

REVIEW

Emodin: A Review of its Pharmacology, Toxicity and Pharmacokinetics

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Emodin is a natural anthraquinone derivative that occurs in many widely used Chinese medicinal herbs, such as *Rheum palmatum*, *Polygonum cuspidatum* and *Polygonum multiflorum*. Emodin has been used as a traditional Chinese medicine for over 2000 years and is still present in various herbal preparations. Emerging evidence indicates that emodin possesses a wide spectrum of pharmacological properties, including anticancer, hepatoprotective, antiinflammatory, antioxidant and antimicrobial activities. However, emodin could also lead to hepatotoxicity, kidney toxicity and reproductive toxicity, particularly in high doses and with long-term use. Pharmacokinetic studies have demonstrated that emodin has poor oral bioavailability in rats because of its extensive glucuronidation. This review aims to comprehensively summarize the pharmacology, toxicity and pharmacokinetics of emodin reported to date with an emphasis on its biological properties and mechanisms of action. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: emodin; pharmacology; toxicology; pharmacokinetics; mechanisms.

INTRODUCTION

Emodin (1,3,8-trihydroxy-6-methylanthraquinone) (Fig. 1) is a naturally occurring anthraquinone derivative and an active ingredient of Chinese herbs, including *Rheum palmatum* (Wang *et al.*, 2011), *Polygonum cuspidatum* (Wang *et al.*, 2012a), *Polygonum multiflorum* (Lee *et al.*, 2011), *Aloe vera* (Naqvi *et al.*, 2010) and *Cassia obtusifolia* (Yang *et al.*, 2003). These herbs have been widely used as traditional medicines in many countries, especially in eastern Asia. Currently, a number of researchers are focusing on the pharmacological effects of this compound. Previous reviews have summarized the anticancer and antiinflammatory properties of emodin (Shrimali *et al.*, 2013; Wei *et al.*, 2013). In the last 3 years, there have been many reports on the anti-tumour and antiinflammatory effects of emodin. Furthermore, emodin has been demonstrated to possess a wide spectrum of pharmacological effects, such as antiviral, antibacterial, anti-allergic, anti-osteoporotic, anti-diabetic, immunosuppressive, neuroprotective and hepatoprotective activities. Moreover, the laxative property of emodin has been its primary mechanism of action for promoting weight loss (Matsuda *et al.*, 2008).

These pharmacological properties suggest that emodin might be a valuable therapeutic option for the prophylaxis and treatment of various diseases, including constipation (Cirillo and Capasso, 2015), asthma, atopic

dermatitis, osteoarthritis, diabetes and diabetic complications, atherosclerosis, Alzheimer's disease (AD), hepatic disease and several types of cancers, such as pancreatic cancer, breast cancer, hepatocellular carcinoma and lung carcinoma. However, an increasing number of recently published studies have reported adverse effects of emodin. The purpose of this review is to provide updated, comprehensive information on the pharmacology, toxicity and pharmacokinetics of emodin in the past few decades to explore the therapeutic potential of this compound and evaluate future research opportunities.

PHARMACOLOGY

Anticancer activity

Induction of apoptosis. Emodin significantly inhibited the cell growth of four bladder cancer cell lines by modulating epigenetic modifications in a dose-dependent and time-dependent manner (Cha *et al.*, 2015). In another study, emodin (IC₅₀ = 3.70 μM) was shown to modulate the expression of apoptosis-related genes to induce growth inhibition and apoptosis in A549 cells. Treatment with emodin helped to enhance apoptosis in A549 cells through up-regulation of the gene expression of Fas ligand (FASL) and disabled damage repair in A549 cells through down-regulation of the gene expression of C-MYC (Li *et al.*, 2014b). Emodin could induce growth inhibition and apoptosis in MCF-7 cells through the modulation of the expression of apoptosis-related genes. The gene expression of FASL was up-regulated,

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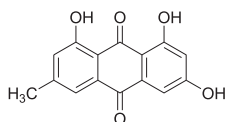


Figure 1. Chemical structure of emodin.

although the expression levels of MCL1, CCND1 and C-MYC were down-regulated (Li *et al.*, 2013b).

Emodin effectively blocked the self-renewal activity of glioma stem cells by suppressing crucial stemness signalling pathways involving Notch-1, b-catenin and STAT3. Emodin induced proteosomal degradation of EGFR/EGFRvIII by interfering with its association with Hsp90, leading to partial induction of apoptosis and sensitization of glioma stem cells to ionizing radiation (Kim *et al.*, 2014b). Wang *et al.* reported that emodin inhibited human cervical cancer HeLa cell proliferation by inducing apoptosis through the intrinsic mitochondrial and extrinsic death receptor pathways (Wang *et al.*, 2013). Furthermore, emodin was also reported to potentiate TNF-related apoptosis-inducing ligand-induced apoptosis through the induction of death receptors and the down-regulation of cell survival proteins in hepatocellular carcinoma cells (Subramaniam *et al.*, 2013).

Emodin significantly inhibited breast cancer cell proliferation by down-regulating ER α protein levels (Huang *et al.*, 2013). Xie *et al.* demonstrated that emodin-provoked oxidative stress induced apoptosis in human colon cancer HCT116 cells through a p53-mitochondrial apoptotic pathway (Xie *et al.*, 2014). A similar study showed that emodin could inhibit LOVO colorectal cancer cell growth via the regulation of the Bcl-2/Bax ratio and by its effect on the mitochondrial apoptosis pathway (Ma and Li, 2014a).

Wnt signalling is involved in the regulation of cell proliferation, differentiation and apoptosis. Emodin suppressed the Wnt signalling pathway in human colorectal cancer cells (SW480 and SW620) by down-regulating T-cell factor/lymphoid enhancer factor transcriptional activity (Pooja and Karunakaran, 2014).

Anti-metastasis. Jia *et al.* demonstrated for the first time that emodin suppressed pulmonary metastasis of breast cancer by inhibiting macrophage recruitment and M2 polarization in the lungs by reducing STAT6 phosphorylation and CCAAT/enhancer-binding protein β expression (Jia *et al.*, 2014b). In another study, treatment with a combination of emodin (10, 20, 40 and 80 μ M) and curcumin (10 μ M) inhibited the proliferation and invasion of breast cancer cells by increasing the expression of miR-34a (Guo *et al.*, 2013b). It has been shown that emodin suppressed human breast cancer cell invasiveness *in vitro* and *in vivo* by antagonizing the P2X7Rs (Jelassi *et al.*, 2013). Moreover, emodin dose dependently inhibited the migration and invasion of human breast cancer MDA-MB-231 cells by down-regulating the expression of MMP-2, MMP-9, uPA and uPAR and by decreasing the activity of p38 and extracellular regulated protein kinases (ERK) (Sun *et al.*, 2015a).

