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Review on some indigenous herbals for neuroprotective effect

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ABSTRACT

Neurodegeneration refers to a condition of neuronal death occurring as a result of progressive disease of long-term and is becoming a major health problem in the 21st century. Neurons degenerated are not replaced resulting in a cognitive loss, many neurodegenerative disorders, such as schizophrenia, depression, Alzheimer's disease (AD), dementia, cerebrovascular impairment, seizure disorders, head injury, parkinsonism. AMP-activated protein kinase (AMPK) boosts SIRT activation by increasing cellular NAD+ levels, which leads to deacetylation and regulation of downstream SIRT1 targets including peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1) (16), a master regulator of mitochondrial biogenesis Thus the herbal plants can be a valuable source of the drug against neurodegenerative disorders which will require high-throughput screening. Glutamate receptor-mediated excitotoxicity has been associated with several diseases of the brain, whereas in vivo and in vitro studies have shown that blocking the NMDA and the non-NMDA receptors simultaneously results in maximum protection against ischemic neurodegeneration. This review will highlight the role of herbal plants and their phytoconstituents against neurodegenerative diseases and other related disorders, focusing on their mechanism of action and therapeutic potential.

Keywords: Apoptosis Herbal medicine, Neurodegenerative diseases, Neuroprotective

INTRODUCTION

NEUROPROTECTIVE TARGETS OF NATURAL COMPOUNDS

Mitochondrial Dysfunction

Because of its high energy requirements, neurons rely heavily on mitochondria for survival. Apoptosis, metabolism, and calcium homeostasis are all essential cellular roles that Mitochondria play[1]. They are both a major cause of reactive oxygen species (ROS) activity and a major target for ROS-induced cellular damage when it comes to oxidative stress. Changes in mitochondrial biology are likely to have effects in a broad range of diseases, including neurodegenerative diseases, given their function as core regulators of cellular death and life (11-13). A clear correlation between mitochondrial dysfunction and anticancer drug neurotoxicity has also been identified[2]. SIRT1, a member of the sirtuin protein family, is a histone and protein deacetylase that is activated by Nicotinamide Adenine Dinucleotide (NAD)(+). SIRT1 stimulation and overexpression have been shown to be neuroprotective of both acute CNS injuries and chronic neurodegenerative disorders in a wide number of reports [3]. AMP-activated protein kinase (AMPK) boosts SIRT activation by increasing cellular NAD+ levels, which leads to deacetylation and regulation of downstream SIRT1

targets including peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1) (16), a master regulator of mitochondrial biogenesis[4]. As a result, in mammalian cells, the AMPK/SIRT1/ PGC-1 axis is closely linked to the orchestration of mitochondrial activity and energy/redox status.

APOPTOSIS

Apoptotic neuronal death is a frequent feature in the brains of patients with a variety of neurodegenerative disorders, and it is regulated by a number of proteins that are either intrinsic (mitochondrial-mediated) or extrinsic (death receptor-mediated) in nature [(5-6)]. By regulating mitochondrial membrane permeability and the release of the pro-apoptotic factor cytochrome c, which facilitates caspase-9 activation, the Bcl-2 protein family plays an important role in the regulation of the intrinsic pathway [7]. Bcl-2 proteins have members that either prevent or facilitate apoptosis (such as Bcl-2, Bcl-w, BclxL, and Mcl-1) (such as Bak, Bad, Bax, Bcl-rambo). A cell's ability to undergo apoptosis is determined by the equilibrium between these members. The caspase cascade, on the other hand, may be triggered at the endoplasmic reticulum (ER) by stress conditions that influence protein folding in the ER lumen. Finally, many stress-sensing transcription factors are activated and involved in AD pathogenesis, in addition to ER-resident proteins and mitochondria [8].

EXCITOTOXICITY

Glutamate is a major excitatory neurotransmitter in the central nervous system, and includes the retina[9] It is released in the presynaptic terminals for very brief periods of time and binds to a variety of receptor-linked channels in the postsynaptic membrane, resulting in the influx of Ca^{++} and the initiation of the action potential. There are three classes of glutamate-gated ion channels, known as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and N-methyl-D aspartate (NMDA) receptors. Glutamate presence in excessive amounts or for excessive periods of time can literally excite cells to apoptotic cell death, mainly due to high Ca^{++} level in the cytosol. Furthermore, the disruption of energy metabolism during acute and chronic neurodegenerative disorders may lead to inefficient glutamate clearance or even inappropriate release, which cause elevated levels of glutamate and increased concentrations of cytosolic Ca++. Finally, excitotoxicity can arise even with normal levels of glutamate, if NMDA receptor is activated [10].

