Pharmacological properties of mangiferin: bioavailability, mechanisms of action and clinical perspectives

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REVIEW

Pharmacological properties of mangiferin: bioavailability, mechanisms of action and clinical perspectives

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Abstract

This review aims to provide an in-depth analysis of the pharmacological properties of mangiferin, focusing primarily on its bioavailability and mechanisms of action, and its potential therapeutic applications, especially in the context of chronic diseases. We conducted a comprehensive examination of in vitro and in vivo studies, as well as clinical trials involving mangiferin or plant extracts containing mangiferin. The primary source of mangiferin is *Mangifera indica,* but it's also found in other plant species from the families Anacardiaceae, Gentianaceae, and Iridaceae. Mangiferin has exhibited a myriad of therapeutic properties, presenting itself as a promising candidate for treating various chronic conditions including neurodegenerative disorders, cardiovascular diseases, renal and pulmonary diseases, diabetes, and obesity. Despite the promising results showcased in many in vitro studies and certain animal studies, the application of mangiferin has been limited due to its poor solubility, absorption, and overall bioavailability. Mangiferin offers significant therapeutic potential in treating a spectrum of chronic diseases, as evidenced by both in vitro and clinical trials. However, the challenges concerning its bioavailability necessitate further research, particularly in optimizing its delivery and absorption, to harness its full medicinal potential. This review serves as a comprehensive update on the health-promoting and therapeutic activities of mangiferin.

Keywords Mangiferin · Pharmacological properties · Mechanisms of action · Chronic diseases · Clinical studies

Introduction

Herbs have historically served as a reservoir of medicinal compounds and continue to underpin many of today's pharmaceuticals (Ginsburg and Deharo 2011). The surge in interest in phytocompounds among the scientific community can be attributed to their cost-effectiveness, superior bioavailability, and lower toxicity when juxtaposed with synthetic therapeutic drugs. While these natural compounds may undergo changes in performance and structure, intrinsic structural resemblances remain among analogs of these compounds. Such similarities often render natural compound ligands more adept at achieving biological objectives than their synthetic counterparts (Ginsburg and Deharo 2011). Polyphenols are extensively found in natural vegetables and fruits and represent a significant group of phytochemicals whose pharmacological activities are widely studied (Jangra

et al. 2020). Mangiferin (MGF), also known as alpizarin or quinoline, with the chemical formula C19H18O11 and IUPAC name 1,3,6,7-tetrahydroxyxanthone C2-β-D-glucoside or 2-β-D-glucopyranosyl-1,3,6,7-tetrahydroxy-xanthone, is a natural xanthone polyphenolic compound (Wilkinson et al. 2008) (Dutta et al. 2023). This compound is found in various plant species belonging to diverse botanical families, as outlined in Table 1. Prominently, it is synthesized by specific plants within the Anacardiaceae, Gentianaceae, and Iridaceae families (Chu et al. 2018). Notably, its presence has been documented in different parts of these plants, including the bark, berries, roots, and leaves (Chu et al. 2018, Jyotshna et al. 2016).

Within the traditional medicine of China, India, and Cuba, MGF-rich plant species have been applied to treat cardiovascular illness, diabetes mellitus, infections, and tumors (Morozkina et al. 2021). The chief source of MGF is the species *Mangifera indica* (Lum et al. 2022). This species, known as mango, is among the most profitable fruits

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Table 1 Significant sources for mangiferin

Genus	Plant species	Family	Reference
Mangifera	*M. indica L*	Anacardiaceae	Kulkarni and Rathod (2018)
	M. odorata		Lasano et al. (2019)
	M. persiformis		Nong et al. (2005)
	M. caesia		Sulaiman and Ooi (2012)
	M. foetida		Sulaiman and Ooi (2012)
	M pentranda		Sulaiman and Ooi (2012)
	M quadrifida		Sulaiman and Ooi (2012)
Gentiana	*G. asclepiadea*	Gentianaceae	Popović et al. (2021)
	G.lutea		Cvetković et al. (2020)
	G.pneumonanthe		Popović et al. (2021)
	G.rhodantha		Xu et al. (2011)
Hypericum	*H. perforatum*	Hypericaceae	Tikhomirova and Gulikova (2021)
Bombax	*B. ceiba*	Malvaceae	Bhargava and Shah (2020)
Anemarrhena	*A.asphodeloides*	Asparagaceae	Chae et al. (2011)
Salacia	*S. chinensis L*	Celastraceae	Ngo et al. (2019)
Aphloia	*A. theiformis*	Aphloiaceae	Grauzdytė et al. (2020)
Pueraria	*P. tuberosa*	Fabaceae	Bulugonda et al. (2017)

grown in tropical and subtropical areas worldwide (Hirano et al. 2010). MGF is extracted from young leaves, bark, and old mango leaves at 172, 107, and 94 g/kg concentrations, respectively (Barreto et al. 2008). The mango plant is utilized in traditional medicine globally to treat conditions and diseases of different organs and systems, such as digestive, pulmonary, auto-immune, metabolism disease, hypertension, insomnia, and tetanus (Ediriweera et al. 2017a). In Ayurveda, mango is utilized to alleviate digestion issues and counteract acidity caused by heat (pitta). Concurrently, in traditional Chinese medicine (TCM), mango is a principal bioactive constituent of more than 40 polyherbal formulations (Jyotshna et al.). This review aims to discuss novel information on the bioavailability, pharmacological effects, and clinical trials of MGF in some commonly encountered chronic diseases except cancer for further development of new medical treatments.

Review methodology

Information on MGF was acquired from specialized databases including PubMed/MedLine, ScienceDirect, Google Scholar, SciFinder, and TRIP Database. The search strategy employed the following MeSH terms: "mangiferin," "bioavailability," "pharmacological studies," "gastroprotective," "cardioprotective," "neuroprotective," "pulmonary AND/OR skin diseases," "metabolism effects," "clinical and preclinical studies," and "safety AND tolerability."

Inclusion Criteria: studies published in English between the years 2002 to 2023; studies containing comprehensive data on the bioavailability, mechanisms of action, and other pharmacological experiments associated with MGF; articles discussing the pharmacological effects and clinical trials of MGF in commonly encountered chronic diseases, excluding cancer.

Exclusion Criteria: abstracts and duplicates; studies that included homeopathic-associated medications; articles published outside the specified date range.

Chemical formulas associated with MGF were cross-referenced with PubChem, while plant taxonomy was verified with World FloraOnline (WFO 2021; PubChem 2022). The essential data were synthesized and displayed in tables and figures.

Bioavailability of *Mangiferin*

Pharmacokinetics and metabolic insights of MGF

MGF's bioavailability has been a topic of extensive research. Many studies emphasize its limited bioavailability upon oral administration, which can be attributed primarily to its poor solubility in aqueous solutions. A case in point, in rat studies, the bioavailability was measured to be a mere 1.2% (Hou et al. 2012). The metabolic processes that MGF undergoes are intricate; starting with its biotransformation, MGF is subjected to a series of reactions: glycosylation, methylation, deglycosylation, glucuronidation, dihydroxylation, and sulfation. After oral administration in rats, MGF and its subsequent metabolites were detected in a wide spectrum of vital organs, which includes the heart, kidneys, intestines, lungs, liver, and spleen.; they were also present in urine, plasma, and feces (Liu et al. 2011) (Fig. 1). Regarding the challenges

of MGF's bioavailability, its lipophilicity is notably poor., this intrinsic characteristic results in diminished permeation through the intestinal membrane, subsequently leading to subpar oral assimilation the therapeutic may be constrained due to its absorption dynamics, especially from the human gastrointestinal tract, there is also the influential aspect of the hepatic first-pass effect to consider. For the pharmacokinetic evaluation, MGF was administered at a dose of 30 mg/kg both orally and intraperitoneally to separate rat cohorts (Kammalla et al. 2015). A detailed assessment of MGF's metabolites was undertaken using ESI-MSn from blood samples. This involved contrasting the retention times with synthesized standards in HPLC. The observations were intriguing; a nominal concentration of MGF was identified in plasma when administered alone, which hints at its extensive metabolism and potential tissue-specific protein binding (Kammalla et al. 2015).

