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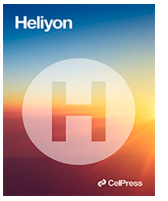

Review article

Therapeutic potential of clinically proven natural products in the management of dementia

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A R T I C L E I N F O

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A B S T R A C T

Dementia is a common neurodegenerative disorder connected to damage to nerve cells in the brain. Although some conventional drugs are available for dementia treatments and are still sanctified for dementia patients, their short- and long-term side effects and other limitations make treating patients more challenging. The authors aimed to explain novel options for treating dementia with natural products and unravel some clinically proven natural products. This article systematically reviewed recent studies that have investigated the role of natural products and their bioactive compounds for dementia. PubMed Central, Scopus, and Google Scholar databases of articles were collected, and abstracts were reviewed for relevance to the subject matter.In this review, we provide mechanistic insights of clinically validated natural products, including like-Yokukansan, Souvenaid, BDW, Hupergene, *Bacopa monnier*, Omega-3, Tramiprostate and Palmitoylethanolamide with which have therapeutic efficacy against dementia in the management of dementia. As shown by studies, certain natural ingredients could be used to treat and prevent dementia. We strongly believe that the medicinal plants and phytoconstituents alone or in combination with other compounds would be effective treatments against dementia with lesser side effects as compared to currently available treatments. Moreover, these products should be studied further in order to develop novel dementia medications.

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1. Introductions

Dementia is a broad term for a loss of memory, language, problem-solving skills, and other ways of thinking that are bad enough to get into daily life [1]. Thus, dementia is not a single disease; it is a general term that encompasses a wide range of specific medical diseases, such as Vascular dementia, Lewy body dementia, Frontotemporal dementia and Alzheimer's disease [2]. More generally, Alzheimer's disease is the most prevalent reason someone develops dementia [3]. In the later stages of dementia, almost 5 out of 6 will also suffer from Behavioral and Psychological Symptoms of Dementia (BPSD) at some point [4,5]. BPSD is typically classified into one of five syndromes: psychosis, aggression, psychomotor agitation, depression, and apathy [6]. For that reason, dementia is seen as the most significant global challenge for health and social care in the 21st century [7].

However, it is estimated that roughly 6% of the world's elderly population is living with dementia [8], which is about 47 million people around the globe [9], and that number is expected to quadruple by 2050 [7,10]. Followed to a report in the United States, 15% of people over the age of 68 have dementia [11], in 2014, approximately 850,000 people were living with dementia in the UK [12]. According to a recent survey, Chinese citizens aged 60 and up had a dementia incidence of 5.30% in 2018 [13]. Notably, the number of dementia patients is slightly fewer in lower and middle-income countries [14]; hence evaluating therapy success is crucial.

By taking a closer look to the treatment of neurological disorders, many existing pharmacological drugs are widely used for neurological patients. Generally, natural compounds are widely used to treat many diseases, including antimicrobial agents [15], anticancer [16–20] neurodegenerative diseases [21], and many other conditions [22]. Throughout history, people have relied on cures made from natural substances such as plants from the land, animal parts, marine life, and the by-products of microbial fermentation [23,24]. Herbal medicines, Ayurveda, and dietary supplements are widely recognized as valuable health resources [25–27]. Some natural phytochemicals such as Punica granatum [27], Flavonoids [28], Ginkgo biloba [29,30], Resveratrol (Vitis vinifera) [31,32], Camilla sinensis [33,34], Theobroma cacao [35,36], *Bacopa monnieri* [37], Crocus sativus [38], Curcumin [39,40] has broad application in the treatment of neurological disorders. Each component in this class of naturally occurring phytochemicals has been shown to engage in unique activities, such as boosting antioxidant levels, reducing inflammation, partially blocking signals, stimulating cell communication, etc.

Thus, natural products' significance and potential for treating dementia are endless. Many plant-based phytochemicals have shown promise as potentially game-changing therapies for dementia and Alzheimer's. Furthermore, this study aimed to provide a mechanistic explanation and additional insight into how some natural compounds are effective in the management of dementia treatment.

2. Methodology

This review article has been written based on a systematic search strategy and preferred reporting items, including the name of natural compounds and relation with dementia according to PRISMA guidelines [41]. For searching relevant articles or databases, we studied the articles of renowned publishers like SciVerse Scopus ® (Elsevier Properties S. A, USA), Web of Science® (Thomson Reuters, USA), and PubMed® (U.S. National Library of Medicine, USA). Search items include – dementia, clinically proven natural products in the treatment of dementia, medicinal plants or herbs in the treatment of dementia, and how medicinal plants/herbs treat dementia etc. A total of 175 non-duplicate articles have been identified in the initial phase. After careful scrutinization, 138 relevant articles have been selected after initial screening. Finally, after 21 exclusions, only 117 more relevant articles have been selected. Non-English articles have been kept out of exploration. The relevant articles' full manuscripts, including title, abstract and conclusive remarks, have been thoroughly read to verify the expedience criterion. For checking data extraction accuracy and discrepancies, a second and third author has been involved when required. BioRender non-professional software was used to generate figures associated with mechanisms of action of these clinical compounds.

3. Natural products in the management of dementia

There are several clinically proven natural products in the management of Dementia.

3.1. Yokukansan

A traditional Japanese herbal medicine Yokukansan (yi-gan san in Chinese), also known as TJ-54 (Tsumura Co., Japan), is a Kampo formula with noticeable curing consequences for neuropsychiatric disorders. TJ-54 is an extracted formulation of seven medicinal herbs containing Angelica acutiloba L. (Umbelliferae), Atractylodes lancea DC. (Compositae), Bupleurum falcatum L. (Umbelliferae), Poria cocos Wolf. (Polyporaceae), Glycyrrhiza uralensis (Leguminosae), Cnidium officinale Makino (Umbelliferae), and Uncaria rhynchophylla Schreb. (Rubiaceae) [42]. The efficacy of Kampo formula in the therapy of dementia is featured particularly in some papers [43]; the preferred utilization of TJ-54 eases BPSD as an advanced drug [44]. The benefits of Yokukansan are clinically well analyzed by Japanese pharmacology experts, which include; improvement of hyperactivity, irritability, agitation, anxiety, insomnia, and behavioral and psychological symptoms of dementia (BPSD) [45,46]. However, this Kampo drug has some gastrointestinal effects like; diarrhea, vomiting, nausea, etc.

