‘Old Wine in a New Bottle’: Harnessing the Therapeutic Properties of Emodin Derivatives

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Abstract

Studies involving mechanism of emodin, an herbal extract, has revealed its potential as anti-inflammatory, anti-oxidant and anti-cancer agent. Emodin has been shown to successfully induce apoptosis, down-regulate cancer inducing genes, proving it to be a therapeutically significant pharmacophore. Modification of emodin and synthesis of various derivatives have successfully increased efficacy of the molecule in regulating various cellular pathway like MAPK signaling pathway, NF-κB signaling pathway, ROS mediated pathways and apoptotic pathways. With the advent of various, anti-bacterial properties of emodin may come in rescue to combat emerging drug resistant microbial and parasitic strains. Different emodin derivatives, including the recently reported haloemodin, which inhibits bacterial topoisomerases, can be designed to generate future drugs against resistant pathogens. Emodin derivatives can also inhibit proteases and microtubule-associated proteins, which play an important role in Alzheimer’s disease. Properly designed drug delivery systems like liposomes and nanoparticles have been reported as efficient emodin carriers and to enhance emodin activity in cancer cell inhibition. Exploitation of these newly reported properties of this age-old drug could prove to be a promising solution for anti-microbial chemoresistance menace and other prevalent non-communicable diseases.

Keywords: Emodin; Anti-inflammatory; Anthroquinones; Anti-proliferative activity; Chloroquine; Water solubility

Introduction

Emodin and its derivatives are anthraquinone skeleton containing compounds having varied therapeutic applications (Figure 1). Rubarb (Rheum rhabarbarum), a herb, which has been widely used in conventional medical treatments in China and eastern-Asian countries was the first source of emodin. HPLC separation in China and Rhubarb extract isolated five compounds with the anthroquinone skeleton among other compounds [1]. Of these five anthroquinone compounds, aloe-emodin (1,3,8-trihydroxyanthraquinone) and emodin (6-methyl-1,3,8-trihydroxyanthraquinone) were notable [1] because of their varied therapeutic properties. Similar isolation techniques are also used for extraction of Aloe emodin and emodin from Aloe vera leaves, Frangula bark (Rhamnus frangula) and Himalayan Rhubarb (Rheum emodi). First reported isolation of emodin was in the year 1858 [2] and the molecular formula, C_{14}H_{14}O_{6} was confirmed in 1876 [3]. Anti-microbial property of emodin was reported for the first time by Ubbink-Kok [4]. Anti-viral properties of emodin were demonstrated by in 1996 [5] and in the same year Chang et al reported that emodin exhibited anti-inflammatory properties [6]. Emodin gained much attention for its overtly reported anti-cancer [7-9] and anti-inflammatory properties [10]. Avecedo-Duncan et al showed anti-tumor effect of Emodin emodin in 2004. Aloe emodin is also reported to induce cell cycle arrest and apoptosis [11]. In order to increase the effectiveness of emodin, it has been subjected to various modification and numerous derivatives have been successfully synthesized with the goal of achieving better therapeutic effects. Modification of plant compounds to improve therapeutic properties is widely used as a part of drug discovery strategies. For example the drugs teniposide and etoposide are derived from podophyllotoxin, which is a non-alkaloid toxin from roots and rhizome of Podophyllum species and topotecan and irinotecan are hydrophilic analogs of the anticancer drug camptothecin obtained from the bark of Camptotheca acuminata. These derivatives show better activity than their parent compounds. Similarly studies with Emodin and Aloe emodin derivatives have also revealed greater therapeutic potential, DNA intercalation property, and reactive oxygen species generation and thereby induction of apoptosis in cancer cells [12]. Such wide spread therapeutic application of emodin led to rise of interest in scientific community leading to development of new synthetic methods and formulation of new derivatives. This review article aims to encompass various therapeutic effects of emodin, aloe emodin and their derivatives in the classical and neo-classical context. From treating simple inflammation, emodin compounds has travelled a long way and have been established as a potent anticancer agent, a possible therapeutic against Alzheimer disease and to deal with resistant parasites and bacteria. This therapeutically beneficial compound can prove itself more useful if used with a proper delivery system. Liposomes and nanoparticles can be the delivery system of choice since they are proven success in several chemotherapeutic strategies.

The Old School Therapeutic Properties of Emodin

Traditionally emodin has been used as laxatives and anti-inflammatory agent for a long time. Scientific study of emodin and aloe emodin has revealed their use for treatment of broad spectrum of diseases, viz. anti-inflammatory, anti-cancer, and few anti-microbial studies.

