Mangiferin in human disease: Multifaceted mechanisms and applications (Review)

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Abstract. Mangiferin (MGF) is a natural C-glucosyl xanthone with multitarget activity relevant to metabolic, inflammatory and cancer diseases. Notably, MGF modulates AMP-activated protein kinase, NF-κB, PI3K/AKT and MAPK signaling; through these pathways, it affects glucose and lipid metabolism, oxidative stress, apoptosis and inflammatory responses. In metabolic disorders, MGF has been shown to improve insulin sensitivity, support mitochondrial function and reduce diabetic complications. In cancer models, MGF suppresses proliferation, invasion and angiogenesis, and can influence antitumor immunity in the tumor microenvironment. Anti-inflammatory actions include decreased cytokine release and regulation of the NLR family pyrin domain-containing 3 inflammasome. Notably, clinical translation remains limited due to its low aqueous solubility, poor oral bioavailability and rapid metabolism. However, benefits of nanocarrier delivery, structural optimization and combination therapy have been reported, which may improve exposure and efficacy in experimental systems. Furthermore, safety signals in animals are favorable at relevant doses, but clinical evidence remains limited. In conclusion, the present review summarizes the pharmacodynamics and mechanisms of MGF across major disease settings and identifies key gaps for translation. Priorities include standardized clinical trials, optimization of delivery strategies, and rigorous assessment of long-term safety and efficacy.

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Abbreviations: AGE, advanced glycation end-products; AMPK, AMP-activated protein kinase; PPAR, peroxisome proliferator-activated receptor; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; SIRT, sirtuin; SOD, superoxide dismutase

Key words: mangiferin, bioavailability, metabolism, anti-inflammatory, anticancer, diabetes, oxidative stress, nanocarrier

Contents

1. Introduction

Mangiferin (MGF) is a yellow crystalline flavonoid with a molecular weight of 422.34 g/mol (Fig. 1). Despite its low water solubility (0.111 mg/ml) (1) and poor oral bioavailability (~1.2%) (2,3), due to its limited lipophilicity and intestinal permeability (4), MGF has been identified in 96 species, 28 genera and 19 families of angiosperms (5). Its unique structure, featuring a catechol moiety and a C-glucosidic linkage, contributes to its interactions with diverse biological targets and underpins its broad pharmacological activities. Moreover,

MGF complies with Lipinski's rule of five, suggesting favorable drug-like properties despite its absorption limitations (6). MGF isolated from indica rice leaves has various pharmacological benefits; notably, it exhibits potent, broad-spectrum antimicrobial activity against diverse fungal and bacterial pathogens, with minimum inhibitory concentration (MIC) values of 1.95-62.5 and 1.95-31.25 μg/ml, respectively (7). In addition, it exerts wide-ranging pharmacological effects by modulating key metabolic pathways, including glycolysis, the tricarboxylic acid (TCA) cycle, and lipid and amino acid metabolism, supporting its potential use in treating metabolic disorders such as hyperlipidemia and hyperglycemia (8). Additionally, MGF has neuroprotective, anti-inflammatory and anticancer effects by reducing oxidative stress, inhibiting proinflammatory signaling, and suppressing tumor proliferation and metastasis. Advances in formulation and drug delivery strategies are expected to further improve its clinical applicability across various diseases (4,9).

The present review has three objectives. First, the current evidence on MGF was organized by mechanism, focusing on AMP-activated protein kinase (AMPK), NF-κB, PI3K/Akt, MAPK and NLR family pyrin domain-containing 3 (NLRP3) pathways, and their relation to metabolic regulation, oxidative stress, apoptosis, angiogenesis and immune modulation. Second, the preclinical efficacy of MGF across metabolic, inflammatory and cancer models was evaluated using reproducible endpoints, such as insulin sensitivity, fibrotic markers, tumor growth, invasion and MMP-9 activity. Third, key barriers to translation, including low solubility, poor oral bioavailability and rapid metabolism, were examined, and delivery and structural optimization strategies that may improve exposure were assessed. Evidence selection prioritized primary studies and systematic analyses with prespecified methods. By integrating data on molecular mechanisms, pharmacology and drug-delivery strategies, the present review aims to identify consistent efficacy signals, highlight areas of uncertainty and propose priorities for future human studies.

Literature search strategy. To ensure the comprehensiveness and reliability of the present review, a structured literature search was conducted in the PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (http://www.webofscience.com/), Scopus (http://www.scopus.com/) and Google Scholar (http://scholar.google.com/) databases. The search included studies published between January 2000 and June 2025. The following key words and their combinations were searched: 'mangiferin', 'pharmacological activity', 'bioavailability', 'metabolism', 'toxicity', 'mechanism of action' and 'therapeutic potential'. The inclusion criteria were as follows: i) Original research or review articles investigating the pharmacological, biochemical or clinical properties of MGF; ii) studies providing mechanistic, pharmacokinetic (PK) or toxicological data; and iii) publications written in English and indexed in peer-reviewed journals. The exclusion criteria were as follows: i) Non-peer-reviewed materials, conference abstracts or duplicated data; ii) studies using complex herbal mixtures without quantifiable MGF content; and iii) articles lacking sufficient methodological detail or outcome data. References were screened by title, abstract and full text, and only those meeting the inclusion criteria were included in the final review.

2. Historical discovery, botanical sources and early pharmacological insights into MGF

The chemical structure of MGF, identified as a 1,3,6,7-tetrahydroxyxanthone C-glucoside, was first elucidated by Aritomi and Kawasaki in 1969 (10). However, detailed structural characterization via nuclear magnetic resonance spectroscopy and X-ray diffraction was not achieved until the early 2000s (11). Between the 1960s and 1980s, MGF and its isomers were isolated from several botanical sources, including *Anemarrhena asphodeloides* Bunge. A subsequent study broadened its known distribution: In 1995, MGF was detected in ferns from New Zealand, and in 2008, markedly high concentrations (up to 6.12%) were reported in the leaves of wild coffee plants (7). MGF is most abundant in members of the Anacardiaceae family, particularly *Mangifera indica* L., but it has also been isolated from other medicinal plants, such as *Prunus dulcis*, *Gentiana manshurica*, *Swertia mussotii* and *Pyrrosia calvata* (12). Advances in phytochemical techniques, including high-performance liquid chromatography and mass spectrometry, have notably improved the precision of MGF identification and quantification across diverse plant matrices.

An early pharmacological study explored the physiological and therapeutic effects of MGF (10). A previous study demonstrated that the substance possesses a spectrum of biological activities beyond its initial inotropic effect on frog hearts, including immunomodulatory, reproductive, antitumor and antiviral properties (13). Metabolic investigations have indicated that MGF is biotransformed by the human intestinal microbiota, with deglycosylation to norathyriol a key step (8). In preclinical PK studies, oral MGF has been shown to exhibit low systemic exposure, which is reflected by its limited detection in the plasma and urine of rodent models (14). These observations have motivated formulation strategies to improve exposure. In 2012, nanostructured lipid carriers were applied to MGF, providing a basis for subsequent nanotechnology-oriented approaches that aim to increase its solubility, stability and oral bioavailability (15).

3. Absorption and metabolism of MGF

Absorption of MGF. Despite its wide pharmacological spectrum, MGF has low oral bioavailability, largely due to its poor solubility and limited membrane permeability. The stability of its C-glycosidic bond prevents enzymatic cleavage and reduces transmembrane transport, thereby restricting passive absorption across the intestinal epithelium (16). A previous *in vivo* study demonstrated that only 1.15% of orally administered MGF (30 mg/kg) is bioavailable in mice, whereas intraperitoneal administration results in markedly increased systemic levels. Additionally, extensive first-pass hepatic metabolism further decreases the amount of active MGF entering systemic circulation (17).

Regional differences in intestinal absorption have been reported in rats. *In situ* perfusion experiments have indicated greater apparent permeability in the duodenum compared with that in the jejunum, and greater permeability in the jejunum than in the ileum, which suggests that the upper small intestine is the principal site of uptake (18). After absorption, MGF is distributed via the circulation to multiple organs, including

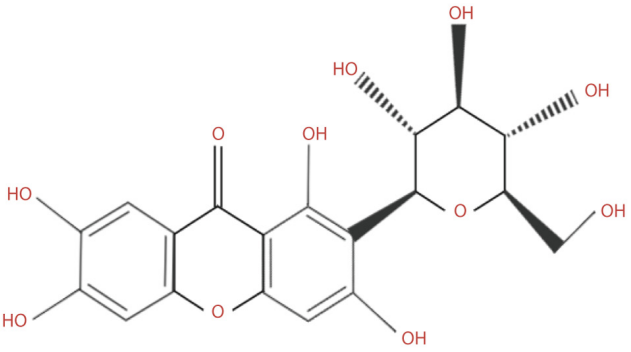

Figure 1. Chemical structure of mangiferin.

the heart, liver, spleen, lungs, kidneys, testes and prostate. In rats administered oral MGF, peak concentrations in the plasma, lungs and kidneys have been reported to occur 4-6 h after dosing. Under the reported analytical conditions, MGF is not detected in brain tissue, which is consistent with limited penetration across the blood-brain barrier in this model (19).

