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Review Article
Alzheimer's Disease and Functional Foods: An Insight on Neuroprotective Effect of its Combination

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease which impairs memory and cognitive function. Currently, AD has no cure and treatments are focused on relieving its symptoms. Several functional plants and foods, such as pomegranate, date fruits, honey, black seeds and figs, possess nutritious properties which alleviate AD. *In vitro* and *in vivo* studies reported that these functional foods exert neuroprotective effects through their antioxidant and anti-inflammatory properties. This review are going to discusses the bioactive components and neuroprotective activities of the functional foods such as pomegranate, dates, honey, black seeds and figs and the potential of functional foods combinations to alleviate AD. Functional food combinations have potential to be consumed for health benefit for the prevention and treatment of AD. This review summarises the functional foods which can be useful for the prevention, treatment and management of AD via oxidative and inflammatory mechanisms. Besides, it provides a new insight on the potential of functional food combinations for the prevention and treatment of AD.

Key words: Functional foods, Alzheimer's disease, phytochemicals, neuroprotective

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INTRODUCTION

Cognitive impairment is a typical condition that occurs during aging[1]. Most people experience a continuous cognitive decline, commonly related to memory for their whole life. Cognitive decline is mostly minor and it may be inconvenienced but it does not disturb the ability to function. Some people may undergo throughout their life without cognitive decline and regarded as successful aging. However, there is another kind of aging that is characterized by further reduce in cognitive function compared to common aging known as mild cognitive impairment (MCI)[2]. MCI is an intermediate phase between typical cognitive aging and dementia[3]. It can be divided into two subtypes: amnestic MCI or non-amnestic MCI[4]. Amnestic MCI is a precursor for AD[5]. A study in Malaysia showed that the incidence rate of MCI was 10.5 per 100 person-years for older adults who did not show MCI at baseline. This rate was greater compared to previous study in China, Italy and Hong Kong[6].

Alzheimer's disease (AD) is the most common age-related neurodegenerative disease which reduces memory and cognitive function[7]. The key pathological hallmark of AD is deposition of amyloid-beta (Aβ) extracellularly in diffuse and neuritic plaques and hyperphosphorylated tau intracellularly as neurofibrillary tangles[8-9]. Early-onset familial AD, which accounts for 1% of AD cases, is due to mutation in the amyloid precursor protein (APP) and in the presenilin-1 and presenilin-2 genes[10,11]. The other 99% are late-onset sporadic cases[10]. Environmental and genetic risk factors contribute to the development of the sporadic form of AD, with aging as the most common environmental risk factor[11]. The incidence rates of AD increase aggressively with age. The World Health Organization (WHO) has reported that neurodegenerative diseases will become the world's second leading cause of death by the middle of the 21st century after cancer[7]. With the rapid growth of the aging population, the number of AD cases is expected to reach[12] 106.8 million in 2050.

Neuroprotection refers to the strategic and relative mechanisms which protect the central nervous system (CNS) against neuronal injury caused by acute (stroke or trauma) and chronic neurodegenerative diseases (AD and Parkinson's disease)[7]. Polyphenols are bioactive compounds in fruits, vegetables and other plant-derived foods which provide numerous health benefits, including enhancing brain function[13,14]. Besides, intake of polyphenol has been proven to protect mental health during aging[15]. Using a single pharmacological target or drug to cure AD is ineffective because of the complex nature of this disease. However, polyphenols with multi-pharmacological targets may be an effective treatment for AD[16]. Polyphenols exert antioxidant, anti-inflammatory, anti-Aβ aggregation and anti-acetylcholinesterase mechanisms for AD treatment[9,16,17]. A study on polyphenol intake among Malaysian population especially from low-middle income groups were still low compared to Western population[15].

Polyphenols may affect human brain function in two ways. Firstly, both plants and mammals may share identical biochemistry and molecular signalling mechanisms[18]. Secondly, polyphenols as secondary metabolites in plants, increase the survival of plants by allowing them to interact with the environment, including microorganisms and insects[14]. Polyphenols are synthesised through natural selection supported with the plant's ability to interact with the CNS of insects. Thus, polyphenols may also interact with the CNS of humans using the same pathways, considering that the CNSs of humans and insects have similarities (most human neurochemicals are present in insects)[14].

Functional foods are natural or processed foods that consist of bioactive compounds that contain health benefits beyond the dietary needs including prevention of risk factors for various diseases and improving specific physiological functions[19-21]. For example, functional foods such as pomegranate and dates were proven to contain high polyphenol content[22]. Many studies indicated the health benefits of polyphenol with various approaches have emerged to advertise polyphenol especially to consumers. These polyphenols can be used for prevention and/or treatment for various diseases especially neurodegenerative disorders as these polyphenols have antioxidant and anti-inflammatory properties[23]. Previous studies have proven that oxidative stress may become a possible factor that can affect cognitive impairment especially in older adults[24,25]. Oxidative stress can occur not only due to free radicals but can also be caused by inadequacy of antioxidant response as seen in MCI and AD patients[26].

