess effective anti-inflammatory, anti-obesity, anti-diabetic, anti-carcinogenic and anti-proliferative properties (Bedel et al., 2017). The principal biological mechanism of punisic acid is the regulation of peroxisome proliferator-activated receptors (PPARs) the differential activity, responsible for controlling transcription of genes related to cell proliferation and differentiation, the regulation of enzymes related to lipid metabolism and glucose homeostasis, and the stimulation of proinflammatory biomarkers (Guerra-Vázquez et al., 2022; Holic et al., 2018).

Punisic acid could be useful for the treatment of AD due to its anti-inflammatory and antioxidant effects (Boroushaki et al., 2016). Moreover, punisic acid may confer benefits over other nutraceutical antioxidants with respect to its impact on pathways that are efficacious in the progression of AD. Furthermore, as pomegranate seed oil is typically derived from pomegranate seeds, which are byproducts of the pomegranate, increasing the utilization of this oil in health and other sectors contributes to both waste recycling and waste prevention, thereby supporting the sustainable nutrition and sustainable development goals that have recently been emphasized (Ozkan et al., 2022). The purpose of the review is to summarise the available evidence on the possible usefulness and effectiveness of pomegranate seed oil and punisic acid in AD.

2. Pomegranate Seed Oil

Pomegranate seed oil (PSO), produced from the seeds of pomegranate, accounts for 12-20% of the total seed weight (Boroushaki et al., 2016; Shrivas et al., 2023). The bioactive compounds of PSO are characterised by a high concentration of diverse saturated and unsaturated fatty acids, steroidal estrogens, non-steroidal compounds, cerebrosides, hydroxybenzoic acid and genistein (Ciccone et al., 2023; George et al., (2023). The steroidal estrogens present in pomegranate seed oil include tocopherol, testosterone, stigmasterol, β-estrolsitosterol, and 17-α-estradiol, while the nonsteroidal estrogens are coumestrol and campestrol (Pirzadeh et al., 2021).

The predominant fatty acid in pomegranate seed oil is punisic acid (cis9, trans11, cis13), while other isomers of CLnAs include α-eleostearic acid (C18:3-9cis, 11trans, 13trans) and catalpic acid (C18:3-9trans,11trans 13cis). Table 1 illustrates the general physical and chemical properties and fatty acid

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composition of pomegranate seed oil. Nevertheless, the oil and fatty acid profile of the seed display considerable variation contingent on the environmental conditions under which it is cultivated (Boroushaki et al., 2016; Ciccone et al., 2023). In a comparative study, Khoddami et al. (2014) evaluated the fatty acid composition of pomegranate seed oil and four commercial edible oils (sunflower, safflower, soya bean and linseed oil). Their findings revealed that pomegranate seed oil exhibited a lower proportion of saturated and monounsaturated fatty acids, whereas the polyunsaturated fatty acid content was either similar or higher.

It is established that unsaturated fatty acids, including linoleic acid, are capable of readily crossing lipophilic biological membranes. In additional to its antioxidant characteristics, β-sitosterol is present in significantly higher concentrations in pomegranate seed oil compared to oils derived from other plants. It is established that β-sitosterol accumulates in the plasma membrane of brain cells, thereby conferring a heightened antioxidant potential upon pomegranate seed oil (Mizrahi et al., 2014; Öğütücü and Yılmaz, 2015). Additionally, pomegranate seed oil comprises gamma-tocopherol, a compound acknowledged for its antioxidant efficacy (Verardo et al., 2014).

Table 1. Chemical and Physical Properties and Fatty Acid Composition of Pomegranate Seed Oil (Chatzikostopoulos et al., 2024)

Chemical/ Physical Features	Specific gravity: 0.92-0.96 g/ cm^3 Acid value: Max. 7 pH Insoluble impurities and Moisture: Max. 0.1 Peroxide value: Max. 10 mcg
Composition of Fatty Acid	Punisic acid: 70-85% Oleic acid: 3-20% Linoleic acid: 3-15% Docosatrienoic acid: 2-5% Palmitic acid: 2-5 % Stearic acid Max. 3% Lignoceric acid Max. 2% Palmitoleic acid Max. 1% Behenic acid Max. 1 % Arachidic acid Max. 1% Erucic acid Max. 1% Eicosenoic acid Max. 1% Other fatty acids: Max. 5%

