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Review

Pharmacotherapeutic Potential of Bitter Gourd (*Momordica charantia*) in Age-related Neurological Diseases

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Abstract

Due to the growth of the elderly population, age-related neurological disorders are an increasing problem. Aging begins very gradually and later leads to several neurological issues such as lower neurotransmitter levels, oxidative stress, neuronal inflammation, and continual neuronal loss. These changes might contribute to brain disorders such as Alzheimer's disease (AD), dementia or mild cognitive impairment, and epilepsy and glioma, and can also aggravate these disorders if they were previously present. *Momordica charantia* (bitter gourd), a member of the Cucurbitaceae family, is a good source of carbohydrates, proteins, vitamins, and minerals. It is used for diabetes and known for its hypoglycemic and antioxidant effects. In this review, we discuss the pharmaceutical effects of *M. charantia* on age-related neurological disorders. We searched several databases, including PubMed and Google Scholar, using MeSH terms. We searched articles published up until 2022 regardless of publication language. *M. charantia* is rich in luteolin, which increases acetylcholine in neurons by binding to enzymes in acetylcholine metabolism pathways, including butyrylcholinesterase and acetylcholinesterase. This binding inhibits the hyperphosphorylation of tau protein by restraining its kinase enzyme. Furthermore, this substance can lower serum cholesterol and has multi-target activity in AD and memory loss. *M. charantia* can also improve memory by decreasing tau protein and it also has potent antioxidant activity and anti-inflammatory effects. This review highlights that *M. charantia* has effects on many age-related neurological disorders, and can be a cost-effective supplement with minimal side effects.

Keywords: bitter gourd; *M. charantia*; age-related neurological diseases; Alzheimer's disease; Parkinson's disease

1. Introduction

Aging has a considerable impact on the central nervous system (CNS). Due to the recognition of diseases related to the CNS, recent estimates show that the neurological diseases included in the Global Burden of Disease (GBD) Study, such as Alzheimer's disease (AD), multiple sclerosis (MS), epilepsy, Parkinson's disease (PD), as well as migraine, medication-overuse headache (MOH), and tension-type headache (TTH), account for 3% of the universal burden of illness. Nevertheless, this accounts for a considerable amount overall. Dementia, especially AD, migraine, epilepsy, and stroke are among the 50 most important agents of disability-adjusted life years (DALYs) [1]. Despite characteristic etiologies, interestingly, aging is the principal risk factor for all the afore mentioned diseases [2–4]. Based on the significant impacts of aging on neurological diseases, to make real progress in terms of medicines, treatment, and control of these diseases, the molecular causes must be accurately characterized. The molecular mechanisms comprise genome instability through mutations, telomere friction, and epigenetic changes. The connections and collaborations between these mechanisms induce the functional decrease in aging organisms [5]. Appropriate therapies and medicines for the diseases mentioned

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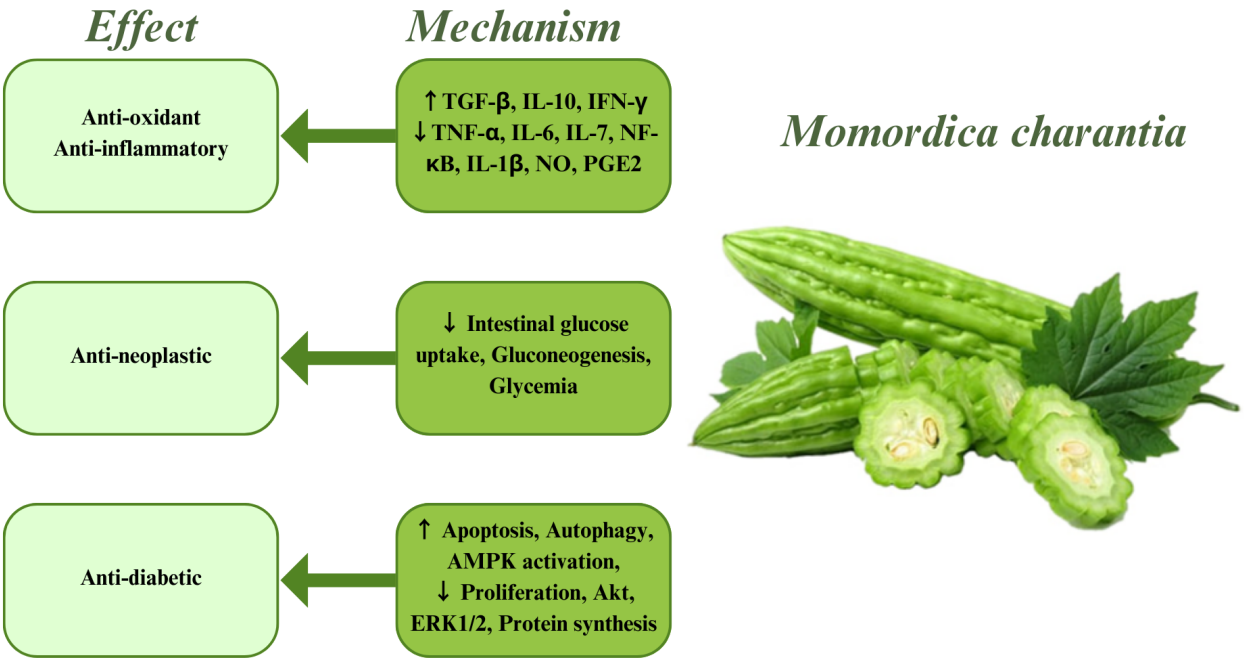

Fig. 1. Effects and related mechanisms of *Momordica charantia*. TGF-β, transforming growth factor beta; IL-10, interlukine-10; IFN-γ, interferon gamma; NK-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; PGE2, prostaglandin E2; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; AMPK, adenosine monophosphate-activated protein kinase; Akt, protein kinase B; ERK1/2, extracellular signal-regulated kinase 1/2.

above have not yet been developed [6]. Considering the previous data and the importance of treating and controlling these diseases that affect health and quality of life, alternative and preventive treatment methods should be sought. Many medicinal plants have been investigated for the prevention and treatment of these diseases [7–17]. One of these plants is *Momordica charantia*, otherwise known as bitter gourd or bitter melon. Fig. 1 outlines current knowledge regarding the potential pharmacotherapeutic effects and mechanisms of *M. charantia* in age-related neurological diseases (ANDs).

2. Retrieval Strategy

We used the online databases Scopus, Google Scholar, and PubMed to retrieve all articles related to the connection between *M. charantia* and neurological diseases, such as AD, dementia, PD, brain tumors (glioma and glioblastoma), neuroinflammation and neurotoxicity, oxidative stress, epilepsy, and seizure among the elderly, without regard for article date. The search was carried out on March 7th, 2022. For each of the databases we used momordica charantia (MeSH) terms with a specific strategy, e.g.,

([bitter gourd] or [momordica charantia]) and ([Alzheimer disease] or [Alzheimer dementia])

([bitter gourd] or [momordica charantia]) and ([glioma] or [glial cell tumor])

([bitter gourd] or [momordica charantia]) and ([Parkinson disease] or [idiopathic Parkinson's disease])

([bitter gourd] or [momordica charantia]) and ([neurotoxicity syndrome] or [neurotoxin disorder])

