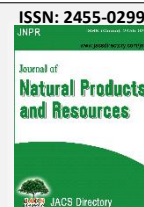




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Pharmacological Properties of Emodin – Anthraquinone Derivatives

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ABSTRACT

Quinones are an important class of naturally occurring compounds widely distributed among all respiring organisms. Anthraquinones comprise the largest group of natural quinones. Natural anthraquinones are widely investigated for their potential therapeutic use. Emodin (1,3,8-trihydroxy-6-methyl anthraquinone), an anthraquinone polyphenol present in several medicinal herbs like in the root and rhizome of *Rheum palmatum*, is an essential component of most Chinese alternative medicine. It exhibits diverse biological activities including anti-inflammatory, anti-microbial, anti-mutagenic properties and modulates the immune system, vasomotor system as well as metabolic processes. Emodin is emerging as a new class of compounds for the treatment of radiation injury, cancer, diabetes, neuronal disorders and inflammation associated disease. This review aims to summarize the pharmacological properties of emodin reported to date with emphasis on its biological activities and the promising mechanism of action.

1. Introduction

Quinones are an important class of naturally occurring compounds widely distributed among all respiring organisms. These are cyclic conjugated diketones formed due to oxidation of aromatic compounds. The simplest quinone is 1,4-benzoquinone. The quinones play essential part in the biochemistry of living cells including photosynthesis, respiration and blood coagulation [1]. Among quinines, anthraquinones constitute the largest group of natural quinines with more than 170 structural variants [2]. These are a group of functionally diverse aromatic compounds structurally related to anthracene with parent structure 9,10-dioxoanthracene (other names include 9,10-anthracenedione, anthradione, 9,10-anthrachionon, anthracene-9,10-quinone and 9,10-dihydro-9,10-dioxoanthracene).

Lower fungi and lichens are the source to a large proportion of the naturally occurring anthraquinones. Among the higher plants, members of the family Bignoniaceae, Fabaceae, Liliaceae, Polygonaceae, Rhamnaceae, Rubiaceae, Scrophulariaceae and Verbenaceae are also rich in anthraquinones [3]. Most of the anthraquinones possess therapeutic properties and are active components of medicinal plants [4]. In general, nitrogen-containing anthraquinone derivatives have been reported to possess antitumor activity; amine ethers are anti-allergic; oximes and alkyl amino derivatives have radio sensitizing and bacteriostatic properties, and sulphur-containing derivatives have radio protective and antimicrobial properties [5].

Natural anthraquinones and their derivatives are among the important compounds investigated to develop new bioactive molecules with potential for biomedical applications. The basic anthrone backbone structure of anthraquinones acts as an electron acceptor. Therefore, a number of structural derivatives of anthraquinone which are found in nature act as antioxidants. A tabulated summary of the potential bioactivity of emodin is given in Table 1.

Table 1 Biological activity of emodin anthraquinone derivatives

Biological Activity	Reference
Anti-cancer	[6, 7]
Anti-metastatic	[6, 7]
Anti-viral activity	[8, 9]
Anti-mitotic	[10]
Anti-oxidant	[11, 12]
Anti-inflammatory	[13]
Anti-hyperglycemic	[14]
Antibacterial	[15, 16]
Anti-fungal	[17, 18]
Anti-viral	[8]
Hepato-protective	[19, 20]
Neuro-protective	[21, 22]
Anti-mutagenic	[23, 24]
Anti-diabetic	[25]
Anti-fibrosis	[26]

2. Occurrence, Chemical Structure and Metabolism of Emodin

Emodin, an anthraquinone polyphenol found in different types of herbs, climbers, shrubs and trees of at least 94 species belonging to 28 genera and 17 families [3]. The root and rhizome of *Rheum palmatum* is a rich source of emodin. Emodin is a major phytoestrogen with an affinity for human estrogen receptors [27] and exhibits diverse biological activities. The biological activity of anthraquinones are closely related to their chemical structure. It has been reported that the hydroxyl, methyl and carbonyl groups of emodin are the key determinants of its biological activity [28]. Markovic and Manojlovic [29] found that all the OH groups at position C1, 3 and 8 can undergo keto-enol tautomerization. They suggested that since the enole forms are stabilized by π -conjugation in the benzene ring, they are more stable than the keto forms. Besides, they observed that the bond dissociation enthalpy of OH bonds at C1 and C8 positions are higher than at C3 position. These observations suggest the importance of C3 hydroxyl group of emodin with regard to its antioxidant potential.