%= percentage, g=gram, cm^3= cubic centimetre, mcg= microgram, max= maximum

3. Pharmacological Effects of Pomegranate Seed Oil

The anti-inflammatory, antioxidant, anti-cancer, anti-tumour, anti-diabetic, anti-osteoporosis, anti-pancreatitis, hepatoprotective, anti-atherogenic, anti-menopausal symptoms and neuroprotective effects of pomegranate seed oil have been well documented (Boroushaki et al., 2016). Additionally, it has been observed that this oil lowers plasma and hepatic triglyceride levels (Boroushaki et al., 2016). It has been observed that pomegranate seed oil exerts favourable effects, such as cytotoxic and anti-tumour activities, the decrease of body fat and the normalisation of lipid metabolism. Moreover, it has been demonstrated that this substance has the capacity to exert preventative effects against a range of

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cancers, including those affecting the prostate, breasts, and colon; to facilitate the reduction of hepatic triglyceride accumulation; and to stimulate epidermal tissue regeneration (Caligiani et al., 2010; Topkafa et al., 2015). The principal characteristics of pomegranate seed oil are anti-inflammatory and antioxidant. These characteristics result from the inhibition of lipid peroxidation and neutrophil activation. In vitro tests to ascertain the antioxidant activity of pomegranate seed oil revealed that pomegranate juice and seed extracts exhibited two to three times the antioxidant activity of red wine or green tea (Jacob et al., 2019). The administration of pomegranate seed oil has been found to result in a reduction in body weight, leptin and insulin levels, as well as an improvement in glucose tolerance, an increase in insulin sensitivity in peripheral tissues, an enhancement of the oxidative capacity of carbohydrates, and inhibition of the progression of type 2 diabetes in humans. Table 2 presents a comprehensive overview of the pharmacological effects of pomegranate seed oil (Boroushaki et al., 2016). The salutary effects of pomegranate seed oil are attributable to its high concentration of CLnAs, comprising three conjugated double-linked (C18:3) octadecatrienoic fatty acid isomers. However, the precise mechanisms of action of CLnAs remain unclear (Boroushaki et al., 2016).

Table 2. Pharmacological Effects of Pomegranate Seed Oil (Boroushaki et al., 2016)

Effect	Mechanism
Anti-inflammation	The compound in question has been observed to up-regulate colonic PPAR-δ expression, which in turn has been shown to increase IL-17 and IFN-γ levels. Moreover, it has been demonstrated that the compound exerts a modulating effect on mucosal immune responses, resulting in a reduction in the expression of TNF-α and IL-6. In addition, it has been shown to inhibit ROS production and TNF-α-induced priming of myeloperoxidase.
Antioxidant	The elevation of antioxidant enzyme levels serves to diminish lipid peroxidation and oxidative stress. The process of facilitating the addition of free radicals to a conjugated double bond in CLnAs was observed.
Anti-cancer/Anti-tumour	The compound induces apoptosis through the processes of protein kinase C pathway activation and lipid peroxidation. It acts as a specific modulator of estrogen receptors, inhibiting the function of estrogen receptors α and β.
Anti-diabetic	It has been demonstrated that this compound suppresses NF-κB, improves insulin sensitivity and activation of TNF-α, and up-regulates PPAR α and γ-responsive genes.
Decreased plasma and hepatic TG levels	It has been demonstrated that this compound increases the levels of α-mRNA and PPAR-γ while simultaneously suppressing Delta-9 desaturation.
Anti-osteoporosis	The inhibition of RANK-RANKL signalling pathways and the reduction in the expression of osteoclast markers in osteoclast-like cells has been observed. Additionally, an increase in the transcriptional levels of major osteoblast lineage markers and alkaline phosphatase activity, including those involved in matrix mineralisation and Wnt/β-catenin signalling pathways, has been noted.
Anti-pancreatitis	The antioxidant and anti-inflammatory mechanisms of pomegranate seed oil have been demonstrated to result in a decrease in the serum levels of both amylase and lipase. In addition, the activity of pancreatic myeloperoxidase is also reduced, as is oedema, leukocyte infiltration and vacuolisation.
Hepatoprotective	A reduction in DNA fragmentation, malondialdehyde (MDA) levels, glutathione reductase (GSR) activity and caspase-3 activity was observed, while an increase in decreased superoxide dismutase (SOD), glutathione (GSH), glutathione S-transferase (GST) and total glutathione peroxidase (t-GPx) activity levels was noted. Consequently, there was a reduction in oxidative stress and apoptosis.

