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Revisión / Review

Neuroprotective natural products: Promising candidates against neurodegenerative diseases

[Productos naturales con propiedades neuroprotectivas: posibles candidatos para el tratamiento de enfermedades neurodegenerativas]

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Abstract: Neurodegeneration is a progressive loss of neurons both structurally and functionally causing neuronal cell death ultimately leading to development of various neurodegenerative diseases. Due to poor pharmacokinetic profile of neurotrophins, there still remains a challenge in their neurotrophic therapy where plants, bacteria and fungi, as natural products, could act as promising candidates against various neurological disorders by modulating the neurotrophic activity. Therefore, these natural products that mimic neurotrophins, could develop novel therapeutic approaches to herbal drug that can ameliorate neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease and other associated neurological disorders. Taking into account the failure of strategies involving single neurotrophins for the treatment of neurodegenerative diseases, we propose a combination of small molecules of natural products that may work synergistically to restore neuronal functions, minimize side effects and target multiple pathways for a more effective treatment.

Keywords: Natural products; Neurodegenerative diseases; Signalling pathways.

Resumen: La neurodegeneración es una pérdida progresiva de neuronas, tanto estructural como funcional, que causa la muerte neuronal, lo que conduce al desarrollo de diversas enfermedades neurodegenerativas. Debido al pobre perfil farmacocinético de las neurotrofinas, existe un desafío en su terapia neurotrófica donde plantas, bacterias y hongos, como productos naturales, podrían actuar como candidatos contra diversos trastornos neurológicos al modular la actividad neurotrófica. Estos productos naturales que asemejan a las neurotrofinas podrían desarrollar enfoques terapéuticos novedosos como medicamentos a base de hierbas que pueden mejorar enfermedades neurodegenerativas como: Parkinson, Alzheimer y otros trastornos neurológicos asociados. Teniendo en cuenta el fracaso de las estrategias terapéuticas de neurotrofinas para las enfermedades neurodegenerativas, proponemos una combinación de pequeñas moléculas de productos naturales que pueden funcionar sinérgicamente para restaurar las funciones neuronales, minimizar los efectos secundarios y apuntar a múltiples vías para un tratamiento más efectivo.

Palabras clave: Productos naturales; Enfermedades neurodegenerativas; Vías de transducción

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ABBREVIATIONS

AD – Alzheimer's disease, **BDNF** – Brain-Derived Neurotrophic Factor, **HD** – Huntington's disease, **IRAK** – Interleukin-1 receptor-associated kinase, **JNK** – c-Jun N-terminal kinase, MAPK – mitogen-activated protein kinase, **NDD** – Neurodegenerative Disease, **NGF** – Nerve Growth Factor, **PD** – Parkinson's disease, **PI3** – phosphoinositide 3-kinase, **PIP2** – Phosphatidylinositol 4,5-bisphosphate, **PLC-γ** – phospholipase C-γ, **p75NTR** – p75 neurotrophin receptor, **ODNM** – (1R, 10S)-2-oxo-3, 4-dehydroxyneomajucin, **Trf** – TNF receptor-associated factor, **Trk** – Tyrosine kinase receptor.

INTRODUCTION

Nervous system is a highly complex part of mammals that controls its own action and coordinates the sensory information by transmitting signals to and from different parts of the body. In vertebrates, this system comprises the Central Nervous system (CNS) and the Peripheral Nervous system (PNS). The CNS comprises of brain and spinal cord whereas PNS comprises nerves that are enclosed bundles of axons that connect the CNS to other parts of the body. Neurons are cells of the nervous system composed of cell body, nucleus, dendrites and axon**s**. Neuronal degeneration is a progressive loss of neurons, both structurally and functionally causing cell death. Therefore, Neurodegenerative disease (NDD) can be defined as a collective term for sporadic and heterogeneous disorders commonly characterized by progressive dysfunction in nervous system resulting from the loss of structure and function of neuronal cells leading to their death (Jellinger, 2010). Most commonly, these diseases are the cause of morbidity and mortality especially among aged people (Erkkinen *et al*., 2018). NDD includes Parkinson disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis and is generally associated with various neurological disorders such as stroke, trauma, and spinal cord injury.

Various efforts are being carried out to understand the NDD mechanisms and it has been found that genetic mutations in unrelated genes are among those candidates that play an important role in causing these diseases (García & Bustos, 2018). These mutations give rise to a number of repetitions of nucleotide triplet CAG known as polyglutamine tract that results in nine types of neurodegenerative diseases including HD and spinocerebellar ataxias (Lieberman *et al*., 2019). Other causes are protein misfolding and aggregation, protofibril formation, mitochondrial dysfunction, dysfunction in ubiquitin proteasome system, oxidative stress, DNA damage, axonal transport, synaptic failure and programmed cell death (Castillo *et al*., 2019).

Neurotrophins are the family of proteins that are crucial for the growth, differentiation during the development of nervous system, and maintain synaptic connectivity. These neurotrophins are composed of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin 3, and neurotrophin 4/5 (Saragovi *et al*., 2019). Chao (2003) reported that neurotrophins orchestrate the neural cell function, survival and development. However, due to their poor pharmacological properties, poor serum stability and limited penetration in the CNS (Longo *et al*., 2007), they have faced significant problems in terms of their therapeutic application in treating NDD. Due to these reasons, some neurotransmitters such as acetylcholine, dopamine and γ-aminobutyric acid were found to overcome these problems and have shown to play an important role in treatment of NDDs and associated neurological disorders (Young, 2009). There are a large number of natural products with small molecules that come from plants, fungi and bacteria mimicking neurotrophins and modulating neural cell transduction pathways. Therefore, these natural products have a high potentiality to act as therapeutic drugs (Schiavone & Trabace, 2018). These small molecules of plants, bacteria and fungi could bypass the limitations of neurotrophins therapeutics (Xu *et al*., 2014) leading to clinical applications in the frontier areas of biomedical research.

In this review, a brief introduction of neurotrophins and the therapeutic approaches of natural products mimicking these neurotrophins to improve neurodegenerative diseases was has been presented. Major focus has been given in discussing various types of natural products obtained from plants, bacteria and fungi having neurotrophic properties proven themselves as emerging candidates to develop novel drugs with neuroprotective potentiality.