Curcumin, major polyphenol in turmeric has protective effect against Alzheimer's disease[19]. Supplementation of curcumin suppressed oxidative damage and synaptophysin loss, decreased microgliosis, improved spatial memory and reduced Aβ deposits in Sprague Dawley rats with cognitive deficits induced by Aβ[27]. Another functional food which consists of garlic also showed neuroprotective effect in Aβ-induced rats. Aged garlic extract improved short term memory and decreased microglia activation and IL-1β levels[28,29]. Both studies showed that antioxidant and anti-inflammatory properties of the functional foods may play a significant protective role against neurotoxic agent such as Aβ, which eventually improved memory function that can lead to neurodegeneration.

It has been previously reported that dietary pattern which included functional foods such as tropical fruits-oats, is associated with successful aging with no cognitive decline[30]. Additionally, diet that rich in fruits or fresh fruits juice possessed neuroprotective effect against MCI[31]. Fruits contained high antioxidant activity and polyphenol content which can protect against cognitive decline[32,33]. Both of these studies showed that consumption of fruits can protect the brain at the early stage and prevent from severe cognitive impairment such as AD.

During the Islamic Golden Age, functional foods were used to treat various diseases. Rhazes (Al-Razi), a Muslim physician in the Islamic Golden Age, started his treatments with diet therapy. He stated that, "if the physician is able to cure with foodstuffs and not medication, then he has succeeded. If, however, he must use medications, then it should be simple medicines and not compound one"[34]. Prophet Muhammad (PBUH) himself preferred food over herbs and medicines. He advised his followers to consume certain foods to prevent or treat diseases[35]. For instance, Ibn 'Abbas: Prophet Muhammad (saw) said, "Healing is in three things: A gulp of honey, cupping and cauterizing. But I forbid my followers to use (cauterisation) branding with fire"[36].

Functional foods widely used during the Islamic Golden Age to treat eczema, burns, cold symptoms, haemorrhoids and wounds include black seeds, honey, dates, figs and pomegranate[34-35]. In his book Canon of Medicines, Avicenna (Ibnu Sina) noted that black seeds enhance and rejuvenate the body's energy[34]. Avicenna (Ibnu Sina) used honey and flour to dress wounds while honey and shredded rose petals to treat tuberculosis in its early stages. In his book Al-Hawi (Encyclopedia of Medicine), Rhazes (Al-Razi) prescribed honey ointments (made with flour) and honey vinegar for skin diseases and nerve injuries and honey water for bladder wounds[35]. Most Muslim scholars derived their inspiration to advance medical knowledge and practice from evidence-based methods in the Al-Quran and hadith[37].

The Al-Quran is a sacred book more than 1400 years old. It has 6600 verses, of which more than 900 verses are advanced scientific findings which are no different from current research findings[38]. It contains complete living guidance and cures for mental and physical diseases[39]. More than 20 identifiable fruits and plants, such as dates, grapes, figs and pomegranates, have been noted in the Al-Quran as gifts from the Divine[37,40].

The hadith is the documented authentic sayings, traditions and actions of Prophet Muhammad (saw). It is viewed as a secondary source of reference for Muslims after the Al-Quran[37,38]. In the hadith, Prophet Muhammad (PBUH) applied and proposed medicinal plants for various diseases. The plants, whether recognised in the Holy Quran or hadiths are acknowledged as having high medicinal value[41]. For instance, black seeds are mentioned in the hadith[40]. Although the health benefits of these foods have been documented, a thorough review of their potential in preventing and treating AD has not been conducted[42]. Thus, this review discusses the bioactive components and neuroprotective activities of the following functional foods (summarised in Table 1): pomegranate, dates, honey, black seeds and Fig. A new insight on the potential of functional food combinations for the prevention and treatment of AD is also provided.

POMEGRANATE (*Punica granatum* L.)

Pomegranate belongs to the family Lythraceae and has been extensively used in different cultures for a long time[43,44]. This fruit is native to Persia and consists of several varieties[43]. Pomegranates were acknowledged as the 'fruit of the dead' in ancient Greek tradition and embellished as the robe of the high priest in Hebrew tradition. Its seeds were viewed as an agent of rebirth by the Babylonians, deemed to grant bravery on battlegrounds by the Persians and represented longevity and immortality to the ancient Chinese[45].

Bioactive components: A study reported that fresh and commercial (conventional and organic) pomegranate juice contains punicalagin isomers, including α-punicalagin and β-punicalagin. Conventional fresh pomegranate juice has higher contents of punicalagin isomers than pomegranate juice produced commercially and by organic farming methods[46].

Another study reported that both fresh and commercial pomegranate juice and extracts of pomegranate peel contain ellagic and gallic acids, in addition to punicalagin. However, commercial pomegranate juice has higher contents of polyphenols than fresh pomegranate juice and peel extract. Commercial production involves pressing intact fruit, which extracts the phenolic compounds and the water-soluble ellagitannins from the rind[47]. In addition, enzymes, thermal conditions and concentration during juice production may contribute to the high level of polyphenols[47,48].

Major phenolic compounds present in pomegranate juice can be divided into numerous groups. The first group includes anthocyanin pigments (cyanidin 3-glucoside, cyanidin 3,5-diglucoside, delphinidin 3-glucoside, delphinidin 3,5-diglucoside and pelargonidin 3-glucoside). The second group includes gallagyl-type tannins (punicalagin isomers).