Metabolism of MGF. MGF undergoes biotransformation through both microbial and host enzymatic systems. A frequently observed pathway is microbial or enzymatic deglycosylation of C-glucoside, generating the aglycone norathyriol (metabolite M1), which has greater membrane permeability than the parent compound (20). Subsequent phase I reactions (for example, dehydroxylation and O-methylation) and phase II conjugations (including glucuronidation and sulfation) yield additional metabolites with distinct physicochemical properties (21). These steps can occur sequentially or in parallel within the gut lumen and microbiota, the intestinal epithelium and the liver, and the relative contribution of each route depends on the species, dose and formulation (21). A schematic overview of these metabolic routes and representative metabolites is provided in Fig. 2. Thus, while the formation of M1 is well documented (20,21), it should be considered a predominant rather than obligatory initial event in the overall metabolic scheme.

Specifically, M1 is dehydroxylated to form 1,3,7-trihydroxyxanthone (M2) and 1,7-dihydroxyxanthone (M4), with M2 being the predominant urinary metabolite in rodents (22). Methylation of M1 yields compounds such as 1,3,6-trihydroxy-7-methoxyxanthone (M3) and methoxy dimethyl xanthone (M5). Conjugation reactions generate glucuronide (M6), sulfate (M7) and mixed derivatives, including dithio-sulfate norathyriol (M8), sulfate norathyriol glucoside (M9), norathyriol glucuronide (M11) and its sulfated form (M10) (11,23).

The gut microbiota serves a critical role in the deglycosylation and subsequent metabolism of MGF, representing a key determinant of its systemic availability and pharmacological effects (24). Although microbial metabolism enables the formation of bioactive metabolites, it remains unclear whether MGF itself modulates the composition and function of the gut microbiota. Further research is needed to clarify this bidirectional interaction, and to characterize the full spectrum of bioactive metabolites relevant to disease prevention and therapy (25).

4. Pharmacological effects of MGF on diabetes

Diabetes mellitus results from impaired pancreatic β-cell function and/or peripheral insulin resistance, ultimately disrupting glucose homeostasis. MGF has notable antidiabetic potential due to its insulinotropic and insulin-sensitizing effects (Fig. 3).

β-cell protection and pancreatic regeneration. MGF supports pancreatic function by preserving and regenerating β cells. In animal models of type 1 and type 2 diabetes, tail vein administration of MGF-loaded polymeric nanocarriers (5-10 mg/kg) have been reported to increase β-cell proliferation, inhibit apoptosis and restored insulin secretion, thereby improving glycemic control (26). Similarly, repeated oral administration of MGF (30 or 90 mg/kg for 14 days) in partially pancreatectomized mice may promote islet regeneration through the upregulation of key cell-cycle regulators (such as cyclin D1 and Ki-67) and pancreatic progenitor markers, including Pdx1 and Ngn3 (27).

Insulin sensitization and glucose metabolism. MGF also alleviates insulin resistance by modulating metabolic, inflammatory and oxidative stress pathways. Activation of the peroxisome proliferator-activated receptor (PPAR)α/γ axis enhances fatty acid β-oxidation and upregulates glucose transporter 4 (GLUT4), thereby improving insulin sensitivity (28). Given that chronic inflammation and oxidative stress are central to the development of diabetes (29), MGF mitigates these processes through the inhibition of HIF-1α and NF-κB signaling, the suppression of JNK phosphorylation, and the reduction in endoplasmic reticulum stress, collectively restoring insulin signaling (30).

In addition, MGF directly regulates glucose metabolism. It promotes glycolysis and glycogen synthesis while inhibiting gluconeogenesis by modulating key enzymes such as glycogen synthase kinase 3β (GSK3β), glucose-6-phosphatase and phosphoenolpyruvate carboxykinase. Furthermore, MGF reverses high glucose-induced impairment of GLUT4 translocation and glucose uptake, partly via AMPK activation and Akt phosphorylation, thereby improving hepatic energy metabolism and overall insulin responsiveness (31).

Structural derivatives and therapeutic effects on diabetic complications. Structural modification of MGF has produced more potent derivatives. For example, compound X-3, a semi-synthetic derivative prepared from MGF, has been reported to markedly reduce hyperglycemia and obesity in mice after 8 weeks of oral treatment (40-120 mg/kg), primarily through AMPK pathway activation (32).

In addition to its ability to control glycemia, MGF has shown activity against diabetic complications in preclinical models. In a mouse model of diabetic pulmonary fibrosis, oral administration of 60 mg/kg MGF every 3 days for 4 weeks has been shown to reduce the progression of fibrosis. Reported effects include the inhibition of endothelial-mesenchymal transition and modulation of the AMPK/FoxO3/sirtuin (SIRT)3 pathway, as evidenced by changes in pathway proteins and fibrosis markers (33). In streptozotocin-induced diabetic mice, oral administration of 15-60 mg/kg/day MGF for 4 weeks may attenuate renal injury, which is consistent with diabetic

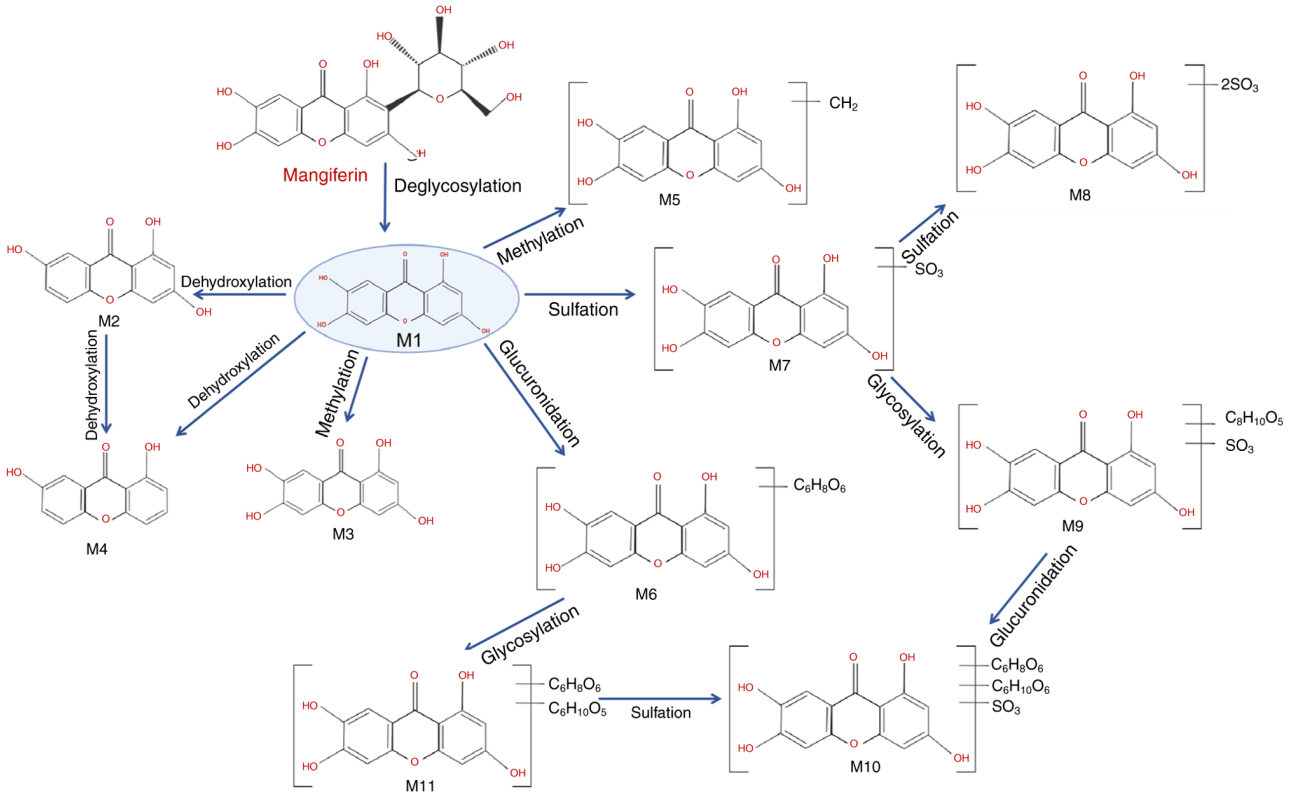

Figure 2. Diagram of the relevant pharmacological properties of mangiferin and its potential mechanism of action. The metabolic pathways include the following: M1, deglycosylation to norathyriol; M2, 1,3,7-trihydroxyxanthone; M3, methylation to 1,3,6-trihydroxy-7-methoxyxanthone; M4, dehydroxylation to 1,7-dihydroxyxanthone; M5, further methylation to methoxy dimethyl xanthone; M6, glucuronidation products; M7, sulfated derivatives; M8, dithio-sulfate norathyriol; M9, sulfate norathyriol glucoside; M10, norathyriol glucuronide sulfate; and M11, norathyriol glucuronide.

