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Review Article

A Mini-Review on the Neuroprotective Effects of Extracts and Metabolites of *Momordica charantia*

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ABSTRACT

This mini-review is on the neuroprotective effects of *Momordica charantia* (MC), a climbing cucurbit better well-known for its anti-diabetic and anti-cancer properties. Commonly known as bitter gourd or bitter melon, MC is a belongs to the family Curcubitaceae. Bitter gourd is rich in bioactive chemical constituents such as polysaccharides, cucurbitane triterpenoids, triterpene glycosides, phenolic acids, flavonoids, essential oils, saponins, fatty acids and proteins. The neuroprotective activities of MC extracts and metabolites can be categorized into different nervous system disorders as targets. They are central nervous system injury, neuronal damage, defective memory, neuronal cancer, neuro-inflammation, cognitive impairment and aging. Studies on the neuroprotective activities of MC juice, extracts, fractions, essential oil and metabolites are based on models of induced brain, cerebral ischemic/reperfusion and neuronal injury. Neuroprotective studies on MC are also based on models of induced neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Research on neurological cancer cells include studies on neuroblastoma and glioma cells. Bioactive metabolites with neuroprotective activities include polysaccharides, protocatechuic acid, charantin and α-eleostearic acid. Aspects for further research are suggested.

Keywords: Charantin; α-Eleostearic acid; Polysaccharides; Protocatechuic acid.

Introduction

Neuroprotection refers to strategies and mechanisms for defending the central nervous system (CNS) against neuronal injury due to both acute (e.g., stroke and trauma) and chronic (e.g., Alzheimer's disease, Parkinson's disease and Huntington's disease) neurodegenerative disorders.[1] Neurodegeneration has oxidative stress and inflammation as its hallmarks,[2] and is accompanied by neuronal cell death with apoptosis and necrosis, the two major death pathways.[3] Neuroprotective natural products from plants are an importance source of herbal medicine for the prevention rather than treatment of neurological disorders.[4] Neuroprotective natural products have the ability to modulate multiple signalling pathways *via* direct effects on enzymes such as kinases, regulatory receptors and proteins. Extracts and metabolites of some plant species possess neuroprotective properties that have potential neuro-therapeutic applications to suppress neurodegenerative, neuropsychiatric, dementia, anxiety, depression, seizures, ischaemic stroke and age-related disorders by improving the memory as well as cognitive functions of the brain.[4,5] Some examples are anthocyanins from *Vaccinium angustifolium*, withanone from *Withania somnifera* and paeonol from *Paeonia suffruticosa* have shown improve memory and other cognitive functions; naringenin from *Citrus* fruits are known to suppress seizures; resveratrol from *Vitis* grapevine has shown to have anti-aging and anti-ischaemic properties, huperzine A from *Huperzia serrata* is a potent acetylcholinesterase (AChE) inhibitor, and curcumin from *Curcuma longa* reduces brain damage and improves memory function.[4-6]

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In this mini-review, neuroprotection, neurodegenerative diseases and plant species extracts and metabolites with neuroprotective properties are topics highlighted in the Introduction. The botany, uses, chemical constituents and pharmacology of *Momordica charantia* (MC) are then described, followed by discussion on the neuroprotective activities of extracts and metabolites of MC. Other *Momordica* species with neuroprotective properties are briefly mentioned. Sources of information in this mini-review were Google, Google Scholar, ScienceDirect, PubMed, J-Stage and PubChem.

Momordica charantia L.

Botany

MC belongs to the family Curcubitaceae and is commonly known as bitter gourd or bitter melon. The annual and herbaceous plant is a pubescent climber 2–4 m in length with twining growth form aided by tendrils.[7-10] Leaves are simple, alternately arranged, deeply lobed and palmately veined (Figure 1). Flowers are solitary, yellow in colour and monoecious in sexual distribution, i.e., male and female flowers are borne on the same plant. Fruits are a pendulous pepo that is fleshy with many seeds and a distinct rind. The exterior of the Chinese varieties of MC is covered with bumps that are warty (Figure 1), while that of the Indian varieties is covered with spikes. The cylindric or fusiform fruit is green when immature bearing white seeds. When mature, the fruit turns orange and splits open revealing bright red seeds. The bitterness of bitter gourd is due to the alkaloid (momordicine) and to triterpene glycosides (momordicosides).[7]

Uses

The bitter taste of MC fruits influences the way it is cooked.[9,11,12] In Asian cuisines, bitter gourd is consumed regularly as a vegetable that has been stir-fried, boiled in soup or curry. The fruit is sometimes pre-boiled with some salt or vinegar or cooked with other vegetables or soya bean paste to reduce its bitter taste. Bitter gourd can be dried or pickled for prolonged use. The leaf and fruit of MC are also drunk as juice or tea.[9,11,12]

Figure 1: Fruits of the Chinese Variety of *Momordica charantia*.

