Pharmacology, Toxicity, Bioavailability, and Formulation of Magnolol: An Update

Yiping Lin1, Yuke Li1, Yuanlian Zeng1, Bin Tian1, Xiaolan Qu1, Qianghua Yuan2 and Ying Song2*

1School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, China, 2Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China

Magnolol (MG) is one of the primary active components of Magnoliae officinalis cortex, which has been widely used in traditional Chinese and Japanese herbal medicine and possesses a wide range of pharmacological activities. In recent years, attention has been drawn to this component due to its potential as an anti-inflammatory and antitumor drug. To summarize the new biological and pharmacological data on MG, we screened the literature from January 2011 to October 2020. In this review, we provide an actualization of already known anti-inflammatory, cardiovascular protection, antiangiogenesis, antidiabetes, hypoglycemic, antioxidation, neuroprotection, gastrointestinal protection, and antibacterial activities of MG. Besides, results from studies on antitumor activity are presented. We also summarized the molecular mechanisms, toxicity, bioavailability, and formulations of MG. Therefore, we provide a valid cognition of MG.

Keywords: magnolol, pharmacology, toxicity, bioavailability, formulation

INTRODUCTION

Magnoliae officinalis cortex, which was first recorded in “Shennong Herbal Classic” (Qin and Han Dynasty, around 221 B.C. to 220 A.D.), is the dry bark, root bark, and branch bark of Magnolia officinalis Rehd. et Wils. or Magnolia officinalis Rehd. et Wils. var. biloba Rehd. et Wils. In traditional medicine, Magnoliae officinalis cortex mainly acts to dry dampness and disperse phlegm, lower Qi, and eliminate fullness. Clinically, it is commonly used to treat asthma, constipation, edema, abdominal distension, malaria, and other diseases by combining different traditional Chinese medicines. For example, the Da Houpo Pill is used to treat abdominal distension (Song Ji Zonglu). The Xiaochengqi decoction is used for the treatment of tidal fever, constipation, and abdominal pain (Treatise on Febrile Diseases). The Banxia Houpo decoction has therapeutic effects on chronic pharyngitis, chronic bronchitis, and esophageal fistula (Synopsis of the Golden Chamber). Recent studies have shown that Magnoliae officinalis cortex has multiple pharmacological activities on the nervous system (Lee et al., 2009; Lee et al., 2013), digestive system (Kim HJ et al., 2018), inflammation (Kim JY et al., 2018), and cancer (Kim et al., 2020). And, its neolignan compounds include MG (a), honokiol (b), 4-methylhonokiol (c), and (R)-8,9-dihydroxydihydromagnolol (d) (Rempel et al., 2013) (Figure 1).

The isomers MG (5,5′-diallyl-2,2′-dihydroxybiphenyl) and honokiol (3,5′-diallyl-4,2′-dihydroxybiphenyl) are biphenyl-type neolignans. They have been recognized as the principal active components of magnolia bark extract, usually accounted for 1–10% of dry bark, depending on the Magnolia species (officinalis or obovata) and extraction method (Sarrica et al., 2018; Oufensou et al., 2019; Lata et al., 2020). Talarek et al. reviewed the chemistry, bioavailability, and
neuroprotective activity of honokiol (Talarek et al., 2017). Woodbury et al. concluded that honokiol has therapeutic potential for anxiety, pain, cerebrovascular damage, epilepsy, and cognitive disorders (Woodbury et al., 2013). Ong et al. and Banik et al. summarized the antitumor mechanisms of honokiol, including the regulation of MAPK, NF-κB, HIF-α, PI3K/Akt/ERK/mTOR, Wnt/β-catenin epidermal growth factor receptor (EGFR), signal transduction and activator of transcription (STAT), and notch signaling pathways (Rauf et al., 2018; Banik et al., 2019; Ong et al., 2020). The metabolism, bioavailability, and pharmacological of honokiol were reviewed by Ong et al. (Ong et al., 2020). Additionally, the antiangiogenesis (Fried and Arbiser, 2009), antioxidation and antibacterial activities (Shen et al., 2010), and molecular mechanisms of honokiol have been summarized.

MG was first isolated from magnolia bark by Japanese scientist Sugii in 1930 and was first synthesized by Swedish scientist H. Erdtmann and J. Runeberg with the p-allylphenol as raw material (Erdtman and Runeberg, 1957). However, the yield was only 25%, and it was challenging to separate and purify. Zhang et al. used 2,2'-biphenol and 1-bromobutane as raw materials to prepare MG (Zhang and Sun, 2011). The reaction process was simple and effective with mild conditions as well as high product purity (>98%), and the yield was increased to 60.2%.

Numerous studies showed that MG possesses extensive biological activities, such as anti-inflammatory (Wei et al., 2014; Lin et al., 2015; Zhang L et al., 2018; Chen H et al., 2019), antitumor (McKeown et al., 2014; Zhang FH et al., 2017; Shen et al., 2017), cardiovascular protection (Liang CJ et al., 2014; Chang et al., 2018), antiangiogenesis (Kim GD et al., 2013; Chen et al., 2013), hypoglycemic (Pulvirenti et al., 2017; Suh et al., 2017; Parry et al., 2018), antioxidation (Baschieri et al., 2017), neuroprotection (Matsui et al., 2016; Kou et al., 2017; Xie et al., 2020), gastrointestinal protection (Chao et al., 2018), and antibacterial activities (Dong et al., 2017) (Table 1).

The studies about MG’s toxicity have been done, suggesting that MG has no genotoxicity and mutagenic toxicity (Saito et al., 2006). As a phenolic polyhydroxy compound, MG’s poor aqueous solubility and low oral bioavailability limit its clinical use. Therefore, various formulations such as liposomes (Shen et al., 2016), solid dispersions (Stefanache et al., 2017a), emulsions (Sheng et al., 2014), and nanoparticles (Wang et al., 2011) have been developed to ameliorate the water solubility and bioavailability of it.

In this review, the pharmacological activities and molecular mechanisms of MG are summarized and updated. Its toxicities, bioavailability, and formulations are reviewed, to identify the benefit of further studies on MG and to find the best method to improve its bioavailability.

MATERIALS AND METHODS

This article collected literature studies related to pharmacology, toxicity, bioavailability, and formulation of MG published from January 2011 to October 2020. All related information about MG was collected by using the keyword of magnolol from globally recognized scientific search engines and databases, such as Web of Science, Springer, ScienceDirect, Elsevier, Google Scholar, and Chinese National Knowledge Infrastructure (CNKI). The source information of Magnoliae officinalis cortex was provided by the 2020 edition of Chinese Pharmacopoeia. The pharmacological activities, molecular mechanisms, toxicity, bioavailability, and formulations of MG are summarized, and the deficiencies of current studies are discussed.

PHARMACOLOGICAL ACTIVITY

Anti-Inflammatory Activity

Inflammation is generally characterized by overexpression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2
| Effect                                      | Model/targets                                      | Dosage          | Result/mechanism/method                                                                 | References                  |
|--------------------------------------------|---------------------------------------------------|-----------------|----------------------------------------------------------------------------------------|----------------------------|
| Anti-inflammatory activity                  | LPS-induced RAW 264.7 cells                       | In vitro: 5, 10, and 15 μM | Inhibited iNOS and COX-2 expression and NF-κB activation via regulating PI3K/Akt and MAPK signaling pathways | Lai et al. (2011)           |
|                                            | MTT-induced U937 cells                            | In vitro: 10–100 μM | Inhibited NO production and expression of p-IκBα, p-P65, IL-1β, and TNF-α. Downregulated phospho-JNK (p-JNK) and p-p38 | Chen H et al. (2018)        |
|                                            | CS7BL/6 mice                                      | DXM (5 mg kg⁻¹) increased colon length and relieved colon pathological injuries | Inhibited iNOS and COX-2 expression and NF-κB activation | Lai et al. (2011)           |
|                                            | DSS-induced male CS7BL/6 mice                    | In vivo: 25, 50, and 100 mg kg⁻¹ (gavage) | Inhibited the expression of TNF-α, IL-1β, and IL-12 by regulating NF-κB and PPAR-γ pathways | Shen P et al. (2018)        |
|                                            | RAW 264.7 cells                                   | In vitro: 5, 10, and 20 μM | Activated p38 MAPK and Nrf2/HO-1 cascade and promoted ROS production | Lu et al. (2015a)           |
|                                            | LPS-induced mammary tissues                       | In vitro: 12.5, 25, 50, 100, and 200 μg ml⁻¹ | Reduced phosphorylation of p65, p38, IκBα, JNK, and ERK. Inhibited TLR4 expression and production of TNF-α, IL-1β, and IL-6 | Wei et al. (2014)           |
|                                            | LPS-induced mouse uterine epithelial cells       | In vitro: 12.5, 25, and 50 μg ml⁻¹ | Reduced phosphorylation of p65, p38, IκBα, JNK, and ERK. Attenuated mice mastitis tissue damage and MPO activity | Luo et al. (2013)           |
|                                            | LPS-induced BALB/c mice                           | In vitro: 5, 10, and 20 mg kg⁻¹ (i.p. injection) | Increased the expression of PPAR-γ. Altered pneumonedia, neutrophil infiltration, ROS production, and proinflammatory factor level | Wei et al. (2014)           |
|                                            | LPS-induced SD rats                               | In vivo: 10 and 20 mg kg⁻¹ (i.p. injection) | Attenuated paw swelling and serum cytokine levels | Lin et al. (2015)           |
|                                            | LPS-induced RAW 264.7 cells                       | In vitro: 15, 30, and 60 μg ml⁻¹ | Downregulated TLR4 expression, NF-κB expression and proinflammatory cytokine activation. Dose-dependently (30–60 μg ml⁻¹) inhibited the IL-1β, IL-6, and TNF-α expression. Suppressed IκBα degradation and phosphorylation of JNK, ERK, and p38 | Fu et al. (2013)            |
|                                            | Human FLS                                         | In vitro: 2.5–25 μg ml⁻¹ | Suppressed cytokine expression and MAPKs and IκB/InB kinetics/NF-κB pathway in a dose-dependent manner | Wang et al. (2012)          |
|                                            | Female Lewis rats                                 | In vivo: 100 mg kg⁻¹ (i.p. injection) | Decreased the expression of inflammatory cytokines and inhibited HIF-1α/VEGF pathway | Yang et al. (2016)          |
|                                            | C57BL/6J mice                                     | In vivo: 10, 25, and 50 mg kg⁻¹ (i.p.) | Decreased the production of inflammatory cytokines and ROS and the expression of TLR2. Prevented p38, ERK, JNK, and NF-κB phosphorylation | Zheng P et al. (2017) |
|                                            | RAW 264.7 cells                                   | In vivo: 25, 50, and 100 μM | Downregulated TLR4 expression, NF-κB expression and proinflammatory cytokine activation. Dose-dependently (30–60 μg ml⁻¹) inhibited the IL-1β, IL-6, and TNF-α expression. Suppressed IκBα degradation and phosphorylation of JNK, ERK, and p38 | Fu et al. (2013)            |
|                                            | A549 cells                                        | In vitro: 6.25, 12.5, 25, 50, 100, and 200 μM | Downregulated TLR4 expression, NF-κB expression and proinflammatory cytokine activation. Dose-dependently (30–60 μg ml⁻¹) inhibited the IL-1β, IL-6, and TNF-α expression. Suppressed IκBα degradation and phosphorylation of JNK, ERK, and p38 | Fu et al. (2013)            |
|                                            | Human aortic endothelial cells                    | In vitro: 5 μM | Suppressed NF-κB and MAPK pathway activation by decreasing the upregulation of intercellular adhesion molecule-1 and phosphorylation of NF-κB, p38, ERK1/2, and SAPK/JNK | Liang CJ et al. (2014) |
|                                            | Antitumor activity                                | In vitro: 20–160 μM | Suppressed the growth, migration, and invasion of CCA cells by regulating cell cycle and expression of cyclin D1 protein, PON1, Ki67, MMP-2, MMP-7, and MMP-9 | Zhang FH et al. (2017) |
|                                            | Cholangiocarcinoma (CCA) cells                    | In vitro: 20–160 μM | Suppressed the growth, migration, and invasion of CCA cells by regulating cell cycle and expression of cyclin D1 protein, PON1, Ki67, MMP-2, MMP-7, and MMP-9 | Zhang FH et al. (2017) |
|                                            | BALB/c nude mice                                  | In vivo: 40 mg kg⁻¹ (i.p. injection) | Suppressed the growth, migration, and invasion of CCA cells by regulating cell cycle and expression of cyclin D1 protein, PON1, Ki67, MMP-2, MMP-7, and MMP-9 | Zhang FH et al. (2017) |
TABLE 1  |  (Continued) Modern pharmacological studies of MG.