Neurotrophic Receptors and Signal Transduction Pathways

Neurotrophins act on receptors of the cell membrane and trigger a specific response that regulate growth and differentiation of neural cells (Huang & Reichardt, 2001; Chao, 2003). They carry out their functions with the help of receptors namely Tyrosine kinase receptor (Trk) and p75 neurotrophin receptor

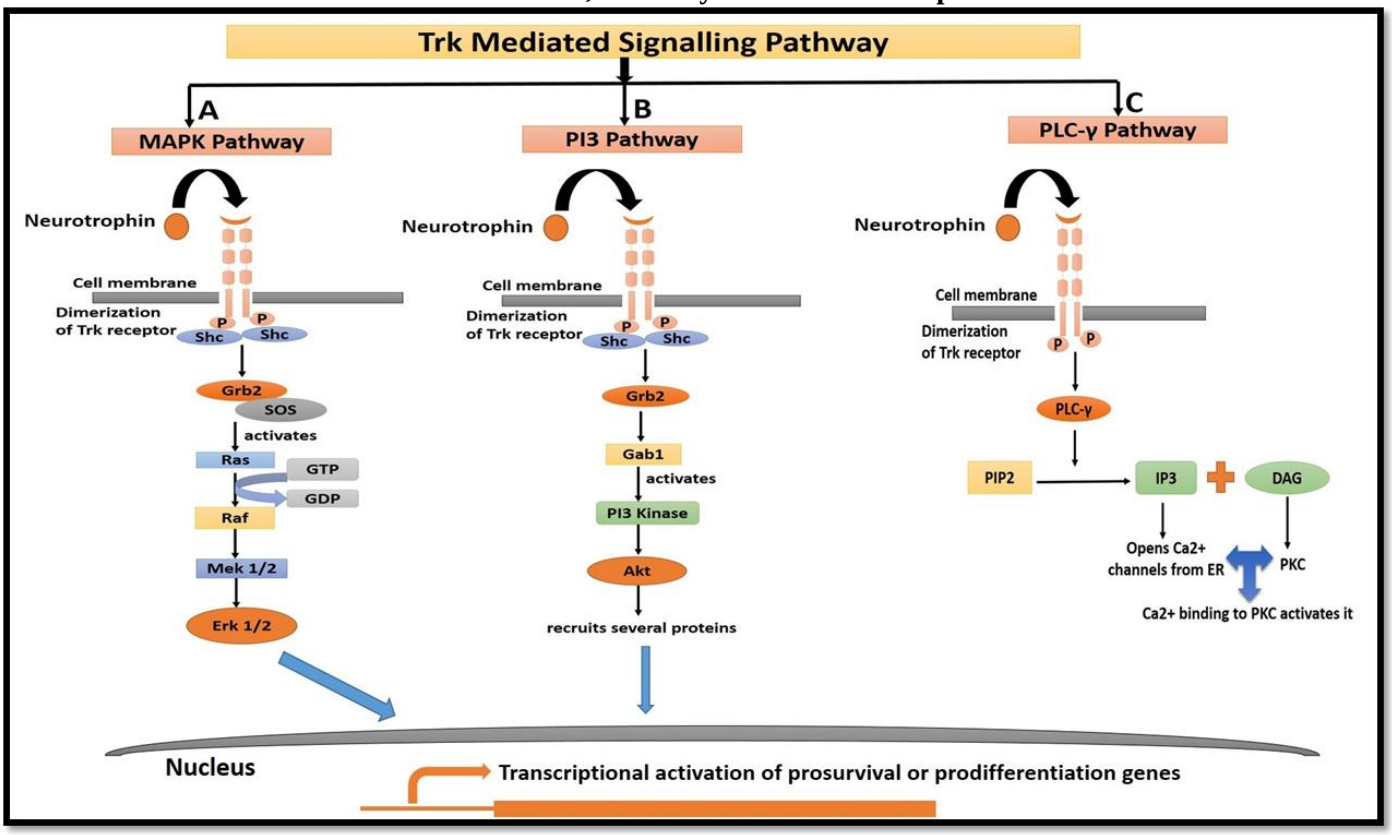
(p75NTR) (Saragovi *et al*., 2019). Trk has shown to enhance growth and survival of neural cells, whereas p75NTR has shown to induce both positive as well as negative signals playing an important role in neural cell development (Fahnestock & Shekari, 2019). The Trk signalling occurs via interconnecting cascades of several transduction pathways namely mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3)/Akt, and phospholipase C-γ (PLC-γ). Neurotrophins binding to Trk induce neural cell survival, differentiation and expression of proteins for proper neuronal functions such as ion channels and neurotransmitters (Huang & Reichardt, 2003), whereas binding to p75NTR triggers apoptosis of neural cells (Dechant & Barde, 2002).

Trk Mediated Signalling pathway

The neurotrophic factors of the neurotrophins bind with Trk receptors that mediated the Trk signalling pathway causing dimerization of the receptor followed by trans-phosphorylation of tyrosine activation loop (Reichardt, 2006). Huang & Reichardt (2001), discussed the major pathways that are activated during Trk mediated signalling, namely Ras, PI3-kinase and PLC-γ pathways. These include GTP mediated activation of Ras through MAPK signalling cascades, activation of Akt through PI3 signalling cascades and generation of Inositol tri-triphosphate (IP3) and diacylglycerol (DAG) through PLC-γ signalling cascades. These three signalling pathways (Figure No. 1) are interrelated among themselves and are result in neuronal development, survival, and preventing neuronal cell death (Yoshii & Constantine-Paton, 2010).

