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Review article

Anticancer potential of emodin

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ABSTRACT

Traditional Chinese Medicine (TCM) is widely used in clinical research due to its low toxicity, low number of side effects, and low cost. Many components of common fruits and vegetables play well-documented roles as chemopreventive or chemotherapeutic agents that suppress tumorigenesis. Anthraquinones are commonly extracted from the Polygonaceae family of plants, e.g., *Rheum palmatum* and *Rheum officinale*. Some of the major chemical components of anthraquinone and its derivatives, such as aloe-emodin, danthron, emodin, chrysophanol, physcion, and rhein, have demonstrated potential anticancer properties. This review evaluates the pharmacological effects of emodin, a major component of *Aloe vera*. In particular, emodin demonstrates anti-neoplastic, anti-inflammatory, anti-angiogenesis, and toxicological potential for use in pharmacology, both *in vitro* and *in vivo*. Emodin demonstrates cytotoxic effects (e.g., cell death) through the arrest of the cell cycle and the induction of apoptosis in cancer cells. The overall molecular mechanisms of emodin include cell cycle arrest, apoptosis, and the promotion of the expression of hypoxia-inducible factor 1α, glutathione S-transferase P, N-acetyltransferase, and glutathione phase I and II detoxification enzymes while inhibiting angiogenesis, invasion, migration, chemical-induced carcinogen-DNA adduct formation, HER2/neu, CKII kinase, and p34cdc2 kinase in human cancer cells. Hopefully, this summary will provide information regarding the actions of emodin in cancer cells and broaden the application potential of chemotherapy to additional cancer patients in the future.

1. Introduction

Numerous researchers have reported the use of phytochemical compounds such as anthraquinone emodin extracts from traditional Chinese medicines (TCM), including *Polygonum multiflorum* [1,2], *P Cuspidatum* [3,4], *Rumex patientia* [5], *Rhamnus catharticus*, *Rhamnus orbiculatus* [6], *Aloe vera* [7], *Acorus tatarinowii* [8], *Cassia obtusifolia* [9], *Cassia occidentalis* [10], *Rheum palmatum* [11], *Rheum officinale* [12], *Eriocaulon buergerianum* [13], *Dendrobium thyrsiflorum* [14], *Fibraurea tinctoria* [15],*Coptis chinensis* [16],*Scutellaria baicalensis* [16], *Isatis indigotica* [17], and *Rumex chalepensis* [18]. Studies on the use of TCM have noted lipid regulation activities and anti-inflammatory, antimicrobial, antiviral, antitumor, and antioxidant effects. To learn more about the therapeutic functions of TCM, experiments are needed to identify the functional ingredients and ascertain the

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molecular mechanisms of these compounds. Recent research is paying more attention to TCM because it may have future applications in clinical medicine. In particular, rhubarb (*Rheum palmatum*) is one of the oldest and most famous Chinese herbal medicines and is still used in various herbal remedies and therapeutic applications. Based on current reports and investigation, we believe rhubarb has clinical potential.

Rhubarb is a well-known treatment for many diseases in TCM [19,20]. Anthraquinones extracted from the rhubarb rhizome exhibit antidiabetic properties, suggesting a metabolic role in the insulin-stimulated glucose transport pathway [21]. Both *in vitro* and *in vivo* studies have reported the antimicrobial activities of extracts from *Sapindus mukorossi* and *Rheum emodin* against *Helicobacter pylori* [22]. Moreover, the antioxidant and anticancer potential of *Rheum emodin* rhizome extracts have demonstrated therapeutic value [23]. Extracts from *Rheum palmatum* have a high level of inhibitory activity against anti-Severe acute respiratory syndrome (SARS) coronavirus 3C-like protease effects [24]. A polysaccharide extracted from *Rheum tanguticum* has been shown to affect 2,4,6-trinitrophene sulphonic acid (TNBS)-induced colitis and $CD4^+$ T cells in rats [25]. Rhubarb has also demonstrated protective effects against experimental severe acute pancreatitis [26]. A study on anti-Oketsu activity indicates that rhubarb II has inhibitory effects against allergies [27]. Hexane extracts from *Rheum undulatum* not only decreases cell viability, thereby triggering apoptotic cell death in oral cancer, but also decreases the expression of specificity protein (Sp1) and its downstream protein, survivin [28].