#1 Bitter Gourd
#2 Momordica charantia
#3 Momordica charantias
#3 #1 or #2
#4 Alzheimer's disease
#5 Alzheimer's dementia
#6 Memory
#7 dementia
#8 glioma
#9 glial cell tumor
#10 glioblastoma
#11 Parkinson's disease
#12 Idiopathic Parkinson's disease
#13 neurotoxicity syndrome
#14 neurotoxin disorder
#15 neuroinflammation
#16 Neuroinflammatory diseases
#17 neuroprotective
#18 neuroprotection
#19 seizure
#20 epilepsy

#21 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20

#22 #21 and #3

(((bitter gourd [Title/Abstract]) OR (Momordica charantia [Mesh]) OR (Momordica charantia [Title/Abstract]) OR (Momordica charantias [Title/Abstract]) OR (charantias, Momordica [Title/Abstract]) OR (Bitter Melon [Title/Abstract]) OR (Bitter Melons [Title/Abstract]) OR (Melon, Bitter [Title/Abstract]) OR (Melons, Bitter [Title/Abstract]) OR (Gourd, Bitter [Title/Abstract]) OR (Bitter Gourd [Title/Abstract]) OR (Bitter Gourds [Title/Abstract]) OR (Gourds, Bitter [Title/Abstract]) OR (Karela [Title/Abstract]))) AND (((Alzheimer Disease [Mesh]) OR (Alzheimer Disease [Title/Abstract]) OR (Alzheimer [Title/Abstract]) OR (Alzheimer dementia [Title/Abstract]) OR (memory [Title/Abstract]) OR (dementia [Title/Abstract]) OR (Glioma [Mesh]) OR (Glioma [Title/Abstract]) OR (glial cell tumor [Title/Abstract]) OR (Glioblastoma [Title/Abstract) OR (Parkinson Disease [Mesh]) OR (Parkinson [Title/Abstract]) OR (idiopathic Parkinson's disease [Title/Abstract]) OR (Neurotoxicity Syndromes [Mesh]) OR (Neurotoxicity [Title/Abstract]) OR (neuroinflammation [Title/Abstract]) OR (Neuroinflammatory Diseases [Mesh]) OR (Neuroprotective [Title/Abstract]) OR ("ALS" [Title/Abstract]) OR ("MS" [Title/Abstract]) OR ("Multiple Sclerosis" [Mesh]) OR ("Amyotrophic Lateral Sclerosis" [Mesh]) OR (Neuroprotection [Title/Abstract]) OR (seizure [Title/Abstract]) OR (epilepsy [Title/Abstract])))

In total, 119 articles were retrieved and 106 articles remained after removing duplicates. We then reviewed the titles and abstracts of these articles, and 64 articles were eligible for assessment of the full text. After full text assessment, 30 articles did not meet the criteria as being an original article or review presenting data on the effectiveness of *M. charantia* on the listed conditions and were excluded. Thirty-four studies remained and were included in this review (Fig. 2).

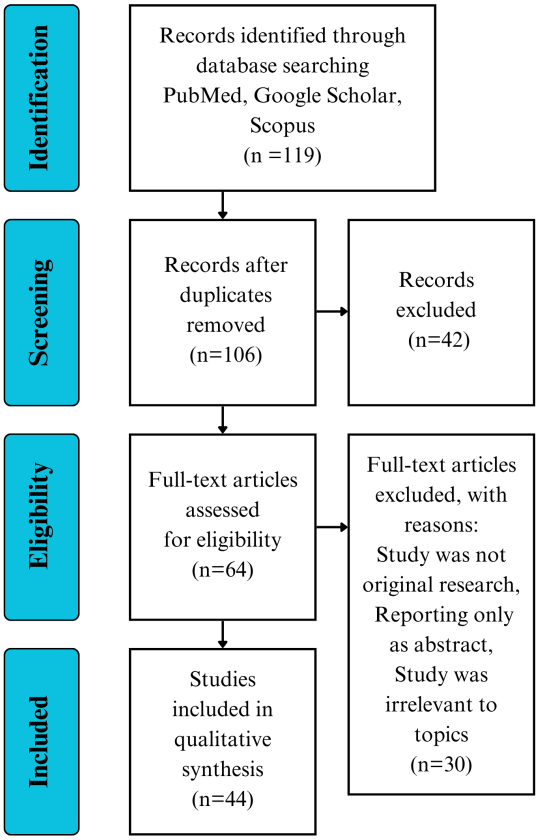

Fig. 2. Outline of the review process.

3. Findings

3.1 Active Components of M. charantia

M. charantia belongs to the genus Momordica and the family Cucurbitaceae. *M. charantia* can grow at high temperatures and is used as an edible vegetable in Asia. This plant grows in a tropical and warm climate; its tree is found in parts of Asia, the Americas, Africa, and the Caribbean. This plant may have therapeutic effects on diabetes, cancer, obesity, and bacterial and viral infections [18].

For centuries, people have used medicinal plants to make products that have been used to prevent and treat diseases. *M. charantia* is widely distributed in tropical and subtropical regions of the world. It is used in folk medicine to treat diabetes, and its fruit has been used as a vegetable for thousands of years [19].

M. charantia contains many substances, including various biological molecules such as proteins and carbohydrates. It also contains minerals such as different vitamins, essential oils, and alkaloids. Other substances found in *M. charantia* include phenolic acids, quinines, and triterpenoids. Fig. 3 shows the structure of some of the small molecules in this plant [20].

M. charantia can inhibit cell death via phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway blockade in glioma and glioblastoma. In addition, in AD, it suppresses amyloid-beta (Aβ) accumulation, reduces tau protein, and positively affects acetylcholine (ACh) and serotonin. In neuroinflammation, it has a role in inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which can produce reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS), cyclooxygenase (COX), and inflammatory cytokines. Moreover, *M. charantia* can suppress acetylcholinesterase and Aβ accumulation, which contribute to ROS production in neurotoxicity.

M. charantia has an anti-cancer effect through the modulation of α- and β-momorcharin, which activates caspase-3 and caspase-9, activating cytochrome C in mitochondria and increasing intracellular Ca^{2+}, enhancing apoptosis of tumor cells.