Different types of derivatives have been synthesized using emodin as parent material which has subsequently shown better therapeutic activity compared to the parent compound. Introduction of a cationic side chain in 4th-position of emodin enhanced its DNA binding

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Affinity [13]. This work further inspired synthesis of emodin derivatives with introduction of quaternary ammonium salt, side chains on the 6-methyl position of emodin, since quaternary ammonium salt can maintain a positive charge at any pH, prolonged DNA intercalation and therefore improved anti-cancer activity was exhibited compared to the parent compound [14]. Synthesis of emodin derivatives containing a hydroxyl group in either 1- or 8-position exhibited better anti-cancer activity, since the hydroxyl group will facilitate uptake of an electron by the anthroquinone moiety, leading to ROS mediated anticancer pathway [15]. Introduction of pyrazole ring in anthroquinone skeleton of emodin produced emodin derivatives with high DNA intercalating activity [16].

Emodin compounds with anti-inflammatory effect

Emodin is an immune response of body to external stimuli like pathogens, irritants or cell injury. Prolonged inflammatory responses can be highly problematic in diseases like rheumatoid arthritis. Inflammatory responses are mediated by NF-kB signaling pathway and treatments for anti-inflammation aims to inhibit NF-kB activation [17]. Activation of NF-kB takes place via phosphorylation and subsequent degradation of IkBα (inhibitor of NF-kB), which can be due to an external stimuli or other signaling pathways like Akt/Phosphoinositide-3-kinase (PI3K) [18] and mitogen activated protein kinase [18]. Emodin has been reported to show anti-inflammatory effect by blocking MAPK pathway and PI3K signaling pathway [19,20] and to inhibit NF-kB activation and iNOS expression [21]. Concentration dependent effect of emodin and aloe emodin in macrophage responsive anti-inflammatory response in RAW264.7 cells by Lipopolysaccharide (LPS) induction was studied by determining Nitric oxide (NO) production, which is a common inflammatory marker [17]. Studies revealed that aloe emodin inhibited transcription and expression of iNOS gene and thereby the decreased amount of NO produced [17]. Emodin was also reported to reduce NO production [17]. Aloe emodin was also reported to suppress the major pro-inflammatory cytokines IL-1β and IL-6 [17]. Expression of IL-1β and IL-6 is regulated by NF-kB signaling pathway, which in turn is activated by IkBα degradation [17]. Aloe emodin reportedly reduced LPS induced IkBα degradation, thus indicating inhibition of NF-kB pathway to show anti-inflammatory property [17] (Figure 2).

Induction of apoptosis and anti-cancer effect of emodin derivatives

Anthroquinones of microbial origin have been successfully used for anticancer treatment, among which, doxorubicin, daunorubicin, epirubicin and some synthetic analogues like mitoxantrone and pixantrone are now in clinical use [22]. Emodin being an anthroquinone was also expected to show similar response against cancerous cells. Scientific studies have been able to provide an insight into the working method of emodin, aloe emodin and their various derivatives. Aloe emodin has been widely studied over the last decade for its anti-cancer effects [23]. Aloe emodin has been reported to downregulate expression of two DNA break repair genes RAD51 and ERCC1 and also to inactivate ERK1/2 pathway, thus inhibiting proliferation of lung cancer cells [24]. Successful use of aloe emodin to inhibit human brain malignant glioma derived glioblastoma cell line U87 has also been reported [25]. Aloe emodin worked in a dose and time dependent manner with the IC50 value becoming half of the initial value within duration of 24 hr. This was due to upregulation of genes like SHARPIN, BCAP31, FIS1 and STAT6 by Aloe emodin, which then played an important role in programmed cell death mechanisms [25]. Thus, Aloe emodin inhibits proliferation of glioblastoma cells by enhancing the apoptotic genes. The study also reported increased expression of MTSSIL (Metastasis suppressor 1-like) gene. Induction of another metastatic suppressor gene NM23 in human hepatocellular carcinoma cell line by aloe emodin has also been reported [26]. This property of suppression of metastasis genes shown by aloe emodin can be exploited further for therapeutic use against breast cancer and lung cancer, which are most common types of cancer showing metastatic property.

