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Review Article

A review on: nutraceutical and neuroprotective approaches of *Momordica charantia* L. fruits against neurodegenerative disease

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ABSTRACT

The *Momordica charantia* is a tropical plant, also known as bitter gourd or bitter melon, is a crucial herbal remedy with a wide range of medicinal properties. People in Indian subcontinent and China consider, *M. charantia* as key components to treats variety of elements such as cancer, diabetes and neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, multiple sclerosis etc. These diseases are described by degeneration or loss of selective neuron populations in a progressive manner. The two main characteristic of neurodegenerative illness are oxidative stress and inflammation, which have been studying using the variety of medicinal herbs and their derivatives. However, very few authors have reported the protective effects of *M. charantia* against neurodegenerative diseases. This short review focus on the neuroprotective effects of *M. charantia*. Based on their anti-oxidant and anti-inflammatory properties, the present study emphasizes to further explore the protective effects of *M. charantia* against neurodegenerative and neuroinflammatory diseases.

Keywords: *In-vivo* studies, *In-vitro* studies, *M. charantia*, Neurodegenerative diseases

INTRODUCTION

Momordica charantia belonging the family of Cucurbitaceae is a herbaceous vine plant with ridged fruits called bitter gourd.¹ *M. charantia* are emerald green in colour while ripened fruits are yellow-orange in colour.² *M. charantia* is a tropical and subtropical plant that has long been utilized in Chinese, Indian, Sri Lankan, and Pakistan for traditional medicines.³ Different varieties of *M. charantia* are available in different habitats.⁴ Proteins, polysaccharides, flavonoids, alkaloids, glycosides, phenolics, tannins, triterpenoids, and steroids are the common phytochemicals present in *M. charantia*.⁵ Moreover, this plant is a rich source for a range of saponins such as momordicin, karavilagenin, and karaviloside.⁶

M. charantia plant has been used against a wide range of diseases including diabetes, cancer, obesity, microbial infections, hypertension, and AIDS, and these medicinal properties are described to the fruits, unripe fruits in the plant.^{7,8} Earlier reviews had discussed the medicinal role of *M. charantia* against obesity and inflammatory diseases.⁹ Other pleiotropic effects such as antitumor effects and anthelmintic effects have also been discussed in recent reviews; however, no review article had specifically pointed out its neuroprotective effects.¹⁰ In this review we discuss the preclinical studies focused on studying the neuroprotective effects of *M. charantia*. Collects from PubMed and google scholar search was done to collect information about Neuroprotective effect of *M. charantia* using the keywords '*Momordica charantia*' and 'Neuroprotective effects', '*Momordica charantia*' and

‘Neurodegenerative diseases’, and ‘*Momordica charantia*’ and ‘Neuroinflammatory diseases’ and also this review paper characterised the efficacy of *M. charantia* as a therapeutic agent against the yet unexplored neurodegenerative and neuro-inflammatory diseases.



Figure 1: *Momordica charantia* L.

Table 1: Commonly used names of *Momordica charantia* L. based on culture of people in a particular locality.¹³

Names of Regions	Used local Names
English	Bitter gourd, Balsam pear, Balsam Apple
Nepali	Teeta, Karela
Arab	Quisaul-Barri
Assam	Kakiral, Kakral
Bengali	Karela, Uchchhe, kerule
Bombay	Kurela, jangro
Gujrati	Karela
Hindi	Karela, Kardi
Kannada	Hagal
Odia	Kalara
Sanskrit	Sushavi, Karavella
Tamil	Pakal, Pavaka, Chedi, Paharkai
Telegu	Koekara, kaaya
Urdu	Karela