| Effect | Model/targets | Positive Dosage | Result/mechanism/method | References |
|--------|---------------|-----------------|--------------------------|------------|
| SKOV3 human ovarian and BT474 human breast cancer cells | In vitro: 6.25, 12.5, 25, 50, 100, and 200 μM | Inhibited the overexpression of HER2 gene by decreasing PI3K/Akt and inhibiting the expression of VEGF, MMP2, and cyclin D1 | Chuang et al. (2011) |
| Human non-small-cell lung cancer cell lines | In vitro: 1, 5, 10, and 20 μM | Inhibited NCI-1299 and A549 cells (IC50 = 5 μM) by blocking cell cycle, destroying cellular microtubule tissue, reducing Akt/mTOR pathway, and promoting autophagy | Shen et al. (2017) |
| Male nude mice | In vivo: 25 mg kg⁻¹ (i.p. injection) | Regulated the Wnt/β-catenin signaling pathway and β-catenin/T-cell factor-targeted downstream genes. Inhibited tumor cell invasion and motility | Kang et al. (2012) |
| Human HCT116, SW480, and HEK293 cells | In vitro: 1, 5, 10, and 20 μM | Inhibited NCI-1299 and A549 cells (IC50 equals 5 μM) by blocking cell cycle, destroying cellular microtubule tissue, reducing Akt/mTOR pathway, and promoting autophagy | Shen et al. (2017) |
| Female nude mice | In vivo: 5 mg kg⁻¹ (i.p. injection) | Regulated the mitochondria and PI3K/Akt-dependent pathways, Bax/Bcl-2 ratio, caspase-3 activation, PI3K/Akt inhibition, and cell apoptosis and induced autophagy | Rasul et al. (2012) |
| Human gastric adenocarcinoma SGC-7901 cells | In vitro: 10, 30, 50, 100, 200, and 300 μM | Altered levels of p53, p21, cyclin D1, CDC25A, and Cdk2, blocked cell cycle progression, and induced mitochondria-related apoptosis | Li et al. (2015) |
| GBC cell lines | In vitro: 10, 20, and 30 μM | Regulated the Wnt/β-catenin signaling pathway and β-catenin/T-cell factor-targeted downstream genes. Inhibited tumor cell invasion and motility | Kang et al. (2012) |
| BALB/c homozygous nude mice | In vivo: 5, 10, 20, 30, and 50 mg kg⁻¹ (i.p. injected) | Suppressed the tumor growth and CDC2 expression and increased caspase-3 activation | Li et al. (2015) |
| Human DU145 and PC3 prostate adenocarcinoma cells | In vitro: 40 and 80 μM | Modulated the cell cycle process of PC3 and DU145 cells. Downregulated the expression of A, B1, D1, E, CDK2, CDK4, and pRBp130. And increased pRBp107 protein expression level | McKeown et al. (2014) |
| Human PC3 cells and LNCaP cells | In vitro: 1, 5, 10, 25, and 50 μM | Affected the expression of insulin-like growth factor-1 (IGF-1), and associated proteins including IGF-binding protein-5 (IGFBP-5), IGFBP-3, IGF-1 receptor, and IGFBP-4 | McKeown and Hurta (2014) |
| HCT-116 cells | In vitro: 1, 5, 10, 25, and 50 μM | Promoted cell apoptosis and inhibited migration and invasion of HCT-116 cells by decreasing Bcl-2 expression, increasing the expression of p53 and Bax, and activating AMPK and caspase-3 | Park et al. (2012) |
| Human lung carcinoma A549 cells | In vitro: 1, 5, 10, 50, and 100 μM | Upregulated the release of lactate dehydrogenase, facilitated caspase-3 activation and poly-(ADP)-ribose polymerases cleavage, and reduced NF-κB/RelA expression level. Inhibited A549 cells growth | Seo et al. (2011) |
| Nude immunodeficient mice | In vitro: 40 mg kg⁻¹ (i.p. injection) | Markedly inhibited the growth of MDA-MB-231 and MCF-7 tumors and MMP-9 level | Liu et al. (2013) |
| Human breast cancer cell lines and nontumorigenic MCF-10A mammary epithelial cells WM1366 (NRAS-mutated) and WM164 (BRAF-mutated) cell lines | In vitro: 10, 20, 30, 40, 50, and 60 μM | Prevented breast cancer cell invasion via inhibiting NF-κB pathway and MMP-9 expression | Liu et al. (2013) |
| In vitro: 10, 20, and 30 μM | Inhibited BRAF/MEK and induced cell death by significantly downregulating PI3K/Akt pathway | Emran et al. (2019) |

(Continued on following page)
| Effect | Model/targets | Positive | Dosage | Result/mechanism/method | References |
|--------|---------------|----------|--------|-------------------------|------------|
| PC3 cells | In vitro: MG 80 μM | Decreased the protein expression of ornithine decarboxylase, R2 subunit of ribonucleotide reductase, p-p38, JNK-1/2, PI3Kp85, p-PI3Kp85, p-Akt, and IκBα, and increased the protein expressions of p-JNK-1, and p-p38, p-PI3Kp85, p-ATK, and IκBα. | McKeown and Hurta (2015) |
| MCF7 cells | In vitro: 20 μM | Increased the expression of the tumor suppressor miRNA | Hagiwara et al. (2015) |
| Antiangiogenic activity | T24 and HUVEC cells | In vitro: 1, 5, and 10 μM | Inhibited HIF-1α/VEGF-dependent pathways, H2O2 formation, and VEGF excretion | Chen et al. (2013) |
| Female athymic nude mice (BALB/c) | In vivo: 2, 5, and 10 mg kg⁻¹ (i.p. injection) | Decreased angiogenesis, HIF-1α, VEGF, and carbonic anhydrase-IX expression | Chen et al. (2013) |
| MES/EB-derived endothelial-like cells | In vitro: 5, 6.25, 10, 12.5, 20, 25, 50, and 100 μM | Inhibited PECAM transcription, translational expression, and MAPKs/PI3K/AKT/mTOR signaling pathway activation | Kim GD et al. (2013) |
| HUVEC cells | In vitro: 10 and 40 μM | Suppressed proliferation, ERK1/2 activity, gelatinase activity, and ROS production and promoted HO-1 level | Kuk et al. (2017) |
| Male NMRI mice | In vivo: 20 μg/ear (transdermally administered) | Inhibited venous remodeling process and decreased endothelial proliferation and MMP-2 abundance. Amplified HO-1-mediated resistance of endothelial cells to ROS-mediated proliferative stimuli | Kuk et al. (2017) |
| Cardiovascular protection | Right coronary arteries from hearts of pigs | In vitro: 1, 3, 10, 30, and 100 μM | Relaxed the coronary artery with an IC₅₀ value of 5.78 μM and dose-dependently inhibited iNOS and COX-2 protein expression | Kuo et al. (2011) |
| Human aortic smooth muscle cells (HASMCs) | In vitro: 10, 20, and 30 μM | Inhibited VSMC migration by suppressing cytoskeletal remodeling and neointima formation | Karki et al. (2013b) |
| Male SD rats | In vivo: 1, 10, and 100 μg kg⁻¹ (intravenous (i.v.) injection) | Reduced the proportion of myocardial ischemic necrosis area. At a concentration of 10 μg kg⁻¹, MG reduced ventricular fibrillation and animal mortality | Karki et al. (2013b) |
| Male SD rats | Ticlopidine 100 mg kg⁻¹ decreased intimal area as well as intimal/medial ratio and increased luminal area | In vivo: 50 and 100 mg kg⁻¹ (gavage) | Attenuated neointima formation, intimal area, and intimal/medial ratio and increased luminal area | Karki et al. (2013a) |
| Male SD rats | In vivo: 10 mg kg⁻¹ (i.p.) | Regulated ACE/Ang II/AT-1R cascade and ACE2. Attenuated the overexpressions of ET-1 and ETA receptor by suppressing Akt/ERK1/2/GSK3β-catenin pathway | Chang et al. (2018) |
| Male spontaneous hypertensive rats | In vivo: 100 mg kg⁻¹ (gavage) | Decreased blood pressure through upregulating PPAR-γ, Akt, and eNOS activity, downregulating TRB3, and improving vascular insulin resistance | Liang X et al. (2014) |
| VSMCs | In vitro: 5, 10, and 20 μM | Suppressed VSMC proliferation and DNA synthesis by inhibiting the expressions of cyclin D1/E, cyclin-dependent kinase 2 and 4, ROS production, and activation of renin–angiotensin system, MEK, and ERK1/2 | Wu et al. (2015) |
| Hypoglycemic activity | 3T3-L1 and HIB1 B preadipocytes | In vitro: 1, 5, 10, and 20 μM | Enhanced adipocyte differentiation and expression of brown adipocyte-specific marker genes and proteins. Promoted browning of 3T3-L1 fat cells via activating AMPK, PPAR, and PKA pathways | Parray et al. (2018) |
| Effect                          | Model/targets                                      | Dosage       | Result/mechanism/method                                                                 | References         |
|-------------------------------|---------------------------------------------------|--------------|----------------------------------------------------------------------------------------|-------------------|
| Gastrointestinal protection   | Castor oil-induced male Kunming mice              | Saline (20 mg kg\(^{-1}\)) relieved diarrhea     | In vivo: 25, 50, and 100 mg kg\(^{-1}\) (gavage)                                         | Pang et al. (2013) |
|                               | ETEC-induced diarrhea male Kunming mice           | In vivo: 100, 300, and 500 mg kg\(^{-1}\) (gavage) | Inhibited diarrhea in mice significantly. Reduced neostigmine-induced small intestinal transit, and increased activity of CAT, SOD, and GSH-Px | Deng et al. (2015) |
|                               | Colonic smooth muscle cells from male SD rats      | In vivo: 1, 3, 10, 30, and 100 μM                  | Regulated the release of IP3-Ca\(^{2+}\) storage, suppressed SK channel, and facilitated the opening of BK\(α\)1 and BK\(β\)3 channels and the closing of BK\(β\)4 channel | Zhang et al. (2013) |
|                               | Kunming mice                                       | In vivo: 5, 10, 15, 20, 25, 30, and 40 mg kg\(^{-1}\) (gavage) | It had significant inhibitory effects on the small intestine charcoal propulsion induced by rhubarb, diarrhea induced by Senna leaf, and gastric emptying inhibition induced by atropine | Zeng et al. (2015) |
| Neuroprotection               | CMS-induced male Kunming mice                     | Fluoxetine (20 mg kg\(^{-1}\)) increased sucrose preference | In vivo: 20 and 40 mg kg\(^{-1}\) (gavage)                                               | Cheng et al. (2018) |
|                               | CMS-induced male ICR mice                         | Fluoxetine (20 mg kg\(^{-1}\)) decreased immobility duration and serum CORT levels | In vivo: 50 and 100 mg kg\(^{-1}\) (gavage)                                             | Bai et al. (2018)  |
|                               | Olfactory bulbectomy male ddY mice                | Fluoxetine (20 mg kg\(^{-1}\)) ameliorated the depression-like behavior | In vivo: 50 and 100 mg kg\(^{-1}\) (gavage)                                             | Matsui et al. (2016) |
|                               | Male SD rats subjected to unpredictable CMS (UCMS) | Fluoxetine hydrochloride (20 mg kg\(^{-1}\)) reversed depression-like behavior | In vivo: 20 and 40 mg kg\(^{-1}\) (gavage)                                             | Li LF et al. (2013) |
|                               | UCMS-induced male SD rats                         | Fluoxetine hydrochloride (20 mg kg\(^{-1}\)) increased the levels of 5-hydroxyindoleacetic acid and 5-HT | In vivo: 20 and 40 mg kg\(^{-1}\) (gavage)                                             | Li et al. (2012) |
|                               | Male Kunming strain mice                          | Diazepam (2 mg kg\(^{-1}\)) prolonged the latency of epileptic seizures and increased the latency of myoclonic jerks | In vivo: 20, 40, and 80 mg kg\(^{-1}\) (i.p. injection)                                 | Chen CR et al. (2011) |
|                               | BV2 cells                                          | In vitro: 2.5, 5, 10, 50, 100, 150, and 200 μM   | Increased Aβ phagocytosis and degradation and ApoE level by activating the target gene liver-X-receptor of PPAR-γ (Continued on following page) | Xie et al. (2020)  |

(Continued on following page)
TABLE 1 | (Continued) Modern pharmacological studies of MG.

