


REVIEW

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# Chinese nutraceuticals and physical activity; their role in neurodegenerative tauopathies

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## Abstract

The onset of neurodegenerative disease has not only been a major cause of scientific worry, but of economic burden to the health system. This condition has been further attributed to mis-stability, deletion or mutation of tau protein, causing the onset of Corticobasal degeneration, Pick's diseases, Progressive supranuclear palsy, Argyrophilic grains disease, Alzheimer's diseases etc. as scientifically renowned. This is mainly related to dysregulation of translational machinery, upregulation of proinflammatory cytokines and inhibition of several essential cascades such as ERK signaling cascade, GSK3 $\beta$ , CREB, and PKA/PKB (Akt) signaling cascades that enhances protein processing, normal protein folding, cognitive function, and microtubule associated tau stability. Administration of some nutrients and/or bioactive compounds has a high tendency to impede tau mediated inflammation at neuronal level. Furthermore, prevention and neutralization of protein misfolding through modulation of microtubule tau stability and prevention of protein misfolding is by virtue few of the numerous beneficial effects of physical activity. Of utmost important in this study is the exploration of promising bioactivities of nutraceuticals found in china and the ameliorating potential of physical activity on tauopathies, while highlighting animal and in vitro studies that have been investigated for comprehensive understanding of its potential and an insight into the effects on human highly probable to tau mediated neurodegeneration.

**Keywords:** Tau, Neurodegenerative diseases, Nutraceutical, Physical activity, Bioactive compounds

## Introduction

At present, neurodegenerative diseases remain a great source of concern to public health, health practitioners and scientists at large, poisoning itself as a major economical headache to health care systems. Critical to the stability of microtubule it is a contaminant identified in 1975 by Weingarten and colleagues called TAU whose aggregates is a pathological indicator of tauopathies [1]. More so, tau has an overall incidence rate of 1.1 cases per 100,000 persons-year and a presumed onset of symptoms at 60 years and above. Psp recorded the highest incidence of tauopathy at a rate of [1.1 in men vs 0–6 in women],

an inverse proportion to incidence recorded in CBS (0.1 in men and 0.3 women) [2]. Conventional tauopathies, includes Alzheimer's disease (AD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Pick's disease (PiD), argyrophilic grain disease (AGD), Huntington's disease (HD), and frontotemporal dementia with Parkinsonism-17 (FTDP-17), all of which are neuro-deteriorating diseases marked by the abnormal deposition of microtubule stability protein tau [3]. In 1975, the tau protein that has a prominent role in the assembly and stabilization of microtubules was first expressed in neurons within the central nervous system [4]. The indispensable role of tau in the transport of axons and neurite eruption cannot be overlooked [5]. Tauopathies such as Neurofibrillary tangles and formation of paired helical tangles (NFTs) can be traced to the withdrawal of tau from microtubules [6, 7], with tau mutations, mis splicing

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and abnormal post translational modifications being the risk factors [8, 9]. Although, tau induced neurodegeneration and mechanisms that leads to the upregulation of tau aggregation are yet to be clarified. AD is characterized by amyloid plaques made up of  $\beta$ -amyloid peptide and neurofibrillary tangles, comprising of hyperphosphorylated Microtubule Associated Protein Tau (MAPT or Tau), leading to loss of neurons and synapses as seen in other tauopathies. [10, 11]. Understanding the roles of these A $\beta$  and tau pathologies is yet to be achieved after decades of research. However, difficulties in restating neurodegeneration via in vitro and in vivo animal models has led to a steady progress. Modulation of oxidative stress and inhibition of neuroinflammation to impede tau induced inflammation at the neuronal level and curb cognitive impairment should be considered towards the mitigation of in vivo oxidative process and aversion of neuronal damage. Thus, administration of nutrients and/or bioactive in combination with persistent exercise might aid the regulation of microtubule tau activity. Furthermore, neurobiological mechanisms (hormones, neurotropic factor levels, neurotransmitter secretion) can be triggered by exercise [12, 13], upregulating growth factors required for brain tissue development [14–16], regulating apoptosis and instigating neurogenesis in specific parts of the brain [17]. This study outlays the role of tau in brain diseases, the reassuring capacity of nutraceuticals found in china and exercise on tau mediated neurodegeneration, with the aim of creating the framework to further elucidate the interaction between these three facets and their effect on neurodegenerative diseases.

### Role of tau in brain diseases

Microtubule associated protein tau encoded by tau gene (MAPT) is an intricate highly domain proteinous macromolecule associated with the axons of neurons enhancing stability of living species [4]. It is a multi-terminal protein, consisting of a highly acidic N-terminal and the neutral C-terminal connected by a central binding basic proline region [18]. Under pathogenic conditions, the multi domain tau builds up in the soma and dendrites of neurons. Strictly regulated by alternative splicing, tau exhibits six isoforms, distinguished by 2 N-terminal repeats (0 N, 1 N, or 2 N) and 3–4 microtubules binding repeats at the C-terminus (3R or 4R) [19]. Although tau plays important roles in the nervous system, uncoupling of microtubule from tau can be severe most significantly a leading cause of tauopathies [6, 7]. To maintain this relationship, tau protein is modulated by post-translational modifications and its isoforms by splicing is thus ensured. The action is thus possible by the down-regulation of 3' untranslated region of target mRNAs by microRNA (miRNA) [20]. Thus, inhibits the formation

of truncated proteins and enhances microtubule-tau stability. With tau having a basic region which is responsible for its non-covalent interactions with the phosphate backbone of RNA [21]. Recent study further described the association of tau with RNA binding proteins U1 [22]. U1 are minute spliceosome nucleoproteins that binds to RNA highly essential in the regulation of RNA metabolism. However, the onset of tauopathies indicates manifestations such as dysregulation and aggregation of U1 ribonucleoprotein [23, 24], aggregation and improper hyper phosphorylation of insoluble tau [25], thereby leading to the detachment of tau from microtubules. Recent in vivo models further affirm that neurodegeneration and splicing defects occurs in U1-ribonucleoprotein tauopathies linked disease [26, 27]. Additionally, at the indication of translational stress, the cytoplasm assembles RNA and proteins to counteract these effects, thus leading to the formation of stress granules [27]. The activation of stress granules impairs proper translational machinery and cleaves RNA binding proteins which in response prevents the synthesis of truncated proteins. This action is possible due to the interaction of tau with proteins responsible for the formation of stress-granules. However, manifestation of brain diseases is characterized by the inactivation of this cascade [28, 29]. Furthermore, several studies have established the association of tau with ribosomes in regulating the translation machinery. This action is essential in maintaining the dendrites and synaptic plasticity of neurons [30–33]. Translational dysregulation has been associated with neurodegenerative diseases involving several complex molecular cascades that converges on the ribosome [34, 35]. Neurotic manifestation of tau-mediated neurodegeneration includes the onset of neurofibrillary tangles (NFT's) as a result of aggregation of insoluble tau, although soluble oligomeric forms of tau have also been developed in neuronal dysfunction and physiological decay [36, 37]. However, the identification of human brain suffering from PSP, AD shows the assembly of oligomeric protein tau and similar brain function decline was observed in P301L mutant mice (rTg4510) [38–40] etc. Mice of familial FLTD-tau, results in the expression of frontotemporal dementia as observed in the articulation of human tau [37, 41]. The reduction in spine density, deterioration of permanent memory and changes in spine morphology was observed at the onset of AD during a mice study [42]. Similarly, the initiation of action potential by the specialized action initial segment and the regulation of neuronal excitability creating a barrier for the axonal compartment was inhibited in acetyl-mimic tau mice, resulting in the destabilization of AIS proteins [43]. Finally, post translational modifications of tau ensures proper stability of tau and microtubules, preventing the inactivation of

stress granules. This extensive modification occurs via the action of several enzymes including kinase, acetylase, ubiquitin-degrading enzyme, methylase, glycosylase and protease enzyme [44]. However, aberrant post-translational modifications are critical in triggering synapse dysfunction and deterioration (Fig. 1).

