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Natural products attenuate PI3K/Akt/mTOR signaling pathway: A promising strategy in regulating neurodegeneration

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Abstract

Background

As common, progressive, and chronic causes of disability and death, neurodegenerative diseases (NDDs) significantly threaten human health, while no effective treatment is available. Given the engagement of multiple dysregulated pathways in neurodegeneration, there is an imperative need to target the axis and provide effective/multi-target agents to tackle neurodegeneration. Recent studies have revealed the role of phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) in some diseases and natural products with therapeutic potentials.

Purpose

This is the first systematic and comprehensive review on the role of plant-derived secondary metabolites in managing and/or treating various neuronal disorders via the PI3K/Akt/mTOR signaling pathway.

Study design and methods

A systematic and comprehensive review was done based on the PubMed, Scopus, Web of Science, and Cochrane electronic databases. Two independent investigators followed the PRISMA guidelines and included papers on PI3K/Akt/mTOR and interconnected pathways/mediators targeted by phytochemicals in NDDs.

Results

Natural products are multi-target agents with diverse pharmacological and biological activities and rich sources for discovering and developing novel therapeutic agents. Accordingly, recent studies have shown increasing phytochemicals in combating Alzheimer's disease, aging, Parkinson's disease, brain/spinal cord damages, depression, and other neuronal-associated dysfunctions. Amongst the emerging targets in neurodegeneration, PI3K/Akt/mTOR is of great importance. Therefore,

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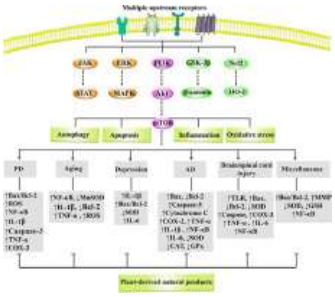
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attenuation of these mediators would be a great step towards neuroprotection in such NDDs.

Conclusion

The application of plant-derived secondary metabolites in managing and/or treating various neuronal disorders through the PI3K/Akt/mTOR signaling pathway is a promising strategy towards neuroprotection.

Graphical abstract



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Keywords

Neurodegenerative diseases; Phytochemicals, Pharmacological targets; PI3K; Akt; mTOR

Abbreviations

Aβ, amyloid-beta; AChE, acetyl cholinesterase; AD, Alzheimer's disease; AEDs, antiepileptic drugs; ALS, amyotrophic lateral sclerosis; AMPK, AMP-activated protein kinase; APP, amyloid precursor protein; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CBP, CREB-binding protein; CML, carboxymethyl lysine; CMS, chronic slight stress; CNS, central nervous system; COX-2, cyclooxygenase-2; CREB, cyclic AMP response element-binding protein; CTFs, C-terminal fragments; CUMS, chronic unpredictable mild stress; DA, dopamine; DCX, doublecortin; DOPET, 3,4-dihydroxyphenylethanol; EGCG, Epigallocatechin 3-gallate; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; ERK, extracellular signal-regulated protein kinase; FGF, fibroblast growth factor; FOXG1, Forkhead Box G1; FST, forced swimming testing; GCLM, γ-glutamate-cysteine ligase modifier; GFAP, glial fibrillary acidic protein; GLT-1, glutamate transporter-1; GPCRs, G protein-coupled receptors; GSH, glutathione; GSK-3β, glycogen synthase kinase-3 beta; HD, Huntington's disease; HO-1, heme oxygenase-1; 5-HT, 5-hydroxytryptamine; Iba-1, ionized calcium-binding adaptor molecule 1; IFN, interferon; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; IRS-1, insulin receptor substrate-1; JAK, Janus kinase; LBCs, lipid-based carriers; LDH, lactate dehydrogenase; L-DOPA, L-3,4-dihydroxyphenylalanine; MAO, monoamine oxidase; MAPK, mitogen-activated protein kinase; MCP, monocyte chemoattractant protein; MDA, malondialdehyde; MMPs, matrix metalloproteinases; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; mTOR, mammalian target of rapamycin; NDDs, neurodegenerative diseases; NLC, nano-structured lipid carriers; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NP, neuropathic pain; Nrf2, nuclear factor erythroid 2-related factor 2; 6-OHDA, 6-hydroxydopamine; O/W, oil in water; PARP-1, poly (ADP-ribose) polymerase1; PD, Parkinson's disease; PHF-1, paired helical filament 1; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKD1, protein kinase D1; PTZ,

pentylenetetrazole; ROCK, Rho-associated protein kinase; RS, reactive species; RTKs, receptor tyrosine kinases; SLCPs, solid lipid curcumin particles; SLNs, solid lipid nanoparticles; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; THSG, 2,3,5,4-Tetrahydroxystilbene-2-O-beta-D-glucoside; TNF-α, tumor necrosis factor-α; TrkB, tropomyosin receptor kinase B