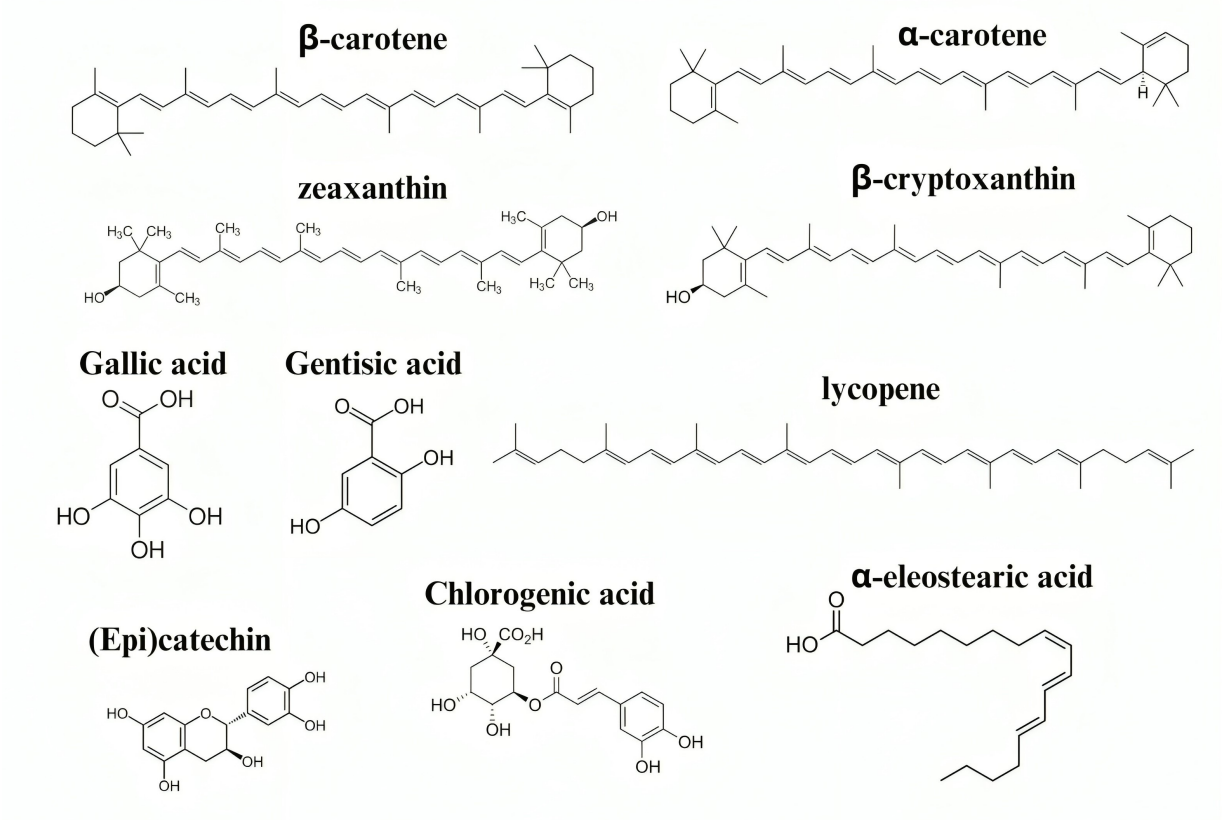

Fig. 3. Structure of some of the active compounds found in *M. charantia* that act against age-related neurological diseases.

M. charantia has neuroprotective roles through the enhancement of soluble guanylate cyclase. In PD, it inhibits 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MTPT), which produces inflammatory cytokines, and also affects toll-like receptor 4 (TLR4), inhibiting the Myeloid differentiation primary response 88 (MyD88)/NF-κB pathway. It can also positively affect dopamine in PD. *M. charantia* can improve memory by reducing tau protein and increasing microtubule-associated protein 2 (MAP2), postsynaptic density protein 95 (PSD95), and beta-site amyloid precursor protein cleaving enzyme 1 (BACE-1).

M. charantia has therefore been used for many different neurological disorders, as shown in Table 1 [21–29].

3.2 Protective Mechanisms

Neuroprotection is defined as the ability of a therapy to prevent neuronal cell death by intervening in and inhibiting the pathogenetic cascade that results in cell dysfunction and eventual death [30].

Ghanta *et al*. [31] analyzed the docking of the phytoconstituents of *M. charantia* with the catalytic domain of guanylate cyclase. A lyase enzyme known as soluble guanylate cyclase is vital in treating cardiovascular and neurodegenerative disorders. Reduced glutamate excitotoxicity caused by modulating soluble guanylate cyclase activity benefits PD [32]. The soluble guanylate cyclase is required for cyclic guanosine monophosphate (GMP) synthesis from guanosine triphosphate (GTP) [33,34]. A heme-containing heterodimer with alpha and beta subunits is also essential [35]. Several subunit isoforms exist: alpha 1, alpha 2, beta 1, and beta 2 [36]. Alpha 1 and beta 1 are the two most common subunits in the human brain [37]. In humans, the heme part of the beta 1 subunit acts as the active site [32].

Numerous studies have been performed to identify the allosteric binding sites of the enzyme that regulates soluble guanylate cyclase activity. The search for binding sites for allosteric enzymes is limited to their catalytic domain. Defects or inhibitions in this region can lead to enzyme dysfunction. 1H-[1,2,4]oxadiazolo-[4,3-a]quinoxalin-1-one (ODQ), a specific inhibitor targeting the catalytic domain of soluble guanylate cyclase, was proven to show antiparkinsonian activity [38].

A water extraction alcohol precipitation process used to process unripe fruit extract from *M. charantia* showed complete inhibition of soluble guanylate cyclase [39]. Several subsequent studies have confirmed *M. charantia*'s ability to inhibit soluble guanylate cyclase [40,41]. *M. charantia* extracts showed neuroprotective effects mainly because of their D-galacturonic acid content [42].

Antioxidants scavenge free radicals from the body's cells and prevent or reduce the damage caused by oxidation. The protective effect of antioxidants continues to be studied around the world. Oxidative stress is caused by the mass production of ROS, primarily because of an imbalance of

Table 1. Summary of studies investigating neurological disorders and *M. charantia* included in our review.

Author	Year	Type of study	Neurological disorder	Outcome
Qiaoli Li *et al*. [21]	2018	*In vitro*	Epilepsy	Momordica charantia polysaccharide (MCP) treatment significantly reduced malondialdehyde levels, increased superoxide dismutase and catalase activities, and mitigated Kainic acid (KA)-induced neuronal loss in the Cornu Ammonis 1 (CA1) and CA3 regions of hypocampus.
Pratibha V Nerurkar *et al*. [22]	2011	*In vivo* mouse	Neuroinflammation	Blue mussel treatment improved blood–brain barrier permeability, normalized neuroinflammatory markers, reduced oxidative stress, and normalized plasma antioxidant enzymes and pro-inflammatory cytokines in mice fed a high-fat diet, reducing glial cell activation, forkhead box O (FoxO), sirtuin 1 (Sirt1) protein expression, and up-regulation of *Sirt3* mRNA expression.
Seung Mi Sin *et al*. [23]	2021	*In vivo* mouse model	Alzheimer's disease (AD)	*M. charantia*'s butanol (BuOH) fraction improved learning and memory by reducing time in the Morris water maze test. It also reduced lipid peroxidation and nitric oxide levels, thus reducing cognitive impairment caused by A25-35.
Hei-Jen Huang *et al*. [24]	2018	*In vivo* mouse	AD	The neuroprotective effect of momordica charantia (MC5), MC3, MC2, and MC5523 is mediated by hyperglycemia or tau hyperphosphorylation. A combination of MC5523 and lithium chloride (LiCl) was administered to ovariectomized mice, boosting survival, increasing neuroprotection, and preventing memory deficits. This suggests that MC5523 and LiCl could be a potential treatment for AD.
Dengjun Guo *et al*. [25]	2021	*In vitro* mouse	Parkinson's disease	1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) treatment can cause brain damage, alter neurotransmitter metabolism, cause inflammation, and induce apoptosis. However, *M. charantia* polysaccharide treatment can reverse these changes, regulating Toll-like receptor 4 (TLR4)/Myeloid differentiation primary response 88 (MyD88)/Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway activation, proving an anti-inflammatory mechanism.
Gunasekar Manoharan [26]	2019	*In vivo*	Glioma	*M. charantia*'s anti-carcinogenic properties were tested on five cancer cell lines. The extract, combined with paclitaxel, significantly decreased cell viability, a significant decrease compared with paclitaxel alone, suggesting its potential for xenobiotic metabolism and oxidative stress.
Zafar Ahmad Malik *et al*. [27]	2011	*In vivo* mouse	Cerebral ischemia	*M. charantia* juice significantly reduced oxidative stress, damage, and neurological impairments in brains, and exhibited dose-dependent antihyperglycemic action in diabetic mice.
Ankur Joshi *et al*. [28]	2017	*In vivo* rat	Memory enhancing activity	*M. charantia* significantly corrected scopolamine-induced amnesia and decreased cholinesterase (ChE) activity in rat brain after 7 and 14 days of administration.
Tamilanban Thamaraikani *et al*. [29]	2020	*In silico*	AD	The study found that MC5523 and LiCl, when combined with streptozotocin, increased neuroprotection and anti-gliosis in ovariectomized (OVX) 3Tg-AD mice. This treatment also prevented memory deficits and enhanced synaptic-related protein expression. Luteolin, a compound responsible for AD, showed high affinity for its target protein, indicating its potential as a potential treatment. The study suggests that MC5523 and LiCl could be a potential treatment for AD.

oxidative and neutralizing processes [43]. Excessive ROS increases age-related disease, triggering inflammation and proatherogenic activities. One of the mechanisms by which antioxidant agents show their effects is reducing the ROS levels in cells. Antioxidants prevent the aging process and age-related and degenerative diseases by helping to balance the production cycle and neutralize free radicals [44–47].