According to Mizukami et al. a cross-over study was designed where 106 patients were randomized and treated. This study was organized in October 2005 to April 2007 in 20 different medical institutes of Japan [47]. This study reveals a significant improvement in total NPI (Neuropsychiatric Inventory) score after 4-wk treatment with TJ-54, alleviated BPSD contrast with non-treatment patients. This cross-over study states that patients have no sink after the termination of TJ-54; thus also manifest at least 4 wk after the last dose

of TJ-54; no rebound-related degeneration was shown. Most significant symptoms, delusions, hallucinations, agitation/aggression, depression, anxiety, and irritability/lability were diminished by TJ-54. Several psychological and behavioral symptoms can be minimized by TJ-54. The study suggests that TJ-54 has promising development for elderly patients with dementia and has no disadvantages on cognitive function in treating BPSD [42]. Another open-label study with a larger was designed to evaluate the efficacy of Yokukansan as a treatment for frontotemporal dementia (FTD). Degeneration of cognitive functions with behavioral disturbances is defined as FTD. A total of 20 patients with FTD were registered at the Kikuchi Hospital, Koshi in Japan, between May 2008 and October 2009. Evaluation using NPI (Neuropsychiatric Inventory) and SRI [48] (Stereotypy Rating Inventory-a sound psychometric tool for measuring stereotypic behaviors) established the behavioral symptoms related to FTD improved by the treatment of Yokukansan [49].

3.1.1. Mechanism of action of yokukansan

5-Hydroxytryptamine (5-HT), or serotonin; is a neurotransmitter that takes part in prime physiological functions such as sleep, temperature regulation, pain, cognition, and clinical circumstances containing mood disorders and anxiety disorders, psychosis, etc. These neurons derived in the raphe nucleus of the brainstem and its project axons control the brain to free serotonin, thus activating receptors to modulate neuronal activities [50]. As per the signal transduction path, there are seven families of 5-HT receptors (5-HT_1 to 5-HT_7), confining 14 subtypes like 5-$HT_{1A/1B/1D/1E/1F}$, 5-$HT_{2A/2B/2C}$etc [51,52]. Several papers proposed that the 5-HT_{1A} receptor is the prime target for TJ-54, an herbal medicinal extract able to resolve behavioral and psychological symptoms of dementia (BPSD) in AD (Alzheimer's disease) patients. It's a G-protein-coupled receptor with seven transmembrane bridge which spreads serotonergic signal to frontal cortex, septum, amygdala, hippocampus and hypothalamus [53,54]. Aggressive behavior of Ad patients happened to the density of 5-HT_{1A} receptors [55]. This behavior turns down by partial agonists of 5-HT_{1A}. A particular component of TJ-54, UncariaeUncis cum Ramaulau (JP Uncaria hook), has a function on 5-HT_{1A} receptors [56] which operate the acetylcholine neurotransmitter system [57]. Activation of the 5-HT_{1A} receptor alleviates serotonergic transmission by suppressing tyrosine hydroxylase synthesis [58]. A recent study revealed 5-HT_{2A} receptor in the mouse prefrontal cortex down-regulation gives rise to time after time treatment with yokukansan [59]. Overall activities of Yokukansan was summarized at Fig. 1.

3.2. Souvenaid

Yogurt-like thick drink [60] Souvenaid ™ is a nutritionally functional food known as antidementia agent. This neutraceutical

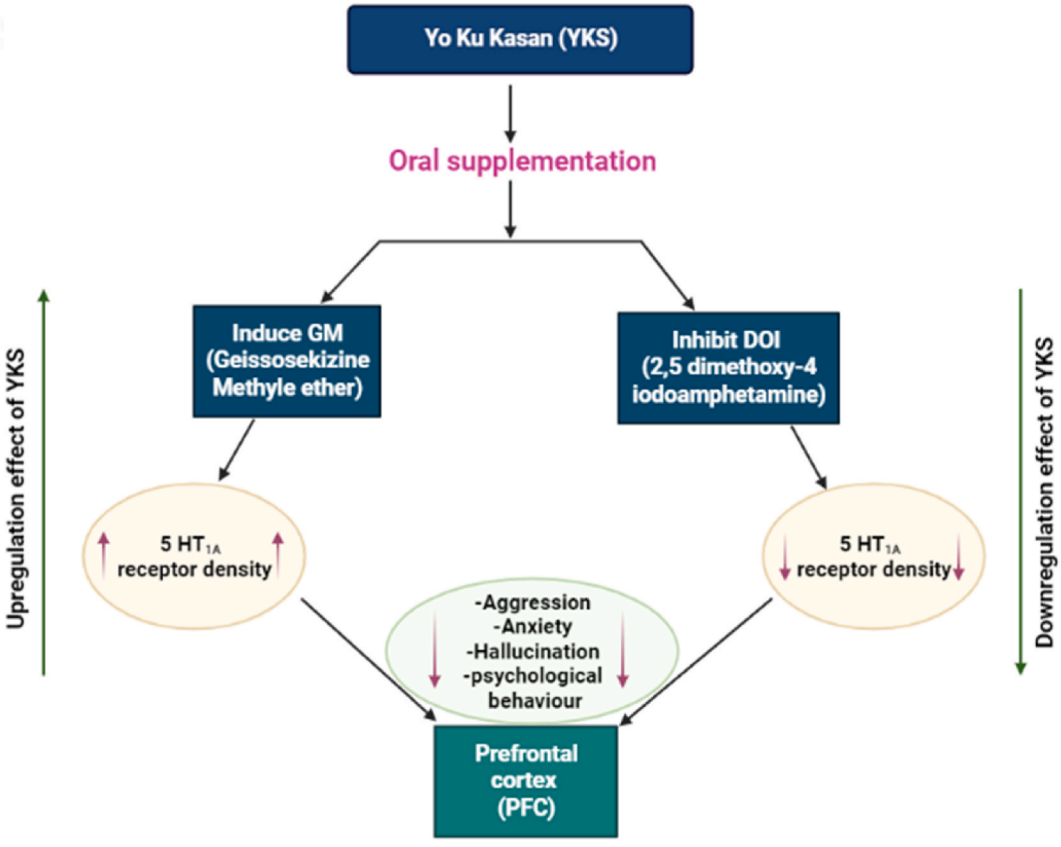

Fig. 1. Neuroprotective effects of yokukansan by regulation of receptors.

compound is composed of uridine (as uridine-mono-phosphate), omega-3 polyunsaturated fatty acids (docosahexaenoic acid and eicosapentaenoic acid), choline, phospholipids, selenium, folic acid, vitamin C, vitamin E, vitamin B6, vitamin B12 [61] and these all are obligatory for the evolution of synaptic membrane [62]. Dutch company Numico Research by "Danone" originally manufactured souvenaid in 2007 [63]. Souvenaid ™ is helpful in reducing behavioral slippage and improve social cognitive skills. Nutrients of Souvenaid ™ support brain phospholipid metabolism. Nutrients present in Souvenaid ™ can elevate neurite outgrowth and dendritic spine, which improves synaptic integrity proved by earlier studies [62,64,65]. Souvenaid ™ drink is also beneficial for mild Alzheimer's patients. Alzheimer's begins due to the lack of ingredients found together in Souvenaid ™. This drink does not apply to those with galactosemia because it comprises milk, soy, and seafood [66].