The effects of rhubarb extracts on experimental chronic renal failure (CRF) indicate that it can reduce proteinuria and the severity glomerulosclerosis within remnant kidneys in rats [29]. Treatment of menopausal symptoms using an extract from the roots of *Rhapontic rhubarb* (plus the results of *in vitro* and *in vivo* experiments) indicate estrogenic actions, especially estrogen receptor β (ERβ)-mediated effects [30]. Oligostilbenes from rhubarb also inhibit low-density lipoprotein and high-density lipoprotein oxidation humans [31], suggesting a pivotal role in the prevention of lipoprotein oxidation.

2. Active ingredients found in the Polygonaceae family

Emodin (1,3,8-trihydroxy-6-methylanthraquinone) (Fig. 1) is an active ingredient in the root and rhizome of *Rheum palmatum* (Polygonaceae) [11]. This herb has been used in TCM for the treatment of gallstones, inflammation, hepatitis, and osteomyelitis and is also a known vasorelaxant and diuretic [32]. It reportedly has antibacterial, anti-inflammatory, antiviral, anti-ulcerogenic, anticancer, immunosuppressive [33–36], and chemopreventive effects [37]. Emodin has also been reported to exert inhibitory effects on cell death in the human lung squamous carcinoma CH27 cell line [36], and-human promyeloleukemic HL-60 cells induce apoptosis by activating the caspase-3 cascade independently of reactive oxygen species (ROS) production [38]. Emodin-induced apoptosis in human cervical cancer Bu 25TK cells occurs through poly (ADP-ribose) polymerase cleavage and the activation of caspase-9, but caspase-8 is not activated [39].

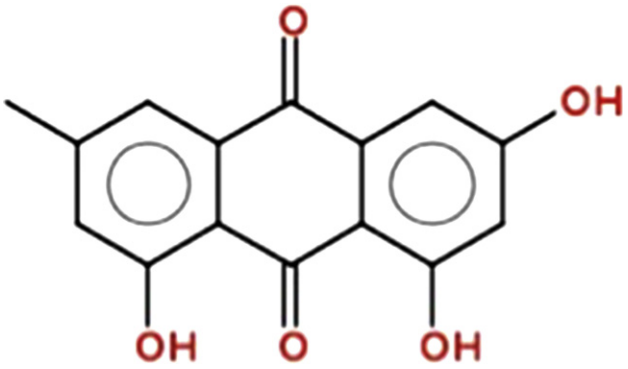

Fig. 1 – Chemical structure of emodin.

Moreover, emodin triggers apoptosis in human hepatoma HepG2/C3A, PLC/PRF/5, and SK-HEP-1 cells through a p53-dependent pathway [40]. In addition, emodin enhances arsenic trioxide-induced apoptosis by generating ROS and inhibiting survival signaling [41], and gene expression alteration occurs in HeLa cells through the redox-dependent enhancement of arsenic cytotoxicity [42]. Our laboratory has proven that Aloe-emodin affects the expression of cytokines and the functions of leukocytes in Sprague Dawley rats [134]. Emodin affects murine myelomonocytic leukemia WEHI-3 cells *in vitro* and enhances phagocytosis in leukemic mice *in vivo* [135].

Emodin downregulates androgen receptors and inhibits the cellular growth of prostate cancer [43]. Emodin inhibits the adhesion of human breast cancer (MDA-MB-231), human cervix epithelioid carcinoma (HeLa), and human hepatocarcinoma (HepG2) tumor cells by suppressing lipid raft coalescence and interfering with integrin clustering and focal adhesion complex (FAC) formation [44]. Likewise, it has been demonstrated that emodin could act as a Janus-activated kinase 2 inhibitor and have cytotoxic activities against multiple myeloma in humans [45]. Emodin selectively inhibits the interleukin–6-induced JAK2/STAT3 pathway and induces apoptosis in myeloma cells via the downregulation of myeloid cell leukemia 1 (Mcl-1) cells [45]. In local ischemic myocardium, emodin mediates protection from acute myocardial infarction through the inhibition of inflammation and apoptosis [46].

