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Neuroprotective effects of *Momordica charantia*: A review from preclinical studies

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ABSTRACT

Momordica charantia L. (*M. charantia*), also referred as bitter gourd or bitter melon, is a cucurbit plant commonly found in tropical and subtropical regions of the world. As an important ingredient in traditional medicine, it has been consumed to treat a wide range of diseases including diabetics and cancer in India, Indian subcontinent and China. This plant contains a rich source of flavonoids, saponins, triterpenes, polysaccharides, proteins, and other phytochemicals. Earlier studies have demonstrated the medicinal properties such as anti-diabetic, anti-cancer, anti-oxidant, anti-inflammatory and anthelmintic properties present in *M. charantia*. Neurodegenerative diseases are the devastating diseases which affect millions of people worldwide. Alzheimer's disease, Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis are some of the common neurodegenerative diseases. These diseases are described by degeneration and /or loss of selective neuron populations in a progressive manner. Oxidative stress and inflammation are the hallmarks of neurodegenerative diseases. Many medicinal herbs and their derivatives have been investigated to treat neurodegenerative diseases. However, very few studies have reported the protective effects of *M. charantia* against neurodegenerative diseases. In this short review, we discuss the preclinical studies with the focus on the neuroprotective effects of *M. charantia*. Based on the anti-oxidant and anti-inflammatory properties, in this review we emphasize to further explore the protective effects of *M. charantia* in neurodegenerative and neuroinflammatory diseases.

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INTRODUCTION

Momordica charantia (*M. charantia*), commonly referred as bitter melon or bitter gourd, is a plant that belongs to the family 'Cucurbitaceae' (Zhang *et al.*, 2016). It is an herbaceous vine plant with cucumber-like fruits. Tender fruits of M. *charantia* are emerald green in color while ripened fruits are yellow-orange in color (Nagarani *et al.*, 2014). M. *charantia* grows in tropical and subtropical regions and has been widely used in folk medicine in India, Sri Lanka, Pakistan and China for ages (Polito *et al.*, 2016). Different varieties of M. *charantia* are available in different habitats (Thakur, 2018). Proteins,

polysaccharides, flavonoids, alkaloids, glycosides, phenolics, tannins, triterpenoids, and steroids are the common phytochemicals present in M. *charantia* (Wang *et al.*, 2017). Moreover, this plant is a rich source for a range of saponins such as momordicin, karavilagenin, and karaviloside (Keller *et al.*, 2011).

M. *charantia* plant has been used against a wide range of diseases including diabetes, cancer, obesity, microbial infections, hypertension, and AIDS (Grover and Yadav, 2004), and these medicinal properties are ascribed to the fruits, unripe fruits in particular, leaves, seeds and roots of the plant (Scartezzini and Speroni, 2000). Earlier reviews had discussed the medicinal role of M. *charantia* against obesity and inflammatory diseases (Fan *et al.*, 2019; Bortolotti *et al.*, 2019). Other pleiotropic effects such as antitumor effects (Fang *et al.*, 2019) and anthelmintic effects (Jiraungkoorskul and Poolperm, 2017) have also been discussed in recent reviews; however, no review article had specifically pointed out its neuroprotective effects.

In this review we discuss the preclinical studies focused on studying the neuroprotective effects of M. *charantia*. In order to collect research articles related to neuroprotective effects we performed PubMed and Google scholar searches using the following key words: '*Momordica charantia*' and 'Neuroprotective effects', '*Momordica charantia*' and 'Neurodegenerative diseases', and '*Momordica charantia*' and 'Neuroinflammatory diseases'. Moreover, we emphasize the potential of M. *charantia* as a therapeutic agent against the yet unexplored neurodegenerative and neuroinflammatory diseases.