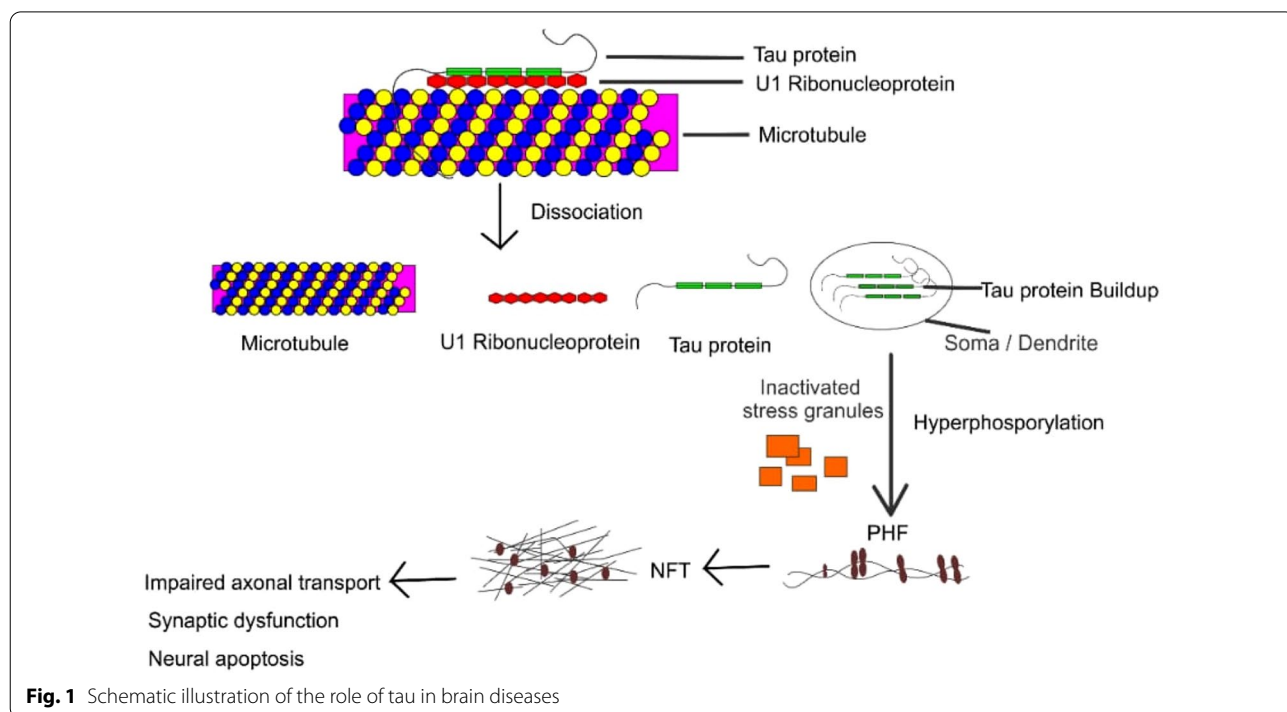
**Neurodegenerative diseases associated to tau**

Neurodegenerative disorder can be defined as the assembly of neurological issues which has impact on a subsection of neurons from a specific part of the focal sensory system and consistently induce their disintegration [45]. The positioning of harmful protein totals, indicate neurodegenerative disorder due to the misfolding and statement in the intra or extra neuronal locale [46]. Neurodegenerative Tauopathies integrate the compulsive state at which the microtubule stability protein tau, undergoes misfolding and gets reserved to shape the neurofibrillary tangles and tau fibers [7, 46]. Dysregulation of translational machinery could lead to a concomitant dissociation of tau protein and microtubules [34, 35]. Neurodegenerative diseases associated with tau (tauopathies) are classified into two, based on the pathological dispersal and the difference in biochemistry [47]. These basics classification namely primary and secondary tauopathies shares similar disease-relevant processes. Indicated by atrophy of the frontal cortex and temporal lobes, primary tauopathies are regularly in mix with decline subcortical mind zones, a member of the frontotemporal lobar

degeneration (FTLD) diseases [48]. Existing isoforms of primary tauopathies includes 4R (AGD, PSP, CD, globular glial tauopathy), 3R (Picks disease) or 3R & 4R (Neurofibrillary tangle diseases) [49–51]. Additionally, the neurodegenerative AD is classified as a secondary 3R/4R isoform tauopathies [52].

**Progressive supranuclear palsy**

PSP is a 4R isoform affiliated by tufted astrocytes, globose neurofibrillary tangles in grey matter and coiled bodies in oligodendrocytes in white matter [53]. It is an intricate clinicopathologic disease mostly affirmed by post mortem activities [54], with the mean age of onset is the mid-sixties and prevalence is estimated at 6 per 100,000 persons [1, 55, 56]. Affirmatively, the onset of ventricular supranuclear palsy and postural instability an indicator of PSP, while the onset of either signifies a clinically possible PSP [57]. Most commonly, PSP occurs with Richardson syndrome (PSP-RS), a nervous targeting disease with high probability of occurrence during autopsy [57–59]. Several existing occurrences of PSP includes, (PSP-PLS) [60, 61], (PSP-CBD) [62], PSP with progressive gait freezing [63, 64] and (PSP-C) [65, 66]. Environmental studies in France revealed that high rate of PSP emerges during the chronic exposure to heavy metals [67, 68]. Studies further revealed that extreme intake of electron transport chain complex inhibitor found in pawpaw [69, 70]. The occurrence of PSP is about 5–6 times increased in aberration or deletion of MAPT gene which is the



**Fig. 1** Schematic illustration of the role of tau in brain diseases

major cause of PSP [71–73]. Several other indicators of PSP include increased oxidative stress, superior frontal cortex activation of lipid peroxidation markers, midbrain and subthalamic activation of lipid peroxidation markers, resulting in the activation of the inflammatory cytokines IL1 $\beta$  is observed in PSP [74]. To contain the damaging effects of PSP, the body defense system upregulates the synthesis and action of essential antioxidants majorly the superoxide dismutase, glutathione [75, 76]. Hyperphosphorylation remains a significant typical element of protein tau in PSP. This is due to the significant rise in reactive oxygen species synthesis, modification of kinase-based signaling cascades via enactment or outflow of the cascade components. In several tauopathies including PSP, increased activity of extracellular-regulated kinase 1 & 2 (ERK-1 /ERK-2), increased expression of stress activated protein kinase (SAPK/ JNK) and calcium/calmodulin-dependent kinase II (CaM Kinase II) overexpression occurs [77], affirming the role of tau phosphorylation. Traditionally, protein kinase p38SAPK activated on the onset of stress is linked with reactive oxygen species induced oxidative stress. Several clinical trial drugs examined for PSP includes valproic acid (NCT00385710, NCT00703677), tideglusib underwent a double-blinded placebo trial which also failed in PSP treatment. Others include salsalate (NCT02422485), CDK5 (NCT04253132) [78] etc.

### Corticobasal degeneration

Corticobasal degeneration (CBD), is a member of the 4R tauopathies basically associated with behavioral, cognitive and motor disorder [79]. It was formerly referred to as a corticodentatonigral degeneration, closely associated with neuronal achromasia [80]. While a clear and definite figure on the prevalence of CBD is currently unavailable, an average of 4.9–7.3 cases in every hundred thousand persons was accounted by eastern European and Asian population study [81]. More so, despite the naming of this condition CBD since 1989, few researchers preferably name it as corticobasal ganglionic degeneration [82–84]. Notably, is the clear differentiation of CBD from corticobasal syndrome (CBS). CBS is clearly a CBD phenotype manifested by the emergence of two or more crooked cortical ignitions such as myoclonus, limb apraxia and parkinsonism [85]. Over expression of the kinase enzyme (responsible for phosphorylation), causes an improper hyperphosphorylation of insoluble tau and a concomitant release of tau protein from microtubule in the brainstems, somatosensory region, basal ganglia, and supplementary motor cortices as the major manifestation of CBD [86]. Thus, causing a loss of microtubule function. Dementia ranging from FTD-AD prototype, CBS, PSP, RD are the frequently occurring CBD phenotype [87]. Pathologically,

the trademark injury of CBD in most cases is astrocytic plaque, caused by the deposition of abnormal tau, abnormal proteins in AD, Parkinson disease and Multiple sclerosis (MS) [88], cohabiting normally with dystrophic neurites and irregularities in discharge of tau muddles by the oligodendroglia cytoplasm [89, 90]. Furthermore, it is characterized by the invasion of neurotransmitters by prion like proteins [91], thus sharing an overlapping clinical and pathological feature with PSP. This effect leads in the expression of proinflammatory interleukin 1beta (1L1 $\beta$ ), interleukin 6 (IL6), and increasing level of tumor necrosis factor alpha (TNF $\alpha$ ), causing plaque and microglia degeneration, a hallmark of neuroinflammation [92]. However, despite the relation of CBD with PSP, biochemical features of both 4R tauopathies differs. Most notably, is a double 37kda band tau fragment as compared to the single 33kda band fragment of PSP [88, 93]. While it is clear that mutation of the encoding MAPT gene, situated on 17q21.31 chromosome is the hallmark of CBD emergence, postmortem examination of CBD patients observed a connection between single nucleotide polymorphisms (SNPs) in MAPT H1 haplotype and the hydrolyzing enzyme Rab GTPase, acting on myelin associated oligodendrocyte basic proteins (MOBP), essential in the effective functioning of myelin sheath [94]. Currently, there still remains no globally accepted therapy for the treatment of CBD, suspected patients may progress from acute to chronic, requiring intensive care, expressing behavioral and cognitive disorders [95]. However, several drugs have been tried in the management of CBD which includes levodopa, benzodiazepines [96], levetiracetam [97], intramuscular administration of botulinum toxin [98]. As science grows each day, the concept of CBD becomes clearer, although autopsy is still the major diagnosis of the 4R tauopathy CBD at present.

