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Unravelling the Recent Trends in Pharmacological and Nanotechnological Potential of Emodin

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Abstract: Emodin is an anthraquinone glycoside primarily found in *Polygonum cuspidatum*, *Polygonum multiflorum*, and rhubarb (Rheum species). Emodin is widely recognized for extensive pharmacological applications, encompassing antiviral, anti-inflammatory, anti-allergic, anti-osteoporotic, anti-arthritic, anticancer, anti-diabetic, and antioxidant effects. It is of considerable importance in alzheimer's disease, asthma, atopic dermatitis, psoriasis, and osteoporosis. Although emodin offers potential therapeutic advantages, its clinical use is hindered by its low solubility, instability, limited bioavailability, and susceptibility to degradation in the gastrointestinal tract. The nanotechnological modification of emodin showed promise for enhancing solubility, reducing degradation rates, minimizing toxicity, and altering the absorption and biological responses of plant-derived bioactive compounds. This review article offers a comprehensive analysis of the pharmacological applications and nanotechnology-based formulations of emodin, encompassing liposomes, solid lipid nanoparticles, polymeric nanoparticles, microspheres, micelles, carbon nanotubes, nano-emulsions, magnetic nanoparticles, and silica nanoparticles, which have attracted considerable interest in recent decades.

Keywords: emodin; bioavailability; solubility; anticancer; nanotechnology; liposomes.

1. Introduction

Phytochemicals have attracted researchers' interest owing to their availability in natural sources such as leaves, fruits, flowers, seeds, and entire plants, and their increasing health benefits without adverse effects [1-3]. The primary categories of phytoconstituents comprise alkaloids, aromatic acids, carotenoids, flavonoids, glycosides, phytosterols, organic acids, and essential oils [4-8]. Emodin is an anthraquinone glycoside characterized by a hydroxyanthraquinone moiety that features an anthracene structure with quinone and a hydroxyl group. Its IUPAC name is designated 1,3,8-trihydroxy-6-methyl-9,10-dihydroanthracene-9,10-dione, empirical formula is $C_{15}H_{10}O_5$, and a molecular weight of 270.23 daltons. The fundamental chemical architecture of anthraquinone is characterized by a phenolic anthracene ring that incorporates two ketone groups at the C9 and C10 positions [9-13]. It is a naturally occurring phytochemical found in *Polygonum cuspidatum*, *Polygonum multiflorum*, and rhubarb (Rheum species), both of which belong to the Polygonaceae family.

It manifests as a red-orange crystalline or powdered substance. Emodin demonstrates solubility in dimethyl sulfoxide while being practically insoluble in water [14-18]. Its limited aqueous solubility, hepatic metabolism, and low oral bioavailability are major challenges for its medicinal use. Previous studies investigated nano-formulations of emodin to improve its solubility and bioavailability, hence augmenting its therapeutic efficacy [19-21].

This review article addresses dual objectives: the pharmacological applications of emodin and its nanotechnological integration. This review offers a concise summary of the pharmacological applications of emodin in Alzheimer's disease, asthma, atopic dermatitis, psoriasis, and osteoporosis, and its role as an antiviral, anti-inflammatory, antiallergic, antiosteoporotic, antiarthritic, anticancer, antidiabetic, and antioxidant agent. This review also focused on nanotechnology-based formulations of emodin, including liposomes, solid lipid nanoparticles, polymeric nanoparticles, microspheres, micelles, carbon nanotubes, nanoemulsions, magnetic nanoparticles, and silica nanoparticles, to improve aqueous solubility and targeted drug delivery. An extensive review of existing literature was conducted using the PubMed, Google Scholar, and ScienceDirect databases, covering articles published between 2000 and 2025.

2. Pharmacological Applications of Emodin

Emodin has been shown to exhibit a diverse range of pharmacological effects, including immune suppression, blood pressure reduction, inflammation alleviation, anticancer properties, hepatoprotection, and antiallergic activities [22,23]. This review offers an inclusive examination of experimental findings that substantiate the pharmacological effects of emodin.

2.1. Laxative.

In recent years, constipation has emerged as one of the most prevalent gastrointestinal conditions. The principal factors contributing to constipation include a fiber-deficient diet, insufficient physical activity, low fluid intake, the use of certain medications, and changes in daily habits or lifestyle [24]. The administration of a dosage of rhubarb containing emodin, aloe-emodin, aloe-emodin anthrone, and physcion demonstrated laxative properties and showed upregulation of c-kit and 5-HT4 expression, while concurrently reducing AQP3 expression in the rat colon [25]. In a preclinical study, administration of emodin via colonic irrigation in chronic kidney disease rats alters the gut microbiota by reducing pathogenic bacteria, such as Clostridium, and boosting bacteria, such as *Lactobacillus*. The reduced systemic inflammation, better renal function, and reduction in uremic toxins may be correlated with microbial change [26].