3. Pharmacological mechanisms against various types of cancer cells

Emodin has shown significant anticancer activities in several tumor cells, both *in vivo* and *in vitro*, while its molecular anticancer mechanisms have not been well explored. This review discusses emodin's pharmacological activities and the mechanisms that induce cell death in many types of human cancer cells, both *in vitro* and *in vivo*. Research findings on emodin-induced cytotoxicity and its protective effects are described below.

3.1. *HER2/neu expression*

Previously published reports in the literature confirm that emodin and its derivatives inhibit p185neu tyrosine kinase via

the suppression of HER2/neu-transformed phenotypes (e.g., by inducing cellular transformations and metastasis-associated potential) [47]. In breast cancer, the emodin derivative, azide methyl anthraquinone, induces mitochondrion-dependent apoptosis in HER2/neu-overexpressing MDA-MB-453 cells and lung adenocarcinoma Calu-3 cells and blocks HER2/neu binding to Hsp90. Azide methyl anthraquinone also induces the proteasomal degradation of HER2/neu in MDA-MB-453 and Calu-3 cells *in vitro* [48].

3.2. *CKII and p34cdc2 kinase*

Emodin inhibits the activity of casein kinase II (CKII) by acting as a competitor at ATP-binding sites. [49]. CKII is involved in the proliferation of human U87 astroglioma cells via stimulation of basal phospholipase D (PLD) activity. [50]. Emodin reportedly induces apoptosis in human tongue squamous cancer SCC-4 cells through ROS and mitochondria-dependent pathways *in vitro* [51]. Aloe-emodin, which is extracted from the rhizome of *Rheum palmatum*, downregulates MMP-2 through a p38 Mitogen-activated protein kinase (MAPK)-Nuclear factor-κB (NF-kB)–dependent pathway, thereby leading to the inhibition of invasion by nasopharyngeal carcinoma cells (NPC-TW 039 and NPC-TW 076) [52].

3.3. *Oncogenes*

It is well documented that nuclear factor-kappaB (NF-κB) plays an important role in the transcription of tumor cells [53,54]. It has been reported that emodin inhibits the proliferation and induction of apoptosis in pancreatic cancer cell lines (SW1990/GZ and SW1990). Emodin not only downregulates NF-κB under unstimulated conditions, but it also inhibits gemcitabine-induced NF-κB protein expression [53]. Aloe-emodin also purportedly induces antiproliferative activities through p53- and p21-dependent apoptotic pathway in the human hepatoma HepG2 and Hep3B cell lines [55]. An attractive target of oncogene-based anticancer drugs derived from natural herbal plants (like emodin), *Polygonum cuspidatum* exhibits strongly selective activities against src-HER2/neu and ras-oncogenes. In other words, emodin might be a oncogenetic signal for the inhibition of transduction [56].

3.4. *Hypoxia-inducible factor 1α*

Heterodimer hypoxia-inducible factor 1α (HIF-1) consists of a β subunit that is constitutively expressed and an oxygen-regulated α subunit. HIF-1 regulates genes that participate in angiogenesis, iron metabolism, glucose metabolism, and cell proliferation/survival [57]. The activity of HIF-1, especially its α subunit, is controlled by the posttranslational modification of the amino acid residues in its subunits [57]. HIF-1 plays a key role in the cellular response to tumor hypoxia that poses a major problem to successful radiotherapy and chemotherapy. The targeting of HIF-1 is now considered to be a pivotal and efficient strategy for treating neurodegenerative maladies like Alzheimer's (AD), Parkinson's (PD), Huntington's Disease (HD), amyotrophic lateral sclerosis (ALS), etc. [58]. It has also been reported that emodin diminishes hypoxia-induced embryotoxicity by upregulating HIF-1 and intracellular superoxide dismutases in whole cultured mouse embryos [59]. As a novel inhibitor of HIF-1, emodin is an adjunct that boosts the efficacy of cytotoxic drugs used for the treatment of prostate cancer DU-145 cells, demonstrating overactivated HIF-1 and potent multidrug resistance (MDR) [60].

