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Role of phytochemicals in neurotrophins mediated regulation of alzheimer's disease

Abstract

The progressive dementia and deterioration of cognitive functions have been characterised as Alzheimer's disease (AD). The most common causes of Alzheimer's disease include aging, nutrition, and toxins. It has been reported to be an unsolved sociomedical problem because of their lack of proper treatment in present scenario. The plant based principles and phytochemicals from traditional herbs might delay the onset or/ and progression of Alzheimer's disease. The phytochemicals may help recovery from Alzheimer's disease because of their antioxidative, anti-inflammatory, and antiamyloidogenic properties by regulating mitochondrial stress, apoptotic factors, free radical scavenging system, and neurotrophic factors. Neurotrophins (BDNF, NT4/5, NT3, and NGF) play important roles (neuronal and non-neuronal responses) in Alzheimer's disease and their depletion accelerates the progression of the disease. Therefore, neurotrophins targeted treatment may act as better strategy to treat Alzheimer's disease. This review presents an updated account of the information available on the phytochemicals mediated signaling pathways (neurotrophin mediated activation of Trk receptors) involved in neuroprotection. The currently available literature suggests that enough attention should be paid towards their clinical trials which still remain to be established. It is necessary to prove the neuroprotective efficacy of such phytochemicals in different preclinical models including humans.

Keywords: neurotrophins, alzheimer's disease, antioxidative, stress, signalling pathways,phytochemicals

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Abbreviations: AD, alzheimer's disease; AChE, acetylcholinesterase; Nrf2, nuclear factor (erythroid-derived 2)-like 2; FOXO, fork head box o; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NT, neurotrophin; Trk, tropomyosin-related kinase; SOD, superoxide dismutase; CAT, catalase; ROS, reactive oxygen species; NO, nitric oxide; TNF-tumor necrosis factor; NF-κB, nuclear factor kappa b; IL, interleukin; iNOS, intrinsic nitric oxide synthase; PG, prostaglandin; ERK, ras/extracellular signal-regulated kinases; and PI3K-phosphatidylinositol 3-kinase

Introduction

Alzheimer's disease (AD) is recognized as one of the most complicated neurodegenerative diseases. It is a chronic neurodegenerative disorder characterized by progressive dementia and deterioration of cognitive function.[1] As a result of aging, the number of people with dementia has been growing rapidly worldwide.[2] According to a consensus the prevalence of neurodegenerative diseases is on the rise worldwide.[3] The main physiological symptoms of neurodegenerative diseases are elevation in the level of oxidative stress, misfolding of protein, aberration in mitochondrial function, loss of synapse and decreased survival of neurons which makes the way easier to apoptosis.[4,5] Neurodegenerative diseases are affected by several factors such as stimulating nuclear factor (erythroid-derived 2)-like 2 (Nrf2), Sirtuin genes, fork head box O (FOXO) transcription factors, chaperones, neurotrophic factors and by acetylcholinesterase (AChE) inhibition.[6]

Neurotrophins play important roles in the survival, maintenance, and regeneration of neuronal population.[7] The neurotrophins that were identified as neuronal survival-promoting proteins in mammals include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and NT-4/5.[8,9] A decrease in neurotrophins has been associated with the pathology of several neurodegenerative diseases and their physiological symptoms.[10] Among the neurotrophins, NGF has been studied extensively as a drug target owing to its strong association to neurodegenerative diseases. The next common targets are antioxidants, anti-inflammatory, inhibitors of acetylcholinesterase (AChE) and anti-stress factors.[11] Neurotrophins are considered to be promising targets for neuroprotective agents against degenerative diseases.[12] The phytochemicals from natural sources have been shown to have potential of controlling the levels of neurotrophin. In particular, a modulator or enhancer targeting the tropomyosin-related kinase (Trk) receptor could be a valuable candidate to reverse neurotrophin loss.[13] Additionally, research has led to an increase in the consumption of specific plant ingredients (phytochemicals) to treat neurodegenerative diseases.[14,15] Natural phytochemicals may be less toxic than novel synthetic drugs. However, since these traditional herbal medicines were prepared from crude plant materials, there are so many questions arises concerning their specific medicinal effects, mechanism of action, and the identity of the active ingredients.[16] Therefore, most recent research has focused on specific active components of an herb rather than on the entire herb/ plant. However, a number of active ingredients should be identified and characterized with regard to their potential therapeutic effects in context to their effects on neurodegenerative diseases. The induction of natural compounds and their effects on neurotrophin have already been reported[3] and were shown to directly or indirectly function as NGF mimetics or inducers.[9,12,17] Overall, phytochemicals can be able to provide an effective way of halting or delaying the progression of neurodegenerative diseases. Phytochemicals and their derivatives induce neuronal cell differentiation and upregulate neurotrophic factors such as NGF and BDNF.[12,18] These compounds may have the potential to prevent and arrest neurodegeneration by inducing neurotrophins and boosting the activity of the antioxidant system, such as superoxide dismutase (SOD) and catalase (CAT).[19] They may also inhibit the production of reactive oxygen species