2.2. Anticancer activity.

Emodin works by lowering signals for oncogenic growth, such as phosphatidylinositol 3-kinase, HER-2 tyrosine kinase, protein kinase B, and Wnt/-catenin, thereby preventing cell growth and multiplication. In addition to controlling cancer cell invasion and spread, this mechanism causes cell death in various cancer cell types [27,28]. Emodin exerts anticancer activities by various pathways, such as via inhibition of cell proliferation by inducing cell cycle arrest, induction of apoptosis, inhibition of angiogenesis, anti-inflammatory effect by inhibition of NF-kB, and modulation of key signalling pathways, i.e., suppression of MAPK and activation of AMPK (Figure 1) [28-30]. In a research study, emodin at a dosage of 40 mg/kg

was administered with gemcitabine at a dosage of 80 mg/kg to tumors in nude mice that had received subcutaneous injections of SW1990 cells. There was an apparent drop in tumor volume, the Ki-67 proliferative index, and the level of expression of the Bcl-2/Bax ratio [27]. In another study, emodin showed suppression of K562 cell development *in vivo* and reduction of the xenografted tumor's volume and weight [31]. In another study, LS1034 cells underwent apoptosis when exposed to emodin up to 30 µM for 48 hours [32]. The proportion of the total apoptotic HL-60/ADR cells increased from 8.25±1.01% to 22.41±5.29% and 32.03±2.59% following 24-hour treatment with 20 µM and 40 µM emodin, respectively [33]. In a preclinical study, emodin showed inhibition of angiogenesis by averting phosphorylation of VEGF receptor-2. By inhibiting NF-κB signalling and downregulating angiogenesis-related proteins, i.e., VEGF, MMP-2/9, and eNOS, emodin reduced tumour growth, invasion, and metastasis, and demonstrated strong antiangiogenic and antiproliferative activity [34-36].

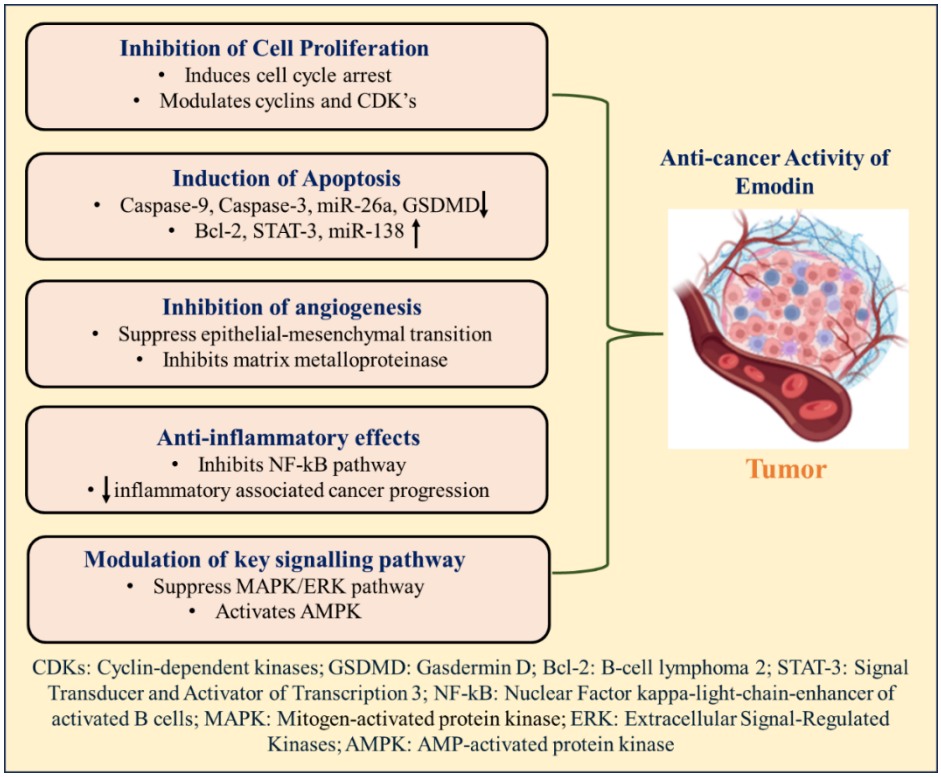

Figure 1. Illustration of key mechanisms underlying the anticancer activity of emodin.