Figure No. 1

Major pathways activated during Trk mediated signalling – (A) MAPK Pathway (B) PI3 Pathway (C) PLC-γ Pathway. The structure of receptors and various protein shown in the diagram is purely hypothetically represented in this figure. IP3 – Inositol 1, 4, 5 triphosphate; MAPK – mitogen-activated protein kinase; PI3 – phosphoinositide 3-kinase; PIP2 – Phosphatidylinositol 4,5-bisphosphate; PLC-γ – phospholipase C-γ, SOS – son of sevenless, Trk – Tyrosine kinase receptor



MAPK pathway

Trans-phosphorylation of tyrosine activation loop creates a phosphotyrosine site on Shc domain that in turn recruits an adapter protein Grb2 that remains bound to another protein called 'son of sevenless. This leads to the activation of Ras protein, which stimulates signalling through Raf-Erk, p38MAP kinase and PI3 kinase pathways (Xing *et al*., 1998; Vanhaesebroeck *et al*., 2001). Ras activation activates protein kinase called Raf, which phosphorylates Mek 1/2 which in turn phosphorylate and activate Erk 1/2 transcription factor (English *et al*., 1999) causing differentiation and survival of neural cells through transcriptional events. Erk 1/2 as well as Erk 5 activates Rsk kinases that along with MAPK activated protein kinase 2 phosphorylate cAMP responsive element binding (CREB) protein, which leads to transcriptional activation of genes essential for prolonged survival of neuronal cells. Wu et al. (Wu *et al*., 2001) reported regarding the sustained MAPK activation where scaffolding proteins Gab2/Shp2 are activated by Trk and involved small G protein, Rap1 on the endosome.

PI3 pathway

Trans-phosphorylation of tyrosine activation loop creates a phosphotyrosine site on Shc domain thereby recruiting an adapter protein Grb2 that in turn recruits Gab1 permitting subsequent binding and activation of PI3 kinase (Holgado-Madruga *et al*., 1997). The activation of PI3 kinase in turn activates the protein kinase Akt that recruits several proteins through phosphorylation determining cell survival and development (Yuan & Yankner, 2000; Brunet *et al*., 2001; Yuan *et al*., 2003) by inhibiting apoptotic signalling (Howe *et al*., 2001).

PLC-γ pathway

The phosphorylated Y785 site on Trk A acts as docking site for PLC-γ enzyme leading to the activation of Trk. PLC then hydrolyses the membrane phospholipid Phosphatidylinositol 4, 5- bisphosphate (PIP2) to generate two classical second messengers namely IP3 and DAG. DAG stimulates the DAG regulated isoforms of protein kinase C (PKC) attaching it to the plasma membrane. On the other hand, IP3 results in opening of IP3 sensitive Ca^{2+} channels from endoplasmic reticulum thereby increasing the cytosolic Ca^{2+} where these ions bind and activate PKC (Putney & Tomita, 2012). Calcium signalling is a very important process for the neuronal synaptic transmission and synaptic plasticity (Kornijcuk *et al*., 2020).

p75NTR mediated signalling pathway

The binding of neurotrophins to p75NTR receptor leads to the activation of p75NTR signalling pathways via activation of NFkB and c-Jun N-terminal kinase (JNK). p75, which is a transmembrane glycoprotein, is a member of TNF receptor or CD40 receptor superfamily and possess conserved structures such as intracellular death domain (Liepinsh *et al*., 1997) as well as extracellular cysteine-rich repeats domain (Yan & Chao, 1991). The signalling cascade of p75NTR mediated two major pathways has been represented in (Figure No. 2).