Significantly, previous research underscores the therapeutic efficacy of MGF derivatives like norathyriol (Guo et al. 2018). Norathyriol, identified as a principal metabolite of MGF, was detectable post both oral and intraperitoneal administrations (Guo et al. 2018). Further, a unique microbial angle emerged with the identification of *Bacteroides* species as the progenitor of a secondary MGF metabolite (Sanugul et al. 2005). This microbial interplay accentuates the importance of gut flora in MGF's metabolic dynamics. Both norathyriol and MGF have been associated with improved glucose utilization and insulin sensitivity, attributable to their regulatory effect on AMPK phosphorylation, and this positions norathyriol as an active metabolite with potential antidiabetic efficacy (Sanugul et al. 2005). The overall metabolic profile of MGF, given different administration routes, revealed its restricted gastrointestinal absorption post-oral intake and its transformation into various metabolites. After undergoing phase II metabolism, MGF's aglycone norathyriol is acted upon by intestinal microbes. A mere 4 h post-administration, MGF and its metabolites were discernible in the liver, intestines, and kidneys. These
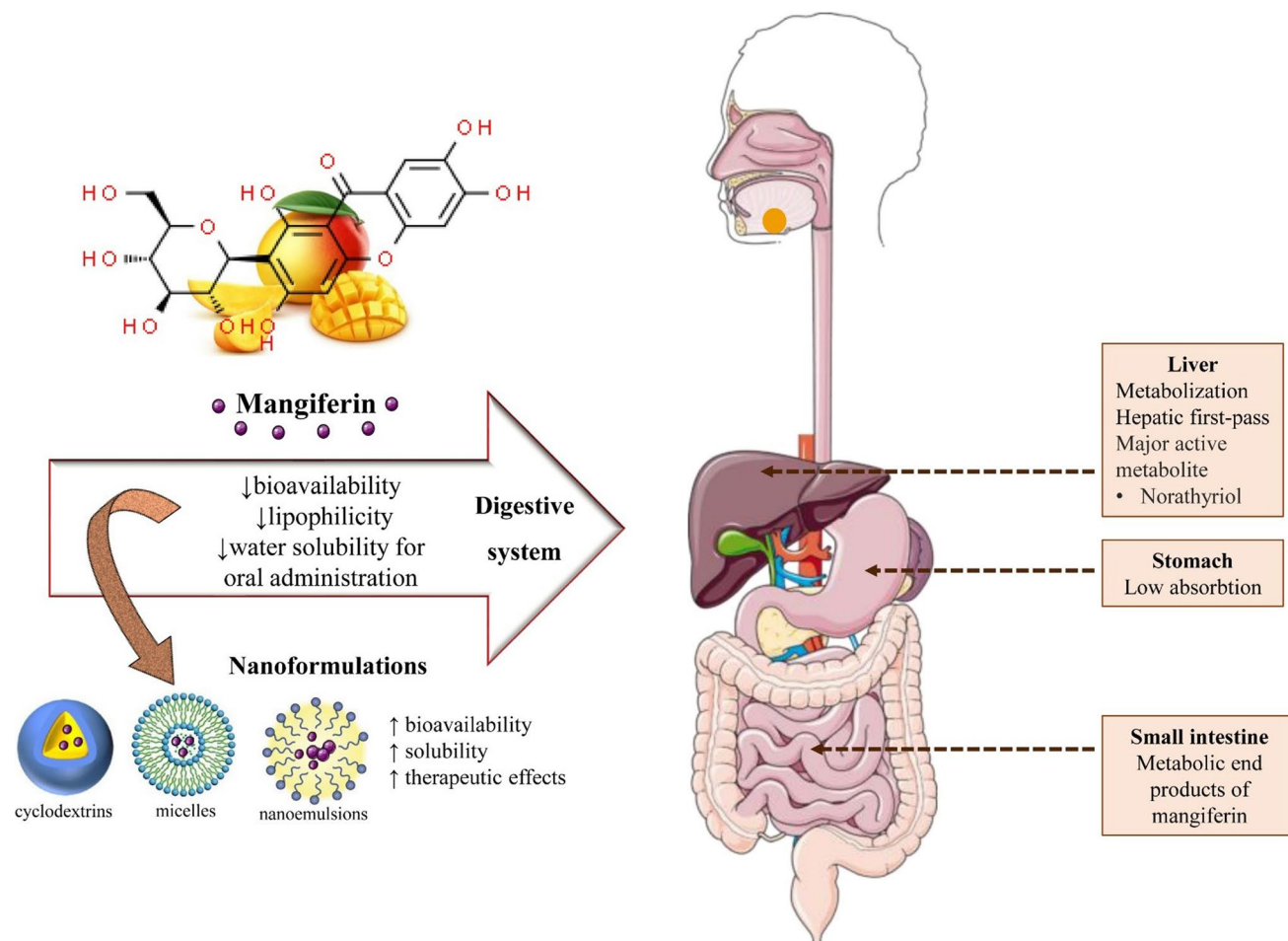

Fig. 1 Illustrative scheme regarding absorption and metabolism of mangiferin. Innovative approaches such as different nanostrategies (nanoparticles, micelles, phytocomplexes, nanoemulsions) enhance the bioavailability of MGF, thus paving the way for its more efficient therapeutic applications. Symbols: ↓decrease, ↑increase

metabolites predominantly find their way out via urine, with a half-life ranging from 4 to 8 h. Further insights, such as MGF's influence on renal expressions and enzymatic activities, were obtained from studies conducted by Li et al. (Li et al. 2020a).

Complexation, nanoformulation, and related technologies applied to mangiferin for enhancing bioavailability and therapeutic effects

The primary challenge associated with MGF therapeutic effects is related to its poor aqueous solubility and low bioavailability upon oral administration. Over the years, researchers have leveraged complexation, nanoformulations, and other cutting-edge technologies to augment MGF's bioavailability and optimize its therapeutic effects (Mei et al. 2023).

Complexation of MGF with phospholipids has shown promising results by forming MGF-phospholipid complexes, the solubility and permeability of MGF in the gastrointestinal tract are enhanced, leading to increased bioavailability. This ingenious complex not only elevates MGF's solubility but also enhances its solubility in rats (Ma et al. 2014). When juxtaposed with standalone MGF, the MGF-phospholipid complex exhibited a marked increase in bioavailability, ranging from 2.3-fold to 9.75-fold (Ma et al. 2014). To amplify the focus on this significant facet of the study, the exploration of MGF's complexation with other compounds warrants its own segment. Notably, the reversible interaction between MGF and human serum albumin was characterized by dominant hydrophobic interactions (Yue et al. 2009). This interaction is worth noting, as in polyherbal formulations, MGF's bioavailability saw a remarkable surge compared to its individual form and it demonstrated a higher affinity towards human serum albumin binding (Yue et al. 2009).

Cyclodextrins, particularly β-cyclodextrins, are cyclic oligosaccharides that can form inclusion complexes with hydrophobic molecules. Complexation of MGF with cyclodextrins can increase its water solubility, thus improving its oral bioavailability (Zhang et al. 2010). Continuing on the path of complexation, Zhang et al.'s research delineated that orally administered MGF complexed with hydroxypropyl-beta-cyclodextrin (HPb-CD) possesses the capability to cross the blood-ocular barrier. Given *Mangiferin*'s limited solubility in water, it was complexed with HPb-CD to enhance its solubility and absorption; HPb-CD has a hydrophilic exterior due to hydroxyl groups and a hydrophobic cavity, making it efficient in forming complexes with hydrophobic molecules like mangiferin. This property ensures HPb-CD's water solubility and positions cyclodextrins as potential solubilizers. These results underpin the potential of MGF in preemptively combatting oxidative stress in ocular conditions (Zhang et al. 2010).

Nanoparticle systems, including polymeric and lipid-based nanoparticles, have been studied for MGF encapsulation (Zhang et al. 2010; Fabián et al. 2023). These nanoparticles can provide protection to MGF from the external environment, increase cellular uptake, and improve its distribution profile (Fabián et al. 2023; Mao et al. 2019). Liposomes are vesicular structures made of phospholipid bilayers that can encapsulate MGF, thereby enhancing its stability and solubility. Liposomal formulations can prolong the release of MGF, offering sustained therapeutic effects (Mao et al. 2019). Nanoemulsions comprising of oil, surfactants, and water, nanoemulsions can solubilize lipophilic drugs like MGF; they present an avenue to improve the dissolution rate and hence the bioavailability of MGF (Pleguezuelos-Villa et al. 2019; Barakat et al. 2022).

Solid dispersion formulations are made by dispersing MGF in a water-soluble carrier matrix, its dissolution rate can be augmented. This approach has been explored to overcome the solubility limitations of MGF (Barakat et al. 2022). Self-microemulsifying Drug Delivery Systems (SMEDDS) are isotropic mixtures of oils, surfactants, and co-solvents/surfactants that can form fine oil-in-water microemulsions when exposed to aqueous phases, such as the gastrointestinal fluid. Incorporation of MGF into SMEDDS can lead to enhanced dissolution and bioavailability (Xuan et al. 2012).

Micelles are formed from surfactants and can encapsulate hydrophobic compounds like MGF, enhancing their solubility and stability in aqueous solutions (Pleguezuelos-Villa et al. 2019; Barakat et al. 2022; Xuan et al. 2012).