### Argyrophilic grain disease

Argyrophilic grain (ArG) is a 25 nm smooth tubules and straight filament, spindle like in shape or a spherical lesion in appearance, identified majorly at the onset of Argyrophilic grain disease (AgD). It is responsive to silver iodide staining techniques, and visible in abnormally phosphorylated tau proteins, for diagnosis purpose [99]. ArG is distributed across trans entorhinal, entorhinal cortices, sub nuclei of amygdala, amygdaloid complex, and in minute cases the basal portions of claustrum [100, 101]. In variant to NFT, ArG are absent in neuronal cell perikaryal [102]. A notable hallmark of AgD is the appearance of coiled bodies, mostly branched oligodendroglia inclusions around the nucleus [103, 104]. They are located around the cortices and subcortices of ArG at the manifestation of AgD, distinguished by hyperphosphorylation, similar to pentangle neurons. More so, the

prevalence of AgD increases in degenerative dementia cases, and also directly proportional to age [105]. Frontotemporal cortical atrophy is also observed upon gross examination [106]. Normal phosphorylation of microtubule tau transpires at Serine (202,214,235,396,404,422) and Threonine (181,205, 231) although excessive kinase activity of tau protein occurs at Ser 262 [107]. These residues are catalyzed by mitogen-activated protein kinase, SAPK/JNK, glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ) & p38 kinases [108]. AgD remains a member of the 4R tauopathies, however immunohistochemistry remains the major diagnosis tool, in detailing the pathologic conditions of an AgD patient.

### Alzheimer's diseases

AD is one of the leading causes of medical challenges, affecting mankind and derailing healthy living. The challenge to contain and improve the management of AD has been on over years since it was coined in 1970. A major pathophysiological protein, relevant to the progression of AD is the microtubule associated tau protein. Present evidences point at the aggregation of abnormal tau at the synapse and nucleus, elucidating a loss of tau function as the pathological mechanism of AD emergence [109–111]. Distinctive features at the hippocampal and temporal cortical regions, identified by the deposition of insoluble hyperphosphorylation tau, NFT, and deposition of  $\beta$ -amyloid (Neurotic plaques) are indicative features of AD. This proceeds to several worrisome conditions such as memory loss, impaired behavioral activities, visuospatial function impairment and loss of cognitive functions [112, 113]. Similarly, lessening in A $\beta$  42, low proportion of A $\beta$  42 to amyloid  $\beta$  1–40 proportions, expansion of t-tau and p-tau, incorporation of amyloid markers (A $\beta$ x-38, A $\beta$ x-40, A $\beta$ x-42 and solvent antecedent protein), complex fiber axonal degeneration, and neuroinflammation indicating protein (chitinase-3-like protein1/YKL-40) are all molecular signatures of AD [114, 115]. Pathologically, four in every five AD patients expresses the deposition of alpha-synuclein in lewy body dementia [116], and about three in every five patients with AD displays lewy-body type synucleinopathy [117]. While 4R tauopathies are histologically indicated in the pathology of AD [11], deposition of TDP-43 deposits, linked to  $\beta$ -amyloid dependent and independent cascades are also recognized in AD brains [118, 119]. Finally, there are several G-protein coupled receptors (GPCR), mediating the phosphorylation of tau protein via kinases majorly via the ERKs, GSK-3 $\beta$ , protein kinases and CDK-5 [120, 121]. Activation of GPCR by either of its activation cascade notably intracellular activation, transactivation, classical activation, diphasic activation, or biased activation cascade, allows for the protection against cell degeneration,

oxidative and cytosolic stress protection [122–124]. However, the progression of AD is characterized by imbalances between GPCR-mediated kinases, thus leading to improper hyperphosphorylation of tau-microtubules [128, 129] (Table 1).

### Role of chinese nutraceuticals in tau neurodegenerative diseases

Emerging from the credible combination of nutrient and pharmaceuticals background is the word termed called nutraceuticals [135]. Also referred to as bioceuticals, they are classified as dietary supplements and food additives by FDA, highly efficient in protecting health and maintaining diseases and as such increase's life expectancy [136, 137]. Statistical evaluation of dietary supplements consumption revealed that 68% [138], 83–86% [139] and about 63–70% consumption rate across United states, Germany, Italy and Australia respectively [139–141]. General to tau neurodegenerative disease is the synthesis of truncated proteins as observed in A $\beta$  in AD, misfolded tau & TDP-43 in TBI, and misfolded A $\beta$  & tau in other tauopathies [142, 143]. These concomitantly leads to the upregulation of detrimental molecular cascades that enhances degeneration. Neurodegeneration occurs when the misfolded proteins activates destructive molecules, most notably free radicals, mitochondrial DNA damage, oxidative stress, iNOS and COX-2 by the overexpression of inflammatory cytokines via the NF- $\kappa$ B cascade induction [144, 145]. On the other hand, CREB, ERK signaling cascade, GSK3 $\beta$  [146], and PKA/PKB (Akt) signaling cascades known to promote protein processing, normal protein folding, cognitive function, and microtubule associated tau stability becomes inhibited [145, 147, 148]. However, nutraceuticals are effective in the management of tauopathies. They act by upregulating ERK, Akt, GSK3 $\beta$  and CREB cascades, along with the exertion of anti-inflammatory, and reactive oxygen species ameliorating capabilities. Thus, preventing oxidative stress and aid cognitive functioning. This study further explores some nutraceuticals found or produced in China and their role in management of tauopathies.

### Garlic (*Allium sativum*)

Belonging to the family of Alliaceae, it is a highly cultivated vegetable believed to originate from central Asia in the past 6000 years ago and used in Chinese medicines in the past 3000 years ago [149]. It is an abundant organo-sulfurous compound, efficient in management of several cardiovascular diseases. Their sulfur compound exists as diallyl sulfide, s-allyl-L-cysteine sulfoxides (Allin), S-allyl-L-cysteine and allicin (diallyl thiosulphate), all generally referred to as Allium compounds [150, 151]. Although containing substantial

**Table 1 Summary of the pathophysiology, disease indicators, current treatment strategies and drugs used in neurodegenerative tauopathies**

Tauopathies	Pathophysiology	Disease indicator	Current treatment strategies	Drugs
Alzheimer's diseases	Characterized by a defined pattern of tangles from the trans-entorhinal cortex → entorhinal cortex → CA1 region of hippocampus and finally to the frontal, temporal, and parietal cortices, thus leading to neuronal loss and atrophy which induces inflammation and amyloid plaques deposition [125]	Formation of senile plaques (SP) [126]	Amyloid- $\beta$ -peptide vaccination Secretase inhibitors Anti-inflammatory agents Cholesterol reducing drugs [127]	Donepezil Galantamine Memantine Rivastigmine [128]
Progressive supranuclear palsy	Characterized by development of NFT in astrocytes with the diffusion of plaques and lewy bodies in the brainstem cell nuclei & cerebral cortex. However, in long standing cases, the purkinje cells of the cerebellum are affected leading to the dilation of the third & fourth ventricles [129, 130]	Gait difficulty and falls Dystonia and personality change Non-specific dizziness Pallialia Compulsive spitting [131]	Drug therapy Electroconvulsive therapy [PSP]	Levodopa Dopamine agonists Pergolide Physostigmine Zolpidem Benzotropine [PSP]
Corticobasal degeneration	Characterized by asymmetric frontoparietal cortical atrophy and asymmetric hyperexcitability of the motor cortex, thus leads to the progression of astrocytic plaques	Ataxic gait Myoclonus Dystonia Dysphagia Dysarthria	Imaging techniques such as computerized tomography scanning (CTS) & Magnetic Resonance Imaging (MRI) Clinical testing and work up (Electroencephalogram; EEG)	Baclofen Botulinum toxin Clonazepam Benzodiazepines
Argyrophilic disease	At the anterior entorhinal cortex, there is mild involvement of the cortical and basolateral nuclei of the amygdala. There is also mild involvement of mammary bodies, nucleus accubens and rare grains in the mid brain, thus leading to impaired UPS function. [132]	Episodic memory loss Cognitive decline and dementia Behavioral abnormalities Emotional imbalances [133, 134]	Anti-phosphorylation strategies Anti-aggregation strategies	Rhodamines Thiacarbocyanines N-phenylalanines Anthraquinones Levodopa

number of macromolecules, (28% CHO, 3.2% protein, 1.5% fibers and 6.5% water), diallylsulphate; an organo-sulfur compound was studied to be responsible for its pharmacological activity [152, 153] (Scheme 1).