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Table 2. Pharmacological Effects of Pomegranate Seed Oil (Boroushaki et al., 2016) (continue)

Anti-atherogenic	A reduction in the ratio of triglyceride (TAG) to high-density lipoprotein cholesterol (HDL-C) was observed.
Neuroprotective	It has been demonstrated that the neutralisation of ROS or the increase in the production of antioxidant genes results in a reduction in the lactate/pyruvate ratio, as well as in the production of extracellular nitric oxide and lactase dehydrogenase: Furthermore, this process has been demonstrated to result in a reduction in lipid oxidation and neuronal loss.

PPAR= Peroxisome proliferator-activated receptor, IL= Interleukin, IFN= Interferon, TNF-α= Tumour necrosis factor-α, ROS= Reactive oxygen compounds, CLnAs= Conjugated linolenic acid, NF-κB= nuclear factor kappa-light chain enhancer of activated B cells, RANK= Nuclear Factor κ B Receptor Activator, RANKL= Receptor Activator of Nuclear Factor κ B ligand

4. Toxicity of Pomegranate Seed Oil

The ingestion of pomegranate and its components has been practised safely for centuries without any adverse effects being observed. The potential adverse effects of pomegranate seed oil remain unknown (Jurenka, 2008). A study was performed to determine the toxicity of PSO. The potential toxicity and mutagenicity of PSO were investigated via a series of tests, including an in vitro Ames test and an in vitro chromosomal aberration test (performed on cultured peripheral human lymphocytes), an in vivo acute oral toxicity test, and an in vivo 28-day dietary toxicity study. The findings of the study indicated that pomegranate seed oil did not exhibit any mutagenic or toxic effects. However, in the 28-day dietary toxicity study with male and female rats, it was observed that consumption of 150,000 ppm pomegranate seed oil (equivalent to 14,214 and 13,710 mg/kg body weight/day in female and male rats, respectively) may potentially influence hepatic enzyme activities and may result in an elevated liver and liver-to-body weight ratio. Nevertheless, it was noted that it was challenging to achieve these levels in the diet (Meerts et al., 2009). It has been advised that high doses of PSO should be avoided due to the lower oxidation stability of punisic acid and conjugated fatty acids in comparison to unconjugated fatty acids. This is attributable to the fact that punisic acid and conjugated fatty acids are acknowledged to demonstrate diminished resilience when subjected to oxidation, which could otherwise prove advantageous in other contexts. However, additional data are necessary to elucidate this issue (Jurenka, 2008).

5. Punisic Acid

Pomegranate seeds are a powerful source of anti-inflammatory and antioxidants due to their high levels of hydrolysable tannins and anthocyanins, but they are also high in fatty acids, especially unsaturated fatty acids. Pomegranate seed oil's main constituent is conjugated linolenic acid (CLnA), representing 70-76% of total oil (Emami Kazemabad et al., 2022). The main natural food source of punicic acid is the pomegranate, although it varies according to the genotype of the fruit. Additional sources include seed oils from various members of the Cucurbitaceae family, which also contain significant levels of punisic acid, including T. nervifolia (52%), Momordica balsamina (50%), Trichosanthes anguina (43%), T. bracteata (42%), T. kirilowii (40%), Fevillea trilobata (30%) and Ecballium elaterium (22%) (Aruna et al., 2016; Xu et al., 2020). Punisic acid is a conjugated isomer of linolenic acid, also identified as tricosanic

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acid (C18H30O2) or octadecatrienoic acid (The Human Metabolome Database [HMDB], 2022; Holic et al., 2018).

Punisic acid biosynthesis starts with de novo synthesis of fatty acids in plant plastids, mainly oleic (18:1Δ9cis), stearic (18:0) and palmitic (16:0) acids being the primary products (Guerra-Vázquez et al., 2022). Punisic acid is an unsaturated acid that is sensitive to deterioration by thermal processes, light and oxidation. Moreover, due to its poor solubility in water and the slow rate of its absorption into the body, the biological availability of punisic acid is very limited. This results in CLA quick metabolisation, which limits the commercial and therapeutic applications of this molecule (Adu-Frimpong et al., 2018). The main biological mechanism of punİsic acid is associated with the regulation of PPARs, regulating the genes transcription implicated in cell proliferation and differentiation, as well as the enzymatic activity implicated in lipid metabolism and glucose homeostasis (Bougarne et al., 2018; Holic et al., 2018).

