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Management of nerve injuries by utilization of nutraceuticals

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Abstract
Nerve injuries leads to loss of function from different organs of patient. It is caused due to dysfunction of neural cell. This dysfunction can occur by different ways like of genetics, protein accumulation in neural cell or any of the sudden accident. The nerve consist of various parts and one axon. The same nerve divides as CNS part and PNS part. The regeneration of nerve axon in PNS can be possible to function but the CNS part of axon cannot be regenerated. This regeneration takes place takes place with injured cell. This injury leads to pain referred as neuropathic pain. The nerve cell injury can be putted into three categories as of Neuropraxia, Axonotmesis and Neurotmesis. The injured neural cell leads to neurodegeneration. There are several treatments available on the basis of nutrients and constituents taken from herbal medicinal plants. Nutraceuticals is a branch known by its food supplements and nutrients of any herbal plant which have positive effect towards patient health and management of related disease. Nutraceuticals have less side and adverse effect towards patient. There are some medications which is derived from herbal medicinal plant such as Ginseng, Ashwagandha, Bacopa monnieri, Ginkgo biloba, Centella asiatica. Some compounds belong to as class of flavonoids, celastrol, trehalose, lycopene, sesamol, resveratrol and curcumin are showing high positive impression. The present scenario demands for the herbal medicinal treatment and for the fulfilment of this need the approach towards nutraceutical are raising high. Neuroprotection mechanism also shown by these nutrients. Apart from neuro regeneration, neuroprotective effect the nutraceutical also show antioxidant, anti-inflammatory effect. Polyphenol compound help to increase neural function.

Keywords: Neuropraxia, axonotmesis, neurotmesis, neuroprotection, polyphenol, neuropath

1. Introduction
Neurological disorders are highly treatable by nutraceuticals. They consist of some specific nutrients which are gained by dietary supplements, food product adding with vitamins and minerals. The improper diet can lead to disturbance in nervous system due to deficiency of essential constituents, so it is most necessary to take a healthy and proper diet. In worldwide more than 1 crore people suffer from the neural disorders and this number is increasing day by day due to increased unhealthy disturbed lifestyle. Neuro-degeneration can be happened by various ways such as aging because it plays a vital role in it.

The term nutraceutical was used initially by Dr Stephen de felice in 1989. From the ancient era till now humans have a good relationship with the herbs. The relationship is maintained till now because of the excellent effect shown by the herbs towards body system. In the present modern era by taking these herbs and medicinal plant their constituents as well as nutrients are to be extracted and form a single dose of it. This approach of dosing preparation is nutraceuticals. The modern science tends to help in human welfare by these nutrients (nutraceutical) in a effective manner. This improves the utilization of phytochemicals with its properties/behaviour from both plant and non-plant source. There are so many variety of compounds which are founded till now and this process is going on as there are many else which will have to found in future. Till now more than 999 plus compounded have been founded. These nutraceuticals majorly include amino acids, vitamins, minerals.

From the beginning of health related education the Ayurveda is playing a vital role in to maintaining a healthy disease free life of humans. In Ayurveda, 'Ayur' referred as age and 'Veda' mean to be way of living the life. There are many herbal medicinal plant included with their mode of administration and therapeutic uses. The herbs showing effective behaviour from over a long time. Ayurveda is written more than 5000 years ago.

The treatment of many diseases include neurological disorders are pointed in Ayurveda by herbal medication with its nutrients. Identification and using of these herbs are simple but their extraction of particular nutrients and constituents is the most important demand for patient for its administration as a nutraceutical to treat the disorder. Hereby the nutraceutical plays major role in improving the patient health and to maintain healthy lifestyle.

2. Nerve Injuries

It is a peripheral nerve injury, patient can be recovered within a month. The injury was firstly discovered by seddon HJ in 1943. The peripheral nervous system includes three types of cells stromal cells, glial cells and neuronal cells. The main work of PNS is to transmit signal from spinal cord to rest of the body system.

Sedddon classified nerve injury into three categories based on damage to axon and demyelination, connective tissue of nerve. Based on focal demyelination the mildest form of injury is called neurapraxia. The second category is axonotmesis in which nerve damages with addition of focal demyelination. Neurotmesis is the most severe form of nerve injury. In neurotmesis complete dysfunction of nerve is noticed.

According to classification scheme given by Sunderland Grade 1 and Grade 4 relates to neuropraxia and neurotmesis. Whereas Grade 2 and Grade 4 are axonotmesis with connective tissue damaging. In nerve injuries some term like neurodegenerative diseases regularly coined because they also happens by degeneration and dysfunction of neuron. Neurodegenerative disease include three major disorders as Parkinson, alzheimer, Huntington and multiple sclerosis. There are variety of herbs which work as a preventive mechanism for the neural injuries, disease and their inhibition.