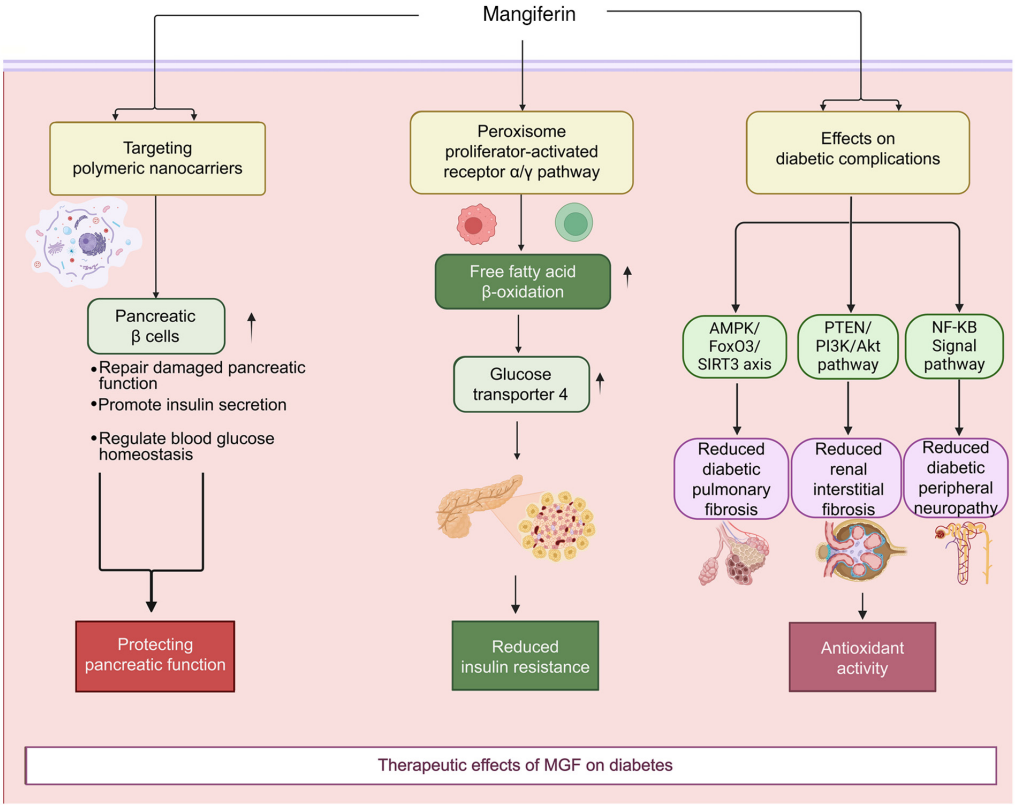

Figure 3. Therapeutic effects of MGF on diabetes. MGF restores islet function, promotes insulin secretion and regulates glucose homeostasis. It enhances fatty acid β-oxidation and glucose transporter 4 expression, alleviates insulin resistance and reduces diabetic complications. The AMPK/FoxO3/SIRT3 and PTEN/PI3K/Akt pathways are crucial targets that contribute to protection against diabetic pulmonary fibrosis, renal fibrosis and peripheral neuropathy. AMPK, AMP-activated protein kinase; MGF, mangiferin; SIRT3, sirtuin 3.

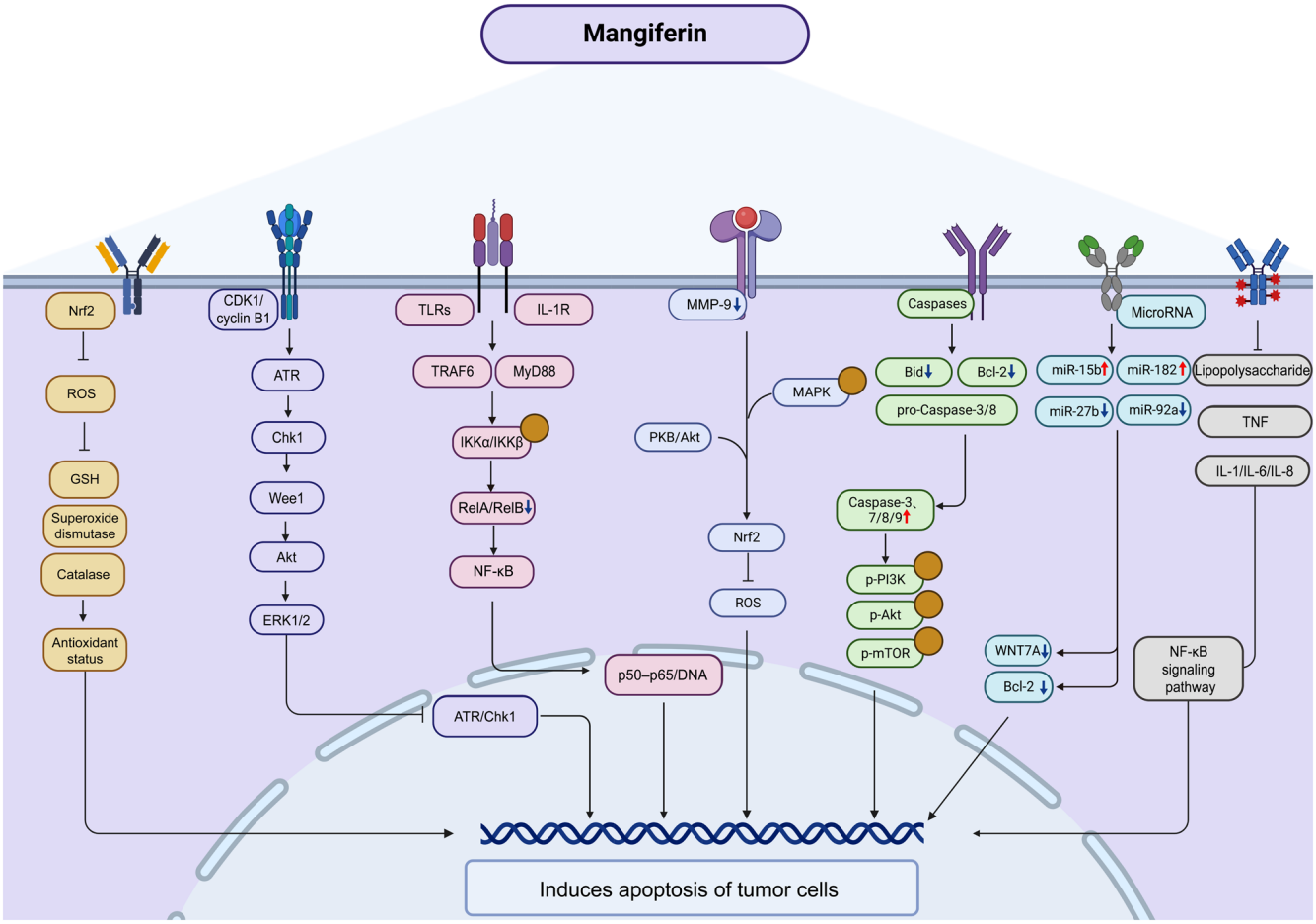

Figure 4. Molecular mechanism of the anticancer effect of MGF. MGF suppresses tumor growth by promoting apoptosis, exerting anti-inflammatory effects, regulating mitochondrial function, modulating autophagy and enhancing immune responses. Upward and downward arrows indicate activation/upregulation or inhibition/downregulation by MGF, respectively. Yellow circles indicate activation of the indicated signaling nodes. GSH, glutathione; IL-1R, IL-1 receptor; MGF, mangiferin; miR, microRNA; Nrf2, nuclear factor erythroid 2-related factor 2; p-, phosphorylated proteins; ROS, reactive oxygen species; TLRs, Toll-like receptors; TRAF6, TNF receptor-associated factor 6.

nephropathy. This previous study reported downregulation of phosphatase and tensin homolog (PTEN)/PI3K/Akt signaling, and reduced expression of fibronectin, collagen I and α-smooth muscle actin (α-SMA), along with decreases in renal fibrosis, inflammation and oxidative stress endpoints (34). Taken together, these data support a potential role for MGF in mitigating pulmonary and renal complications of diabetes under experimental conditions, while confirming that the proposed mechanisms, including inhibition of endothelial-mesenchymal transition and modulation of AMPK/FoxO3/SIRT3 signaling in diabetic pulmonary fibrosis, and downregulation of PTEN/PI3K/Akt signaling with reduced fibronectin/collagen I/α-SMA expression in diabetic nephropathy, are supported by molecular endpoints measured in these models (33,34).

In models of diabetic peripheral neuropathy, MGF alleviates neuroinflammation by reducing TNF-α, TGF-β1, IL-1β and IL-6 levels in the sciatic nerve. Concurrently, it enhances antioxidant defenses and upregulates nerve growth factor, thereby promoting nerve regeneration and functional recovery (35).