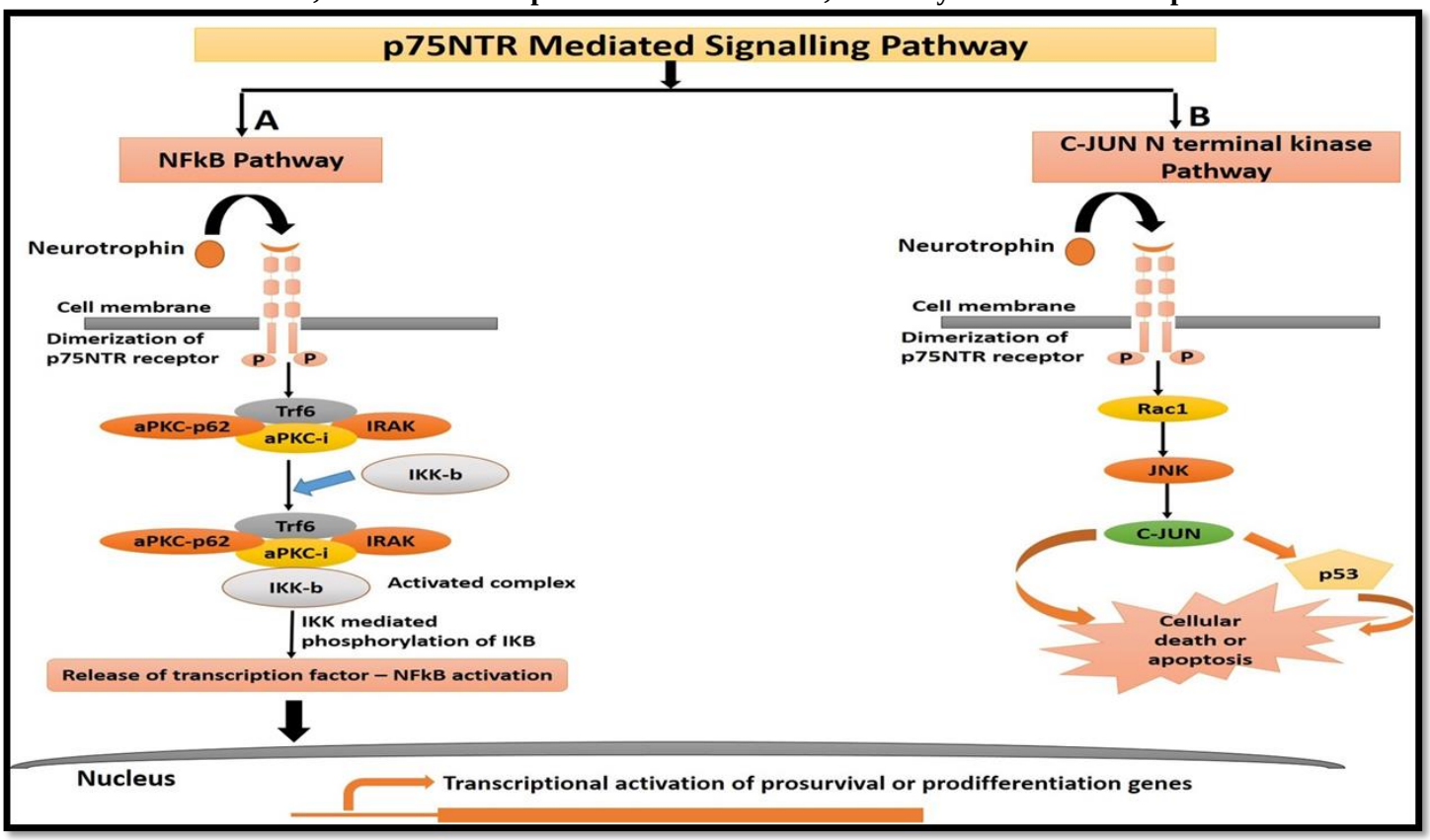
Activation via NFkB signalling pathway

The binding of neurotrophins to p75NTR leads to the activation of NFkB through the interaction of Trf6, a member of TNF receptor-associated factor (Trf) family thereby promoting the expression of genes involved with pro-survival neurons (Middleton *et al*., 2000). This is successfully demonstrated in glia Schwann cells and fibroblast cell lines (Khursigara *et al*., 1999). Binding of neurotrophins as for example NGF facilitates the association of Trf6 at the cytoplasmic domain of the receptor which in turn recruits Interleukin-1 receptor-associated kinase (IRAK) forming a complex. This complex recruits the necessary factors i.e., an atypical protein kinase C-i interacts with protein p62 (Vandenplas *et al*., 2002) that are required for the activation of transcription factor NFkB. Finally, IkB kinase-b (IKK-b) gets recruited to this complex and phosphorylation of IkB results in release of NFkB that enters the nucleus inducing expression of pro-survival genes.

Activation via JNK signalling pathway

The binding of neurotrophins with p75 NTR stimulates a distinctive pathway known as JNK signalling pathway. This pathway is also thought to be activated as a result of ceramide production (Verheij *et al*., 1996). It has been reported that binding of NGF to p75NTR via JNK pathway leads to apoptosis in oligodendrocytes (Yoon *et al*., 1998) and activation of caspase 1, caspase 2 and caspases 3. Binding of neurotrophins recruit a small GTPase protein, Rac 1 that in turn activates c-Jun N-terminal kinase (JNK). The cJUN then activates p53 protein ultimately resulting in p75 mediated cellular death or apoptosis.

Figure No. 2
Major pathways activated during p75NTR mediated signalling – (A) NFkB Pathway (B) c-JUN N-terminal kinase Pathway. The structure of receptors and various protein shown in the diagram is purely hypothetically represented in this figure. aPKC-i – atypical protein kinase C-i; aPKC-p62 – atypical protein kinase interacting protein p62; IKK-b – IkB kinase-b; IKK-b – IkB kinase-b; IRAK – Interleukin-1 receptor-associated kinase; JNK – c-Jun N-terminal kinase; p75NTR – p75 neurotrophin receptor; SOS – son of sevenless; Trf6 – TNF receptor-associated factor 6; Trk – Tyrosine kinase receptor



Natural products mimicking neurotrophins

There are huge number of natural products obtained from plants belonging to division namely Bryophytes (Agnieszka & Yoshinori, 2020), Pteridophytes (Baskaran *et al*., 2018), Gymnosperms (Rivadeneyra-Domínguez & Rodríguez-Landa, 2014) and Angiosperms (Dey *et al*., 2020) that have shown potentiality in mimicking neurotrophic factors of neurotrophins and help in the structural and functional development of neuronal cells. In this review important groups of natural products derived from plants, bacteria and fungi has been discussed concerning their neurotrophic properties that could be applied in treatment of neurodegenerative disorders. As shown in Table No. 1, natural products provide insight in neuroprotective functions in the developing of neural cells.

***Illicium* derived Sesquiterpenes**

Illicium spp. are the flowering plants belonging to family Schisandraceae, commonly known as anise tree or star anise. Trzoss *et al*. (2013) reported the presence of majucin type sesquiterpenes namely jiadefenolide, jiadefenin and (1R, 10S)-2-oxo-3, 4-dehydroxyneomajucin (ODNM) that have shown to mimic neurotrophic factors. Earlier, merrilactone A (Huang *et al*., 2000), bicycloillicinon (Fukuyama *et al*., 1997), tricycloillicinone (Fukuyama *et al*., 1995) have also been reported to be isolated from this genus. These natural products have shown to possess complex caged structure having neurotrophic properties and have played a role in the promotion of neurite outgrowth in primary cell cultures of fetal rat's cortical neurons, at low concentrations, between micromolar to nanomolar.

Table No. 1
Important groups of Natural Products mimicking neurotrophic function. ODNM – (1R, 10S)-2-oxo-3, 4-dehydroxyneomajucin, ChAT – choline acetyltransferase, AChE – acetylcholine esterase, NGF – Nerve growth factor, BDNF – Brain-derived neurotrophic factor, MAPK – Mitogen-activated protein kinases (* indicates data not available/not reported)