| Effect Model/targets | Positive Dosage | Result/mechanism/method | References |
|----------------------|-----------------|--------------------------|------------|
| Male SD rats         | In vivo: 30 mg kg⁻¹ (i.p. injection) | Attenuated brain water content and neurological deficits and restored the BBB by reducing giall cell stimulation, neutrophil infiltration, and production of IL-1β, TNF-α, and MMP-9 | Zhou F et al. (2019) |
| TMT-induced HT22 cells and BV-2 cells | In vitro: 5, 10, 15, and 20 μM | Inhibited neuronal death and microglial activation by suppressing ROS production and activation of JNK, p38 MAPKs, and NF-κB | Kim and Kim (2016) |
| TMT-induced male ICR mice | In vivo: 25 mg kg⁻¹ (i.p. injection) | Reversed a large number of neuronal injury and oxidative stress induced by TMT. Decreased giall cells and iNOS expression and blocked the activation of JNK and P38 | |
| Glutamate-induced neurons | In vitro: 0.1, 1 μM | Attenuated intracellular Ca²⁺ levels, [Ca²⁺]i increase, cytotoxicity, and cell swelling | |
| Male SD rats         | In vivo: 25, 50, 100, 150, and 200 mg kg⁻¹ (i.p.) | The infarct area was significantly reduced by 30.9–37.8%, and neurobehavioral scores were improved | Lee et al. (2012) |
| Stroke male SD rats  | In vivo: 10 and 30 mg kg⁻¹ (i.p. injection) | Reduced cerebral infarction volume and neuronal apoptosis. Increased the expression of transforming growth factor-β1 | Wang CC et al. (2013) |
| LPS-induced microglial cells, brain microvascular endothelial cells | In vitro: 0.01, 0.1, 1, and 10 μM | Attenuated the BBB hyperpermeability in a dose- and time-dependent manner. Reduced levels of iNOS, TNF-α, and IL-1β and p65 subunit expression | Liu et al. (2017) |
| I-R-induced Kunming mice | Eadaravone (3 mg kg⁻¹) reduced about 33% of the white infarct areas and failed to inhibit Evans blue secretion and brain edema | Reduced infarct volume, cerebral water content, and Evans blue secretion | |
| Fluid percussion-induced male SD rats | In vivo: 2 and 2 mg kg⁻¹ (i.v. injection) | Reduced cerebral infarction volume and neuronal apoptosis. Increased the expression of transforming growth factor-β1 | Gong et al. (2012) |
| Neuronal NG108-15 cells | In vitro: 10, 30, and 100 μM | Inhibited the voltage K⁺ and voltage-gated Na⁺ channels with IC₅₀ values of 21 and 15–30 μM | Duan et al. (2015) |
| Male SD rats         | In vivo: 50 mg kg⁻¹ (gavage) | Inhibited CYP1A and 2C significantly | |
| Interaction with CYP450 enzyme | In vitro: 8, 10, 16, 32, and 64 μM | Inhibited human CYP3A4 and rat CYP1A2 with IC₅₀ values of 56.2 and 10 μM, respectively | Duan et al. (2015) |
| Rat/human CYP enzymes (1A2/1A2, 2D/2D6, 3A/3A4, 2E1/2E1, and 2C/2C9) | | | |
| Human CYP2C19 | The IC₅₀ value of 1.37 μM for loratadine | Noncompetitive inhibition of CYP2C19 with IC₅₀ and Ki values of 1.37 μM and 10.0 μM, respectively | Zhang T et al. (2018) |
| SD rat CYP2D | | | |
| CYP2C, CYP2D6, CYP2E1, CYP3A4, CYP1A2, and CYP2B6 | In vitro: 0.1, 0.25, 0.5, 0.75, 1, 1.5, and 2 μM | Inhibited the CYP2D in a dose-dependent manner, with an IC₅₀ value of 39.9 μM. And inhibited rat CYP2C8, CYP2E1, and CYP2A1/2 and human CYP2E1 and CYP2A6 with IC₅₀ values > 100 μM | Liu et al. (2016) |
| Male SD rats         | In vivo: 0.5–50 μM | The IC₅₀ values of MG for the metabolism of phenacetin and diclofenac were 19.0 and 47.3 μM, respectively | Kim SB et al. (2018) |
| CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A | | | |

(Continued on following page)
TABLE 1 | Modern pharmacological studies of MG.

| Effect                          | Model/targets                                                                 | Positive                                                                 | Dosage                                                                 | Result/mechanism/method                                                                                   | References          |
|---------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|---------------------|
| Antibacterial activity          | Aeromonas hydrophila strains                                                  | In vitro: 2, 4, 6, 8, and 16 μg ml⁻¹                                   |                                                                     | The MIC values ranged from 32–64 μg ml⁻¹                                                               | Dong et al. (2017)  |
|                                 | MRSA, MSSA, and ATCC 25923                                                     | In vitro: 8–128 mg L⁻¹                                               |                                                                     | The MIC50/MBC50 values of MSSA and MRSA were 32/32 and 18/16 mg L⁻¹, respectively                     | Zuo et al. (2015)   |
|                                 | 64 Candida spp. strains                                                       | In vitro: 0.5–256 μg ml⁻¹                                           |                                                                     | The range of MIC value was 16–64 μg ml⁻¹                                                              | Behbehani et al. (2017) |
|                                 | 32 Fusarium spp. strains                                                      | In vitro: 5–400 μg ml⁻¹                                              |                                                                     | MG had similar bactericidal activity compared with fluconazole; however, compared with terbinafine, it was less effective at all selected concentrations | Oufensou et al. (2019) |
|                                 | A. actinomycetemcomitans, S. mutans, S. aureus, and E. coli                   | In vitro: 0.5, 1, 3, and 7 μg ml⁻¹                                     |                                                                     |                                                                                                         |                     |
|                                 | Alternaria alternata (Fr.) Keissl, Penicillium expansum (Link) Thom, Alternaria dauci f.sp. solani, Fusarium moniliforme J. Sheld, Fusarium oxysporum Schmitt, Valsa maif Miyabe & G. Yamada, and Rhizoctonia solani J.G. Kühn A | In vitro: 0.001, 0.005, 1, 3, and 7 μg ml⁻¹                                      |                                                                     |                                                                                                         |                     |
| Antioxidative activity          | Acrolein-induced SH-SYSY human neuroblastoma cells                            | In vitro: 8, 16, and 32 μM                                           |                                                                     | Played roles in protecting against oxidative stress and prolonging the vitality in acrolein-induced SH-SYSY cells by altering JNK/mitochondria/caspase, P38K/MEK/ERK/Akt/O subfamily of FoxO 1 signaling pathways | Dong et al. (2013)  |
|                                 | AA-induced HK-2 cells                                                         | In vitro: 5 and 10 μM                                               |                                                                     | Effectively reduced oxidative stress, suppressed cell proliferation, and prevented the G2/M arrest induced by AA.  | Bunel et al. (2016) |
|                                 | Male C3H/HeOuJ mice                                                           | In vivo: 20 mg g⁻¹ (i.v. injection)                                   |                                                                     | Attenuated lung injury by significantly reducing pulmonary edema, iNOS expression, MPO activity, and plasma peroxynitrite | Shih et al. (2012)  |
| Antiphotoaging activity         | UVB-induced HR-1 hairless male mice                                           | In vivo: 40 μL of the formulation containing 0.25% MG (topically applied) |                                                                     | Reduced the mean length and depth of wrinkles and levels of MMP-1, MMP-9, and MMP-13                 | Im et al. (2015)    |
| I nhibition of osteoclast       | RAW 264.7 macrophages                                                         | In vitro: 2.5, 5, 10, and 20 μM                                      |                                                                     | Suppressed MAPK/c-fos/AP-1/NF-κB signaling and ROS production. Increased HO-1 expression               | Lu et al. (2015a)   |
| differentiation                  | TDSCs                                                                         | In vitro: 5, 10, or 20 μM                                         |                                                                     | Inhibited ALP activity and calcium deposits                                                          | Zhou et al. (2019)  |
|                                 | Male SD rats                                                                  | In vivo: 20 mg kg⁻¹ (p.o. injection)                                  |                                                                     | Suppressed the expressions of RUNX2, OCN, and BMP2                                                   |                     |
|                                 | M C3T3-E1 cells                                                               | In vitro: 0.01, 0.1, and 1 μM                                       |                                                                     | Significantly downregulated the production of osteoclast differentiation-inducing factors such as RANKL, TNF-α, and IL-6 and inhibited mitochondrial electron transport   | Kwak et al. (2012) |
|                                 | RANKL-induced RAW 264.7 macrophages                                           | In vitro: 75, 100, and 150 μM                                     |                                                                     | Decreased osteoclast differentiation, tartrate-resistant acid phosphatase activity of differentiated cells, and resorption pit area caused by osteoclasts in a concentration-dependent manner | Lu et al. (2013)   |
|                                 | Male SD rats                                                                  | In vivo: 100 mg kg⁻¹ (p.o.)                                         |                                                                     | Significantly suppressed alveolar bone resorption, the number of osteoclasts on the bony surface, expression of RANKL, MMP-1, MMP-9, iNOS and COX-2, and TNF-α activation | Lu et al. (2013)   |
Currently, commonly used treatment methods include (COX-2) and excessive synthesis of nitric oxide (NO) and prostaglandins (PGEs) (Chen H et al., 2019). Mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) are the most crucial signaling pathways in the inflammatory process. MAPK includes four subfamilies: extracellular signal-regulated kinase (ERK), stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK), big mitogen-activated protein kinase 1 (BMK1)/ERK5, and p38MAPK, which participates in cell growth, differentiation, apoptosis, immune regulation, etc. Furthermore, NF-κB consists of isotype or heteromorphic p50 and p65 protein, which affects the expression of inflammatory and growth factors, chemokines, COX-2, and iNOS involved in the processes of inflammation, apoptosis, tumorigenesis, etc. (Lu et al., 2015b). MG exhibited anti-inflammatory activity by inhibiting Toll-like receptor2 (TLR2)/TLR4/NF-κB/MAPK/peroxisome proliferator-activated receptor-γ (PPAR-γ) pathways and downregulating the expression of inflammatory cytokines (Luo et al., 2013; Wang et al., 2014; Wei et al., 2014; Lin et al., 2015; Lu et al., 2015a; Yang et al., 2016; Zhang L et al., 2018; Chen H et al., 2019; Piasecka et al., 2020).

MG (5–15 μM) could exhibit anti-inflammatory activity in lipopolysaccharide (LPS)-induced RAW 264.7 cells. It decreased the translocation of p50 and p65 subunits and downstream NF-κB transcription through downregulating inhibitor kappa B (IκB) degradation and phosphorylation. Additionally, MG blocked the phosphorylation of ERK1/2, JNK1/2, and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signal, interfered with the activation of PI3K/Akt, MAPK, and NF-κB pathway, and thus inhibited iNOS and COX-2 protein and gene expression (Lai et al., 2011). MG (5–20 μM) significantly suppressed inflammatory reaction, production of pro-inflammatory cytokines, PGE2, and nitrite, expression of iNOS and COX-2, and activation of NF-κB. Meanwhile, it elevated nuclear factor-erythroid 2-related factor 2 (Nrf2) nuclear translocation and heme oxygenase (HO)-1 expression (Lu et al., 2015b).

MG (20 mg kg⁻¹, intraperitoneal i.p. injection) played roles in significantly ameliorating pathological characteristics and inhibiting the inflammatory reaction of acute lung injury in male Sprague Dawley (SD) rats. It could attenuate pneumonia edema, neutrophil infiltration, reactive oxygen species (ROS) production, iNOS and COX-2 expression, and NF-κB activation and upregulate PPAR-γ expression (Lin et al., 2015). MG (25 mg kg⁻¹, i.p.) exhibited therapeutic effect for pathological retinal angiogenesis and glial dysfunctions by decreasing the expression of inflammatory cytokines and inactivating the HIF-1α/VEGF pathway (Yang et al., 2016).

The above results showed that MG has the effect of treating inflammation. However, most of the studies lacked positive groups. Positive groups should be set in follow-up studies.

**Antitumor Activity**

In the past few decades, in order to elucidate the molecular mechanisms of tumor formation and tumorigenesis and explore therapeutic methods, a mass of studies have been done. Currently, commonly used treatment methods include
radiotherapy, chemotherapy, and surgery. However, present chemotherapeutic drugs have adverse reactions such as vomiting, hair loss, kidney damage, and bone marrow destruction. It is an important challenge to find effective and economic antitumor drugs with minimum side effects. A large number of literature studies have shown that MG has antitumor activity against colon cancer (Kang et al., 2012; Park et al., 2012), prostate cancer (McKeown et al., 2014), liver cancer, lung cancer (Seo et al., 2011; Shen et al., 2017), gastric cancer (Rasul et al., 2012), cholangiocarcinoma (Zhang FH et al., 2017), oral cancer (Hsieh et al., 2018), ovarian cancer (Chuang et al., 2011), breast cancer (Liu et al., 2013), and melanoma (Cheng et al., 2020). MG suppressed the growth, migration, and invasion of tumor cells and promoted apoptosis as well as autophagy by acting on caspase-8, caspase-3, and other proteins participated in the p53, MAPK, NF-κB, TLR, HIF-1α/VEGF, PI3K/Akt/ERK/mTOR, and Wnt/β-catenin signaling pathways (Chen et al., 2013; Liu et al., 2013; Li et al., 2014; Kang et al., 2012; Park et al., 2012), number of literature studies have shown that MG has antitumor activity by regulating TLR signaling pathways. Honokiol also can regulate STAF, EGFR, and notch signaling pathways to exhibit antitumor activities (Leeman-Neill et al., 2010; Liu et al., 2012; Kaushik et al., 2015). Further experiments in vivo are needed, and attention should be paid to whether MG could cause side effects.

**Antiangiogenesis Activity**

Angiogenesis, the essential procedure of embryonic angiogenesis, organ regeneration, and wound healing, is involved in many pathological illnesses, such as cancer, rheumatoid arthritis, and diabetic retinopathy. It is of great significance to study the molecular mechanism of angiogenesis, find relevant new drugs, and provide potential lead candidates. Studies have shown that ROS can participate in the signal transduction cascade in the key steps of angiogenesis and regulate the growth and migration of endothelial cells. MG inhibited angiogenesis through regulating the PI3K/Akt/mTOR signaling pathway and HIF-1α/vascular endothelial growth factor (VEGF)-dependent pathway and inhibiting ROS production (Kim GD et al., 2013; Chen et al., 2013).