Bachmann and Schlatter [30] studied the pharmacokinetics of emodin in rats using radioactive labeling. They reported that the highest concentrations emodin in peripheral blood could reach within 2 hr of the exposure which decreases to about 30% in the next 24 hr period. Liang et al. [31] showed that the serum profile of emodin in rabbits follows a two-

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compartment model. The observed distribution half-life of emodin was 6.8 min and the elimination half-life was 227 min. The blood level of emodin has been reported to be significantly higher in female rats compared to male rats [32].

3. Pharmacological Properties

3.1 Gastrointestinal Effects

Emodin exhibited hepatoprotective effects on carbon tetrachloride (CCl₄) as well as D-galactosamine (D-GalN)-induced liver damage [33]. Studies have shown that emodin is a potent agent in the management of clinical and experimental acute pancreatitis via accelerating pancreatic repair and regeneration process. These effects have been attributed to the ability of emodin to promote up regulation of the epidermal growth factor (EGF) and transforming growth factor beta1 (TGF-β1) gene expression [34]. In murine test system, emodin enhanced small intestinal peristalsis by promoting secretion of motilin by lowering the content of somatostatin and inhibiting Na⁺-K⁺-ATPase activity of the intestinal mucosa [35]. Jung et al. [36] reported hydroxyl radical inhibitory and/or scavenging activities and hepatoprotective activity of emodin on taurine-induced cytotoxicity in HepG2 cells. Emodin has the effect of promoting liver regeneration and improving liver function in rats after reduced size transplantation by improving proliferation of liver cell and protecting liver cells from injury [37]. Emodin has a protective effect on hepatocytes and alleviate cholestatic hepatitis by antagonizing pro-inflammatory cytokines and mediators, inhibiting oxidative damage, improving hepatic microcirculation, reducing impairment signals, and controlling neutrophil infiltration [38]. Alisi et al. [39] demonstrated that emodin can prevent hepatosteatosis, preserving liver from pro-inflammatory and pro-oxidant damage caused by high-fat/high-fructose diet. Recently Liu et al. [40] showed that protective role of emodin in alcohol-mediated liver steatosis. Emodin pre-treatment has also been reported to protect against Con A-induced liver injury in mice and the effects could involve differential regulation of helper T as well as macrophages and modulation of the p38 MAPK-NF-κB pathway [20].

3.2 Renal Protective Effect

Mesangial cells play a significant role in the genesis of the cellular damage observed in nephritis. The increase in the number of mesangial cells or the amount of mesangial matrix are characteristics of renal lesion sites. Emodin showed strong suppressive effect on human mesangial cell proliferation activated by interleukin (IL)-1β and IL-6 [41]. Emodin ameliorated the high glucose-induced matrix synthesis via suppression of the activation of protein kinase C and cAMP binding protein in mesangial cells. Moreover, emodin inhibited proliferation and promoted apoptosis in renal fibroblasts isolated from lupus nephritis patients. This may be important in suppressing interstitial fibrosis and improve prognosis of lupus nephritis [42]. Emodin effectively ameliorated renal dysfunction in diabetic nephropathy rats probably by inhibiting p38 MAPK pathway and fibronectin down regulation [43], thus represents a promising strategy to prevent renal dysfunction in early-stages of diabetes mellitus [38]. Yang et al. [21] reported that emodin inhibited DNA-binding and transcriptional activity of NF-κB resulting in down regulation of TGF-β1 and FN expression. They suggested that emodin-mediated inhibition of NF-κB pathway could protect against diabetic nephropathy. Ali et al. [22] showed that emodin had protective role against cisplatin-induced nephrotoxicity in rats. Emodin were shown to inhibit high glucose induced proliferation of rat renal mesangial cells via inducing cell cycle arrest at G1 phase as well as cellular apoptosis via up regulation of pro-apoptotic mediators bax and caspase activation, and showed promising treatment of diabetic nephropathy [44].

3.3 Anti-Fungal and Anti-Microbial and Anti-Viral Effects

Emodin showed important antifungal activity against *Botrytis cinerea*, *Erysiphe graminis*, *Phytophthora infestans*, and *Rhizoctonia solani* [45]. However, Chrysai-Tokousbalides and Kastanias [46] reported that emodin had no noticeable effect on *Sclerotinia minor*, *Sclerotinia sclerotiorum* or *Botrytis cinerea*. Emodin delayed the development of subcutaneous abscesses due to infection of *Trichomonas vaginalis* and oral administration inhibited the trichomonas induced intra-vaginal infection [47]. Meanwhile, Wang and Chung [48] reported that emodin suppressed the growth of *Helicobacter pylori* (which is closely related to peptic ulcer disease) and proposed that the effect could be due to induction of DNA damage. Emodin showed efficacy against both human fungal pathogens (inhibiting both spore germination and hyphal growth) and several strains of bacteria [18]. Antibacterial activity of emodin at against methicillin-