Studies on the efficacy of different emodin derivatives against various cancer cell lines like HepG2, MCF-7, DU-145 and PC-3 and normal non-transformed cell line HEK-293 were also reported [22]. The derivatives used in the study were 11 O-alkylated emodin derivatives, 2 amide derivatives and 2 ester derivatives. IC50 values for all 15 synthesized compounds against the reported cell lines were less than the parent compound emodin. Notably the O-alkylate d compound with a basic amine group showed IC50 value lower than the market available drug Epirubicin against HepG2 and PC-3 cell lines [22].
This compound was further used in apoptotic studies and cell cycle analysis study against HepG2 cell line showing increased apoptosis in compound treated cell lines. The cell cycle study indicated an increase of S-phase cells, which clearly shows S-phase arrest of HepG2 cells and thereby suggesting a mechanism for anti-proliferative activity [22] of the O-alkylated compound. There was an increase in caspase-3 activation with increasing concentration of this specific compound confirming the apoptotic pathway induced by the compound to be caspase dependent (Figure 3) [22].

**Therapeutic efficacy of emodin compounds through DNA intercalation**

Mitoxantrone and Daunorubicin (Figures 4A and 4B) are anthr quoquinone-based drugs, are widely used DNA intercalators, which act as antitumor agents [16]. Presence of planar polycyclic aromatic system and presence of one or two side chains containing polymethylenamine or sugar derivatives with a strictly defined orientation to chromophore are the properties exhibited by most
DNA binders. They bind DNA with intercalative association in the major and minor grooves and backbone leading to conformational change in DNA. Such conformational change distorts the regular double helical structure of DNA, unwinds the binding site and most importantly interferes with DNA binding enzymes like topoisomerases and DNA polymerases [27]. The above mentioned drugs follow the same mechanisms and inhibit DNA topoisomerase II, thus inducing breaks in DNA double strands of tumor cells leading to cell death [16]. Though Mitoxantrone and Daunorubicin are outstanding DNA binders and antitumor agents, they have undesirable side effects in cancer therapy, especially cardiotoxicity [28]. This kind of harmful side effect has led to modification of anthroquinones to yield compounds with less harmful side effect and high antitumor activity. Losoxantrone is such an anthrapyrazole derivative of anthroquinone (Figure 5A) with lower cardiotoxicity than Mitoxantrone [29]. Though emodin itself has low DNA binding activity, it belongs to the same class of co-planar anthroquinones as of the above mentioned drugs, so incorporation of a pyrazole ring in its anthroquinone chromophore can increase the resistance of the chromophore to enzymatic reduction into radical species, thus lowering cytotoxicity of the compound (Figure 5B) [16]. Further enhancement of DNA binding capacity of anthrapyrazole derivatives of emodin with different cationic amino side chains attached to the pyrole ring exhibited greater efficiency [16]. The compounds were tested for their DNA binding property against Calf Thymus (CT) DNA and all the compounds exhibited enhanced DNA binding capability compared to the parent compound, emodin. The spectral changes reported in the study imply that binding method for most of the derived compounds to the CT DNA was intercalative association. Cytotoxicity study revealed a much lower IC50 value for the anthrapyrazole derivatives against three tumor cell lines (B16, HepG2, LLC) as compared to the parent compound [16]. O-alkylated and C-alkylated derivatives of emodin (Figure 6), which showed much more efficacy than emodin and comparable efficacy as epirubicin (a well marketed anticancer drug) were shown to be used as an anti-proliferative agent against cancer cell lines (HepG2 and MDA-MB-231) [12]. The study showed that the mechanism underlying the anti-proliferative activity is due to DNA intercalating property of the compounds. An ethidium bromide (EtBr) displacement assay using CT DNA showed that these compounds competitively bind DNA and displaces EtBr. These derivatives showed similar efficiency as that of doxorubicin, a known DNA intercalator, suggesting these compounds as potent drugs for anti-cancer therapeutics.

The New Age Therapeutic Effects of Emodin

Increasing resistance of bacterial and parasitic strains towards conventional antibiotics is an alarming threat to the developing countries [30], which desperately calls for new therapeutic techniques. Commonly used broad spectrum antibiotics are no longer adequate for treating bacterial or parasitic diseases, necessitating formulation of novel drugs. Emodin, being traditionally used as an antibacterial...
agent, can prove to be a potent lead compound for synthesis of new drugs, which will be effective against these resistant strains. Emodin also possesses apoptosis inducing properties, which makes it potential anticancer agent. Apoptosis is not only relevant in cancer treatment; it also plays an important role in acquired immunodeficiency disease and neurodegenerative diseases [31]. The apoptotic inductive character of emodin can be exploited for production of a new line of therapeutics to treat these diseases.