Emodin treatment significantly suppressed metastasis to the lungs in an orthotopic hepatocellular carcinoma mice model and CXCR4 expression in tumour tissues (Manu *et al.*, 2013). Way *et al.* demonstrated that emodin significantly inhibited TWIST1-induced cell migration

and invasion by inhibiting the β -catenin and Akt pathways (Way *et al.*, 2014).

Cell cycle arrest. An MTT assay, flow cytometry and electron microscopy were used to investigate the inhibitory effect of emodin on the human hepatoma cell line SMMC-7721. The results showed that the proliferation of SMMC-7721 cells was inhibited in a time-dependent and concentration-dependent manner, that cells in G2/M phase increased significantly and that the proportion of S-phase cells gradually declined (Zhang *et al.*, 2015a).

Reversion of multidrug resistance. The overexpression of multidrug resistance (MDR) in tumour cells poses a serious obstacle to successful chemotherapy (Wesolowska, 2011). Our investigations demonstrate that emodin could sensitize tumour cells to chemotherapeutic agents via inhibiting pathways. Emodin/cisplatin co-treatment inhibited the growth of human ovarian carcinoma cells and gallbladder carcinoma cells *in vivo*. This mechanism might involve the down-regulation of MRP1 expression (Ma *et al.*, 2014b) and ABCG2 expression (Li *et al.*, 2012b). In addition, the combination of emodin (25 μ M) and cisplatin (3.0 μ M) induced a relatively higher inhibitory effect on gastric cancer cells than that of individual treatment with emodin or cisplatin by inducing apoptosis and cell cycle arrest (Huang *et al.*, 2015).

Chen *et al.* showed a synergistic growth-inhibitory effect of azidothymidine and emodin in K562/ADM cells. This effect might be mediated by S cell cycle arrest and decreased MDR1 mRNA/p-gp protein expression (Chen *et al.*, 2013). Furthermore, the gene and protein expression levels of nuclear factor- κ B (NF- κ B), X-linked inhibitor of apoptosis and survivin were suppressed in Bxpc-3/Gem cells treated with the combination of emodin and gemcitabine (Zhang *et al.*, 2013).

Emodin inhibits cell growth in several types of cancer cells and regulates genes and proteins related to the control of cell apoptosis, cell invasion, metastasis and cell cycle arrest. Moreover, the synergistic enhancement of apoptosis is important in combination chemotherapeutic agents for cancer and has attracted attention as a promising avenue of treatment.

Antiinflammatory activity

Nuclear factor- κ B is involved in the transcription of various pro-inflammatory genes involved in disease progression. The antiinflammatory effect of emodin has been associated with the inhibition of the pro-inflammatory transcription factor NF- κ B. Gao *et al.* elucidated the antiinflammatory active components of Jiashitang scar removal ointment, including saffimin, emodin, salvianolic acid, tanshinone and triterpenoid saponin derivatives. Among these active ingredients, emodin was predicted to exert NF- κ B-inhibiting effects through the mitogen-activated protein kinase (MAPK), PI3K/AKT and NIK-IKK pathways (Gao *et al.*, 2014). In a collagen-induced arthritic mouse model, emodin exhibited its anti-arthritis effects through inhibition of the NF- κ B pathway and pro-inflammatory mediators (Hwang *et al.*, 2013; Zhu *et al.*, 2013). Moreover, emodin could improve the corneal structure and reduce corneal

injure by suppressing the activation of NF- κ B, c-JunN-terminalkinase (JNK) and the expression of ICAM-1 (Kitano *et al.*, 2007; Chen *et al.*, 2009a, 2015a). In a severe acute pancreatitis (SAP) model group, emodin treatment significantly decreased the expression of Bip, inositol-requiring-1 α (IRE1 α), TNF receptor-associated factor 2 and ASK1 and inhibited phosphorylation of JNK and p38 MAPK by inhibiting ER stress transducers IRE1 α and its downstream molecules (Wu *et al.*, 2013). Jia *et al.* found that emodin could halt the transition from simple steatosis to non-alcoholic steatohepatitis by suppressing Erk1/2 and p38 signalling in *in vitro* experiments (Jia *et al.*, 2014a).

Reports also have shown that emodin has a protective role in rats with acute necrotizing pancreatitis by increasing the expression levels of mCD14 and inhibiting the serum expression levels of TNF- α , IL-6 and IL-1 β (Ni *et al.*, 2014; Yao *et al.*, 2015). In lipopolysaccharide (LPS)-induced mouse mastitis, emodin could reduce LPS-induced mammary gland injuries and inflammatory cell infiltration, decrease myeloperoxidase (MPO) activation in the mammary gland, down-regulate the expression of TNF- α , IL-6 and IL-1 β and activate PPAR- γ in a dose-dependent manner (Yang *et al.*, 2014b; Li *et al.*, 2013a). A similar study showed that emodin considerably decreased the levels of TNF- α , IL-6, MPO, malondialdehyde (MDA), CINC-1, MIP-2 and ICAM-1. However, the levels of nitric oxide and inducible nitric oxide synthase were markedly increased (Ding *et al.*, 2008).

Emodin could attenuate pulmonary oedema and inflammation, enhance alveolar epithelial barrier function and promote the expression of claudin-4, claudin-5 and occludin in lung tissues (Xia *et al.*, 2010). Furthermore, emodin treatment effectively inhibited allergen-induced inflammation by reducing the Th2 immune response, suppressing MMP-9 expression and inducing HO-1 expression in a murine model of asthma (Wang *et al.*, 2015b). LTs synthesized by the 5-LOX reaction are believed to play an important role in atopic dermatitis, and Jin *et al.* demonstrated that emodin possessed a 5-LOX inhibitory action (Jin *et al.*, 2011).