resistant *Staphylococcus aureus* have been reported [49]. Emodin showed direct antibacterial activity against *Vibrio vulnificus*, a good model organism of bacterial septicemia has also been reported [50]. It is a potent anti-herpes simplex virus (HSV) agent that inhibits the yields of HSV-1 via the suppression of a novel target, UL12 [38]. Emodin could inhibit Cocksackievirus B₄ (CVB₄) induced apoptosis *in vitro* and *in vivo* [9]. Dey et al. [51] reported antitubercular and antibacterial activity of emodin against multi-drug resistant *Mycobacterium tuberculosis* and other bacterial pathogens. Li et al. [16] reported the *in vitro* antibacterial action of emodin against *Haemophilus parasuis* and showed that emodin as a candidate for treating Glässer's disease. Emodin has also been reported to show inhibitory effect on HBV replication *in vivo*, which may function as a supplementary modality in the treatment of hepatitis B infection [8]. Cao et al. [52] proposed that the antibacterial activity of emodin *S. aureus* could be the result of disruption of cell wall/membrane integrity in the host organism.

3.4 Anti-Cancer Activities of Emodin

A number of studies have analyzed the anti-tumour properties of emodin and suggested possible mechanisms of such effects [7]. Studies on emodin and various other anthraquinone derivatives have revealed that the C1 and C3 positions of emodin are important for its antitumor function [53]. Emodin has been reported to have differential cytotoxicity against ras-transformed bronchial epithelial cells compared to the normal human bronchial epithelial cells. On the other hand, reports to the contrary have been published [38]. The observed differences could at least in part be due to the cell lines and the concentrations of the test agents used. Studying on murine splenocytes, Sharma and Tiku [54] reported that emodin up to a concentration of 100 μM failed to produce significant cytotoxic effects and suggested that normal and tumor cells may have differential sensitivity towards emodin.

Perturbation of cell cycle progression has been a primary target of cancer chemotherapy, thus restricting cancer cell proliferation and metastasis. The effect of emodin on the regulation of cell cycle has been demonstrated on various cancer cells. Emodin has been reported to cause cell cycle arrest at G2/M in v-ras-transformed cells and HepG2/C3A cells [55]. Shieh et al. [55] proposed that the G2/M arrest could be effected through up regulation of p53 and p21 genes. Besides its effects on G2/M arrest, emodin has been implicated in the blockage of G1 to S transition in HCT-15 carcinoma cells [56] as well as breast cancer MDA-MB-453 cells [57]. Emodin has also been reported to cause down regulation of the TCF/LEF transcriptional activity in human colorectal cancer cells (SW480 and SW620), thus interfering in the Wnt signalling pathway [38]. Hwang et al. [58] found that emodin attenuated radio resistance in the HepG2 cells via up regulation of the apoptotic signals and down-regulation of the proliferative signals. Sun et al. [59] reported that inhibition of metastasis and cancel invasion observed following emodin exposure could be mediated through decreased activity of p38 and ERK as well as down regulation of uPA, uPAR, MMP-9 and MMP-2 expressions. Emodin has also been reported to produce synergistic cytotoxic and antiproliferative effects in combination with other agents like curcumin in different cancer cell lines [60].

Apart from cell cycle perturbation, another important mechanism of the potential anti-cancer effect of emodin is the induction of apoptosis. The ability of emodin to induce apoptosis in cancer cell lines has been reported by a number of studies [7]. During metabolism, the quinone structure of emodin is converted to semiquinone which generates ROS due to interaction with oxygen. Generation of ROS during the metabolism of the semiquinone is considered to be the causative factor of emodin-induced apoptosis [61]. Bras et al. [62] reported that ROS contributes to mitochondrial injury, reduction of mitochondrial trans-membrane potential, cytochrome C and Smac release, and subsequent caspase activation resulting induction of apoptosis.

The mitochondrial pathway of emodin induced apoptosis could involve the anti-apoptotic protein Bcl-2 proteins. It has been shown that emodin-induced apoptosis is closely related with the down regulation of Bcl-2 gene expression which could be mitigated through ectopic expression of Bcl-2 [61]. Besides, increased expression of the pro-apoptotic proteins Bax and Bak following emodin exposure has also been reported [63]. Recently, Ma et al. [64] reported that emodin-induced inhibition of tumour angiogenesis and metastasis could be related to down regulation of the transcription factor Runx2 and inhibition of matrix metalloproteinases (MMPs) and vascular endothelial growth factor receptor-2 (VEGFR-2).