(ROS), nitric oxide (NO), tumor necrosis factor alpha (TNF-α), nuclear factor kappa B (NF-κB), interleukin (IL)-1β, intrinsic nitric oxide synthase (iNOS), and prostaglandin (PG) E2. NGF triggers the Trk A signaling pathway [12,18] by inhibiting caspase protein expression[20] and via degradation of beta amyloid oligomers in the brain.[21] This review focuses the phytochemicals that have the potential to treat neurodegenerative diseases or arrest the degeneration and/or loss of neurons by targeting neurotrophins.

Cellular interactions of neurotrophins with their receptors

Neurodegenerative diseases might be treated by regulating neuron proliferation, differentiation, and survival. Phytochemicals that inhibits acetylcholinesterase (AChE) can regulate intracellular signaling and prevent damage to cognitive function of patients with Alzheimer's disease by up regulating neurotransmitter (ACh).[22] The discharged neurotransmitter targets receptors on pre/postsynaptic cells. Once activated, these receptors facilitate various intracellular signaling mechanisms, which promote both various cellular responses in developing and mature neurons.[23] Similarly, the cells respond to external stimuli via extracellular receptors and neurotrophins individually activate members of the Trk receptor family (TrkA, TrkB, and TrkC show high affinity towards NGF, BDNF, and NT 4/5 and NT-3, respectively).[24] Many neurotrophic factors such as NGF, BDNF, NT-3, NT 4/5, erythropoietin and basic fibroblast growth factor-2 protect neurons. Therefore, they are able to reverse the degeneration of neurons by interacting with Trk receptor and promoting the survival, growth, differentiation and maintenance of neurons.[25] Among the neurotrophins, NGF was the first growth factor to be identified and has been found to promote the survival of neurons and neurite ganglia outgrowth in terrestrial birds by using mouse sarcoma tissue.[26] The binding of neurotrophins to their receptors facilitates different intracellular signaling pathwaws including the Ras/extracellular signal-regulated kinases (ERK), phospholipase Cγ and phosphatidylinositol 3-kinase (PI3K)/AKT pathways.[27] Neurotrophins also activate downstream signaling pathways to regulate cell survival and promotes recovery from neurodegeneration.[28] Neurotrophins promote transcriptional expression of the Trk receptor via Kruppel-like factor 7, Brn3a, cyclic adenosine monophosphate (cAMP) response element binding (CREB) protein, c-Jun, and NeuroD.[29] An absence of neurotrophins suppresses Trk receptor expression and may cause cognitive neuronal defects. Neurotrophins also show weak affinity towards the p75 neurotrophin receptor (p75NTR) owing to structural similarities with the Trk family receptors.[30] Interestingly, p75NTR mediates the cell-death-promoting tumor necrosis factor (TNF) receptor super family. Tumor necrosis factor (TNF) plays an important role in modulating neuronal and immune interactions.[7] Dimeric neurotrophins interact with p75NTR monomers by forming a disulfide bond with cysteine-rich intracellular repeating domains and inducing a conformational change in the receptor. This change then causes enzymatic activation of an adaptor protein via NF-κB and c-Jun N-terminal kinase (JNK), which facilitates proliferation and survival via Bcl-2, or cell death through caspases.[31] Neurotrophin binding triggers the activation of the Trk receptor, causing oligomerization and transautophosphorylation in intracellular domain, which leads to the activation of an intracellular signaling pathway with activation of Ras/mitogen activated protein kinase (MAPK), which results in CREB-dependent neurotrophin secretion and Bcl-2 expression, promoting survival, proliferation and differentiation of the cell.[32] Therefore, the study of phytochemicals that can be able to potentiate neurotrophins is necessary to find out new natural agents to combat effectively with neurodegenerative diseases.