2.3. Alzheimer's disease.

The presence of extracellular beta-amyloid accumulation in the form of plaques and neuritic tangles, and intracellular buildup of hyperphosphorylated tau as neurofibrillary tangles, are fundamental neuropathologic markers for diagnosing Alzheimer's disease [37]. The amyloid hypothesis is the predominant pathophysiological theory behind Alzheimer's disease, highlighting the role of Aβ generation and Aβ-induced neurotoxicity in the progression of the disorder. Emodin showed potential to inhibit Aβ-induced cytotoxicity, Aβ aggregation, and parenchymal plaque formation. In Alzheimer's disease, plaque formation contributes to oxidative stress, leading to alterations in kinase/phosphatase activity, tau hyperphosphorylation, and intracellular neurofibril entanglement. Emodin showed the prevention of the formation of reactive oxygen species responsible for mitochondrial dysfunction via inhibition of Aβ accumulation. In a separate pathway, emodin prevents dysregulation of autophagy in neuroblastoma cells by inhibiting PI3K/AKT/mTOR and

activating the Bcl-2 pathway, and by preventing the degradation of synaptic and neural proteins (Figure 2) [38-40]. A research study revealed the neuroprotective effect of emodin in Alzheimer's disease by the Nrf2 signaling pathway in U251 cells and APP/PS1 mice [41]. In a preclinical study in an Alzheimer's disease-induced mouse model, emodin activated Nrf2/HO-1, leading to improved protein kinase C phosphorylation and cognitive performance, reduced oxidative stress and inflammation, and enhanced antioxidant effects. Emodin reduced tau and β-amyloid pathology, altered mitochondrial apoptosis regulators (Bcl-2/Bax), and improved cognitive function and neuroprotection in a disease-induced rat model [42].

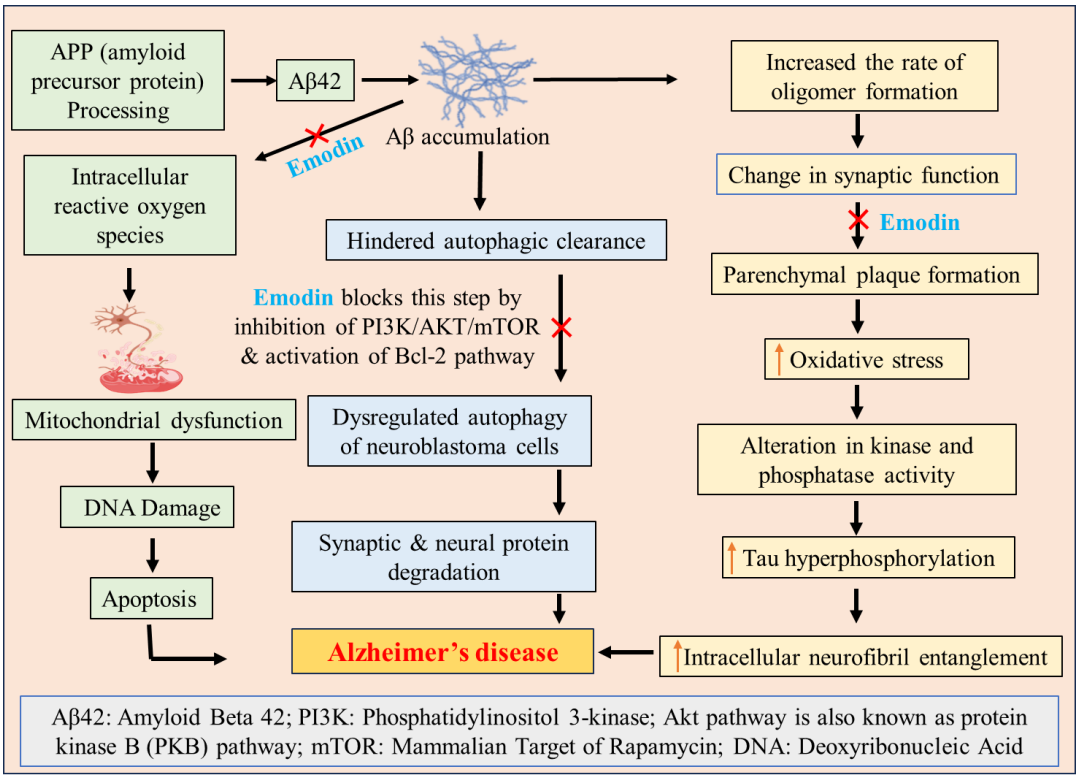

Figure 2. Illustration of underlying pathways for therapeutic effects of emodin in Alzheimer's disease.