Table 1: Neuroprotective effects of functional foods

Funtional foods	Study design	Neuroprotective effects	References
Pomegranate (*Punica granatum* L.)	Transgenic mice (APPsw/Tg2576) received pomegranate juice or sugar water in drinking bottles from 6-12.5 months of age. The amount of polyphenol consumed was approximately 0.3-0.6 mg/day	Pomegranate juice reduced amyloid load (both insoluble and soluble Aβ-42) and improved learning and memory in cued and spatial water maze learning tasks along with faster swim speeds by the treated groups	Hartman *et al.*[49]
	Healthy and aluminium chloride-induced male mice fed with pomegranate juice in drinking water with concentration of 20% for 29 days	Pomegranate juice improved learning and memory and reduced anxiety by decreasing time needed to find baited arms, reduced entry errors, increased avoidance response and increased curiosity, but did not inhibit oxidative damage in the brain tissue	Abdul Malek *et al.*[108]
	Transgenic females (APPsw/Tg2576) and non-transgenic mice fed with 4% pomegranate fruit or regular diet for 15 months	Pomegranate fruit reduced oxidative stress by reducing lipid peroxidation and protein carbonyls and improved antioxidant enzymes (SOD, catalase, GPx, GSH, GST), also reduced AChE and increased Na^+ K^+-ATPase activities	Subash *et al.*[51]
	Transgenic females (APPsw/Tg2576) and non-transgenic mice fed with 4% pomegranate fruits or regular diet for 15 months	Pomegranate fruits supplementation attenuated brain Aβ (Aβ-40 and Aβ-42) levels and inflammatory cytokines (IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, TNF-α and eotaxin)	Essa *et al.*[52]
	Ellagic acid and punicalagin were tested on BACE 1, α-secretase (TACE), chymotrypsin, trypsin and elastase enzyme assays kit *in vitro*	Ellagic acid and punicalagin were β-secretase inhibitors (BACEI) but less inhibitory to TACE, chymotrypsin, trypsin and elastase	Kwak *et al.*[54]
	Aβ-42 pre-incubated with or without ellagic acid added on SH-SY5Y cells for 48 h *in vitro*	Ellagic acid reduced Aβ-42 oligomers level and Aβ-42-induced cytotoxicity	Feng *et al.*[56]
Date palm fruits (*Phoenix dactylifera*)	Transgenic females (APPsw/Tg2576) and non-transgenic mice fed with 4% date fruits or regular diet for 15 months	Date fruits supplementation attenuated brain Aβ (Aβ-40 and Aβ-42) levels and inflammatory cytokines (IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, TNF-α and eotaxin)	Essa *et al.*[52]
	Transgenic mice (APPsw/Tg2576) fed with 2 and 4% date fruit and regular diet for 14 months	Date fruits supplementation improved learning and memory, motor coordination and deceased anxiety by improving locomotors, improved escape latency, improved reversal learning of left-right discrimination and increased preference time spent duration in open arm as well as significant reduced in the plasma Aβ-40 and Aβ-42 levels	Subash *et al.*[67]
	Gallic acid and p-coumaric acid were tested on BACE1, α-secretase (TACE), chymotrypsin and trypsin enzyme assays kit *in vitro*	Gallic acid and p-coumaric acid inhibited BACE1 but showed no significant reduction in TACE, chymotrypsin and trypsin	Youn and Jun[68]
	Primary cultured rat cortical neurons treated with 0.1 and 1 μM gallic acid 15 min prior to the treatment with Aβ (25-35), neurons treated with Aβ (25-35) for 24 h *in vitro*	Gallic acid inhibited Aβ (25-35)-induced apoptosis by preventing glutamate release and ROS production especially at dose 1 μM	Ban *et al.*[69]
	Transgenic females APP/Presenilin 1 (APPswe/PSIdE) treated with 5.3 or 16 mg kg^{-1}/day of ferulic acid for 6 months	Ferulic acid supplementation significantly enhanced novel object recognition test and reduced cortical Aβ-40 and Aβ-42 levels especially at lower dose 5.3 mg kg^{-1}/day, both doses reduced IL-1β levels	Yan *et al.*[70]
	Transgenic PSAPP and wild type mice fed with 30 mg kg^{-1} ferulic acid or vehicle for 6 months	Ferulic acid improved behavioural deficits by preventing hyperactivity, improved novel object exploration frequency, increased alternation behaviour, reduced latency to reach platform and swam in the goal quadrant longer, additionally, ferulic acid reduced Aβ deposition (Aβ-40 and Aβ-42), reduced BACE 1, reduced neuroinflammation(reduced activated astrocytes and microglia, TNF-α, IL-1β) and reduced oxidative stress markers (SOD, GPx and catalase)	Mori *et al.*[71]
Honey	Healthy and chronic cerebral hypoperfusion rats induced by permanent bilateral common carotid arteries ligation fed with or without 1.2 g kg^{-1} Malaysian Tualang honey	Malaysian Tualang honey improved pathological changes in the hippocampus region and reduced neuronal cell loss	Saxena *et al.*[80]
	Healthy and lead-induced neurotoxicity rats fed with distilled water or UNILORIN honey (1 or 1.5 mL kg^{-1}) for 28 days	Honey improved memory function, locomotor and reduced anxiety by improved exploratory activities, shorter latency period and increased time spent in goal quadrant, additionally, honey increased SOD, GST and GSH activities	Abdulmajeed *et al.*[82]