More acknowledgeable, is the unique flavor attributed to freshly prepared garlic, which is notably due to the presence of alkyl thiosulfonates, thiosulfonates, *s*-alkyl-substituted cysteine sulfoxide derivatives, pyruvate, and NH<sub>3</sub> [154]. Several studies have highlighted the therapeutic potential attributed to garlic; thus, the medicinal efficacy of garlic is well renowned. These include immunodialatory, antitumor, anti-inflammatory, antioxidant, antimicrobial, cardioprotective, anticancer and neuroprotective potential [155–158]. As earlier explained, neurodegenerative tauopathies occurs when misfolded proteins upregulate the inflammatory cytokines, activating the NF-κβ signaling cascade and further downregulate ERK, CREB and Akt pathways. However, research has affirmed the efficacy of garlic via its bioactive compound *s*-allyl cysteine (SAC). SAC was found to inhibit TNFα and IL1β [159], downregulates NF-κβ signaling cascades [160, 161] and further limits the activity of iNOS [162]. Furthermore, the neuroprotective potential of *Allium sativum* has been explored. Several such studies include remediation of neuronal damage by SAC [163, 164], neuroprotective potential in mice model [165], improved behavioral activity in mice [166] and finally memory enhancing effects of aged garlic extract [167]. While Aβ induced neurotoxicity remains an indicator of neurodegenerative tauopathies, Jeong et al. [168] further stressed the ameliorative potential of garlic. Finally, *Allium sativum* is classified as a member of GRAS (Generally Recognized as Safe) by FDA, due to its limited adverse effect, as such it is

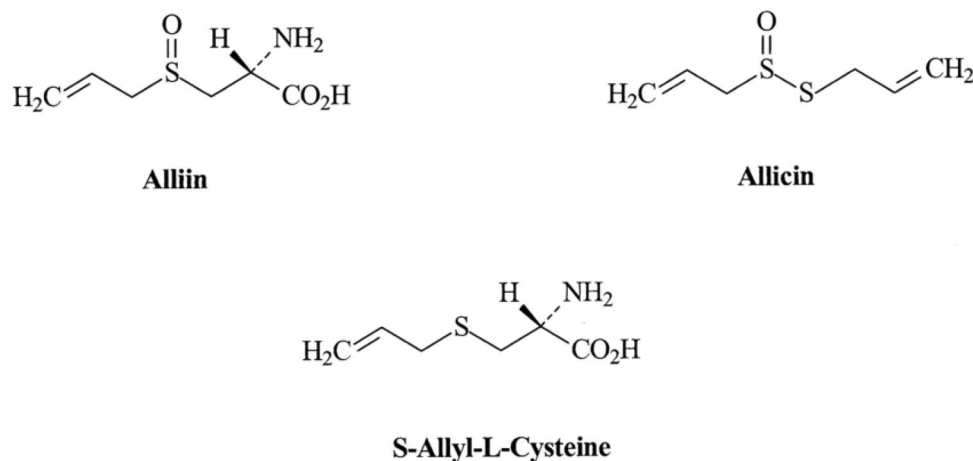
acknowledgeable to encourage the use of garlic for human consumption (Fig. 2).

#### **Withania somnifera**

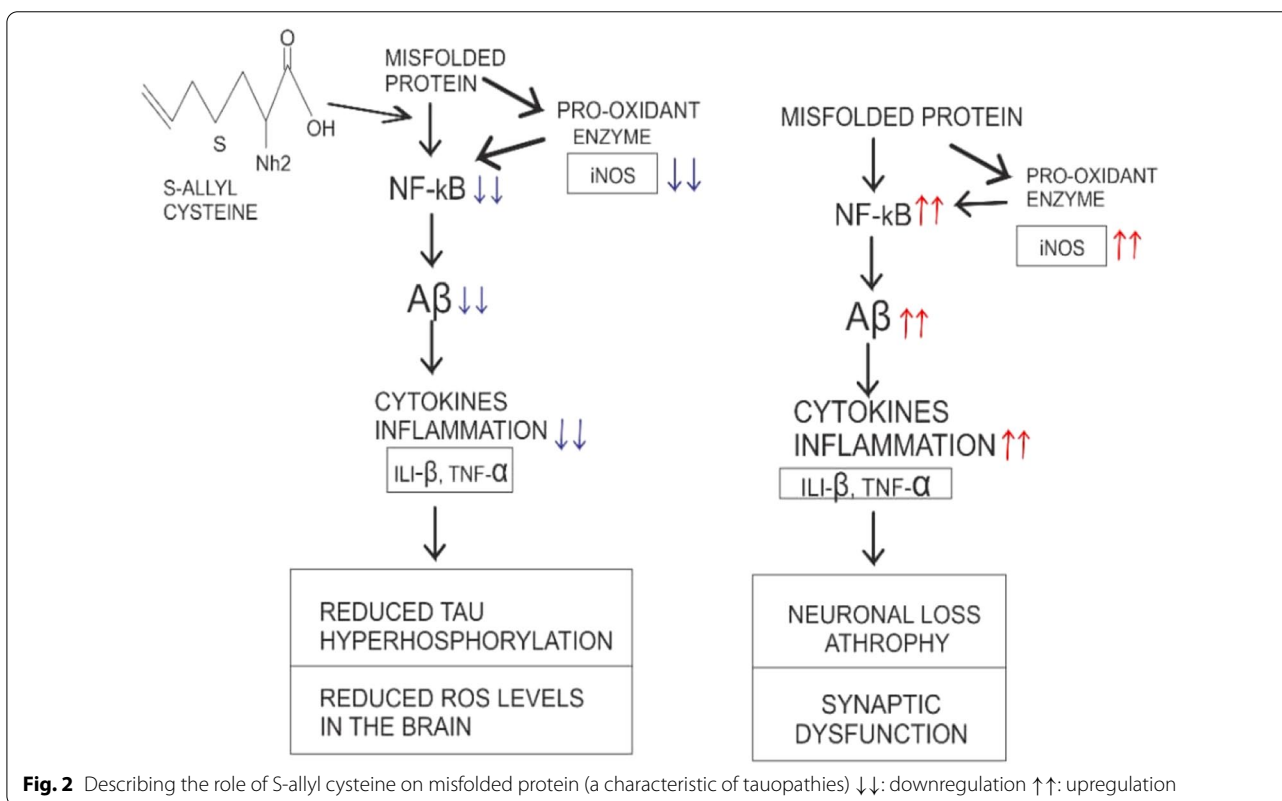
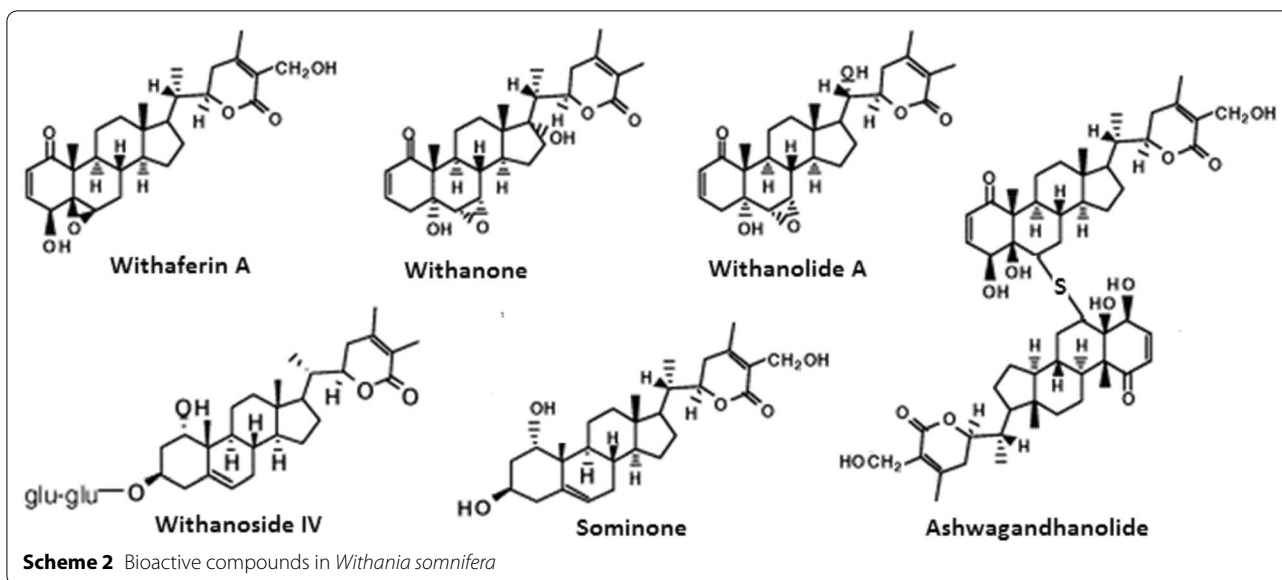
*Withania somnifera* (WS) is popularly referred to as Ashwagandha, belonging to the family Solanaceae and identified by a small green shrub with long roots. Distributed across south Africa, middle east India and China, WS have had its part exploited since ages in the management of various human diseases [169, 170]. Biochemically composed of a combined steroidal alkaloids and lactones called Withanolide [171]. Withanolide are side chain steroidal nucleus decorated by six membered lactone rings [172, 173], consisting of essential alkaloids such as withanine, tropine, choline, anaferine amidst others. Evaluation of the toxicological properties of WS by several studies and FDA, considers WS as a safe drug for human consumption, having been explored and revealed antioxidant capabilities, sedative, anti-inflammatory potential, memory enhancing capabilities, pain relief and antimicrobial potential [174–176]. The neuroprotective potential of WS has undergone extensive studies (Scheme 2).