The study results reflect that emodin is capable of inhibiting the activation of NF- κ B, JNK, p38 MAPK, Erk1/2 and 5-LOX, suppressing the expression of TNF- α , IL-6, IL-1 β , MPO, MDA, CINC-1, MIP-2, ICAM-1 and MMP-9 and enhancing the levels of mCD14, nitric oxide and inducible nitric oxide synthase. Emodin has been shown to exhibit potential therapeutic effects in the treatment and prevention of various inflammatory disorders.

Antivirus activity

Severe acute respiratory syndrome (SARS) is an emerging infectious disease caused by a novel coronavirus (Ho *et al.*, 2007). In a model of *Xenopus* oocytes, emodin could inhibit the 3a ion channel of coronavirus SARS-CoV and HCoV-OC43 and inhibit virus release from HCoV-OC43 with a $K_{1/2}$ value of approximately 20 μ M (Schwarz *et al.*, 2011). Moreover, emodin significantly blocked the S protein and ACE2 interactions in a dose-dependent manner and inhibited the infectivity of S protein-pseudotyped retrovirus to Vero E6 cells. The results suggested that emodin might be considered as a

potential lead therapeutic agent in the treatment of SARS (Ho *et al.*, 2007). Dang *et al.*, for the first time, demonstrated that emodin had a weak but long-lasting inhibitory effect on HBV replication *in vivo* (Dang *et al.*, 2009). *In vitro* experiments showed that exposure of HepG-2 cells to emodin resulted in time-dependent and concentration-dependent inhibition of hepatitis B virus DNA replication and hepatitis B surface antigen secretion (Dang *et al.*, 2006). Similarly, emodin reduced Cocksackievirus B₄ entry and replication on HepG-2 cells in a concentration-dependent and time-dependent manner. The results implied that emodin might act as a biological synthesis inhibitor against Cocksackievirus B₄ infection rather than directly inactivating the viruses or blocking their absorption to the susceptible cells (Liu *et al.*, 2013). In a biochemical assay, emodin specifically inhibited the nuclease activity of herpes simplex virus-1 UL12 alkaline nuclease. Furthermore, emodin possessed antiviral activities through the disruption of the phospholipid bilayer and the inhibition of CK2 (Hsiang and Ho, 2008).

Therefore, these results suggest that emodin might be a potent viral inhibitor with a broad spectrum of antiviral activities, indicating that emodin might act as an antiviral drug by blocking virus infection and replication in a time-dependent and concentration-dependent manner.

Antibacterial activity

Emodin exhibited a remarkable bacteriostatic effect on the Gram-positive bacteria tested, especially *Bacillus subtilis* and *Staphylococcus aureus*. The bioactive minimum inhibitory concentration (MIC) values of emodin were 28.9 and 14.4 μ M. However, emodin was not active against two Gram-negative bacteria (*Klebsiella pneumoniae* and *Escherichia coli*) at the highest concentration (1851.9 μ M) tested (Chukwujekwu *et al.*, 2006). Similarly, emodin has been reported to exhibit antimycobacterial and broad spectrum antibacterial activity, particularly against *M. tuberculosis* (lowest MIC = 0.9 μ M) and Gram-positive bacteria (lowest MIC < 14.8 μ M) of clinical origin (Dey *et al.*, 2014). Cao *et al.* investigated the anti-methicillin-resistant *S. aureus* (anti-MRSA) activity and chemical compositions of ether extracts from *Rhizoma Polygoni Cuspidati* (ET-RPC). The results showed that ET-RPC could significantly inhibit bacterial growth of MRSA strains. Moreover, emodin was identified as the major compound with anti-MRSA activity, which was related to the destruction of the integrity of the cell wall and cell membrane (Cao *et al.*, 2015).

Emodin also significantly attenuated the growth, acid production and insoluble glucan synthesis of *Streptococcus mutans* *in vitro* and suppressed the development of dental caries in rats. The results suggested that the natural compound emodin might be a novel pharmacological agent for the prevention and treatment of dental caries (Xu *et al.*, 2014). Chen *et al.* reported for the first time that emodin functioned as a competitive inhibitor against *Helicobacter pylori*, which might be associated with occupying the entrance of the tunnel or embedding into the tunnel to prevent the substrate from accessing the active site (Chen *et al.*, 2009b).

Overall, like many herbal monomers, emodin has a potential antimicrobial property. Emodin itself could

be used as a potential lead compound for further anti-bacterial drug discovery.

Anti-allergic activity

Allergic reactions are triggered when allergens cross-link with the high-affinity IgE receptor (FcεRI) on mast cells. To assess the anti-allergic activity of emodin, an *in vivo* passive anaphylaxis animal model and *in vitro* mouse bone marrow-derived mast cells were used to investigate the mechanism of its action on mast cells. The results demonstrated that emodin attenuated the mast cell-dependent passive anaphylactic reaction in IgE-sensitized mice. Therefore, emodin inhibited mast cell activation and thereby the anaphylactic reaction through the suppression of the receptor-proximal Syk-dependent signalling pathways (Lu *et al.*, 2011).

An increase in the intracellular calcium (Ca²⁺) concentration also triggers degranulation, bypassing receptor activation. Emodin significantly inhibited TNF-α production and degranulation through the regulation of IKK2 and PKC activation, suggesting that emodin inhibits mast cell activation through the FcεRI-mediated proximal signalling pathway and through the Ca²⁺ influx-mediated downstream signalling pathway (Kim *et al.*, 2014a). In rat basophilic leukaemia (RBL-2H3) cells, Wang *et al.* evaluated the inhibitory effects of emodin on the IgE-mediated allergic response by measuring the release of granules and cytokines. Emodin suppressed degranulation and cytokine production by increasing the stability of the cell membrane and inhibiting extracellular Ca²⁺ influx (Wang *et al.*, 2012b).

Emodin significantly suppresses mast cell degranulation by either FcεRI or calcium ionophore stimulation, suggesting that emodin could be further developed as a therapeutic agent for immediate and chronic allergic diseases.