BIOGRAPHICAL AND BOTANICAL DESCRIPTION

Momordica charantia, commonly known as bitter melon, is a tropical and subtropical vine of the family Cucurbitaceae, widely grown for its edible fruit. The plant is indigenous to Africa and Asia; it thrives well in hot climates, mostly seen growing up trellises or fences.¹¹ The vine displays deeply lobed leaves and bright yellow flowers, which form into a distinctively warty, oblong fruit. The fruit is green when unripe and turns yellow or orange as it ripens, exposing bright red seeds within.¹² Bitter melon is highly regarded for its sharp, bitter flavor and has been used extensively in various gastronomic traditions and folk medicine, particularly in Asian and African cultures and the various local names are used in

various region of world described in Table 1.¹³ Biographically, it had been used for thousands of years, mostly for blood sugar control and as a digestive aid.¹⁴ Its botanical properties and varied uses make it an important plant in both horticulture and ethnobotany, leading to its continued cultivation and cultural significance around the world.¹⁵

Traditional uses of *Momordica charantia* L.

Bitter melon is often eaten cooked while it is green or in early fading. Shoots and leaves of Bitter melon can be consumed as greens. The fruit is bitter when raw, but it may be soaked in cold water and drained to reduce part of the bitterness. Bitter melon or *Momordica charantia* is appreciated in Chinese cuisine for its bitter flavour, and it is commonly used in stir-fries (usually with pork and douchi), soups, and herbal teas like gohyah tea. It has also been used as a bittering additive instead of hops in some beers in China and Okinawa.¹⁶

The plant has been used in traditional and folk medicines for various medical applications, including treating T2DM, hypertension, obesity, cancer, bacterial and viral infections, and AIDS.¹⁷ In Ayurveda medicine, bitter melon, known as karela, are used for thousands of years. The juice is used for joint pain relief, chronic fever, jaundice, liver and digestive system illnesses, and treating burns, boils, and rashes. In Turkish folk medicine, the oil from ripe fruits is used for gastric ulcers.¹⁸

Nutraceutical approaches of *Momordica charantia* L.

The fruits of *M. charantia* are mineral-rich and loaded with vitamins with the bitter melon fruit having the highest antioxidant capacity. Its major constituent is phenolic acid, which aids in fighting against oxidative stress and other deleterious molecules.¹⁹ The intake of *M. charantia* as a dietary food imparts cell reinforcement advantages against asthma, sensations of consuming, clogging, colic, diabetes, hack, fever, gout, helminthiasis, skin ailments, ulcers, and wounds.²⁰ The juice of the fruit is also used for treating liver diseases, cardiac oedema, and hypertrophy.²¹ Fruits of *M. charantia* are used for treating ulcers, diseases of the liver and spleen, diabetes, high cholesterol, parasites in the digestive tract, gas in the stomach, and wound healing.²² For its hypoglycemic effect, *M. charantia* is beneficial in the management of diabetes mellitus. The fruit contains charantin, vicine, and polypeptide-p, all of which contribute to its glucose-lowering capabilities. Charantin, a steroidal saponin, and polypeptide-p, an insulin-like compound, enhance glucose uptake and glycogen synthesis in the liver, muscle, and adipose tissues, mimicking the action of insulin.²³

Additionally, *M. charantia* exhibits strong antioxidant properties, primarily due to its high content of phenolic compounds and flavonoids.²⁴ These antioxidants combat oxidative stress, which is implicated in the pathogenesis of various chronic diseases, including cardiovascular

diseases and cancer.²⁵ By neutralizing free radicals and reducing oxidative damage, *M. charantia* helps in mitigating inflammation and protecting cellular integrity. The anti-cancer potential of *M. charantia* has also been a focal point of recent studies. The bioactive compounds in bitter melon, such as cucurbitane-type triterpenoids, have demonstrated the ability to inhibit cancer cell proliferation and induce apoptosis in various cancer cell lines, including breast, prostate, and colon cancers.²⁶ These compounds interfere with multiple cellular pathways, including those involved in cell cycle regulation, apoptosis, and metastasis, highlighting their potential as chemopreventive and therapeutic agents.²⁷ Moreover, *M. charantia* extracts have shown to inhibit angiogenesis, which is crucial for tumour growth and metastasis.²⁸ In terms of cardiovascular health, *M. charantia* has been noted for its lipid-lowering effects. The fruit and its extracts can reduce levels of low-density lipoprotein (LDL) cholesterol and triglycerides while increasing high density lipoprotein (HDL) cholesterol. These lipid-modulating effects are beneficial in preventing atherosclerosis and other cardiovascular diseases.²⁹ Furthermore, *M. charantia* has shown promising anti-inflammatory and immune modulatory properties and are primarily known to inhibit the key inflammatory mediators such as cyclooxygenase (COX) and nitric oxide synthase (NOS).³⁰ By downregulating the production of pro-inflammatory cytokines and enzymes, bitter melon helps in managing inflammatory conditions like rheumatoid arthritis and inflammatory bowel disease. Another significant aspect of *M. charantia*'s nutraceutical is its potential role in weight management. The fruit's high fiber content aids in promoting satiety and reducing overall calorie intake, while its compounds enhance lipid metabolism and inhibit adipogenesis, the process of fat cell formation.³¹