According to a proof-of-concept study, 26 patients with the behavioral variant of frontotemporal dementia (bv-FTD) were registered based on: age, disease duration, and no other admissible neurological or psychiatric co-morbidities. As per Post-hoc tests, showed notable deterioration in NPI (Neuropsychiatric Inventory) CGI-S (Clinical Global Impression-Severity), and RMET (The Reading the Mind in the Eyes Test) outcomes in Souvenaid ™ medication in contrast to the placebo group [67]. This scenario of Post-hoc tests shows reverse NPI, CGI-S, and RMET outcomes in patients who replaced Souvenaid ™ with a placebo. Remarkable boost in behavioral impairment and social cognition with proliferate ToM (Theory of Mind) skills in bv-FTD patients observed after the treatment of Souvenaid ™. The study proposed that termination of Souvenaid ™ results in elevated behavioral slippage with reduced ToM skills, proving the positive impact of Souvenaid ™ medication in the bv-FTD community [66,68].

3.2.1. Mechanism of action of souvenaid

Due to the failure of nerve cells in the peripheral nervous system bv-FTD, Alzheimer's, like many neurodegenerative disorders, prevails. Difficulties in synapses should be a promising target of neutraceuticals in neurodegenerative diseases [68]. Synapse permits a nerve cell to pass signals (electrical or chemical) to another nerve cell in the nervous system through which the brain receives sensory code assimilating information, thus useful for decision-making and supervising motor activity [69]. The presynaptic part is found on a neurite in numerous synapses, and the postsynaptic part is on a dendrite [70]. The pre-and post-synaptic neuron clings jointly by synaptic adhesion molecules (SAMs), which support synapses' generation, function, and stabilization [71]. Various micronutrients, including vitamin B complex, vitamin C, E, selenium as antioxidants, polyunsaturated fatty acids, and phospholipids, activate neural plasticity, restoring synapses stabilization, and thus alleviating neurodegenerative processes [72,73]. Lack of these nutrients causes synaptic dysfunction, leading to many neurodegenerative complications, mostly dementia-like bv-FTD in Alzheimer's patients. Choline, DHA (docosahexaenoic acid) EPA (eicosapentaenoic acid), and uridine with vitamins and antioxidants jointly expedite the formation of the synaptic membrane. Stabilization of synapses induces transmission of neurotransmitter that modulates receptor to boost pre- and post-synaptic neuron arise receptor signaling mechanism thus develop memory function [74]. Souvenaid™ comprise

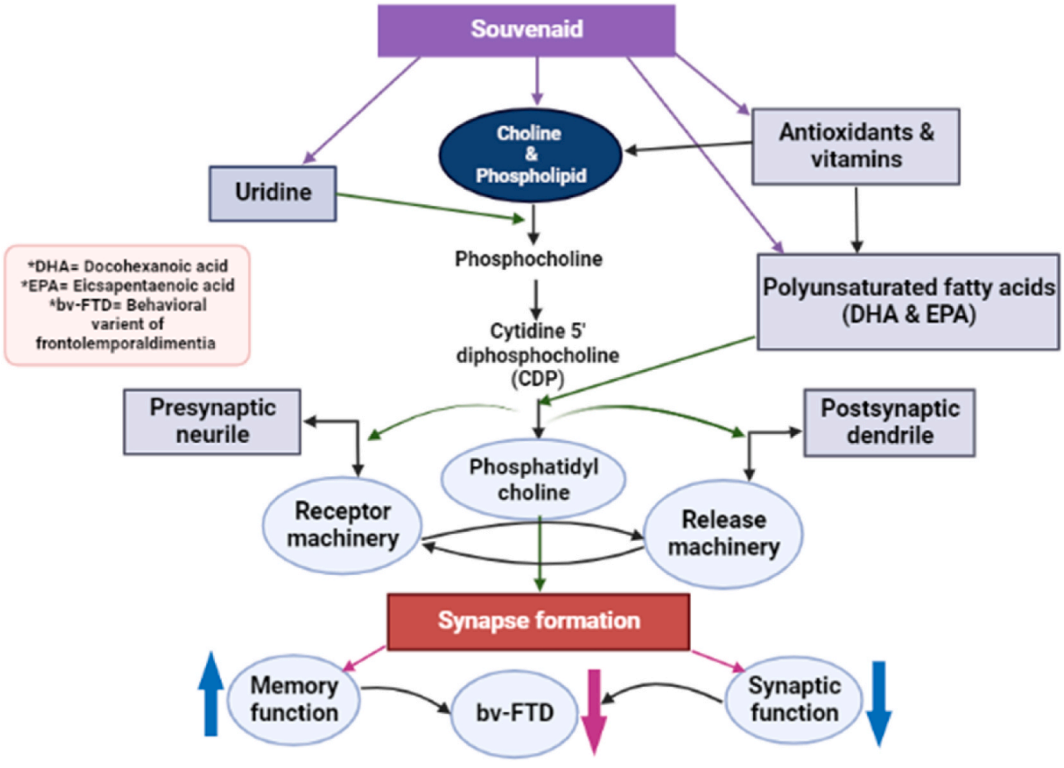

Fig. 2. The neuroprotective properties of souvenaid are controlled by a number of signaling mechanisms and receptors.

above ingredients which acts on the target region on synaptic dysfunction to restoring synaptic consequences with rectifying memory function, behavioral variant by frontotemporal dementia (bv-FTD) in Alzheimer's disease. (Fig. 2).

3.3. BDW

Ba Wei Di Huang Wan or BDW (hachimi-jio-gan in Japanese) is a classical herbal Chinese therapeutics also known as Rehmannia eight principles prepared from Liu wei Di huang tang strategy that manipulates to boost cognitive task and memory ruination in patients who have dementia [75]. This medicinal course is composed of eight herbs containing Radix Rehmanniae praeparata (shu di huang), Fructus Corni (shan zhu yu), Rhizoma Dioscoreae (shan yao), Poria (fu ling), Cortex Moutan (mu dan pi), Rhizoma Alismatis (ze xie), Radix Aconiti Lateralis preparator (pao fu zi) and Cortex Cinnamomi (rou gui) [76]. Rehmannia eight concepts support mitigating Hypertension, Diabetes mellitus, Asthma, Renal impairment, disorders of the immune system, cold agitation, cognitive activity, dementia, and so on [75]. BDW accumulated central cholinergic system to persuade scopolamine-induced memory impairment in rat model also archived [77,78]. A promising outcome of BDW is the depletion of cerebrovascular refusal, thus raising cerebral blood flow [79].

In accordance with the double-blind, randomized, placebo-controlled trial, 33 patients with mild to severe dementia was incorporated with hypertension, diabetes mellitus, and hypercholesterolemia sign up from Akiba Hospital, Japan of May 2002 to September 2002. Following Tukey-Kramer post hoc test that reveals elevated MMSE (Mini-Mental State Examination) score and the Barthel Index in BDW therapy contrast to the placebo category [43]. Depleted PI (The pulsatility index) appears in the BDW section and neither in the placebo. After the withdrawal of BDW therapeutics contrary layout with poor MMSE score and the Barthel Index with elevated PI, this study recommended BDW stimulate cognitive function rather than placebo in patients with dementia [43,80].