5. Anticancer mechanisms of MGF

MGF exerts potent anticancer activity through multiple mechanisms that target key cellular processes underlying tumor initiation and progression. These include the induction of cell cycle arrest, the promotion of apoptosis through various intracellular pathways, the inhibition of tumor invasion and metastasis, the modulation of immune responses, and the enhancement of radiosensitivity in cancer such as glioblastoma (GBM) (36,37). Fig. 4 schematically summarizes the major signaling pathways [such as nuclear factor erythroid 2-related factor 2 (Nrf2)/reactive oxygen species (ROS), ATR/Chk1, CDK1/cyclin B1, NF-κB, PI3K/Akt, MAPK, caspases and microRNAs (miRNAs/miRs)] through which MGF induces apoptosis of tumor cells.

According to previous cancer-related experiments, MGF most consistently modulates four signaling axes that share common upstream triggers and downstream responses (38,39). For NF-κB, typical engagement is inferred from reduced IKKα/IKKβ phosphorylation, stabilization of IκBα, and reduced nuclear p65 DNA binding, with downstream decreases in pro-survival and invasive effectors, such as BCL2L1, BIRC5 and MMP-9 (40-43). For Nrf2, evidence includes diminished Kelch-like ECH-associated protein 1-mediated ubiquitination, increased nuclear Nrf2, and the induction of heme oxygenase (HO)-1, NAD(P)H quinone dehydrogenase 1 (NQO1) and other phase II enzymes, aligning with decreased ROS and lipid peroxidation (44,45). MAPK modulation is context dependent;

a number of models show attenuation of ERK1/2, JNK and p38 phosphorylation, reduced activator protein (AP)-1 activity, and consequent decreases in proliferation and cytokine output (38,46). For PI3K/Akt, changes in Akt Thr308/Ser473, and downstream GSK3β and mTOR complex 1 lead to reduced protein synthesis and survival signaling in tumor cells, whereas in metabolic tissues, they support GLUT4 translocation and glycogen synthesis (16,47-54). Notably, crosstalk is evident: AMPK activation can suppress NF-κB priming and MAPK activity, whereas redox shifts through Nrf2 dampen inflammasome priming, which converges on MMP-9 and invasion programs. To aid interpretation, each subsequent subsection in the present review reports on the model, exposure, phosphorylation status of key signaling proteins and a disease-relevant functional endpoint (for example, apoptosis markers, invasion or tumor growth), and provides a brief appraisal of sample size and risks of bias.

Cell cycle arrest via CDK1/cyclin B1. In HL-60 cells, some studies have reported increased CDK1 and cyclin B1 mRNA following MGF exposure, indicating regulation at the transcriptional level in this model (55). However, across tumor cell systems, the functional consequence remains G_2/M arrest, with reduced proliferation and increased susceptibility to apoptosis. This outcome is consistent with reports of decreased CDK1/cyclin B1 activity, altered phosphorylation of CDK1 with reduced activating phosphorylation and increased inhibitory phosphorylation, and engagement of checkpoint signaling, including ATR-dependent Chk1 activation, in other tumor cell lines exposed to MGF (56,57). This evidence supports multilevel regulation of the CDK1/cyclin B1 axis by MGF. Differences at the mRNA level are plausibly attributable to the assay, timing, dose and cellular context, whereas the consistent phenotype is G_2/M blockade with growth suppression (55-57).

Apoptosis pathways

Caspase activation. The induction of apoptosis via caspase activation is a well-established anticancer mechanism. Caspases are a family of cysteine proteases that execute programmed cell death through a proteolytic cascade. Initiator caspases (such as caspase-8 and -9) activate effector caspases (including caspase-3, -6 and -7), leading to degradation of intracellular components and apoptotic cell death (58,59). MGF has been shown to promote this cascade through multiple upstream regulators, including the Bcl-2 protein family and cytochrome *c*-mediated pathways (60).

MGF induces apoptosis in nasopharyngeal carcinoma cells by modulating the mitochondrial pathway, decreasing antiapoptotic Bcl-2 and increasing proapoptotic Bax expression (61). In HeLa cervical cancer cells, ethanolic mango peel extract enriched with MGF downregulates Bid, Bcl-2 and pro-caspase-3 and -8, while activating caspases-3, -7, -8 and -9, and cleaving poly(ADP-ribose) polymerase (PARP)-hallmarks of caspase-mediated apoptosis (62).

In SGC-7901 gastric cancer cells, MGF suppresses Bcl-2, Bcl-xL and Mcl-1 expression, and increases Bax, Bad, and cleaved caspase-3 and -9 levels. Additionally, it inhibits the PI3K/Akt/mTOR signaling axis, further promoting apoptosis and suppressing cell survival (47).

Modulation of miRNAs. miRNAs are short, noncoding RNAs that post-transcriptionally regulate gene expression and serve dual roles in cancer as oncogenes or tumor suppressors (63). MGF influences the expression of several miRNAs associated with tumor suppression and apoptosis.

In glioma cells, MGF upregulates miR-15b, which induces apoptosis by downregulating the expression of oncogenic targets such as WNT7A (37,64). Similarly, in prostate cancer PC3 cells, MGF elevates miR-182 levels, leading to decreased Bcl-2 expression and increased apoptotic activity (65). In lung adenocarcinoma models, MGF reduces the expression of miR-27b and miR-92a, two oncogenic miRNAs highly expressed in tumor tissues, thereby inhibiting tumor cell proliferation and promoting apoptosis (66).

Induction of the mitochondrial pathway. MGF also initiates intrinsic apoptosis via the mitochondrial pathway (67). Disruption of mitochondrial membrane potential is a critical early event in the apoptotic cascade and is often regulated by intracellular calcium homeostasis and endoplasmic reticulum stress (68). MGF reduces the mitochondrial membrane potential in HT29 colon cancer cells, leading to mitochondrial outer membrane permeabilization and apoptosis (69). In lung cancer mouse models, MGF alters mitochondrial metabolism by increasing lipid peroxidation and suppressing key TCA cycle and electron transport enzymes, including isocitrate dehydrogenase, succinate dehydrogenase, malate dehydrogenase and α-ketoglutarate dehydrogenase (70). Notably, in models of fluoride-induced neurotoxicity, MGF restores mitochondrial integrity by inhibiting proapoptotic proteins (Bax, caspase-3 and caspase-9) and upregulating Bcl-2. These protective effects are mediated via JNK inhibition and activation of the Nrf2/HO-1 pathway (71). Thus, the ability of MGF to induce mitochondrial dysfunction in cancer cells and preserve mitochondrial health in normal cells reflects its selective cytotoxic potential.

Induction of oxidative stress. ROS serve a paradoxical role in cancer, contributing to tumor initiation while also serving as apoptotic triggers when in excess (72). MGF modulates oxidative stress pathways by interacting with both pro-oxidant and antioxidant systems. MGF activates the Nrf2 pathway, stabilizing Nrf2 protein levels by inhibiting its ubiquitination, which leads to increased transcription of antioxidant enzymes, such as NQO1 (73,74). This activity suppresses intracellular ROS accumulation and induces apoptosis in leukemia HL-60 cells (75). In neuroblastoma SK-N-SH cells, MGF reduces ROS production and the activity of key antioxidants, such as glutathione (GSH), superoxide dismutase (SOD), catalase and GSH peroxidase (GSH-Px), pushing the redox balance toward apoptosis (9,76). Additionally, MGF enhances phase II detoxifying enzymes, including GSH S-transferase, quinone reductase and UDP-glucuronosyltransferase, while reducing lipid peroxidation in lung cancer models (77,78).

In a diethylnitrosamine-induced hepatocellular carcinoma rat model, treatment with MGF has been shown to improve hepatic oxidative stress markers, as follows: Malondialdehyde (MDA) content was reduced, whereas SOD activity and GSH levels were elevated, and tumor formation was attenuated (79). In colorectal cancer, an azoxymethane-induced rat model treated with MGF has been shown to exhibit improved antioxidant enzyme activity, reduced aberrant crypt foci formation

and modulation of apoptotic proteins, such as Bax, Bcl-2 and caspase-3, have been reported, linking redox control to tumor suppression in colon tissue (80).

In malignant contexts where antioxidant defenses become critically depleted, MGF-mediated redox modulation may serve as an initiating event that dictates cell fate. Sustained ROS accumulation disrupts mitochondrial integrity, diminishes the membrane potential and promotes apoptotic signaling, as observed in tumor and myoblast models (81). In addition to this proapoptotic cascade, accumulating evidence has suggested that redox regulation itself constitutes a primary mechanistic axis rather than a subordinate branch of apoptosis, reflecting broader control of mitochondrial and metabolic homeostasis (82,83).

In malignant settings with severely depleted antioxidant defenses, persistent ROS elevation can damage mitochondria, impair membrane potential and promote apoptotic signaling. However, available data suggest that MGF-driven restoration of redox homeostasis represents a central mechanistic axis of its antitumor activity, rather than merely a downstream branch of apoptosis (84,85).