The polysaccharides in *M. charantia* are found to be antioxidants. According to an *in vivo* study, *M. charantia* polysaccharide could play a role in detoxification, improving immunity, and decreasing blood sugars [48]. Furthermore, the polysaccharide may increase chloramphenicol acetyltransferase (CAT) and superoxide dismutase (SOD) in mouse serum, liver, and spleen. It can also reduce malondialdehyde (MDA) in these tissues [49]. MDA is considered one of the most vital products in the process of membrane lipid peroxidation. The polysaccharides found in *M. charantia* might therefore possess antioxidant properties [21]. Another study showed that using the polysaccharides found in *M. charantia* for treating kainic acid-induced epileptic mice could decrease MDA levels and increase the function of SOD and CAT in the rat hippocampus. As a result, the antioxidant and free radical scavenging activities of *M. charantia* polysaccharides can significantly reduce neuronal damage in the brain and central nervous system [50].

In addition, Chen *et al*. [50] found that phosphorylated polysaccharides and sulfated polysaccharides of *M. charantia* have different sugar levels. Introducing phosphate and sulfate can therefore enhance the anti-lipid peroxidation capability and scavenging capacity of superoxide anions in the *M. charantia* polysaccharides [51].

M. charantia is also rich in phenolic compounds. Gallic acid is the main phenolic acid found in *M. charantia*. Several studies support that the phenolic compounds of *M. charantia* have antimutagen and antioxidant effects [52,53]. The antioxidant effect signified by the Half maximal inhibitory concentration (IC_{50}) index, a 50% decrease in radical absorbance, was higher in solvent and Soxhlet than in subcritical water extraction, meaning the second extraction had better antioxidant activity. Therefore, the authors suggest *M. charantia* as a good source of antioxidants [52]. Lin *et al*. [53] examined the antioxidant effects of *M. charantia* in various aspects over time and at different temperatures. The results showed that the antioxidant activity was significantly reduced after 3 days of storage, and the reduction rate was more significant at higher temperatures. Abbas *et al*. [46] divided *M. charantia* into separate groups to achieve higher amounts of antioxidants. The investigators concluded that treating at the seedling stage can affect the amount of antioxidants in *M. charantia*.

The antioxidant effect of aqueous extract and phenolic extract of *M. charantia* in protecting against damage from hydrogen peroxide (H_2O_2) and hypoxanthine-xanthine oxidase (HX-XO) was evaluated in a cell-based assay. The aqueous extract had no toxic effect at the same dose as the phenolic extract. According to this study, *M. charantia* extract is rich in phenolics; it has vigorous antioxidant activity and effective radical removal [54,55].

Neurotoxicity occurs when exposure to natural or manufactured toxic substances (neurotoxicants) alters the normal activity of the nervous system. This can eventually disrupt or even kill neurons, key cells that transmit and process signals in the brain and other parts of the nervous system [56]. Neurotoxicity can result from exposure to substances used in chemotherapy, radiation treatment, drug therapies, and organ transplants, as well as exposure to heavy metals such as lead and mercury, certain foods and food additives, pesticides, industrial or cleaning solvents, cosmetics, and some naturally occurring substances. Symptoms may appear immediately after exposure or after a delay [57]. They may include limb weakness or numbness, memory loss, vision. Individuals with certain disorders may be especially vulnerable to neurotoxicants [58].

In 2021, Kumar *et al*. [58] experimented with the anticholinesterase and antioxidant activity of *M. charantia* in *Danio rerio* (zebrafish). They used trimethyltin chloride (TMT) to induce neuronal death. Six groups were used in this *in vivo* study as follows: control, TMT (day1), TMT (day2), TMT + food and drug administration (FDA)-approved drug for AD (donepezil), TMT + *M. charantia*, and TMT + (*M. charantia* + mesoporous silica nanoparticle) [59–61]. Their results showed that *M. charantia* causes no adverse changes in behavior and mortality during treatment. Furthermore, no pathological changes were seen in the brain histopathological analysis of *M. charantia*-treated fish. The results of the acetylcholinesterase activity assay indicated that *M. charantia* at the concentration of 50 g/mL caused significant inhibitory activity of acetylcholinesterase compared with the positive control group (donepezil-treated group). In addition, the aqueous *M. charantia* showed significant antioxidant activity compared with ascorbic acid, the standard antioxidant in the positive control, according to 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity, a method for evaluating antioxidant potential. The results of the total antioxidant assay indicated a significant total antioxidant activity of *M. charantia* compared with the positive control (ascorbic acid). In addition, the lipid peroxidation assay showed that *M. charantia* had significant lipid peroxidation activity compared with MDA (as a standard antioxidant, positive control) [62].

3.3 Potential Pharmacological Applications in Neurological Disorders

3.3.1 Role of M. Charantia in Neuroinflammation

Neuroinflammation is a crucial part of the general pathology of several chronic and severe problems in the CNS [63]. The occurrence of neurologic diseases in people over 65 years is 1.8 and 2.6 for people aged 85 to 90 years, per 100 population [64]. The aggregation of dam-

aging products caused by oxidative stress, such as glycated products, oxidized proteins, and lipid peroxidation, results in the destruction of neurons, which is more noticeable in brain disorders. Cerebrovascular diseases are characterized by vascular lesions that cause cognitive decline and dementia in old age [65].

Signaling molecules generated throughout the process of neuroinflammation meditate a number of pro-apoptotic pathways. In operating microglial cells, a transcription factor named NF-κB induces and controls the expression of many vital components in inflammatory and immune feedback systems in the CNS and neurodegenerative disorders [65].

Kim *et al*. [66] found that protocatechuic acid (PA), an active phenolic compound of *M. charantia*, reduced the increased levels of NF-κB, cyclooxygenase-2 (COX-2), and *iNOS* mRNA due to H_2O_2-induced oxidative stress. In addition, PA attenuated the production of interleukin (IL)-6 and reduced nitric oxide (NO) induced by endotoxin lipopolysaccharide (LPS) and interferon-gamma (IFN-γ) together. Furthermore, it reduced mRNA expression of *iNOS* and *COX-2* induced by LPS and IFN-γ [22].

M. charantia supplementation significantly reduced high-fat diet-induced brain oxidative stress in C57BL/6 mice, reducing blood–brain barrier (BBB) leakage, neuroinflammatory cytokines, NF-κB1 expression, glial cell activation, and oxidative stress, while improving systemic inflammation [67].