In traditional medicine, *M. charantia* is well-known for its anti-diabetic properties.[13,14] Other uses include the treatment of ailments such as dysmenorrhea, eczema, emmenagogue, malaria, galactagogue, gout, jaundice, abdominal pain, kidney stone, leprosy, leucorrhea, piles, pneumonia, psoriasis, rheumatism, fever and scabies.[12]

Chemical Constituents

Bitter gourd is rich in bioactive chemical constituents such as polysaccharides, cucurbitane triterpenoids, triterpene glycosides, phenolic acids, flavonoids, essential oils, saponins, fatty acids and proteins.[9,15,16] Some of the isolated metabolites such as kuguacin J, karaviloside XI, kuguaglycoside C, momordicoside Q−U, charantin and *α*-eleostearic acid, and proteins such as *α*-momorcharin, ribonuclease MC2, (RNase MC2) and *Momordica* anti-viral protein 30 kDa (MAP30) possess potent biological activity.[9,15]

Pharmacology

Bitter gourd is reported to possess pharmacological properties such as antioxidant, anti-inflammatory, anti-cancer, anti-diabetic, hypolipidemic, hypotensive, antimicrobial, anthelmintic, anti-obesity, anti-dementia, neuroprotective and immunomodulatory activities.[9,10,15,17,19] Anti-cancer activity of extracts and metabolites of MC is very diverse covering a wide range of cancers.[20,21] Metabolites with anti-cancer properties include MAP3, BG-4, α-momorcharin, RNase MC2, kuguacin J, *α*-eleostearic acid, charantosides I & II and momordicine I.[18,21,22] Other pharmacological properties of MC include the enhancement of female fertility and foetal well-being in rats by momordicilin, a triterpenoid from the leaf extract,[23] and the cardioprotective ability of the fruit extract by being a potent activator of sirtuin 1 (SIRT-1) protein.[24]

Neuroprotective Activities

The neuroprotective activities of MC juice, extracts, fractions, essential oil and metabolites including their underlying molecular mechanisms are summarized in Table 1. These activities can be categorized into different nervous system (NS) disorders as targets. They include central nervous system (CNS) injury (10), neuronal damage (6), defective memory (5), neuronal cancer (5), neuro-inflammation (3), cognitive impairment (2) and aging (2). Many of these disorders are inter-related. Examples are: a) defective memory, cognitive impairment and aging; and b) diabetes and neuropathy or nerve damage. Most are *in vivo* studies using rats and mice, with only a few *in vitro* studies that use neural stem cells (NSCs), neuronal cells and astrocytes.

Studies on the neuroprotective activities of MC are based on models of induced brain, cerebral ischemic/reperfusion and neuronal injury. Neuroprotective studies on MC are also based on models of induced neurodegenerative diseases such as Alzheimer's disease (AD),[25-29] and Parkinson's disease (PD).[30] Research on neurological cancer cells include those on neuroblastoma[31,32] and glioma cells.[33]

Neuroprotective Metabolites

Neuroprotective activities of bioactive metabolites from MC have been reported especially those of polysaccharides.[30,34,35,39,54,57,58] Other neuroprotective metabolites include protocatechuic acid,[28,45,55] charantin[52] and *α*-eleostearic acid.[38] Their chemical structures are described below.

Polysaccharides (PS)

PS are the major active ingredients of MC that have attracted much scientific interest because of their bioactivities such as hypoglycemic, anti-cancer, antioxidant, antimicrobial, immunomodulation and hepatoprotective properties.[59,60] PS have complex chemical structures as reflected in their sugar compositions, molecular weights, sugar backbone, and position of the functional groups. A water-soluble PS isolated from the fruit of MC has a molecular weight of ranging from 85–100 kDa and comprises the monosaccharides of arabinose, xylose, galactose and rhamnose.[61] Galacturonic acid (GalA) is the major monosaccharide component of PS up to 93.7% in content.[35] Among eight monosaccharide components of PS isolated, GalA has the second highest molar ratio of 15.[62]

Protocatechuic Acid (PA)