Important Groups	Natural Products	Derived Sources	Neuroprotective effects	Experimental models	Papers referred
***Illicium* derived Sesquiterpenes**	Jiadefenolide, jiadefenin	*Illicium jiadifengpi* (plant)	Promotion of neurite outgrowth in the primary cultures of neurons at 0.1 μM jiadefenin and at 0.1nM jiadefenolide	Fetal rats	Trzoss *et al*., 2011, Trzoss *et al*., 2013
	ODNM	*Illicium majus* (plant)	Promotion of neurite outgrowth in the primary cultures of neurons at 0.1 μM	Fetal rats	
	Merrilactone A	*Illicium merrillianum* (plant)	Promotion of neurite outgrowth in the primary cultures of neurons at 0.1 μM – 10 μM	Fetal rats	Huang *et al*., 2000
	Bicycloillicinone, tricycloillicinone	*Illicium tashiroi* (plant)	Upregulation of ChAT promote neurite outgrowth	Fetal rats	Fukuyama *et al*., 1995, Fukuyama *et al*., 1997
Cyathane derived Diterpenoids	Cyrneines A and B	*Sarcodon cyrneus* (fungi)	Induce neurite outgrowth at high concentration in PC-12 cells without causing significant cytotoxicity	Mouse	Marcotullio *et al*., 2006
	Erinacines A – F	cultured mycelia of *Hericium erinaceum* (fungi)	Induce NGF secretion of astroglia cells at a concentration ranging from 1-5 mM	Mouse	Kawagishi *et al*., 1996
	Scabronines A – C	mushroom *Sarcodon scabrosus* (fungi)	Induce secretion of neurotrophic factors from 1321N1 astrocytoma cells along with their enhancement in mRNA expression patterns	Human astrocytoma cells	Obara *et al*., 1999
Lactacystin	Lactacystin	broth culture of *Streptomyces* sp. (bacteria)	Non-protein neurotrophic natural product that have significant neurotrophic activity in neuroblastoma cell lines	*	Omura *et al*., 1991
***Lycopodium* derived Alkaloids**	Huperzine A	*Huperzia serrata* (plant)	Act as potent reversible inhibitor of AChE. This alkaloid has shown its promise in the treatment of AD and myasthenia gravis.	Mouse	Liu *et al*., 1986
			Increment of both NGF and p75NTR levels in PC-12 cells.	Mouse	Tang *et al*., 2005
			Increment in concentration of various proteins namely NGF, BDNF and phosphorylated MAPK when administered at 0.2 mg/kg.	Mouse	Wang *et al*., 2006
	Complanadines, Lyconadins	*Lycopodium complanatum* (plant)	Have shown their efficacy in enhancing mRNA expression of NGF in glial cells	Human	Ishiuchi *et al*., 2006; Morita *et al*., 2005
Steroids	Anicequol	*Acremonium* sp. (fungi)	Induction of neurite outgrowth in PC-12 cells	*	Nozawa *et al*., 2002

	Withanolide A	*Withania somnifera* (plant)	Shown neurite outgrowth in neuroblastoma cells	Human	Zhao *et al*., 2002
			Induction of synaptic reconstruction and axonal regeneration in damaged cortical neurons in rats and impaired brain in mouse	Rats, Mouse	Kuboyama *et al*., 2005

Plant products jiadefenolide, a pentacyclic sesquiterpene and jiadifenin were reported to be isolated from *Illicium jiadifengpi* whereas ODNM has been isolated from the plant *Illicium majus*. Various reports suggest that jiadefenin and ODNM has shown their potentiality in promoting neurite outgrowth in the primary cultures of fetal rat's cortical neurons at 0.1 μM concentration, whereas jiadefonolide exhibited a potent neurite outgrowth at much lower concentration of 0.1nM, showing to act like neurotrophins. Many potent small molecules were identified during the evaluation of the neurotrophic activity in these compounds that have shown to strongly increase the NGF activity in phaeochromocytoma, PC12 cell lines (Trzoss *et al*., 2013). These small molecules of natural products enhance NGF signalling pathways by itself rather than mimicking NGF (Trzoss *et al*., 2011).

Merrilactone A isolated from *Illicium merrillianum* has been reported to exhibit neurite outgrowth in the primary cultures of fetal rat's cortical neurons ranging from concentrations of 10 to 0.1 μM (Huang *et al*., 2000). Bicycloillicinone and tricycloillicinone isolated from *Illicium tashiroi* by Fukuyama et al. in the years 1997 and 1995 respectively, reported significant evidence regarding the upregulation of choline acetyltransferase that promote neurite outgrowth. In addition to this, choline acetyltransferase upregulation also represent a probable treatment strategy for AD patients since in AD patients, the level of acetylcholine is usually low.

Cyathane derived diterpenoids

Cyathane Diterpenoids possess unusual tricyclic structures and are reported to be isolated from Basidiomycetous fungi *Cyathus sp*. (Figure No. 3A), belongs to family Nidulariaceae commonly known as "bird's nest fungi". Besides this, cyathane diterpenoids have also been reported from *Sarcodon* and *Hericium* species. There are a numerous bioactivity reports of cyathane diterpenoids till date including its anti-cancer, anti-inflammatory and anti-microbial activity (Enquist & Stoltz, 2009). Many researchers have isolated various secondary metabolites namely cyrneines (Marcotullio *et al*., 2006), erinacines (Kawagishi *et al*., 1996), Scabronines (Obara *et al*., 1999) and reported their activity in inducing NGF synthesis in 1321N1 human's astrocytoma cells and mouse's astroglia cells. Besides these natural products at their lower concentrations, they also promote neurite outgrowth in PC12 cell lines.

Cyrneines A and B isolated from fungus *Sarcodon cyrneus* has been reported to induce neurite outgrowth at high concentration in PC12 cell lines without causing significant cytotoxicity. Marcotullio *et al*. (2006), also reported their activity in upregulating the transcription factors NF-κB and activator protein-1 (AP-1). Obara *et al*. (2007), through their studies also reported that Rac-1, a GTPase protein regulates the promotion of neurite outgrowth through Rac-1-dependent mechanism.

Kawagishi *et al*. (1996), isolated erinacines A – F from the cultured mycelia of *Hericium erinacium* and these cyathane xylosides has been reported to trigger the secretion of NGF in astroglial cells of mouse at a concentration ranging from 1 to 5 mM. Shimbo *et al*. (2005), studied the effect of erinacines A on rats and reported that this natural product is capable of increasing the secretion level of both NGF and homovanillic acid. Erinacines E has the ability to selectively bind to κ-opioid receptors to initiate a biological response (Saito *et al*., 1998) and this activation of receptors are reported to increase hyperalgesia i.e, enhances pain response in rats (Stein *et al*., 1989).

Obara *et al*. (1999), isolated natural products scabronines A–C from mushroom *Sarcodon scabrosus* of family Bankeraceae and again in the year 2001 (Obara *et al*., 2001), their group isolated newly synthesized Scabronines G from this particular mushroom. These compounds have been reported to induce secretion of neurotrophic factors from 1321N1 human astrocytoma cell line along with their enhancement in mRNA expression patterns. These natural products are not able to induce enough NGF secretion required for differentiation of PC12 cell. Scabronines G-methylester (ME) has been reported to

induce the secretion of Interleukin 6 (IL-6) from 1321N1 human astrocytoma cells and neuronal differentiation of rat PC12 cells.