MG (10 μM) reduced the accumulation of HIF-1α protein by enhancing the activity of prolyl hydroxylase and reducing the synthesis of HIF-1α protein (Chen et al., 2013). MG (20 μM) has been shown to significantly inhibit the transcription and translation activity of platelet endothelial cell adhesion molecules and induce the production of ROS by mediating mitochondria and apoptosis. Furthermore, MG inhibited the activation of MAPKs and PI3K/Akt/mTOR signaling pathways in mouse embryonic stem (MES)/embryoid body (EB)-derived endothelial-like cells (Kim GD et al., 2013). MG (10 and 40 μM) suppressed the proliferation of human umbilical vein endothelial cells (HUVECs), ERK1/2 activity, gelatinase activity, and ROS production and promoted HO-1 levels (Kuk et al., 2017). In a word, MG and honokiol suppress the proliferation, migration, and invasion of tumor cells and promote apoptosis as well as autophagy by regulating MAPK, NF-κB, HIF-α, PI3K/Akt/ERK/mTOR, and Wnt/β-catenin signaling pathways (Tse et al., 2005; Vavilala et al., 2014; Lin et al., 2016; Lee et al., 2019).

In addition, MG shows antitumor activity by regulating TLR signaling pathways. Honokiol also can regulate STAF, EGFR, and notch signaling pathways to exhibit antitumor activities (Leeman-Neill et al., 2010; Liu et al., 2012; Kaushik et al., 2015). Further experiments in vivo are needed, and attention should be paid to whether MG could cause side effects.
and MMP-2 abundance by amplifying the HO-1-mediated resistance of endothelial cells to ROS-mediated proliferative stimuli and blocking the proteolytic activity upon biomechanical load (Kuk et al., 2017).

**Cardiovascular Protection**

Cardiovascular disease is a large class of diseases, including coronary artery disease, hypertension, dyslipidemia, congenital heart disease, valve disease, and arrhythmia. With the improvement of people’s living standards, the incidence of cardiovascular diseases is gradually increasing. MG showed activities of inhibiting the migration and hyperplasia of vascular smooth muscle cells (VSMCs), such as antiplatelet, antithrombotic, and antihypertensive via inhibiting MAPK family activation, Akt/ERK1/2/GSK3β-catenin pathway, and angiotensin-converting enzyme (ACE)/angiotensin II (Ang II)/Ang II type 1 receptor (AT-1R) cascade and upregulating PPAR-β/γ and NO/guanosine 3′,5′-cyclic phosphate/PKG pathways (Shih and Chou, 2012; Karki et al., 2013b; Liang X et al., 2014; Wu et al., 2015; Chang et al., 2018).

Under pathological conditions, the proliferation and migration of VSMCs to the intima can lead to vascular diseases such as atherosclerosis and restenosis after balloon angioplasty (Karki et al., 2012). MG (20 and 30 µM) inhibited VSMCs migration, β1-integrin expression, focal adhesion kinase (FAK) phosphorylation, RhoA and cell division cycle 42 (Cdc42) activation, and collagen-induced stress fiber formation (Karki et al., 2013b). MG (20 µM) suppressed VSMC proliferation and DNA synthesis by inhibiting the expression of cyclin D1/E and cyclin-dependent kinase 2 and 4, ROS production, and activation of renin–angiotensin system, MEK, and ERK1/2 (Karki et al., 2013a; Wu et al., 2015). Additionally, it (1–100 µM) could play the role of vasodilator and eliminate superoxide anion by relaxing right coronary arteries (separated from hearts of pigs) in a dose-dependent manner and controlling the expression levels of iNOS and COX-2, with an IC50 value of 5.78 µM (Kuo et al., 2011). Further pharmacological research in this field was needed to reveal the mechanism by which MG inhibited homocysteine-induced endothelium-dependent vasodilation damage.

In vivo, MG (50 and 100 mg kg⁻¹, gavage) caused attenuation of neointima formation, intimal area, and intimal/media ratio and increase of luminal area via significantly decreasing the expression of cyclin D1/E and CDK4/2 mRNA and protein (Karki et al., 2013a). In male SD rats with pulmonary hypertension (PHA), MG (100 mg kg⁻¹, i.p. injection) exerted a therapeutic effect of PHA by altering the Akt/ERK1/2/glycogen synthase kinase 3β (GSK3β)-β-catenin pathway. It upregulated ACE2 and significantly downregulated the expression of iNOS, endothelin-1 (ET-1), and ETA receptors and O²⁻ production (Chang et al., 2018).

**Hypoglycemic Activity**

Diabetes is a metabolic disease characterized by hyperglycemia, which is caused by insufficient insulin excretion and impaired biological effects. Long-term hyperglycemia can contribute to chronic injury and dysfunction in numerous tissues, especially eyes, kidneys, and heart. Type 2 diabetes, formerly known as adult-onset diabetes, mostly occurs after 35–40 years of age and accounts for more than 90% of diabetic patients (Maddaloni et al., 2020). Numerous studies have reported that MG exhibits the hypoglycemic activity and protein tyrosine phosphatase 1B (PTP1B) inhibition by mediating AMPK/silent information regulator 1 (SIRT1)/PGC-1α, PPAR-γ, and protein kinase A (PKA) pathways, enhancing the activities of glyoxalase 1, PDX1, Ins2, and GPX genes, stimulating Akt phosphorylation, and inhibiting α-glucosidase (Choi et al., 2012; Wang HY et al., 2013; Onoda et al., 2016; Pulvirenti et al., 2017; Suh et al., 2017; Parray et al., 2018).

Low-dose MG (0.01–1 µM) inhibited the death of RIN-m5F cells and the decrease of insulin secretion induced by methylglucosyl, thereby exerting hypoglycemic activity (Suh et al., 2017). It could upregulate the expression of Ins2 and PDX1, the levels of SIRT1 and PGC1α, AMPK phosphorylation, and glyoxalase 1 activity. Moreover, it attenuated the level of methylglyoxal-modified protein adducts and protected protein glycosylation (Alonso-Castro et al., 2011). In L6 myotubes, honokiol (3–30 µM) and MG (3–30 µM) stimulated glucose uptake in a dose-dependent manner and promoted the translocation of glucose transporter-4 to the cell surface as well as Akt phosphorylation. Their activity to stimulate glucose uptake could be blocked by the phosphatidylinositol 3-kinase inhibitor, wortmannin (Choi et al., 2012). MG (20 µM) reduced metabolic disorders, oxidative stress, and fat formation by promoting the adipocyte differentiation and browning of 3T3-L1 C3H10T1/2 cells adipocyte-specific marker genes (uncoupling protein 1, CD137, Tbx1, etc.) and protein expression (Parray et al., 2018). It upregulated key fatty acid oxidation and lipid biomarkers (carnitine palmitoyltransferase 1C, acyl-CoA synthase long-chain family member 1, SIRT1, and perilipin) and activated AMPK, PPAR-γ, and PKA pathways. Honokiol and MG inhibited α-glucosidase with IC50 values of 2.3 and 0.4 µM, respectively (Wang HY et al., 2013). Moreover, their inhibition at 1.5 µM was 3.9 and 29.8%, respectively (Pulvirenti et al., 2017). The inhibitory effect of honokiol on α-glucosidase was lower than that of MG.

C57BL/6J mice were fed a high-fat diet (45 kcal% fat) with or without honokiol (0.02%, w/w) or MG (0.02%, w/w) for 16 weeks. The results showed that honokiol and MG significantly lowered the weight of white adipose tissue, adipocyte size, and proinflammatory gene expression, protected against insulin resistance, and elevated plasma IL-10 level. In particular, honokiol could significantly decrease the plasma resistin level and increase the plasma adiponectin level compared to the control group (Kim Y et al., 2013).

It can be seen that MG and honokiol have similar mechanisms to play a hypoglycemic role, such as inhibition of α-glucosidase and stimulation of glucose uptake. The difference is that MG has a better inhibitory effect on α-glucosidase, while honokiol can significantly decrease the plasma resistin level and increase the plasma adiponectin level.

**Gastrointestinal Protection**

In vitro, MG (3–100 μM) inhibited the spontaneous contraction, acetylcholine (ACh)- and Bay k8664-induced contraction, L-type
**Table 2 | Toxicity of MG.**

| Activity                        | Cell lines                                                                 | Dosage        | Application | References                      |
|--------------------------------|----------------------------------------------------------------------------|---------------|-------------|---------------------------------|
| Inhibition of cell viability   | U937 and LO-2 cells                                                        | 10–100 µM     | In vitro    | Chen H et al. (2019)            |
| Inhibition of cell viability   | MMMECs                                                                     | 50–200 µg ml⁻¹| In vitro    | Wei et al. (2014)               |
| Inhibition of cell migration   | VSMCs                                                                      | 40 µM         | In vitro    | Karki et al. (2013a)            |
| Inhibition of cell viability   | Murine 3T3-F442A preadipocytes and human normal subcutaneous preadipocytes | 30–100 µM     | In vitro    | Alonso-Castro et al. (2011)     |
| Inhibition of cell growth      | mES-derived endothelial-like cells                                         | 50–100 µM     | In vitro    | Kim GD et al. (2013)            |
| Inhibition of cell viability   | MCF-10A, MCF-7, SK-BR3, MDA-MB-453, MDA-MB-433S, MDA-MB-231, and MDA-MB-468 cells | IC₅₀: 70.52 ± 5.09, 36.46 ± 2.38, 59.40 ± 8.24, 35.69 ± 4.91, 25.39 ± 3.26, 25.32 ± 2.72, and 24.79 ± 3.06 µM, respectively | In vitro | Liu et al. (2013) |
| Inhibition of cell viability   | HCT-116 cells                                                             | 1–50 µM       | In vitro    | Park et al. (2012)              |
| Inhibition of cell viability   | OC2 cells                                                                  | 20–100 µM     | In vitro    | Hsieh et al. (2018)             |
| Inhibition of cell viability   | AS49 cells                                                                 | 6.25–200 µM   | In vitro    | Wu et al. (2014)                |
| Inhibition of cell viability   | DU145 and PC3 cells                                                       | 40 and 80 µM  | In vitro    | McKeown et al. (2014)           |
| Induction of cell apoptosis    | GBC cells                                                                  | 10–30 µM      | In vitro    | Li et al. (2015)                |
| Induction of cell apoptosis    | SGC-7901 cells                                                            | 10–300 µM     | In vitro    | Rasul et al. (2012)             |
| Induction of cell proliferation| SKOV3 and TOV21G cells                                                   | 6.25–100 µM   | In vitro    | Chiang et al. (2011)            |
| Induction of cell proliferation| QBC-939, SK-Cha-1, MZ-Cha-1, and RBE cells                                 | 20–160 µM     | In vitro    | Zhang FH et al. (2017)          |

**Ca²⁺ current, and the contraction of colonic smooth muscle through decreasing L-type Ca²⁺ channel activity (Zhang et al., 2013).**

In the Kunming mouse model of diarrhea induced by castor oil, MG (25, 50, and 100 mg kg⁻¹, gavage) significantly inhibited diarrhea, reduced small intestinal transport, and increased catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) (Pang et al., 2013). Zeng et al. found that the antiarrhythmic mechanism of MG and honokiol was similar, but in vivo experiments showed that MG had a higher antiarrhythmic activity than honokiol (Zeng et al., 2015). The reason might be related to the inhibition of the liver CYP450 enzyme. Deng et al. reported that MG (100, 300, and 500 mg kg⁻¹, gavage) and honokiol (100, 300, and 500 mg kg⁻¹, gavage) regulated the release of IP3-Ca²⁺ storage, suppressed SK channel, and facilitated the opening of BKα1 as well as BKβ3 channels and the closing of BKβ4 channel by blocking the IP3-Ca²⁺ channel, inhibiting the activation of IP3 receptor I and CaM, and regulating protein kinase P (PKC) (Deng et al., 2015). In this study, the dose of MG and honokiol was too high and there was no positive control, so the dose should be reduced, and a positive control should be set for further research.

In conclusion, both MG and honokiol can exhibit gastrointestinal protective activity with similar mechanism, while MG’s antiarrhythmic activity is better than that of honokiol.