**Therapeutic formulations of emodin used to treat Alzheimer’s disease**

Alzheimer disease (AD) is a neurodegenerative disease leading to memory loss and cognitive behaviour [32]. Two major forms of calpain and a cytosolic calcium activated cysteine-protease have predominantly been linked to Alzheimer disease [33]. These two forms are calpain 1 and calpain 2 (also known as μ-calpain and m-calpain). Calpain 1 is abnormally activated in AD brain [34] whereas activated calpain 2 is increased in neurites of neuronal cells developing neurofibrillary pathology and binds neurofibrillary tangles (NFTs) in patients of AD [35]. Calpastatin, the endogenous inhibitor for calpain is reduced in Alzheimer disease [33]. Recently, it has been shown that, effectiveness of 10-deoxycitreorosein; a derivative of ω-hydroxy-emodin, and emodin carbaldehyde (Figure 7) can inhibit μ-calpain [36]. The compounds 10-deoxycitreorosein and emodin carbaldehyde showed 3.1 and 2.4 times more activity than E64d, a known calpain inhibitor. Aggregation of a microtubule associated protein “Tau” has been linked to AD, correlating its aggregation with type and severity of cognitive impairment in AD patients. Though various tau inhibitors have been reported, there remains a question about their bioavailability, pharmacokinetics and in-vivo activity [37]. 2,ω-Dihydroxyemodin, derived from secondary metabolite of the fungi Aspergillus nidulans, has shown effective inhibition of tau aggregation with more potency than emodin [38], which is generally considered as a strong inhibitor of tau [37]. These studies show that emodin and their derivatives can be used and modified to form potent drugs to be used for treatment of AD.

**Emodin derivatives as potent anti-parasitic agents**

Chloroquine is the most widely used drug for primary chemotherapeutic treatment of malaria since decades [39]. But with
instances of Chloroquine resistance being reported from majority of malaria-endemic countries including Southeast Asia and South America, synthesis of novel drugs for treatment of Chloroquine resistant malaria parasite have become a major requirement [39]. Another major drawback of anti-microbial agents is their cytotoxicity. Reviving on the effectiveness of emodin as an efficient anti-microbial agent, new study reports the synthesis of a variety of emodin derivatives, which were tested for their anti-malarial activity against Chloroquine resistant and sensitive strain of \textit{Plasmodium falciparum}, PfK1 and Pf3D7, respectively, [40] along with their extents of cytotoxicity. While most of the derivatives exhibited better inhibition of both the strains as compared to parent compound emodin, it was found that O-alkylation of emodin improved activity in both strains, but C-alkylation only improved activity against Chloroquine sensitive strain Pf3D7 [40]. Among the emodin derivatives, three Mannich base derivatives (Figure 8) showed IC50 value comparable to the drug Chloroquine and also good therapeutic index against the PfK1 strain (Chloroquine resistant) [40]. Also, the compounds did not show any notable cytotoxicity when studied with VERO cell line. Emodin was reported to be isolated from \textit{Cassia siamea} stem bark and its inhibitory effect was studied against PfK1 strain [41]. Efficient anti-plasmodial activity with a notable IC50 value was reported [41].

**Anti-bacterial activity of emodin compounds**

Antibiotics like tetracycline, streptomycin, penicillin and their derivatives as well as fluoroquinolones have long served as classical therapeutic agents against different bacterial strains. Tetracycline and streptomycin inhibits protein synthesis in bacteria, whereas penicillin cleaves the \(\beta\)-lactum ring, inhibiting formation of peptidoglycan linkages in bacterial cell wall. However, over time, many bacterial strains have gradually adapted themselves to the existing antibiotics by spontaneous genetic mutations, thus become resistant to existing line of treatment [30]. This is an alarming problem as resistant bacterial strain poses more threat and is difficult to treat as compared to non-resistant strains. This situation calls for new approaches in drug discovery with novel strategies to target bacterial strains.