Neuroprotective properties

Neurodegenerative diseases (NDs) are untreatable and debilitating diseases, described by degeneration and /or loss of selective neuron populations in a progressive manner, which differs from the cell death, occurs due to any metabolic or toxic stress (Dugger and Dickson, 2017). There are different types of NDs including Alzheimer's disease (AD), Parkinson's disease (PD), and Multiple Sclerosis (MS), Motor neuron diseases (MND), Huntington's disease (HD), and Prion disease. Among these, AD, PD, MS and HD are the most commonly occurring NDs (Hussain *et al.*, 2018). 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 lead to neurodegeneration (Chi *et al.*, 2018). Number of preclinical studies demonstrated the neuroprotective effects of crude extract or purified compounds of *M. charantia* by attenuating oxidative stress, neuroinflammation and cell death.

In vitro studies

Anti-oxidant properties of *M. charantia* have been demonstrated in *in vitro* studies. Choi et al. showed that *M. charantia*-derived phenolic protocatechuic acid significantly reversed C6 glial cell damage induced by hydrogen peroxide (H_2O_2) and AD-associated amyloid beta 25-35 ($A\beta_{25-35}$). In this study, ROS production was controlled by protocatechuic acid (Choi *et al.*, 2014). 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 and inhibited mitogen-activated protein kinase (MAPK) signaling by suppressing MAPK phosphorylation (Kim *et al.*, 2018). 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 (Tamilanban, 2018).

Gong et al. found that *M. charantia* polysaccharides exerted neuroprotection against primary rat hippocampal neuronal cells subjected to oxygen glucose deprivation (Gong *et al.*, 2015). 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* NDs models. Neuronal cell loss followed by memory impairment is a characteristic feature in AD. 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 AD mice by blocking lipid peroxidation and acetyl cholinesterase activity (Pathakota, 2017). Similar anti-amnesic activity was reported in by scopolamine-induced rat AD model (Joshi *et al.*, 2017). In a recent study, hydroalcoholic extract of *M. charantia* fruits showed to restore the memory in scopolamine-induced mouse model (Miri *et al.*, 2019). In another important study, co-administration of *M. charantia* fruit powder was found to reduce the side effects of Lithium Chloride-mediated treatment in 3×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 AD.