Inhibition of tumor invasion via MMP-9 suppression. MMPs, particularly MMP-2, MMP-9 and MMP-11, are critical enzymes involved in tumor invasion, metastasis and angiogenesis (86). Among these proteins, MMP-9 serves a central role in degrading extracellular matrix components, facilitating tumor cell dissemination. MGF has been demonstrated to have a selective inhibitory effect on MMP-9, making it a promising candidate for antimetastatic therapy (87).

MGF inhibits tumor invasion in part by selectively suppressing MMP-9 expression and activity. In human glioma models, MGF reduces phorbol 12-myristate 13-acetate-induced MMP-9 without materially affecting other MMP family members, which is consistent with decreased NF-κB and AP-1 binding to the MMP-9 promoter, and with upstream attenuation of Akt and MAPK signaling (41). A Computational study has provided support for direct interactions between MGF derivatives and the MMP-9 catalytic site, which may contribute to enzymatic inhibition (88).

MGF has also been shown to sensitize glioma cells by modulating signaling pathways involved in MMP-9 regulation, including the NF-κB and PKB/Akt pathways. In metastatic melanoma models, low-dose MGF enhances the antitumor activity of citrus-derived glycosides, partly by increasing TNF-α expression and inhibiting metastasis (89).

Immunomodulatory activity

Suppression of NF-κB signaling. In addition to its downstream effects on apoptosis, NF-κB signaling represents a key immunomodulatory axis. Chronic inflammation drives tumorigenesis in ~20% of cancers (90), largely through activation of the NF-κB pathway (91,92). MGF interferes with multiple nodes of NF-κB signaling, thereby limiting inflammation-driven carcinogenesis (93). NF-κB transcription factors, particularly RelA (p65) and RelB, promote the expression of pro-survival and proinflammatory genes (94). MGF suppresses RelA and RelB expression, reduces NF-κB transcriptional activity, and induces apoptosis in malignancies such as multiple myeloma (95).

In the canonical NF-κB pathway, extracellular stimuli such as pathogen-associated molecular patterns or proinflammatory cytokines (such as IL-1 and TNF-α) activate Toll-like receptors and IL-1 receptor (IL-1R), leading to recruitment of the MyD88-IL-1R-associated kinase 1/4-TNF receptor-associated factor 6 complex (96,97). This initiates downstream signaling via TAK1-TAB1/2 and the IKK complex (IKKα, IKKβ and NEMO), ultimately phosphorylating IκB and releasing the NF-κB p50/p65 dimer for nuclear translocation (98).

MGF effectively interferes with this cascade. *In vitro* studies have shown that pretreatment with MGF or its enriched extract Vimang reduces the phosphorylation of IKKα and IKKβ without altering their total protein levels (99). Furthermore, MGF impairs the nuclear translocation and DNA-binding activity of p65 in response to TNF-α stimulation (100), thereby disrupting NF-κB-driven transcription and weakening the survival response in tumor cells (101). This NF-κB inhibition is accompanied by classical apoptotic hallmarks. MGF upregulates proapoptotic markers, including cleaved caspase-3, cleaved PARP-1, p53, phosphorylated-p53 and p53-upregulated modulator of apoptosis, while downregulating antiapoptotic proteins, such as survivin and Bcl-xL (40). Additionally, MGF suppresses NF-κB-inducing kinase, further reinforcing the blockade of both the canonical and noncanonical NF-κB pathways, ultimately limiting cancer cell proliferation, metastasis and survival.

MGF also modulates stress and survival pathways that converge on NF-κB. In HL-60 leukemia cells, MGF activates Nrf2 and lowers intracellular ROS, which is consistent with the attenuation of oxidative stress (75). In epithelial cancer models, MGF enhances the cytotoxic effects of chemotherapeutics while suppressing NF-κB activation. In HeLa and HT29 cells, this suppression coincides with improved responses to oxaliplatin and reduced drug resistance. In A549 lung cancer cells, MGF increases the antiproliferative impact of chemotherapy in association with G_2/M arrest and inhibition of the PKC-NF-κB axis (56). These apoptotic outcomes are considered secondary to the primary immunomodulatory role of MGF through NF-κB inhibition.

Modulation of immune cells and cytokine responses. In addition to its direct cytotoxicity, MGF modulates host immune responses, enhancing antitumor immunity. It influences various immune cell populations, including macrophages, neutrophils, splenocytes and natural killer (NK) cells, which are critical components of the tumor microenvironment (78). MGF induces cytoskeletal rearrangement in macrophages, alters their morphology and enhances their phagocytic capacity (102). It also modulates immune responses triggered by lipopolysaccharides (LPS), TNF-α and IL-1, potentially limiting tumor-induced DNA damage in normal tissues and mitigating tumor-promoting inflammation (103).

In MDA-MB-231 breast cancer cells, MGF disrupts Rac1/WAVE2 signaling and inhibits cytokine secretion (for example, IL-6 and IL-8), thereby reducing invasive capacity and inflammatory crosstalk (104). Dose-dependent immunostimulatory effects have also been observed in murine models; low concentrations (5-40 mg/ml) enhance the proliferation of splenocytes and thymocytes, whereas higher doses inhibit tumor cell proliferation. MGF activates splenocytes, facilitates

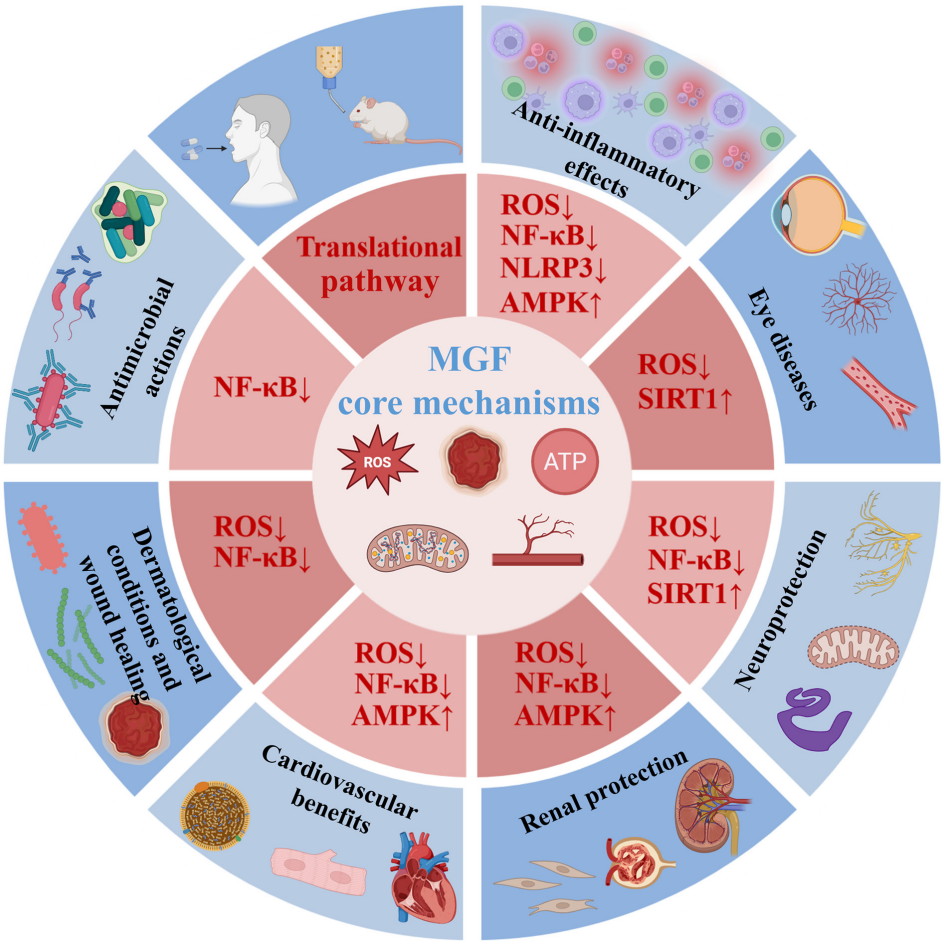

Figure 5. Representative therapeutic applications of MGF and its core molecular mechanisms. MGF exhibits broad pharmacological activity across multiple organ systems, which is primarily mediated through the attenuation of oxidative stress and inflammatory signaling. The core mechanisms include a reduction in ROS levels, suppression of NF-κB and NLRP3 inflammasome activation, and activation of the AMPK and SIRT1 pathways. These convergent regulatory effects underpin the diverse protective actions of MGF in inflammatory, neurodegenerative, ocular, renal, cardiovascular, dermatological and infectious diseases. The listed conditions represent key examples rather than an exhaustive account of the therapeutic potential of MGF, highlighting its versatility as a pleiotropic bioactive compound. AMPK, AMP-activated protein kinase; MGF, mangiferin; NLRP3, NLR family pyrin domain-containing 3; ROS, reactive oxygen species; SIRT, sirtuin.

plant lectin agglutination and stimulates NK-resistant tumor cell killing by macrophages (105,106).