Obesity increases the development of T-helper (Th) 17 cell genealogy, leading to inflammation [68]. IFN-γ, IL-17, and IL-22 are major cytokines liberated from Th1 and Th17 CD4+ cells. *M. charantia* decreases inflammation by reducing the liberation of plasma pro-inflammatory cytokines, IFN-γ, and IL-17 with tumor necrosis factor-alpha (TNF-α), exotoxin-2, lymphotactin, and IL-1β in mice fed with blue mussels (BM). Furthermore, *M. charantia* adjusted the Th2 cytokines IL-5, IL-10, and IL-13 to preserve obesity-associated inflammation [69]. However, in another study, the results were different, and Th2 cytokines such as IL-4 were shown to aggravate weight gain and high fat diet (HFD)-related hypothalamic inflammation [70]. In some studies, *M. charantia* adjusted neuroinflammatory and peripheral reciprocation by regulating the BBB [71–75]. Increased expression of IL-22 in the brains of HFD-fed mice may indicate glial cell activation, and feeding HFD to Sprague-Dawley rats reduced Sirtuin 1 (SIRT1) levels in the cerebral cortex and hippocampus, promoting oxidative stress. The observed 25% decrease of SIRT1 protein in the brains of HFD rats is lower than the 81% decrease reported by Wu *et al*. [75] in the cerebral cortex and hippocampus of HFD-fed mice. The levels of SIRT1 were different in the studies by Wu *et al*. [75] and others.

Horax *et al*. [76] reported that *M. charantia* contains various flavonoids, bitter triterpene aglycones, non-bitter cucurbitane, and glycosides that transmit antioxidants. Horax *et al*. [76] also showed that catechin is a major polyphenol in the seeds of BM and pericarp.

Deng *et al*. [77] used the chronic social defeat stress (CSDS) mouse model to assess the efficacy of Momordica charantia polysaccharide (MCP). MCP prohibits depressive-like behaviors brought on by CSDS. Moreover, MCP diminishes the amount of pro-inflammatory cytokines and restrains The c-Jun-NH(2)-terminal kinase (JNK3) and c-Jun production in the hippocampus. Furthermore, MCP protects against depressive-like behaviors in mice. Consequently, the protective efficacy of MCP in CSDS mice against depressive-like behaviors could be because of reduced neuroinflammation and down-regulation of the JNK3/PI3K/Akt pathway in the hippocampus [78].

In 2020, Kung *et al*. [78] studied the effects of wild bitter melon (WBM) on mouse models with spinal cord injuries (SCI), which induced secondary neuroinflammation. The investigators also used astrocyte-like cells stimulated by LPS for *in vitro* studies of astrocyte inflammation. They found that WBM reduces spinal cord injury. Furthermore, WBM, which contains alpha-eleostearic acid (α-ESA), increases the viability and survival ability of astrocyte-like cells.

Mitochondrial malfunction and inflammation can lead to irreparable neuronal deficits. Chitosan/gelatin/sodium hyaluronate (CGSH) iron-sulfur domain 2 is a protein located on the outer membrane of mitochondria and is involved in maintaining the integrity of mitochondria and inhibiting apoptosis [79,80]. Furthermore, CGSH iron-sulfur domain 2 reduces inflammatory responses caused by CNS injuries. Aging downregulates the expression of CGSH iron-sulfur domain 2, which aggravates mitochondrial malfunction and increases inflammatory responses [81,82]. Spinal cord injury-induced downregulation of IL-4 is reduced by WBM because losing IL-4 increases microglial polarization from M2 to M1 [83]. WBM can increase the volume of M2 microglia, which are anti-inflammatory. The anti-inflammatory effects of WBM are therefore facilitated through the increase of CGSH iron-sulfur domain 2 in mice with spinal cord injuries and astrocyte-like cells stimulated with LPS. In addition, its protective effects in mice are shown by the deactivation of astrocytes and the downregulation of NF-κB [83].

3.3.2 M. Charantia and Headaches, Amyotrophic Lateral Sclerosis, and MS

There have been reports of headaches following the consumption of *M. Charantia* seeds; however, there is no information regarding amyotrophic lateral sclerosis and headache severity or duration, or effectiveness as a treatment [84].

3.3.3 M. Charantia and MS

Macrophages are part of the first line of defense against injury, mediating the innate non-specific immune

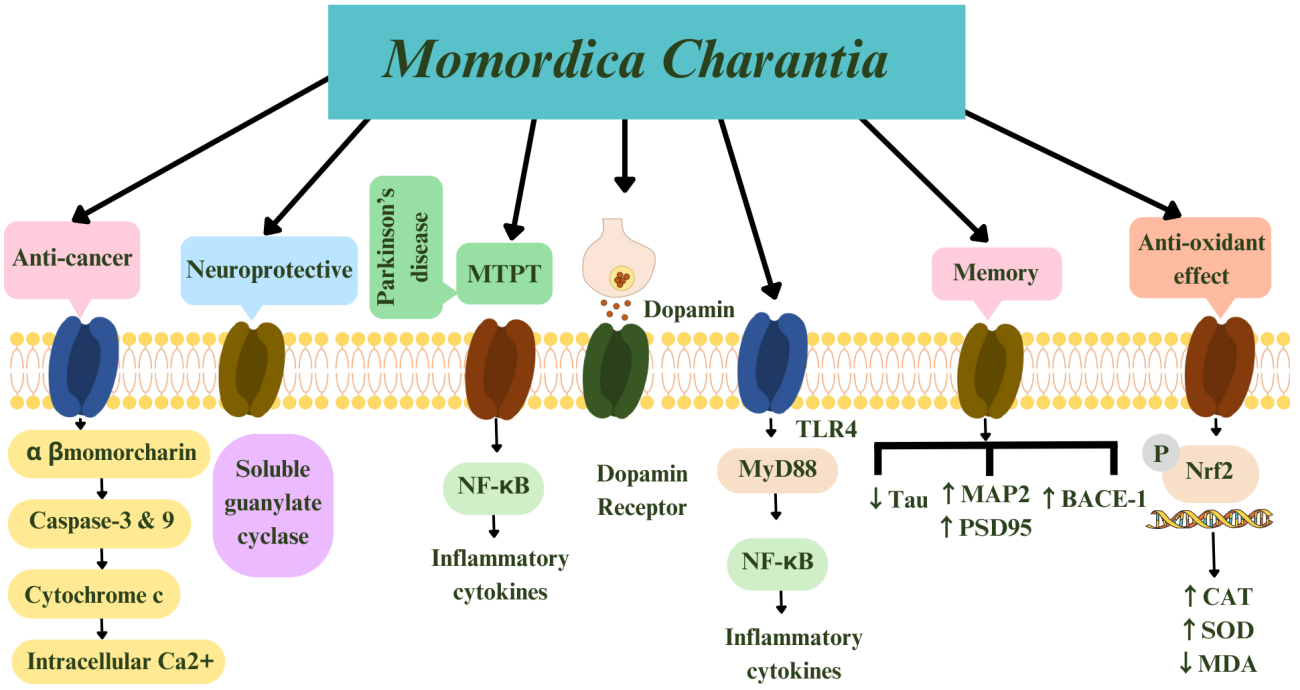

Fig. 4. Summary of *Momordica charantia*'s effects including anti-oxidant, anti-cancer, anti-glioma, anti-Alzheimer's disease, and anti-Parkinson's disease. Arrows indicate mechanism of actions of *M. charantia*. Keap1 is the factor accommodating Nrf2. MTPT, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TLR4, toll-like receptor 4; MAP2, microtubule-associated protein 2; BACE-1, beta-site amyloid precursor protein cleaving enzyme 1; PSD95, postsynaptic density protein 95; Nrf2, nuclear factor erythroid 2-related factor 2; CAT, chloramphenicol acetyltransferase; SOD, superoxide dismutase; MDA, malondialdehyde; MyD88, myeloid differentiation primary response 88; P, phosphorylation; CAT, chloramphenicol acetyltransferase; Tau, tubulin associated unit.