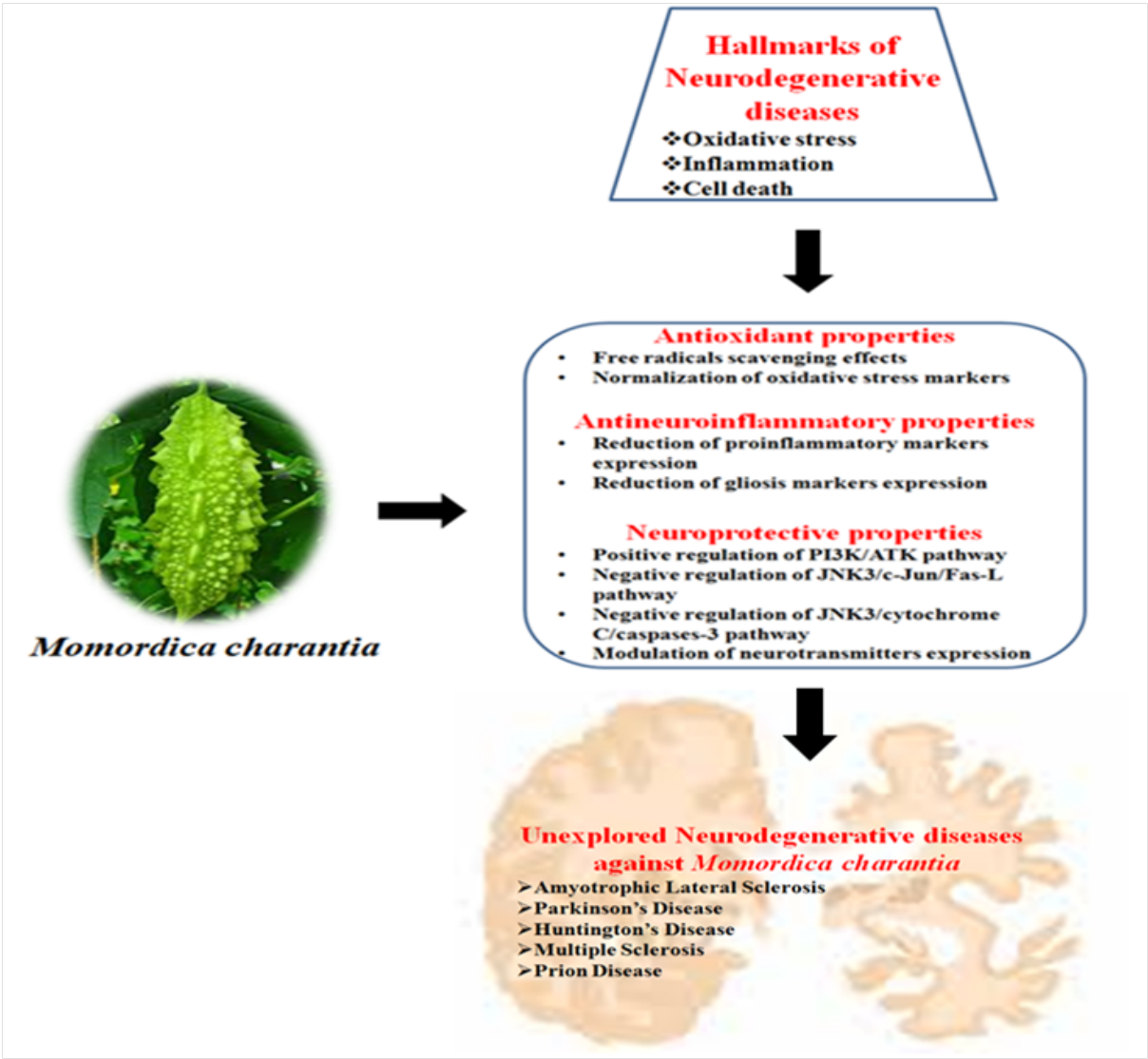

Figure 1: The medicinal properties and underlying molecular mechanisms of M. *charantia*,and its possible protective effects against the yet unexplored neurodegenerative diseases

Typical AD pathological features including extensive neuronal loss, gliosis, oligomeric Aβ formation, and hyperphosphorylated tau protein level were substantially reduced by *M. charantia* (Huang *et al.*, 2018). Thus, these studies showed that *M. charantia* shall be a promising phytotherapeutic drug candidate plant to treat AD.

Nerurkar et al. demonstrated anti-oxidant and anti-neuroinflammatory properties of *M. charantia* in high-fat diet associated oxidative stress and neuroinflammation 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-κB1 were markedly reduced in mouse brain by *M. charantia*. In addition, gliosis markers Iba1, CD11b, GFAP and S100β were decreased in *M. charantia*-fed mice (Nerurkar *et al.*, 2011). A recent study by Deng et al. reported that *M. charantia* downregulated the hippocampal expression of pro-inflammatory cytokine markers tumor necrosis factor-alpha (TNF-α), IL-6, and IL-1β 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-110β was reduced and activity of negative inflammation mediators phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT) was increased in *M. charantia*-treated mice (Deng *et al.*, 2019). Thus, these studies showed effective anti-neuroinflammatory properties of *M. charantia* fruits.

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 $GABA_A$ergic neurons (Ishola *et al.*, 2013).

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, c-jun, and caspase-3 (Duan *et al.*, 2015). In another study, *M. charantia* polysaccharides were proved to execute protective effects in rat model of cerebral ischemia-reperfusion injury. Data from this study were in line with Duan et al. as the polysaccharides of *M. charantia* blocked the stimulation of JNK3/c-Jun/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,O_2^- and $ONOO^-$ (Gong *et al.*, 2015). Malik et al. demonstrated 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 (Malik *et al.*, 2011). In 2013, the same group reported neuroprotective effect of *M. charantia* in Streptozotocin-driven mice diabetic neuropathy model. Serum markers associated with oxido-nitrosative stress were reduced in *M. charantia*-treated diabetic mice, which eventually protected against diabetes-induced neuropathy (Malik *et al.*, 2013). Altogether, these studies revealed the neuroprotective effects of *M. charantia* against different *in vivo* neuronal injury models. 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 1.