3. Role of Nutraceuticals

The nutraceuticals work as of protective mechanism of nerve from neural inflammation. These nutraceutical work function as protection from neuroinflammation, neuroprotective effect and immunomodulant effect. There are variety of nutrients, constituents and compounds obtained from herbal medicinal plant in the form of their extract and then make its preparation called as branch of nutraceutical.

This is a series of nutraceutical really shown excellent effect towards nerve injury and they all are listed below with their constituents.

3.1 Nutraceuticals for improving the nerves from neurodegeneration

Protein misfolding is one of the main cause of neurodegeneration. These protein mainly include τau and amyloid-β. For managing this cause the nutraceutical can be used and it will directly replace synthetic drug. Due to its availability, affordable price and less side effect nutraceuticals can improve and prevent neural cells from their degeneration.

Table 1: This table include the nutraceutical responsible for neuroprotection from neurodegeneration and source and constituents

Source of Nutraceutical	Nutrients/phytoconstituents
Gingko biloba	Quercetin and Kaempferol
Ashwagandha	Withanine
Bhallaatak	Bhilawanol
Gotu kola	Asiatic Acid

3.1.2 Quercetin and Kaempferol

The brain fibers can be disturb by any of the disorder. Here quercetin and Kaempferol have widely seen to reduced free radicals. These nutraceutical prove too functioned as prevention from increased inflammatory cytokines which include mainly interleukins. The main source of obtaining these phytoconstituents is from the leaf part of gingko biloba. It has been seen to cure the cognitive disorders. The neurodegenerative disease Alzheimer's is treated by these constituents and also it improves blood circulation into the brain [1]. They are most commonly found polyphenols also founded from some fruits and vegetables. Kaempferol is a type of flavonoid also act somewhere as chemopreventive agent for cancer treatment. It blocks plenty of signalling pathway which make signalling pathway for survival of cancer cells. This nutraceutical also activates P53 and work to suppression of cell cycle genes for inducing apoptosis in breast and in cancer cells. Quercetin also fights widely from cancer and heart diseases. It improves blood circulation into the brain [2].

3.1.3 Withanine

The main source of Withanine is from Ashwagandha. It commonly known by name of Indian ginseng. From the ancient period its property is seen for enhancing neurocognitive property and memory enhancing. It inhibits the enzyme acetylcholinesterase, this enzyme is responsible for neurodegeneration. It show high property for the treatment and management of Alzheimer's disease. Withanine blocks nitric oxide from its activation then process of oxidative stress reversed. It provide neuroprotection and memory inhancing effect.

3.1.4 Bhilawanol

It is obtained from bhallaatak. It is a lipid soluble compound mainly found from semecarpus anacardium. This is herb which work by enhancing memory. This compound also inhibits acetylcholinesterase enzyme. The neural cells affected by stress are seen to manage by these constituents [4].

3.1.5 Asiatic Acid

This phytoconstituent is responsible for the neuroprotective effect. Asiatic acid increases the levels of glutathione. Asiatic acid is mainly extracted from *Gotu kola*. According to ayurveda it also show memory enhancing property. It decreasing the levels of malondialdehyde (it is the final product of polyunsaturated fatty acid peroxidation in cell) [3].

3.2 Neural protection

The proper functioning of signals in the body is regulated by the nerve cell; present in the body. These neural cells present in the count of millions in human body and they consist various synapse function as a joint between neurons. It is important for transmission of sensory and motor signals into various organs of the body. And this complete process is only be done by neurons located at various sites of the human body. If neuron will be damaged, injured or misfold by any of ways then it will not be function as usual. So, for prevention of the neuron and for its proper functioning it is necessary to get rid of arising unwanted factors. There are various herbs, plants available which are very good source

of nutrients helpful in neuroprotection. The various nutraceutical available for the neuroprotection.

Table 2: Nutraceutical responsible for neuroprotective affect with their source and constituents

Source of Nutraceutical	Obtained nutrients/phytoconstituents
Crocus sativus.	Crocin.
Nigella sativa.	Linoleic acid, oleic acid, Palmitic acid, Arachidic acid, Eicosadienoic acid, Stearic acid, Linoleic acid and Myristic acid, p-cymene, Thymoquinone, carvacrol and thymol.
Coriandrum sativum.	Linalool, linolenic acids.
Ferula assafoetida.	Propyl sec-butyl disulfide and germacrene B.
Thymus vulgaris.	Phenols, thymol and carvacrol.
Zataria multiflora.	Dihydroxyaromadendrane, luteolin and a-tocopherolquinone.
Curcuma longa.	Curcumin tumerone, atlantone and zingiberone.