Neuroprotective activity

The accumulation of β-amyloid protein (Aβ) in the brain plays an important role in the pathogenesis of AD. Emodin up-regulated Bcl-2 and also blocked amyloid-β_{25–35}-induced autophagy through the activation of the ER/PI3K/Akt pathway and the class III phosphatidylinositol 3-kinase/Beclin-1/B-cell lymphoma 2 pathway, respectively (Liu *et al.*, 2010; Sun and Liu, 2015b). The results provided confirmatory evidence for the application of emodin in the prevention and treatment of AD. Furthermore, emodin raised the survival rate of oxygen-glucose-deprived neuron-like cells, increased activin A expression and decreased caspase-3 expression, indicating that emodin could inhibit neuronal apoptosis and alleviate nerve cell injury after oxygen-glucose deprivation through the activin A pathway (Guo *et al.*, 2013a). Yang *et al.* observed the interventional effects of emodin in epileptic rats and elucidated a possible mechanism of action. The findings suggested that emodin could influence the effects of cyclooxygenase-2 in brain tissue and block *N*-methyl-D-aspartate-mediated overexpression of MDR1, thereby achieving anti-epileptic effects (Yang *et al.*, 2015).

In chronic unpredictable mild stress mice, emodin treatment (20, 40 and 80 mg/kg) reversed the

behavioural deficiency. Emodin normalized the change of the plasma corticosterone level and up-regulated the hippocampal glucocorticoid receptor (GR) (mRNA and protein) and brain-derived neurotrophic factor (BDNF) (mRNA) expression levels (Li *et al.*, 2014a). It was shown for the first time that emodin treatment led to induced neurite outgrowth through the PI3K/Akt/GSK-3β signalling pathway in Neuro2a cells (Park *et al.*, 2015). Zhou *et al.* demonstrated that emodin induced BV-2 cell apoptosis and consequently eliminated inflammatory microglia through the induction of TRB3, suggesting that emodin is a candidate for treating intracerebral haemorrhages and other neurodegenerative disorders that involve microglial activation (Zhou *et al.*, 2011). The P2X_{2/3} receptors play a crucial role in facilitating the transmission of pain in neuropathic pain states. Emodin could decrease the expression of the P2X_{2/3} receptor during chronic pain and inhibit primary afferent transmission mediated by the P2X_{2/3} receptor (Gao *et al.*, 2011).

Based on the aforementioned studies, emodin could act as an effective neuroprotective drug for treating AD and epilepsy and could antagonize ischemia-reperfusion brain injury and glutamate-induced neuronal damage.

Immunosuppressive activity

Emodin has been developed as an immunosuppressive agent. Emodin (1, 10 and 100 μM) was observed to exert immunosuppressive actions by inhibiting the growth of human T cells and inducing apoptosis in a dose-dependent and time-dependent manner. Furthermore, emodin disrupted the mitochondrial membrane potential and increased the cytosolic level of cytochrome C and levels of activated cleavage fragments of caspase-3, -4, and -9 in human T cells (Qu *et al.*, 2013). *In vivo* and *in vitro* experiments showed that emodin ameliorated the proliferation of peripheral blood mononuclear cells, promoted Th2-type cytokine IL-4 and reduced the Th1-type cytokine IL-2, showing immunosuppressive potential (Liu *et al.*, 2009b).

Emodin played a key role in the inhibition of the differentiation and maturation of dendritic cells and enhancement of Tregs production, which might be helpful for the modulation of immune rejection after liver transplantation (Zhang *et al.*, 2012). Emodin treatment also prolonged the liver allograft survival time and inhibited histopathologic changes of acute graft rejection. The mechanisms underlying this effect might be associated with polarizing the Th1/Th2 paradigm to Th2 (Tong *et al.*, 2011).

The studies demonstrated that emodin exerts a broad range of actions on the immune system. The potential immunosuppressive mechanism might be the suppression of lymphocyte proliferation and cytokine production, which might be helpful for the modulation of immune suppression and the induction of immune tolerance.

Anti-osteoporotic activity

Emodin has been used to treat bone diseases for thousands of years. In the mouse model of LPS-mediated

osteoporosis, Kang *et al.* demonstrated that emodin treatment showed the anti-osteoporotic effect by the marked suppression of bone resorption (Kang *et al.*, 2014). Furthermore, emodin could increase the number of osteoblasts, the bone mineral density and the connectivity density in ovariectomized mice. The gene and protein expression levels of osteogenesis markers, such as Runx2, osterix, collagen type I, osteocalcin or ALP, were up-regulated (Yang *et al.*, 2014a). A similar study showed that emodin also increased alizarin red-mineralization activity and the expression of osteogenesis markers (Runx2, osteocalcin and ALP) and activated the p38-Runx2 pathway, which enhanced osteoblast differentiation. However, emodin suppressed receptor activator of NF- κ B ligand (RANKL)-induced osteoclast differentiation of bone marrow macrophages and the bone-resorbing activity of mature osteoclasts by inhibiting RANKL-induced NF- κ B, c-Fos and NFATc1 expression (Kim *et al.*, 2014c). In another study, Lee *et al.* reported that emodin at low concentrations could accelerate the osteoblast differentiation by the induction of the BMP-2 gene by activating the PI3K-Akt and/or MAP kinase-NF- κ B signalling pathways (Lee *et al.*, 2008).

Summarizing the beneficial effect of emodin on bone health, our studies elucidate the pharmacological roles of emodin in the prevention of osteoporosis and provide the initiative in the early drug discovery and development for osteoporosis.

Anti-diabetic activity

Recent studies have suggested that emodin has a PPAR γ -activating effect. Intraperitoneal injections with emodin for 3 weeks notably ameliorated the symptoms of diabetic animals, and this effect was likely associated with the regulation of the PPAR γ pathway (Xue *et al.*, 2010). A similar study showed that emodin effectively ameliorated p38 over-activation and hypocontractility in high glucose-induced mesangial cells via activation of PPAR γ (Liu *et al.*, 2009a). In differentiated 3T3-L1 adipocytes, emodin exhibited a high binding affinity to PPAR γ by inducing an increase in glucose uptake and increases in GLUT1 and GLUT4 mRNA expression (Yang *et al.*, 2007).