Radiosensitization in GBM. GBM is a highly aggressive brain tumor with a poor prognosis and a limited response to conventional radiotherapy. While radiotherapy remains a cornerstone of GBM treatment, tumor recurrence due to radioresistance remains a major challenge. Radiosensitizers are pharmacological agents that increase tumor sensitivity to radiation while minimizing harm to normal tissues, representing an attractive adjunct strategy in GBM management.

Recent evidence has suggested that MGF enhances radiosensitivity in GBM through multiple mechanisms. It synergistically inhibits the proliferation of U87 and U118 GBM cells in a dose- and time-dependent manner when combined with radiation. MGF exerts these effects by downregulating MMP-9 expression and modulating miR-15b, thereby disrupting tumor cell survival and invasion (35). Notably, MGF selectively inhibits the nonhomologous end joining pathway, a major DNA repair mechanism in GBM cells, thereby impairing DNA repair following radiation and enhancing radiotherapeutic efficacy. By sensitizing tumor cells to radiation-induced DNA damage, MGF improves therapeutic outcomes without necessitating an increase in radiation dose (36). A comprehensive summary of the targets, dosages, study models, signaling pathways and mechanistic insights associated with MGF across different cancer-related contexts is presented in Table I (4,5,7,8,13-17,55,56,107-114).

6. Applications in other diseases

In addition to its well-characterized roles in diabetes and cancer, MGF exerts protective effects across a broad spectrum of pathological conditions. These include inflammatory, neurodegenerative, ocular, renal, cardiovascular, dermatological and infectious diseases (7,36,106,115-118). Although the mechanistic depth of investigation in these fields is comparatively limited, accumulating preclinical and early clinical evidence has underscored the versatile pharmacodynamic (PD) profile of MGF. Its therapeutic actions converge on several core molecular pathways, particularly the suppression of oxidative stress and NF-κB-mediated inflammation, and the activation of AMPK and SIRT1 signaling (119-121). Fig. 5 provides an overview of these

Table I. Summary of representative studies on MGF and the underlying molecular mechanisms.

Target/pathway	Dose and duration	Experimental model/sample size	Type of study	Major signaling pathways	Principal findings/cellular products	Limitations/ remarks	(Refs.)
Apoptosis	12.5-200 μM	CNE2, SGC-7901 gastric carcinoma cells	*In vitro*	Caspase; PI3K-Akt	Bax (up), Bad (up), Bcl-2 (down); activation of caspase-3/9;	Limited to gastric cell lines	(4,5)
miRNA modulation	12.5-100 mg/ml	H2030/H1299/ A549 lung cancer cells	*In vitro*	miR-92a, miR-27b	Downregulated oncogenic miRNAs; suppressed proliferation and induced apoptosis in LUAD cells	No animal or human data	(7)
miRNA modulation	25-100 μM	Human U87 glioma cells	*In vitro*	MMP-9/ miR-15b	MMP-9 (down), miR-15b (down); attenuated invasion	Mechanism indirect; requires *in vivo* validation	(8)
Mitochondrial pathway	1/50/400 μM	HT-29 colon adenocarcinoma cells (ATCC HTB-38)	*In vitro*	PPAR, SIRT, NF-κB, STAT3, HIF, Wnt	Multitargeting of mitochondrial oxidoreductases and β-oxidation; inhibited proliferation, metastasis, angiogenesis	*In vitro* only; pharmacokinetic data were not available	(13)
Mitochondrial pathway	10/25/50 μM	SH-SY5Y neuroblastoma cells	*In vitro*	JNK; Nrf2/HO-1	Normalized mitochondrial dynamics, reduced oxidative stress	Limited neuronal model	(14)
Lipid peroxidation	10 μg/ml	U-937 macrophages	*In vitro*	NF-κB	Inhibited TNF-induced lipid peroxidation; catalase (up); apoptosis protection	Preclinical only	(15)
Lipid peroxidation	50 mg/kg	Benzo(a)pyrene-induced lung cancer in Swiss albino mice (n=6/group)	*In vivo*	NF-κB; mitochondrial genes	Reduced mitochondrial lipid peroxidation; altered TCA/ETC enzymes; induced apoptosis	No chronic safety data	(16)
Oxidative-stress pathway	50/100/ 200 mg/kg x14 days	Wistar rats (n=8/group)	*In vivo*	Nrf2	Breg levels, activated Nrf2 antioxidant pathway; proinflammatory mediators (down)	Rodent model; needs clinical validation	(17)
Cell-cycle proteins	0.5/0.75/ 1 μM	HL-60 leukemia cells	*In vitro*	CDK1/ cyclin B1	Increased cyclin B1; triggered G_2/M arrest	Short-term exposure; lacks mechanistic protein validation	(55)

Table I. Continued.

Target/pathway	Dose and duration	Experimental model/sample size	Type of study	Major signaling pathways	Principal findings/cellular products	Limitations/ remarks	(Refs.)
Cell-cycle proteins	10/50/ 100 mg/kg	A549 lung carcinoma cells	*In vitro*	CDK1/ cyclin B1	Induced G_2/M-phase arrest; apoptosis via NF-κB inhibition	Only cell-line data; no *in vivo* validation	(56)
Pharmacokinetics/ absorption	30 mg/kg (single oral dose)	Wistar rats (n=6)	*In vivo*	-	Peak tissue level in small intestine at 0.5 h (754 ng/ ml); nonlinear absorption	No human PK association	(107)
Anti-invasion/ anti-metastasis	1 mg/ml; 50 μl/well	U87MG/ U373MG/ CRT-MG glioma cells	*In vitro*	MMP-9; PI3K-Akt; MAPK	Suppressed MMP-9 via inhibition of NF-κB and AP-1; Akt/MAPK phosphorylation (down)	No *in vivo* validation	(108)
Anti-inflammatory	4.2 mg	RAW 264.7 macrophages	*In vitro*	NF-κB	IL-12 (down), TNF-α (up), IL-1 (up), IL-6 (down); anti-inflammatory shift	Lacks time-course data	(109)
miRNA modulation	10/20/40 μM	PC3 human prostate cancer cells	*In vitro*	Bcl-2/miR-182	Bcl-2 (down), miR-182 (up); promoted apoptosis	Single-cell model	(110)
Mitochondrial pathway	100 mg/kg x 21 days	ER^- breast-cancer xenograft mice (n=8)	*In vivo*	NF-κB; caspase-3	Tumor volume reduced by ~89%, comparable to cisplatin (91.5%)	Short duration; no toxicity endpoints	(111)
Inflammatory models	20-40 μM/ 5-20 mg/kg	RAW264.7 cells and mouse air-pouch model (n=6/group)	*In vitro* and *in vivo*	ROS; NF-κB	Reduced ROS; blocked NF-κB nuclear translocation; suppressed cytokines	Dose-dependent effects only short term	(112)
Safety/toxicity	≤1,000 mg/ kg x 28 days	Sprague-Dawley rats (n=10/group)	*In vivo*	-	No abnormal hematology; LD_{50} >2,000 mg/kg	Limited to 28 days	(113)
Clinical cognition study	300 mg/day x 7 days	60 healthy adults, randomized double-blind	Clinical	Cognitive/ antioxidant	Improved attention and working memory; no adverse events	Short duration; healthy subjects only	(114)

'(up)' indicates upregulation; '(down)' indicates downregulation. AP-1, activator protein-1; ER, estrogen receptor; HO-1, heme oxygenase-1; LD_{50}, lethal dose 50%; LUAD, lung adenocarcinoma; miRNA/miR, microRNA; ETC, electron transport chain; MNF, mangiferin; Nrf2, nuclear factor erythroid 2-related factor 2; Breg, regulatory B cell; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SIRT, sirtuin; TCA, tricarboxylic acid; -, not applicable.

shared mechanisms and representative disease contexts, illustrating the diverse yet interconnected pharmacological potential of MGF beyond metabolic and oncological disorders.

Anti-inflammatory effects. Chronic inflammation is a key driver of various pathological conditions, including degenerative, autoimmune and metabolic diseases. MGF, characterized by its C-glucosyl and polyhydroxylated xanthone structure, exhibits potent antioxidant and anti-inflammatory activities by scavenging free radicals and modulating key signaling pathways.

In intervertebral disc degeneration, MGF has been shown to attenuate mitochondrial dysfunction and reduce ROS in human nucleus pulposus cells. It suppresses TNF-α-induced NF-κB activation and downregulates the expression of apoptosis-related markers, including pro-apoptotic caspases and Bcl-2 family proteins, indicating its therapeutic potential for treating degenerative disc disorders (122).

In a rat model of rheumatoid arthritis, MGF (15-45 mg/kg, 2-week administration) inhibits the MAPK and NF-κB pathways, thereby reducing inflammatory cell proliferation, migration and cytokine secretion. MGF also promotes inflammatory apoptosis and attenuates the pathogenic activity of fibroblast-like synoviocytes in arthritic rats (123).