3.5 Anti-Inflammatory and Immunosuppressive Effects

Chronic inflammation promotes cancer development during tumour progression [65]. A number of chemicals with anti-inflammatory effect can protect animals against the toxic and carcinogenic effects of chemicals and

microbes [66]. Emodin was reported to suppress the proliferation of several activated cell lines, including primary human T lymphocytes, mononuclear cells, mesangial cells and RAW 264.7 macrophages [38]. The mechanisms of this inhibition are related to (a) the attenuation of IL-2 and TNF- α mRNA level expression, (b) decrease of IL-1, IL-2, IL-4 and TNF- α cytokine production, (c) hydrogen peroxide generated from semiquinone, and (d) suppression of NF κ B activation. Emodin has been reported to inhibit inflammation in C2C12 myotubes and 3T3-L1 adipocytes [67]. Sharma and Tikku [13] showed that emodin inhibited concavaline-A induced inflammation and proliferation by modulating cytokines (Th1/Th2/Th17) response in murine splenocytes *in vitro*. They found that administration of emodin showed therapeutic effects on the progression of hypertrophic scarring characterized by inflammation. The underlying mechanism of this may be due to inhibition of the PI3K/Akt signalling pathway [68]. Emodin suppressed p-I κ B/ α I κ B ratio and reduced NF- κ B subunit p50 in the nuclear fraction, and modulated LPS-induced innate immune response in adipocytes by altering expression of PTEN [69]. Emodin showed therapeutic potential against allergic bronchial asthma by exhibiting anti-inflammatory effects in the airway inflammation in mouse model [70], and in acute lung injury in mice possibly through NF- κ B inactivation [71]. Recently it showed that emodin be used as a natural anti-neuroinflammatory agent that exerts its effects by inducing HO-1 and NQO1 via AMPK/Nrf2 signalling in microglia [72]. In RAW264.7 cells, emodin suppresses LPS-induced inflammation through a PPAR γ -dependent pathway [73].

Emodin has been reported to increase host survival by preventing post-orthotopic transplantation rejection possibly through protection of hepatocytes against apoptotic death and inhibition of CD4(+) T cell proliferation in plasma [38]. Immunomodulatory effects of emodin may have been attributable, in part, to the anti-proliferative effects on lymphocytes and a shift within the TH1/TH2 and TH17/Treg balance (towards TH2 and Treg) [13]. Inhibition of extracellular Ca²⁺ influx and protection of cell membrane are proposed as a possible mechanisms of the anti-allergic activity of emodin [74].

3.6 Anti-Mutagenic Effect

The anti-mutagenic effect of emodin has been reported in many studies. In *Salmonella typhimurium* (TA98) and *E. coli* PQ37, emodin prevented the formation of DNA adducts induced by 1-nitropyrene [75]. In addition, emodin markedly inhibited benzo(a)pyrene-mediated DNA damage in comet assay system [76]. Emodin is shown to protect DNA damage induced by radiation in pBR322 plasmid [13]. Recently Wang et al, [77] showed radio-protective action of emodin on mice by reducing mortality and intestinal injury via inhibition of apoptosis and modulation of p53. Nucleotide excision repair (NER) is the main DNA repair pathway by which mammalian cells remove UV- or carcinogen-induced DNA damage. Emodin increased unscheduled DNA synthesis for UV-induced damage and reduced the cytotoxicity of cisplatin to W138 cells, a human lung diploid fibroblast cell line, suggesting that emodin may promote NER activity. Emodin increased the expression of key subunits of NER complex. Besides, since UV-induced NER is Ca dependent, emodin elevated the Ca²⁺ influx which might lead to its enhancement of DNA repair [23].

In addition to NER enhancement, inhibition of cytochrome P4501A1 activity might be another mechanism by which emodin displays its anti-mutagenic effect. Emodin was reported to suppress the mutagenicity of one of the heterocyclic amines, 3-amino-1-methyl-5H-pyrido(4,3-b)indole, through inhibiting the activity of cytochrome P4501A1 [24]. However, emodin was not carcinogenic, neither in rats or nor in mice [78] but induced dose-dependent estrogenic activities in yeast strains (*Saccharomyces cerevisiae*) that expressed human estrogen receptors ER α or ER β .