Emodin has been reported to be a novel AMP-activated protein kinase (AMPK) activator. Emodin had a positive effect on glucose metabolism in 3T3-L1 adipocytes, which was primarily due to increases in glycolysis and might be mediated by the AMPK signalling pathway (Zhang *et al.*, 2015b). Chen and Song *et al.* also demonstrated that emodin regulated glucose utilization through activating the AMPK signalling pathway (Chen *et al.*, 2012; Song *et al.*, 2013). Moreover, emodin displayed an inhibitory effect on the high-level glucose-induced phosphorylation of ERK 1/2 and p38 MAPK (Gao *et al.*, 2015). Wang *et al.* demonstrated that long-term emodin (3 μ M) administration improved glucose tolerance and ameliorated other metabolic disorders in *ob/ob* mice by the inhibition of 11 β -HSD1 activity in adipose tissue (Wang *et al.*, 2012c). Emodin has been reported to exhibit protective effects against diabetic cardiomyopathy by regulating the AKT/GSK-3 β signalling pathway (Wu *et al.*, 2014).

Diabetic nephropathy (DN) is a major cause of end-stage renal disease (Baylis *et al.*, 2003). Emodin (40 mg/kg/day) was efficient to ameliorate renal dysfunction in DN rats likely by its inhibition of the activation of the p38 MAPK pathway and down-regulation of the expression of fibronectin (Wang *et al.*, 2006). Yang *et al.* also reported that emodin significantly decreased NF- κ B-mediated TGF- β 1 and fibronectin expression (Yang *et al.*, 2013). Furthermore, emodin (20 mg/kg/day) repressed renal integrin-linked kinase and desmin expression, preserved nephrin expression and ameliorated albuminuria in streptozotocin-induced diabetic rats (Chen *et al.*, 2015b). In rat mesangial cells cultured under high glucose, emodin suppressed hyperglycaemia-induced cell proliferation and fibronectin expression by inhibiting the p38MAPK pathway and cellular FLICE-inhibitory protein (cFLIP), suggesting a potential role of emodin in the treatment of DN (Gao *et al.*, 2014; Li *et al.*, 2009).

In summary, our results show that emodin ameliorates the symptoms of diabetic animals, and this effect is likely associated with the activation of the PPAR γ and AMPK signalling pathways. Therefore, emodin holds great promise for the eventual use of a therapeutic agent to treat diabetes mellitus and its complications.

Hepatoprotective activity

Emodin was found to ameliorate ethanol-mediated liver steatosis and decrease alanine aminotransferase (ALT), aspartate aminotransferase and hepatic triglycerides. Moreover, emodin significantly reduced liver α -smooth muscle actin and collagen type I, whereas it increased the mRNA levels of PPAR- γ (Liu *et al.*, 2014). In another experiment, emodin was shown to attenuate the ethanol-induced cytotoxicity of HepG2/CYP2E1 cells by the inhibition of Gamma-glutamyltransferase (GGT) activity and CYP2E1 protein expression in a dose-dependent manner, indicating that emodin might be beneficial in patients with alcoholic liver disease (Qian *et al.*, 2011). In a rat model with CCl₄-induced liver fibrogenesis, the activities of serum ALT and aspartate aminotransferase and the hepatic hydroxyproline content were significantly reduced by the administration of emodin. The mRNA and protein levels of TGF- β 1, Smad4 and α -SMA were also down-regulated in liver tissues (Dong *et al.*, 2009). Lee *et al.* demonstrated that emodin might be valuable for the protection of CCl₄-induced liver injury by reducing lipid peroxidation and by positively modulating inflammation (Lee *et al.*, 2012). Emodin also had the ability to prevent CCl₄-induced liver damage through reversing hepatic oxidative insults, CYP enzymatic activity and ultrastructural changes (Bhadoria *et al.*, 2009). In addition, emodin at a dose of 30 mg/kg (po) possessed optimum hepatoprotective ability against acetaminophen (APAP)-induced toxicity via diminishing oxidative stress (Bhadoria, 2010).

Yin *et al.* showed that emodin could effectively prevent LPS-induced fulminant hepatic failure, and this beneficial effect might occur by the blockade of TLR4/MD2 complex expression on the cell surface of macrophages, which could lead to the deactivation of the p38 MAPK and NF- κ B signalling pathways and inhibition of TNF- α production (Yin *et al.*, 2014). Similarly, emodin treatment protected against concanavalin

A-induced liver injury by inhibiting the activation of the p38 MAPK and NF- κ B signalling pathways in CD4+ T cells and macrophages, indicating that emodin can be applied as a potential candidate for the prevention and intervention of clinical fulminant hepatic failure (Xue *et al.*, 2015).

We may be able to conclude from these findings that emodin exhibits hepatoprotective effects in ethanol-induced hepatosteatosis and CCl₄ or APAP-induced liver injury, indicating that emodin might have therapeutic applications in the prevention of fulminant hepatitis.

TOXICITY

Through *in vivo* and *in vitro* experiments, Wang *et al.* investigated the toxicity and target organs of rhubarb in the rat and compared the toxicity of the essential components of rhubarb. In these studies, emodin was the primary toxic component of rhubarb, and the toxic target organs were predicted to be the kidney and liver (Wang *et al.*, 2007b). Emodin (30 μ M) led to significant apoptosis in a time-dependent manner, as determined by morphological changes in L-02 cells (Li *et al.*, 2012a). Furthermore, emodin had the potential to disturb glutathione (GSH) and fatty acid metabolism in human liver cells (Liu *et al.*, 2015). In addition, emodin exerted its cytotoxic effects in the hepatic cells of grass carp via apoptosis by directly affecting the mitochondria, indicating that high concentrations of emodin are not suitable for use in fish (Cui *et al.*, 2014).

The US National Toxicology Program showed that emodin exposure resulted in increased incidences of renal tubule pigmentation in male and female mice and increased incidences of nephropathy in female mice (National Toxicology Program, 2001). The administration of emodin (40 and 80 μ M) for 24 h resulted in a significant decrease in cell viability by approximately 29% and 45%, respectively, which was mediated through the induction of apoptosis in the caspase 3-dependent pathway and the mitochondrial pathway (Wang *et al.*, 2007a, 2015a). Another study demonstrated that emodin also significantly inhibited the proliferation of HK-2 cells, with IC₅₀ values of 130.65 μ M (Wang *et al.*, 2007c).

Emodin has been reported to exert reproductive toxicity. In male reproductive organs/tissues, the toxicity study of emodin indicated that it has testicular toxicity because of the disruption of the expression of testicular genes (Oshida *et al.*, 2011). Luo *et al.* demonstrated that emodin also inhibited human sperm functions by reducing sperm [Ca²⁺]_i and suppressing tyrosine phosphorylation *in vitro* (Luo *et al.*, 2015). Ethanol solution extracts of *R. patientia*, which contain anthraquinones, such as emodin and chrysophanol, as active ingredients, caused irreversible pathological changes at very high doses (4000 mg/kg), although lower doses and aqueous extracts produced either non-significant or reversible changes (Islam *et al.*, 2015). Therefore, long-term administration of high doses of anthraquinones extracts should be avoided altogether during pregnancy.