Pharmacological studies of mangiferin: evidence based on in vitro and in vivo studies

Neuroprotective effect

Neurological disorders are more prevalent in aging populations, making it important to explore adjuvant natural treatments. In this sense, MGF exhibited various beneficial effects on the central nervous system in vitro and in vivo (Table 1). Mangiferin (MGF) has been highlighted for its neuroprotective qualities (Sekar 2015). Specifically, it has been shown to counteract cognitive impairments and AlCl3-driven reductions in the brain-derived neurotrophic factor (BDNF) within the hippocampus (Kasbe et al. 2015a). Further investigations revealed MGF's capability to mitigate lipopolysaccharide (LPS)-triggered cognitive decline, simultaneously diminishing LPS-induced IL-6 levels in the hippocampus (Fu et al. 2015a). Additionally, Infante-Garcia et al. (2017) documented MGF's effectiveness in attenuating inflammation and TAU hyperphosphorylation in neural

regions like the cortex and hippocampus, fostering the restoration of both episodic and spatial memories. Moreover, MGF demonstrated potential antidepressant properties, alleviating stress-induced behavioral disruptions. This effect can be attributed to the suppression of NLR Family Pyrin Domain Containing 3 (NLRP3), the adaptor protein ASC, and caspase-1, leading to decreased synthesis of pro-inflammatory markers like IL-1β and IL-18 (Cao et al. 2017). In a model of spinal cord harm, MGF regulated the oxidative stress reactions (reactive oxygen species (ROS), H_2O_2, superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT)) (Li et al. 2018b). Furthermore, it inhibited the mitochondrial pathway apoptotic markers (SKIP, ASK1, Fas, tBid, APAF-1, and caspase-3). The protective properties of MGF (10 mg/kg) were evaluated against spinocerebellar ataxia type-2 (SCA-2) characterized by induced memory disorder in female transgenic mice for one year. According to the authors, MGF ameliorated memory recognition but did not impact in memory of SCA-2 mice (Pardo Andreu et al. 2010). The oral administration of MGF at doses of 50, 100, and 200 mg/kg was employed for 4 months to assess the effect on the spatial memory of lead-induced neurotoxicity in rats (Li et al. 2013). At a high dose, it improved rats' spatial learning and decreased the hidden platform's latency time (Li et al. 2013). Also, Liu et al. administered MGF orally for 9 weeks to Sprague–Dawley rats of STZ-induced cognitive impairment at three different doses: 15, 30, and 60 mg/kg (Liu et al. 2013). As a result, MGF improved the cognitive functions indicated by suppressing the escape latency and increasing the time spent in a dose-dependent manner. Mechanistically, MGF triggered methylglyoxal hyperactivity. The neuropharmacological study of MGF (applied in doses 10, 20, and 40 mg/kg) was conducted intraperitoneally in scopolamine(sco)-generated amnesia in juvenile and aged Swiss albino mice for 2 weeks (Biradar et al. 2012). The results indicated that MGF exhibited the ability to reverse scopolamine-induced memory deficits and enhance learning performance, and this was demonstrated by reduced transfer latency in an elevated plus maze test (EPM) and increased step-down latency in the passive avoidance test (PAT) (Biradar et al. 2012). Furthermore, only the high dose of MGF reinstated the activity of brain cholinesterase and biogenic amines such as dopamine and norepinephrine in the brain (hippocampus) (Biradar et al. 2012). In another scopolamine-induced memory deficit study, oral administration of 20 mg/kg of MGF inhibited acetylcholinesterase (AChE) activity with IC_{50} value of 62.8 μM in male mice (Jung et al. 2009). Then, the results indicated a decrease in the escape latency in training trials and swimming times in the Morris maze test and PAT. Furthermore, MGF attenuated TNF-α production and NF-κB signaling pathways in scopolamine or TNF-α-stimulated BV-2 microglial cells (Jung et al. 2009). Feng et al. (2017)

conducted a study on MGF (40 mg/kg, orally) to evaluate its effect on sleep deprivation (SD)–induced memory damage in Swiss albino mice for 2 weeks (Feng et al. 2017). Results from the Morris water maze assessment and novel object recognition (NOR) showed a decrease in escape latency conjugated and a rise in the crossing number over the platform position. MGF also improved the recognition index without affecting the total exploratory time (Feng et al. 2017). In the old APP/PS1 transgenic mice model, a long-time oral administration of 50 mg/kg of MGF caused significant amelioration of spatial and episodic memory of APP/PS1 mice (Infante-Garcia et al. 2017). Also, Fu et al. analyzed the neural effects of MGF (50 mg/kg) on lipopolysaccharide (LPS)-induced neural damage and cognitive deficiency in Kunming male mice of 1-month-old for twelve days (Fu et al. 2015b). The oral administration significantly reduced the escape latency and the time spent, suggesting the potential effect of MGF to ameliorate LPS-induced memory impairment, and learning disabilities in mice (Fu et al. 2015b). In a similar study of LPS-triggered neurological disorder of mice, the oral administration of MGF (20 and 40 mg/kg) enhanced the anxiety-like behavior in EPM and light–dark box and open-field tests (Jangra et al. 2014). It also ameliorated the anhedonia behavior and social communication time. It abolished the depressive effect evoked by LPS, as demonstrated by a forced swim and tail suspension test. Additionally, it reduced the hippocampal glutathione (GSH) content, SOD, and CAT activities along with the hippocampal interleukin-1 beta (IL-1β) production leading to the inhibition of neuroinflammation in the hippocampus and prefrontal cortex. Yang et al. assessed the protective effect of MGF on cerebral ischemia–reperfusion damage in Wistar male rats (Yang et al. 2016). The intragastric application of MGF (25, 50, and 100 mg/kg) significantly amended the neurological impairment, water content, IL-1 β and tumor necrosis factor (TNF-α), lipid peroxidation, and brain antioxidants (GSH and SOD) in the brain tissue of cerebral ischemic rats. Then, MGF modulated the expressions of the nuclear factor erythroid 2-related factor-2 (Nrf-2) and heme-oxygenase-1 (HO-1). The neuroprotective activity of MGF (20 and 40 mg/kg) was proven to aluminum chloride ($AlCl_3$)-induced cognitive dysfunction and neurotoxicity in mice (Kasbe et al. 2015b). This study was conducted for 42 days. A high dose of MGF reduced the retention latency accompanied by an increased crossing number over a platform and recognition index, as evidenced in MWM and NOR findings. It lessened the hippocampal oxide-nitrosative stress and proinflammatory cytokines (Kasbe et al. 2015b). In another model of lipopolysaccharide (LPS)-activated primary rat microglia, MGF (1–50 μM) effectively modulated the microglial activation as evidenced by the attenuation of LPS-induced prostaglandin E2 (PGE2) and 8-iso-prostaglandin F2a (8-iso-PGF2a) production (Bhatia et al. 2008). It

downregulated the expression of LPS-induced cyclooxygenase (COX-2) protein in a dose-dependent way. Not observed effects in p38 mitogen-activated protein kinase (p38 MAPK) phosphorylation or inducible nitric oxide synthase (iNOS) or TNF-α production (Bhatia et al. 2008). Another study investigated MGF's behavioral and neurological outcomes (applied i.p. in doses 10, 50, or 100 mg/kg) in normal male Wistar rats (Pardo Andreu et al. 2010). MGF immediately boosted NOR memory post-training but did not affect NOR 6 h post-training. The locomotion or motivation was not affected (Pardo Andreu et al. 2010). In a different study, MGF isolated from *Hypericum aucheri* (Clusiaceae) contributed to the antidepressant effect via the suppression of inhibited MAOA ($IC_{50} = 40.1$ mM) and MAOB ($IC_{50} = 1$ mM) dose-related action in hepatic mitochondria in rats (Dimitrov et al. 2011). The forced swimming test (FST) produced a decreased immobilization time in rats treated with MGF. Moreover, MGF provoked anti-dementia effects via improved learning, memory retention, and lipid peroxidation in a senescence-accelerated mouse-prone 8 (SAMP8) mouse model (Du et al. 2019). It lowered the damage to hippocampal neurons and mitochondria and downregulated amyloid-β (Aβ1-40 and Aβ1-42) expression, reducing its deposition in the brain tissues. However, it did not affect amyloid precursor protein (APP) within the brain of SAMP8 mice. In this study, the human U138-MG glioblastoma cells upregulated cell proliferation, nerve growth factor (NGF), and TNF-α. The authors concluded that MGF induced recognition. It enhanced memory cognition in mechanisms related to neurotrophin and cytokine levels. In a recent study, it has been investigated the antinociceptive properties of MGF (10 to 100 mg/kg) using chemical models (acetic acid, formalin, and capsaicin) and thermal models (hot-plate and tail-flick) in male Swiss mice (Lopes et al. 2013). The oral treatment remarkably reduced pain in the chemical models in a naloxone-sensitive way in a mechanism related to endogenous opiates, KATP channels, and adenosine receptors. However, it did not modulate the thermal nociception in hot-plate and tail-flick test models, indicating that its analgesic actions are merely peripheral rather than central. Therefore, interestingly, the above studies reveal that oral administration is sufficient to achieve an effect in the brain and intravenous or intranasal administration is not necessary, as prevails for some molecules of low solubility, stability and bioavailability.