Moreover, *M. charantia* has antimicrobial properties that can protect against various pathogenic bacteria, viruses, and fungi. The fruit's extracts have demonstrated efficacy in inhibiting the growth of harmful microorganisms, which is attributed to the presence of bioactive compounds such as momordicin, a protein that exhibits antifungal and antibacterial activity.

NEUROPROTECTIVE PROPERTIES

Neurodegenerative diseases (NDs) are incurable, fatal disorders characterized by degeneration and loss of selective neuron populations in a progressive manner, which differs from the cell death, occurs due to any metabolic or toxic stress.³² There are different types of Neuro degenerative diseases (ND) including Alzheimer's disease (AD), Parkinson's disease (PD), and Multiple Sclerosis (MS), Motor neuron diseases (MND), Huntington's disease (HD), and Priondisease. Among these, AD, PD, MS and HD are the most commonly occurring Neuro-Degenerative Diseases (NDs).³³ Neuronal cell death is considered as a major hallmark of NDs. Neurotoxic molecules such as reactive oxygen species (ROS) and protein aggregates induce

neuroinflammation or neuronal cell death, which eventually leads to neurodegeneration.³⁴ Number of several studies demonstrated that the neuroprotective effects of crude extract or purified compounds of *M. charantia* helps in attenuating oxidative stress, neuroinflammation and cell death.

IN-VITRO STUDIES

Choi et al report that *M. charantia* derived phenolic protocatechuic acid significantly reversed C6 glial cell damage induced by hydrogen peroxide (H₂O₂) and AD-associated amyloid beta 25-35 (Aβ₂₅₋₃₅). In this study, ROS production was controlled by protocatechuic acid.³⁵ Similar antioxidant and anti-apoptotic effects were exerted by ethanol extract of *M. charantia* fruits against oxidative stress-induced SK-N-MC human neuroblastoma cell death. Results from this study showed that the extract blocked mitochondria dependent apoptotic pathways, which is also inhibited mitogen-activated protein kinase (MAPK) signalling by suppressing MAPK phosphorylation.³⁹ In another study, Tamilanban et al. proved that charantin derived from the fruits of *M. charantia* efficiently protected human SH-SY5Y neuroblastoma cells against neurotoxins 1-methyl-4-phenylpyridinium (MPP) and tunicamycin.³⁶ Gong et al. found that *M. charantia* polysaccharides exerted neuroprotection against primary rat hippocampal neuronal cells subjected to oxygen glucose deprivation.³⁷ Altogether, these in vitro studies found substantial anti-oxidant and neuroprotective effects of *M. charantia*.