Lactacystin

Lactacystin is a natural product from bacteria first isolated by Omura *et al*. (1991), from a broth culture of *Streptomyces sp.* (Figure No. 3B & Figure No. 3C). They reported this organic compound as the first non-protein neurotrophic natural product that have shown significant neurotrophic activity in neuroblastoma cell lines. They also found bipolar and multipolar morphology when they exposed the cells for 1, 3 or 4 days respectively. The neurites became increasing branched on much longer exposure to lactacystin. This phenomenon is dependent upon protein synthesis (de novo), actin polymerization and microtubule assembly (Fenteany *et al*., 1994; Fenteany *et al*., 1995). Fenteany *et al*. (1994), investigated the mode of action of lactacyctin in MG-63 human osteosarcoma cell lines and Neuro 2A cells and found that this natural product is capable of inhibiting cell cycle progression at both G0/G1 and G2/M phases of cell cycle. Fenteany *et al*. (1995), also reported useful findings that provide a link between differentiation of neurons and proteasomal inhibition.

Lycopodium derived Alkaloids

Lycopodium spp. (Figure No. 3D) are flowerless, vascular plants of family Lycodiaceae, commonly known as club mosses of division Pteridophyta. The genus *Lycopodium* is subdivided into four genera namely *Lycopodium*, *Lycopodiella*, *Diphasiastrum* and *Huperzia*. These pteridophytes has shown to possess extraordinary healing medicinal properties and are being used as homeopathic medicine for years to treat different human ailments. Several reports suggest that alkaloids isolated from *Lycopodium* spp. showed potentiality to mimic neurotrophic factors and display their neurotrophic profiles (Hirasawa *et al*., 2006).

Liu *et al*. (1986), isolated an alkaloid huperzine A of the plant *Huperzia serrata* where this natural product has shown to act as potent reversible inhibitor of acetylcholine esterase. This alkaloid has shown its promise in the treatment of AD and myasthenia gravis. Xu *et al*. (1995), reported that huperzine A could cross blood-brain barrier effectively without any cytotoxic effects with minimal side effects. Tang *et al*. (2005), performed studies in PC12 cells where they reported the increase of both NGF and p75NTR levels in the presence of this particular alkaloid. Wang *et al*. (2006), on other hand demonstrated the increase in the concentration of various proteins namely NGF, BDNF and phosphorylated MAPK in mice when huperzine A was administered at 0.2 mg/kg. Huperzine A is considered as an approved drug in China for its potentiality in treating cognitive deficiencies associated with neurodegenerative disease AD and is also being used as herbal medicine in USA (Ma *et al*., 2007; Ha *et al*., 2011). Researchers working on *H. serrata*, have also detected huperzine J, huperzine K and huperzine L and their potentiality in treating AD. These alkaloids not only occur in this particular species but also in other species of genera *Huperzia*.

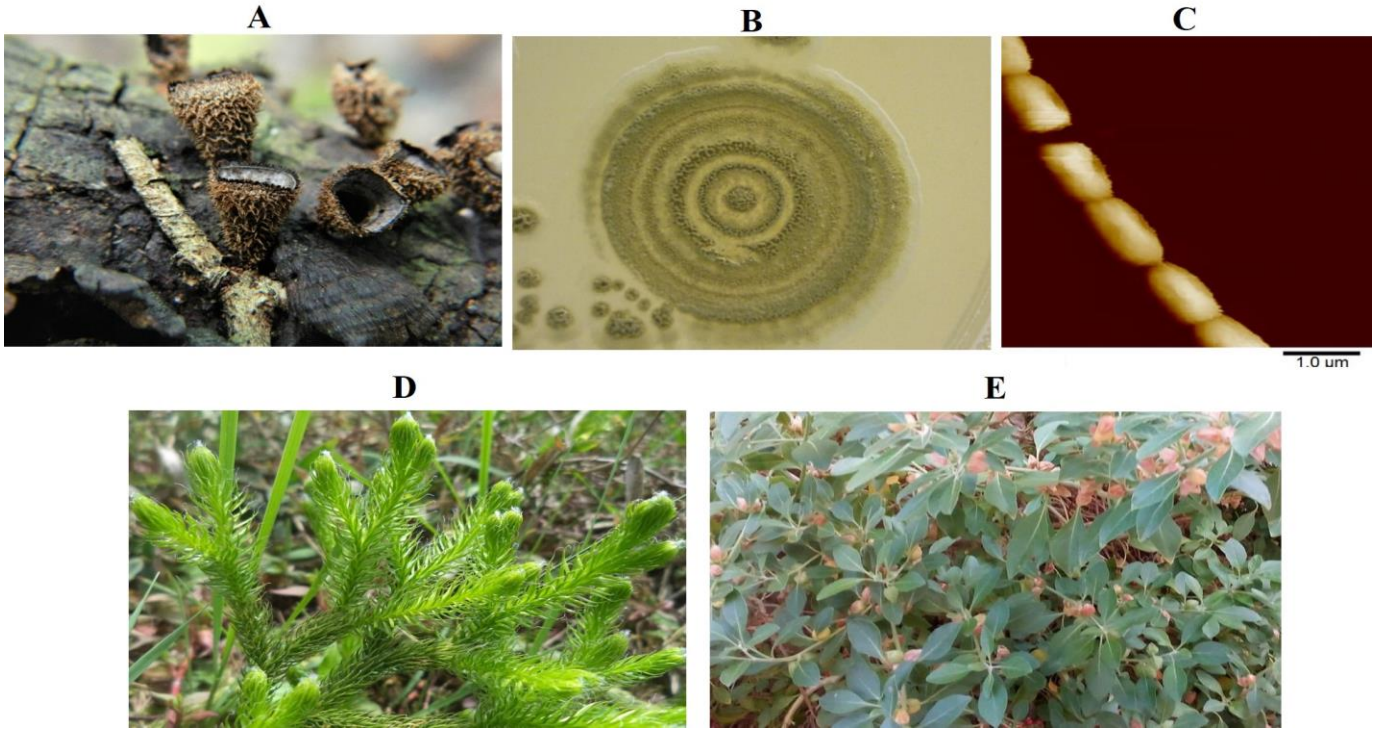
Kobayashi *et al*. (2000) and Kobayashi *et al*. (2001), isolated alkaloids Complanadines and Lyconadins respectively from the plant *Lycopodium complanatum*. These plant products have shown their efficacy in enhancing mRNA expression of NGF in 1321N1 human astrocytoma cell lines (Morita *et al*., 2005; Ishiuchi *et al*., 2006). Recent research on Lyconadins have reported Lyconadins C-E along with previously reported Lyconadin A and Lyconadin B. Cheng *et al*. (2016), have reported the presence of rare lyconadin G and lyconadin H in *L. complanatum*. Lyconadins have also been reported to show modest cytotoxicity against human epidermal carcinoma KB cells and murine lymphoma L1210 cells (Kobayashi *et al*., 2001). On other hand small molecules, Complanadine B and Obscurmines A-B have been reported in *L. complanatum* and *Lycopodium obscurum*. Complanadine A together with Complanadine B has shown to induce neurotrophic factors secretion from human astrocytoma cells (Morita *et al*., 2005). Hirasawa *et al*. (2004), isolated another natural product from *Lycopodium hamiltonii* and this alkaloid has shown to possess neurotrophic activity in human astrocytoma cells (Hirasawa *et al*., 2006). However, further biological investigation is still required to reveal the biological potentiality of these *Lycopodium* alkaloids.