3.5. *N-acetyltransferase activity*

Our previous studies have demonstrated how emodin and aloe-emodin inhibit N-acetyltransferase (NAT) activity and gene expression in mouse leukemia L1210 cells [61], human melanoma cells (A375.S2) [62], and strains of *H pylori* in peptic ulcer patients [63,64].

3.6. *Cell cycle arrest*

The cell cycle is classified into the G0/G1, S, and G2/M phases; if an agent induces apoptosis, then those will be sug-G1 phase [65]. In clinic settings, some anticancer agents can induce cell cycle arrest (arrest during the G0/G1, S, and/or G2/M phase) [65,66]. It has been reported that emodin and docosahexaenoic acid (DHA) increase arsenic trioxide interferon–α-induced cell death in human T-cell leukemia virus type 1 (HTLV-I)–transformed cells via ROS generation and the inhibition of Akt and activator protein 1 (AP-1) [67]. Emodin inhibits the growth of hepatocellular carcinomas, such as Huh7, Hep3B, and HepG2, through anticancer pathways (e.g., G2/M arrest and increased expression levels of the involved genes, both at the mRNA and protein levels) [68]. Emodin also reportedly inhibits vascular endothelial growth factor-A–induced angiogenesis [69]. Other investigators have demonstrated how emodin induces apoptosis through the p53-dependent pathway in human hepatocellular carcinoma cells [40], as well as growth arrest and death through ROS and p53 in human vascular smooth muscle cells [70].

Aloe-emodin also induces G2/M arrest in human promyelocytic leukemia HL-60 cells [71], cervical cancer HeLa cells [72], and through activated alkaline phosphatase in human oral cancer KB cells *in vitro* [73]. It has also been reported that aloe-emodin induces apoptosis through protein 53 (p53)-dependent apoptotic pathways in human bladder cancer T24 cells [74]. Aloe-emodin induces destabilization of caspase-8 and -10-associated RING protein (CARP) mRNA, indicating that caspase-8–mediated p53-independent apoptosis in human carcinoma cells [75] and human nasopharyngeal carcinoma cells induces caspase-3, -8, and -9–mediated activation of the mitochondrial death pathway [76]. Still, the antiproliferative activity of aloe-emodin occurs via p53- and p21-dependent apoptotic pathways in human hepatoma HepG2 cell lines [55,77]. Other evidence indicates that aloe-emodin and emodin inhibit schisandrin B in gastric cancer cells *in vitro* [78].

3.7. *Apoptosis*

It is well documented that the best strategy for killing cancer cells is via the induction of apoptosis [79] and that the best way for chemotherapeutic agents to kill cancer cells is to trigger apoptosis in tumors [79,80]. In human hepatoma Huh-7 cells, apoptosis is mediated by the downregulation of calpain-2 and ubiquitin-protein ligase E3A [81]. Emodin has strong antioxidative and anticancer actions and abrogates cisplatin-

induced nephrotoxicity in rats [82]. Other reports have cited the antitumor and apoptosis-promoting properties of emodin, an anthraquinone derivative, against pancreatic cancer in mice by inhibiting Akt activation [12]. Emodin enhances apoptosis in cisplatin-induced gallbladder carcinomas in a ROS-dependent manner and suppresses survivin expression [83]. Emodin downregulates X-linked inhibitor of apoptosis protein (XIAP) expression [84] and inhibits NF-κB against human pancreatic cancer [53], thereby enhancing the antitumor efficacy. Emodin induces apoptosis in the mouse microglial BV-2 cell line via Tribbles homolog 3 (TRB3) and eliminates inflammatory microglia, thereby exerting neuroprotective effects [85].