Table 1: Continue

Funtional foods	Study design	Neuroprotective effects	References
Black Seed (*Nigella sativa*)	Aβ-40 induced neuronal cell death in primary cultured cerebellar granule neurons (CGNs) were treated with 0.1 and 1 μM thymoquinone *in vitro*	Thymoquinone restored cell viability, decreased LDH, preserved intact cell bodies and neurite network, reduced condensed chromatin, slightly attenuated free radical production and suppressed the caspase 3, 8 and 9 activations	Ismail *et al.*[96]
	Aβ-42 was introduced to primary hippocampal and cortical cultures with or without thymoquinone (0.1-100 nM) simultaneously for 72 h *in vitro*	Thymoquinone improved cell survival and mitochondrial function, reduced intracellular ROS production, enhanced neurotransmission, sustained firing frequency and reduced Aβ-42 aggregation	Alhebshi *et al.*[97]
	Primary cerebellar granule neurons pre-treated with 1, 10 and 100 μg mL^{-1} of black seed oil and its fractions (hexane, ethyl acetate and water fractions) for 5 h before incubating with Aβ-40 for 24 h	Black seed oil and water fraction inhibited cell death and reduced LDH activity compared to hexane and ethyl acetate fractions, at the highest dose, water fraction showed prooxidant activity, both black seed oil and water fraction were effective in scavenging the DPHH-general radicals	Ismail *et al.*[98]
Fig (*Ficus carica*)	Transgenic females (APPsw/Tg2576) and non-transgenic mice fed with 4% fig fruits or regular diet for 15 months	Fig fruits supplementation attenuated brain Aβ (Aβ-40 and Aβ-42) levels and inflammatory cytokines (IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, TNF-α and eotaxin)	Essa *et al.*[52]
	Transgenic females (APPsw/Tg2576) and non-transgenic mice fed with 4% fig fruits or regular diet for 15 months	Fig fruits supplementation enhanced learning and memory deficit by improving escape latency in Morris water maze, reduced plasma Aβ-40 and Aβ-42, reduced lipid peroxidation and protein carbonyl levels, enhanced antioxidant enzymes activities(SOD, GPx, CAT, GR), maintained GSH activity, reduced AChE and increased Na^+ K^+-ATPase activities	Subash *et al.*[105]
	Transgenic females (APPsw/Tg2576) and non-transgenic mice fed 4% fig fruits or regular diet for 15 months	Fig fruits supplementation improved spatial memory, motor coordination, learning ability and anxiety by sustained the locomotor activity, improved escape latency, increased preference time spent duration in open arm and improved position discrimination	Subash *et al.*[106]

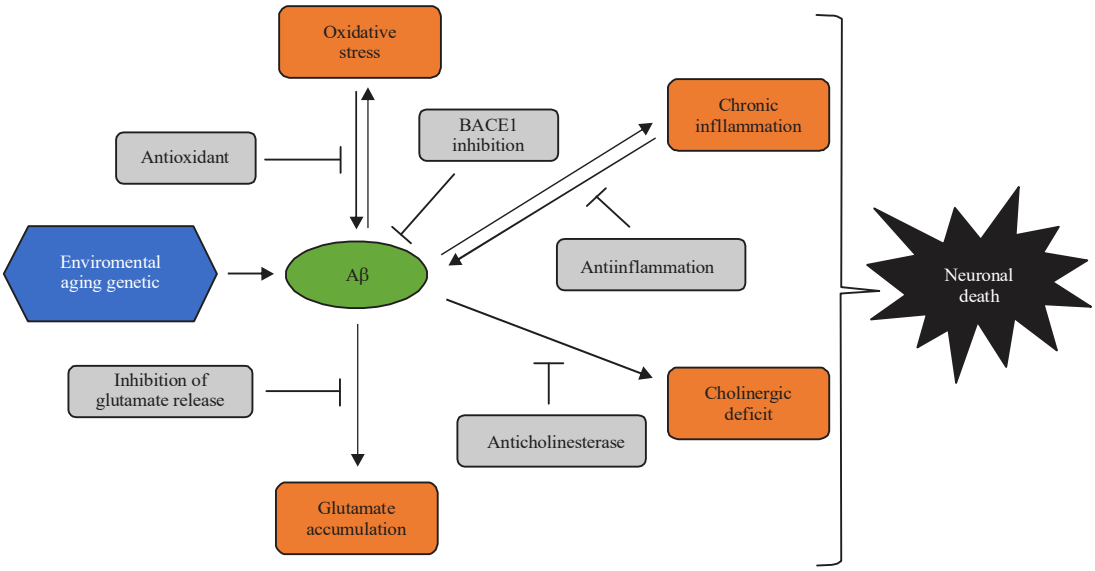

Fig. 1: Various targets for neuroprotective effects of functional foods in AD[11,51,52,54,68,69,71,105]

The third group comprises ellagic acid and its derivatives and the last group consists of other hydrolysable tannins (galloyl glucose)[48].

Neuroprotective activity: The neuroprotective effect of pomegranate juice was evaluated in APP transgenic mice. Results showed that the amyloid load, which includes fibrillary Aβ deposition and soluble Aβ-42, is decreased in APP transgenic mice. In addition, pomegranate juice improves cognition and behaviour in the brain[49]. This result is consistent with another finding that pomegranate juice supplementation improves learning and memory in mice with an AD-like condition induced by aluminium chloride. However, pomegranate juice does not inhibit oxidative damage of the brain tissue in these rodents[50] (Fig. 1).