Gastroprotective effect

Gastrointestinal (GI) diseases encompass a broad range of conditions that affect the digestive system and they can range from benign, self-limiting symptoms like heartburn or indigestion to severe, life-threatening conditions such as gastric, colorectal cancers and inflammatory bowel disease (GBD collaborators 2022, Lazarus et al. 2023). Given the scope and symptoms of these diseases, there's a growing emphasis on identifying potent, natural bioactive compounds that can prevent or mitigate their effects (Zhou et al. 2022; Morais et al. 2015b). MGF, isolated from *Curcuma amada* (Zingiberaceae), was encapsulated in β-lactoglobulin (β-LG) to produce spherical nanoparticles with uniform particle size (≈70 nm) (Telange et al. 2021). The nanoparticles resisted enzymatic digestion and were released in the colon fluid, provoking an anti-microbial effect against *Staphylococcus aureus* and *Escherichia coli*. Interestingly, the nanocarrier did not exert any toxic properties against the probiotics of the colon. MGF (3, 10, 40, or 100 mg/kg) is beneficial in regulating gastrointestinal transit (GIT) disturbances in normal and constipated rats (Cavalcante Morais et al. 2012). Compared to tegaserod, a standard medication, MGF increased GIT in normal and constipated mice. Also, it accelerated fecal production without affecting the water content in the fecal mass. Additionally, it did not induce any diarrheic effect. An in vivo study tested the protective effect of MGF (3, 10, and 30 mg/kg) against ethanol and indomethacin-induced gastric mucosal injury (Carvalho et al. 2007). MGF restored the protein-free sulfhydryl content of gastric mucosa in mice. Also, it inhibited ethanol-induced gastrointestinal damage by 63% at a high dose (Carvalho et al. 2007). In another gastric ulcer rat model, MGF produced a gastroprotective effect by a mechanism related to the upregulation of Nrf2, HO-1, and PPAR-γ along with the downregulation of NF-κB and iNOS in a dose-dependently (Mahmoud-Awny et al. 2015). It augmented antioxidant capacity manifested by increased glutathione content and reduced lipid peroxidation near normal values. Interestingly, it elicited an anti-apoptotic activity displayed by raised Bcl-2 levels and reduced caspase-3 (Mahmoud-Awny et al. 2015). Complementarily, MGF-modified colitis's oxidative and inflammatory mediators in mice as a model of inflammatory bowel syndrome (IBS) via the down-expression of TNF-α and MMP-9 (Somani et al. 2016). The molecular modeling trials revealed an efficient binding of MGF with TNF-α and MMP-9. Also, it improved inflammation in intestines and gastroenteric motility disturbance in the postoperative ileus mouse model via the reduction of the myeloperoxidase activity, TNF-α, IL-1β, IL-6, and MCP-1 level (Morais et al. 2015a). Additionally, Dou et al. informed that MGF inhibited the dextran sulfate sodium (DSS)-induced diarrhea (Dou et al. 2014). Mechanistically, it significantly downregulated the colon's proinflammatory mediators such as iNOS, ICAM-1, TNF-α, IL-1β, and IL-6. Moreover, MGF inhibited IκBα degradation and NF-κB p65 phosphorylation.

Cardioprotective effect

Heart disease is the leading cause of death in several countries with a possible scene of further complications in the following decades. In this context, MGF (15 mg/kg) exhibited a reduction in the atherosclerotic plaque size, low-density lipoprotein cholesterol (LDL), triglycerides, and total cholesterol in apo-E$^{-/-}$ mice, along with the improvement in the high-density lipoprotein cholesterol (HDL) and cholesterol transfer efficiency. Furthermore, mechanistically, it induced cholesterol efflux via the modulation of ATP binding cassette A1/G1 (ABCA1/G1), liver X receptor-α (LXRα), and peroxisome proliferator-activated receptor-γ (PPAR-γ) pathway (Ren et al. 2019).

MGF ameliorated STZ-triggered cardiac toxicity in diabetic rat models by reducing the lipid peroxidation cascade (Muruganandan et al. 2002). The oral administration of MGF (20 mg/kg) attenuated the translocation of NF-κB and the expression of different inflammatory cytokines such as TNF-α and IL-1β (Hou et al. 2016). Moreover, MGF was proven to be an antihypertensive agent by reducing intracellular nitric oxide (NO) radicals and ROS. It potentially modulated the expressions of several signaling pathways, such as NOS-II, iNOS, TNF-α, and TGF-β (Mujawdiya and Kapur 2015). Also, MGF improved cardiac performance and prohibited diabetic cardiomyopathy (DCM) by reducing myocardial collagen accumulation (Hou et al. 2013). It acted by mechanisms related to regulating the balance between matrix metalloproteinase-2 (MMP-2) and MMP-9 that are included in cardiac collagen content, thereby causing cardiac fibrosis. In a specific study, MGF was protective against post-infarction myocardial remodeling and intercellular fibrosis progression (Zheng et al. 2012). It suppressed the cascade of phosphorylated p38 MAPK, facilitating the reduction of apoptosis and fibrosis in myocardium remodeling. Therefore, the evidence to date suggests that MGF acts through a pleiotropic mechanism with adequate concentration-dependent cardioprotective benefits.

Nephroprotective effect

Kidney diseases can be life-threatening for patients and may arise from underlying health issues like diabetes or from direct problems such as cancer, stones, or infections. (Tirichen et al. 2021; Ishimoto et al. 2018) Therefore, several studies have reported the protective effect of MGF on nephrons in various in vitro and in vivo models, highlighting its beneficial effects attributed to its antioxidant and anti-inflammatory properties. For example, a study in vitro on tBHP-induced cytotoxicity in human kidney epithelial cells indicated that MGF and its antioxidant effect induced the expression of PI3K (Saha et al. 2016). In addition, a study in vivo on cisplatin-induced acute kidney damage in

rats proved the nephroprotective effect of MGF through the modulation of MAP kinase signaling cascade (Sahu et al. 2019), and the upregulation of Nrf-2 mediated pro-survival signaling cascades through PI3K initiation (Sadhukhan et al. 2018). Moreover, Song et al. demonstrated the protective effects of MGF on renal interstitial fibrosis in streptozotocin-induced mice with diabetes via its anti-inflammatory and antioxidant effect by decreasing the TGF-β1-mediated raising of Col I, FN, and α-SMA through the PTEN/PI3K/Akt pathway (Song et al. 2020). Furthermore, the administration of MGF inhibited renal glomerulus fibrosis in rats with diabetes mellitus due to osteopontin suppression achieved via the inactivation of the NF-κB pathway (Zhu et al. 2015). Also, He et al. reported that MGF protected against sepsis-induced acute kidney damage in CLP-induced septic mice for NLRP3 inflammasome inhibition and Nrf2 up-regulation, together with decreasing lowering serum levels of IL-1β and IL-18 and suppression of apoptosis of tubular epithelial cells (He et al. 2014). The mechanism by which MGF reduced serum uric acid levels was studied. The results suggested that MGF promoted intestinal urate excretion by upward regulation of ABCG2 expression, downregulating GLUT9 expression, and elevation of AQP2-related urinary uric acid excretion (Li et al. 2020b). In addition, another study reported that doses of 1.5, 3.0, and 6.0 mg/kg of MGF lowered serum urate concentrations in the hyperuricemia-induced mice by inhibiting xanthine dehydrogenase (Niu et al. 2012b).

Protective effects on lung diseases

The most common lung diseases include asthma, chronic obstructive pulmonary disease, lung cancer, and pneumonia. Interestingly, MGF has shown protective effects on lung diseases. The protecting capacity of MGF against arsenic-induced lung toxicity in mice was studied. The findings demonstrated that MGF exhibited suppressive effects on inflammatory cell infiltration, decreased oxidative stress, and inhibited lung apoptosis, these effects were attributed to the upregulation of the Nrf2/HO1 axis (Mahalanobish et al. 2019). Complementarily, the administration of 20 mg/kg of MGF in bleomycin-induced pulmonary fibrosis reduced the histopathological lesions and death rate through its antioxidant and anti-inflammatory outcome and the suppression of TLR4/NF κB signaling. It reduced matrix metalloproteinase-9 (MMP-9) mediated via the TGF-β/Smad2/3 pathway (Jia et al. 2019). MGF attenuated LPS-induced acute lung damage in mice as a result of the downregulation of vascular permeability, inhibition of MMP-9 expression, and anti-inflammatory and antioxidant effects (Zhang et al. 2020). In a recent investigation, MGF was found to protect against lung injury by inhibiting the initiation of NLRP3 inflammasome in an NF-κB-dependent way in macrophages (Li

et al. 2021). In addition, the MGF has anti-asthmatic effects; for example, 200 mg/kg of MGF administered to an OVA-induced asthmatic mouse model inhibited the cascade of signaling and the activators of transcription (STAT) proteins (Guo et al. 2014); in the same animal model, Yun et al. revealed that the anti-asthmatic activity of MGF was due to the reduction in Th9 and Th17 and the elevation of Treg responses (Yun et al. 2019).