3.3.1. Mechanism of action of BDW

Acetylcholine, a neurotransmitter found in all motor neurons throughout transmission, conciliated to cholinergic synapses, thus functional for motivation, attention, learning, cognition and memory [80]. A reaction assembled by choline acetyltransferase in nerve terminals is acetylcholine formulated from acetyl coenzyme A and choline [81]. Dementia or cognitive decline is associated with an inadequate cholinergic system. According to the cholinergic hypothesis alleviated, acetylcholine fusion in synaptic cleft originates Alzheimer's disease (AD) [82]. Consequently, the modern remedial blueprint of AD focuses on inhibiting acetylcholinesterase act. BDW amplifies the action of choline acetyltransferase, thus mediates the absorption of acetylcholine in the frontal cortex and diminishes acetylcholinesterase activity like donepezil [83]. BDW can obstruct the disintegration of acetylcholine; therefore,

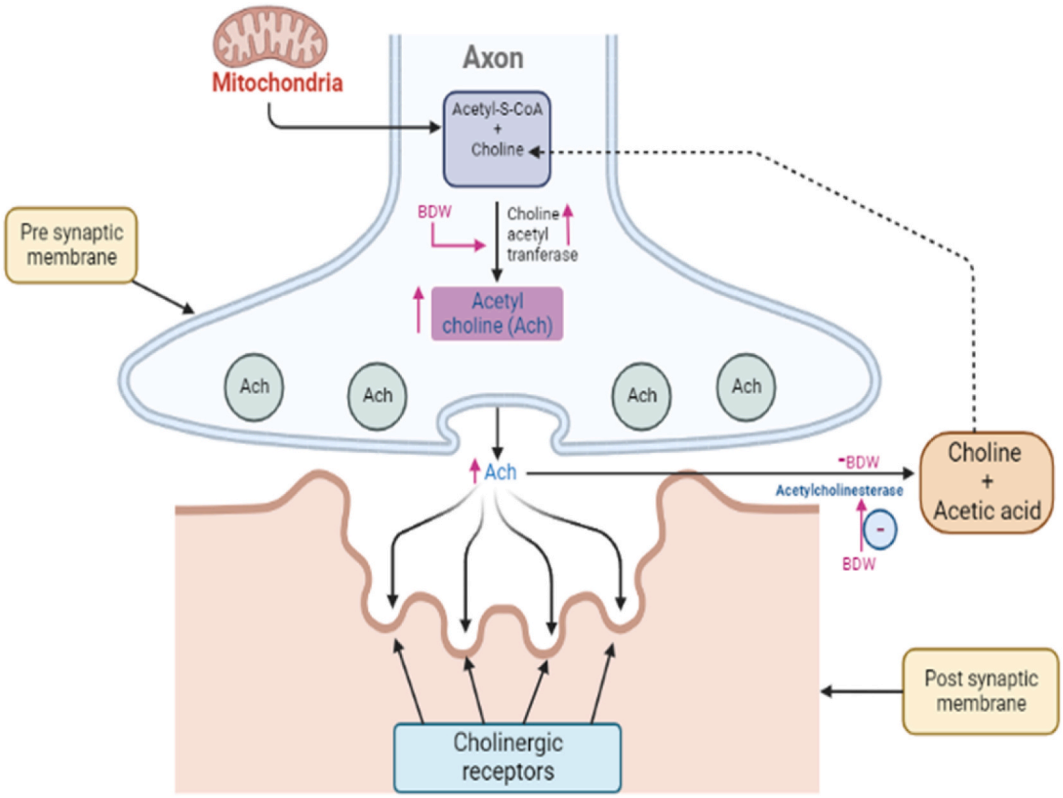

Fig. 3. The possible neuroprotective mechanism of BDW is controlled by achetylcholine receptors.

accumulations of acetylcholine in the synapse efficiently transmit chemical signals to other cells, consequently recovering cognitive decline or dementia. Therefore cognitive breakthrough with BDW is notable than cholinesterase inhibitors. (Fig. 3).

3.4. Hupergene

An active acetylcholinesterase inhibitor (AChEI), Huperzine A (Hup A) that was extracted from classical chinese medicine, Qian Ceng Ta discovered in 1980 by Chinese scientists [84]. It belongs to club moss Huperzia serrata; authorized as an anti-Alzheimer's remedy in China in 1996, and accessible nutraceuticals in the US [85]. Contrary to galantamine, donepezil, tacrine, and so on, Hup A show prolonged action duration, thus enhanced blood-brain barrier dispersion with less adverse reactions exhibited along animal and human safety appraisal [86]. Hup A occasionally boosts energy, reduces depression, assists in the conduct of myasthenia gravis, and is supposed to improve learning and memory to avoid cognitive decline [87]. Nausea, diarrhea, vomiting, constipation, blurred vision, restlessness, loss of appetite, contraction of muscle fibers, uncontrolled urination, high blood pressure, dizziness, sleeplessness, and retards heart rate are possible leftover of Hup A [88].

In accordance with a randomized, double-blind, placebo-controlled phase II assay, 210 patients were signed up owing to age, diagnosed with feasible AD, and any sensible alternative use of narcotic analgesics. According to Alzheimer's disease Assessment Scale–cognitive subscale (ADAS-Cog) score, 400g BID of Hup A is more effective in alleviating memory and learning impairment and improving cognitive functions compared to placebo & 200g BID supplementation. The outcome of another statistical survey, the Activities of Daily Living scale (ADL), and Neuropsychiatric Inventory (NPI) infrequently notable for both doses [89].

3.4.1. Mechanism of action of Hupergene

Cognition, learning, and memory performance are mediated through cholinergic neurotransmission of Acetylcholine [89]. Acetylcholinesterase (AchE) cleaves acetylcholine (Ach) in the synaptic cleft, thus diminishing Ach's linkage to cholinergic receptors in neurodegenerative disorders. As a result, chemical signals from synapses to other cells collapse. Having good brain dispersion quality, Hup A blockade AchE; therefore, the concentration of Ach is elevated to clinch receptors, stabilizing neurotransmission & alleviate neurotoxicity [90].This overwhelming inhibitor has also non-cholinergic characteristics in the therapy of Vascular Dementia (VD) & AD by the cessation of Aβ access into mitochondria. Although ameliorated mitochondrial malfunction observed due to the ROS quelling that boost up mitochondrial cohesion, resolving oxidative stress. Hup A is also considered to cerebral NMDA receptor antagonist that obstructs cytoxicity. Substantially Hup A supposed to be a potent antidote with a definite cognitive effect in patients with mild to moderate AD which are the ethical objectives of late dementia [91]. (Fig. 4).