Some of which includes; enhancement of dendrites formation in neuroblastoma cell [177], memory enhancement via withanoside IV induced RET modulation [178], regeneration and reconstruction of axons and synapses in mice damaged brain [179] and protection against cellular brain damage [180]. Recall that neurodegenerative tauopathies are characterized by the onset of Aβ toxicity, however, WS bioactive compound withanolide protected against pheochromocytoma cells against Aβ toxicity and inhibited fibril formation [181, 182].

Furthermore, the antedementia potential of WS in mice model of AD shows upregulation of low-density



**Scheme 1** Structures of bioactive compounds present in *Allium sativum*



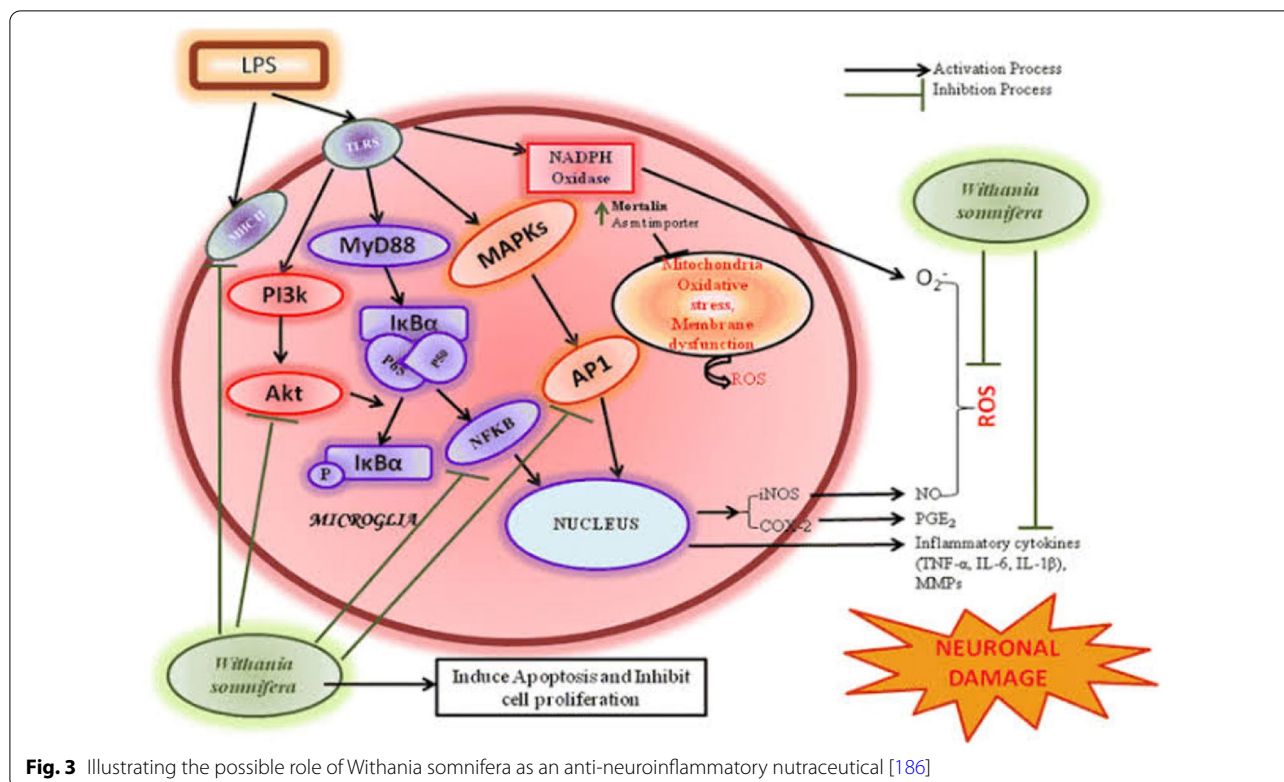
lipoprotein receptor in AD pathology reversal and improved cognitive functioning [183], all pointing at the neuroprotective potential of WS in the amelioration of neurodegenerative tauopathies. Finally, WS has been affirmed in regulating oxidative stress, inhibiting lipid peroxidation [184], and increasing ROS scavenging

activity by upregulating SOD and catalase activity [185] (Fig. 3).

**Bacopa monnieri**

Bacopa monnieri (Brahimi; BM) is a perennial, highly branched, succulent herb characterized by a fleshy,



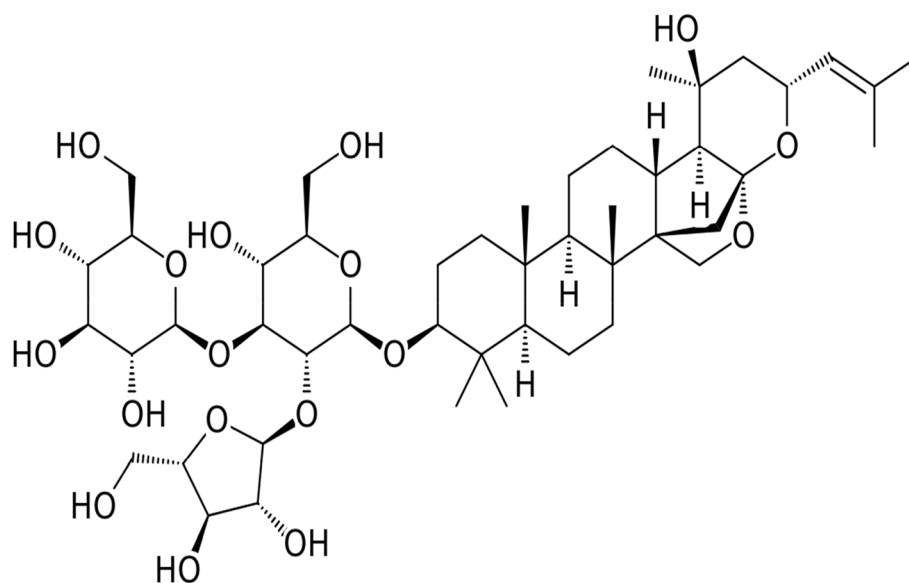


**Fig. 3** Illustrating the possible role of *Withania somnifera* as an anti-neuroinflammatory nutraceutical [186]

spatulate and sessile leaves, singly arranged pale blue flower, bivalve ovoid capsule fruits and minute seeds [187]. They are distributed across India, Africa, Pakistan and China; mostly grown for medicinal purposes [188]. Acclimating a height of about 2–3 feet tall, Brahimi has been phytochemically analyzed to be a multi-functional compound with multiple bioactive compounds [189]. Some of which includes triterpenoids saponins, glycosides, alkaloids and alcohols. Looking inward, their alkaloid contains brahmine, nicotine and herpestine, their glycoside contains pseudojujubogeuin (3-O-[ $\alpha$ -L-arabinofuranosyl (1–2)  $\beta$ -D-glucopyranosyl]), and their triterpenoids contains Bacoside A3 (chemically known as triterpenoid saponin 3- $\beta$ -[O- $\beta$ -D-glucopyranosyl (1–3)-O-[ $\alpha$ -L-arabinofuranosyl (1–2)]-O- $\beta$ -D-glucopyranosyl]oxy)), and Bacoside A [190] (Scheme 3).

However, Bacoside A and Bacoside B is attributed to be responsible for the neuroprotective potential of Brahimi, with respect to the presence of several saponins including Bacoside A3, bacopaside, jujubogenin and bacoposaponin C [191]. Notable therapeutic efficacy of BM includes neuroprotection against AD [192], memory dysfunction [193] and dementia [194]. However, further studies have explained its role in enhancing cognitive functioning [195], anti-inflammation capabilities [196], hepatoprotective potential [197] and anti-aging capabilities [198]. A hallmark of oxidative stress induced cellular damage is

the oxidation of intracellular proteins resulting in neurodegenerative diseases [199], however, BM reduces protein carbonyl levels in cytosol and mitochondrial fragments in prevention of oxidative damage [200]. More so, the irreversible damage caused of cellular organelles caused by lipid peroxidation has showed BM as an efficient cellular protective compound in protecting the prefrontal cortex, striatum in rat models [201] and reducing MDA levels [202]. Furthermore, the maintenance of SOD levels [203, 204], glutathione activity [200, 205] and glutathione peroxidase activity reduction [205–207]. Designated as a memory booster, and considered as a nootropic herbal drug, BM has showed its efficacy in igniting cognitive functioning [192, 208]. While the decline in cognitive functioning still remains as a manifestation in neurodegenerative tauopathies, the improvement in logical thinking, sense of judgement and problem-solving skills relays the therapeutic potential of BM. Similarly, the aggregation of A $\beta$  and tau proteins in AD and other tauopathies have been shown to be on decline in WS and BM treatment [209]. This efficacy is attributed to the neuroprotective potential of Bacoside A, against A $\beta$  induced cytotoxicity in SH-S454 cells [210]. Terneehooheep et al. [211], in his study reflected on the ameliorating potential of BM extract on tauopathies suggests that BM prevents the hyperphosphorylation of tau proteins and as such attenuates tau-mediated toxicity. Neuroinflammation of

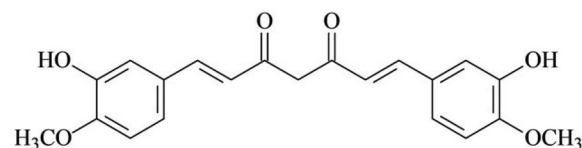


**Scheme 3** Structure of Bacoside

tauopathies is triggered by the deposition of tau protein aggregates which in principle activates proinflammatory cytokines TNF  $\alpha$  and IL1 $\beta$ ; i.e. the exposure of A $\beta$  fibers, triggers the activation of proinflammatory cytokines, causing neuroinflammation [212]. However, a study by Viji et al. [213], explained the anti-inflammatory potential of BM via the inhibition of NF-K $\beta$  and ERK signaling cascades, thus improving learning, memory and consequently synapse functioning. More so, the inhibition of TNF  $\alpha$  by the bioactive compound triterpenoids and bacoside has further been elucidated [214]. Finally, the efficacy of BM in the reduction of IL1 $\beta$  in an in vivo brain damage rat study, results in improved cognitive functioning [215].