In metabolic inflammation, MGF improves insulin sensitivity and lipid metabolism. In a rodent model of high-fat diet-induced nonalcoholic fatty liver disease (NAFLD), MGF (25-100 mg/kg, 12 weeks) activates AMPK and suppresses NLRP3 inflammasome signaling, reducing hepatic inflammation and steatosis (124). An additional study has confirmed the ability of MGF to inhibit the NF-κB and JNK pathways, with reduced body weight and plasma triglyceride and cholesterol levels in NAFLD mouse models (125).

In models of acute lung injury, pre-administration of MGF (100 mg/kg) suppresses LPS-induced NLRP3 inflammasome activation in macrophages via NF-κB inhibition. This results in reduced inflammatory cytokine production and amelioration of pulmonary pathology (126).

Eye diseases. Oxidative stress serves a central role in the pathogenesis of ocular disorders such as diabetic retinopathy and macular degeneration. MGF has demonstrated therapeutic benefits in preclinical models of retinal and lens injury through antioxidant and antiangiogenic mechanisms (127).

In ischemic retinal injury, MGF downregulates HIF-1α and glial fibrillary acidic protein while upregulating SIRT1, thereby protecting retinal ganglion cells from oxidative damage in mouse models (128). In diabetic retinopathy, MGF inhibits angiogenesis and endothelial cell migration by targeting the PI3K/Akt/mTOR pathway, suggesting potential for clinical translation (129).

Notably, the capacity of MGF to cross the blood-retinal barrier enhances its therapeutic efficacy (130). In streptozotocin-induced diabetic rats, biochemical analysis has revealed that MGF increases antioxidant enzyme activity (SOD, GSH-Px), reduces lipid peroxidation (MDA), and decreases advanced glycation end-products (AGEs) and sorbitol levels in the lens and serum, thereby contributing to the prevention of diabetic ocular complications (131).

Neuroprotection. MGF exhibits robust neuroprotective properties across multiple animal models of neurodegeneration, ischemia and cognitive impairment. Its mechanisms include the modulation of oxidative stress, mitochondrial protection and anti-inflammatory signaling (132).

In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse models and α-synuclein overexpression transgenic mouse models of Parkinson's disease, MGF reduces neuroinflammation and oxidative stress by inhibiting NF-κB signaling, resulting in improved motor coordination and neuronal survival in the substantia nigra (133). It also improves memory by enhancing cholinergic transmission through acetylcholinesterase inhibition and NF-κB suppression (134).

In hypoxia/reoxygenation-induced N2a neuroblastoma cell models of ischemic injury, MGF activates the SIRT1/PPARγ coactivator-1α axis to preserve mitochondrial function and reduce neuronal damage (135). A placebo-controlled human study demonstrated that acute MGF administration enhances attention, long-term memory and cognitive performance in healthy adults (136).

MGF also protects against β-amyloid-induced oxidative damage, restoring redox balance and preserving mitochondrial integrity in Alzheimer's disease models, such as amyloid β-treated neuronal cultures and APP/PS1 transgenic mice (137). In aging mice, MGF improves memory, reduces hippocampal pathology, and decreases the β-amyloid burden and lipid peroxidation (138). Furthermore, it enhances hippocampal neuronal excitability and cognitive processing, supporting its potential as a neurocognitive enhancer (139).

Renal protection. Renal dysfunction, often driven by oxidative stress and inflammation, contributes to the pathogenesis of acute and chronic kidney diseases. MGF has demonstrated renoprotective effects across a range of kidney injury models by modulating inflammation, oxidative stress and fibrotic signaling pathways (140).

In vitro studies have shown that MGF suppresses IL-6 and IL-8 production by inhibiting the MAPK and NF-κB pathways, thereby attenuating inflammatory responses in renal epithelial cells (141). In a mouse model of ischemia-reperfusion injury, MGF (10, 30 or 100 mg/kg) protects renal tubular cells by reducing inflammation and apoptosis through activation of the adenosine-CD73 pathway (141). Similarly, in D(+)-galactosamine-induced nephrotoxicity, MGF exhibits antioxidant properties by inhibiting inducible nitric oxide synthase and downregulating NF-κB signaling, leading to improved renal function and histology (142).

MGF (20, 50 or 100 mg/kg) also protects against sepsis-induced acute kidney injury in an LPS-induced sepsis mouse model by preserving the endothelial glycocalyx component syndecan-1, reducing ROS and MDA production, enhancing tight junction integrity, and limiting vascular leakage and inflammation (142).

Diabetic nephropathy is a common microvascular complication of type 1 and type 2 diabetes (143). MGF (50 mg/kg) mitigates renal injury in streptozotocin-induced diabetic mice by modulating hexokinase II-mitochondrial interactions and inhibiting NADPH oxidase 4, thereby reducing oxidative stress (144). Moreover, MGF (12.5, 25 or 50 mg/kg) enhances autophagic flux via AMPK-mTOR signaling, delaying the progression of diabetic nephropathy (145).

MGF also attenuates renal interstitial fibrosis, a hallmark of diabetic kidney disease. In streptozotocin-induced diabetic mice, MGF (15, 30 or 60 mg/kg) suppresses inflammation and oxidative stress by modulating the PTEN/PI3K/Akt pathway,

leading to reduced expression of fibrotic markers such as collagen I, fibronectin and α-SMA (34).

Cardiovascular benefits. MGF has lipid-lowering, antioxidant and anti-inflammatory properties that contribute to cardiovascular protection. A randomized, double-blind clinical trial demonstrated that MGF supplementation can markedly decrease serum triglyceride and free fatty acid levels in overweight individuals with hyperlipidemia, highlighting its clinical potential (146).

In high-fat diet-induced hyperlipidemic rats, MGF (50, 100 or 150 mg/kg, orally administered for 6 weeks) has been shown to activate hepatic AMPK, resulting in improved lipid metabolism and reduced circulating free fatty acids (147). Furthermore, in high-fat diet-induced hyperlipidemic rats, MGF-loaded N-succinyl-chitosan-grafted alginate nanoparticles enhance therapeutic efficacy by increasing the hepatic expression of PPARα, carnitine palmitoyltransferase I and FAT/CD36, while suppressing lipogenic genes, such as SREBP-1c, ACC, DGAT2 and MTP (148).

In rat models of diabetic cardiomyopathy, MGF (20 mg/kg for 16 weeks) has been shown to notably decrease ROS production and AGE accumulation, partly through the inhibition of NF-κB signaling. This preserves myocardial function and delays cardiomyopathic remodeling (149).

Dermatological benefits and wound healing. In murine models of contact dermatitis induced by oxazolone, MGF suppresses TNF-α-stimulated macrophage activation and inhibits NF-κB pathway activation, resulting in decreased production of inflammatory mediators and oxidative stress markers (150). Its C-glucosylxanthone structure contributes to its efficacy as a skin-targeted anti-inflammatory compound.

Oxygenated anthraquinone derivatives of MGF, including isobavachalcone, gartanin and glucosylated xanthone, have demonstrated antimicrobial activity against acne-causing bacteria such as *Staphylococcus epidermidis*. These compounds also inhibit inflammatory pathways, including PPAR and prostaglandin cascades, suggesting their therapeutic potential in both acne and inflammatory dermatoses (151).

In wound healing, MGF-loaded hydrogels or liposomes (10, 20 and 40 μM) have been reported to accelerate flap regeneration in rat models of skin injury. This treatment may inhibit oxidative stress-induced apoptosis, increase the Bcl-2/Bax ratio and decrease cleaved caspase-3 expression (29). MGF also enhances PPARγ expression and suppresses NF-κB activity, further promoting anti-inflammatory and cytoprotective effects in dermal tissues (29).

Antimicrobial actions. MGF possesses broad-spectrum antimicrobial activity against both fungal and bacterial pathogens, including strains involved in drug resistance and biofilm formation. Purified MGF has MIC values ranging from 1.95 to 62.5 μg/ml for fungi and from 1.95 to 31.25 μg/ml for bacteria, with a time-kill study confirming its bactericidal and fungicidal efficacy (1). Extracts from mango leaves, which are rich in MGF, have shown inhibitory activity against gram-positive bacteria (*Staphylococcus aureus, Bacillus subtilis, Streptococcus pneumoniae*) and gram-negative pathogens (*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Shigella* spp.) (114,152,153). Furthermore, MGF derivatives have demonstrated efficacy against *K. pneumoniae* by disrupting biofilms, impairing virulence factor expression and increasing antibiotic susceptibility (154).

In a murine periodontitis model, oral administration of MGF (50 mg/kg for 8 weeks) has been reported to suppress *Porphyromonas gingivalis*-induced alveolar bone loss, downregulate TNF-α production and inhibit NF-κB and JAK1/STAT1/3 phosphorylation in the gingival epithelium (155). In *Caenorhabditis elegans* models infected with *P. aeruginosa*, MGF compounds regulate quorum sensing pathways and reduce bacterial virulence in both dauer larvae and adult stages, further supporting their anti-infective potential (156).