Future directions

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 NDs, for ex., AD and neuronal injury. As mentioned earlier, oxidative stress and inflammation are the key pathological hallmarks of NDs. 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 NDs.

CONCLUSIONS

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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REFERENCES

Bortolotti, M., Mercatelli, D., Polito, L. 2019. Momordica charantia, a Nutraceutical Approach for Inflammatory Related Diseases. *Frontiers in Pharmacology*, 10:486–486.

Chi, H., Chang, H. Y., Sang, T. K. 2018. Neuronal Cell Death Mechanisms in Major Neurodegenerative Diseases. *International Journal of Molecular Sciences*, 19(10):3082–3082.

Choi, J. R., Choi, J. M., Lee, S., Cho, K. M., Cho, E. J., Kim, H. Y. 2014. The protective effects of protocatechuic acid from Momordica charantia against oxidative stress in neuronal cells. *Korean Journal*

of Pharmacognosy, 45(1):11–16.

Deng, Z., Yuan, C., Yang, J., Peng, Y., Wang, W., Wang, Y., Gao, W. 2019. Behavioral defects induced by chronic social defeat stress are protected by Momordica charantia polysaccharides via attenuation of JNK3/PI3K/AKT neuroinflammatory pathway. *Annals of Translational Medicine*, 7(1):6–6.

Duan, Z. Z., Zhou, X. L., Li, Y. H., Zhang, F., Li, F. Y., Su-Hua, Q. 2015. Protection of Momordica charantia polysaccharide against intracerebral hemorrhage-induced brain injury through JNK3 signaling pathway. *Journal of Receptors and Signal Transduction*, 35(6):523–529.

Dugger, B. N., Dickson, D. W. 2017. Pathology of Neurodegenerative Diseases. *Cold Spring Harbor Perspectives in Biology*, 9(7):a028035–a028035.

Fan, Kim, Choi, Tang, Moon 2019. The Role of Momordica charantia in Resisting Obesity. *International Journal of Environmental Research and Public Health*, 16(18):3251–3251.

Fang, E. F., Froetscher, L., Scheibye-Knudsen, M., Bohr, V. A., Wong, J. H., Ng, T. B. 2019. Emerging Antitumor Activities of the Bitter Melon (Momordica charantia). *Current Protein & Peptide Science*, 20(3):296–301.

Gong, J., Sun, F., Li, Y., Zhou, X., Duan, Z., Duan, F., Shen, J. 2015. Momordica charantia polysaccharides could protect against cerebral ischemia/reperfusion injury through inhibiting oxidative stress mediated c-Jun N-terminal kinase 3 signaling pathway. *Neuropharmacology*, 91:123–134.

Grover, J. K., Yadav, S. P. 2004. Pharmacological actions and potential uses of Momordica charantia: a review. *Journal of Ethnopharmacology*, 93(1):123–132.

Huang, H. J., Chen, S. L., Chang, Y. T., Chyuan, J. H., Hsieh-Li, H. 2018. Administration of Momordica charantia Enhances the Neuroprotection and Reduces the Side Effects of LiCl in the Treatment of Alzheimer's Disease. *Nutrients*, 10(12):1888–1888.

Hussain, R., Zubair, H., Pursell, S., Shahab, M. 2018. Neurodegenerative Diseases: Regenerative Mechanisms and Novel Therapeutic Approaches. *Brain Sciences*, 8(9):177–177.

Ishola, I., Akinyede, A., Sholarin, A. 2013. Antidepressant and Anxiolytic Properties of the Methanolic Extract of Momordica charantia Linn (Cucurbitaceae) and its Mechanism of Action. *Drug Research*, 64(07):368–376.