response via inflammation, and playing an important role not only in host defense but also in tissue homeostasis, repair, and pathology development, including MS. RAW 264.7 mouse derived macrophages have been widely used as an *in vitro* model to study the modulatory effects of various compounds using LPS for activation. It has been observed that treatment with Bitter Gourd (BG)-4 peptide extracted from *M. Charantia* has anti-inflammatory effects. In the investigation conducted by Nieto-Veloza *et al.* [84], BG-4 doses up to 375 g/mL had no effect on macrophage viability. It is known that LPS can activate NF-κB, which acts as a master regulator of the inflammatory response by promoting the release of signaling and effector molecules such as pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) and NO that act as mediators of inflammation during the host immune response. MS and other inflammatory problems can be caused by the destruction of normal and healthy tissue caused by a continuous inflammatory condition; therefore, reducing the quantity of these pro-inflammatory produced molecules can lead to the management and treatment of these diseases. BG-4 dose-dependently inhibits NO and IL-6 production in LPS-activated RAW 264.7 macrophages. Moreover, BG-4 reduces the expression of iNOS and COX-2 [85].

3.3.4 M. Charantia and AD

AD is among the most prevalent of neurological diseases. Oxidative stress and the abnormal increases in Aβ are the most common causes of AD. Dementia is seen in patients with AD and occurs when Aβ accumulates in brain tissue, including in the cerebral cortex. Common treatments are cholinesterase inhibitors and receptor antagonists, but they cannot efficiently treat patients [23,86,87].

According to an *in vivo* study by Sin *et al.* [23], 100 and 200 mg/kg/day of butanol (BuOH) fraction derived from *M. charantia* can improve memory and learning in the Aβ (25-26)-induced AD mouse model. Furthermore, oral prescription decreased HNO_3 and lipid peroxidation in the brain compared with the control group [24]. Combination therapy including *M. charantia* and lithium chloride in ovariectomized AD female mice reduced gliosis, neuronal loss, and tau hyperphosphorylation, suggesting the potential for AD treatment [88].

In an *in-silico* study [89], luteolin, extracted from *M. charantia*, increased ACh in neuronal cells by attaching to acetylcholinesterase and butyrylcholinesterase. The authors suggested luteolin as a multi-target molecule against AD. Luteolin can therefore effectively act as a multi-target

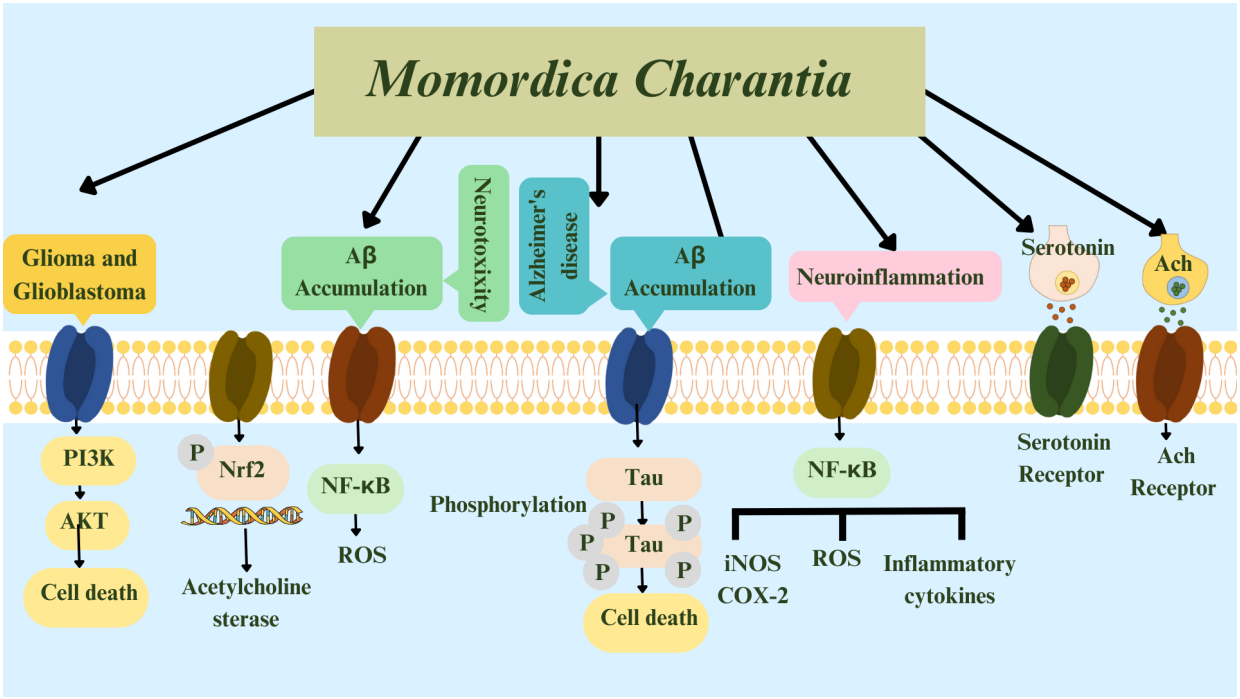

Fig. 5. Summary of pathways: *Momordica charantia* acts in Gliomas, Glioblastomas, neurotoxicity, and Alzheimer's disease, and on neuroinflammation, serotonin, and acetylcholine. Glutamate-activated AMPA and NMDA receptors mediate Aβ accumulation. ROS, reactive oxygen species; ACh, acetylcholine; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-D-aspartate; PI3K, phosphoinositide 3-kinases; Akt, protein kinase B; P, phosphorylation; Aβ, amyloid-beta.

molecule against AD. The summarized effects of *M. charantia* on age-related neurological disorders is shown in Figs. 4,5.

A study [90] reviewed the therapeutic role of α-ESA, an isomer of conjugated linolenic acids produced from wild bitter melon (*Momordica charantia* L. var. *abbreviata* Seringe), and curcumin in CNS illnesses. In addition, the authors highlighted the probable role of glia-mediated neuroinflammation, mitochondrial dysfunction, CDGSH iron-sulfur domain 2 (CISD2) loss, and NF-κB activation in CNS traumas and disorders. Their review enhances our understanding of the CNS pathology–CISD2–NF-κB axis and clarifies the possible therapeutic role of these natural chemicals [90].

A study [90] investigated the neuroprotective benefits of sulforaphane (SFN) on cognitive illnesses such as AD, PD, Huntington's disease, amyotrophic lateral sclerosis, MS, autistic spectrum disorder, and schizophrenia in a separate review. they described the anti-AD-like action of SFN and how it reduced levels of AD biomarkers, including Aβ, tau, inflammation, oxidative stress, and neurodegeneration in AD-like animal and cell models. In addition, the authors concentrated on the probable mechanisms behind the neuroprotective benefits of SFN. This review reveals that SFN has multiple neuroprotective effects on the pathophysiology of AD, highlighting the necessity to continue SFN research [90].