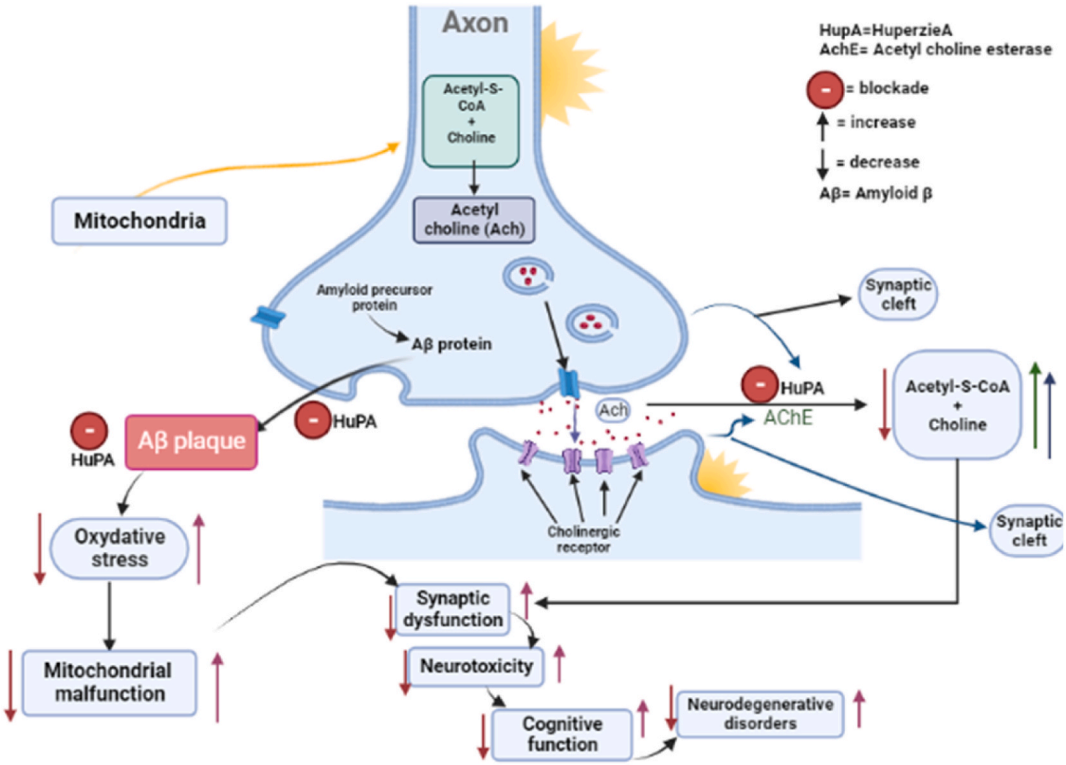

Fig. 4. The potential neuroprotective action of huperzine in the fight against dementia.

3.5. Bacopa monnieri

In Ayuvedia (conventional Indian medicine) *Bacopa monnieri* (BM) also known as 'Brahmi' a primitive herb thus found in India, Australia, Europe, Africa, Asia, and America [92] practiced for memory retention, cognitive boost up, anxiety, stimulant to fight stress alike dementia and Alzheimer's Disease (AD) [93]. Synthetic part of BM is comprised of brahmine, herpestine and nicotine, saponin monierin, hersaponin, and bacoside that are familiar to be healthy in humans [94,95]. Bacosides and bacosides found in BM may hoist cognitive function, learning, and memory confinement, suppress inflammation in the brain also work on oxidative stress reservations [93]. Nausea, stomach cramps, and flu-like symptoms are some of the unpleasant upshots of this herbal formula [95].

As per randomized, double-blind, placebo-controlled appraisal, 54 (Fifty-four) participants were enrolled from the community to a clinic in Portland based on age, and deficient clinical signs of dementia. Applicants who take BM extract possess upgraded Auditory Verbal Learning Test (AVLT) using Blessed Orientation Memory Concentration test (BOMC) thus conducted by analysis of variance (ANOVA) compared to placebo. The remarkable outcome was also found with BM association in Stroop Task, Center for Epidemiologic Studies Depression scale (CESD-10) scores using the same analysis likewise placebo. That is why applicants with BM consumption ameliorate memory processes with developed cognitive function thus mitigating difficulties of AD as well as dementia [96].

3.5.1. Mechanism of action of Bacopa monnieri

This ayurvedic formula revealed bacosides/bacopasides ease the deposition of amyloid plaque on synaptic cleft that trivializes oxidative stress in the case of the animal model assay acknowledged with memory reinforcement, cognitive promoter, and diminish mitochondrial malfunction [97]. Different investigation reveals the cholinergic effects of BM thus manifesting the disintegration of acetylcholine depleted in the synaptic cleft by the suppression of acetylcholine esterase (AchE). Therefore this neurotransmitter becomes accomplished to proceed with receptors for the propagation of signal transduction on other cells to alleviate neurotoxicity that is seen in AD foremost dementia [98]. In rat model observations, BM also conveys its execution on 5HT receptor activation thus recommending memory improvement with significant cognitive properties on AD thereby leading to dementia [99]. (Fig. 5).

3.6. Omega-3

Polyunsaturated fatty acids (PUFAs); Omega-3 (ω-3) fatty acids are one of the prime integrants of human physiology & nutrition, thus specified by a double bond aside from the closing methyl group.

α -linolenic acid (ALA), essential ω-3-fatty acids acquired from that also used to form another two ω-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [100]. However, because our bodies do not efficiently produce some ω-3 fatty acids from marine sources, it is necessary to obtain adequate amounts through fish and fish oil products. An organosulfur fusion α-lipoic acid, also well known as lipoic acid (LA) acts as an antioxidant and is thus consumed from the gastrointestinal tract swiftly [101]. Foods such as red meat, heart, kidneys, liver, rice bran, carrots, beets, spinach and broccoli are high provenience of lipoic acid (LA) [102].