Effects on metabolisms: antidiabetes and antiobesity

Obesity is a chronic disease that affects a considerable number of countries. There is a close relationship between type 2 diabetes preceded by a condition of obesity (GBD collaborators 2023). In this sense, MGF was reported to positively affect insulin metabolism in several studies of diabetes mellitus (Li et al. 2018a; Niu et al. 2012a; Sellamuthu et al. 2009; Dutta et al. 2023).

Additionally, it enhances lipid metabolization through pathways dependent on AMP-activated protein kinase (AMPK) (Xu et al. 2018). In this study, it has been evaluated the therapeutic impact of MGF, a glucosylxanthone known for its positive effects on glucose and lipid homeostasis, on perivascular adipose tissue (PVAT). The research aimed to determine if MGF aids in regulating insulin action within the endothelium; it has been observed that Palmitate stimulation induced ROS-related endoplasmic reticulum stress (ER stress) and NLRP3 inflammasome activation in PVAT. Upon MGF treatment, there was: an increase in LKB1-dependent AMPK activity; suppression of ER stress, coupled with a decline in TXNIP induction; inhibition of NLRP3 inflammasome activation, identified by decreased NLRP3; cleaved caspase-1 expression, lower IL-1β secretion; restoration of insulin-mediated Akt and eNOS phosphorylations, resulting in raised NO production. Immunohistochemistry assessments of adipocytes and endothelial tissue from high-fat diet-fed mice revealed that MGF ingestion curtailed ER stress and NLRP3 induction in PVAT. This helped in effectively combatting insulin resistance in the vessel endothelium. As a result, MGF successfully prevented endothelial insulin resistance. This study proposes that correcting PVAT dysfunction could serve as a viable therapeutic approach to deter endothelial insulin resistance (Xu et al. 2018).

In another study, MGF upregulated glucose transporter 4 (GLUT4) mRNA and protein expression in skeletal muscles and pancreas. Furthermore, it stimulated peroxisome proliferator-activated receptor-γ (PPAR-γ), causing enhancement of insulin sensitization and glucose metabolism (Singh et al. 2018). In this study, researchers extracted two compounds, MGF and naringenin, from the leaves of *Salacia oblonga*. To investigate the potential antidiabetic effects of these compounds, they were given to diabetic male Albino rats (induced by streptozotocin) in doses of 50 and 100 mg/kg daily over a 15-day period. They examined various parameters, including blood glucose levels, weight, serum lipid profiles oxidative stress markers, and studied potential molecular interactions using docking studies on specific diabetes-related targets. The results showed that both compounds reduced blood glucose levels; restored body weight; normalized serum lipid concentrations; improvement in oxidative stress markers in the liver and pancreas. Docking studies highlighted a strong binding affinity of both compounds towards peroxisome proliferator-activated receptor gamma (PPARγ) and glucose transporter type 4 (GLUT4). Further molecular investigations (using real-time reverse transcription polymerase chain reaction and western blot techniques) validated increased expression levels of PPARγ and GLUT4 genes and proteins in pancreatic tissues. The findings indicate that the antidiabetic effects of these compounds stem from the activation of PPARγ/GLUT4 signaling pathways; additionally, NMR-based metabolic analysis demonstrated that both compounds corrected the imbalances of metabolites related to diabetes in the serum (Singh et al. 2018). Skeletal muscle changes related to obesity involve muscle atrophy, slow to rapid fiber-like transformation, and reduced mitochondrial oxidative ability. They are associated with enhancing insulin resistance. Then, the treatment with MGF (15 mg/kg/day) after 8 weeks achieved maintaining skeletal muscle mass, cross-sectional fiber size, and fiber-type composition and boosted the oxidative capacity of oxidation of muscle fibers in the obese Zucker rats. At the same time, hypoglycemic response significantly decreased in a unified glucose tolerance test relative to the placebo group (Acevedo et al. 2017).

Protective effects on skin diseases

MGF also possesses the potential for the management of skin conditions. It was found that this bioactive compound can penetrate the epidermis and dermis in a considerable amount and reversibly inhibit the action of elastase and collagenase (Ochocka et al. 2017). Studies in vitro have shown the potential capacity of MGF-loaded glycethosomes in managing psoriasis and other skin diseases. The results showed that 2, 4, 6, and 8 mg/mL concentrations protected the fibroblasts against hydrogen peroxide-induced skin damage (Pleguezuelos-Villa et al. 2020). Also, the glycoltransfersomes loaded with MGF and modified with mucin allowed better deposition of MGF on skin layers, protected fibroblasts from oxidative stress, and promoted fibroblast proliferation and wound healing (Allaw et al. 2020). Additionally, MGF revealed a hopeful activity against skin inflammation such as dermatitis via inhibiting the NF-κB (Zhao et al. 2017). Antiviral studies in vitro of MGF against acyclovir-resistant herpes

simplex virus (HSV-1) indicated an $IC_{50} = 2.9$ μg/mL for the AR-29 and 3.5 μg/mL for the KOS strains (Rechenchoski et al. 2020). The in vivo study in Balb/c mice treated with a topical formula of 0.7% MGF produced diminished vesicle lesions, delaying their appearance compared to the control group (Rechenchoski et al. 2020).

Table 2 and Fig. 2 summarize the primary data regarding biological activities and mechanisms of MGF in different chronic diseases.

Human clinical studies

Mangifera indica leaf extract is marketed in the USA as an ingredient in dietary supplement industries with the category "Generally Recognized As Safe regulatory" (Reddeman et al. 2019).

A clinical study evaluated MGF to prevent and treat mixed osteoarthritic pain. The efficacy and safety of *M. indica* L extract (MSBE) supplementation was examined in fifty individuals suffering from knee pain as a result of osteoarthritis and these participants had previously undergone a full year of conventional treatment, which included paracetamol and non-drug-based interventions (Garrido-Suárez et al. 2022). The participants received 900 mg of extract daily, standard treatment, and placebo for 4 months. The effect was measured using the average daily pain score (ADPS) and applying the Likert scale. Also, the evaluators used a multifaceted measuring of pain, stiffness, and functioning disability. At the same time, the researchers assessed knee osteoarthritis (OA) patients using the Western Ontario and McMaster Universities (WOMAC) index and chronic ultrasonographic signs of synovitis, such as effusion and synovial depth. Remarkable improvements were observed in pain and functional disability WOMAC sub-scores and the number of joints with synovial thickness and effusion. At the same time, non-experimental effects were observed in the experimental group. The quantitative results of this study were as follows: (i) regarding Average Daily Pain Diary Score (ADPS): 2 weeks post MSBE supplementation, there was a notable reduction in ADPS, an effect that persisted and amplified by the 120-day mark; placebo group's scores shifted from 5.5 to 4.0 (down by 27.2%) while MSBE group saw a drastic dip from 5.6 to 0.1 (down by 98.2%). The gap between these two groups in terms of reduction was 71.0%.; (ii) WOMAC Index for Knee osteoarthritis outcomes: MSBE participants exclusively registered significant positive shifts in the WOMAC pain and functional disability metrics when set against the baseline data; while both groups recorded a reduction in WOMAC stiffness scores from their starting points, the group taking MSBE reported a more pronounced improvement; (iii)

ultrasonographic results: starting off, 80.9% of the MSBE group (spanning 22 joints) exhibited synovial thickness (averaging 6.4 ± 0.7 mm), while in the control group, 47% (over 13 joints) had a thickness average of 7.2 ± 1.1 mm.; only the MSBE group saw a significant decline in the number of joints affected by synovial hypertrophy; considering joint effusion, initial data showed the experimental group (MSBE) had 66.6% of its participants (over 17 joints) with deep effusion (measured at 5.5 ± 0.3 mm); in the control group, the count was 58.8% (across 13 joints) averaging 4.9 ± 0.2 mm; 4 months into the treatment, MSBE users reported no joint effusion, whereas over half (52.9%) of the non-supplemented group still had joint effusion present. Furthermore, specific inflammatory lesions linked to knee pain, like chondropathy by synovial plica and popliteal tendonitis, were observed. Initial findings showed that all participants had one or more such lesions; at the end of the study, there were 23 lesions in the MSBE group and 18 in the placebo group. While both groups showed improvement by the study's end, MSBE users had a more considerable decline in the total percentage of these lesions (Garrido-Suárez et al. 2022).

In another human clinical study, Na et al. investigated the MGF effect on serum lipid profiles in overweight patients with hyperlipidemia (Na et al. 2015). The study aimed to assess the impact of mangiferin on the serum lipid profiles of overweight patients who had hyperlipidemia. The trial was a double-blind randomized controlled study and included overweight patients having hyperlipidemia (defined by serum triglyceride ≥ 1.70 mmol/L, and total cholesterol ≥ 5.2 mmol/L). The participants were randomized to receive either 150 mg/day of mangiferin or a placebo for 12 weeks and the key metrics analyzed included serum lipid profiles, mangiferin, glucose, L-carnitine, β-hydroxybutyrate, and acetoacetate at the beginning and end of a 12-week period.