The pharmacological effect of punisic acid is attributable to CLnA. The precise mechanisms of action of CLnAs remain unclear; however, they are characterised by a range of properties, including antimicrobial, antioxidant, immunomodulatory, anti-carcinogenic, anti-diabetic, anti-inflammatory and lipid metabolism regulation (Boroushaki et al., 2016). The anti-inflammatory effect of punisic acid indicates that it may have a preventive, therapeutic, or symptom-reducing impact on the inflammatory pathways associated with AD.

5.1. Metabolism of Punisic Acid

Lipids are highly prevalent in the brain, where they fulfil a multitude of functions related to the structure of the brain. These processes encompass signal transduction, neurogenesis, neural communication, synaptic transmission, membrane compartmentalisation and the regulation of gene expression (Calvano et al., 2021). Punisic acid is metabolised to circulating CLA via a saturation reaction (Pereira de Melo et al., 2019). CLA is primarily metabolised by the liver into phospholipids and/or neutral lipids. CLA isomers c9, t11 and t10, c12 undergo metabolic processes involving extension and desaturation reactions, while retaining their conjugated diene structures (Mele et al., 2013). The two isomers are processed differently. Punisic acid is converted to CLA cis-9, trans-11, and subsequently undergoes β-oxidation to form conjugated diene (CD) 16:2 or is metabolised by Δ6-desaturase to CD 18:3, which is then subjected to further processing to yield CD 20:3 and CD 20:4. CD 18:3, 20:3 and 20:4 are mainly integrated into CLA phospholipids. Simultaneously, CD 20:3 and CD 18:3 are partitioned to neutral lipids (Mele et al., 2013). In the body, it has been shown that punisic acid is converted to c9, t11 and taken up in tissues like red blood cells and plasma (Yuan et al., 2009).

6. Effects of Pomegranate Seed Oil on Alzheimer's Disease

The polyphenols in pomegranate have been shown to have neuroprotective properties. Studies have demonstrated the pomegranate seed oil extract to possess the highest polyphenol concentration (Sarkaki et al., 2013). Mizrahi et al. (2014) administered high concentrations of PSO to mice in five different ways. The first three groups were administered PSO in the feed (1 kg feed was dissolved in water and 25 ml PSO was added), the fourth group was given nano-PSO five times a week (150 µl/day) through a probe, and the fifth group was given nano-PSO in drinking water. Findings showed that PSO

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was able to delay disease development in young transgenic (Tgs) mice. Furthermore, smaller doses of nano-PSO demonstrated a meaningful retardation of disease development in asymptomatic TgMHu2ME199K mice and a delay in the exacerbation of disease in mice that were already exhibiting symptoms. It can therefore be surmised that PSO formulations may have an effect on neurodegenerative diseases (Mizrahi et al., 2014).

In a study to assess the efficacy of PSO on aversive memory in oestrogen-deficient cognitively impaired rats, it was shown that PSO supplementation enhanced both memory and sensory-motor performance in a dose-related manner. The aforementioned benefits have been attributed to the phytoestrogenic and antioxidant effects of PSO, indicating its possible therapeutic value in alleviating memory impairment (Sarkaki et al., 2015). A study in rats found that 3-nitropropionic acid (3-NP) increased ROS and decreased antioxidant status, whereas PSO increased antioxidant activities and scavenged ROS. Conversely, PSO was observed to scavenge ROS and enhance antioxidant activities. The study indicates that the oil has the capacity to mitigate oxidative stress by reinstating cellular vitality and sustaining antioxidant defences. The results of this study highlight the possible use of PSO as a therapeutic compund in the treatment of neurodegenerative conditions (Al-Sabahi et al., 2017). In a study, an attempt was made to form a stabile microemulsion for galantamine hydrobromide (GHBr) using PSO as an excipient. The proportion of PSO and GHBr in the microemulsion was optimised and evaluated for its protecting efficacy towards amyloid-β (Aβ)-induced toxicity in a cellular model. The resulting microemulsion demonstrated positive efficacy in protecting against Aβ-induced cell death, exhibiting antioxidant activity and reducing toxicity. The authors of the study posit that PSO is capable of enhancing the efficacy of anti-AD pharmaceuticals in the treatment of the disease (Shrivas et al., 2023). The additional hypothesis posits that PSO can impede the activity of enzymes, diminish the concentration of ROS, forestall microglial stimulation, safeguard synaptic plasticity, prevent hyperphosphorylation of tau protein, suppress beta secretase-1 (BACE-1) and demonstrate anti-inflammatory properties. Despite the dearth of human studies, there is compelling evidence to suggest that PSO may mitigate several risk factors linked to AD, including offering neurological protection and decelerating the ageing process (George et al., 2023).