Translational aspects

PK, and absorption, distribution, metabolism and excretion overview. Orally administered MGF shows low aqueous solubility and limited intestinal permeability, resulting in poor systemic exposure at conventional doses (157-160). After uptake in the proximal small intestine, extensive first-pass metabolism and gut microbiota-mediated deglycosylation (yielding norathyriol and downstream conjugates) further reduce parent drug levels (21,160-162). The tissue distribution in rodents indicates measurable concentrations in the liver, kidney and lung with delayed plasma peaks, whereas brain penetration appears limited under standard conditions (107,163). These properties underscore the need to link PD readouts to exposures achievable with clinically realistic regimens, and to report unbound concentrations where possible.

Key barriers to translation. The main obstacles include: i) Low solubility and permeability [constraining C_{max}/area under the curve (AUC) after oral dosing] ((164-166), ii) metabolic lability and conjugation that curtails exposure to the parent compound MGF (21,167,168), iii) variability introduced by microbiome-dependent deglycosylation (165,169), and iv) inconsistent reporting of dose-exposure relationships across preclinical studies (170,171). These issues complicate cross-study comparisons and dose selection for human studies.

Delivery/formulation strategies. Multiple approaches have improved exposure in preclinical systems, including nanostructured lipid carriers, polymeric and chitosan-based nanogels, phospholipid complexes (2,172,173), and targeted nanoparticles designed to enhance intestinal uptake or lymphatic transport and to stabilize MGF against rapid metabolism (172,174-176). Early structure-led strategies (for example, monosodium salts/derivatives) have also reported increased apparent potency or improved tissue delivery in disease models (166,177,178). In the future, head-to-head comparisons using common dose units, matched controls and standardized PK endpoints (AUC, bioavailability, tissue-plasma ratios) will be essential for identifying clinically scalable options (170,179).

Safety/toxicity signals. A nonclinical study has previously reported favorable tolerability at pharmacologically relevant exposures, with adverse findings emerging at substantially higher doses (180). However, several safety uncertainties remain: i) Limited chronic toxicity datasets for purified MGF (as opposed to plant extracts) (108); ii) sparse evaluation of drug-drug interaction risks given pathway cross-talk (for example, with PI3K/Akt, AMPK or NF-κB modulators) (181-183); and iii) incomplete reporting of standardized

laboratory safety assessments and histopathology in a number of efficacy-focused studies (184). Extract-based toxicology (such as that assessing mango leaf preparations) should not be overextrapolated to the purified compound without compositional bridging.

Clinical evidence and next steps. Early human data are limited, heterogeneous (often extract-based) and not yet definitive for purified MGF. Small studies suggest metabolic or performance signals in select contexts, but they seldom include rigorous PK/PD integration, dose-ranging or long-term safety monitoring (139,166,185). The next steps include: i) Phase I studies with single- and multiple-ascending doses of purified MGF and exposure-enhancing formulations; ii) assessment of the effects of food intake on MGF PKs and bioequivalence for leading delivery platforms, including nanostructured lipid carriers, phospholipid complexes and chitosan-based nanoparticles; iii) PK/PD modeling anchored to validated mechanistic biomarkers (such as p65 nuclear translocation, Nrf2 target induction) and disease-relevant functional endpoints; and iv) randomized, controlled phase II trials using clinically translatable doses and standardized safety surveillance.

7. Evidence gaps

Preclinical findings regarding MGF are promising; however, the evidence base shows important gaps that limit translation. Notably, the results vary across cell lines and animal strains, and several mechanisms that are frequently cited (for example, NF-κB or MMP-9 modulation, G_2/M arrest and AMPK activation) appear to be highly context dependent, with inconsistent replication under different stimuli or dosing conditions (4,13,117,124,186,187). A number of studies rely on single models, small or unreported sample sizes, and pretreatment designs rather than therapeutic intervention after disease onset, which reduces external validity (117,188). PK constraints remain under-characterized, including oral exposure at clinically relevant doses, the relative contribution of metabolites such as norathyriol, tissue penetration in target organs and the variability introduced by different formulations (21,159,162). Material standardization is uneven, with frequent use of extracts or nanoparticles without full reporting of purity, content uniformity or release profiles, making cross-study comparisons difficult and weakening conclusions regarding the active entity (161,181). Mechanistic claims often rely on surrogate protein readouts, such as changes in pathway marker proteins (for example, NF-κB p65 nuclear translocation or AMPK phosphorylation), without orthogonal validation or causal rescue experiments, and dose-response and time-course data are incomplete for several indications (13,186,189). Comparative efficacy vs. standard of care is rarely tested, and combination studies seldom include PK or PD interaction assessments. Furthermore, safety reporting is inconsistent, with limited long-term toxicity, immunomodulatory risk and drug-drug interaction data, and with few studies that stratify patients by sex or age (184,185,190). Human evidence remains sparse, with a lack of standardized endpoints, validated translational biomarkers, and prospective trials that incorporate randomization, blinding and predefined primary outcomes (184,191). Addressing these gaps will require well-powered, rigorously controlled studies that integrate exposure-response relationships, prespecified functional end points and reproducible materials, together with head-to-head and combination designs that reflect real clinical use.

8. Conclusion and future prospects

MGF, a natural C-glucosylxanthone, has broad pharmacological effects, including antidiabetic, anticancer, anti-inflammatory, antioxidant and neuroprotective activities, with low toxicity and good biocompatibility, making it a promising therapeutic candidate.

Notably, the clinical use of MGF is limited by poor solubility and low oral bioavailability. Advances such as nanogels, lipid carriers and phospholipid complexes have improved absorption and stability (23,192,193). Structural modifications and derivatives such as monosodium MGF also enhance efficacy, partly via the modulation of oxidative stress pathways (194). Future work should focus on optimized delivery systems, rational structural designs, and rigorous clinical trials to confirm safety and dosing (170). Building on the growing preclinical base, next-step studies should prioritize clinically scalable formulations, such as polymeric or lipid nanocarriers, self-microemulsifying drug delivery systems (forming fine oil-in-water microemulsions in the gastrointestinal tract) and solid lipid nanoparticles (lipid-based colloidal carriers), cyclodextrin inclusions and phospholipid complexes, supported by standardized chemistry, manufacturing and controls characterization and direct PK comparisons with conventional extracts (195,196). This approach is justified by consistent improvements in solubility, uptake and systemic exposure demonstrated in nanodelivery research, as well as by early human PK findings that MGF monosodium salt substantially increases bioavailability compared with the parent compound (166,195). These PK advantages make dose finding and scheduling practically feasible in phase I/II trials. To ensure translational credibility, forthcoming clinical studies should integrate exposure-response analysis and biomarker verification, quantifying indicators such as Nrf2 target induction, NF-κB suppression, and oxidative or DNA damage markers in accessible tissues or circulating immune cells. Consistent with the development principles proposed by previous scholars, these strategies effectively integrate formulation, dosage and PDs into a coherent translational framework (166,195,197).

Deeper investigations into signaling pathways, including the NF-κB, Nrf2 and AMPK pathways, will further clarify the underlying mechanisms of MGF and support its clinical translation (184,198,199). Mechanistically enriched studies should define, for each indication discussed in this review (for example, cancer, inflammatory disorders and liver disease), the predominant signaling axis, distinguishing between redox-regulated Nrf2 signaling, inflammatory NF-κB activation and metabolic AMPK modulation, as summarized in reviews of the molecular mechanisms of MGF in cancer/inflammation and liver disease, including the NF-κB, Nrf2 and AMPK pathways (198,199). Such resolution will guide rational combinations, for example, pairing MGF with radiotherapy or cytotoxic drugs where redox priming or DNA-repair interference is desired or combining with immunomodulators where NF-κB/innate signaling is dominant (200-202). This

pathway-specific combination strategy, which pairs MGF with radiotherapy or cytotoxic agents for redox priming or DNA-repair interference, or with immunomodulators that act on the dominant NF-κB/innate signaling pathway, is inspired by prior 'redox-directed' therapeutic approaches, and is further supported by MGF studies showing Nrf2-centred and AMPK-linked anti-inflammatory effects (75,120). Together, a biomarker-driven, pathway-specific strategy may result in MGF progressing from a broadly-acting pleiotropic lead compound to a precisely targeted therapeutic candidate for defined patient subgroups.

In conclusion, MGF represents a compelling natural compound with substantial therapeutic potential. With continued advancements in formulation science, structural modification and clinical validation, MGF may emerge as a clinically valuable agent in modern pharmacotherapy. Overcoming its current limitations through interdisciplinary innovation will be essential to determining its full potential in the prevention and treatment of metabolic, inflammatory, infectious, degenerative and neoplastic diseases.

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Authors' contributions

YD, QH and MT contributed equally to the conception and design of the review, performed the literature search, screened the articles, extracted and synthesized the data, and drafted the initial manuscript. SZ and ZW participated in the literature search and data extraction, performed extensive analysis and interpretation of the data, summarized and organized the extracted findings, and assisted with figure and table preparation. CJ contributed to the organization and interpretation of the extracted data, and critically revised the manuscript for important intellectual content. ZL and SS conceived and supervised the study, resolved discrepancies in study selection and data interpretation, provided critical revision of the manuscript, and are the corresponding authors. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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