Li *et al.* found that emodin possessed genotoxicity and DNA-damaging properties by stabilizing Topo II-DNA cleavage complexes and inhibiting ATP hydrolysis (Li *et al.*, 2010). Moreover, emodin exerted a toxic function on interstitial cells of Cajal, which could lead to

membrane damage and energy metabolism disorders by inhibiting the activity of Na⁺-K⁺-ATPase and Ca²⁺-ATPase and increasing the activity of IP₃ and cAMP (Peng *et al.*, 2013).

PHARMACOKINETICS

In pharmacokinetic experiments, emodin was predominantly found in the liver and the brain after oral intake of *P. cuspidatum* (Lin *et al.*, 2012). After intragastric administration at doses of 20 and 40 mg/kg, emodin rapidly underwent phase II metabolism to form its glucuronide, and the parent form of emodin was almost undetectable *in vivo*. Even when administered at higher dose (82.4 mg/kg), the *in vivo* emodin levels detected remained very low (Shia *et al.*, 2010). In a Caco-2 cell culture model, Liu *et al.* demonstrated that glucuronidation metabolism appeared to be one of the main reasons for the very poor oral bioavailability of emodin (Liu *et al.*, 2012). Moreover, Ma *et al.* was the first to demonstrate that 2,3,5,4'-tetrahydroxystilbene-2-O- β -D-glucoside (TSG) could inhibit the phase II metabolism of emodin *in vivo* through down-regulation of the expression of UGT1A8 (Ma *et al.*, 2013). A similar study showed that piperine significantly increased the C_{max} and area under concentration-time curve (AUC) of emodin and decreased the AUC and C_{max} of emodin glucuronide. However, the detailed mechanisms of the improved bioavailability of emodin need to be further investigated (Di *et al.*, 2015). Traditional oral administration would not be the best method of application of emodin because of poor intestinal absorption, fast elimination and low bioavailability *in vivo*. The pharmacokinetics of emodin could be improved by inhibiting its glucuronidation metabolism. In further research, we should pay attention to the ability of emodin to lead to other toxicity problems due to the increase in its content.

Future perspectives and conclusions

Emodin, the major bioactive ingredient of *R. palmatum*, is available in common foods and is used as an alternative medicine. *In vitro* and *in vivo* pharmacological studies have revealed that emodin exhibits a variety of pharmacological benefits, including anticancer, anti-inflammatory, antiviral, antibacterial, anti-allergic, anti-osteoporotic, anti-diabetic, immunosuppressive, neuroprotective and hepatoprotective effects. Emodin has been widely used in the treatment of cancer, asthma, osteoarthritis, diabetes, atherosclerosis, AD and hepatic disease. Furthermore, many recent studies have shown that emodin in conjunction with various chemotherapeutic agents is effective in the elimination of tumour cell growth. Therefore, it is important to evaluate the effect of emodin on other drug metabolism before emodin can be safely used in combination with other drugs.

Emodin strongly inhibits the expression of proteins and genes, such as C-MYC, MCL1, CCND1, CK2, IKK2, PKC, TGF- β 1, Smad4 and Bcl-2/Bax. However, the expression levels of BDNF, Runx2, osterix, collagen type I, osteocalcin and ALP are up-regulated. Moreover, emodin affects the NF- κ B, MAPK, PI3K/AKT, NIK-IKK, PPAR γ , MMPs and activin A signalling pathways. The evidence provided strongly supports the