3.2.1 *Crocus sativus*
It is known as a herbal remedy. It is used to treat cognitive disorder, relaxing the smooth muscles and for neural disorder [5, 6, 7]. *C. sativus* also reported for anti-Alzheimer properties. The administration of *C. sativus* extract before inducing in cerebral ischemia from middle cerebral artery (MCAO) showed reduction of glutamate and aspartate concentrations in the rats [8]. It is beneficial for depression also and act as anti-depressant agent in humans.

3.3.2 *Nigella sativa*
N. sativa belongs from the family of ranunculaceae. It is medicinally used as an anti-oxidant. It improves memory and nourishes cells. In a study it is seen that N. Sativa reduced the serum level, also improved the inflammatory responses and function as reduction of oxidative stress in patients with rheumatoid arthritis [9]. It works as neuroprotection and management of alzheimer disease and epilepsy [10].

3.2.3 *Coriandrum sativum*
Coriandrum sativum is belongs to the family of apiaceae. From the ancient Indian period it is widely used as a digestive agent. This medicinal plant is widely used for its properties like anti-oxidant and analgesic. A study was done in which a possible preventive effect of the hydro-alcoholic extract of the plant on neural damages was examined in rat model. And the result came as the total 3 dose of the extract able to prevent production of dark neuron as well as apoptotic cell in areas (hippocampus) compared to PTZ group. *C. sativum* have antioxidant property and by that it prevents from neuronal damage in PTZ rat model of seizure. Here seizure is a sudden attacks on behavioural changes and physiological characteristics [11].

3.2.4 *Ferula asafoetida*
It is obtained from the tap roots of the plant. *F. asafoetida*. It consist high nutritional properties. The root part of the plant is used as antipyretic. The plant constituents widely able to manage and in the treatment of different activities and responses like in intestinal parasites, weak digestion, influenza, asthma, epilepsy, stomach pain, flatulence. In a study it seen to be acts as a neural protective agent and neuro simulative agent in peripheral neuropathy [12]. Neurodegenerative disorder such as Parkinson's and Alzheimer's diseases can be manage by a therapy given from this system by *F. asafoetida* [13]. On *in vivo* and *in vitro* study in snail nervous system the property of inhibition of acetylcholinesterase is reported. It enhance memory.

3.2.5 *Thymus vulgaris*
Belong to lamiaceae family. It was used in tea as a herbal remedy from the ancient time till now by some group of humans. Some common activity can be seen from T. vulgaris like antitussive, antispasmodic, antioxidant, antimicrobial and expectorant effects [17, 18]. It can tailor some cholinergic function by enhancing synaptic acetylcholine as well as nicotinic receptor activity [14]. Thymol functioned as neuroprotective effects by inhibition of synaptic transmission by GABA mediation [15].

3.2.6 *Zataria multiflora*
The management of Alzheimer's disease can be possible by *Zataria multiflora*. It also functioned as restoration of memory impairments in rats by administration of *Z. multiflora* [16].

3.2.7 Curcuma longa
It widely found in south Asian countries. It prevents from neuropathic pain. Curcumin is mainly found in some plants as a polyphenolic compound. Neurodegenerative disease are managed by use of curcumin [19]. Curcuma longa have been reported to have inhibition effects in cytokines production, platelet aggregation [20, 21]. Protection from renal damage has been reported by *C. longa*. Curcumin seems to have neuroprotective effects in neurodegenerative diseases as well as cerebro-ischemic [22, 23].

3.3 Approach of nutraceutical for neurodegenerative by some natural compound with properties

Table 3: Consist of various nutraceuticals effective against neural dysfunction

Source	Main Ingredient	Effect and activity	References
Celasterol	Triptolide	Inhibition of cytokine production Minimize loss of dopamine and related neuron.	[24, 25]
Coffee bean extract	Caffeine	Helps in combination of adenosine receptors present in brain Minimize neurotoxicity (dopaminergic)	[26]
Flavonoid		Inhibition of synthesis of nitric oxide scavenging ROS and Reactive nitrogen species	[25, 27]
Sesame	Sesamol	Neuroinflammation protection and improves neurotransmission, synaptic plasticity	[28, 25]
Convolvulus pluricaulis extract	Convolvulus pluricaulis	Inhibition of enzymatic activity of acetylcholine esterase Helps in management of mRNA	[29]
Trehalose	Trehalose	Increased autophagic activity Inhibition of protein aggregation, beta amyloid	[25, 30, 31]
Lycopene	Lycopene	Minimize biochemical changes	[25, 32, 33]

3.4 Effective nutraceuticals against Alzheimer's disease

Alzheimer is a neurological disorder and in this disease the condition of memory loss arises significantly. Antioxidant nutraceutical can manage AD and also oxidative stress. The intake of antioxidant in patient can reduce the high risk of AD disorder. There are the food supplements which are rich in polyunsaturated fatty acids have ability to inhibit neurodegeneration [34].