Subash *et al.*[51] showed that pomegranate fruit reduces oxidative stress and acetylcholinesterase (AChE) and Na^+ K^+-ATPase activities in APPsw (Tg2576) mice, suggesting that this fruit exerts some neuroprotection against oxidative stress in the transgenic mouse model of AD. However, how the antioxidants in pomegranate protect against AD and the mechanism of anti-cholinesterase and Na^+ K^+-ATPase activities of pomegranate warrant further investigation.

Apart from antioxidant activities, pomegranate also shows anti-inflammatory activities by suppressing cytokines and reducing brain Aβ-40 and Aβ-42 levels in APPsw/Tg2576 mice supplemented with 4% pomegranate for 15 months compared with control APPsw/Tg2576 mice[52]. The neuroprotective properties shown might be due to the polyphenols contained in the pomegranate[49]. In addition, reducing the Aβ levels may improve tau pathology in the AD brain[53].

Punicalagin and ellagic acid are polyphenolic compounds present in pomegranate[47,48]. Both are β-secretase inhibitors which can suppress Aβ formation[54]. Aβ is formed by the endoproteolysis of parental amyloid precursor protein (APP), which is obtained by the sequential cleavage of APP by groups of enzyme complexes, including β-secretase. This APP processing is divided into non-amyloidogenic and amyloidogenic pathways. The amyloidogenic pathway leads to Aβ production mediated by β-secretase[55].

However, another study has shown that ellagic acid enhances Aβ aggregation into fibrils with significantly reduced pathogenic Aβ-42 oligomer levels and Aβ-42 cytotoxicity toward SH-SY5Y[56]. This result is in contrast to the previous finding that pomegranate reduces the amyloid plaque load in the brain instead of increasing the Aβ aggregation[49]. The differences in the mechanism of actions of pomegranate juice and ellagic acid may be due to the polyphenol contents in both treatments. Pomegranate juice contains various polyphenol combinations, including ellagic acid, which may act together with synergistic or additive effects. By contrast, ellagic acid may have different pathways when acting alone. Given the different pathways of neuroprotection, further studies are required to explore the protective and therapeutic potential of pomegranate and its phytochemicals in AD.

DATE PALM FRUITS (*Phoenix dactylifera*)

Date palm belongs to the Arecaceae family and its fruits are a source of low-cost food, an essential component in the Arabian diet. It is also a staple food in certain places of the world and consumed by Muslims during the holy month of Ramadan to break the fast[57,58].

Bioactive components: Gallic acid is the major free phenolic acid in all dates cultivars in Algeria. The other phenolic acids are ferulic acid, p-coumaric acids and small amounts of caffeic acid. Several flavonoids have also been detected, including isoquercetin, rutin and quercetrin. Flavonoids such as quercetin and luteolin have been detected in some varieties[59]. Another study found that ferulic, p-coumaric and sinapic acids are the main compounds in Algerian dates. Some flavonoids, primarily flavone glycosides, flavanone glycosides and flavonol glycosides, have also been detected. Unfortunately, the identities of these compounds cannot be determined because their concentrations are too low[60].

In Oman varieties of dates, gallic acid is the major phenolic acid. Caffeic acid, p-coumaric acid, vanillic acid and syringic acid are the other phenolic acids detected[61]. Al-Farsi *et al.*[62] detected nine phenolic acids (gallic acid, protocatechuic acid, p-hydroxybenzoic acid, vanillic acid, syringic acid, caffeic acid, p-coumaric acid, ferulic acid and o-coumaric acid), both free and bound, in Oman varieties of fresh and sun-dried dates. The total concentration of both free and bound phenolic acids is significantly higher in sun-dried dates than in fresh dates. Among the free phenolic acids, vanillic acid, syringic acid and ferulic acid are the major compounds detected in different varieties. For the bound phenolic acids, protocatechuic acid, ferulic acid, p-coumaric acid and o-coumaric acid are among the major compounds detected in different varieties[62].

Gallic acid is the major phenolic acid and quercetin is the major compound in all date cultivars in Saudi. The other phenolic and flavonoid compounds detected include caffeic acid, ferulic acid, protocatechuic acid, catechin, p-coumaric acid, resorcinol, chlorogenic acid, syringic acid, luteolin, isoquercetin, apigenin and rutin[63]. Thirteen flavonoid glucosides of luteolin, quercetin and apigenin have been identified in mature Deglet Noor dates[64]. The differences observed between the phenolic compounds in each variety are due to such factors as variety, growing conditions, stage of ripeness, season, geographic origin, storage conditions, fertilisers used, soil types and amount of sunlight received[62].

Neuroprotective activity: An animal study investigated the effect of date fruit supplementation on APPsw/Tg2576 mice as an *in vivo* model for AD. Date fruit supplementation for 15 months in APPsw/Tg2576 mice attenuates the brain Aβ-40 and Aβ-42 levels and inflammatory cytokines compared with the control APPsw/Tg2576 mice. Date palm fruits contain flavonoid glycosides of luteolin, quercetin and apigenin, which demonstrate anti-inflammatory activities[52]. Neuroinflammation is a pathological indication of AD, of which inflammatory pathways can be activated during the early or later stage of AD or even before AD development[65,66]. Date fruits may provide protection against inflammation in AD by reducing the risk, delaying the onset or slowing down its progression.