The results of this clinical study showed the next MGF's impacts on lipids: (i) significant reduction in serum levels of triglycerides (TG) and free fatty acids (FFAs) in the mangiferin group compared to the placebo group; (ii) significant increase in high-density lipoprotein cholesterol (HDL), L-carnitine, β-hydroxybutyrate, and acetoacetate in the mangiferin group; (iii) no significant change in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL) in the MGF group post-intervention. Regarding the impact on the metabolic variables, MGF supplementation led to a significant increase in serum mangiferin levels and reduced the insulin resistance index (HOMA-IR) relative to the placebo group, and no significant differences were noted in serum glucose and insulin levels between both groups. Compared to placebo, MGF reduced triglycerides (TG), free fatty acids (FFAs), and insulin resistance index (HOMA-IR) by 14.5%, 8.5%, and 8.5% respectively; it also

Table 2 Preclinical pharmacological studies and mechanisms of action of mangiferin

Pharmacological property	Experimental model in vitro/in vivo	Mechanisms/key results	References
Neuroprotective	Rats model of spinal cord injury in vivo	↓oxidative stress response: ↓ROS, ↓H_2O_2, ↓SOD, ↓GPX, ↓CAT ↓apoptotic markers: ↓SKIP, ↓ASK1, ↓Fas, ↓tBid, ↓APAF-1, ↓caspase-3	(Li et al. 2018b)
	Female transgenic mice spinocerebellar ataxia type-2 (SCA-2) induced memory disorder in vivo	↑memory recognition not impact on inhibitory avoidance of memory	(Pardo Andreu et al. 2010)
	Rats lead-induced neurotoxicity in vivo	↑spatial learning ↓latency time of the hidden platform	(Li et al. 2013)
	Sprague–Dawley rats STZ-induced cognitive impairment in vivo	↑cognitive functions ↓escape latency, ↑the time spent in a dose-dependent manner ↓methylglyoxal hyperactivity	(Liu et al. 2013)
	Young and aged Swiss albino mice scopolamine induced amnesia in vivo	↓scopolamine-induced memory deficits ↑learning performance in an elevated plus maze test ↓step-down latency in the passive avoidance test ↑cholinesterase, ↑biogenic amines: ↑dopamine, ↑norepinephrine in the hippocampus	(Biradar et al. 2012)
	Male mice scopolamine-induced memory deficit in vivo TNF-α-stimulated BV-2 microglial cells in vitro	↓AChE ↓latency in training trials and swimming times in the Morris maze test and PAT ↓TNF-α, ↓NF-κB	(Jung et al. 2009)
	Swiss albino mice sleep-deprivation (SD)-induced memory damage in vivo	↓latency conjugated with the rise in the crossing number over the platform position in Morris water maze (MWM) and novel object recognition (NOR) tests ↑recognition index	(Feng et al. 2017)
	Old APP/PS1 transgenic mice model in vivo	Amelioration of spatial and episodic memory	(Infante-Garcia et al. 2017)
	LPS-induced neural damage and cognitive deficiency in Kunming male mice in vivo	↓LPS-induced memory dysfunction ↓learning disability	(Fu et al. 2015b)
	LPS-triggered neurological disorder in mice in vivo	↓anxiety-like behavior in EPM and light–dark box and open field tests ↓anhedonia behavior ↓depressive effect evoked by LPS ↓neuroinflammation in the hippocampus and prefrontal cortex ↓GSH, ↓SOD, ↓CAT, ↓IL-1β	(Jangra et al. 2014)
	Cerebral ischemia–reperfusion injury in Wistar male rats in vivo	↓neurological impairment ↓IL-1 β, ↓TNF-α, ↓GSH, ↓SOD, ↓Nrf-2, ↓HO-1	(Yang et al. 2016)
	AlCl$_3$ induced cognitive dysfunction and neurotoxicity in male Swiss albino mice in vivo	↓retention latency accompanied by increased crossing number over a platform and recognition index ↓oxido-nitrosative stress ↓proinflammatory cytokines Dose = 20 and 40 mg/kg	(Kasbe et al. 2015b)
	LPS-activated primary rat microglia In vitro	↓PGE2, ↓8-iso-PGF2a, COX-2, p38 MAPK, iNOS, ↓TNF-α	(Bhatia et al. 2008)
	Normal male Wistar rats in vivo	↑NOR memory post-training locomotion or motivation was not affected	(Pardo Andreu et al. 2010)
	Senescence-accelerated mouse prone 8 (SAMP8) mouse model in vivo hippocampal neurons in vitro	Anti-dementia effects ↑learning, ↑memory ↓amyloid deposition in the brain tissues ↓amyloid precursor protein ↓Aβ1-40, ↓Aβ1-42	(Du et al. 2019)
	Human U138-MG glioblastoma cells in vitro	↓cancer cells proliferation ↑NGF, ↓ TNF-α	(Lopes et al. 2013)

Table 2 (continued)

Pharmacological property	Experimental model in vitro/in vivo	Mechanisms/key results	References
Gastroprotective	Normal and constipated rats in vivo	Regulation of the GIT not induced diarrheic effect	(Cavalcante Morais et al. 2012)
	Ethanol and indomethacin-induced gastric mucosa lesions in mice in vivo	Restored the gastric mucosal non-protein sulfhydryl content ↓ethanol-induced gastrointestinal damage	(Carvalho et al. 2007)
	Gastric ulcer model rats in vivo	↑gastroprotective effect ↑Nrf2, ↑HO-1, ↑PPAR-γ, ↓NF-κB, ↓iNOS antioxidant effect ↑glutathione, ↓lipid peroxidation ↓apoptosis, ↑Bcl-2, ↓caspase-3	(Mahmoud-Awny et al. 2015)
	Model of inflammatory bowel syndrome in mice in vivo	↓inflammatory mediators in colitis ↓TNF-α, ↓MMP-9 ↓IL-1β, ↓IL-6, ↓MCP-1	(Morais et al. 2015a)
Cardioprotective	Apo-E⁻/⁻ mice in vivo	↓LDL, ↑HDL, ↓triglycerides, ↓total cholesterol: ABCA1/G1, LXRα, PPAR-γ ↓atherosclerotic plaque size	(Ren et al. 2019)
	STZ-triggered cardiac toxicity in diabetic rats in vivo	↓lipid peroxidation ↓NF-κB, ↓TNF-α, ↓IL-1β ↓diabetic cardiomyopathy, ↓myocardial collagen Accumulation ↓MMP-2, ↓MMP-9, ↓p38 MAPK ↓cardiac fibrosis, ↓apoptosis	(Muruganandan et al. 2002) (Hou et al. 2016) (Zheng et al. 2012)
	Hypertensive rats in vivo	Antihypertensive effect ↓NO, ↓ROS, ↓NOS-II, ↓iNOS, ↓TNF-α, ↓TGF-β ↑cardiac performance	(Mujawdiya and Kapur 2015) (Hou et al. 2013)
Nephroprotective	tBHP induced cytotoxicity on normal human kidney epithelial cells (NKE) in vitro	↓Cyclin d1, ↓NFκB, ↓HO-1, ↓SOD2, ↓PI3K/Akt	(Saha et al. 2016)
	Cisplatin-induced acute kidney damage in rats in vivo	Nephroprotective effect ↓MAP kinase ↑Nrf-2 mediated pro-survival signaling cascades ↑PI3K	(Sahu et al. 2019) (Sadhukhan et al. 2018)
	Renal interstitial fibrosis diabetic mice induced by streptozotocin in vivo	Anti-inflammatory, antioxidant ↓TGF-β1, ↓Col I, ↓FN, ↓ α-SMA, ↓PTEN/PI3K/Akt	(Song et al. 2020)
	Renal glomerulosis in diabetic rats induced by streptozotocin in vivo	↓osteopontin ↓NF-κB	(Zhu et al. 2015)
	Sepsis-induced acute kidney injury in CLP-induced septic mice in vivo	↓apoptosis of tubular epithelial cells ↓NLRP3, ↑Nrf2, ↓IL-1β, ↓IL-18	(He et al. 2014)
	Hyperuricemic nephropathy in mice in vivo	↑intestinal elimination of urates ↑ABCG2, ↓GLUT9, ↑AQP2	(Li et al. 2020b) (Niu et al. 2012b)
Protective effects on pulmonary diseases	Arsenic-induced lung toxicity in mice in vivo	↓inflammatory cell infiltration ↓oxidative stress ↑Nrf2-HO1	(Mahalanobish et al. 2019)
	Bleomycin-induced pulmonary fibrosis in mice in vivo	Antioxidant anti-inflammatory ↓TLR4/NF-κB, ↓MMP-9, ↓TGF-β/Smad2/3	(Jia et al. 2019)
	LPS-induced acute lung injury in mice in vivo	antioxidant, anti-inflammatory ↓MMP-9	(Zhang et al. 2020)
	OVA-induced asthmatic mouse model in vivo	↓STAT ↓Th9, ↓Th17, ↑Treg	(Guo et al. 2014)
Antidiabetes Antiobesity	Perivascular adipose tissue Sprague–Dawley rats and ICR mice in vivo	↓insulin resistance ↓TXNIP ↓endoplasmic reticulum stress regulates lipid metabolism, ↑AMPK	(Xu et al. 2018)
	Diabetic rats induced by streptozotocin in vivo	↑GLUT4 mRNA, ↑PPAR-γ ↑protein expression in skeletal muscles and pancreatic tissues	(Singh et al. 2018)
	Obese ucker rats in vivo	maintained skeletal muscle mass, transversal fiber size, and fiber composition hypoglicemic effec	(Acevedo et al. 2017)