Phytochemicals as neuroprotectant

The brain uses a major proportion of the nutrients consumed by a person. Therefore, certain diets might improve brain function.[33] Consuming dietary macro and micronutrients derived from different traditional medicinal plants has been shown to enhance cognitive function[34] and can partly penetrate the Blood Brain Barrier. The properties of these phytochemicals can effectively reverse the age-related decline in cognitive function by inducing the expression of neurotrophins via the Trk signaling pathway in the hippocampus.[34] In addition to their special biological activities, phytochemicals mainly act as antioxidants, scavenging free radicals in the brain and thus induces neuronal regeneration, and neuroprotection activities that lead to improved neuronal survival, differentiation, LTP, and memory enhancement.[35] The phytochemicals which have reported to be used as neuroprotectant are listed in Table 1.

Table 1 List of phytochemicals having neuroprotective property

S. No.	Phytochemicals	Plant	Family	Potective Function	Mechanism (S)	References
1	(−)-3,5-Dicaffeoylmuco-quinic acid and quinic acid	*Aster scaber*/ *Doellingeria scaber*	Asteraceae	Neuroinflammation and neuroprotection	Activates Trk/ERK1/2/PI3K-mediated neurotrophic mimetic action	26
2	3,5-*O-trans*-dicaffeoylquinic acid methyl ester and 1-*O-trans*-*p*-coumaroyl-5-*O-cis-p* coumaroylquinic acid	*Pimpinella brachycarpa*	Apiaceae	Neuroinflammation	Inhibits the production of NO and iNOS, and boosts antioxidant system	26
3	6α,7α-Dihydroxyannonene, 7α,20-dihydroxyannonene, clerodane diterpenoid	*Ptychopetalum olacoides*	Olacaceae	Neuroprotection	Through neurotrophic mimetic action	36
4	α-Iso-cubebene, dibenzocyclooctadiene lignans, nigranoic acid, schisanchinins A-D	*Schisandra chinensis*	Schisandraceae	Neuroinflammation and neuroprotection	Activates PKA/B/Ca2+-CaMKII/ERk1/2-mediated CREB and Nrf2 pathway, induces the expression of BDNF and c-fos, and inhibits the production of NO and PGE2	37

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S. No.	Phytochemicals	Plant	Family	Potective Function	Mechanism (S)	References
5	6-shogaol	*Zingiber officinale*	Zingiberaceae	Neuroinflammation and neuroprotection	Induces NGF, BDNF and GDNF secretion, increases the levels of SOD, Bcl-2, and Bcl-xL and inhibits the level of Cox 2, TNF-α, NF-κB, IL-1β, NO, p38, iNOS, Bax, PG-E2, and ROS	38
6	Apigenin-8-*C*-β-digitoxopyranoside, apigenin- 8-*C*-β-boivinopyranoside, luteolin-8-*C*-β-boivinopyranoside	*Passiflora edulis*	Passifloraceae	Anxiolytic, neuroinflammation, and neuroprotection	Inhibits NO, iNOS, and PGE2-mediated modulation of ERK 1/2, p38 MAPK and JNK pathway	39
7	Berberine	*Coptis chinensis*	Ranunculaceae	Neuroinflammation and neuroprotection	Activates AKT/GSK-3β/Nrf2-mediated regulation, induces NGF and BDNF secretion and inhibits the levels of iNOS, Cox2, TNF-α, NF-κB and IL-1β	40
8	Curcumin	*Curcuma longa*	Zingiberaceae	Neuroinflammation, and neuroprotection	Activates PKC/ERK-mediated CREB regulation and AKT/GSK-3β mediated regulation, induces BDNF secretion, and inhibits Cas3, TNF-α, andNF-κB levels	41
9	Diosniposide B, 3,7-dihydroxy-2,4,6-trimethoxy-phenanthrene, sapogenin	*Dioscorea nipponica*	Dioscoreaceae	Neuroinflammation, and neuroprotection	Activates Trk signaling pathway, induces secretion of NGF and inhibition of NO	12
10	Epigallocatechin-3-galate	*Camellia sinensis*	Theaceae	Neuroinflammation and neuroprotection	Activates Trk signaling pathway, induces secretion of NGF and BDNF	42
11	Ginsenoside Rg3, panaxynol	*Panax ginseng*	Araliaceae	Neuroinflammation and neuroprotection	Activates cAMP/MAPK & Trk, TNF-α, NF-κB, IL-1β, iNOS and neurotrophic mimetic action	43
12	Geniposidic acid	*Eucommia ulmoides*	Eucommiaceae	Anti-apoptotic, and neuroprotection	Activates PI3K/AKT, p38 MAPK/ERK1/2 inhibition of LDH, PARP, cleaved caspase 3, MMPs and cytochrome C, increase in Bcl-2, Bcl-xL, BDNF level of expression, and inhibition of AChE	44
13	Ginkgolide B	*Ginkgo biloba (L)*	Ginkgoaceae	Antidepressant, dementia, neuroprotective, antioxidant, and neuroinflammation	Activates Trk/Ras/MAP, induces secretion of BDNF and reduces the ROS, LDH, caspase3, and proapoptotic factors	45
14	Honokiol, magnolol	*Magnolia officinalis*	Magnoliaceae	neuroinflammation and neuroprotection	Induces secretion of NGF and BDNF, inhibition of TNF-α, NF-κB, IL-1β, IL-6, ROS, and increases the activity of Akt	46
15	Huperzine A	*Huperzia serrata*	Huperziaceae	Neuroinflammation and neuroprotection	Activates Trk/MAPK/ERK, induces NGF and BDNF secretion, reduces the levels AChE, TNF-α, NF-κB, IL-1β, and MDA, increases the level of SOD, GSH-Px, Cat, Bcl-2, Bcl-xL, and TGF-β	47