Jiraungkoorskul, W., Poolperm, S. 2017. An update review on the anthelmintic activity of bitter gourd, Momordica charantia. *Pharmacognosy Reviews*, 11(21):31–31.

Joshi, A., Soni, P., Malviya, S., Kharia, A. 2017. Memory enhancing activity of Momordica charantia by scopolamine induced amnesia in rats. *Indian J Clin Anat Physiol* , 2:11–18.

Keller, A. C., Ma, J., Kavalier, A., He, K., Brillantes, A.-M. B., Kennelly, E. J. 2011. Saponins from the traditional medicinal plant Momordica charantia stimulate insulin secretion in vitro. *Phytomedicine*, 19(1):32–37.

Kim, K., Lee, S., Kang, I., Kim, J. H. 2018. Momordica charantia Ethanol Extract Attenuates H2O2-Induced Cell Death by Its Antioxidant and Anti-Apoptotic Properties in Human Neuroblastoma SK-N-MC Cells. *Nutrients*, 10(10):1368–1368.

Malik, Z. A., Singh, M., Sharma, P. L. 2011. Neuroprotective effect of Momordica charantia in global cerebral ischemia and reperfusion induced neuronal damage in diabetic mice. *Journal of Ethnopharmacology*, 133(2):729–734.

Malik, Z. A., Tabassum, N., Sharma, P. L. 2013. Attenuation of experimentally induced diabetic neuropathy in association with reduced oxidative-nitrosative stress by chronic administration of Momordica charantia. *Advances in Bioscience and Biotechnology*, 04(03):356–363.

Miri, A., Askari, S. F., Shahraki, E. 2019. Examining The Effects Of Hydro-Alcoholic Extract Of Momordica Charantia Fruit On Avoidance Memory Alterations In Mice Using Step- Through Model. *J Fundam Appl Sci*, 11(1):101–116.

Nagarani, G., Abirami, A., Siddhuraju, P. 2014. Food prospects and nutraceutical attributes of Momordica species: A potential tropical bioresources – A review. *Food Science and Human Wellness*, 3(3-4):117–126.

Nerurkar, P. V., Johns, L. M., Buesa, L. M., Kipyakwai, G., Volper, E., Sato, R., Shah, P., Feher, D., Williams, P. G., Nerurkar, V. R. 2011. Momordica charantia (bitter melon) attenuates high-fat diet-associated oxidative stress and neuroinflammation. *Journal of Neuroinflammation*, 8(1):64–64.

Pathakota, R. 2017. Neuroprotective Effects Of Momordica Charantia On Scopolamine Induced Alzheimer's Disease. *World Journal of Pharmacy and Pharmaceutical Sciences*, 6(4):2141–2155.

Polito, L., Bortolotti, M., Maiello, S., Battelli, M., Bolognesi, A. 2016. Plants Producing Ribosome-Inactivating Proteins in Traditional Medicine. *Molecules*, 21(11):1560–1560.

Scartezzini, P., Speroni, E. 2000. Review on some plants of Indian traditional medicine with antioxi-

dant activity. *Journal of Ethnopharmacology*, 71(1-2):23–43.

Tamilanban, T. 2018. In vitro neuroprotective effect of charantin from Momordica charantia against neurotoxin and endoplasmic reticulum stress-induced cell death in SH-SY5Y cells. *International Journal of Green Pharmacy (IJGP)*, 12(03).

Thakur, V. 2018. Yield and yield contributing traits of bitter gourd (Momordica charantia L.) genotypes. *J. Pharmacogn. Phytochem*, 7(3):844–846.

Wang, S., Li, Z., Yang, G., Ho, C. T., Li, S. 2017. Momordica charantia: a popular health-promoting vegetable with multifunctionality. *Food & Function*, 8(5):1749–1762.

Zhang, F., Lin, L., Xie, J. 2016. A mini-review of chemical and biological properties of polysaccharides from Momordica charantia. *International Journal of Biological Macromolecules*, 92:246–253.