Yoshinori Okada and Mizue Okada [90] evaluated the protective effects of plant seeds against Aβ-induced neurotoxicity in hippocampal neurons. They examined the aqueous extracts of 15 plant grains for their ability to inhibit Aβ (25-35)-induced cell death using hippocampal neurons. The aqueous juices showed antioxidant properties. Furthermore, intracellular cumulative ROS resulting from Aβ declined when cells were cured with some of these extracts. Kale, bitter melon, red shiso, kaiware radish, and corn inhibited TNF-α in Aβ-stimulated neurons and, in all instances, Japanese honeywort displayed better cell survival. This study showed that some plant seed juices offer protection against Aβ-mediated death in cells.

Katsouri *et al.* [91] showed promising results regarding a lithium chloride (LiCl) compound, including increased cognition and short-term memory, as well as decreased amounts of oligomer, tau protein phosphorylation, and BACE-1 expression, and improved expression of synaptic plasticity-related proteins. Other neuroprotective results have been reported by synthesizing LiCl with L-dopa or other histone deacetylase inhibitors [67,92–101]. Many studies showed that synthesizing therapies with multifold drugs has better therapeutic potential for AD [102–105].

3.3.5 M. Charantia and Epilepsy

Epilepsy is a common condition that affects the brain and causes frequent seizures. Seizures are bursts of electrical activity in the brain that temporarily affect how it works, causing many symptoms. Epilepsy can start at any age but usually it starts in childhood or in people over 60 years [106]. The drugs that are currently available to treat epilepsy might adversely affect human health. The herbal medicines that have been used in the past and traditional medicines have fewer side effects [107].

Soliman *et al*. [107] investigated the anticonvulsant potential of *M. charantia* in rats. Thirty minutes after treatment, ear electrodes were used to give rats a 150 mA shock. According to the reported results, *M. charantia* might have tremendous anticonvulsant effects against maximal electroshock-induced seizures and reduce the duration and delay the onset of seizures [108].

3.3.6 M. Charantia and PD

PD is the second most common neurodegenerative disease after AD [109,110]. The cause of PD is not yet well understood, but genetic and environmental factors, including poisons, are proven to contribute to its development [111]. In PD, dopaminergic neurons in the substantia nigra compact area are lost, and Lewy bodies accumulate in the brain [112]. The active metabolite of 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) is N-methyl 4-phenylpyridinium (MPP^+). MPTP is a neurotoxin that specifically targets dopaminergic neurons and causes PD [113]. Evidence indicates that inflammatory damage and oxidative stress can accelerate the disease [25].

Natural ingredients such as polysaccharides in plants delay aging and protect the brain. Momordica charantia polysaccharides (MCPs) have been studied for their antioxidant, anti-inflammatory, anti-tumor, hypoglycemic, and anti-diabetic effects [19]. Little is known about their role in the regulation of neurogenesis [114]. However, MCPs reduce nerve damage after stroke by scavenging free radicals [42].

MCPs showed neuroprotective effects in MPTP- and MPP^+-induced PD in mice. A study on mice reported that MCPs alleviated the exercise instability and loss of coordination caused by MPTP, inhibited the release of inflammatory factors and oxidative stress products in the brain, and, as a result, increased dopamine levels. Regarding cell function, MCPs inhibit apoptosis and oxidative stress induced by MPP^+. The authors also observed that MCPs can protect against oxidative stress by inhibiting the transcription of Toll-like receptor 4 (TLR4)/Myeloid differentiation primary response 88 (MyD88)/NF-κB [114]. The TLR4/MyD88/NF-κB pathway is thought to play a vital role in the inflammatory process [115,116]. Observing the changes in this signaling pathway showed that MCPs can affect the status of the TLR4/MyD88/NF-κB pathway. There are various TLR4 inhibitors, among which Resatorvid (TAK-242) is a bioavailable TLR4 inhibitor that inhibits extensive inflammation [117]. As a result of the combined use of MCPs and TAK-242 in the PD condition, the investigators found that TAK-242 could reverse the protective effects of MCPs, therefore proving the effectiveness of MCPs on the TLR4/MyD88/NF-κB signaling pathway [114].

3.3.7 Anti-Cancer Effects of M. Charantia

Increasing the average life expectancy is one of the most significant achievements of the past century [118,119]. However, a healthy lifestyle and life expectancy free of disease have not increased as much [118,120]. In addition to disability and reduced physical strength, aging is a risk factor for chronic diseases and cancer, and it has become a pervasive challenge [118,121,122]. Research to identify the causes of these destructive changes in the body that occur with the aging process and find a solution to reduce these changes will therefore help to increase quality of life and personal productivity. Cancer and tumors are a group of age-related diseases that we are facing more often due to increases in the average age of society. Prolonged exposure to endogenous and exogenous factors contributing to oxidative stress can eventually lead to gene mutations and inflammatory processes [123]. Antioxidant therapy is therefore accepted as one of the main methods to limit cell damage caused by oxidative stress [124,125]. Many studies have been conducted to find effective natural and artificial antioxidants for fighting excess free radicals. Currently, people older than 65 years comprise around 60% of all patients with malignant tumors, and they make up 69% of whole cancer deaths [126]. Based on etiology, some highlighted common causes of aging and cancers include oxidative damage and deoxyribonucleic acid (DNA) damage [127–130], cellular senescence [131], and insulin/insulin-like growth factor-1 (IGF-1) signaling [132].

In a study by Manoharan *et al*. [132], the impacts of α- and β-momorcharin (200-800 µM) on WERI-Rb-1, SK-MEL, 1321N1, COR-L23, and U87-MG cancer cells lines were compared with the normal and balanced L6 myocytes line. α- and β-momorcharin decreased viability, increased cytochrome c release, and enhanced calcium concentration in treated cells. The authors reported 800 µM as the most effective concentration. Furthermore, other studies have suggested that α- and β-momorcharin can trigger a receptor on the membrane surface of cancer cells or may infiltrate the cell by its osmotic effect [133–135]. This substance is also assumed to damage the cancer cells' mitochondria, leading to apoptosis by improving the caspase-3 and caspase-9 processes, releasing cytochrome c and intracellular Ca^{2+} [136,137]. In conclusion, *M. charantia*, which contains α- and β-momorcharin, can effectively lead to cancer cell apoptosis and may be a suitable anti-cancer option.

M. charantia is a plant with medical effects, such as anti-inflammatory [138–145] and anti-cancer effects,

as well as anti-diabetic and antiviral activities [146,147]. Its evaluation is therefore valuable for discovering its influential factors. Previous studies identified some of its beneficial components, including the ribosome-inactivating proteins α- and β-momorcharin, cucurbitacin B, and momordin, and the chemical analog MAP30 protein [148–151]. A few study found two new triterpenoids, D [146] and E [147] charantagenin. A novel sterol, 7-oxostigmasta-5,25-diene-3-O-β-D-glucopyranoside, was isolated [152] in addition to eight known compositions [153–159]. The results confirmed that this novel composition was more abundant than the others and that another (guaglycoside D) contained an O-Methyl (OMe) substituent in the side chain, which was effective against cancer cells and had impressive cytotoxic effects. In addition, they had lower IC_{50} values compared with other components. It is worth noting that IC_{50} is applied to measure drug efficacy, as it corresponds to the potency of the drug. These findings suggest the level of OMe may be associated with the cytotoxic activity of cucurbitane-type triterpenoids. The cucurbitane-type triterpenes, especially from *M. charantia*, therefore probably have potential anti-cancer effects similar to chemotherapy.