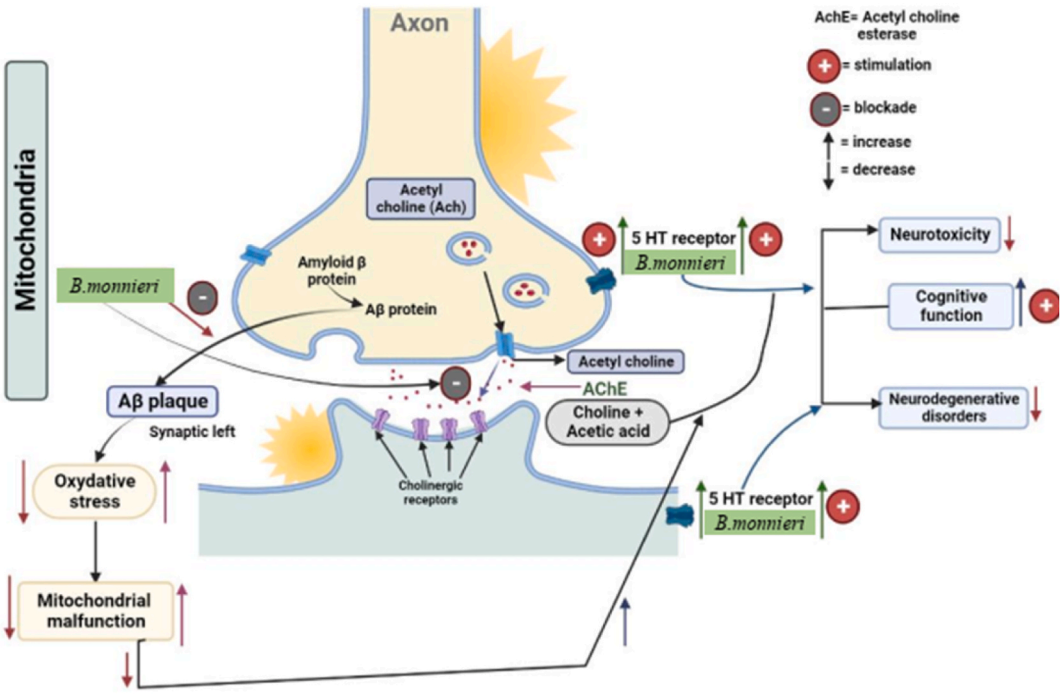

Fig. 5. The potentiality of *Bacopa monnieri's* neuroprotective properties in the battle against dementia.

Fish-derived ω-3 fatty acids are generally consumed to EPA and DHA in the liver and marginal in the brain [103]. Studies have shown that EPA and DHA are essential for proper fetal development and may affect many aspects of cardiovascular function, including inflammation, peripheral artery disease, major coronary events, and anticoagulation; they also have promising results in the management of cognitive function in those with very mild Alzheimer's disease. Lipoic acid thus salvages supplemental antioxidants like vitamin C, E, and glutathione with anti-inflammatory acreage and notably conveys refinement in learning and memory reservations. Nausea, vomiting, headache, stomach upset, flu, dizziness etc. were proclaimed upshot for ω-3 fatty acids and LA [104].

In obedience to randomized placebo-controlled pilot scrutiny, 39 subjects were enrolled based on age, dementia with probable AD, and any alternative sensible neurological along with psychiatric co-morbidities in Alzheimer's Disease (AD) those were endorsed by Oregon Health & Science University's Institutional Review Board (Portland, USA [105]. This pilot study explored the addition of ω-3 solely and ω-3 + LA consequences contrary to placebo on peripheral F2-isoprostane levels as the succession of Ad fused with oxidative stress. Beyond linear regression analysis has been an analogy on F2-isoprostane levels among groups specified in this dissertation. As per Alzheimer Disease Assessment Scale cognitive subscale (ADAS-cog) and Activities of Daily Living/Instrumental Activities of Daily Living (ADL/IADL), ω-3 +LA and ω-3 haven't notable variations in the placebo group. In contrast to placebo, reduced ω-3+LA arose, applying Mini-Mental State Examination (MMSE) and IADL thus revealed collaboration of ω-3+LA dictated sluggish cognitive and functional wane in AD randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease [105,106].

3.6.1. *Mechanism of action of Omega-3*

Owing to the accumulation of amyloid β (Aβ1-42) protein in synapse; form neurotoxic oligomers that give rise to neuroinflammation, oxidative damage, and synaptic dysfunction [105,107], thus stimulus neurodegeneration and progression of AD. DHA and EPA with antioxidants jointly provide structural and chemical resources requisite to synaptic functioning [106]. Stabilization of synapses accelerates the transmission of neurotransmitters, notably conveys refinement in learning and memory reservations [108–111]. Due to the elevation of F2-isoprostane that enhances lipid peroxidation can cause oxidative damage in AD where DHA is

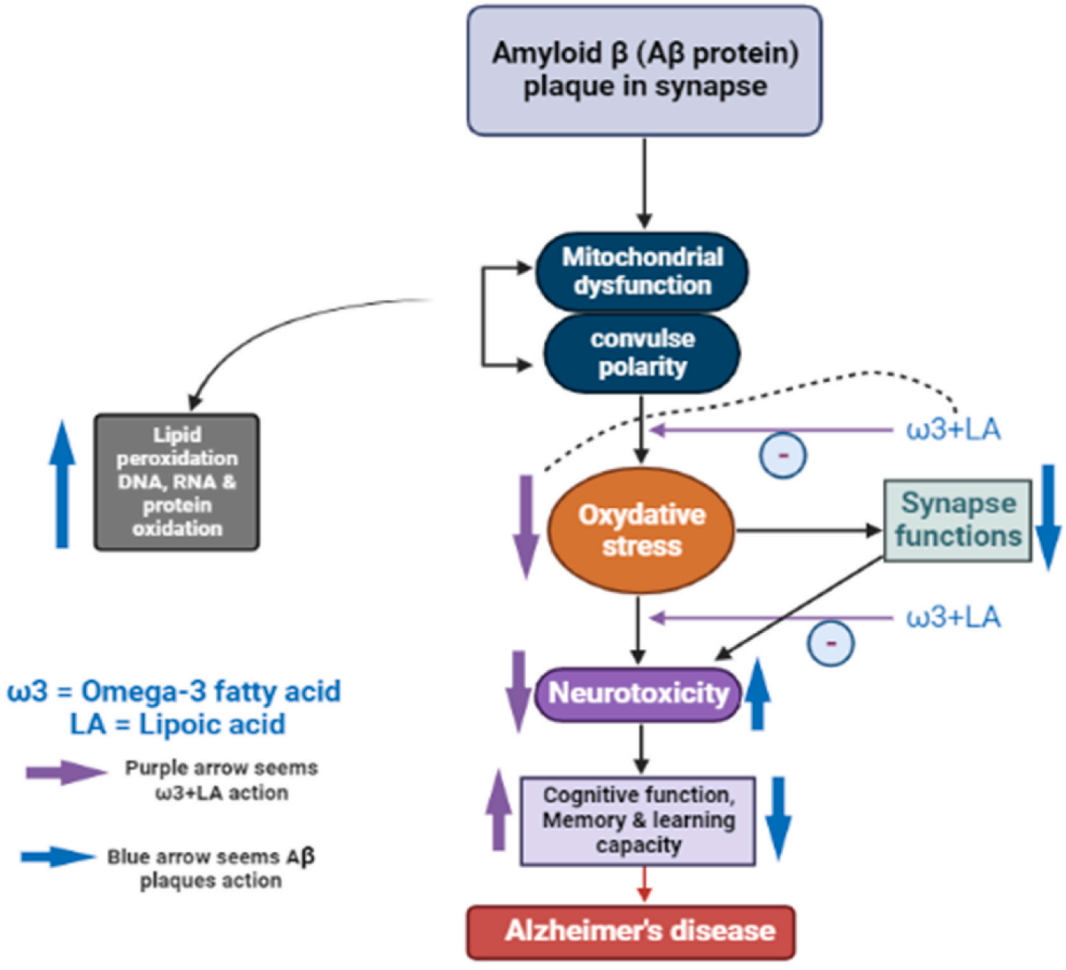

Fig. 6. The potential mechanism of Omega-3 (ω-3) fatty acids to protect the brain against dementia.