Glutamate receptor-mediated excitotoxicity has been associated with several diseases of the brain, whereas in vivo and in vitro studies have shown that blocking the NMDA and the non-NMDA receptors simultaneously results in maximum protection against ischemic neurodegeneration.[11] Furthermore, myricetin inhibited glutamate-induced excitotoxicity in neurons; specifically, it affected NMDAR receptor (NMDAR) phosphorylation, which had, as a result, reduction of intracellular Ca++ overload. Myricetin also inhibited the glutamate-induced ROS production and the activity of caspase-3 by interacting withit.

Table:1 Neuroprotective medicinal plants

MEDICINAL PLANTS	COMMON NAME	FAMILY	MAJOR CONSTITUENTS	GEOGRAPHICAL SOURCES	MEDICINAL USES
Crocus sativus[11]	Saffron	Iridaceae (Crocoideae family)	• Saffranal (Volatile) • Crocetin (Non-Volatile)	Iran Afghanistan Turkey Spain	• Cognitive disorders, Neural disorders, relax smooth muscles • Treat the mild to moderate depression
Nigella sativa[12]	Black Cumin (Annual herbaceous)	Ranunculaceae	• Anethole, P-Cymene • Carvone. • Linoleic acid (55.6%) • Oleic acid (23.4%) • Palmitic acid (12.5%)	Mediterranean region Western Asia Middle East and Eastern Europe	• Anti-oxidative effects of N. sativa oil on the patients with rheumatoid arthritis • Reduce serum level • oxidative stress and anxiety • Improved the inflammatory response • Improved scopolamine • Induce the learning and memory impairment
Coriandrum sativum[13]	Corriander (Chinese Parsley)	Apiaceae	• Linalool (57.57%) • Geranyl acetate (15.9%) • Caryophyllene (3.26%) • P- Cymene (2.5%)	Mediterranean region	• Seed extract used as lotions and shampoos • Produce anti-microbial and anti-rheumatoid effects • Act as digestive agent • relieve anxiety and insomnia • Extracts decrease the duration of tonic seizures and showed a significant anticonvulsant activity in the maximal electro shock test

Ferula asafoetida[15]	Asafoetida (Devil's dung)	Apiaceae, Umbelliferae	● Resin (40-64%) ● Gum (25%) ● Essential oil (10-17%)	India Iran	● Leaf - anthelmintic , carminative and diaphoretic properties ● Roots – Antipyretic properties ● Treat the asthma, epilepsy , stomach ache, flatulence, intestinal parasites, weak digestion and influenza
Thymus vulgaris[16]	Garden thyme /Common thyme	Lamiaceae Labiatae	● p-cymene (8.41%) ● Thymol(47.59%)	Southern Europe Spain Mediterranean region	● It posses anti-oxidant, antimicrobial, anti-tussive, anti-spasmodic and expectorant effects. ● Thymol acts centrally via mimicking or facilitating GABA ction and modulate GABAA receptor and therefore it shows anti-convulsant and anti-epileptogenic effects
Zataria multiflora[17]	Satar	Lamiaceae	● Thymol, Carvacrol, ● p- Cymene, ● Gamma terpinene	Iran Pakistan Afghanistan	● Analgesic, antiseptic, antibacterial, Immuno- regulatory and anti-inflammator effects ● Essential oil – has anti-oxidant , anti-bacterial and anti-fungal properties in *invitro* studies
Curuma longa[18]	Turmeric	Zingiberaceae	● Curcumin (diferuloylmethane, the primary constituent , it is responsible for yellow colour of turmeric) ● Demethoxycurcumin ● Bisdemethoxycurcumin ● Volatile oils including tumerone, atlantone, and zingiberone	South or southeast Asia from Vietnam, China or Western India	● Water soluble extract raise dopamine, norepinephrine and 5 –HT levels in CNS ● It has Anti-inflammatory and anti- oxidant effects ● Curcumin therapeutic potential for neurodegenerative disease has garnered great interest in recent years

MATERIALS AND METHODS

PLANT DESCRIPTION

VITIS VINIFERA – GRAPES

Grapevines belong to the family of ViStaceae. As a source of grape, it is economically important both for direct fruit consumption and for the production of wine by fermentation. Grape vines are studied and cultivated as wine. Hermaphrodite flora has reproductive structures for both men and women. These flowers are grouped in so-called flora. It yields fruit in shoots derived from buds produced in the last growing season. Wine growing is one of the foundations behind the growth of the previous year's so-called "One Year Wood" which includes winter shoots that have become hard and woody. Vines will be pruned either into a cane which will support 8 to 15 buds or to a smaller spur which holds 2 to 3 buds. Flower buds are formed late in the growing season and overwinter for blooming in spring of the next year.