Table 1. Pharmacology of emodin

Pharmacological effect	Cell lines/model	Activity/mechanism(s) of action	Application	Reference	
Anticancer activity	Bladder cancer cell	Modulates epigenetic modifications	<i>In vitro</i>	Cha <i>et al.</i> (2015)	
	Human lung adenocarcinoma A549 cells	Modifies the extrinsic apoptotic pathways and induces cell cycle arrest	<i>In vitro</i>	Li <i>et al.</i> (2014b)	
	OECM-1 cells	Inhibits the β -catenin and Akt pathways	<i>In vitro</i> <i>In vivo</i>	Way <i>et al.</i> (2014)	
	Glioma stem cells	Inhibits the stemness signalling	<i>In vitro</i>	Kim <i>et al.</i> (2014b)	
	Human cervical cancer HeLa cells	Intrinsic mitochondrial pathway; extrinsic death receptor pathway	<i>In vivo</i>	Wang <i>et al.</i> (2013)	
	Human breast cancer cell	Inhibits the P2X7 receptor; down-regulates ER α protein levels, MCL1, CCND1, C-MYC, MMP-2, MMP-9, uPA and uPAR expression; reduces STAT6 phosphorylation and C/EBP β expression; and increases the expression of miR-34a	<i>In vitro</i> <i>In vivo</i>	Wang <i>et al.</i> (2013); Huang <i>et al.</i> (2013); Guo <i>et al.</i> (2013b); Li <i>et al.</i> (2013b); Jia <i>et al.</i> (2014b); Sun <i>et al.</i> (2015a)	
	Human colon cancer cell	Mitochondrial apoptosis pathway; p53-mitochondrial apoptotic pathway; Down-regulates TCF/LEF transcriptional activity, cell survival proteins, CXCR4 expression Induces death receptors	<i>In vitro</i> <i>In vivo</i>	Xie <i>et al.</i> (2014); Ma and Li (2014a); Pooja and Karunakaran (2014); Subramaniam <i>et al.</i> (2013); Manu <i>et al.</i> (2013)	
	Human ovarian carcinoma cell	Down-regulates MRP1 expression	<i>In vivo</i>	Ma <i>et al.</i> (2014b)	
	Gallbladder carcinoma cell	Down-regulates ABCG2 expression	<i>In vivo</i>	Li <i>et al.</i> (2012b)	
	Gastric cancer cells K562/ADM cells	Induces apoptosis; Induces cell cycle arrest Decreased MDR1 mRNA/p-gp protein expression	<i>In vitro</i> <i>In vitro</i>	Huang <i>et al.</i> (2015) Chen <i>et al.</i> (2013)	
	Antiinflammatory activity	Severe acute pancreatitis model	Inhibits ER stress transducers IRE1 α and its downstream molecules; the serum expression levels(TNF- α , IL-6, IL-1 β); increases the expression levels of mCD14	<i>In vitro</i> <i>In vivo</i>	Wu <i>et al.</i> (2013); Xia <i>et al.</i> (2010); Ni <i>et al.</i> (2014); Yao <i>et al.</i> (2015)
		Collagen-induced arthritic mice model	Inhibits the NF- κ B pathway; pro-inflammatory mediators	<i>In vivo</i>	Huang <i>et al.</i> (2013); Zhu <i>et al.</i> (2013)
		LPS-induced mouse mastitis	Activates PPAR- γ	<i>In vivo</i>	Yang <i>et al.</i> (2014b); Li <i>et al.</i> (2013a)
LPS-induced mouse corneal injury		Suppresses the activation of NF- κ B, JNK and the expression of ICAM-1	<i>In vitro</i> <i>In vivo</i>	Kitano <i>et al.</i> (2007); Chen <i>et al.</i> (2009a); Chen <i>et al.</i> (2015a)	
Non-alcoholic steatohepatitis model		Suppresses Erk1/2 and p38 signalling	<i>In vitro</i>	Jia <i>et al.</i> (2014a)	
Ovalbumin-induced mouse model Atopic dermatitis mouse model		Suppresses MMP-9 expression;Induces HO-1 expression Inhibits 5-LOX action	<i>In vivo</i> <i>In vivo</i>	Wang <i>et al.</i> (2015b) Jin <i>et al.</i> (2011)	
Antivirus activity	Vero E6 cells	Blocks the S protein and ACE2 interaction	<i>In vitro</i>	Ho <i>et al.</i> (2007)	
	Rhabdomyosarcoma cells	Inhibits the 3a ion channel of coronavirus SARS-CoV and HCoV-OC43	<i>In vitro</i>	Schwarz <i>et al.</i> (2011)	
	Human hepatoma 2.2.15 cells African green monkey kidney cells	Inhibits the replication of hepatitis B virus Disrupts phospholipid bilayer; inhibits CK2 and UL12	<i>In vitro</i> <i>In vitro</i> <i>In vitro</i>	Dang <i>et al.</i> (2006); Dang <i>et al.</i> (2009) Hsiang and Ho (2008)	
Antibacterial activity	The bacterial strain MRSA252	Destructs the integrity of the cell wall and cell membrane	<i>In vitro</i>	Cao <i>et al.</i> (2015)	
	<i>S. mutans</i> ATCC 25175	Suppressed the synthesis of insoluble glucans	<i>In vitro</i> <i>In vivo</i>	Xu <i>et al.</i> (2014)	
	Standard <i>H. pylori</i> strains SS1 and ATCC 43504	Occupies the entrance of the tunnel or embeds into the tunnel	<i>In vitro</i>	Chen <i>et al.</i> (2009b)	
Anti-allergic activity	RBL-2H3 cells	Increases the stability of the cell membrane; inhibits extracellular Ca ²⁺ influx	<i>In vitro</i>	Wang <i>et al.</i> (2012b)	
	Female C57BL/6 mice	Inhibits the PKC or PKC–IKK2 pathways	<i>In vivo</i>	Kim <i>et al.</i> (2014a)	

(Continues)

Table 1. (Continued)