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Introduction

Neurodegenerative diseases (NDDs) as debilitating and incurable conditions refer to a heterogeneous disorder with progressive degeneration and neuronal cell death (Gitler et al., 2017; Poh and Kong Thoo Lin, 2018). The nerve cells are not usually capable of being regenerated or replaced; the condition results in functional changes of the peripheral/central nervous system. This procedure causes several acute or chronic neurological diseases like Alzheimer's disease (AD), aging, Parkinson's disease (PD), central nervous system (CNS) [brain/spinal cord] injuries, ischemia, depression, epilepsy, neuropathic pain (NP), Huntington's disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and autism (Ahmed et al., 2018; Fakhri et al., 2019a, 2019b; Gitler et al., 2017; Menzies et al., 2015). The aforementioned progressive/debilitating disorders affect the life quality of millions of people worldwide and an increasing population of the elderly population (Gitler et al., 2017; Thrall, 2005).

From the pathophysiological point of view, recent reports have introduced complex dysregulated signaling pathways behind neurodegeneration; however, the exact mechanisms remained unclear (Fakhri et al., 2020c). Of those dysregulated pathways, oxidative stress, inflammation, apoptosis and autophagy play critical destructive roles towards neurodegeneration (Fakhri et al., 2018a; Gravandi et al., 2021; Shabab et al., 2017). Oxidative stress and mitochondrial dysfunction employ reactive oxygen species (ROS) to play major roles in the progression of neuronal dysfunction (Bhat et al., 2015). Besides, the over-activation of neuroinflammation plays cytotoxic effects, through releasing pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α), nitric oxide (NO), cyclooxygenase-2 (COX-2), interleukin-6 (IL-6), IL-1β, and superoxide in classical activation state (Hu et al., 2015; Tang and Le, 2016). Like the other potential causes of NDDs, genomic instability, cell senescence, disruption in the synthesis and/or release of neurotransmitters, and abnormal protein synthesis are of potential importance (Park et al., 2020; Singh et al., 2017). Therefore, regulating oxidative stress, cytokines/chemokines release, and other destructive mechanisms play beneficial roles in managing and/or treating multiple NDDs. Thus, there is a crucial need to develop effective and multi-target agents to target multiple dysregulated pathways and mechanisms involved in NDDs.

Since ancient times, natural products have been a source of disease-modifying agents. They have several biological and pharmacological activities, possessing a major burden of safety and efficacy, regarding gaining considerable attention for the development of novel therapeutic agents (Newman and Cragg, 2020; Poh and Kong Thoo Lin, 2018; Sengupta and Mehta, 2018). Natural products exert beneficial effects on various NDDs by targeting different signaling pathways, including oxidative stress, inflammation and apoptosis pathways and many other cellular and molecular mechanisms. They also down-regulate inflammatory cytokines/chemokines release, enhancing antioxidative performance by preventing mitochondrial damages and neutralizing free radicals (Jin et al., 2019; Mohd Sairazi and Sirajudeen, 2020; Poh and Kong Thoo Lin, 2018; Wang et al., 2019c). Of those signaling cascades,

phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is of great importance. We also previously showed the critical role of PI3K/Akt/mTOR in the pathological procedure of various diseases (Zarneshanetal., 2020).

Recent reviews have revealed the role of PI3K/Akt/mTOR in cancer, and natural products with anticancer potential (Fakhrietal., 2020a; Fakhrietal., 2020b; Tewarietal., 2019; Xuetal., 2020). Also, in a recent review, the role of this pathway has been shown in NDDs (Xuetal., 2020). However, to the best of authot's knowledge, this is the first systematic review with a complete focus on the critical role of modulating PI3K/Akt/mTOR by phytochemicals in NDDs. Therefore, in the present review, we highlight the neuroprotective effects of plant-derived natural products, which are exerted by modulation of PI3K/Akt/mTOR and close interconnected mediators as a promising strategy in regulating neurodegeneration.

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Study design and methods

A systematic and comprehensive review was done based on the PubMed, Scopus, Web of Science, and Cochrane electronic databases. The keywords (“neuron” OR “brain” OR “spinal cord injury” OR “multiple sclerosis” OR “Parkinson's disease” OR “Alzheimer's disease” OR “depression” OR “aging” OR “autism” OR “stroke” OR “epilepsy” OR “seizure” OR “Huntington's disease”) AND (“PI3K” OR “Akt” OR “mTOR” OR “m-TOR”) were searched in [title/abstract/keywords]. The interconnected pathways/mediators to …

Neuroprotective responses: Pivotal role of PI3K/Akt/mTOR pathway

PI3K/Akt/mTOR plays pivotal roles in plenty of mechanistic procedures, including apoptosis, angiogenesis, as well as cell proliferation and migration towards body homeostasis. Instead, during pathological procedures, the aforementioned pathway tends to be engaged in several dysregulated situations.