PA is a phenolic metabolite in MC. It is a promising *in vitro* anti-neuroinflammatory molecule for neurodegenerative diseases.[55] The experiment was done using C6 glial cells and oxidative stress was induced by hydrogen peroxide (H_2O_2) and amyloid beta (A*β*) that caused the decrease of cell viability and over-production of reactive oxygen species (ROS).[45] Treatment with PA significantly elevated cell viability, inhibited the overproduction of ROS and recovered the cellular damage induced by A*β*. Another component of the experiment was the assessment of the protective effects of PA against cognitive impairment in an A*β*-induced AD mouse model.[28] The PA groups showed significantly decrease in lipid peroxidation (LPI) and nitric acid (NO) production in the brain, kidney and liver tissues. Furthermore, the PA groups showed attenuated Aβ-induced neuroinflammation by down-regulating inflammatory mediators, inducible nitric oxide synthase and cyclooxygenase-2 (COX-2) in the brain. The PA groups demonstrated cognitive improvement through behavioral tests, including T-maze, object recognition and the Morris water maze test. The PA groups showed more use of novel routes, better novel object recognition, and improved learning and memory ability.

Charantin

Charantin is an insulin-like peptide with hypoglycemic property that has an ability to lower blood sugar, equivalent to that of insulin.[63] Charantin comprises equal amounts of *β*-sitosterol glucoside ($C_{35}H_{60}O_6$) and 5,25-stigmasteryl glucoside ($C_{35}H_{58}O_6$). Their molecular weights are 576.8 g/mol and 574.8 g/mol.[52] The content of charantin is higher in the fruit and leaf of MC. In the fruit, the content of charantin was the highest in flesh part (0.16 mg/g) followed by the whole fruit (0.11 mg/g) and the skin (0.08 mg/g).[64] Charantin from MC exhibited *in vitro* neuroprotection against neurotoxin and endoplasmic reticulum (ER) stress-induced death in SH-SY5Y cells, suggesting its potential as a memory enhancer in AD dementia.[52]

α-Eleostearic Acid (α-ESA)

α-ESA ($C_{18}H_{29}O_2$) is a conjugated linoleic acid that is found in the seed oil of MC[9,65] with a content of 60%.[66] In dried and fresh fruits of MC, the content of α-ESA was 7.1 g/kg and 0.42 g/kg, respectively.[30] Major bioactivity of *α*-ESA is anti-cancer.[65-69] The neuroprotective properties of *α*-ESA from MC had an elevating effect on the expression of CDGSH iron-sulfur domain 2 (CISD2) gene in mice with spinal cord injury (SCI).[38] The CISD2 is a pro-longevity gene that plays an important role in slowing down aging. A higher level of CISD2 appears to prevent age-associated organ dysfunction, prolong a healthy lifespan, and improve the quality of life during old age.[70]

Table 1: Neuroprotective activities of *Momordica charantia* extracts and metabolites.