Date fruit supplementation for 14 months also significantly enhances learning and memory, improves motor coordination, decreases anxiety and reduces plasma Aβ-40 and Aβ-42 levels in APPsw/Tg2576 mice[67]. However, the underlying mechanism remains to be determined. The anti-inflammatory properties of date fruits may contribute to their neuroprotective effects. AD involves various pathways, thus, dates containing such phenolic contents as gallic acid, ferulic acid and p-coumaric acid may act on a different pathway.

An in vitro study showed that gallic acid and p-coumaric inhibit β-secretase (BACE1) in a dose-dependent manner. BACE1 is an important enzyme in Aβ production[68]. In addition, gallic acid inhibits the apoptosis of cultured cortical neurons in vitro by preventing the Aβ (25-35)-induced release of glutamate and the production of reactive oxygen species (ROS)[69]. Moreover, ferulic acid significantly enhances performance in novel-object recognition test, decreases IL-1β levels and reduces cortical Aβ-40 and Aβ-42 levels in APPswe/presenilin 1 mice. A low dose (5.3 mg kg^{-1}/day) of ferulic acid is more effective than a high dose (16 mg kg^{-1}/day)[70].

In addition, ferulic acid treatment of the PSAPP mouse model of AD-like pathology for 6 months reduces Aβ deposition in different brain regions (e.g., cingulate cortex, hippocampus and entorhinal cortex), improves behavioural deficits and reduces the amounts of BACE1 protein. Ferulic acid also shows anti-inflammatory and antioxidant properties by reducing both microglial and astrocyte activation, including reducing both TNF-α and IL-1β expression in the brain mRNA and significantly reducing the expression of oxidative stress markers (super oxide dismutase (SOD), catalase and glutathione peroxidase (GPx) to baseline levels[71].

These studies showed that the phytochemicals in dates exert their neuroprotective effects via their antioxidant and anti-inflammatory properties and by their abilities to reduce Aβ levels and production.

HONEY

Honey is a sweet substance made from plant nectar by honey bees. Bees collect honey, convert the substance by mixing with particular substances of their own, deposit, dehydrate, store and allow to mature in the honeycombs[72]. Traditionally, honey has been used as a sweetener and medicine for the treatment of burns, cataracts, ulcers and wound healing[73].

Bioactive components: Honey is a complex substance because its composition relies on various factors, including geographical and floral origins, season, storage and harvest method, soil type, temperature, genetic factors and bee species[74-76].

An analysis of Malaysian honey, such as gelam, nenas, acacia, tualang and kelulut honey, revealed that gelam honey contains high levels of benzoic acid, ferulic acid, hesperetin and p-coumaric acid with ellagic acid as its main compound. In acacia and tualang honey, naringenin and ellagic acid are the major phenolic compounds, whereas nenas honey contains benzoic acid and syringic acid as the dominant compounds. Ellagic acid and benzoic acid are major compounds in kelulut honey[77].

In Polish honey, the major phenolic acids in lime, nectar honeydew, rape, honeydew and acacia honeys are p-coumaric acid and gallic acid. Buckwheat honey contains gallic acid, caffeic acid and p-coumaric acid as the major phenolic acids, whereas multi-flower honey contains p-coumaric acid and ferulic acid. With respect to flavonoid content, lime, nectar-honeydew, rape, honeydew and multi-flower honeys contain naringenin. The major flavonoid in acacia honey is kaempferol. Quercetin is the major flavonoid in buckwheat honey[78]. In Australian jelly bush honey, myricetin is the major flavonoid and gallic acid and coumaric acid are the major phenolic acids. New Zealand Manuka honey consists mainly of quercetin and isorhamnetin as the main flavonoids and gallic acid as the main phenolic acid[79].

Neuroprotective activity: Treatment of Malaysia tualang honey on male Sprague-Dawley rats with chronic cerebral hypoperfusion induced by permanent bilateral common carotid arteries ligation (2VO), revealed that the treatment group has an improvement in hippocampal cells in their normal structure and decreased neuronal cell loss compared with the control group[80]. 2VO reduces cerebral blood flow (CBF) significantly in the rats, which can lead to severe damage in the neuron cells in the CA1 region of the hippocampus. Even though the main risk factor for AD is aging, reduction of CBF in chronic cerebral hypoperfusion is also a factor that can also cause AD[80,81]. Malaysia tualang honey can be used as a neuroprotective agent in the prevention and treatment of AD.

In another study involving Wistar rats, co-administration of honey with lead can improve memory function, increase locomotion and reduce anxiety in lead-exposed rats receiving treatment[82]. In addition, honey can enhance antioxidant activities by increasing brain SOD, glutathione (GSH) and glutathione S-transferase (GST) activities. Lead is a neuro-toxicant that causes oxidative stress in the brain, leading to brain dysfunction[82,83]. Honey has high antioxidant properties that reduces oxidative stress, an early characteristic of AD[84,85].

BLACK SEED (*Nigella sativa*)

Nigella sativa, usually known as black seed or black cumin, black caraway or coriander seeds in Asia, is also known as 'Love in a Mist' in English, Shonaiz in Persian, Al-Habat-El-Sauda or Haba-Al-Barka (seed of blessing) in Arabic countries, Hak Jun Chou in China and Kalonji in India[86-89].