solely inadequate to alleviate the toxicity in brain thus required antioxidant interventions like LA [45,46,112]. Aβ cluster in synapses promotes oxidative damage with extortionate mitochondrial defects in CSF where peroxidizable DHA is concentrated. So brain penetrable LA, a mitochondrial coenzyme with antioxidant actions like vitamin C, E, and glutathione, was proposed as a combined intervention with DHA for mitochondrial shielding. By dint of its influential antioxidant capacity of LA improves cognitive function, learning and memory reservations, preserves, improves cerebral damage, and alleviating peripheral oxidative damage and neurodegeneration in the hippocampal region. Therefore, LA can be a curative candidate fusion with DHA for the remedy of Alzhemier's disease by fortifying neurons from β-amyloid neurotoxicity and suppressing the evolution of β-amyloid fibrils [68,80,97]. (Fig. 6).

3.7. Palmitoylethanolamide (PEA)

An endocannabinoid (eCB) like bioactive lipid mediator called palmitoylethanolamide (PEA) is a member of the N-acyl-ethanolamine (NAE) fatty acid amide family [113,114]. It exists in all tissues, including the brain, and has a localized action. It develops within the lipid bilayer [115,116]. Soy lecithin, milk, alfalfa, egg yolk, peanuts and peanuts are also excellent sources of PEA.

3.7.1. Mechanism of action for palmitoylethanolamide

According to recent observation, PEA appears to be a molecule that functions as a pro-homeostatic protective response to cellular damage and is typically up-regulated in disease circumstances [115,117]. It has analgesic, anticonvulsant, antibacterial, antipyretic, antiepileptic, immunomodulatory, and neuroprotective effects [118,119]. Because the endocannabinoid structure stimulates nerve end extension, supervision, neuron growth, and its functions, PEA's neurotrophic consequence certainly help out people's cognitive, behavioral, and mental wellness [120–122].

Seventeen individuals suspected of having FTD, encompassing both the behavioral variant (bvFTD) and primary progressive aphasia (PPA), participated in a study, conducted in accordance with the latest clinical diagnostic criteria [123]. This study report that, PEA-LUT modulates cortical oscillatory activity and GABA(B) ergic transmission, which may lessen behavioral abnormalities and improve frontal lobe functions in patients with frontotemporal dementia [123].

Moreover, a recent inquiry has unveiled a positive outcome associated with PEA in maintaining muscle function among individuals diagnosed with amyotrophic lateral sclerosis (ALS), a situation exhibit both pathophysiological and clinical traits akin to FTD [124]. Furthermore, a newfound role of PEA, involving the augmentation of GABA neurotransmission by regulating the production of the endocannabinoid 2-AG, has recently emerged into our understanding [125]. GABA transmission is disrupted in FTD, as demonstrated by the loss of GABAergic bound calbindin-D28k local-circuit nonpyramidal neurons in upper cortical layers [126]. Moreover, GABAergic inhibitory neurons play a pivotal role in regulating cortical oscillatory rhythms [127], particularly the construction of gamma oscillations, which hold investigational to be reduced in the frontal lobes of individuals with FTD. Given these considerations, PEA emerges as a promising candidate for potential use as an adjunctive treatment in neurodegenerative conditions like FTD, as it has the capacity to modulate both neuroinflammation and GABAergic neurotransmission. (Fig. 7).

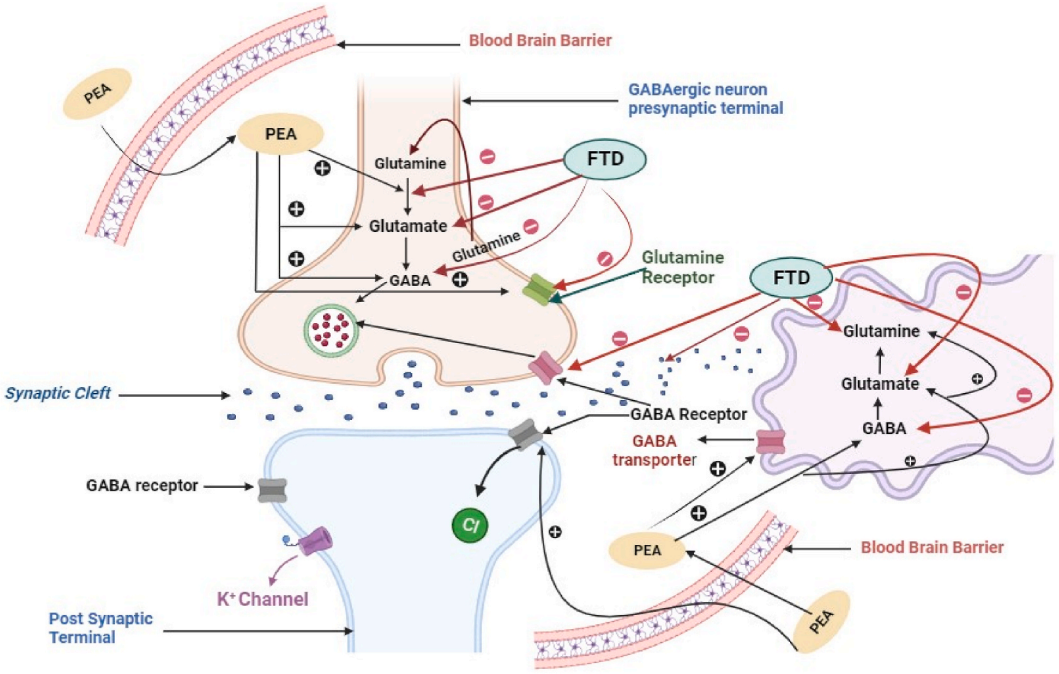

Fig. 7. Beneficial mechanism of palmitoylethanolamide in the treatment of dementia.

3.8. Tramiprosate

Homotaurine, also known as 3-amino-1-propanesulfonic acid (3-APS), is a naturally occurring compound that has been studied for its potential therapeutic effects, particularly in the context of neurodegenerative diseases [128]. Research on homotaurine's effects on dementia is still in its early stages, and findings are not yet conclusive. However, there are several possible mechanisms through which homotaurine might exert its effects on dementia like modulation of neurotransmitters,anti-inflammatory effect,Beta-Amyloid reduction, and enhancement of cognition.