Pharmacological effect	Cell lines/model	Activity/mechanism(s) of action	Application	Reference
Neuroprotective activity	Cortical neurons cell	Activates ER/PI3K/Akt pathway	<i>In vitro</i>	Liu <i>et al.</i> (2010)
	PC12 cells	Activates class III phosphatidylinositol 3-kinase/Beclin-1/ B-cell lymphoma 2 pathway	<i>In vitro</i>	Sun and Liu (2015b)
	Neuro2a cells	PI3K/Akt/GSK-3 β signalling pathway	<i>In vitro</i>	Park <i>et al.</i> (2015)
	ICR mice	Up-regulates GR and BDNF levels	<i>In vivo</i>	Li <i>et al.</i> (2014a)
	Rat epilepsy model	Inhibits MDR1 gene and its associated genes	<i>In vivo</i>	Yang <i>et al.</i> (2015)
	PC12 cells	Activin A pathway	<i>In vitro</i>	Guo <i>et al.</i> (2013a)
	BV-2 cells	Eliminates inflammatory microglia	<i>In vitro</i>	Zhou <i>et al.</i> (2011)
Immunosuppressive activity	Chronic constriction injury (CCI) model	P2X _{2/3} receptor	<i>In vitro</i> <i>In vivo</i>	Gao <i>et al.</i> (2011)
	Human T cells	ROS-mediated ER stress; mitochondrial dysfunction	<i>In vitro</i>	Qu <i>et al.</i> (2013)
	Dendritic cells (DCs)	Inhibits the differentiation and maturation of DCs	<i>In vitro</i>	Zhang <i>et al.</i> (2012)
	Liver transplantation rats model	Modulated the deviation of the Th1/Th2 paradigm to Th2	<i>In vitro</i>	Tong <i>et al.</i> (2011)
Anti-osteoporotic activity	Peripheral blood mononuclear cell	Suppresses lymphocyte proliferation	<i>In vitro</i> <i>In vivo</i>	Liu <i>et al.</i> (2009b)
	LPS-mediated osteoporotic mouse model	Suppresses bone resorption	<i>In vitro</i>	Kang <i>et al.</i> (2014)
	Bone marrow cell	Up-regulates Runx2, osterix, collagen type I, osteocalcin and ALP; down-regulates adipogenesis, PPAR γ , C/EBP α and ap2	<i>In vitro</i> <i>In vivo</i>	Kim <i>et al.</i> (2014c); Yang <i>et al.</i> (2014a)
Anti-diabetic activity	Mouse osteoblastic MC3 T3-E1 subclone 4 cells	Activates the PI3K-Akt; MAP kinase-NF- κ B signalling pathways	<i>In vitro</i>	Lee <i>et al.</i> (2008)
	STZ-induced diabetic mice	Regulates the PPAR γ pathway	<i>In vivo</i>	Xue <i>et al.</i> (2010)
	High-glucose-induced mesangial cells	Activates the PPAR γ pathway	<i>In vitro</i>	Liu <i>et al.</i> (2009a)
	3 T3-L1 cells	Promotes adipocyte differentiation; increases glucose uptake	<i>In vitro</i>	Yang <i>et al.</i> (2007)
	3 T3-L1 preadipocytes C57Bl/6 J mice	Activates the AMPK signalling pathway	<i>In vitro</i> <i>In vivo</i>	Chen <i>et al.</i> (2012); Song <i>et al.</i> (2013)
	Human umbilical vein endothelial cells	Suppresses activation of p38 MAPK and ERK1/2	<i>In vitro</i>	Gao <i>et al.</i> (2015)
	3 T3-L1 adipocytes	Inhibits NF- κ B, ERK signalling pathways	<i>In vitro</i> <i>In vivo</i>	Zhang <i>et al.</i> (2015b)
	Mesangial cells	Inhibits NF- κ B; inhibits cellular FLICE-inhibitory protein generation	<i>In vitro</i>	Yang <i>et al.</i> (2013); Gao <i>et al.</i> (2014)
	In ob/ob mice	Inhibits the 11 β -HSD1 activity	<i>In vitro</i> <i>In vivo</i>	Wang <i>et al.</i> (2012c)
	STZ-induced diabetic rats with cardiomyopathy	Regulates the AKT/GSK-3 β signalling pathway	<i>In vivo</i>	Wu <i>et al.</i> (2014)
Hepatoprotective activity	STZ-induced diabetic rats with nephropathy	Inhibits the activation of p38 MAPK pathway	<i>In vivo</i>	Wang <i>et al.</i> (2006)
	HG-stimulated podocytes; STZ-induced diabetic rats	Inhibits ILK and desmin expression; restores nephrin expression	<i>In vitro</i> <i>In vivo</i>	Chen <i>et al.</i> (2015b)
	LPS-elicited RAW264.7 mouse macrophage cells	Inhibits TNF- α production; deactivates MAPKs and NF- κ B; blockades TLR4/MD2 complex expression	<i>In vitro</i> <i>In vivo</i>	Yin <i>et al.</i> (2014)
	CD4+ T cells and macrophages	Inhibits activation of the p38 MAPK-NF- κ B signalling pathway	<i>In vitro</i> <i>In vivo</i>	Xue <i>et al.</i> (2015)
	CCl ₄ -induced hepatic damage in rats	Reverses hepatic oxidative insult, CYP enzymatic activity and ultrastructural changes	<i>In vivo</i>	Bhadoria <i>et al.</i> (2009)
	Clone 9 cell; CCl ₄ -induced liver damage of SD rats	Modulates inflammation	<i>In vivo</i>	Lee <i>et al.</i> (2012)
	APAP-induced hepatic damage in rats	Diminishes oxidative stress	<i>In vivo</i>	Bhadoria (2010)
HepG2/CYP2E1 cells	Inhibits the GGT activity and CYP2E1 protein expression	<i>In vitro</i>	Qian <i>et al.</i> (2011)	

Table 2. Toxicity of emodin

Cell lines/model	Activity/mechanism(s) of action	Application	Reference
Human proximal tubular epithelial (HK-2) cells	Induces apoptosis in caspase 3-dependent pathway and mitochondrial pathway	<i>In vitro</i>	Wang <i>et al.</i> (2007a, 2007c) Wang <i>et al.</i> (2015a)
L8824 cells	Induces apoptosis by directly affecting the mitochondria	<i>In vitro</i>	Cui <i>et al.</i> (2014)
L-O2 cells	Induces apoptosis GSH metabolism and fatty acid metabolism pathway	<i>In vitro</i>	Li <i>et al.</i> (2012a); Liu <i>et al.</i> (2015)
TK6 cells, HL-60 cells, and HL-60/MX2 cells	Stabilizes Topo II-DNA cleavage complexes; inhibits ATP hydrolysis	<i>In vitro</i>	Li <i>et al.</i> (2010)
Interstitial cells of Cajal	Inhibits activity of Na ⁺ -K ⁺ -ATPase and Ca ²⁺ -ATPase; raises activity of IP3 and cAMP	<i>In vitro</i>	Peng <i>et al.</i> (2013)
Male reproductive organs/tissues	Disrupts the expression of testicular genes	<i>In vivo</i>	Oshida <i>et al.</i> (2011)
Human sperm	Reduces sperm [Ca ²⁺]; suppresses tyrosine phosphorylation	<i>In vitro</i>	Luo <i>et al.</i> (2015)

ability of emodin to inhibit diverse events involved in cell apoptosis, cell metastasis and cell cycle arrest and clearly supports its traditional use in the treatment of cancers. This paper summarizes the pharmacological properties and molecular mechanisms of emodin (in Table 1) and strongly supports the view that emodin has a broad application prospect.

Rhein, which is similar to emodin, has many pharmacological properties, including hepatoprotective, nephroprotective, antiinflammatory, antioxidant, anticancer and antimicrobial activities (Zhou *et al.*, 2015). Aloe-emodin (AE) also has attracted increasing attention for its anticancer properties. Numerous studies have revealed that AE exerts therapeutic effects through multiple pathways, including differentiation, apoptosis, invasion and migration (Chen *et al.*, 2014).

Another issue is that emodin shows both hepatoprotection and hepatotoxicity, which appears to be contradictory. Based on an examination of the literature, we speculate that the reasons are for these effects are likely the administration dosage and delivery time. High doses and long-term drug delivery are more likely to result in liver toxicity, whereas low doses and short-term drug delivery might result in liver protection. Therefore, this issue requires further study.

We also summarized the toxicity of emodin, including the hepatotoxicity, nephrotoxicity, genotoxicity and reproductive toxicity (in Table 2). The number of reports regarding the adverse effects of emodin is increasing. The primary toxicity among these reports is hepatotoxicity and nephrotoxicity, which are of wide concern worldwide. Emodin shows hepatotoxicity and nephrotoxicity by inducing apoptosis in the caspase 3-dependent pathway and the mitochondrial pathway. In addition, GSH metabolism and the fatty acid metabolism pathways are also involved. Therefore, further studies are needed to attenuate the toxicity of emodin.

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Conflict of Interest

The authors have declared that there is no conflict of interest.

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