The initial study on PSO in humans within this field was a randomised controlled trial conducted by Chatzikostopoulos et al. (2024) with 100 individuals diagnosed with mild cognitive impairment (MCI) and an mean age of 69.53 years. The objective of the research was to examine the potential impact of PSO on cognitive function in individuals with MCI through a comprehensive neuropsychological assessment. The control group was provided with only the Mediterranean diet, whereas the experimental group was given the Mediterranean diet in conjunction with five drops of cold-pressed PSO per day. A neuropsychological assessment was conducted at the outset of the study and at six-month and one-year intervals to ascertain the status of the patients. The tests conducted were the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the ADAS-cog changes in global cognition, In addition to the Rivermead Behavioural Verbal Learning Test. Verbal memory is

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evaluated using the Rey Auditory Verbal Tilt Test (RAVLT), while visuospatial memory and cognitive functions are assessed with the Rey-Osterrieth Complex Shape Test and Trail Making Test Part B (TMT B). The outcomes of this study suggest that PSO has the capacity to augment visual-spatial capability, processing velocity, and executional function, as assessed via the verbal and learning episode memory assessments of the RAVLT, and global cognition, as assessed via the ADAS-cog, which is one of the most extensively utilized psychometric instruments in clinical research. In a specifically designated experimental group, statistically significant improvements were observed in the RAVLT, TMT B and ADAS-cog at the one-year treatment follow-up assessment. Additionally, mean scores on all other neuropsychological tests demonstrated improvement however, the difference in MoCA values did not reach statistical significance. A one-year treatment period has demonstrated that PSO can be an effective intervention for individuals with HBB, as it has been shown to enhance various cognitive domains (Chatzikostopoulos et al., 2024).

7. Effects of Punisic Acid on Alzheimer's Disease

Punisic acid is currently understood to possess a diverse range of biological properties. Punisic acid has been demonstrated to have strong antioxidant and anti-inflammatory properties. In vitro studies and animal rat models have demonstrated that punisic acid is capable of inducing a substantial decline in lipid peroxidation, reinstating superoxide dismutase, catalase and glutathione peroxidase levels, while concurrently reducing glutathione and nitric oxide (NO) synthase levels in the pancreas and blood (Viuda-Martos et al., 2010). Furthermore, punisic acid has been demonstrated to mitigate the inflammatory impact of pro-inflammatory cytokines, specifically IL-6 and TNF-α (Fayaz et al., 2017). PPAR has been demonstrated to reduce neuroinflammation and tau hyperphosphorylation, while simultaneously reducing the formation and aggregation of Aβ. Punisic acid acts as a PPAR and has been demonstrated to inhibit the action of calpain and cyclin-dependent kinase 5 (CDK5), thereby restricting the hyperphosphorylation of tau protein and reducing Aβ formation. Additionally, it has been shown to increase GLUT4 protein production, which regulates glucose metabolism in the brain, reduces hyperphosphorylation of tau proteins and reduces insulin resistance. Furthermore, it may increase paraoxonase 1 (PON1) activity and, HDL antioxidant properties as part of its potent antioxidant effects, reducing ROS formation and lipid peroxidation (Anusree et al., 2018; Khajebishak et al., 2019; Frid et al., 2020). A study has demonstrated that punisic acid is capable of reducing the inflammatory response induced by the proinflammatory cytokines TNF-α and IL-6 in 3T3-L1 pre-adipocytes. Similarly, it has been demonstrated that punisic acid increases the expression of PPAR-y, which has the capacity to reduce the transcription of the Nuclear Factor Kappa B (NFκB) p65 component, as well as to decrease mRNA synthesis of the inhibitor of cytokine signalling 3 (SOCS3) and to attenuate protein tyrosine phosphatase 1B (PTP1B) stimulated by TNF-α (Anusree et al., 2018). In a separate study, punisic acid was observed to reduce the expression of genes involved in lipid metabolism, including PPAR-α, PPAR-β and PPAR-γ, as well as genes associated with fatty acid synthesis and sterol regulatory element binding transcription factor (Srbp1). Additionally, the expression of antioxidant genes, such as aldehyde oxidase 1 (Aox1), was also found to be decreased. The expression of NAD(P)H quinone dehydrogenase

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1 (Nqo1), peroxiredoxin 1 (Prdx1) and glutathione S-transferase A4 (Gst4) was elevated, while the values of TNF-α and IL-6 were reduced (Zamora-López et al., 2020).