NS disorder	Effect & mechanism	Reference
CNS injury	PS exerted protective effects such as anti-inflammatory, antioxidative stress, and anti-apoptosis, and improved brain function on PD mice by regulating activation of the TLR4/ MyD88/NF-*κ*B pathway.	30
	PS protected against IH-induced BI rats by scavenging ROS, attenuating neuronal cell death, and inhibiting the JNK3 signaling pathway.	34
	PS protected against CIRI in rats by inhibiting free radical-mediated oxidative stress mediated JNK3 signaling pathway.	35
	PS promoted differentiation of NSCs *via* activation of the SIRT1/β-catenin pathway using the CIRI cell model and the MCAO stroke rat model.	36
	Ethanol extract of MC mitigated the injury-induced by down-regulation of CISD2 gene in mice with SCI and in LPS-stimulated ALT astrocytes.	37
	α-ESA from MC had an elevating effect on CISD2 in SCI mice, a potential therapeutic target for CNS injuries and diseases.	38
	PS promoted NSC proliferation by increasing SIRT1 activity in CIRI rats, suggesting their potential use to promote stroke recovery.	39
	ELNs from MC are able to cross the BBB, and protected against ischemic BI *via* inhibition of MMP-9 and activation of the AKT/GSK3β signaling pathway.	40
	The aqueous extract of MC has a ME effect by mitigating the cognitive impairment, attenuated cholinergic and purinergic dysfunction, and suppressed oxidative stress in the brain of DOX-treated rats.	41
	The MC fruit juice has neuroprotective activity in CIRI and ND of the brain of rats, suggesting its potential treatment of stroke.	42
Neuronal damage	The MC fruit juice has potent neuroprotective activity against CIRI, ND and neurological deficits in diabetic mice.	43
	Freeze-dried MC powder protected mice against diabetic neuropathy in association with attenuation of hyperglycemia and oxidative-nitrosative stress.	44
	Protocatechuic acid from MC exerted neuroprotective effect on C6 glial neuronal cells through attenuation of oxidative stress.	45
	PS exerted neuroprotective effects by attenuating KA-induced neuronal damage in the brain of mice through their free radical scavenging activities.	46
	TCD, a triterpenoid from MC, reduced synaptosomal release of glutamate and protected against KA-induced neuronal death in the CA3 hippocampus region of rats.	47
	The ethanol fruit extract of MC protected hippocampal neuronal cells against PAH-induced neurotoxicity in rats. Possible mechanisms involved the p38 MAPS pathway, with vitamin E and stigmasterol as active constituents.	48
Defective memory	The extract of MC lowered serum cholesterol, elevated ACh level in the brain and enhanced the memory of rats with scopolamine-induced amnesia (AD).	25
	The ethanol extract of MC improved the memory of mice with amnesia (AD) by inhibiting LPO and decreasing AChE activity in the brain.	26
	Administration of the extract of MC5523, a cultivar of MC, enhanced the memory of mice with AD and reduced the side effects of LiCl.	27
	The ethanol extract of MC restored the memory of mice with scopolamine-induced defective memory using the step-through model.	49
	The ethanol extract of MC enhanced the memory of rats with aspartame-induced spatial memory impairment.	50
Neurological cancer	The ethanol extract of MC attenuated H_2O_2-induced cell death in SK-N-MC neuroblastoma cells by improving cell viability and apoptosis. Mechanisms involved its antioxidant and anti-apoptotic properties. Inhibition of apoptosis included the suppression of mitochondria-dependent apoptosis pathway and MAPK signaling pathway.	31
	The ethanol extract of MC exerted neuroprotective effect on H_2O_2-induced cell death in neuroblastoma SH-SY5Y cells. Mechanisms included improved intracellular ROS production, reduced caspase activation, improved cell viability and suppressed apoptosis.	32

	Extracellular vesicles-like nanovesicles derived from MC inhibited proliferation, migration and invasion of glioma cells by regulating the PI3K/AKT signaling pathway.	33
	MC extract exerted neuroprotective effects against H_2O_2-induced cytotoxicity in SK-N-MC neuroblastoma cells.	51
	Charantin from MC exhibited *in vitro* neuroprotection against neurotoxin and ER stress-induced death in neuroblastoma SH-SY5Y cells, suggesting its potential as a memory enhancer in AD dementia.	52
Neuro-inflammation	High brain oxidative stress induced by HFD in mice was reduced by BM supplementation, *via* the reduction in FoxO, normalization of Sirt 1 expression and up-regulation of Sirt 3 mRNA expression.	53
	PS protected mice against depressive-like behaviors in CSDS *via* attenuation of the JNK3/PI3K/AKT NI pathway.	54
	Protocatechuic acid from MC protected mice against H_2O_2-induced oxidative stress and NI in C6 glial cells.	55
Cognitive impairment	Protocatechuic acid from MC protected mice against cognitive impairment in an Aβ-induced Alzheimer's disease mouse model.	28
	Oral administration of the butanol fraction from MC exerted positive cognitive improvement effects on mice in a Aβ-induced cognitive impairment AD mouse model.	29
Aging	The ethanol extract of MC improved the cognitive impairment in D-galactose-induced aging mice by activating the PI3K/AKT signaling pathway.	56
	PS ameliorated D‑galactose‑induced aging in mice. The anti-aging mechanism involved the Nrf2/β‑catenin signaling pathway.	57

Abbreviations: Aβ = amyloid beta, ACh = acetylcholine, AChE = acetylcholine esterase, AD = Alzheimer's disease, AKT = serine/threonine kinase, BBB = blood-brain barrier, BI = brain injury, CIRI = cerebral ischemic/reperfusion injury, CISD2 = CDGSH iron-sulfur domain 2, CNS = central nervous system, CSDS = chronic social defeat stress, DOX = doxorubicin, ELNs = exosome-like nanoparticles, ER = endoplasmic reticulum, α-ESA = α-eleostearic acid, FoxO = forkhead box class O transcription factor, GSK = glycogen synthase kinase, HFD = high-fat diet, H_2O_2 = hydrogen peroxide, IH = intracerebral hemorrhage, JNK3 = c-jun N-terminal protein kinase, KA = kainic acid, LiCl = lithium chloride, LPO = lipid peroxidation, LPS = lipopolysaccharide, MAPK = mitogen-activated protein kinase, MC = *Momordica charantia*, MCAO = middle cerebral artery occlusion, ME = memory enhancing, MMP-9 = matrix metalloproteinase 9, mRNA = messenger ribonucleic acid, ND = neuronal damage, NF-κB = nuclear factor kappa B, NI = neuroinflammation, Nrf2 = nuclear erythroid p45-related factor 2, NS = nervous system, NSC = neural stem cell, PAH = polycyclic aromatic hydrocarbons, PD = Parkinson's disease, PI3K = phosphoinositide 3-kinase, PS = polysaccharides, ROS = reactive oxygen species, SCI = spinal cord injury, SIRT = sirtuin and TCD = 3β,7β,25-trihydroxycucurbita-5,23(*E*)-dien-19-al.