**Neuroprotection**

It is worth noting that MG can cross the blood–brain barrier (BBB) (Ranaware et al., 2018). A great quantity of research studies has demonstrated that it has generous pharmacological activities in the nervous system. Cannabinoid (CB) receptors are composed of CB1 and CB2 (Geiger et al., 2010). CB1 receptor activation is involved in the regulation of memory, cognition, and motor control, for example, relieving pain, vomiting, reducing hyperexcitability in epilepsy, stimulating appetite, and euphoria. CB2 receptor activation brings about antinociceptive and inflammatory activities (Fuchs et al., 2013). Studies have found that MG was a partial agonist of CB1 (EC₅₀ = 18.3 ± 8.6 µM) and CB2 (EC₅₀ = 3.28 ± 2.10 µM), while honokiol was a full agonist of CB1 (EC₅₀ > 10 µM) and an inverse agonist of CB2. 4′-O-Methylhonokiol was a CB2 receptor agonist and a potent COX-2 SSI (Chicca et al., 2015). In addition, MG had no activity on GPR-55, while honokiol was an antagonist of GPR-55 (Rempel et al., 2013; Coppola and Mondola, 2014; Fuchs et al., 2014). MG showed a certain preference for CB2 in binding studies with Ki values for CB1 and CB2 of 3.19 and 1.44 µM, respectively. Ki values of honokiol at CB1 and CB2 were 6.46 and 5.61 µM, respectively (Schuehly et al., 2011; Rempel et al., 2013). The Ki values of 4′-O-methylhonokiol at CB1 and CB2 were 2.4 µM and 188.5 nM, respectively (Chicca et al., 2015). MG played an antidepressant role by adjusting the hypothalamic–pituitary–adrenal (HPA) axis and hippocampal neurotransmitters and increasing the...
**TABLE 3 | Formulations of MG.**

| Carrier | Proportion | Drug loading (%) | Entrapment efficiency (%) | Solubility (mg ml<sup>-1</sup>) | Bioavailability | References |
|---------|------------|------------------|---------------------------|-----------------------------|----------------|------------|
| Pluronic F127 and L61 (8:1; MG-M) | — | 27.58 ± 0.53 | 81.57 ± 1.49 | 3.62 ± 0.02 | The C<sub>max</sub>, AUC<sub>0-inf</sub>, T<sub>max</sub>, and T<sub>1/2</sub> values of MG-M were 0.823 mg ml<sup>-1</sup>, 4.673 ± 0.31 mg/ml h, 0.75 ± 0.158 h, and 2.982 ± 0.528 h, respectively. The relative bioavailability of MG-M was 283% greater than that of raw MG. Shen H et al. (2018) |
| SOL: HS15 40:10 | — | 4.12 ± 0.16 | 98.37 ± 1.23 | — | The C<sub>max</sub>, AUC<sub>0-inf</sub>, T<sub>max</sub>, and T<sub>1/2</sub> values of MG-H were 0.837 ± 0.050 μg ml<sup>-1</sup>, 5.127 ± 0.988 μg/ml h, 0.708 ± 0.188 h, and 3.656 ± 1.212 h, respectively. The relative oral bioavailability of MG-H increased by 2.98-fold. Ding et al. (2018) |
| SOL: TPGS 50:6 | — | 4.03 ± 0.19 | 94.61 ± 0.91 | — | The C<sub>max</sub>, AUC<sub>0-inf</sub>, T<sub>max</sub>, and T<sub>1/2</sub> values of MG-T were 0.918 ± 0.040 μg ml<sup>-1</sup>, 6.027 ± 0.963 mg/ml h, 0.750 ± 0.158 h, and 3.407 ± 1.212 h, respectively. The relative oral bioavailability of MG-T increased by 2.39-fold. Ding et al. (2018) |
| Phospholipids, cholesterol, and mPEG2000-DSPE | Phospholipids: cholesterol: mPEG 2000-DSPE: MG 60:8:3:20 | — | 98.22 | — | Compared with MG solution, the liposome had a sustained-release effect. Shen et al. (2016) |
| Soy lecithin | Soy lecithin: MG 0.27:0.8 | — | — | — | The cumulative dissolution rate was 96.3%, in 12 h. And the bioavailability was increased by 1.38 times, with the value of C<sub>max</sub> for 533.62 ± 59.01 ng ml<sup>-1</sup>. Liu et al. (2020) |
| PVP K30 | PVPK30:MG 0.27:1.35 | — | — | — | The cumulative dissolution rate was 76.4%, in 12 h. And the bioavailability was increased by 2.12 times, with the value of C<sub>max</sub> for 721.73 ± 103.44 ng ml<sup>-1</sup>. Li et al. (2020) |
| Povidone S-630 (PS-630) | PSS-630: MG 6:1 | — | — | — | The value of relative bioavailability, AUC<sub>0-t</sub>, T<sub>1/2</sub>, and C<sub>max</sub> was 137.22%, 823.81 ± 152.63 ng/L h, 6.066 ± 1.879 h, and 304.59 ± 136.48 ng L<sup>-1</sup>. Li et al. (2019) |
| HPC | HPC: MG 6:1 | — | — | — | The values of bioavailability, AUC<sub>0-t</sub>, T<sub>1/2</sub>, and C<sub>max</sub> were 170.88%, 1025.90 ± 149.93 ng/L h, 17.63 ± 5.020 h, and 151.75 ± 26.37 ng L<sup>-1</sup>, respectively. Lin et al. (2019) |
| Eudragit EPO (EPO) | EPO: MG 6:1 | — | — | — | The values of bioavailability, AUC<sub>0-t</sub>, T<sub>1/2</sub>, and C<sub>max</sub> were 79.50%, 477.30 ± 159.46 ng/L h, 13.81 ± 11.780 h, and 83.49 ± 22.37 ng L<sup>-1</sup>, respectively. Lin et al. (2014) |
| EPC and DPPC | 0.075 mg mL<sup>-1</sup> MG | — | 74.13 ± 1.97 (EPC), 64.26 ± 2.92 | — | The EPC and DPPC liposomes enhanced the activity of inhibiting VSMC. Chen (2008) |
| PVP | PVP: MG 1:1 | — | — | 105 | The C<sub>max</sub>, AUC<sub>0-inf</sub>, and T<sub>max</sub> values of solid dispersion were 0.6 ± 0.1 nmol mt<sup>-1</sup>, 679.0 ± 130.0 nmol mt<sup>-1</sup> min, and 275.0 ± 272.6 min, respectively. Lin et al. (2014) |

(Continued on following page)
### TABLE 3 | (Continued) Formulations of MG.

| Carrier                        | Proportion                                            | Drug loading (%) | Entrapment efficiency (%) | Solubility (mg ml\(^{-1}\)) | Bioavailability | References |
|--------------------------------|--------------------------------------------------------|------------------|---------------------------|-----------------------------|------------------|------------|
| CHC                            | MG concentration from 0.05 to 0.2 mg ml\(^{-1}\)      | 79.3 ± 2.2       | —                         | —                           | —                | Wang et al. (2011) |
|                                | (0.2 mg ml\(^{-1}\)), 88.4 ± 2.3 (0.2 mg ml\(^{-1}\)), and 91.6 ± 0.4 (0.2 mg ml\(^{-1}\)) |                  |                           |                             |                  |            |
| Oil phase mass fraction of 20 wt% and an aqueous phase mass fraction of 80 wt% | The amount of MG was 2.0 g/100 ml                      | —                | —                         | —                           | —                |            |
| Distearyl phosphatidylcholine (DSPC), DPPC, and dimyristoyl phosphatidylcholine (DMPC) | —                                                       | 84.87 ± 1.97 (DSPC), 75.05 ± 3.93 (DPPC), and 67.19 ± 2.92 (DMPC) | —                         | —                           | —                | Chen (2009) |
| HP-β-CD                        | HP-β-CD: MG 10:1                                       | —                | —                         | —                           | —                | Qiu et al. (2016) |
| Uio-66(Zr)                     | —                                                      | 72.16 ± 2.15     | —                         | —                           | —                | Santos et al. (2020) |

Compared with free MG, MG-CHC nanoparticles showed better cell uptake efficiency, antiproliferation, and inhibition of VSMC migration.

The absolute bioavailability of MG is 17.5 ± 9.7%. The \( \text{AUC}_{0-\infty} \), \( T_{1/2} \), CL/F, and Vd/F values of MG emulsion (25 mg kg\(^{-1}\), i.v.) were 6,875 ± 1,080 μg/ml h, 5.49 ± 1.77 h, 2.9 ± 0.9 ml/h/kg, and 0.37 ± 0.059 ml/kg, respectively. The \( C_{\text{max}} \), \( \text{AUC}_{0-\infty} \), \( T_{\text{max}} \), \( T_{1/2} \), CL/F, and Vd/F values of MG emulsion (50 mg kg\(^{-1}\), oral administration) were 426.4 ± 273.8 mg ml\(^{-1}\), 2,665 ± 1,306 μg/ml h, 1.2 ± 1.6 h, 4.9 ± 3.0 h, 2.2 ± 1.0 ml/h/kg, and 13.9 ± 5.1 ml kg\(^{-1}\), respectively.

The three kinds of lipid could increase the inhibition activity of MG to VSMC, and the efficacy of inhibition was DMPC > DPPC > DSPC.

The water solubility of HP-β-CD-MG was more than 500 times higher than that of MG, and the stability of HP-β-CD-MG was significantly increased.

The \( C_{\text{max}} \), \( \text{AUC}_{0-\infty} \), \( T_{\text{max}} \), and \( T_{1/2} \) values of MG@Uio-66(Zr) (100 mg kg\(^{-1}\), oral administration) were 3.77 ± 0.33 μg ml\(^{-1}\), 2099.95 ± 148.48 μg/ml min, 196.97 ± 17.38 min, and 206.21 ± 27.95 min, respectively. The \( C_{\text{max}} \), \( \text{AUC}_{0-\infty} \), \( T_{\text{max}} \), and \( T_{1/2} \) values of MG@Uio-66(Zr) (100 mg kg\(^{-1}\), i.p.) were 5.65 ± 2.41 μg ml\(^{-1}\), 3831.72 ± 451.57 μg/ml min, 114.27 ± 7.09 min, and 606.35 ± 114.37 min, respectively. The relative bioavailability increased almost two-fold.
TABLE 3 (Continued) Formulations of MG.

| Carrier                  | Solubility (mg ml$^{-1}$) | Entrapment efficiency (%) | Bioavailability |
|--------------------------|---------------------------|----------------------------|-----------------|
| Soluplus VR and Poloxamer 188 (1:12:1) | 5.46 ± 0.65% (MMs) and 42.3% ± 1.27% (MNs) | 89.58 ± 2.54% (MMs) | 0.285 h, respectively. The gastrointestinal absorption of MG was increased by 2.85 and 2.27 times by MM and MN, respectively. |
| MG, Soluplus VR, Poloxamer 188 and Polysorbate 80 (1:1:M) | 0.346 ± 0.037 mg ml$^{-1}$, 0.792 ± 0.102 h, and 3.142 ± 0.256 h (MMs) | 5.49 ± 0.91% (MNs) | 0.285 h, respectively. The gastrointestinal absorption of MG was increased by 2.85 and 2.27 times by MM and MN, respectively. |
| MG, Poloxamer 188 and Polysorbate 80 (1:1:M) | 0.286 ± 0.192 mg ml$^{-1}$, 0.792 ± 0.102 h, and 3.142 ± 0.256 h (MMs) | 5.49 ± 0.91% (MNs) | 0.285 h, respectively. The gastrointestinal absorption of MG was increased by 2.85 and 2.27 times by MM and MN, respectively. |
| MG, PVP K-30:1:1 | 0.286 ± 0.192 mg ml$^{-1}$, 0.792 ± 0.102 h, and 3.142 ± 0.256 h (MMs) | 5.49 ± 0.91% (MNs) | 0.285 h, respectively. The gastrointestinal absorption of MG was increased by 2.85 and 2.27 times by MM and MN, respectively. |

expression levels of brain-derived neurotrophic factor (BDNF), serotonergic system activity, such as nerve inflammation, and the prefrontal cortex oxidative stress (Li et al., 2012, Li LF et al., 2013; Matsui et al., 2016; Bai et al., 2018; Cheng et al., 2018). MG was a dual agonist of PPAR-γ (EC$_{50}$ = 0.93 ± 0.91 µM) and RXRa (EC$_{50}$ = 3.91 ± 1.08 µM) (Dreier et al., 2017). In addition, MG and honokiol could improve both phasic and tonic GABAergic neurotransmission in hippocampal dentate granule neurons (Alexeev et al., 2012). Honokiol had a stronger positive regulatory effect on GABAA receptors than MG (Fuchs et al., 2014). In α1β2γ2 receptor and β1 containing subtype, the EC$_{50}$ value was at approximately 20 µM for honokiol (Rycek et al., 2015). MG exhibited the activities of anti-AD, antiepileptic, and neuroprotection by acting on PPAR-γ targets, GABA/benzodiazepine receptor complex, NF-κB, JNK/mitochondrial/caspase, and PI3K/Akt/forhead transcription factor (FoxO) 1 pathways, alleviating inflammation, promoting microglia phagocytosis and Aβ degradation, reducing the seizure mortality, prolonging seizure time, and inhibiting apoptosis (Chen CR et al., 2011; Wang CC et al., 2013; Chen et al., 2014; Chen et al., 2014; Rycek et al., 2015; Kou et al., 2017; Zhou F et al., 2019; Zhou F et al., 2019; Li J et al., 2020; Xie et al., 2020).

In BV2 cells, MG (10 µM) attenuated Aβ-induced AD by inhibiting the luciferase activity of NF-κB and the target gene of inflammatory cytokines, activating luciferase and liver X receptor activity, reducing ROS production induced by Aβ, upregulating apolipoprotein E (ApoE), and promoting microglial phagocytosis and Aβ degradation (Xie et al., 2020). MG (EC$_{50}$ = 3.49 µM) and honokiol (EC$_{50}$ = 2.65 µM) promoted the transcriptional activities of PPAR-γ in a dose-dependent manner. They also dose-dependently increased the luciferase activity of PPAR-γ-LBD. MG and honokiol could fit into the protein pocket of PPAR-γ-LBD with IC$_{50}$ values of 3.745 and 16.13 µM, respectively. What is more, MG had two hydrogen bonds at Glu343, which maintained the binding stability, while honokiol had one hydrogen bond at Glu343, and SER342, respectively. What is more, MG had two hydrogen bonds at Glu343, which maintained the binding stability, while honokiol had one hydrogen bond at Glu343 and SER342, respectively, indicating that MG was more effective in enhancing PPAR-γ luciferase levels than honokiol (Xie et al., 2020). MG (5 µM) significantly inhibited trimethyltin (TMT)-mediated neuronal death and microglial activation by inhibiting ROS production and the activation of JNK, p38 MAPKs, and NF-κB in HT22 cells and BV-2 cells (Kim and Kim, 2016). Both MG (12.5 µM) and honokiol (6.25 µM) showed effective behavioral and electrophysiological antiepileptic activities in pentylenetetrazole and ethyl ketopentenoate models (Li G et al., 2020).