In a very recent work, F.Duan \textit{et al}. reported synthesis of a series of halogenated emodins. Among these haloemodins, one compound (Figure 9) efficiently inhibited methicillin resistant \textit{Staphylococcus aureus} and \textit{Staphylococcus epidermis} (MRSA and MRSE) and vancomycin

![Figure 8: Structure of Mannich base derivatives of emodin, which potently inhibit Chloroquine resistant PfK1 strain.](image)
resistant *Enterococcus faecium* (VRE) strains with minimum inhibitory concentration (MIC) value much less than the antibiotic cefoxitin for MRSA and MRSE strains [42]. For VRE strain, the reported compound exhibited much lower MIC value than that of vancomycin. This haloemodin was reported to selectively bind bacterial DNA Gyrase and inhibit kDNA decatenation [42]. The compound also inhibited *E.coli* Topo I and had no activity against human topoisomerase Topo IIα [42]. In contrast, Emodin showed little inhibitory activity against bacterial DNA Gyrase and none against bacterial Topo I, but had strong inhibitory activity against Human Topo IIα. The compound was also therapeutically effective against *S. aureus* induced keratitis in rabbit model [42]. The characteristic of the haloemodin as a novel bacterial Topoisomerase inhibitor and the fact that it differs structurally from the conventionally used antibiotics like β-lactums, quinolones, glycopeptides, makes it a preferable choice for therapeutics development against different drug resistant bacteria and parasites.

**Emodin Derivatives with Increased Permeability**

Polypeptides and protein macromolecules are poorly permeable against mucosal cells due to their hydrophobic nature. Use of absorption enhancer molecules causes better absorption of these molecules and has been reported to enhance permeability against transepithelial membrane. Mast cell derived inflammation mediators like histamine; platelet activating factors and nitric oxide are known molecules responsible for increased permeation and disrupting barrier function [43]. Aloe emodin derivative, Aloe Emodin Anthrone (AEA) was found to have histamine releasing activity in isolated rat mast cells. In a study aloe emodin antherone was used as permeation enhancer for water-soluble poorly permeable compounds in rat colonic mucosal cells [44]. Carboxyfluorescein, a water-soluble tracer dye, was used as a model compound. AEA treatment showed a notable increase in permeability coefficient of carboxyfluorescein as compared to permeability coefficient in absence of AEA. The underlying mechanism was reported to be AEA stimulated release of histamine from of mast cells of colonic mucosa aiding in increasing the permeation coefficient of mucosal cells.

**Efficient Delivery of Emodin, Aloe Emodin and their Derivatives**

Like many other poor water-soluble drug, emodin also faces the challenge of poor oral bioavailability due to its poor water solubility, which is a common phenomenon for most anthraquinone-based drugs. It is practically insoluble in water with highly soluble in alcohol and belongs to BCS classification II, suggesting that it has low solubility but high permeability [45]. Aloe emodin also shows hydrophobicity and is found to crystallize in aqueous solution [46]. Liposomes, self-enclosing spherical lipid vesicles, and nanoparticles have been widely used as drug delivery vesicles for targeted and efficient delivery of anticancer drugs [46]. Same approach with emodin and aloe emodin has resulted in successful delivery of the drugs to desired target cells.

**Liposomal delivery of Aloe emodin and Emodin**

Liposomes are most common and abundantly used drug delivery vessels because of their biocompatibility, biodegradability, low toxicity and ability to enclose both hydrophilic and hydrophobic drugs [46]. Also, encapsulation of drugs by liposomes significantly increases pharmacokinetics and biodistribution of drugs because of controlled release. Liposome encapsulated aloe emodin when studied against skin cancer cells (A431, SCC25, A375, Hs68, HaCaT) was reported to successfully cross skin barrier and showed higher cytotoxicity against A431 and SCC25 cell lines than free aloe emodin and DMSO:emodin solution. Surface modification of liposomes loaded with emodin by silk-fibroin coats showed localized drug delivery, increased residence time and specific cell recognition as compared to uncoated liposomes, which contain emodin [46]. Also, silk fibroin modified liposomal emodin showed better uptake and retention of emodin in MDA-MB-453 cells (breast cancer cell line) compared to uncoated emodin loaded liposomes [46]. Silk fibroin modified liposomal emodin inhibits MAPK pathway in addition to phosphorylating Her2/neu phosphorylation, the latter is achieved by uncoated liposomal emodin as well but to a lesser extent [46]. Besides silk fibroin coated liposomes also show better delivery of emodin without any alteration at the target site. Surface modification of liposomes with cationic surfactant also increases their permeability with respect to neutral liposomes [47]. Gemini based cationic formulations have successfully increased permeability of undissociated aloe emodin proving it as a suitable strategy for delivery of this hydrophobic compound [47].