Emodin induces ROS generation and the activation of the ATM-p53-Bax–dependent signaling pathway in human lung adenocarcinoma A549 cells [86]. It has been reported that emodin exerts potential anticancer effects in pancreatic cancer cells by downregulating the expression of survivin and β-catenin [87]. Emodin also demonstrates potential as an antiatherosclerosis agent by inhibiting the proliferation of Tumor necrosis factor (TNF)-alpha–induced human aortic smooth muscle cells (HASMC) through mitochondrial- and caspase-dependent apoptotic pathways [88]. Emodin induces apoptosis via the caspase-3–dependent pathway in human renal proximal tubule HK-2 cells [89] and inhibits human prostate cancer LNCaP cell proliferation via androgen receptor and p53-p21 pathways [90]; pyrazole emodin derivatives inhibit the growth of and induce apoptosis in human hepatocellular carcinoma HepG2 cells [91]. Pyrazole emodin derivative also induce apoptosis in human cervical cancer cells via the activation of caspase-3 and -9 and the cleavage of poly (ADP-ribose) polymerase [39]. Aloe-emodin induces apoptosis in human lung nonsmall carcinoma H460 cells through Cyclic Adenosine monophosphate (cAMP)-dependent protein kinase, protein kinase C, Bcl-2, caspase-3, and the p38 signaling pathway and induces human lung squamous cell carcinoma CH27 cell death via the Bax and Fas death pathways [92,93]. Emodin not only successfully suppresses acute graft rejection *in vivo*, thereby prolonging the survival of the recipient rats by inhibiting hepatocellular apoptosis and modulating Th_1/Th_2 balance [94], but also mediates protection against acute myocardial infarction [46] in local ischemic myocardium. Emodin can reverse gemcitabine resistance in pancreatic cancer cells via mitochondria-dependent pathways *in vitro* [95].

3.8. *Glutathione S-transferase and glutathione peroxidase*

The function of glutathione S-transferase has implications in cell growth and oxidative stress as well as disease progression and prevention, which are present in subcellular compartments (e.g., cytosol, mitochondria, endoplasmic reticulum, nucleus, plasma membrane) [96]. Glutathione peroxidase (GPx), a selenoenzyme, plays a key role in the protection of organisms from oxidative damage by catalyzing the reduction of harmful hydroperoxides using thiol cofactors [97]. The function of GPx is to regulate hydroperoxide levels, but it might have dual roles [98,99]. The role of glutathione and glutathione-dependent enzymes in antioxidative processes is the maintenance and regulation of cell status, glutathionylation, and deglutathionylation, redox-dependent signaling, and apoptosis [100].

Emodin also demonstrates hepatoprotective effects against CCl_4-induced liver injury [101]. Emodin induces apoptosis in Dalton's lymphoma cells in association with the modulation of hydrogen peroxide-metabolizing antioxidant enzymes [102]. Emodin affects the mitochondrial capacity of ATP generation and antioxidant components as well as susceptibility against ischemia-reperfusion injury in rat hearts, although there is a sex difference [103]. Emodin also reportedly demonstrates antioxidant actions *in vivo* [104] and myocardial protective effects [105].

3.9. *Carcinogenesis*

Novel functions of emodin have been reported, namely that emodin enhances the repair of UV- and cisplatin-induced DNA damage and might even promote nucleotide excision repair (NER) capabilities in human fibroblast cells (WI38) [106] and human tongue cancer SCC-4 cells following DNA damage and the inhibition of DNA repair genes [107]. Emodin also demonstrates a proven ability to inhibit mutagenicity and the formation of 1-nitropyrene–induced DNA adducts in *Escherichia coli* PQ37 [108].