Table 4: This table include mainly nature and activity of nutraceutical compound helpful in the treatment of Alzheimer's disease

Nutraceutical	Constituent	Nature	Activity	Reference
Carotenoids	Lutein, zeaxanthin, lycopene and β-cryptoxanthin, including α and β carotenes	Neuroprotective compound	Antioxidant activity, prevent mitochondria	[35]
Cyanidin		Neuroprotection	Anti-inflammatory and neuroprotective action, inhibition of activation of proinflammatory cytokines	
Luteolin		Neuroprotective activity	Prevent DNA against hydrogen peroxide induced toxicity, prevention from inflammation and cell damage	[36, 37]
Flavonoids	Catechin, epicatechin, epigallocatechin, and epigallocatechin gallate	Polyphenolic compounds	Cerebral blood flow, synaptic plasticity and repair of neuronal functions	[38]

3.5 Nutraceuticals in neuropathic pain

Nerve injury can lead to neuropathic pain. Pain is the common symptom of body by which patient get to know about the defect, dysfunction, injured area or any effective site of body from some type of sensation response. Here a term neuropathic meant for any type pain having on neuron due to its injury or any disorder. Pain is a type of signal from patient and it is due to protection of tissues from the injury. Chronic pain can precisely caused by direct neuronal tissue injury, which results in specific conditions like neuropathic pain [39]. Central neuropathic pain results disorder in the central nervous system whereas peripheral part refers to disorder associated with peripheral nervous system.

Table 5: It include all the nutraceutical which have good approach towards neuropathic pain arises due to nerve injury

	Nutraceutical	Source	References
1.	Zerumbone	Zingiber zerumbet rhizomes	
2.	Phlorotannins	Fucaceae, Sargassaceae and Araliaceae	[40]
3.	Papain	Carica papaya	
4.	Naringenin	Grapefruit, citrus fruits	[41]
5.	Linalool	Lavender, rosewood, bergamot	(Soh Katsuyama *et al*., 2012)
6.	α-Terpineol	Melaleuca leucadendra, Citrus aurantium, and Nepeta dschuparensi	[42]
7.	Lappaconitine	Aconitum Sinomontanum (Ranunculaceae)	
8.	Koumine	Gelsemium elegans	[43, 44, 45]
9.	Incarvillateine	Incarvillea sinensis	(Y. Chi *et al*., 1990)
10.	Hesperidin	Grapefruits, citrus fruits	
11.	Hecogenin acetate	Leaves of agave sisalana	(J. S. S. Quintans *et al*., 2014)
12.	Diosmin	Rutaceae family, scrophularia nodosa	[46]
13.	Dehydrocorybulbine	Corydalis yanhusuo	(L. Wang *et al*., 2016; Y. Zhang *et al*., 2014)
14.	Chlorogenic acid	Coffee	
15.	β-caryophyllene	Cannabis sativa, Syzygium aromaticum, Piper nigrum, Rosmarinus officinalis and Origanum vulgare	[47]
16.	Capsaicin	Fruits of Capsicum	

Activity of these nutraceutical

3.5.1 Zerumbone

This shows anti-inflammatory activity and due to this it can be beneficial for the treatment of neuropathic pain. Zerumbone can relief pain, in the current study as by the involvement of L-arginine-nitric oxide-cGMP-K + ATP pathways as a potential mechanism [48].

3.5.2 Phlorotannins

It is polyphenolic metabolites. They have antioxidant capacity [49]. This can show action of pain relaxation in injured nerve by the presence of phlorotannins [50].

3.5.3 Papain

Papain breaks peptide bonds present in basic amino acids as arginine, lysine and phenylalanine. This show various pharmaceutical, medicinal and nutritional activity included anti-inflammatory, analgesic and immunomodulatory activity [51]. Papain manage neuropathic pain by decreasing oxidative stress.

3.5.4 Naringenin

It shows neuroprotective effect. It suppress pro-inflammatory mediators in the spinal cord and inactivate glial cells [52]. In combination with it alters inflammatory cytokine release, oxidative nitrosative stress, and matrix metalloproteinases [53].