3.7 Is emodin an Anti-Oxidant or Oxidant?

Emodin has been reported to have varying effects, from being an antioxidant to a pro-oxidant and is a major inhibitor of inducible nitric oxide synthase [38]. In some cell-free experimental system, emodin was found to inhibit the superoxide radical production, and lipid peroxidation using the thiocyanate method [12]. However, it did not show inhibitory activity in reactive oxygen- and nitrogen-mediated reactions [79]. In pBR322 plasmid relaxation assay, it works as an antioxidant and protects DNA from radiation induced ROS damage [54]. On the other hand, under cell culture experimental system, emodin has been reported as a free radical generator, which contributes to its immunosuppressive effect and induction of apoptosis [38]. The formation of ROS including superoxide anions and hydroxyl radicals are proposed to be the metabolic consequences of the redox cycling reactions between the quinines and their corresponding semiquinones [80]. These studies suggest that

emodin can serve as a natural and low toxicity ROS generator, and lead to various anti-tumour effects. On the contrary, emodin has been reported to protect against oxidative stress in cultured human kidney (HEK 293) cells induced by cisplatin and murine splenocytes from gamma radiation [54]. Likewise, Wu et al. [81] showed protective effects of emodin against calcium overload and endoplasmic reticulum (ER) stress in an acute pancreatitis model *in vitro*. In another report [82] showed that while emodin induced gene mutations and DNA; it also exhibited free radicals scavenging activity. Thus, reported studies indicate emodin may have differential effects on normal and transformed cells.

3.8 Other Pharmacological Effects

Myocardial protective effect of emodin was observed using isolated perfused rat hearts after ischemia-reperfusion (IR) injury; it associated with significant reduction in the extent of IR-induced reduced glutathione (GSH) depletion [83]. Pre-treatment with emodin per se at 1.2 mmol/kg was found to protect against ischemia-reperfusion injury as assessed by measuring the level of lactate dehydrogenase (LDH) leakage. The muscle contraction induced by emodin was premediated in the mouse isolated diaphragm and sarcoplasmic reticulum membrane vesicles [84]. This effect was due to the oxidation of the ryanodine receptor and influx of extracellular Ca²⁺ through voltage-dependent and subsequent release of Ca²⁺ channels of the plasma membrane, and from sarcoplasmic reticulum. Another study showed that emodin modulated the intracellular Ca blocking Ca²⁺ concentration in isolated brain cells through dependent release of glutamate from the Schaffer collaterals in the hippocampal area [85]. Emodin showed neuroprotective effects in primary rat cortical neurons apoptosis induced by hydrogen peroxide and inhibited aggregation of pathological tau and prevents β -amyloid-induced neuronal death *in vitro* [86]. Culture of human umbilical vein endothelial cells with high concentrations of glucose resulted in damage to the cells; emodin was able to alleviate these impairments which related to the inhibition of CCL5 expression and subsequent cell stress/inflammatory events possibly mediated by activation of MAPK signalling pathways [38]. Recently, Park et al. [87] reported that emodin induced neuronal differentiation of Neuro2a cells via PI3K/Akt/GSK-3 β pathway. In diabetic cardiomyopathy, perturbation of Akt/GSK-3 β signalling pathway by emodin has been reported [88]. Emodin is emerging as a potential natural compound for the treatment of metabolic syndrome or type 2 diabetes. The activation of PPAR gamma and the modulation of metabolism-related genes were likely involved in the anti-diabetic effects of emodin. Emodin may be an effective preventive agent for ethanol-induced teratogenesis [89]. The combination of emodin with irbesartan may provide a better anti-fibrosis effect than the single application [26]. Zhou et al. [90] reported that emodin showed cardiovascular protective effect by increasing the secretion of atrial natriuretic peptide (ANP) through activation of K⁺ATP and inhibition of L-type Ca²⁺ channels.

4. Conclusion

Naturally occurring quinines, especially anthraquinones and their derivatives are widely reported to have range of bioactivity which could be put into therapeutic use. Emodin, one of the most studied anthraquinone derivatives has been reported to have potential therapeutic properties like protection against toxicities to gastrointestinal, liver, kidney and nervous system. Emodin has also been reported to provide beneficial effects against human ailments related to respiration, allergy and inflammation and diabetes. A large number of studies have provided evidence for the anti-viral, anti-bacterial, anti-parasitic and anti-fungal properties of emodin. In addition, significant amount of literature is available highlighting the anti-proliferative and anticancer potential emodin either alone or in combination of other therapeutic agents. Recent evidence suggests that emodin can protect against radiation-induced damage as well as modulates a host of metabolic processes. However, the mechanism action for such diverse group of functions is not clear. The redox cycling of quinines and the corresponding semiquinones can lead to the formation of ROS. Therefore, considerable controversies exist regarding the anti- or prooxidant nature of these compounds, which need further investigations, especially *in vivo*.

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