Table 2 (continued)

Pharmacological property	Experimental model in vitro/in vivo	Mechanisms/key results	References
Protective effects on skin diseases	3T3 mouse fibroblasts in vitro inflammatory mice models applying topically TPA in vivo	Protects the fibroblasts against hydrogen peroxide-induced skin damage protects fibroblasts against oxidative stress ↑fibroblast proliferation, ↑wound healing	(Pleguezuelos-Villa et al. 2020)
	Vero cells in vitro Balb/c mice in vivo	↑antiviral effect against acyclovir-resistant herpes simplex virus (HSV-1) mangiferin topical formula (0.7%) ↓vesicle lesions	(Rechenchoski et al. 2020)

Abbreviations and symbols: ↑ increase, ↓ decrease, *ROS* reactive oxygen species, *SOD* superoxide dismutase, *GPX* glutathione peroxidase, *CAT* catalase, *SKIP* sphingosine kinase interacting protein, *ASK1* apoptosis signal-regulating kinase 1, *Fas* apoptosis antigen 1, *tBid* truncated bid protein, *APAF-1* apoptosis protease-activating factor-1, AChE (Acetylcholinesterase), *PAT* passive avoidance test, IC_{50} inhibitory concentration, *TNF-a* tumor necrosis factor α, *NF-kB* nuclear factor kappa-light-chain-enhancer of activated B cells, *MWM* Morris water maze, *NOR* novel object recognition, *LPS* lipopolysaccharide, *EPM* elevated plus maze, *GSH* hippocampal glutathione, *IL-1b* interleukin 1b, *Nrf-2* nuclear factor erythroid 2-related factor 2, *HO-1* hemeoxygenase-1, *PGE2* prostaglandin E_2, *8-iso-PGF2a* 8-150-prostaglandin $F_{2\alpha}$, *COX-2* cyclooxygenase, *p38 MAPK* p38 mitogen-activated protein kinases, *iNOS* inducible nitric oxide synthase, *Ab1-40* amyloid beta peptide 1-40, *Ab1-42* amyloid beta peptide 1-42, *NGF* nerve growth factor, *GIT* gastrointestinal regulation, *PPAR-g* peroxisome proliferator-activated receptor gamma, *MMP-2* matrix metallopeptidase 2, *MMP-9* matrix metallopeptidase 9, *p38 MPAK* p38 mitogen-activated protein kinases, *NOS II* nitric oxide synthase II, *TGF-b* transforming growth factor beta, *PI3K* phosphoinositide 3-kinase, *Akt* protein kinase B, *NLRP3* NLR family pyrin domain containing 3, *ABCG2* ATP-binding cassette super-family G member 2, GLUT9 glucose transporter 9, AQP2 aquaporin-2, TLR4 toll-like receptor 4, Smad 2/3 mothers against decapentaplegic homolog 3, *STAT* signal transducer and the activator of transcription), *Th9* (T helper type 9 cells), *Th17* T helper type 17 cells), *TXNIP* thioredoxin-interacting protein), *AMPK* (AMP-activated protein kinase, *GLUT4* glucose transporter 4, *mRNA* messenger ribonucleic acid, *HSV-1* herpes simplex virus
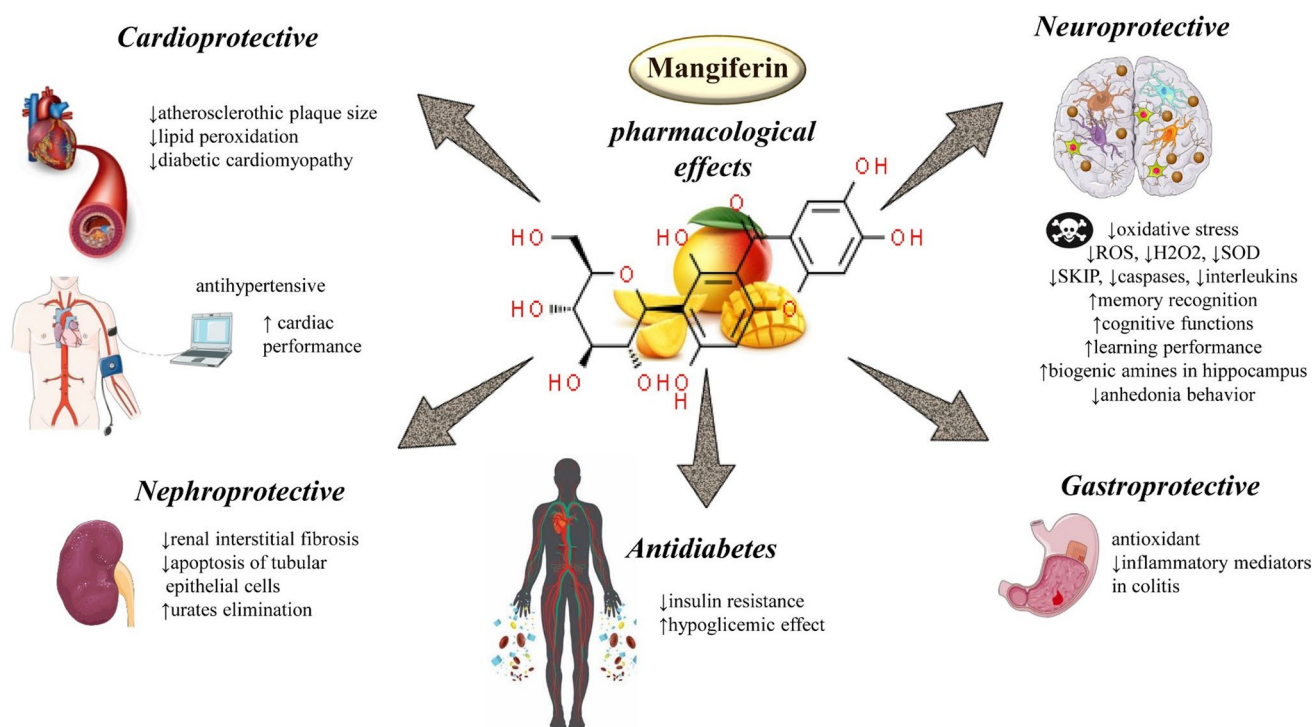

Fig. 2 Illustration of the most important pharmacological effects of mangiferin. Symbols: ↑ increase, ↓ decrease. ROS (Reactive oxygen species), SOD (Superoxide dismutase), SKIP (Sphingosine kinase interacting protein)

increased serum levels of high-density lipoprotein (HDL), Lipoprotein lipase (LPL), L-carnitine, β-hydroxybutyrate, and acetoacetate by figures like 41.3%, 4.60%, 15.2%, 11.0%, 17.2%, and 16.4% respectively. The total serum fatty acids, including saturated (SFA), mono-unsaturated (MUFA), poly-unsaturated (PUFA), n-3, and n-6 fatty acids,

decreased significantly in the mangiferin group versus controls. The results of this study showed that MGF supplementation can benefit the serum lipid profile, especially by lowering serum TG and FFAs in overweight hyperlipidemia patients and this is partly attributed to the promotion of FFA oxidation (Na et al. 2015).

Safety and tolerability

Predictions about the potential application of MGF in humans as a novel medicinal compound require exhaustive toxicity assessment. Only a few studies have been performed so far to describe the possible toxicological effects of MGF. Prado et al. analyzed oral, skin, and intraperitoneal toxicity assays of MGF in rodents in a 28-day-long repetitive doses investigation. After oral application of 2000 mg/kg and a 14-day observation period, no alterations in any organ were reported in Sprague–Dawley rats and Balb/C mice of both sexes. According to the same study, i.p. exposure to one dose of 2000 mg/kg induced death in treated animals (Prado et al. 2015). According to Jagetia and Baliga, MGF LD_{50} after acute i.p. application to $DBAxC_{57}BL$ mice was 400 mg/kg (Jagetia and Baliga 2005).

Therapeutic perspectives, limitations, and clinical pitfalls

Traditional acclaims of plants containing MGF and their correlation with recent pharmacological reports

Mangiferin, a polyphenolic xanthone glucoside, is not unique to just one plant but is present in various species across different geographical regions. The most notable source is the mango tree (*M. indica*), but other plants like *Anemarrhena asphodeloides* and certain bamboo species are also known to contain this compound. These plants have been historically revered in their respective traditional medicine systems for their wide array of therapeutic applications (Dutta et al. 2023).