3.5.5 Linalool

In *in vivo* study it is seen that this compound show sedative, hypnotic and anticonvulsant effects of this compound on the CNS [54].

3.5.6 α-Terpineol

It is used in many cosmeceutical preparation as ell as in various fragments. TPN can be beneficial for management

of fibromyalgia pain [55]. TPN also reduce mechanical allodynia and thermal hyperalgesia.

3.5.7 Lappaconitine
This compound show various effects like analgesic, antifebric, anti-inflammatory, local anesthetic and cardiac arrhythmias. It also use in the treatment of neuropathic pain.

3.5.8 Koumine
Administration of koumine resulted in the reduction in mechanical hyperalgesia which further results in the deduction of neuropathic pain. It inhibit spinal neuroinflammation and activation of the translocator protein which have been linked to pain reduction (B. J. Xiong *et al*., 2017).

3.5.9 Incarvillateine
It is an excellent antinociceptive molecule. It show anti-inflammatory activity and can be helpful in the treatment of neuropathic pain. (M. L. Wang *et al*., 2015).

3.5.10 Hesperidin
It show neuroprotective effect as well as used in the treatment and management of neuropathic pain. It reduces pro-inflammatory mediators as like cytokines [56]. This molecule can be used in management of peripheral and central neuropathic pain, by binding with dopamine, GABA receptors. (A.I. Carballo-Villalobos *et al*., 2017)

3.5.11 Hecogenin acetate
Mechanical hyperalgesia might reduce by HA via cytokine-inhibitory mechanisms and neuronal transmission blockage in the spinal cord (J.S.S. Quintans *et al*., 2014). This nutraceutical can treat neuropathic pain.

3.5.12 Diosmin
It lowers the levels of IL-1, IL-8, and NO while increasing the level of IL-10 which can beneficial for inflammatory conditions [57]. Diosmin can inhibit neuropathic pain and it inhibit the stimulation of cytokine level and glial cells.

3.5.13 Dehydrocorybulbine
The neuropathic pain arises by any of injured nerve can be manage by Dehydrocorybulbine. This lowers interleukins level whereas it blocks P2X4 receptor expression and reduces ATP-induced intracellular Ca^{++} concentration in spinal cord injury.

3.5.14 Chlorogenic acid
It includes antioxidant, antibacterial, hypoglycemic, hypolipidemic, and anticancer activity [58]. This phenolic compound shows anti neuropathic effect against diabetic animals**.** This also reduces inflammatory responses. And finally it can treat neuropathic pain [59].

3.5.15 β-caryophyllene
It is a highly nutritional source and also used for flavouring agent. It binds with CB2 receptors, which are important therapeutic targets for inflammatory and painful conditions. It lowers inflammatory mediator levels and activates CB2 receptors [60].

3.5.16 Capsaicin
It shows some therapeutic effects such as cardioprotective, anti-inflammatory, anti-lithogenic, thermogenic and chemo-preventive. It can manage peripheral neuropathic pain [61]. Capsaicin can treat pruritis and gastritis caused by nonsteroidal anti-inflammatory drugs. It inhibits the synthesis of proinflammatory mediators.

Conclusion
Nutraceuticals are highly beneficial for the human health. It consist of a extracted form of nutrients, phytoconstituents. It has been seen that every nutraceutical shows some common effects and properties among other and these are as anti-oxidant, anti-inflammatory and in some as neuroprotection also. They all are also preventing from neurotoxicity. There are so many factors responsible for nerve injury as by of sudden accident, neural disorder or by some biological activities. These are some factor which leads to neural injury whereas neural injury consist of three stages and they named as neuropraxia, Axonotmesis, Neurotmesis Neurodegenerative disease like AD, PD, HD causes apoptosis, necroptosis and inflammation. The above mentioned nutraceutical provide neuroprotective effect by reducing inflammatory cytokines and enhance anti-inflammatory cytokines. It can be managed and treat by nutraceuticals. These all nutraceuticals provide protection against chronic diseases and improves health. Nutraceutical used for improving human health by its various properties whereas also improves the nerve health. In this review here is a listings of all the nutraceuticals included with their source, phytoconstituents and properties which have tendency to treat nerve injuries and neuropathic pain. There is a need of more study and making formulation from nutraceutical for its better usage. Making it popular among the humans required more awareness. The use of nutraceutical in patients is safe.

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Conflict of interest
The author declare that there is no conflict of interest in this study.

Credit authorship contribution statement
Karan Suyal: Main author, Student, writing, Project administration, validation, review and editing. Navin Chandra Pant: Mentor. Dr. Abhijeet Ojha: Supervision.

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