3.10. *Gene expression*

Several studies have reported that emodin affects the gene expression of human breast carcinoma BCap-37 cells [109] and downregulates the expression of transient receptor potential vanilloid 1 (TRPV1) ion channel protein mRNA and its functions in Dorsal root ganglion (DRG) neurons *in vitro*, thereby inhibiting inflammatory stimuli-induced hyperalgesia [110]. Emodin-mediated cytotoxicity in human lung adenocarcinoma H1650 (CRL-5883), human bronchioloalveolar carcinoma A549, lung squamous cell carcinoma H520, and H1703 cells is suppressed by Excision repair cross-complementary 1 (ERCC1) and Rapid Application Development (Rad)51 expression via extracellular regulated protein kinase 1/2 (ERK1/2) inactivation [111]. It has also been reported that emodin induces DNA damage and inhibits the expression of DNA repair genes in human tongue cancer SCC-4 cells [107]. Studies also show that emodin induces toxicological effects to the murine testicular gene expression profile [112] and inhibits the cytotoxic actions of tumor necrosis factor [113]. On the other hand, it has also been reported that emodin inhibits the migration and invasion in human tongue cancer SCC-4 cells due to the inhibition of the gene expression of matrix metalloproteinase (MMP)-9 [114].

3.11. *Glutathione S-transferase P expression*

Glutathione S-transferase P (GSTP) has been reported to regulate the S-glutathionylation of specific clusters of main proteins; it also plays a negative modulating role in some kinase pathways through ligand or protein interactions. GSTP is ubiquitously expressed in human tissue [115] and is linked to two cell-signaling functions critical to survival. It can sequester and negatively regulate c-jun N-terminal kinase (JNK) [116]. Catalytic reversal of S-glutathionylation is well characterized, but the role of GSTP in catalyzing the forward reaction contributes to the glutathionylation cycle [116].

Emodin reportedly induces neuroprotective effects in rat cortical neurons against β-amyloid–induced neurotoxicity [117]. Emodin induces apoptosis via an ROS-dependent mitochondrial signaling pathway in human lung adenocarcinoma A549 cells [118]. Emodin inhibits invasiveness, suppresses MMP-9 expression through the suppression of AP-1 and NF-κB in human cancer HSC5 cells (skin squamous cell carcinoma) and MDA-MB-231 cells (human breast cancer cell line) [119]. Likewise, emodin effectively suppresses hyaluronic acid (HA)-induced matrix metalloproteinase (MMP) secretion and the invasion of glioma through the inhibition of focal adhesion kinase (FAK), extracellular regulated protein kinase (ERK)1/2, and Akt/protein kinase B (PKB) activation and the partial inhibition of the transcriptional activities of activator protein-1 (AP-1) and nuclear factor-κB (NF-κB) [33].

3.12. *Angiogenesis*

Therapeutic antiangiogenesis is widely viewed as a useful approach for the treatment of cancer, cardiovascular diseases, bone fractures, rheumatoid arthrities, and other diseases [120]. In tumor formation, angiogenesis plays a vital role in development, reproduction, and wound repair. Many studies describe natural and synthetic compounds with antiangiogenic activities, attracting notice to their potential applications in cancer prevention and treatment [121]. Emodin reportedly inhibits tumor-associated angiogenesis through the inhibition of ERK phosphorylation [122] and inhibits vascular endothelial growth factor-A–induced angiogenesis by blocking receptor-2 (KDR/Flk-1) phosphorylation [69]. Vascular endothelial growth factor (VEGF) has been studied for its role as a stimulant in angiogenesis and vascular permeability. Several studies show that emodin and its anthraquinone derivatives inhibit the angiogenesis and proliferation [123] of primary cultured bovine aortic endothelial cells in the absence or presence of basic fibroblast growth factor (bFGF) or the presence of VEGF in a dose-dependent manner [124,125]. Likewise, emodin inhibits VEGF receptors in human colon cancer cells [126], upregulates urokinase plasminogen activator (uPA) and plasminogen activator inhibitor-1, and promotes wound healing in human fibroblasts [127]. Emodin has been used in cancer therapies for the treatment of autoimmune diseases with anti-VEGF or anti-VEGFR (receptor) effects [69,126]. It has also been reported that emodin induces antiproliferative and antimetastatic effects in human pancreatic cancer SW1990 cells [128]. In human neuroblastoma SH-SY5Y cells, emodin inhibits the level of MMP, thus inhibiting migration and invasion *in vitro* [129].