Traditional acclaims

M. indica (Mango tree) is predominantly used in Ayurvedic and Unani systems of medicine; leaves, bark, and kernels were commonly prescribed for ailments such as diarrhea, dysentery, and ailments related to inflammation like rheumatism (Ediriweera et al. 2017b). Additionally, they were also considered beneficial for oral health, with the bark's decoction used as a mouthwash for inflamed

gums (Ediriweera et al. 2017b). The plant *Anemarrhena asphodeloides* is a staple in Traditional Chinese Medicine (TCM), it is known for its anti-pyretic properties and for alleviating coughs (Liu et al. 2023). Bamboo species are embedded in various Asian traditional medicine practices; the shoots, rich in mangiferin, have been utilized for their anti-inflammatory effects and are also believed to possess anti-aging benefits (Cheng et al. 2023).

Correlation with recent pharmacological studies

Antioxidant and anti-inflammatory activities *Mangiferin's* traditional use for inflammation, especially in rheumatism, correlates with modern discoveries of its potent antioxidant and anti-inflammatory activities (Ain et al. 2023).

Regulation of blood glucose and glucidic metabolism The traditional use of mango bark in managing hyperglycemia finds validation in recent studies. Modern research has demonstrated *Mangiferin's* potential in modulating blood glucose levels and enhancing insulin sensitivity (Meng et al. 2023).

Neuroprotective effect Though not directly anchored in a specific traditional claim, contemporary research has unveiled *Mangiferin's* neuroprotective effects, suggesting its possible therapeutic application against neurodegenerative diseases (Zhou et al. 2023).

Anticancer properties While traditional systems might not have recognized mangiferin-bearing plants for their anticancer properties, recent pharmacological studies have highlighted their role in modulating cell proliferation, inducing apoptosis, and other antitumor activities (Mirza et al. 2021).

The ancient therapeutic uses of plants rich in mangiferin, deeply rooted in traditional medicine, find echoing affirmations in modern pharmacological studies. The journey of mangiferin from traditional remedies to contemporary research elucidates the continuum of knowledge and underscores the importance of understanding and valuing ancient wisdom as we forge ahead in the realm of modern medicine.

Limitations and clinical pitfalls

Studies in vitro and in vivo based on MGF activities revealed that it has a therapeutic effect on multiple pathological conditions through different mechanisms of action. As described, it possesses broad antioxidant, anti-lipid peroxidation, wound healing, anti-neurodegenerative, and antidiabetic activities. In addition, MGF modulates the immune response and cardiac tension. Due to its numerous bioactivities, MGF is

a promising prospect for nutraceutical and functional food development applications (Mei et al. 2021). Contrary to the comprehensive pharmacological evaluation of MGF, the fact that only some studies have analyzed its pharmacokinetics has compromised its clinical usability. MGF belongs to the Biopharmaceutics Classification System (BSC) IV class compounds, and its clinical application and subsequent development are primarily restricted to its low water and fat solubility, limited absorption, and low bioavailability (Amidon et al. 1995). However, even though MGF exhibits promising therapeutic potential, its clinical use is restricted due to its poor oral bioavailability (Tan et al. 2021). For an investigational new drug approval, one of the critical roles playing in drug development is pharmacokinetic studies. While a limited number of clinical trials have highlighted the benefits of MGF adjuvant therapy on human health, it's essential to weigh its pros and cons based on the patient's health condition, the nature of the disease, the regular medications prescribed, and potential drug interactions. To fully understand its implications, there is a need for more extensive randomized clinical trials for a broader spectrum of chronic diseases.

Conclusion

MGF possesses a wide range of therapeutic properties representing promising candidates for application in developing nutraceutical and functional food products. As a result of insufficient bioavailability, the daily doses must be enhanced to accomplish the required result, resulting in increased cost of treatment. Another characteristic that stands out from the in vitro and in vivo tests is the high dose required, which is why drug delivery systems and drug targeting with MGF can be a technological challenge. In this review, we have also outlined various literature reports attributed to the pharmacokinetic parameters of MGF. In-depth investigations should concentrate on the following elements in the future to promote their development and utilization. First, creating advanced pharmaceutical formulations may help improve MGF's bioavailability. Secondly, further studies should research the structure–activity relationship to influence strategies to enhance its efficacy. Also, additional clinical studies should be designed to evaluate the effectiveness of MGF in specific diseases.

Abbreviations α-SMA: alpha smooth muscle actin; A1/G1 (ABCA1/G1): ATP binding cassette; AChE: acetylcholinesterase; Ab1-40: amyloid beta peptide 1–40; Ab1-42: amyloid beta peptide 1–42; ABCG2: ATP-binding cassette superfamily G member 2; ADPS: average daily pain diary score; AKT: protein kinase B; AMPK: AMP-activated protein kinase; APAF-1: apoptosis protease-activating factor-1; APP: amyloid precursor protein; APP/PS1: mouse model of Alzheimer's disease; AQP-2: aquaporin-2; AR-29: *Anoxybacillus* sp. AR-29 strain; ASC: artificial cerebrospinal fluid; ASK1: apoptosis signal-regulating kinase 1; ATP: adenosine triphosphate; β-LG: β-LACTOGLOBULIN; Bcl-2: B-cell lymphoma 2; BCS: biopharmaceutics Classification System; BDNF: brain-derived neurotrophic factor; BV-2: immortalized murine microglial cell line; CAT: catalase; CLP: cecal ligation and puncture; Col I: collagen type I alpha 1; COMT: catechol-O-methyltransferase; COX-2: cyclooxygenase; DCM: diabetic cardiomyopathy; DSS: dextran sulphate sodium; E2(PGE2): prostaglandin E2; EEG: electroencephalogram; EPM: elevated plus maze; ESI-MSn: electrospray ionization mass spectroscopy; F2a(8–150-PGF2a): 8–150-prostaglandin F2α; Fas: apoptosis antigen 1; FFA: free fatty acids; FN: formononetin; FST: forced swimming test; GIT: gastrointestinal regulation; GLUT4: glucose transporter 4; GLUT9: glucose transporter 9; GPX: glutathione peroxidase; GRAS: generally recognized as safe; GSH: hippocampal glutathione; HDL: high-density lipoprotein cholesterol; HO-1: hemeoxygenase-1; HPLC: high-performance liquid chromatography; HSV-1: herpes simplex virus; IBs: inflammatory bowel syndrome; IC50: inhibitory concentration; ICAM-1: intercellular adhesion molecule 1; IκBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; IL-1b: interleukin 1b; IL-6: interleukin 6; IL-18: interleukin 18; iNOS: inducible nitric oxide synthase; IUPAC: International Union of Pure and Applied Chemistry; KATP-channels: ATP-sensitive potassium channel; KOS: herpes simplex virus type 1 (HSV-1) strain KOS; LD50: lethal dose; LDL: low-density lipoprotein cholesterol; LPS: lipopolysaccharide; LXRα: liver X receptor-α; MANG: bacteroides; MAOA: monoamine oxidase A; MAOB: monoamine oxidase B; MAP: mitogen-activated protein; MCP-1: monocyte chemoattractant protein 1; MeSH: medical subject headings; MGF: mangiferin; MMP-2: matrix metallopeptidase 2; MMP-9: matrix metallopeptidase 9; mRNA: messenger ribonucleic acid; MWM: Morris water maze; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; NGF: nerve growth factor; NLRP3: NLR family pyrin domain containing 3; NO: nitric oxide; NOR: novel object recognition; NOS-II: nitric oxide synthase II; Nrf-2: nuclear factor erythroid 2-related factor 2; OAT1: organic anion transporter 1; OVA: ovalbumin; p38 MAPK: p38 mitogen-activated protein kinases; PGE2: prostaglandin E2; PAT: passive avoidance test; PI3K: phosphoinositide 3-kinase; PPAR-γ: peroxisome proliferator-activated receptor gamma; PTEN: fosfatidilinositol-3,4,5-trisfosfato 3-fosfatasa; ROS: reactive oxygen species; rRNA: ribosomal ribonucleic acid; SAMP 8 : senescence-accelerated mouse; SCA-2: spinocerebellar ataxia type 2; SD: sleep deprivation; SKIP: sphingosine kinase interacting protein; Smad2/3: mothers against decapentaplegic homolog 3; SOD: superoxide dismutase; STAT: signal transducer and the activator of transcription; STZ: streptozotocin; TAU: tubulin-associated unit; tBHP: t-butyl hydroperoxide; tBid: truncated bid protein; TCM: traditional Chinese medicine; TG: serum thyroglobulin; TGF-β: transforming growth factor beta; TGF-β1: transforming growth factor beta 1; Th9: T helper type 9 cells; Th17 : T helper type 17 cells; TLR4: toll-like receptor 4; TNF-a: tumor necrosis factor α; TRIP : turning research into practice; TXNIP: thioredoxin-interacting protein; U138-MG: glioblastoma cells; URAT1: solute carrier family 22 (organic anion/cation transporter), member 12S; WOMAC: Western Ontario and Mc Master Universities

Data availability Not applicable.

Declarations

Ethics approval and consent to participate Not Applicable.

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