Furthermore, abnormal activation of PI3K/Akt pathway is closely associated with cancer, diabetes mellitus, PD, AD, and other neurological diseases. PI3K/Akt pathway, in turn, is regulated by upstream …

Phytochemicals and Neurodegenerative Diseases: Focusing on PI3K/Akt/mTOR

In recent years, we have also drawn a promising future for natural products in treating NDDs (Nouri et al., 2019). Focusing on the critical PI3K/Akt/mTOR pathway and close interconnected mediators, phytochemicals pave the road against AD, aging, PD, CNS (brain and spinal cord) injuries, MS, HD, ALS, depression, epilepsy, NP, and autism. …

Clinical potential of plant-derived natural products

As described, various phytochemicals have shown pre-clinical evidence to be used against NDDs. Although limited clinical studies are provided to reveal their effectiveness and associated pharmacological mechanism in the human body. We have previously revealed the clinical potentials of natural compounds in combating NDDs through modulating apoptosis/autophagy, and interconnected inflammatory/oxidative pathways (Abbaszadeh et al., 2020). Focusing on the PI3K/Akt/mTOR pathway, phytochemicals are …

Phytochemicals novel delivery systems: targeted therapy and nanoformulations

Nanomedicine is the medical application of nanotechnology, which uses biocompatible, and low toxicity nanoparticles in various fields of medicine (Pelaz et al., 2017). The composition and activity of many phytochemicals have already been investigated and appointed. Phytochemicals are showing great potential of neuroprotective effects in both *in vivo* and *in vitro* studies. As an obstacle, many of these compounds have shown insufficient absorption profiles because of difficulty passing the lipid …

Conclusions and future perspective

Recent reports are indicating the critical role of PI3K/Akt/mTOR in the central nervous system. Growing evidence also highlights the dysregulated PI3K/Akt/mTOR pathway and interconnected mediators in the pathogenesis of NDDs. Besides, the present side effects and drug-resistance of the conventional neuroprotective agents urge the need for providing alternative therapies. So, providing natural multi-target agents for simultaneous targeting of the aforementioned mediators, with higher efficacy …

Author Contributions

Conceptualization, S.F., M.H.F., and J.E.; drafting the manuscript, S.F., A.I., M.M.G., M.R., and M.B.M.; software, S.F.; review and editing the paper: S.F., M.H.F., J.E., Y.Q., M.W., P.L. and J.X. All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy. …

Declaration of Competing Interest

None. …

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(Fakhri et al., 2018b, 2019a) …

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References (259)

F. Abbaszadeh *et al.*
Targeting apoptosis and autophagy following spinal cord injury: Therapeutic approaches to polyphenols and candidate phytochemicals
Pharmacological research (2020)

M. ArunSundar *et al.*
3, 4-Dihydroxyphenylethanol assuages cognitive impulsivity in Alzheimer's disease by attuning HPA-axis via differential crosstalk of A7 NAChR with MicroRNA-124 and HDAC6
ACS chemical neuroscience (2018)

G. Bao *et al.*
Tetrandrine protects against oxygen-glucose-serum deprivation/reoxygenation-induced injury via PI3K/AKT/NF-κB signaling pathway in rat spinal cord astrocytes
Biomedicine & Pharmacotherapy (2016)

A.H. Bhat *et al.*
Oxidative stress, mitochondrial dysfunction and neurodegenerative diseases; a mechanistic insight
Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie (2015)

J. Cao *et al.*
Hyperoside alleviates epilepsy-induced neuronal damage by enhancing antioxidant levels and reducing autophagy
Journal of ethnopharmacology (2020)

Q. Cao *et al.*
Amentoflavone protects dopaminergic neurons in MPTP-induced Parkinson's disease model mice through PI3K/Akt and ERK signaling pathways
Toxicology and applied pharmacology (2017)

C.S. Cătană *et al.*
Natural products with anti-aging potential: Affected targets and molecular mechanisms
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Neurosci Lett (2010)

W.-F. Chen *et al.*
Neuroprotective properties of icariin in MPTP-induced mouse model of Parkinson's disease: Involvement of PI3K/Akt and MEK/ERK signaling pathways
Phytomedicine (2017)

H. Daitoku *et al.*
Regulation of FoxO transcription factors by acetylation and protein-protein interactions

Biochimica et biophysica acta (2011)

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(Fakhri et al., 2018b, 2019a)

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