Black seed is commonly used in the Indian subcontinent, Arabian countries and Europe for cooking and as a natural treatment for various diseases and conditions, such as asthma, hypertension, diabetes, inflammation, cough, polio, kidney stones and abdominal pain[86,90]. Muslims recognise black seed as one of the best remedy as Abu Hurairah (ra) narrated that Prophet Muhammad (PBUH) said, 'Use this black seed. For indeed it contains a cure for every disease except As-Sam' and As-Sam is death[91,92].

Bioactive components: Black seed essential oil contains up to 49.8% p-cymene and black seed volatile oil contains trans-Anethole (38.3%), p-cymene (14.8%), limonene (4.3%), carvone (4.0%), thymoquinone (77.2%-86.2%) and o-cymene (5.4-11%)[93-95]. Other constituents detected at lower amounts are carvacrol, limonene, methyl chavicol, terpinen-4-ol, trans-sabynil acetate, longifolene, α-thujene and γ-terpinene[95].

Neuroprotective activity: Pre-treatment of thymoquinone, a bioactive component of black seed, inhibits Aβ-40-induced

neuronal cell death in primary cultured cerebellar granule neurons. Thymoquinone increases cell viability, decreases lactate dehydrogenase release, maintains cell bodies, improves neurite network, mitigates condensed chromatin, attenuates the production of free radical and suppresses the activation of caspase 3, 8 and 9, compared to those treated with Aβ-40 alone[96]. Thymoquinone also improves cell viability, decreases intracellular ROS, improves synaptic vesicle recycling inhibition which enhances neurotransmission, maintains firing frequency and suppresses Aβ-42 aggregation in primary hippocampal and cortical neurons cultures[97].

Apart from thymoquinone, pre-treatment of black seed oil and its fraction (water fraction, hexane fraction and ethyl acetate fraction) improves cell viability even at a lower dose, that is, water fraction (1 μg mL^{-1}) in Aβ-induced cell death in primary rat cerebellar granule neurons. However, at the highest dose, water fraction (100 μg mL^{-1}) exhibits prooxidant activity[98]. Further study is required to determine the exact mechanism underlying the protective effects of black seed.

FIG (*Ficus carica*)

Ficus carica Linn. belongs to the family Moraceae and is commonly known as fig[99]. The word 'ficolin' which is similar to Ficus is indicated as a combination of a lectin-like compound with the initial parts of the words 'fibrinogen' and 'collagen'[100]. Figs are called as 'Teen' in Arabic[101]. It has been utilised traditionally for the treatment of metabolic, cardiovascular and respiratory diseases through its anti-spasmodic and anti-inflammatory effects[102].

Bioactive components: Quercetin-3-O-rutinoside is the dominant compound of dried Tunisia fig fruits. Other compounds, such as ferulic acid and quercetin, have been detected at lower quantities[103]. In the Turkish varieties (Sarilop and Bursa siyahi), phenolic acids are higher in the Bursa than in the Sarilop varieties. Chlorogenic, ellagic and p-coumaric acids have been detected in the skin and gallic acid in the pulp of fresh figs. Both varieties of dried figs have higher contents of gallic acid than fresh figs[104].

With respect to flavonoid compounds, rutin is the principal compound in both varieties of figs. The majority of rutin is located in the fruit skin. Other flavonoid compounds detected in both fig varieties are quercetin-3-glucoside, kaempferol-rutinoside and quercetin derivatives. The drying process reduces rutin, kaempferol-rutinoside and quercetin-3-glucoside compounds in the Sarilop variety. For the Bursa variety, the drying process results in a loss in quercetin-3-glucoside and quercetin derivatives but increases rutin and kaempferol-rutinoside[104].

Neuroprotective activity: Supplementation of fig fruits for 15 months attenuates brain Aβ levels and inflammatory cytokines in APPsw/Tg2576 mice as an *in vivo* model for AD. Compared with control APPsw/Tg2576 mice, APPsw/Tg2576 mice fed with fig fruits have significantly reduced inflammatory cytokines[52]. Given their anti-inflammatory activities, figs protect against neurodegenerative diseases, such as AD.

Fig fruits also exhibit their neuroprotective effect via their antioxidant activities. Dietary supplementation of 4% figs for 15 months in Tg2576 mice enhances learning and memory deficit in Tg2576 mice, reduces the plasma Aβ (1-40 and 1-42), reduces AChE and improves Na^+ K^+-ATPase activities as compared with control[105]. Another study showed that dietary supplementation of 4% figs for 15 months improves spatial memory, learning ability and anxiety in the Tg2576 mouse model of AD[106]. The neuroprotective effect of figs may be due to its antioxidant activities as fig supplementation reduces MDA and protein carbonyl levels while increases SOD, catalase, GPx, GSH and glutathione reductase levels[105].

POTENTIAL OF FUNCTIONAL FOODS COMBINATION TO TREAT VARIOUS DISEASES

Previous *in vitro* study on the mixed concentrated juice consisted of pomegranate, dates and honey combination showed that these functional foods in combination contained high antioxidant content and it is suggested to consume this juice as a supplement[107]. Another study on different functional mixed fruit juice of pomegranate, guava and roselle in combination, also contained high total phenolic content and antioxidant activity[108]. These showed that these functional foods in combination may have potential to manage various diseases especially for diseases that have oxidative stress as its prevalent process to cause diseases.