#### Role of tumeric in neurodegenerative tauopathies

Turmeric, also known as *Curcuma longa* is a plant prominently grown in Southeast Asia, including China. The dried rhizomes are eaten as spice and is related to the family of ginger. Curcumin is an essential component of turmeric, responsible for its brownish-yellow color. Amongst its other bioactive compounds are desmethoxycurcumin and bisdemethoxycurcumin which can collectively be known as curcuminoids [216]. Curcumin, with the chemical nomenclature ((1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is classified as a beta-diketone molecule enabling both chemical and medicinal activities such as anti-oxidant, anti-inflammatory and anti-cancer activities, as well as a "cleanser of the body"[217] (Scheme 4).



**Scheme 4** Structure of curcumin

Curcumin has been of great interest because of its strong efficacy and affinity for fibrillar amyloid proteins [218]. Anti-amyloid properties of curcumin result in decreasing A $\beta$  production, inhibiting A $\beta$  aggregation and promotion of A $\beta$  clearance. Curcumin binds readily with other  $\beta$  pleated proteins such as A-Synuclein, p-tau & AD and prion proteins [219, 220]. The major chemical feature of A $\beta$  is the presence of two aromatic end group which has effect on its activity if altered. Due to the lipophilic property of curcumin, brain tissue enables it to bypass the blood brain barrier and binds to plaques thus, inhibiting the aggregation of A $\beta$  proteins [221].

One of the major characteristics of tauopathies is inflammation of nerve cells. Inflammation is therefore reduced by curcumin mainly by inhibiting Egr-1 DNA binding activity in THP-1 cells (a major inflammatory transcription factor) [222, 223]. Curcumin also serve as an anti-inflammatory agent by inhibiting the enzyme cyclooxygenase (Cox-2), 5-Lipoxygenase(5-Lox), enzymes responsible for biosynthesis of prostaglandins [224]. NF-kB, a neuroinflammatory marker protein is also downregulated by Turmeric [225], as well as the expression of IL-1, IL-6 and TNF- $\alpha$  in LPS-stimulated BV2

microglia, is reduced by curcumin [226, 227]. A $\beta$  aggregate and generation of ROS in various neurodegenerative diseases can be produced by heavy metal such as copper (cu), zinc (zn), lead(pb) and manganese [228, 229]. Considering the chemical structure of curcumin, the presence of two phenolic group and one active methylene group makes it a perfect binding agent for any metal ion attached by coordinate bonds preventing neurotoxicity [230]. A coordinate bonds is formed when curcumin binds with copper, iron and zinc causing the non-availability of metals to produce amyloid protein aggregation.

There is also increase in the expression of NF-KB levels by heavy metals causing neuroinflammation. Since it has been noted that curcumin check inflammation by obstructing NF-kB levels, possibly, this is carried out by metal chelation [231, 232].

A study carried out by Kozmon and Tvaroska 2015, revealed the association between A $\beta$  peptide and copper ions and curcumin and was observed that curcumin not only chelated heavy metals (cu, pb, zn) but also form "curcumin—cu<sub>2</sub>+—A $\beta$  and curcumin-A $\beta$  complexes when curcumin is directly attached to A $\beta$  thereby decreasing toxic B-sheets structure [233]. Turmeric shows properties of antioxidants i.e. curcumin, the major active component protects cells from damage caused by free radicals. This damage occurs when there is accumulation of ROS which in return affect polyunsaturated fatty acids. Antioxidant properties of curcumin help to increase superoxide dismutase, glutathione peroxidase, glutathione transferase activities which in return preserves the level of glutathione and decreases malonaldehyde accumulation [234]. Along with the antioxidant effects, curcumin has also been noted to eliminate NO-based radicals [235]. An In-vivo study revealed suppression in the level of carbonyl protein in transgenic mouse models

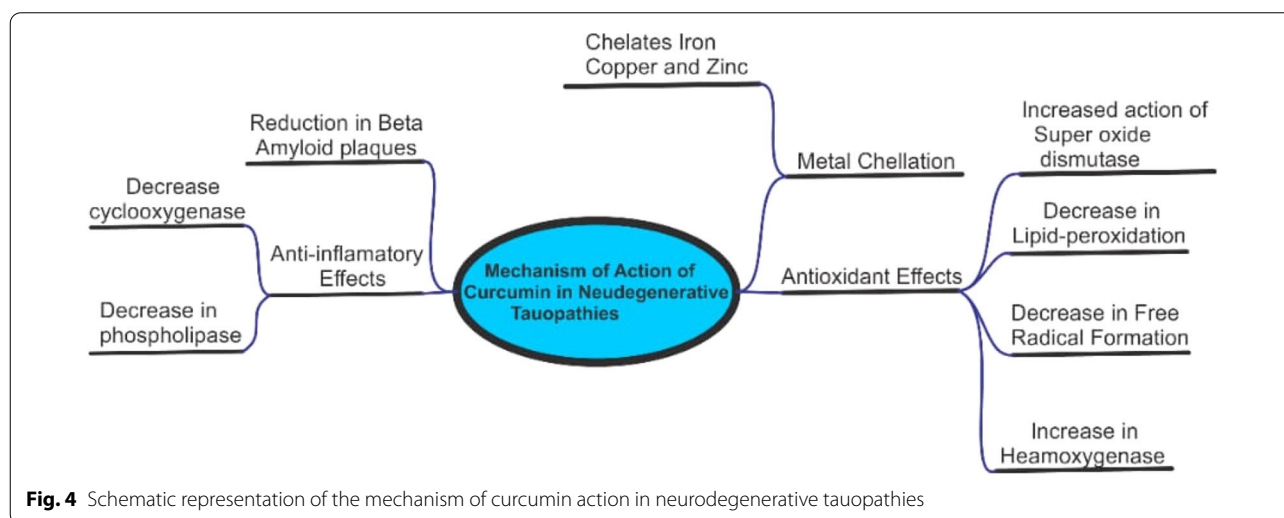
exhibiting human Alzheimer's disease gene when administered curcumin. Thus, it was deduced that curcumin prevent oxidative damage caused by lipid peroxidation, which induce carbonyl compounds (hydroxynomenal), while also inhibiting the activity of AP1; a transcription factor involved in expression of amyloid [236] (Fig. 4).

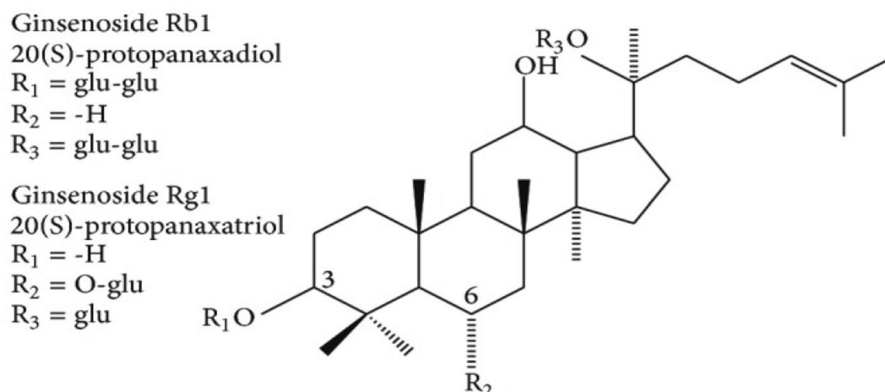
#### Role of ginseng in neurodegenerative tauopathies

Ginseng is known to be one of the popular traditional plants of the family are Araliaceae (perennial plant) and genus "panax". It has its name originated from "Jen Sheng" a Chinese word meaning "man herb" due to the shape of the root which is human like shape [237], "panax" a Greek word meaning "all heal", this shows that it can cure all kind of diseases [238]. The commonly studied Ginseng are "Panax ginseng", "Panax quinquefolium" and Panax notoginseng [239] exhibiting a lot of biological effects [237]. The active constituents of ginseng called "ginsenosides" shows neuroprotective effects and enhances memory [240] (Scheme 5).