**Nanoparticle based delivery of Emodin derivatives**

To achieve therapeutically effectiveness, solubility of emodin can be enhanced by using appropriate modifications by crosslinking the hydroxyl group of emodin to borate ion, since addition of borate to any polymer chain aids the latter to behave as a polyelectrolyte [48]. Water-soluble emodin-borate (EmB) can be further loaded onto polymer microgels to achieve controlled release of the drug [49]. Also, release of emodin from phenylboronic acid nanoparticles showed better cytotoxicity against HepG2 cells than MC-3T3-E1 cells (normal cell line) [50]. Controlled release of emodin from silver nanoparticles loaded into porous silicon (PSI) nano-structured layers showed emodin release without any aggregate formation by emodin [51]. Solid lipid nanoparticles or SLNs are promising drug delivery system for anticancer drugs because of their advantageous properties.
of controlled release, efficient targeting and prevention of loaded drugs from degrading. Also, it is an attractive means of delivery of lipophilic drugs, like emodin. Emodin and aloe emodin released from solid-lipid nanoparticles or SLNs were reported to have higher cytotoxicity against breast cancer cell lines MCF-7 compared to free drug [45,51]. Emodin:SLNs were also effective against MDA-MB-231 cells. E-SLNs, AE-SLNs and blank SLNs were nontoxic to human mammary epithelial cell line, MCF-10A, confirming safety to normal cells [45,51]. So, use of SLN mediated delivery of emodin and aloe emodin in anticancer therapeutics can be a promising way of combating the disease with increased efficacy of emodin.

Conclusion

Emodin has undergone wide modification and evolved from Traditional Chinese Medicine (TCM) to a compound of immense scientific interest. Antibacterial property exhibited by the recently reported haloemodins against drug resistant Gram-positive bacterial strain opens a new horizon in treatment of drug resistant bacteria, which are now related with every type of disease. Further study on the properties of these compounds and their modifications may give rise to more potent drugs. One of the studies mentioned in this review showed an emodin derivative assisting in increasing permeability of poorly permeable molecules across colonic mucosa [43] while other derivatives exhibited potent anti-parasitic activities along with reduced cytotoxicity. This specific modification can be added onto halogen modification, to produce a mixed bag of derivatives capable of binding bacterial Topo I and bacterial DNA Gyrase. A combination of different beneficial modifications on emodin can be generated in silico and thereafter their parameterization can be carried out to obtain their 3D coordinates. Such mixed bag derivatives can then be used to dock onto essential metabolic enzymes of microbes e.g., DNA Topo I and/or DNA gyrase, so as to obtain the derivative with highest docking efficiency in terms of most stable docked structure. Thereafter laboratory synthesis of these specific derivatives will generate a drug with high specificity towards essential microbial enzymes such as bacterial topoisomerases as well as exhibit, reduced cytotoxicity and/or increased cell permeability. A lowered cytotoxicity and increased efficiency of emodin derivatives would thus yield a highly efficient pharmacophore that can act against both sensitive and resistant microbes. Specialized methods of drug delivery can be devised for the above-mentioned drugs so as to obtain an efficient and target specific delivery of the drug. For example modified haloemodin will be present in the inside core while the permeability enhancing drug will be in the outer core. If a nanoparticle is so designed that the drug in the outside core is leached as it reaches the target organ, to enhance cell permeability, an easy entry of the core drug haloemodin would be achieved, thus causing efficient destruction of the target organism.

Leishmania are kinetoplastid protozoa having an interconnected network of maxicircles and minicircles inside the kinetoplast, which is efficiently resolved by topoisomerases. Hence DNA intercalating derivatives of emodin such as anthrapyrazole derivatives, O-alkylated derivatives and C-alkylated derivatives can be further modified to make them non-cytotoxic to mammalian cells and can be used for treating Leishmaniasis caused by Leishmania sp. These compounds can bind and intercalate kinetoplastid DNA of L. donovani and inhibit the binding of topoisomerases to kDNA proving fatal to the protozoa. Inhibition of cysteine proteases and microtubule-associated proteins by ω-hydroxymodin and 2, ω-Di hydroxymodin, respectively, has made emodin a potential future drug for treatment of Alzheimer disease [36,38]. Armed with modern techniques of drug delivery systems and chemical modifications, which enhances its activity, emodin has traversed a long path from being a laxative and anti-inflammatory drug of old China and seems to be the answer to most of the problematic questions of therapeutic research of recent times.

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