3β,7β,25-Trihydroxycucurbita-5,23(E)-dien-19-al (TCD)

TCD is a cucurbitane triterpenoid isolated from the leaf and vine of MC.[47,71] It has anti-cancer and anti-diabetic properties. TCD from the fruit of MC inhibited SAS tongue squamous cancer cells but not HFB skin fibroblast cells.[72] TCD induced the hypoglycemic effect by acting as a peroxisome proliferator-activated receptor γ (PPARγ) ligand and by inducing glucose uptake in the muscles *via* Glut4 translocation.[73] In neuroprotection, TCD reduced synaptosomal release of glutamate and protected against kainic acid (KA)-induced neuronal death in the CA3 hippocampus region of rats, suggesting its potential for treating diseases related to neuronal excitotoxicity.[47] The latter is involved in the pathogenesis of acute and chronic brain diseases.[74,75]

Other *Momordica* Species

Besides MC, other *Momordica* species have also been reported to possess neuroprotective properties. They include *Momordica cymbalaria* Fenzi ex Naudin and *Momordica cochinchinensis* (Lour.) Spreng.

A triterpenoid saponin isolated from the root of *M. cymbalaria* possessed neuroprotective activity in streptozotocin (STZ)-induced diabetic mice by showing improved diabetic neuropathy.[76] The triterpenoid saponin from *M. cymbalaria* also displayed protective effect on high-glucose induced neuropathy in NB-41A3 mouse neuroblastoma cells.[77] The same group of scientists reported that STZ-induced diabetic rats treated with the saponin from *M. cymbalaria* showed improved diabetic neuropathy *via* the polyol pathway.[78] The *in vivo* neuroprotective effects on the rats included improvement in muscular grip strength, in reaction to heat and pain, and in nerve conduction velocity. An *in vitro* component of the study used cultured sciatic nerves exposed to high glucose concentration. When treated with the saponin, the cells showed improved diabetic peripheral neuropathy (DPN) *via* a significant reduction in aldose activity and intracellular accumulation of sorbitol.[78]

The neurotrophic effects of plant species were screened were screened for their ability to induce neurite outgrowth in PC12 dopaminergic cells.[77] Results showed that the seed extract of *M. cochinchinensis* exerted nerve growth factor (NGF) mimetic effects through early endoplasmic reticulum kinase (pERK) signaling, and neurite branching and outgrowth. A recent study reported that supplementation of oil from *M. cochinchinensis* fruit mitigated cognitive decline in aluminum chloride-induced rats through the regulation of AD markers and autophagy *via* gut-brain communication.[80]

Conclusion

MC has been associated with a wide range of health benefits. Notable pharmacological properties are anti-diabetes, anti-obesity and anti-cancer. The anti-diabetic properties of PS are well-demonstrated. MC have shown to be able to regulate blood glucose level and lipid metabolism. The hypoglycemic effects and blood glucose-lowering effects of MC are well-established in animal studies. Blood sugar levels of mice fed with MC juice, extracts, fractions, essential oils or metabolites were significantly reduced. PS exhibited promising anti-obesity properties in mice on high fat diet. The potent anti-diabetic and anti-obesity activities of PS suggest that they could be developed as dietary or weight-loss supplements. The anti-cancer activity of extracts and metabolites of MC is very diverse with susceptibility shown in many types of cancer. The use of extracts and metabolites of MC in the management of the neurological disorders including neurodegenerative and neuropsychiatric diseases is of great interest. More in-depth exploration on the molecular mechanisms of neuroprotective properties of MC present exciting prospects. Much research needs to be

undertaken before clinical trials and drug development can be considered. There are more questions than answers and the development of potential therapeutic strategies for treatment is far away in the distant horizon.

Conflict of Interest

The authors declare no conflict of interest.

Author's Declaration

The author hereby declares that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by him.

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