A $\beta$  is coined for peptides constituting 36–43 amino acid residues. A $\beta$  formation is from A $\beta$  precursor protein (APP) present in neurons through successive hydrolysis of protein with an enzyme beta secretase 1(BACE1) and  $\gamma$ -secretase [241].

Some ginsenosides are BACE1 inhibitors. Their inhibiting ability is in decreasing order: Rc>Rg1>Rg2>Rb1>Rg3>Re [241]. Gintonin acts in ameliorating tauopathies via the reduction of accumulated amyloid plaque. Hyperphosphorylated tau protein inhibits Panax ginseng by upregulating the activities of phosphatase activities in SY5Y cells. However, Ginsenosides Rd and Rb1 reduces hyperphosphorylated tau by increasing phosphatase 2A level (PP2A) [242]. Rg1 also reduces A $\beta$  formation and decreases





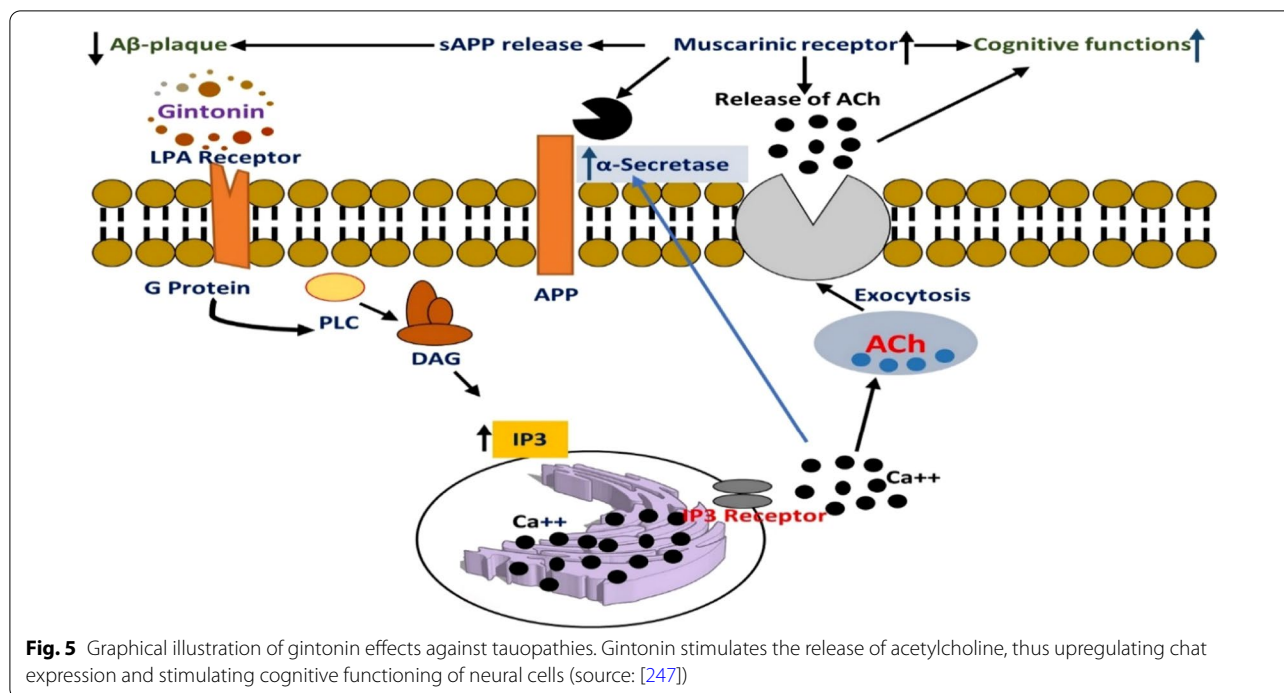
**Scheme 5** Structure of ginsenosides

hyperphosphorylated tau. One of the major treatments of AD is a principal Acetylcholine (ACh) neurotransmitters in which cognition and memory process is reduced in AD [237]. This neurotransmitter is terminated by an enzyme known as Acetylcholinesterase (AChE), and butyryl cholinesterase (BChE), which is present in patients with AD as well as inhibiting of choline acetyltransferase (ChAT) activity (an enzyme responsible for ACh metabolism) [243]. Studies have shown that Rb1, Rb2, Rc, Re, Rg1 and Rg3 have a reducing property on AChE and BChE [243, 244]. Rg2 also decreases intracellular Ca<sup>2+</sup> level and ROS which is caused by the presence of A $\beta$  also reduce lipid peroxidation that is produced by glutamate. Ginsenosides Rb1 and Rb5 (in-vitro) and ginsenoside Rd (in-vivo) are capable of reducing the expression of anti-inflammatory factors such as IL-1B, IL-6, TNF- $\alpha$  by inhibiting the activation of NF- $\kappa$ B [245]. Cox-2 and NOS 2, a major enzyme in the biosynthesis of prostaglandins and neurotransmitter that helps in learning and memory mechanism respectively is seen to be increased in models of tauopathies and the level of NOS1 reduces. Nonetheless, management of tauopathies using ginsenosides Rg5 reduces the level of Cox-2 and NOS 2 [245], while the increase in the level of NOS 1 increases and Cox-2 decreases with the treatment of Rb1 [246] (Fig. 5).

#### Role of physical activity in neurodegenerative tauopathies

Physical activity and exercise is defined as contraction of skeletal muscle expressing the movement of the body, yielding energy expenditure. Nevertheless, the major difference between physical activity and exercise is that the former includes various types of movement while the latter is a type of physical activities which helps in the improvement and maintenance of physical fitness by planned and structural activities [248]. Due to the pleiotropic favorable impact on human tissues e.g. Muscles,

vascular, heart and brain, constant physical activities are considered as an important component of a healthy living resulting in inhibition and resistance of various chronic pathological disease such as cardiovascular, metabolic and neurodegenerative diseases [249]. Some benefits of exercise have been found to ameliorate special learning, working memory, executive and cognitive function [250, 251]. In addition, it causes many neurobiological operations e.g. regulating giving off of neurotransmitters [12], regulating hormones and neurotrophic factor levels [252] to be produced on brain areas activating both acute and chronic biological effects. Many factors affecting growth required in the growth of correct brain tissue, e.g. Fibroblast growth factor-2 (FGF-2) [253], insulin-like growth factor-1 (IGF-1) [254], vascular endothelial growth factor (VEGF) [255], and brain derived neurotrophic factor (BDNF) [256] are through exercise increased in level. The decrease of OS at brain level in addition to the regulation of these factors [257], and the regulation of cell death and inauguration of neurogenesis in precise area of the brain [258], is accountable for defensive consequences of exercise as regards neurodegenerative diseases [12]. Much likely defensive procedure, essential for the impact of physical activity on dementia danger have been suggested as well as rise in brain derived neurotrophic factor (BDNF), decrease in cardiovascular disease and metabolic syndrome risk, with rise in flow of cerebral blood [259]. Eminently, there is an association of decrease in danger of a number of dementia types, in addition to AD emerging to be most sensitive with regulation of the afore-mentioned elements via increase in physical activity [260]. Consequently, it's rational to postulate that variations of mechanism and deterioration of A $\beta$  and tau are significantly essential procedures expected amid exercise and AD risk. Extracellular amyloid plaques are formed by the aggregation of A $\beta$  peptides resulting to decrease



in cognitive functions and neuronal death in tauopathies. Major components of amyloid plaques is the lengthy, and more fibrillar isoform of A $\beta$ , A $\beta$  1–42[261]. It had been identified by autopsy evaluation of AD brains that there is amyloid deposit initially detected in the cingulate cortex, accompanied by the temporal and parietal cortices and the caudate. There is formation of plaques located in occipital, sensory and motor brain region at the subsequent stage of this neuropathological process [262]. Identifying individuals with AD, it has been proven within living human studies that quantification of A $\beta$  in the cerebrospinal fluid and brain (through positron emission tomography, PET, and A $\beta$  binding agent) have proven responsive and precised [263]. Instead of complete inhibition, there is likelihood that exercise hold back and also decrease A $\beta$  accumulation. Which reflects the importance of exercise being commenced before start of symptoms (preclinical period). Additionally, Um et al. [264] for seventeen months, measured A $\beta$ , noticing impact of exercise on decreased A $\beta$  1–42 deposition. Following physical activity and exercise, it has been reported from many animal studies that there is reduction in phosphorylation of tau present in brain and tau pathology [265–269], and reduction in hippocampal tau pathology [266, 267, 270] using intervention varying from 2 to 5 months and 2–9 months have been observed from studies. In the effect of physical activity and exercise on brain tau, it is uncertain whether specific aspects of intervention involve in a key function from the findings

made. In respect of tau reduction, as it may be postulated that greater potency running can evoke better favorable impact. Yet, research applying forced running [266, 267] and voluntary wheel running probably at a reduced intensity [265, 270] detect result on both phosphorylation and accumulation. Over a certain period of 2 months, it is feasible that steady aerobic exercise evokes decrease in tau using animal specimen. However, a review disclosed rise in insoluble tau levels and phosphorylation of tau at the C terminus implementing physical activities [271]. Notwithstanding, there is a complex correlation amid exercise, inflammation and neurodegenerative processes: Decreased AD pathology is linked to increase and decrease in inflammatory marker, having ranging (increase to decrease) adaptive inflammatory response to exercise [272, 273]. In detecting brain tau, varying techniques were used, such as western blotting [267, 268, 271, 274], enzyme linked immunosorbent assays [270], Sarkozy extraction [265], and immunofluorescence [269]. Although it still remains obscure, how these varying procedures could impact the reported results because of the all-round procedures used. According to Gratuze et al. (2017) [265], described none impact of voluntary wheel moving on some tau kinases (GSK3, CDK5, C-JUN N terminal kinases (JNK) and calmodulin -dependent protein kinase 11 (camk11)) nor phosphatase (which dephosphorylate tau in vitro) in their animals. It has been shown that a lack in 2 cholesterol binding proteins, Niemann-pick disease, type C1 (NPC1) and type 2 (NPC2), give