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Table Continued...

S. No.	Phytochemicals	Plant	Family	Potective Function	Mechanism (S)	References
16	Limonoid, 1α,3-dihydroxyl-7α-tigloyloxy-12α-ethoxylnimbolinin and 12-*O*-ethyl-1-deacetyl-nimbolinin B	*Melia toosendan*	Meliaceae	Neuroprotective and neuroinflammatory	Activates PKA/ERK1/2, induces secretion of NGF, and decreases the level of LDH activity	48
17	Ligraminol E4-*O*-β-d-xyloside, juniperigiside	*Abies holophylla*	Pinaceae	neuroinflammatory	Inhibits production of NO and activates production of NGF	49
18	Oleuropein	*Olea europaea*	Oleaceae	Neuroprotection and neuroinflammation	Induces secretion of NGF and BDNF	50
19	Quercetin, gallic acid	*Morus alba (L)*	Moraceae	Cognitive disorders, antiaging, and neuroprotection	Induces PI3K/ERK1/2, CREB activation, and NGF secretion	51
20	Resveratrol	*Vitis vinifera*	Vitaceae	neuroinflammation, and neuroprotection	Activates ERK, regulates CREB, induces NGF, GDNF, and BDNF secretion, and inhibits caspase3, TNF-α, NF-κB, IL10, IL-1β, MCP1, MDA levels and increases SOD level	52
21	Rosmarinic acid, citronellal, isomenthone, ε-caryophyllene, ursolic acid	*Melissa officinalis (L)*	Lamiaceae	Antidepressant, cognitive disorders, neuroinflammation, and neuroprotection	NGF mimetic, activates ERK1/2, improves cholinergic activity and NF-κB pathway, and inhibits IL-1β, TNF-α, and caspase 3	53

Conclusion

A variety of dietary phytochemicals may serve as promising candidates for the treatment of neurodegenerative diseases. Several evidences suggesting that the naturally occurring phytochemicals that affect neurotrophins should be a first-line treatment of neurodegenerative disease. Phytochemicals offer a safe approach towards the protection against neuronal damage and loss caused by neurotrophin deficits in patients with neurodegenerative disease. In particular, the importance of the role of neurotrophins and the value of phytochemicals in regulating neurodegenerative disease has been reported similar activities for phytochemicals through (i) reducing oxidative-stress induced by free radicals, (ii) boosting the phagocytic properties of immunological cells, (iii) increasing the concentration of neurotransmitter by inhibiting neurotransmitter cleaving enzymes and (iv) adapting to the prevailing stress conditions by affecting the differentiation properties of neurons. As nerve growth factor are just responsible for the growth and survival of developing neurons. Phytochemicals may not be the absolute cure, but they may serve to delay or prevent the onset of neurodegenerative diseases. Furthermore, phytochemicals do not appear to be cytotoxic, they may provide the maintenance of mature neurons and allow them to regenerate. As a result, phytochemicals that induces the neurotrophins expression or mimic neurotrophins like functions and activate Trk receptors can potentially prevent neurodegenerative diseases. Hence, phytochemicals that regulate neurodegenerative disease by targeting neurotrophins might be a promising future. Even the prevailing gap exists between pharmacognosy and pharmacological approaches to the treatment and cure of the disease the phytochemicals that regulate neurodegenerative diseases are still needs to be more attention in preclinical and clinical studies. Particularly, in-depth study is needed towards the phytochemicals which regulates neurodegenerative diseases by regulating NGF-Trk A signaling.

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Conflicts of interest

Author declares there are no conflicts of interest.

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