IN-VIVO STUDIES

Neuroprotective effects of *M. charantia* have been considerably investigated in limited number of In vivo Neurodegenerative diseases (ND) models. Neuronal cell loss followed by memory impairment is a characteristic feature in Alzheimer's Disease. In (Figure 3), it is mentioned that the medicinal properties and underlying molecular mechanisms of *M. charantia*, and its possible protective effects against the yet unexplored neurodegenerative diseases. Pathakotla et al. demonstrated the neuroprotective effect of *M. charantia* fruits in scopolamine induced mouse AD model. The data of this research showed that ethanolic extract of *M. charantia* fruits attenuated the memory loss and improved learning and memory in Alzheimer's disease (AD) mice by blocking lipid peroxidation and acetyl cholinesterase activity.³⁸ Similar anti-amnesic activity was reported in by scopolamine-induced rat AD model.³⁹

In a recent investigation, Deng et al, report hydro alcoholic extract of *M. charantia* fruits showed to restore the memory in scopolamine-induced mouse model.⁴⁰ In another important study, *M. charantia* fruit powder was found to reduce the side effects of Lithium Chloride-mediated treatment in Tg AD mice and in streptozotocin-induced AD mice. The results of this study provided more

details on the underlying neuroprotective mechanisms of *M. charantia* in Alzheimer's disease.

Typical AD pathological features including extensive neuronal loss, gliosis, oligomeric Amyloid β protein formation, and hyperphosphorylated tau protein level were substantially reduced by *M. charantia*.⁴¹ Thus, these studies showed that *M. charantia* shall be a promising Phyto-therapeutic drug candidate plant to treat AD. Nerurkar et al. demonstrated anti-oxidant and anti-neuro inflammatory properties of *M. charantia* in high-fat diet associated oxidative stress and neuro-inflammation in mice. Anti-oxidant markers glutathione, glutathione peroxidase, catalase, and superoxide dismutase were significantly normalized while pro-inflammatory markers interleukin-16 (IL-16), IL-17R, IL-22, and NF κ B1 were markedly reduced in mouse brain by *M. charantia*. In addition, gliosis markers Iba1, CD11b, GFAP and S100 β were decreased in *M. charantia* fed mice.⁴² A recent study by Deng et al report that *M. charantia* down-regulated the hippocampal expression of pro-inflammatory cytokine markers tumour necrosis factor-alpha (TNF- α), IL-6, and IL-1 β in mouse model associated with chronic social defeat stress. Moreover, hippocampal expression of positive inflammation mediators c-jun N-terminal kinase (JNK3), c-Jun, P-110 β was reduced and activity of negative inflammation mediators' phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT) was increased in *M. charantia*-treated mice.⁴³ Thus, these studies demonstrates effective anti-neuroinflammatory properties of *M. charantia* fruits. Findings of Ishola et al. showed anti-depressant and anxiolytic effects of methanolic extract of *M. charantia* in mice subjected to depression and anxiety.

They found that anti-depressant mechanism was attributed to the activation of receptors for serotonergic, noradrenergic, dopaminergic, and muscarinic cholinergic neurons and anxiolytic mechanism was attributed to the activation of receptors for GABAergic neuron.⁴⁴ Neuroprotective effects of *M. charantia* have been examined in *in vivo* neuronal injury models. In rat intracerebral hemorrhage-induced brain injury model, polysaccharide obtained from *M. charantia* exerted neuroprotection via negatively regulating the expression of pro-apoptotic factors JNK3, cjun, and caspase-3.⁴⁵ In another study, *M. charantia* polysaccharides were proved to execute protective effects in rat model of cerebral ischemia-reperfusion injury.⁴⁶ Data from this study were in line with Duan et al. as the polysaccharides of *M. charantia* blocked the stimulation of JNK3/cJun/Fas-L and JNK3/cytochrome C/caspases-3 signaling pathways in brain regions damaged with ischemic injury. In addition, scavenging effects was also noticed against free radicals including NO, O₂ and NO₃.⁴⁷ Malik et al demonstrates the neuroprotective effect of *M. charantia* against neuronal cell death induced by cerebral ischemia-reperfusion model in diabetic mice. In this study, it was observed that *M. charantia* reduced the cerebral infarct size and free ROS generation.⁴⁸ In 2013, the same group report

neuroprotective effect of *M. charantia* in Streptozotocin-driven mice diabetic neuropathy model. Serum markers associated with oxidonitrosative stress were reduced in *M. charantia* treated diabetic mice, which eventually protected against diabetes-induced neuropathy.⁴⁹ Altogether, these studies revealed the neuroprotective effects of *M. charantia* against different *in vivo* neuronal injury models.⁵⁰ The medicinal properties and underlying molecular mechanisms of *M. charantia*, and its possible protective effects against the yet unexplored NDs have been presented in Figure 3.