**Table 2** Illustrating the types of exercise, impacts and effects on tau activity

Exercise type	Duration	Physical activities	Impacts	Safety tips	Changes to tau activity	References
Endurance exercise	Minimum of 150 min per week	Jogging, dancing, swimming, biking, hills climbing, playing tennis	Improves fitness levels Aids daily tasks Improves the health of the heart, lungs and circulatory system Prevent cardiovascular diseases	Easy walking before and after endurance exercise Prevent injuries Drink fluids that makes you sweat	Inhibition of free radical activities in the brain Activates AKT/PKB cascades, thus consequently reduces tau hyperphosphorylation	[278, 279]
Strength exercise	Minimum of two days per week	Push-up, squats, digging, weight lifting, use of resistance bands	Increases bone density Improves cardiac function Keeps muscle strong Prevents falls and fall related injuries	Never hold breath during strength exercise Breathe out as you lift and breathe in as you relax Prevent injuries	Downregulation of phospho-PKA levels and upregulating PKC levels Reduces tau hyperphosphorylation	[280]
Flexibility exercise	2 to 3 days per week at 15- 30 s repeated 2-4 times	Shoulder rolls, neck & shoulder release, chest mobiliser, ankle stretch, calf stretch	Improves flexibility Improves balance Stretches muscles	Warm up prior to stretching Don't stretch if it hurts Breathe normally while holding a stretch	Downregulation of phospho-ERK1/2, phospho JNK and p38 levels were thus inhibiting the over expression of tau protein	[280]
Balance exercise	2 to 3 days per week	Step up, Heel to toe walk, one-leg stand, sideways walking	Prevent falls Improves core muscles Improves balance	Use a sturdy chair when necessary Prevent injuries	Inhibition of GSK3β, a kinase mediating tau hyperphosphorylation	[281]

rise to tau Pathology. Belarbi and partners in their mice following voluntary wheel running, observed upregulation of NPC1 and NPC2 mRNA [270]. There is a further requirement of extensive research considering the numerous potentially mediating factors such as kinases and phosphatases. Baker et al. [275] discovered a lower CSF tau in healthy group only to be associated with high-intensity physical activity: It is certain that insufficient intensity or volume of exercise might be undertaken by MCI group to discover a connection with CSF tau. The relationship between habitual physical activity levels and CSF biomarkers of AD has been evaluated with the use of objectively measured physical activity (actigraphy), [276]; a lesser proportion of total tau/A $\beta$ 1-42 and phosphorylated tau /A $\beta$  1-42 (showing a less cerebral pathology) was seen in people spending adequate time participating in moderate physical activity. Lately, Brown et al. [277] reported the greatest levels of exercise showing lesser extent of PET calculated tau in reasonably elderly persons and also, pathological extent of tau protein is not yet reached even with those having "greater" extent of tau in the brain. With the recent studies on tau neuroimaging, the association between physical activity and brain tau in people is a great research work in the coming years (Table 2).

## Conclusion

As explored in this study, tau have proved essential in triggering neurodegenerative diseases cascade, representing a great hurdle to human health of the twenty-first century. Since induction of oxidative stress, instability of microtubule, upregulation of proinflammatory cytokines and cognitive repression are involved in the progression of neurodegenerative tauopathies, potential ameliorating strategies to traditional pharmacological treatments (such as dietary administration of nutraceuticals and moderate physical activity) should focus on modulation of microtubule tau activity. Essentially, nutraceutical-containing nano systems, for targeted neuronal activity have a great potential neuronal remediation strategy, as they could bypass blood brain barriers for targeting neuronal cells, thus enhancing the bioactive effects. Tailored interventions with targeted nutraceuticals to reduce neuroinflammation, improve cognitive functioning and to induce enzymes with a great antioxidant potential, together with the activation of exercise in increasing the levels of growth factors involved in correct brain tissue development, such as fibroblast growth factor-2 (FGF- 2), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and brain derived neurotrophic factor (BDNF), thus contributing to the improvement of the pathological profile of diverse oxidation-related brain neuropathology. However, despite the promising

relationship between tau, physical activity, nutraceuticals and neurodegenerative tauopathies, the challenge to conform in vivo study model to human model still remains and is still to be fully elucidated.

## Future perspective

Apart from explored therapeutic target, biomarkers and drugs available, the quest for complete treatment of tauopathies still persist. While the synergism between pharmacological and non-pharmacological treatments is applaudable, the role of secondary metabolites in Chinese nutraceuticals is praiseworthy. However more robust preclinical and clinical trials against novel drug target with minimal adverse effect for the complete suppression of tauopathies modulation should be carried out.

Transformation achievements belonging to tauopathies such as therapeutic employment of neuro-imaging, identification of molecular cascades involving mediating tau-induced neuronal loss, atrophy, development of tau-based immunotherapy and antisense oligonucleotides are rapidly evolving the biological comprehension, management and diagnosis in treatment of tauopathies, thus offering a great hope for the future.

Finally, nanotechnology has made great stride in diseases managements and drug design in recent years. Thus, future studies should explore the role of nanotechnology in neurodegenerative tauopathies as well as creating a novel therapeutic target.

## Abbreviations

MDA5: Melanoma differentiation-associated protein 5; NF- $\kappa$ B: Nuclear factor kappa light chain enhancer of activated B cells; IRF: Interferon regulatory transcription factor; IFNAR: Interferon  $\alpha$  and  $\beta$  receptor 1; JAK: Janus Kinase; A $\beta$ :  $\beta$ - Amyloid peptide; AD: Alzheimer's disease; FGF-2: Fibroblast growth factor-2; IGF-1: Insulin-like growth factor-1; VEGF: Vascular endothelial growth factor; NFTs: Neurofibrillary Tangles; HD: Huntington's disease; PHFs: Paired helical filaments; BDNF: Brain derived neurotrophic factor; NPC1: Niemann-Pick disease, type C1; NPC2: Niemann-Pick disease type C2; CamKII: Calmodulin-dependent protein kinase II; JNK: C-Jun N terminal kinases; PET: Positron emission tomography; BDNF: Brain-derived neurotrophic factor; FGF-2: Fibroblast growth factor-2; IGF-1: Insulin-like growth factor-1; MAPT: Microtubule associated protein tau; VEGF: Vascular endothelial growth factor; FTDP-17: Frontotemporal dementia with Parkinsonism-17; TNF $\alpha$ : Tumor necrosis factor alpha; IL1 $\beta$ : Interleukin 1 beta; BM: Bacopa monnieri; WS: Withania somniferous; SAC: S-allyl cysteine; GRAS: Generally Recognized as Safe; GSK3 $\beta$ : Glycogen synthase kinase 3 beta; CREB: CAMP response element-binding protein; Akt: Protein Kinase A/ Protein Kinase B: PKA/PKB; MAPK/ERK: Mitogen-activated protein kinase; SAPK/JNK: Stress-activated protein kinase; AgD: Argyrophilic grain disease; ArG: Argyrophilic grain; MOBP: Myelin associated oligodendrocyte basic proteins; MS: Multiple sclerosis; CBS: Corticobasal syndrome; CBD: Corticobasal degeneration; SAPK/JNK: Stress activated protein kinase; PSP: Progressive supranuclear palsy; OS: Oxidative stress; PSP-CBD: PSP with corticobasal degeneration; FTLD: Frontotemporal lobar degeneration; CBD: Corticobasal degeneration; PID: Pick's disease; AGD: Argyrophilic grain disease; FDA: Food and Drug Administration; GDP: Gross Domestic Product; CHO: Carbohydrate; EGR1: Early Growth Response 1; THP-1: Human leukemia monocytic cell line; DAG: Diacylglycerol; IP3: Inositol trisphosphate; LPA receptor: Lysophosphatidic acid receptors; PLC: Phospholipase C.

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