Glioblastoma multiforme (GBM), also referred to as a grade four astrocytoma, is a fast-growing and aggressive brain tumor. It invades the nearby brain tissue but does not spread to distant organs. Gliomas are tumors that have a peak incidence in middle-aged humans [160]. Gliomas account for over half of all intracranial tumors [161]. The average annual age-adjusted incidence rate of glioma is estimated at 6 per 100,000 population [162]. These tumors are the most common primary tumors in the brain, originating from different glial cells, including oligodendrocytes, astrocytes, and ependymal cells [163]. Standard of care includes surgery, radiation therapy, and chemotherapy. However, due to the exceedingly invasive capability of glioblastoma cells, tumors develop over time and integrate into surrounding brain tissue [164].

Wang *et al*. [161] found that *M. charantia* impedes viability and reduces the multiplication of U251 glioma cells, repressing their influx, which has an anti-glioma effect. However, it had no considerable efficacy in the apoptosis of these cells. Moreover, *M. charantia*-derived extracellular vesicle-like nanovesicles exert anti-glioma effects by adjusting the PI3K/Akt signaling route [165]. In an *in vitro* study the effects of the anti-tumor activity of *M. charantia* (MAP30) on proliferation, migration, and invasion of the U87 and U251 cell lines were assessed [166,167]. MAP30 inhibited U87 and U251 cell viability in a dose- and time-dependent manner and decreased colony formation of these cell lines. It also induced apoptosis and S-phase cell cycle arrest by breaking the bonds of the adenine-ribose glycoside. The invading proportions of the cells treated with MAP30 were significantly lower than their control counterparts. Western blot analysis indicated decreased leucine rich repeat containing G protein-coupled receptor 5 (LGR5) expression and increased Smac (activator of intrinsic apoptosis) expression in cells treated with MAP30. The Wnt/β-catenin and LGR5 signaling pathways play a vital role in the tumorigenesis of gliomas [26,168–171]. Manoharan [26] investigated the performance of α- and β-momorcharin obtained from *M. charantia* by combining cyclophosphamide with the cellular mechanisms. Compared with cyclophosphamide's effect, the results showed significant decreases in cell viability for each cell line in the presence of active substances [172].

Furthermore, 800 µg of the crude water-soluble *M. charantia* extraction in combination with 250 µg of paclitaxel showed a significant decline in cell viability of five cell lines mentioned earlier [173]. Another study on the U87G Glioblastoma cell line showed that *M. charantia* extraction displays a cytotoxic and anti-proliferative role and might be helpful as a therapeutic agent against GBM [174]. According to these studies, *M. charantia* can be considered a plant with pharmacological and nutritional properties. Its compounds make this plant a potential anti-carcinogenic agent and therapeutic aid for the treatment of glioma.

3.3.8 M. Charantia and Ischemia

Stroke is the second leading cause of disability and death worldwide, and has the most concerning and excessive burden in countries with revenue deficiency. The universal number of incidents was 13.7 million in 2016, and it is estimated that 87% of those were ischemic stroke [27]. Furthermore, stroke is one of the world's most prevalent vascular ailments and remains the fifth leading cause of death in the United States [175]. Brain ischemia could be focal or multifocal and is caused by an abrupt cessation or diameter reduction of the artery supply of a region in the brain. The decreased brain blood supply leads to hemodynamic dysfunction, which contributes to damage to the brain tissue [28]. There are some uncommon causative agents of ischemia. Rarely, dissection of cervical blood vessels causes brain ischemia and may cause stroke in younger patients. Another rare cause of brain ischemia is vasospasm. An infection can also lead to stroke.

It should be noted that an increased stroke incidence has occurred with the COVID-19 pandemic [174]. Aging and related conditions, including diabetes, could be important factors in ischemia manifestation. Special attention must therefore be paid to ischemia as an age-related disorder.

The potential neuroprotective effect of the freeze-dried juice of fresh *M. charantia* in cerebral injury caused by ischemia-reperfusion was studied by Malik *et al*. [27] using cerebral infarct size, measuring thiobarbituric acid reactive substances (TBARS) and immediate memory and motor activity. Cerebral oxidative stress and damage with a shortfall in neurological functions were observed related to the dosage. The authors reported that the manifesta-

tions were extenuated by lyophilized *M. charantia* juice pre-treatment. *M. charantia* might therefore be an efficient option with neuroprotective activity in treating patients with stroke [27].

4. Conclusions

The aging process begins with molecular changes, such as epigenetic changes, telomere weakening, and the buildup of mutations, which causes genomic instability. These defects increase rapidly over time, with a "snowball effect", and finally lead to a functional and morphological worsening of the brain, which includes excessive inflammation, reduced amounts of neurotransmitters, progressive neuronal damage, and damaged integrity of vessels, leading to microbleeds and infarction. Furthermore, the reduced effectiveness of the DNA repair systems makes us more vulnerable to spontaneous mutagenesis and ROS, leading to age-related neoplasia. In addition, the malabsorption and malnutrition usually seen in older people may lead to a deficiency in folic acid and vitamin B12, leading to vascular damage. These factors cause brain injuries in the elderly and increase the risk of CNS diseases such as epilepsy, dementia, PD, stroke, and AD [175].

M. charantia is used for diabetes, AD, glioma, neuroinflammation, seizure, and PD. Its antioxidant compounds, including luteolin, increase acetylcholine in neurons, reduce cholesterol, and treat memory loss [28,29]. It seems that *M. charantia* can also improve memory by decreasing tau protein and increasing MAP2, postsynaptic density protein 95 (PSD95), and beta-site amyloid precursor protein cleaving enzyme 1 (BACE-1) [166]. The neurotoxin MPTP targets dopaminergic neurons and causes PD [61]. MCPs reduce exercise instability and coordination loss caused by MPTP, inhibit inflammatory factors and oxidative stress products in the brain, and increase dopamine levels. MCPs also inhibit apoptosis and oxidative stress caused by MPP^+, an active metabolite of MPTP. Additionally, MCPs protect against oxidative stress by inhibiting the transcription of TLR4/MyD88/NF-κB [152]. *M. charantia* contains different types of phenolic acid, including gentisic acid, gallic acid, epicatechin, and catechin, which are more abundant in its flesh than in its seeds. Phenolic acids inhibit lipid oxidation and have potent antioxidant activity [52,53]. Moreover, *M. charantia* extracts were found to possess neuroprotective properties partly because of their high level of D-galacturonic acid [42].

M. charantia liposomes are specific for brain tumor cell lines such as U87-MG, GOS-3, and astrocytoma cell line1321N1 and not human astroglial cells (SVGP12), the standard glial cell line. When compared with paclitaxel (an anti-cancer medicine), the side effects of *M. charantia* were far less, and whereas paclitaxel could inhibit 44–66% of glioma cells without affecting normal glial cells, the *M. charantia* liposomes inhibited 60–80% of them [176]. Extracts of the seeds of *M. charantia* contain ethanolic, which can be used for treating maximal electroshock and pentylenetetrazole seizures. These anticonvulsant effects are due to their phytochemical constituents [108].

This review has highlighted that *M. charantia* has effects on many ANDs, and it can be a cost-effective drug with minimal side effects. We recommend further *in vitro* and *in vivo* studies to fully understand its mechanisms, in addition to clinical trials to investigate the effects of this plant on patients.

Author Contributions

Study concept and design: ND. Acquisition of data: SMHHA, OJKA, AA, RT, SB, MF, MR, MSS, SH, SP, DA, MP, HA, SAM, RK. Drafting of the Manuscript: SMHHA, OJKA, AA, RT, SB, MF, MR, MSS, SH, SP, DA, MP, HA. Critical revision of the manuscript for important intellectual content: SAM, MF, RK. Study supervision: ND. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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