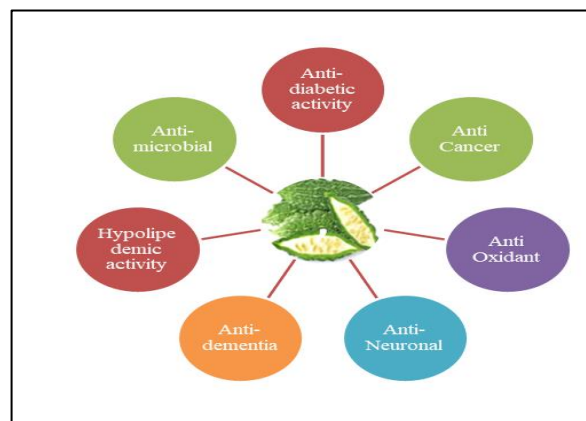


Figure 2: Nutraceutical properties of *Momodica charantia* L.

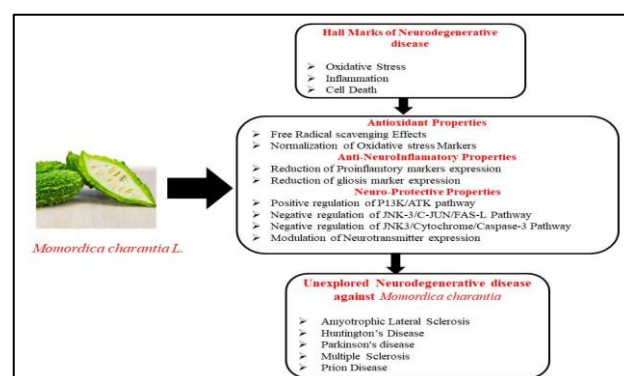


Figure 3: The medicinal properties and underlying molecular mechanisms of *Momodica charantia* L., and its possible protective effects against the yet unexplored neurodegenerative diseases.

FUTURE PROSPECTIVE

Medicinal properties of *M. charantia* have been largely explored in preclinical studies linked to diabetes and cancer. Very few experiments have been attempted to investigate its efficacy in neurodegenerative diseases (ND) for example, AD and neuronal injury. As mentioned earlier, oxidative stress and inflammation are the key pathological hallmarks of neurodegenerative diseases (ND). Research in recent years has been focusing on finding traditional herbs or their novel phytochemicals that may target multiple pathological conditions via

antioxidant and anti-inflammatory properties. Moreover, they modulate free radical scavenging activity, mitochondrial stress, apoptotic factors, and neurotrophins expression. Preclinical studies revealed that the extract of *M. charantia* provide neuroprotection via its exemplary antioxidant and anti-inflammatory properties. At molecular level, *M. charantia* was found to modify PI3K/ATK, JNK3/c-Jun/Fas-L and JNK3/cytochrome C/caspases-3 signaling pathways which are key pathways associated with inflammation. By considering these data we propose that therapeutic efficacy of *M. charantia* plant must be explored against NDs like ALS, PD, HD and MS using appropriate in vitro and in vivo models. Pathways targeted phytocompounds identification and isolation from *M. charantia* shall be initiated and studied in large scale using suitable model systems. Based on the results, clinical trials shall be promoted to treat patients with Neuro degenerative diseases (ND).

CONCLUSION

M. charantia is used in traditional medicine to treat diabetes, cancer, inflammatory diseases, viral diseases, hypercholesterolemia and other diseases. NDs are incurable, life-threatening diseases with severe oxidative stress and inflammation. The presence of effective natural anti-oxidant and anti-inflammatory compounds and supportive preclinical studies suggested the usage of *M. charantia* as a promising therapeutic plant candidate against NDs. Additional and new in vitro and in vivo models are guaranteed to decipher the role of *M. charantia* in ND treatment.

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