Steroids

The first discovered steroid with neurotrophic activity is Anicequol, denoted by developmental code NGA0187 has been isolated from fungi *Acremonium* sp. TF- 0356 (Nozawa *et al*., 2002) of the family Hypocreaceae. They reported that the natural product isolated from fermentation broth induced the neurite outgrowth in PC12 cells. Another steroid, Withanolide A has been isolated from *Withania somnifera* (Figure No. 3E) of family Solanaceae commonly known as ‘aswagandha’ and considered as

Indian ginseng. This showed neurite outgrowth in human neuroblastoma cells (Zhao *et al*., 2002). Kuboyama *et al*. (2005), reported that withanolide A, a natural product from the Indian herbal drug Ashwagandha (root of *Withania somnifera*) is able to induce synaptic rebuilding and axonal regeneration in damaged cortical neurons of rats as well as in impaired brain in mice. Dominguez *et al*. (2004), reported another steroid β-estradiol that has the potentiality of inducing neurite outgrowth via the MAPK signalling pathway. In addition to this, Yokomaku *et al*. (2003) reported also the enhancement in the expression of synaptophysin caused by β-estradiol via the p44 MAPK pathway. Besides these, steroids namely S19159, allopregnanolone, deoxygedunin also have been reported to possess neurotrophic activity and they act across the MAPK mediated signalling pathways.

Figure No. 3
Shows some examples of fungus, bacteria and plants that possess neuroprotective factors which mimic neurotrophins, as described in this Review.
A – *Cyathus sp.* (fungi), **B** – colony of *Streptomyces sp.* (bacteria), **C** – Magnified view of *Streptomyces myrophorea*, (bacteria), and plants **D** – *Lycopodium* sp. (Division Pteridophyta), **E** – *Withania somnifera* (Division Angiosperms).



Probable therapeutic targets for treatment of neurodegenerative diseases and their associated disorders

Neurodegenerative diseases are a collective term for range of conditions that lead to progressive dysfunction and neuronal cell death. Neurons do not regenerate and therefore they finally die. Calabrese *et al*. (2007) focussed on the role of vitagenes namely heme-oxygenase-1, sirtuins, heat shock proteins 70, thioredoxin that are able to counteract the reactive oxygen species mediated damage of neuronal cells, showing thereby the potentiality of antioxidants in amelioration and treatment of neurodegenerative diseases and associated disorders.

However, there is currently no permanent cure for these type of diseases since these neurodegenerative diseases lead to the progressive degeneration of the neural cells ultimately causing ataxias and dementias. Dementias account for almost 60-70 percent of the cases in neurodegenerative patients. Common neurodegenerative diseases include Parkinson's disease, Alzheimer's disease, Huntington's disease, Motor neurone diseases, Amyotrophic lateral sclerosis, spinocerebellar ataxia,

Prion disease. In this review, the therapeutic approaches to PD and AD has been discussed briefly.

Parkinson's disease

Parkinson Disease is a neurodegenerative disease where degeneration of neuronal cells occurs in the substantia nigra of the brain that causes inability of these cells to secrete the neurotransmitter dopamine. Many reports have been demonstrated that around 80 % of patients suffering from PD cannot produce sufficient dopamine in the substantia nigra therefore people with Parkinson's acquire symptoms like tremor, imbalance, rigidity and slowness in muscular movements. Nunnari & Suomalainen (2012), reported the redox as well as mitochondrial dysfunctions as related to the pathogenesis of PD. Mitochondrial dysfunction may result from the mutation of PTEN-induced kinase 1 (PINK1), a mitochondrial specific kinase and Parkin, a E3 ubiquitin ligase as well as mitochondrial associated protein (Hertz *et al*., 2013). Therefore, activation of PINK1/Parkin pathway (Arena *et al*., 2013) opened an area for the researchers for developing therapeutic drugs obtained either from natural sources or developed synthetically against PD and associated neurological disorders. Most of the therapeutic strategies for treatment of PD rely on dopamine secretion level and Maguire-Zeiss (2008) reviewed the role of α-synuclein in PD pathogenesis and discussed about α-synuclein as probable therapeutic target that is able to ameliorate neurological disorders associated with PD. Johnson *et al*. (2009), reported the pharmacological modification of metabotropic glutamate receptors (mGluRs) as probable therapeutic target for developing novel pharmacological therapies against PD since mGluRs possess the ability to fine tune their neurotransmission process. Moreover, they developed various mGluRs antagonists and activators as therapeutic drugs and studied the effect of drugs in animal models concluding that these drugs apart from reversing motor deficits also provide neuroprotection. Hong & Sklar (2014), reported GTPases as therapeutic target area for treatment of PD since dysfunction of GTPases at molecular level is related with PD pathogenesis as GTPases regulates the mitochondrial fission and fusion, axon maintenance, neuronal inflammation and the increment in oxidative stress. The functioning of NOX1, a free radical producer, regulated by GTPase Rac1 has been seen to accumulate in dopaminergic neurons of patients suffering from PD and associated neurological disorders (Choi *et al*., 2012). Meng *et al*. (2017), studied the expression of the gen CHCHD2 in cells of both mammalian and the mutant *Drosophila chchd2* and observed that such mutation plays an important role in PD disease. This mutation in cells of *Drosophila* led to an abnormal development of matrix structures and impaired oxygen respiration in mitochondria, what implicate the loss of dopaminergic neurons together with dysfunction of motor neurons. They also showed that the mutation in cells of *Drosophila* could be reversed by the introduction of human CHCHD2. Therefore, the upregulation of CHCHD2 could be another therapeutic approach to treat PD and associated disorders. Recently, Liss & Striessnig (2019) reviewed the role of L-type calcium channel blockers like dihydropyridine and isradipine, which have been implicated in the neuroprotective therapy in patients suffering with PD.