Calpains are calcium-dependent cysteine proteases that are implicated in the pathogenesis of a range of neurodegenerative diseases, particularly AD. Calpains play a crucial role in neuroplasticity and synaptic function, they are highly expressed in the brain. They act as neuroprotective agents at basal concentrations, whereas excessive activation of calpains has been linked to neurotoxicity and their hyperactivation has been linked to the progression of neurodegenerative diseases (Ahmad et al., 2018). Calpain-1 is expressed at elevated levels in the final stages of AD, resulting in the production of toxic tau fragments in reaction to treatment of Aβ aggregate. Conversely, Calpain-2 was observed to display enhanced initial activity in the aetiology of AD in a mouse model. Furthermore, it was identified as a factor associated with reduced cognitive functioning and elevated levels of Aβ levels in neocortical tissue specimens obtained from patients diagnosed with AD (Ahmad et al., 2018; Chen et al., 2018). Calpain inhibitors have been shown to possess neuroprotective effects, leading pharmaceutical companies to investigate their potential use as therapeutic agents for Alzheimer's disease (Paul et al., 2020). The neuroprotective activity demonstrated with the nanoformulation of PSO, commercialised as GranaGard®, may be attributed to its calpain inhibition effects. The nanoformulation was observed to inhibit the formation of Aβ, prevent the accumulation of CDK5 and inhibit cytochrome c oxidase activity in transgenic mice (Binyamin et al., 2019).

Furthermore, it is commonly observed that a disruption in metabolism of glucose and the functionality and regulation of glucose transporters occurs alongside a number of neurodegenerative diseases. In Alzheimer's disease, there is a diminution in glucose metabolism as a consequence of a decline in the regulation of glucose transporters throughout the brain (Szablewski et al., 2021). GLUT-4 is an insulin-sensitive glucose transport protein that is present in multiple parts of the brain, including the pituitary, hippocampus, cerebellum, sensorimotor cortex and hypothalamus. The physiologic role of this substance remains uncertain, however, indications are that it is involved in several functions, including glucose sensing, modulation of insulin-mediated glucose transport in various brain regions, and facilitation of glucose transport to motor neurons during periods of increased demand (Głuchowska et al., 2021; Szablewski et al., 2021). In Alzheimer's disease, a reduction in the number of glucose transporters (GLUTs) in the most active parts of the human brain, including the hippocampus, cerebral cortex and microvessels (Gil-Iturbe et al., 2020; Głuchowska et al., 2021; Szablewski et al., 2021). The diminished GLUT-4 expression in hippocampal neurons may be linked with the impairment of short-term memory and lack of orientation observed in patients with Alzheimer's disease (Wang et al., 2020). In studies examining GLUT-4, an important pathway in Alzheimer's disease, it was determined that three-day PSO capsule supplementation increased the expression of the GLUT-4 gene, while punisic acid supplementation increased mRNA and protein expression of GLUT-4 in 3T3-L1 adipocytes (Anusree et al., 2018; Khajebishak et al., 2019).

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8. Conclusion

The findings of animal and human studies suggest that pomegranate seed oil and punisic acid may have the potential to delay the onset of Alzheimer's disease or to alleviate its symptoms. This is due to the anti-inflammatory, antioxidant and neuroprotective properties of these substances, which have been demonstrated in scientific studies. The outcomes of these studies indicate that pomegranate seed oil and punisic acid may represent a promising avenue for the development of new strategies for the treatment and prevention of Alzheimer's disease. Further evidence is required to substantiate these effects and elucidate the underlying mechanisms of action. To this end, in addition to experimental studies, further research is required to examine the physiological and metabolic effects in the human body.

Authors Contributions

Topic selection: ZŞ, HYİ; Design: ZŞ, HYİ; Planning: ZŞ, HYİ; Data collection and analysis: ZŞ, HYİ; Writing of the article: ZŞ, HYİ; Critical revision: ZŞ, HYİ.

Conflict of Interest

There is no conflict of interest between the authors.

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