At concentrations of 50 and 100 mg kg$^{-1}$, MG alleviated depression-like behavior in male ICR mice by reducing corticosterone (CORT) level and increasing NE, 5-hydroxytryptamine (5-HT), and BDNF protein levels (Bai et al., 2018). It could improve depressive behavior and hippocampal nerve damage in male ddY mice (Matsui et al., 2016). The phosphorylation of Akt, ERK, and cyclic AMP-responsive element-binding protein was significantly increased. In a male Kunming mouse model of chronic mild stress (CMS),
MG (20 and 40 mg kg\(^{-1}\), gavage) downregulated the levels of interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) in the prefrontal cortex, suppressed the activation of microglia and the proliferation of HPA axis and oxidative stress, and reversed malondialdehyde increase and SOD as well as GSHPx decrease to produce antidepressant-like effect (Cheng et al., 2018). MG (10 and 30 mg kg\(^{-1}\), i.p. injection) downregulated the expression of bax and Ac-FOXO1 and production of NOS, 4-HPETE, iNOS, phosphorylated p38MAPK, and C/EBP homologs, while upregulated the expressions of Bcl-2 and SIRT1. The regulation effect of MG on ischemic damage factors may be through inhibiting the production of ROS and upregulating p-Akt and NF-κB (Chen et al., 2014). MG (40 and 80 mg kg\(^{-1}\)) exhibited antiepileptic activity by prolonging the latency of seizure onset and decreasing the number of seizure spikes, through acting on GABAA/benzodiazepine receptor (Chen CR et al., 2011).

As indicated by the above results, both MG and honokiol can act on CB1 and CB2 receptors. The difference is that MG is a partial agonist of CB1 and CB2, while honokiol is a full agonist of CB1 and an inverse agonist of CB2, and MG has no activity on GPR-55, while honokiol is an antagonist of GPR-55. MG and honokiol can improve both phasic and tonic GABAergic neurotransmission in hippocampal dentate granule neurons; however, honokiol has a stronger positive regulatory effect on GABAA receptors than MG. In addition, MG and honokiol promote the transcriptional activities of PPAR-γ in a dose-dependent manner. They also dose-dependently increased the luciferase activity of PPAR-γ-LBD. However, MG is more effective in enhancing PPAR-γ luciferase levels than honokiol. MG had antidepressant, anti-AD, anti-convulsant, anti-neurological deterioration, and protective effects to brain injury in the nervous system. Honokiol can regulate CB2 receptor, PPAR-γ targets, GABAA, and NF-κB and inhibit the levels of IL-1β, IL-6, IL-8, and TNF-α, production of ROS, RNS, COX2 as well as iNOS, and expression of PI3K/Akt, MAPKs, ERKs, INKs, and p38 to exert neuroprotective effects (Talarek et al., 2017).

**Interaction with CYP450 Enzyme**

CYP450 is an important enzyme system involved in drug metabolism in vivo (Tota and Rettie, 2005). Among them, CYP2C8, CYP2C9, CYP2E1, and CYP2A6 accounted for about 40% of the total CYP450 enzymes in the liver (Zhang P et al., 2017). It is of great significance to study the interaction between the active components of traditional Chinese medicine and CYP450 for clinical safety. Studies have shown that MG can inhibit many CYP enzymes in humans and rats.

The IC\(_{50}\) values of MG on human CYP1A, CYP2C, CYP3A, CYP3A4, CYP2C19, CYP2C8, and CYP2B6 were 5.56 ± 5.13, 35.0, 56.2, 0.527, 1.62, and 44.9 µM, respectively. And the IC\(_{50}\) values of MG on rat CYP2C, CYP2D6, CYP2E1, CYP3A4, CYP1A2, CYP2B6, CYP1A, CYP3A, CYP2C11, and CYP2D were 5.56 ± 2.87, 65.42 ± 4.46, 67.93 ± 9.51, 52.36 ± 17.32, 97.80 ± 3.83, 28.69 ± 1.46, 5.56, 3.8, 84.5, and 39.9 µM, respectively. In addition, IC\(_{50}\) values of CYP2C8, CYP2A1, and CYP2A2 in rat liver and CYP2E1 and CYP2A6 in the human liver were greater than 100 µM. The inhibition types of MG on CYP1A (Ki: 1.09–12.0 µM), CYP2C9 (Ki: 0.449 μM), CYP2C (Ki: 10.0–15.2 µM), 3A (Ki: 93.7–183 µM), and CYP1A2 (Ki: 10.0 µM) were competitive inhibition. The IC\(_{50}\) values of honokiol on human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, and CYP3A4 were 3.5, 18.8, 40.8, 9.6, 32.9, >50, >50, and 43.9 µM, respectively. Moreover, the IC\(_{50}\) values of honokiol on rat CYP2C, CYP2A6, CYP2D6, CYP2E1, CYP3A4, CYP1A2, and CYP2B6 were 41.86 ± 4.24, >100, 43.43 ± 2.34, 58.10 ± 3.02, >100, 95.24 ± 7.81, and 53.22 ± 0.66 µM, respectively. The inhibition type of honokiol on CYP1A2 (Ki: 6.2 µM) was competitive inhibition, and the inhibition types of honokiol on CYP2E1 (Ki: 11.1 µM) and CYP2C19 (Ki: 0.702 µM) were noncompetitive inhibition (Joo and Liu, 2013; Duan et al., 2015; Kim SY et al., 2015; Liu et al., 2016; Zhang P et al., 2017; Huang et al., 2019; Kim S. B. et al., 2015).

Kim et al. proved the feasibility of MG and honokiol to modulate CYP activity in vivo by using the phenacetin and diclofenac as probe substrates for rat CYP1A and 2C, respectively. The result indicated that the mean IC\(_{50}\) values of MG for the metabolism of phenacetin and diclofenac were 19.0 and 47.3 µM, while those of honokiol were 8.59 and 44.7 µM, respectively. The inhibitory effect of MG and honokiol on CYP1A activity was stronger than that of CYP2C activity rat liver microsomes (Kim SB et al., 2018). Huang et al. revealed that different CYP450 enzyme isoforms showed different activities in the in vitro metabolism of MG and honokiol in rat liver microsomes (Huang et al., 2019). The CYP2E1 subtype managed the oxidation of MG and honokiol terminal double bonds to epoxy metabolites, CYP3A4 seemed to be the main subtype responsible for further hydrolytic metabolism, while CYP1A2 might promote the decarboxylation of metabolites. CYP2A6 might be the key subtype leading to MG hydrogenation. It is necessary to further study the pharmacokinetic interaction between MG and CYP substrate drugs in vivo and in vitro.

**Antibacterial Activity**

According to the literature review, MG has antibacterial activities. It could inhibit the Aeromonas hydrophila strains, with the minimal inhibitory concentration (MIC) value range of 32–64 µg mL\(^{-1}\) (Dong et al., 2017). MG and honokiol exhibited similar inhibitory activity against methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-susceptible S. aureus (MSSA), with the MIC/minimal bactericidal concentration (MBC) value range of 16–64 mg L\(^{-1}\) (Zuo et al., 2015). Honokiol and MG dose-dependently inhibited the MRSA strain with the MIC values of 33 and 20 µg mL\(^{-1}\), respectively (Kim SY et al., 2015). They inhibited multidrug-resistant and MRSA with MIC values in the range of 8–16 ppm (Liu et al., 2014). Choi et al. reported that honokiol and MG caused significant cellular immune-modulatory effect and decreased the production of ROS and inflammatory cytokines/chemokines during S. aureus infection. Honokiol upregulated type I and II interferon mRNA expression in response to MSSA infection and inhibited the growth of MSSA at 2.5 µg mL\(^{-1}\) and MRSA at 5 µg mL\(^{-1}\), whereas MG inhibited the growth of both
bacterial cells at 5 µg ml\(^{-1}\) after 24 h of growing (Choi et al., 2015). MG and honokiol could inhibit S. mutans to prevent dental caries, with an MIC value of 10 µg ml\(^{-1}\). And MG (50 µg ml\(^{-1}\)) had better bactericidal activity against S. mutans biofilm than honokiol (50 µg ml\(^{-1}\)) and chlorhexidine (500 µg ml\(^{-1}\)) at 5 min after exposure (Saka et al., 2016).

In addition, in the seven pathogenic fungi including Alternaria alternata (Fr.) Keissl, Penicillium expansum (Link) Thom, and Alternaria dauci F.Sp. solani, MG inhibited their growth by more than 57% (Chen Y-H et al., 2019). Moreover, the MIC value ranged from 16 to 64 µg ml\(^{-1}\) for the 64 Candida spp. strains, and the MICs of Candida CSC27907, CDC27897, CDC28621, and ATCC24433 were 64, 32, 16, and 32 µg ml\(^{-1}\), respectively. And the average inhibition rate of biofilm was 69.5% (Behbehani et al., 2017). Honokiol exhibited better antimicrobial activity than MG on Aggregatibacter actinomycetemcomitans, S. mutans, S. aureus, MRSA, and Escherichia coli with MIC/MBC values of 10/10, 10/20, 10/20, 10/90, and > 100/> 100 g ml\(^{-1}\), respectively, while those of MG were 10/20, 10/20, 10/30, 20/90, and > 100/> 100 g ml\(^{-1}\), respectively (Chiu et al., 2020).

Oufensou et al. tested the antifungal activities of MG and honokiol (5–400 µg ml\(^{-1}\)) against 32 Fusarium spp. strains. The terbinafine (0.1–10 µg ml\(^{-1}\)) and fluconazole (1–50 µg ml\(^{-1}\)) were used as positive controls. The results revealed that MG had similar bactericidal activity compared with fluconazole, whereas honokiol had a better effect of inhibiting the mycelium growth compared to this fungicide. Compared to terbinafine, honokiol exhibited similar antifungal activity, whereas MG was less effective at all selected concentrations (Oufensou et al., 2019).

### Antioxidant Activity

Amorati et al. explored the chemistry behind the antioxidant activity of MG and honokiol. They found that MG trapped four peroxyl radicals, with a kinh of 6.1 × 104 M\(^{-1}\)s\(^{-1}\) in chlorobenzene and 6.0 × 103 M\(^{-1}\)s\(^{-1}\) in acetonitrile, while honokiol trapped two peroxyl radicals in chlorobenzene (kinh = 3.8 × 104 M\(^{-1}\)s\(^{-1}\)) and four peroxyl radicals in acetonitrile (kinh = 9.5 × 103 M\(^{-1}\)s\(^{-1}\)). Their different behavior was due to the combination of intramolecular hydrogen bonding among the reactive OH groups (in MG) and of the OH groups with the aromatic and allyl π-systems (Amorati et al., 2015). MG has a bisphenol core with two allylic side chains, and its antioxidant activity is attributed to hydroxyl and allyl groups (Baschieri et al., 2017). MG downregulated myeloperoxidase (MPO) activity and the expression of TNF-α, iNOS, and IL-6 by altering JNK/mitochondrial/caspase and PI3K/Akt/FOXO1 signaling pathways (Shih et al., 2012; Dong et al., 2013). In vitro, MG (16 µM) protected against acrolein-induced oxidative stress in human SH-SY5Y cells via acting on JNK/mitochondrial/caspase and PI3K/Akt/FOXO1 signaling pathways and inhibiting intracellular glutathione consumption as well as ROS accumulation (Dong et al., 2013).

It was found that MG (20 mg g\(^{-1}\), i.v. injection) could significantly reduce MPO activity and the expression of iNOS, TNF-α, and IL-6 to inhibit oxidative stress and reduce mesenteric reperfusion caused lung injury in male C3H/HeOuJ mice (Shih et al., 2012). In aristolochic acid (AA)-induced HK-2 cells, MG (10 µM) and honokiol (10 µM) effectively reduced oxidative stress and suppressed cell proliferation by blocking the cell cycle at the G1 phase and preventing the G2/M arrest (Bunel et al., 2016).

### Other Activities

Besides these pharmacological activities mentioned above, MG also has the following activities: inhibition of osteoclast differentiation, antiphotoaging, antiparasitic, antiviral activity, and reduction of multidrug resistance.