Alzheimer's disease

Alzheimer's disease is the most common cause of dementia that leads to the inability of a person to think and behave independently, coordinate the things occurring around, forget current or recent conversations ultimately disrupting the ability of that person to function independently. The main cause of Alzheimer's disease has been identified as a protein misfolding disease (proteopathy), caused by plaque accumulation of abnormally folded amyloid ß protein and tau protein in the brain that initiates a signalling cascade leading to the death and degeneration of neural cells. Even before AD onset, one may able to detect the abnormality in metabolism of amyloid ß (Buchhave *et al*., 2012). So far, any compounds have been reported to interfere with the process of amyloid ß aggregation and there are reports suggesting that abnormal amyloid ß metabolism could be the area that has become the possible target for therapeutic interventions. Usually the AD is developed and observed in animal models, which are then translated into clinical practise (Karran & Hardy, 2014) that may be sometimes misleading as the human system is more complex as compared to mice or rat models. Therefore, researchers are trying to focus on small molecules of natural products that has the potentiality to act on amyloid ß aggregation, investigating and developing novel compounds that can be used for the treatment of AD.

Mandelkow & Mandelkow (1998), reported another important marker protein 'tau' that remain associated with microtubules that also plays an important role in AD pathogenesis. Ittner *et al*. (2010), reported the role of tau in regulating dendritic

function during AD by mediating toxicity of Aβ protein in mouse models. Therefore, both amyloid ß protein and tau protein have become important targets for the development of drugs to ameliorate AD and related disorders. Illes *et al*. (2019), reported that microglial cells are also responsible for causing AD and identified microglial P2X7 receptors to cause degeneration of neurons thereby opening a new therapeutic target that can be developed either from synthetic methods or from natural products for treatment of AD and associated neurological disorders. Recently, researchers from University of South Florida, United States, developed symptoms of AD in transgenic or knockout mice to investigate the role of antagonist of Apolipoprotein E (Apo-E) that have shown to be a potential genetic risk factor in developing this neurodegenerative disease (Sawmiller *et al*., 2019). They reported the antagonist called 6KApoEp works by blocking the interaction of Apo-E with N-terminal of amyloid precursor protein. Besides this, 6KApoEp has shown to reduce the Aβ protein aggregation and tau hyper-phosphorylation in brain, opening another therapeutic target that can ameliorate AD.

Challenges in neurotrophic therapy: benefits of natural products with small molecules

There are many challenges faced in neurotrophic therapy in terms of their clinical usage and direct application of the neurotrophic factors of neurotrophins to combat neurodegenerative disease. One such challenge is related to the methods as how they could be injected inside the cell using viral vectors. These limitations are due to the deficient knowledge of their pharmacokinetic properties and their poor permeability to cross the blood-brain barrier (Upadhyay, 2014). Hence, researchers have found the benefit of natural products with small molecules because they have the potentiality to behave as therapeutic drug. These small molecules bind any one of the neurotrophin receptors at the same time. They bind either Trk (Trk A/Trk B) or p75NTR and this action has shown to attenuate side effects. Natural products mimicking BDNF has been reported to have a high specificity towards TrkB receptor. They promote survival of neurons and induce neuronal differentiation in cultured hippocampal neurons (Massa *et al*., 2010). Massa *et al*. (2010), also applied these natural products mimicking BDNF in mouse models infected with different neurodegenerative diseases (AD, PD, HD) and found that they were able to prevent cellular death similar as BDNF. Schmid *et al*. (2012), also reported that natural products mimicking BDNF when binds to TrkB receptor, improves their potentiality to carry out different neuroprotective functions. Various researchers are carrying out a number of clinical trials with these small molecules derived from natural products having medicinal properties with neuroprotective applications. These will permit them to discover novel therapeutic approaches for treatment against the neurodegenerative diseases and associated neurological disorders.

CONCLUSIONS

Neurodegeneration is a progressive loss of neurons both structurally and functionally causing neural cell death. Common neurodegenerative diseases include Parkinson's disease, Alzheimer's disease, Huntington's disease, motor neuron diseases, amyotrophic lateral sclerosis, spinocerebellar ataxia and Prion disease (reference). There is currently no permanent cure for these diseases that finally produce ataxias and dementias. These dementias occur in an amount of about of 60 - 70 % of the cases of patients with neurodegenerative diseases. The neurotrophins play an important role in preventing such neurodegeneration. Because the pharmacokinetic properties of the neurotrophins are poor and present a limited penetration of in the CNS, it has been observed that the therapeutic potentiality to treat NDD have faced significant problems. Therefore, an immediate effort must be taken globally to unveil unexplored areas and fill the gap still existing in this research area. This is a reason to focus the need of search new areas for a novel development in the finding of a most effective therapeutic treatment in neurodegenerative diseases. To solve this problem, we emphasis the properties that are contained in many of the natural products that show very similar neurotrophic factors that mimic those of neurotrophins and therefore they may be an important alternative as tools for drug design in this context. Further research with natural products like plants, fungi and bacteria may be the solution to develop new areas using biochemical or pharmacological techniques to the treatment of neurodegenerative diseases. This may open up combinatorial therapies involving both natural products together with neurotrophins. There are being development by neuroscientists in conjunction with pharmacologists to target multiple pathways instead of single one. This approach has proved to be effective for the treatment of those neurodegenerative diseases as well as some associated neurological disorders.

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