3.8.1. Mechanism of action for tramiprosate

Tramiprosate substances can generate and increase fibrillogenesis and Aβ aggregation, both of which have damaging effects on neurons. On the other hand, homotaurine has been demonstrated to be able to inhibit Aβ fibrillogenesis, hence lessening the detrimental effects on neurons.

Furthermore, initial human trials revealed that homotaurine led to a dose-dependent reduction in cerebrospinal levels of A1-42 in individuals with Alzheimer's disease [129], along with a decline in brain atrophy [130] and positive cognitive outcomes. These potential neuroprotective benefits might aid patients with Mild Cognitive Impairment (MCI) in staving off the decline in their Cognitive faculties [131].

Modifications in the amyloid precursor protein (APP) and its enzymatic processing believed to play a significant role in the development of Alzheimer's disease. An imbalance between the amyloidogenic pathway, which involves beta and gamma-secretases, and the non-amyloidogenic pathway, involving alpha-secretase, may contribute to the excessive generation of insoluble amyloid peptides. As these peptides gradually accumulate and their clearance diminishes, they promote the aggregation of Aβ peptides into toxic oligomers and fibrils, which harm neurons. Consequently, this leads to substantial alterations in synaptic plasticity mechanisms, such as impaired long-term potentiation (LTP), extended long-term depression (LTD), reductions in spine size and density, and ultimate neuronal degeneration [132]. Homotaurine, also recognized as tramiprosate, is a glycosaminoglycan (GAG) compound known for its capacity [128] to stimulate and enhance fibrillogenesis and Aβ aggregation, leading to neurotoxic consequences for neurons. In opposition, research has demonstrated that homotaurine can impede Aβ fibrillogenesis, thus reducing the harmful impacts on neurons. Indeed, homotaurine treatment suppressed the formation of Aβ fibrils, mitigated brain pathology, and facilitated the development of physiological long-term potentiation (LTP) [133] development in experimental animals. These characteristics suggest that homotaurine may possess neuroprotective [134] attributes that could prove effective in early-stage Alzheimer's disease treatment strategies. Additionally, owing to its affinity for GABAA receptors (GABAARs), homotaurine directly influences neuronal function as an enhancer of excitatory neurotransmission, besides its anti-amyloid properties. Fig. 8 summarises the therapeutic efficacy of tramiprosate against dementia.

4. Conclusion and future perspective

Even though the precise molecular pathways underlying dementia pathogenesis are yet unknown, the mortality and complication rates related to this dementia are still rising globally. Therefore, it urgently necessitates developing an alternate treatment with minimal side effects, especially from natural resources. It encourages researchers to develop new medicines from natural products, i.e., phytochemical-based therapeutic, which could provide significant clinical benefit in managing dementia patients. Phytochemicals from medicinal plants remain crucial for developing new pharmacological drugs against dementia. So therapeutics advantage of

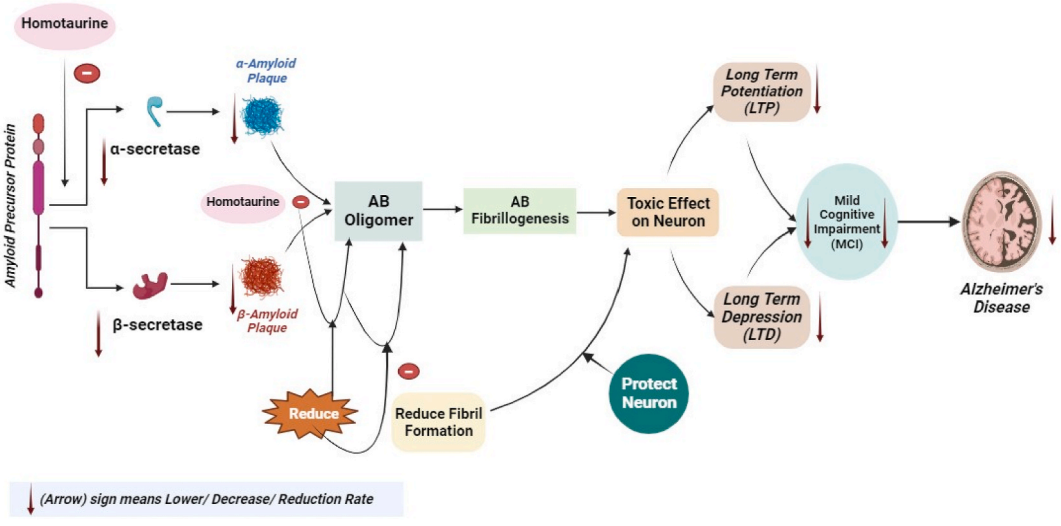

Fig. 8. Therapeutic efficacy of tramiprosate against dementia.

clinically proven compounds from the natural plant in treating dementia cannot be denied. According to clinical studies, it can be anticipated that natural compounds mediate their anti-dementia efficacy through modulating multiple pathways. Altogether, due to their therapeutic benefits, this review contends that phytochemicals could serve as an additional and alternative anti-dementia agents for treating dementia patients. We recommend consuming these natural products as a dietary supplement until final drugs are available in the pharma market. Although clinically proven compounds have worked as therapeutic agents in dementia, some limitations should be solved. Besides trial information, there was a lack of overall toxicities. So authors suggest identifying all compounds and testing some *in silico* approaches between phytochemicals and several dementia targets with more preclinical trials.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Data will be made available on request.

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Farzana Ansari: Writing – original draft, Formal analysis. **Md Sohel:** Writing – original draft, Software. **Md Mahfujul Haque Haidary:** Writing – original draft. **Md Saqline Mostaq:** Writing – original draft, Data curation. **Shamima Akter:** Writing – original draft. **Asrafun Nahar:** Writing – original draft. **Fatematuz Zohora Labony:** Writing – original draft, Conceptualization. **Arman Ahmed:** Validation, Resources, Investigation, Data curation. **Mohammed Shamim Hasan:** Validation, Resources, Data curation. **Mohammad Hasem Babu:** Resources, Formal analysis. **Mohammad Nurul Amin:** Writing – review & editing, Validation, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

BPSD	Behavioral and psychological symptoms of dementia
FTD	Frontotemporal dementia
SAMs	Synaptic adhesion molecules
DHA	docosahexaenoic acid
EPA	Eicosapentaenoic acid
MMSE	Mini-Mental State Examination
AD	Alzheimer's disease
AChEI	Acetylcholinesterase inhibitor
Hup A	Huperzine A
ADAS-Cog	Alzheimer's disease Assessment Scale–cognitive subscale
VD	Vascular Dementia
BM	Bacopa monnieri
AVLT	Auditory Verbal Learning Test
BOMC	Blessed Orientation Memory Concentration test
PUFAs	Polyunsaturated fatty acids

LA Lipoic acid
bv-FTD Behavioral variant of frontotemporal dementia

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