3.13. *Drug resistance*

The overexpression of multidrug resistance (MDR) in tumor cells poses a serious obstacle to successful chemotherapy [130]. Treating cancer with chemotherapeutic agents and radiation leads to complications, such as the development of tumor resistance to therapy (radio- or chemoresistance). Emodin might sensitize tumor cells to radiation therapy and chemotherapeutic agents by inhibiting the pathways that lead to treatment resistance. Emodin has also been found to protect against therapy-associated toxicities [131]. Emodin induces the mechanisms that involve the ROS-mediated suppression of MDR and HIF-11 [60]. Our studies demonstrate emodin's cytotoxic and protective effects in rat C6 glioma cells: the survival effects involve Mdr1a, MRP2, MRP3, MRP6, and NF-κB [132]. Emodin may be involved in reducing the glutathione level and downregulating MDR-related protein 1 (MRP1) expression in gallbladder SGC996 cancer cells. In tumor-bearing mice, it has also been indicated that co-treatment with emodin/cisplatin suppresses tumor growth *in vivo* by increasing cancer cell apoptosis and downregulating MRP1 expression [61,133].

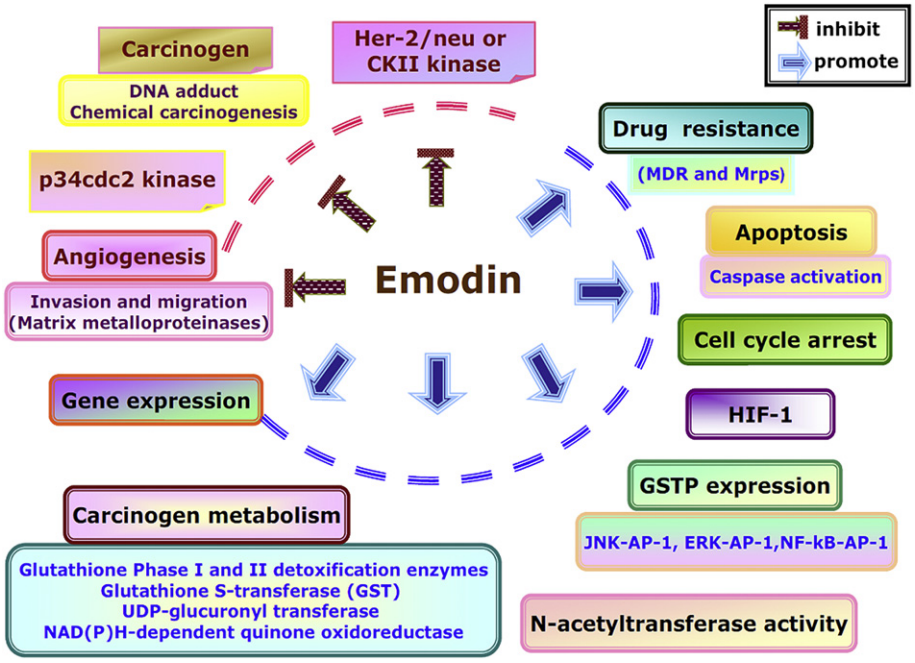

Fig. 2 – The pharmacology of emodin as a possible anti-cancer therapy.

4. Conclusion

Despite the fact that TCM research has been greatly accelerated with the advent of new technologies, we still need to work hard to gain stronger evidence that confirms the clinical applications of herbal medicines. Based on our observations and the results of previously reported studies, emodin can act as an anticancer agent against many human cancer cell lines through its effects across multiple signaling pathways. Over these past several years, our laboratory has evaluated agents that affect cell cycle arrest, apoptosis, metastasis, and angiogenesis in human cancer cell lines, both *in vitro* and *in vivo*, in addition to tumor cell growth, invasion, migration, and metastasis that are also involved in angiogenesis. Based on these observations regarding the effects of emodin, these findings may offer information that could be used in the design of novel therapeutic agents that inhibit tumor cells. Accordingly, we also summarize the pharmacology of emodin as a possible anticancer agent (Fig. 2).

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