In an *in vivo* study, the effectiveness of combined functional foods have been reported to prevent and treat various diseases. A combination of black seeds and honey used to treat heart disorders (induced by food additives) in male rats improves serum and heart lipid profiles and enzyme activities and reduces oxidative stress. Even though the honey treatment is more effective than the black seed treatment, the effect is stronger when the combined treatment is used than when each treatment is used alone[109].

A human study reported that a combination of black seeds and honey ameliorates gastric infection due to *Helicobacter pylori* in patients with positive *H. pylori* infection. The patients did not have serious adverse effects. This study shows that this food combination is a potential anti-dyspeptic agent[110]. Further study is required to determine the mechanism by which this food combination reduces H. pylori infection. Concrete evidence is needed because this study is a pilot study with a small sample size.

Another study determined the anti-hyperlipidemic effect of a polyherbal mixture (which includes the combination of black seeds, pomegranate, garlic, cinnamon and few other herbs) in streptozotocin-induced diabetic rats. This polyherbal mixture improves blood glucose level and lipid profiles, showing that this mixture can be used as a food supplement for diabetes management[111]. Such functional food combinations show promising results in the management of cardiovascular disease, bacterial infection and diabetes. Moreover, these food combinations exhibit antioxidant activity in vitro and in vivo and improve glucose levels, both of which are important in brain aging. Thus, determining the potential of functional food combinations for the management of neurodegenerative diseases (especially AD) is interesting.

HEALTH BENEFITS OF FOOD COMBINATION ON ALZHEIMER'S DISEASE

AD is a multi-factor and heterogeneous disease with an unclear pathogenesis[112]. Various factors, such as age, lifestyle, dietary preferences and genetics, affect the progress of this disease[113,114]. The mechanisms that cause the brain to age pathologically are obscure, even though oxidative stress is a prevalent process to both brain aging and AD[115,116]. Other processes prevalent in brain aging are increased inflammation, decreased mitochondrial function and impaired glucose metabolism[117-120].

Due to the complex and extensive pathological mechanisms in AD, multi-targeted approaches may be required to treat and prevent AD effectively. Various phenolic compounds are present in functional foods and a combination of these foods may act on different pathways. Thus, the additive and synergistic effects of phytochemicals in the foods are probably responsible for their health benefits. The complex mixture of phytochemicals in these foods may act via completing and complementary mechanisms, such as oxidative agents, immune system induction, hormone metabolism, anti-bacterial and anti-viral effects[121-123]. These phytochemicals are different in molecular size, polarity and solubility, which may influence the bioavailability and distribution of each compound in different macromolecules, subcellular organelles, cells, organs and tissues[121].

Various previous studies as stated above proved that single purified phytochemicals (e.g., ellagic acid, ferulic acid and punicalagin) and whole functional foods (e.g., date fruits and pomegranate) provide health benefits for AD treatment. Even though isolated pure compounds provide health benefits, especially in AD, dietary supplements containing purified phytochemicals do not provide similar health benefits compared to whole foods which are rich in the combinations of phytochemicals. The reason is that purified phytochemicals may lose their bioactivity or may not act similar to the mixture of compounds in the whole foods[121]. Thus, a combination of functional foods as mentioned in the Al-Quran and hadith can provide the same or better health benefits compared to a single purified phytochemical.

Few studies have proven the beneficial effects of a combination of foods/dietary supplements for the prevention or treatment of AD. A medical food cocktail consisting of curcumin, piperine, epigallocatechin gallate, α-lipoic acid, N-acetylcysteine, B-vitamins, vitamin C, vitamin E and folate supplemented for 6 months improves learning and memory in a transgenic mouse model of AD and also decreases Aβ levels and oligomerisation[114].

Furthermore, a medical food cocktail containing N-acetyl cysteine and R-alpha lipoic acid, turmeric, green tea and black paper extracts improves spatial attention in a canine model of human aging. A medical food cocktail improves spatial attention and motivation in patients with AD. However, spatial memory and Aβ level in the brain and cerebrospinal fluid are not affected by the cocktail[124].

In addition, Hutton *et al.*[125] conducted a study using a prevention approach to determine the neuroprotective effects of polyphenol-containing multiple ingredient dietary supplement (MDS) consisting of 30 ingredients, such as gingko biloba, ginseng, green tea, garlic, curcumin, vitamin C and melatonin, on both sexes of triple transgenic (3xTg-AD) mice for 2 months. Results show that 3xTg-AD mice (both sexes) treated with MDS is prevented from deteriorating in working and spatial learning compared with untreated-3xTg-AD mice. However, MDS is unable to preserve recognition memory. This study suggests that a combination of supplements may protect against AD-related behavioural changes.

CONCLUSION

Functional foods such as pomegranate, honey, date fruits, black seed and figs have beneficial health effects, especially in the management of neurodegenerative diseases, including AD that is multifactorial. Thus, combination of functional foods may act via multi-mechanism simultaneously for their neuroprotective effects and eventually provide health benefit for the prevention and treatment of AD compared to single treatment.

SIGNIFICANCE STATEMENT

This review discovers the potential of health benefits of the functional foods combination in the prevention and treatment of neurodegenerative disease especially AD. This provides a new insight for the management of AD as many researchers still continuously finding cure for AD due to its complexity.

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