Vitis is distinguished from other genera of Vitaceae by having petals which remain joined at the tip and detach from the base to fall together as a calyptra or 'cap'. The flowers are mostly bisexual, pentamerous, with a hypogynous disk. The calyx is greatly reduced or non-existent in most species and the petals are joined together at the tip into one unit but separated at the base. The fruit is a berry, ovoid in shape and juicy, with a two-celled ovary each containing two ovules, thus normally producing four seeds per flower. Other parts of the vine include the tendrils which are leaf-opposed, branched in *Vitis vinifera*, and are used to support the climbing plant by twining ontosurroundingstructuressuchasbranchesorthetrellising ofavine-trainingsystem. In the wild, all species of *Vitis* are normally dioecious, but under domestication, variants with perfect flowers appear to have been selected[19].

GUAVA- *PSIDIUM GUAJAVA*

It is an evergreen shrub or small tree native to Caribbean, Central and South America. It is pollinated by insects mainly by honey bee, *Apismellifera*. It is widely cultivated in tropical and subtropical regions. It can range in size from as small as an apricot to as large as a grapefruit. Cultivars have white, pink, or red flesh, and a few also feature red (instead of green or yellow) skin. Cuttings, grafting, and air layering are more commonly used as a propagation method in commercial groves. Highly adaptable, guavas can be easily grown as container plants in temperate regions, though their ability to bloom and set fruit is somewhat less predictable. Several species are grown commercially; apple guava and its cultivars are those most commonly traded internationally. Guavas also grow in southwestern Europe, specifically the Costa del Sol on Málaga, (Spain) and Greece where guavas have been commercially grown since the middle of the 20th century and they proliferate as cultivars .

Psidium species are used as food plants by the caterpillars of some Lepidoptera, mainly moths like Ello Sphinx (*Erinnyisello*), *Eupseudosoma aberrans*, *E.involutum, and Hypercompeicasia*Mites, like *Pronematuspruni*and*Tydeusmunsteri*, are known to be crop pests of the apple guava (*P. guajava*)[20] . *Erwinia psidii*causes rot diseases of the apple guava. Although the fruit is cultivated and favored by humans, many animals and birds consume it, readily dispersing the seeds in their droppings and, in Hawaii, strawberry guava (*P. littorale*) has become an aggressive invasivespecies threatening extinction to more than 100 other plant species. By contrast, several guava species have become rare due to habitat destruction and at least one (Jamaican guava, *P. dumetorum*), is already extinct.

PAPAYA – *CARICA PAPAYA*

Papaya is a sparsely branched tree, usually with a single stem growing from 5 to 10 m tall, with spirally arranged leaves confined to the top of the trunk. The lower trunk is conspicuously scarred where leaves and fruit were borne. The leaves are large, 50–70 cm in diameter, deeply palmately lobed, with seven lobes[21]. All parts of the plant contain latex in articulated laticifers. Papayas are dioecious. The flowers are 5-parted and highly dimorphic, the male flowers withthe stamens fused to the petals. The female flowers have a superior ovary and five contorted petals loosely connected at the base. Male and female flowers are borne in the leaf axils, the males in multi flowered dichasia, and the female flowers in few-flowered dichasia. The fruit is a large berry about 15–45 cm (5.9–17.7 in) long and 10–30 cm (3.9–11.8 in) in diameter[22].

CONCLUSION

The management of neurodegenerative diseases remains a challenge in the modern medicine because of their complicated pathogenesis. Protein misfolding and their accumulation inside or outside of neurons is the key pathological feature in several neurodegenerative diseases including Alzheimer's, Parkinson's Huntington's disease. Herbal medicines are regarded as effective and promising sources of potential neuroprotective agents because of their cognitive benefits and more significantly, their mechanisms of action with respect to the fundamental pathophysiology of the diseases. Our review has acknowledged several herbal medicines such as *Vitis vinifera*,*Psidium guajava* and***Carica Papaya*** with potential therapeutic effects for neurodegenerative diseases. It is anticipated that

the information provided through this review should help the researcher to provide some evidence and conceptual detail of the benefit of a wide range of herbs as neuroprotective agents**.**

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