MG (0.1 µM) significantly downregulated the production of osteoclast differentiation-inducing factors such as RANKL, TNF-α, and IL-6 and inhibited mitochondrial electron transport (Kwak et al., 2012). In RANKL-induced RAW 264.7 macrophages, MG (75–150 µM) decreased osteoclast differentiation, tartrate-resistant acid phosphatase activity of differentiated cells, and resorption pit area caused by osteoclasts in a concentration-manner (Lu et al., 2013). MG (10 µM) inhibited IL-1-induced RANKL expression and osteoclast differentiation by suppressing COX-2 expression and PGE2 production (Hwang et al., 2018). MG (2.5–20 µM) attenuated RANKL-induced osteoclast differentiation by suppressing MAPK/c-fos/AP-1 and NF-κB signaling, inhibiting ROS production, and increasing HO-1 expression (Lu et al., 2015a). In tendon-derived stem cells (TDSCs), MG (5–20 µM) prevented calcium deposition and osteogenic differentiation of tendon-derived stem cells through influencing PI3K/Akt/β-catenin pathway induced by PEG-2 (Zhou et al., 2019). In liguature-induced rats, MG (100 mg kg\(^{-1}\), p.o.) significantly suppressed alveolar bone resorption, the number of osteoclasts on the bony surface, and the expression of RANKL. Moreover, it could reduce the expression of MMP-1, MMP-9, iNOS, and COX-2 and TNF-α activation (Lu et al., 2013). MG (25 mg kg\(^{-1}\), i.p. injection) inhibited the activities of osteogenic factors runt-related transcription factor 2(RUNX2), OCN, and bone morphogenetic protein 2 (BMP2) in male SD rats. Moreover, it inhibited ossification of tendon ossification by reducing heterotopic ossification of Achilles tendon (Zhou et al., 2019).

After treating HR-1 hairless male mice with 40 µl of the 0.25% MG preparation, it significantly reduced the average length and depth of wrinkles and inhibited the expression of MMP-1, MMP-9, and MMP-13 to play a role in antiphotoaging activity (Im et al., 2015).

MG significantly inhibited HBV activities. The IC\(_{50}\) values of HBV surface antigen (HBsAg), HBV e antigen (HBeAg), and replication of HBV DNA were 2.03, 3.76, and 8.67 µM, respectively, and without cytotoxicity to HBsAg and HBeAg (Li J et al., 2013). MG (2.51 ± 0.51 µg ml\(^{-1}\)) and honokiol (3.18 ± 0.61 µg ml\(^{-1}\)) stimulated the expression of immune-related genes to resist grass carp reovirus infection in Ctenopharyngodon idella kidney (CIK) cells. MG significantly increased the expression of interferon (IFN) regulatory factor (IRF) 7 and IL-1β to activate type I IFN (IFN-1) but failed to induce the molecules in NF-κB pathways. The difference was that honokiol promoted the expression of IL-1β, TNFa, NF-κB, IFN-β, promoter stimulator 1, IRF3, and
IRF7 but failed to increase IFN-1 expression, showing that it could enhance the host innate antiviral response to grass carp reovirus infection by regulating NF-kB pathway (Chen et al., 2017).

What is more, MG (1–50 μM) reduced the multidrug resistance of cancer cells to antitumor drugs through downregulating P-glycoprotein expression in a concentration- and time-dependent manner and increased the intracellular accumulation of calcine in NCI/ADR-RES cells (Han and Van Anh, 2012).

**TOXICITY**

So far, a large number of studies have shown that MG has cytotoxicity (Table 2). MG (10–100 μM, 24 or 48 h) was used to investigate the toxicity on human normal hepatocyte U937 and LO-2 cells. The results showed that MG at low concentration could promote the cell survival rate in a dose-dependent manner. At a concentration of less than 60 μM, MG could promote the survival of U937 cells. When exposed to MG at a concentration of less than 70 μM after 48 h, the mortality of LO-2 cells was lower than 20% (Chen H et al., 2019). Additionally, at a concentration range from 50 to 200 μg ml⁻¹, MG could cause toxicity and inhibit MMEC survival (Wei et al., 2014).

Karki et al. reported that MG at a concentration of 40 μM possessed cytotoxicity on VSMCs (Karki et al., 2013a). MG (100 μM) reduced the murine 3T3-F442A preadipocyte viability by 25% and human normal subcutaneous preadipocyte viability by 36%. MG (50 μM) reduced the murine cell viability by 16% and human cell viability by 22%. Otherwise, honokiol (50 μM) significantly decreased the murine and human cell viability by 30 and 39%, and the combined application of honokiol and MG (100 μM each) markedly decreased the cell viability by 73% (murine) and 80% (human). The combined application of honokiol and MG (50 μM each) also markedly reduced murine (31%) and human (37%) cell viability. On the contrary, the simultaneous application of honokiol and MG (30 μM each) only moderately affected the murine (15%) and human (21%) cell viability (Alonso-Castro et al., 2011). When the concentration of MG was > 50 μM, it would be toxic to mES-derived endothelial-like cells (Kim GD et al., 2013). Liu et al. studied the cytotoxicity of MG on human breast cancer cell lines and normal human mammary epithelial cells. The results showed that MG had moderate cytotoxicity to MCF-10A, MCF-7, SK-BR3, MDA-MB-453, MDA-MB-435S, MDA-MB-231, and MDA-MB-468 cells with IC₅₀ values of 70.52 ± 5.09, 36.46 ± 2.38, 59.40 ± 8.24, 35.69 ± 4.91, 25.39 ± 3.26, 25.32 ± 2.72, and 24.79 ± 3.06 μM, respectively (Liu et al., 2013). Park et al. treated HCT-116 colon cancer cells with various concentrations of MG (0–50 μM) for 24 and 48 h. MG induced cell death in a dose- and time-dependent manner. Treatment with 50 μM MG for 24 h resulted in significant decreases in cell viability with 75.3% of the cells surviving after 24 h and 81.7% of the cells surviving after 48 h. Moreover, MG (50 μM) induced apoptosis in 76.1% of the cells after 24 h, indicating that MG inhibited cell proliferation and induced apoptosis in HCT-116 cells (Park et al., 2012). When OC2 cells were treated with MG (20–100 μM) for 24 h, the cell viability decreased in a dose-dependent manner (Hsieh et al., 2018). After treating A549 cells with 6.25, 12.5, 25, 50, 100, and 200 μM of MG for 24 and 48 h, cell viability for 24 h was 98.1 ± 2.7, 86.4 ± 2.3, 79.5 ± 4.6, 68.7 ± 2.3, 55.9 ± 1.1, and 12.8 ± 3.1%, respectively, while for 48 h was 92.5 ± 3.5, 80.1 ± 4.7, 70.2 ± 2.8, 56.6 ± 3.4, 36.3 ± 2.6, and 3.1 ± 0.9%, respectively. When the dose of MG was ≤ 6.25 μM, there was almost no inhibitory effect on A549 cells, while 25 μM of MG significantly inhibited the proliferation of A549 cells. MG inhibited the proliferation of A549 cells in a dose- and time-dependent manner (Wu et al., 2014). In DU145 cells, the viability was reduced by 30 and 60% at 40 and 80 μM, respectively, after 6 h of MG treatment, and 49 and 76% were reduced at 40 and 80 μM, respectively, after 24 h of MG treatment. After treating PC3 cells with 80 μM MG for 6 and 24 h, its viability decreased to 50 and 48%, respectively (McKown et al., 2014). Li et al. treated GBC cells with MG at concentrations of 10, 20, and 30 μM for 48 h. The results showed that the apoptosis index of GBC cells was significantly higher than that of the control group (Li et al., 2015). SGC-7901 cells were treated with different concentrations of MG (0, 10, 30, 50, 100, 200, and 300 μM) for 48 h. It was observed that MG inhibited cell growth in a dose-dependent manner. Compared with the control group, exposing cells to 40, 60, and 80 μM of MG for 48 h resulted in a significant reduction in the number of cells (Rasul et al., 2012). MG significantly suppressed the proliferation of SKOV3 and TOV21G cells in a dose-dependent (6.25, 12.5, 25, 50, and 100 μM) and time-dependent (48 and 72 h) manner (Chuang et al., 2011). The QBC939, SK-ChA-1, MZ-ChA-1, and RBE cells were treated with different concentrations of MG (20, 40, 80, and 160 μM) for 24, 48, and 72 h. The results demonstrated that MG significantly suppressed the proliferation of the above cell lines in a concentration- and time-dependent manner (Zhang FH et al., 2017).

Fujita et al. investigated the ability of MG and honokiol to inhibit UV-induced mutation in Salmonella typhimurium TA102. The results suggested that both MG (5 μg/per plate) and honokiol (5 μg/per plate) could inhibit against UV-induced mutations by scavenging -OH generated by UV irradiation. The relative mutagenic activities of MG and honokiol were 62 ± 1% and 62 ± 4%, respectively, while that of control was 100% (Fujita and Taira, 1994). MG significantly inhibited the mutagenicity induced by indirect mutagens but did not affect the direct mutagens. It strongly and competitively inhibited the activities of ethoxyresorcinol-O-demethylase and methoxyresorcinol-O-demethylase, indicating that it could inhibit indirect mutagen-induced mutations by suppressing the activities of CYP1A1 and CYP1A2 (Saito et al., 2006). The genotoxicity of Magnolia bark extract (MBE) was studied by Li et al., which was composed of 94% MG and 1.5% honokiol. The results revealed that MBE was not genotoxic under the conditions of the in vitro bacterial reverse mutation test and in vivo micronucleus test and supported the safety of MBE for dietary consumption (Li et al., 2007).

In general, the abovementioned cytotoxicity is mostly related to the antitumor and antiangiogenic activities of MG. Additionally, studies have shown that MG not only has no
mutagenic and genotoxic activity but also even has antimutagenic activity. In summary, MG was found to be fairly nontoxic.

**BIOAVAILABILITY AND FORMULATION**

MG is a dimeric phenolic neolignan (Pulvirenti et al., 2017) with strong lipid solubility, and its absorption in the gastrointestinal tract is mainly through a lipid-like pathway (Niu et al., 2015). Hattori et al. studied the absorption, metabolism, and excretion of MG through oral administration and intraperitoneal injection of [ring-14C] MG. The results showed that MG participated in enterohepatic circulation (Hattori et al., 1986). After oral administration of MG (50 mg kg$^{-1}$), the MG sulfates and glucuronides were predominant in the bloodstream. And MG was mainly distributed in the liver, kidney, brain, lung, and heart; among these organs, the concentration of MG and MG glucuronides in the liver was the highest (Lin et al., 2011). Additionally, MG's main metabolite excreted in bile was magnolol-2-O-glucuronide, and the main route of excretion of MG after oral or intraperitoneal injection was through the alimentary tract (Hattori et al., 1986). After 24 h of oral administration of [ring-14C] MG, the main fecal derivatives of oral MG in rats were MG and a series of free form metabolites, which accounted for more than 90% of the total dose; only 6% were glucuronic acid and sulfate (Hattori et al., 1986). The MG metabolites tetrahydromagnolol and trans-isomagnolol showed an increasing trend after repeated administration, indicating that their formation was related to the induction of metabolic enzymes in animal tissues and/or intestinal bacteria. It was mainly excreted through liver metabolism and renal excretion (Hattori et al., 1986). The absorption half-life, elimination half-life ($T_{1/2}$), maximum concentration-time ($T_{max}$), and maximum concentration ($C_{max}$) of MG were 0.63 h, 2.33 h, 1.12 h, and 0.16 µg ml$^{-1}$, respectively. The water solubility and gastrointestinal absorption of MG were poor, with the oral bioavailability of only 4.9% (Tsai et al., 1996), limiting its clinical use. The low bioavailability might be partly due to the high metabolism of the intestine and liver and the low solubility in gastric juice.

In recent years, the bioavailability of MG has been significantly improved by various formulations including solid dispersion (Ochiuz et al., 2016; Tang et al., 2016; Stefanache et al., 2017b; Stefanache et al., 2017a; Li et al., 2019), phospholipid complex (Liu et al., 2020), liposome (Chen, 2008; Chen, 2009; Shen et al., 2016), nanoparticles (Wang et al., 2011), emulsion (Sheng et al., 2014), mixed micelles (Shen H et al., 2018; Ding et al., 2018), β-cyclodextrin inclusion compound (Qiu et al., 2016), and Zr-based organometallic framework (Santos et al., 2020) (Table 3).

Liu et al. prepared MG solid dispersion, MG solid lipid nanoparticles, and MG phospholipid complex and studied their bioavailability. The results showed that the cumulative dissolution of MG was 30.6% within 12 h, while the cumulative dissolution of MG solid dispersion, MG solid lipid nanoparticles, and MG phospholipid complex increased to 96.3, 76.4, and 45.9%, respectively. The pharmacokinetic parameters such as $C_{max}$ and area under the curve (AUC$_{0-1}$ and AUC$_{0-\infty}$) were significantly improved. Moreover, compared with raw MG, their relative bioavailability increased to 1.38, 2.12, and 3.45 times, respectively (Liu et al., 2020). All three preparations could improve the oral absorption bioavailability of MG, but the effect of MG solid lipid nanoparticles was more obvious. Lin et al. prepared a solid dispersion of MG with polyvinylpyrrolidone K-30 (PVP) and studied its bioavailability by oral administration (50 mg kg$^{-1}$). The results indicated that compared with raw MG, the solid dispersion of MG with PVP significantly increased the systemic exposures of MG and MG sulfates/glucuronides by 80.1 and 142.8%, respectively (Lin et al., 2014). For the solid dispersion prepared by MG and croscarmellose sodium (1: 5), the in vitro cumulative dissolution rate of MG reached 80.66% at 120 min, which was 6.9 times that of the raw MG (11.74%) (Tang et al., 2016). Stefanache et al. incorporated MG into the pores of amino-functionalized mesoporous silica particles to increase the dosage of MG and delay its release (Stefanache et al., 2017a).

After gavaging the emulsion (50 mg kg$^{-1}$) in male SD rats, the 1.20 h average plasma concentration of MG was 426.4727 ng ml$^{-1}$, and the absolute bioavailability was 17.579%, indicating that preparing an emulsion could improve the bioavailability of MG (Sheng et al., 2014).

Chen used 1,2-diacyl-Sn-glycero-3-phosphocholine (EPC) and 1,2-dipalmitoyl-Sn-glycero-3-phosphocholine (DPPC) liposomes to encapsulate MG with entrapment efficiencies of 74.13 ± 1.97% and 64.26 ± 2.92%, respectively. The results showed that EPC and DPPC liposomes enhanced the inhibitory effect of MG on VSMCs, and the inhibitory effect of EPC liposome-encapsulated MG on VSMCs was better than that of DPPC liposome (Chen, 2008). Qiu et al. utilized hydroxypropyl-β-cyclodextrin (HP-β-CD) to prepare MG-HP-β-CD inclusion complex (HP-β-CD: MG 10:1). The stoichiometric ratio of the inclusion compound was 1:1, and the stability constant ($K_c$) was calculated as 2206 M$^{-1}$. In addition, the aqueous solubility of the MG-HP-β-CD inclusion complex was more than 500-fold that of free MG, and it had better stability and stronger antitumor activity in vitro (Qiu et al., 2016). Santos et al. used Uio-66 (Zr) as the MG carrier. After oral or intraperitoneal administration of 100 mg kg$^{-1}$ of MG and MG@Uio-66(Zr), the AUC$_{0-720}$ of MG@Uio-66(Zr) (op:1823 ± 167.31 µg/ml min, i.p.: 2312.67 ± 253.76 µg/ml min) was significantly higher than the AUC$_{0-720}$ of free MG (op: 823.3 ± 139.10 µg/ml min, i.p.: 2582.67 ± 150.48 µg/ml min). The relative bioavailability of MG increased almost twofold by using Uio-66(Zr) (Santos et al., 2020).

The drug loading efficiency of MG-carboxymethyl-hexanoyloxy chitosan (CHC) nanoparticles was in the range of 91.6 ± 0.4 to 79.3 ± 2.2%, depending on the initial MG concentration of 0.05–0.2 mg mL$^{-1}$. MG-CHC nanoparticles had excellent cell uptake efficiency. Compared with free MG, it could be effectively delivered within the cell, which increased the resistance proliferation and inhibition of VSMC migration (Wang et al., 2011).

Mixed Soluplus (SOL) and Solutol HS15 (HS15), SOL, and D-alpha-tocopheryl polyethylene glycol 1,000 succinate (TPGS) were used to prepare MG-loaded mixed micelles (MG-M) MG-H and MG-T, respectively. The relative oral bioavailability of MG-T and MG-H were increased by 2.39- and 2.98-fold, respectively, compared to that of raw MG, indicating that MG-H and MG-T
could promote the absorption of MG in the gastrointestinal tract (Ding et al., 2018). Shen et al. also prepared MG-M by pluronic F127 and L61, and its drug loading efficiency and entrapment efficiency were 81.57 ± 1.49% and 27.58 ± 0.53%, respectively. In vitro release test showed that MG had sustained release behavior after being encapsulated in micelles. The permeability of MG through the Caco-2 cell monolayer was enhanced, and the relative bioavailability of oral MG-M was 2.83 times higher than that of the raw MG (Shen H et al., 2018). It can be seen that the mixed micelle drug delivery system can improve the poor water solubility and bioavailability of MG.

In general, the existing formulations can not only improve the water solubility and bioavailability of MG but also improve its stability, enhance its pharmacological effects, and enable MG to have a sustained release behavior, which will provide strategies for future clinical applications of MG.

CONCLUSION

In 2011, Chen et al. summarized the pharmacological activities and molecular mechanisms of MG. According to the review, MG could exhibit anti-inflammatory activity by inhibiting the production of inflammatory enzymes/cytokines and activation of NF-κB and leukocyte. It also exerted antitumor effects by inhibiting cell proliferation and metastasis and inducing apoptosis. The molecular mechanisms mainly include the increase of p21, p27, cell proliferation and metastasis and inducing apoptosis. The proliferation of smooth muscle cells and could attenuate VCAM-1, ICAM-1, MCP-1, and MMP9, inhibit the activation, CYP1A1, CYP1A2, MMP-9 as well as MMP-2 activity PTEN/AKT pathway, ERK1/2, NF-κB, P38, iNOS, and COX2 activation, CYP1A1, CYP1A2, MMP-9 as well as MMP-2 activity and Bcl-2 expression, induction of cytochrome C, and AIF release and activation of the mitochondrial death receptor pathway. MG could attenuate VCAM-1, ICAM-1, MCP-1, and MMP9, inhibit the proliferation of smooth muscle cells and fibroblasts, and obtain arrhythmia from I/R injury to show cardiovascular protection. It could also exert neuroprotective activities by inhibiting the production of PGE2, regulating (GABA)A receptor subtypes and central serotonergic activity, retaining cholinergic neurons in the forebrain, and inhibiting cortical 5-HT release. MG had a therapeutic effect on gastrointestinal diseases by regulating serotonergic and gastrointestinal system functions and relaxing gastrointestinal smooth muscles. Moreover, it exhibited hypoglycemic activity by activating PPAR and increasing basal and insulin-stimulated glucose uptake (Chen YH et al., 2011).

In this review, in vivo and in vitro studies demonstrated that MG has a wide range of pharmacological activities including anti-inflammatory, antitumor, antioxidant, hypoglycemic, cardiovascular protection, antiangiogenesis, and antibacterial. MG inhibited TLR2/TLR4/NF-κB/MAPK/PPAR-γ pathways and decreased the expression of inflammatory cytokines to exhibit anti-inflammatory activity. It suppressed the growth, migration, and invasion of tumor cells and promoted apoptosis as well as autophagy, through acting on caspase-8, caspase-3, and other proteins participated in the p53, MAPK, NF-κB, TLR, PI3K/Akt/mTOR, and Wnt/β-catenin signaling pathways. It also protected the nervous system through multiple systems and multiple targets. Moreover, it has a wide range of antibacterial activity. MG is a candidate drug for anti-inflammatory, anticancer, and neuroprotective activities. However, MG’s in vivo effect with CYP enzymes is not clear yet, and there is no clinical research on MG, which cannot fully provide the pharmacological activities of it.

MG and honokiol have similar pharmacological activities. Both of them can exhibit antitumor activities by regulating MAPK, NF-κB, HIF-α, PI3K/Akt/ERK/mTOR, and Wnt/β-catenin signaling pathways. MG shows antitumor activity by regulating TLR signaling pathways, and honokiol can regulate STAF, EGFR, and notch signaling pathways to exhibit antitumor activities. They have inhibitory activity on α-glucosidase and stimulation of glucose uptake to play a hypoglycemic role, while MG has a better inhibitory effect of α-glucosidase. Moreover, both MG and honokiol exhibit gastrointestinal protective activity with similar mechanism, while MG’s antiarrheal activity is better than that of honokiol. MG is a partial agonist of CB1 and CB2; however, honokiol is a full agonist of CB1 and an inverse agonist of CB2. MG has no activity on GPR-55, while honokiol is an antagonist of GPR-55. Honokiol has a stronger positive regulatory effect on GABAA receptors than MG; however, MG is more effective in enhancing PPAR-γ luciferase levels than honokiol. What is more, the inhibition types of MG on CYP1A, CYP2C19, CYP2C, CYP3A, and CYP1A2 were competitive inhibition. The inhibition type of honokiol on CYP1A2 was competitive inhibition, and the inhibition types of honokiol on CYP2E1 and CYP2C19 were noncompetitive inhibition. Both honokiol and MG have antimicrobial activity. The difference is that honokiol exhibits better antimicrobial activity than MG on Aggregatibacter actinomycetemcomitans, S. mutans, S. aureus, MRSA, Escherichia coli, and Fusarium spp.

MG is nontoxic and is used in dietary supplements and cosmetic products, such as added to toothpaste to play antibacterial and antiperiodontitis effects. However, the low water solubility, poor bioavailability, and skin irritation hamper its application. To overcome this problem, numerous studies have been conducted. By preparing solid dispersions, nanoparticles, phospholipid complexes, liposomes, emulsions, etc., the bioavailability and stability of MG significantly improved, which will greatly promote its clinical application. Aside from its formulations, structural modification is becoming an increasingly promising method for obtaining MG derivatives with better therapeutic effects and higher bioavailability. The synthesis and research of MG derivatives are beyond the scope of this study, so we will not go into details. Consequently, the design and research of MG derivatives are of great significance in the future.

In summary, this article comprehensively reviews the pharmacology, toxicity, bioavailability, and formulations of MG.

AUTHOR CONTRIBUTIONS

YL and YS contributed to the conception and design of the study; YL, YL, and YZ prepared the original draft; BT, XQ, and QY reviewed and edited the manuscript; YS supervised the study.
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GLOSSARY

(iNOS) inducible nitric oxide synthase
(COX-2) cyclooxygenase-2
(NF-κB) nuclear factor-κB
(MAPK) mitogen-activated protein kinase
(PGEs) prostaglandins
(ERK) extracellular signal-regulated kinase
(BMK1) big mitogen-activated protein kinase 1
(SAPK) stress-activated protein kinase
(JNK) c-Jun N-terminal kinase
(NO) nitric oxiditric oxide
(TLR) Toll-like receptor
(Pi3K) phosphatidylinositol 3-kinase
(Akt) Protein kinase B
(LPS) lipopolysaccharide
(IκB) inhibitor kappa Binhibitor κB
(Nrf2) nuclear factor-erythroid 2-related factor 2
(HO) heme oxygenase
(SD) Sprague Dawley
(PPAR-γ) peroxisome proliferator-activated receptor-γ
(ROS) reactive oxygen species
(MMP) matrix metalloproteinase
(PCNA) proliferating cell nuclear antigen
(CCA) cholangiocarcinoma
(Bcl-2) B-cell lymphoma-2
(mTOR) mammalian target of rapamycin
(PKC) protein kinase C
(VSMC) vascular smooth muscle cell
(NO) nitric oxiditric oxide
(cGMP) guanosine 3',5'-cyclic phosphate
(ACE) angiotensin-converting enzyme
(Ang II) angiotensin II
(AT-1R) Ang II type 1 receptor
(FAK) focal adhesion kinase
(MEK) mitogen-activated protein kinase
(eNOS) endothelial nitric oxide synthase
(MES) mouse embryonic stem
(EB) embryoid body
(VEGF) vascular endothelial growth factor
(HIF-1a) hypoxia-inducible factor-1a
(ET-1) endothelin-1
(TNF-α) tumor necrosis factor-α
(PAH) pulmonary arterial hypertension

(DSS) dextran sulfate sodium
(IL-1β) interleukin-1β
(IκB) inhibitor kappa Binhibitor κB
(ICAM-1) intercellular adhesion molecule-1
(Cdk2) cyclin-dependent kinase 2
(IGF-1) insulin-like growth factor-1
(IGFBP-5) IGF-binding protein-5
(IGF-1R) IGF-1 receptor
(MPO) myeloperoxidase
(PKA) protein kinase A
(AD) Alzheimer’s disease
(CYP) cytochrome P450 monooxygenase
(SOD) superoxide dismutase
(GSH-Px) glutathione peroxidase
(CORT) corticosterone
(GSH) glutathione
(AA) aristolochic acid
(MIC) minimal inhibitory concentration
(MBC) minimal bactericidal concentration
(SIRT1) silent information regulator 1
(NE) norepinephrine
(BDNF) brain-derived neurotrophic factor
(HPA) hypothalamic–pituitary–adrenal
(5-HT) 5-hydroxytryptamine
(4-HNE) 4-hydroxynonenal
(FoxO) O subfamily of forkhead transcription factors
(HASMCs) human aortic smooth muscle cells
(Cdc42) cell division cycle 42
(GSK3β) glycogen synthase kinase 3β
(HEK) human embryonic kidney
(I-R) ischemia–reperfusion
(CMS) chronic mild stress
(BBB) blood–brain barrier
(LC50) lethal concentration
(CAT) catalase
(p-JNK) phospho-JNK
(MRSA) methicillin-resistant Staphylococcus aureus
(MSSA) methicillin-susceptible S. aureus
(CDC) cell division cycle gene
(PS-630) Povidone S-630
(HPC) hydroxypropyl cellulose
(EPO) Eudragit EPO
(PVP K30) polyvinylpyrrolidone K30
(CMC) carboxymethylcellulosecroscarmellose sodium
(BMP2) bone morphogenetic protein 2
(RUNX2) runt-related transcription factor 2
(ApoE) apolipoprotein E
(i.v.) intravenous
(i.p.) intraperitoneal
(CMC) carboxymethylcellulosecroscarmellose sodium

(AUC) area under the curve
(T1/2) elimination half-life
(Tmax) maximum concentration-time
(Cmax) maximum concentration
(GBC) gallbladder carcinoma
(TMT) trimethyltin