2.4. Asthma.

The hallmark of asthma is reversible airflow restriction together with inflammation and hyperresponsiveness. Due to exposure to inhaled allergens, e.g., pollens, cockroaches, animal dander, fungus, and house dust mites, the majority of asthma cases often begin in infancy. The increase in T-helper type 2 cells is prompted by inhaled allergens, resulting in production and secretion of Th2 cytokines and interleukins [43]. Emodin demonstrated a dosage-dependent suppression of serum levels of histamine, leukotriene C4, and prostaglandin D2 [44]. Emodin showed suppression of airway inflammation and hyperresponsiveness, resulting in strong antiasthmatic benefits in a diseased mouse model with cough variant asthma. By suppressing notch receptors and delta-like ligand 4 expression, emodin showed controlled notch signaling pathway, reduction in immune cell infiltration and inflammatory cytokines such as IL-5, IL-17, and IFN-γ, and enhanced tissue remodeling and pulmonary function [45].

2.5. Diabetes Mellitus.

Diabetes mellitus is classified into three types. Type 1 diabetes is characterized by an inability to release and form insulin and an autoimmune disruption of β-cells in the pancreas. Type 2 diabetes is characterized by the body's abnormal resistance to insulin and its inability

to produce insulin. Type 3 diabetes usually affects pregnant women, which is a type of glucose intolerance [46]. In the study, it was demonstrated that administration of emodin by the intraperitoneal route in the diabetic mouse model significantly reduced the levels of total cholesterol, blood glucose, and triglycerides. Emodin exhibited an increase in mRNA expression level of PPARγ and modulation in the mRNA expression levels of FABPs (ap2), lipoprotein lipase, and fatty acid translocation/cluster of differentiation in adipocytes and liver tissues [47]. Emodin suppressed local glucocorticoid action and 11β-HSD1 activity, thereby increasing insulin sensitivity and adipocyte glucose uptake, exerting an antidiabetic effect. *An in vivo preclinical study in diabetic mice demonstrated increased glucose tolerance, PPARγ and adiponectin levels, and reduced* insulin resistance and blood glucose levels, whereas an *in vitro* study demonstrated amelioration of adipocyte dysfunction [48].

2.6. Antiviral.

Emodin has shown antiviral properties against poliovirus and hepatitis B virus [40]. It can suppress acute respiratory syndrome-coronavirus infection by blocking the spike protein of human coronavirus, thereby exerting an antiviral effect [49]. In a study involving intraperitoneal injection of emodin at a dosage of 50 mg/kg administered once daily for three consecutive days in female Kunming mice, survival rate in emodin treated mice group was significantly higher than control group in context of Pseudorabies infection which might be attributed to modulation of serum levels of TNF-α, IL-6, IFN-γ, and IL-4 in infected mice [50]. Emodin, isolated from *Polygonum cuspidatum*, showed suppression of Coxsackievirus B4 by averting viral entrance and replication without deactivating viral particles. It showed a decrease in myocardial viral titers and viral-induced apoptosis while increasing the mouse lifespan. Emodin also showed antiviral activity against pseudorabies virus and human coronavirus NL63 by targeting viral proteins and ion channels, modulating immune responses, and inhibiting NF-κB signaling [51].

2.7. Anti-inflammatory and antioxidant activity.

The accumulation of cells and exudates in inflamed tissues is referred to as inflammation, which constitutes a response to injury that serves to protect against further damage. Reactive oxygen radicals, like hydroxyl radicals, can damage cell membranes through oxidative stress, which can result in a number of diseases like AIDS, diabetes, cancer, arthritis, and alzheimer's [52]. The research has shown aloe-emodin derivatives' significant potential as antityrosinase, antibacterial, and antiinflammatory agents [53]. Co-administration of lipopolysaccharide and emodin by the intraperitoneal route in male C57BL/6 mice reduced IL-1β production. In a lipopolysaccharide-induced endotoxin shock model in mice, emodin reduced the severity of symptoms associated with NLRP3 inflammasome activation [54]. Emodin showed reduction in inflammation and nociception by lowering COX-2, PGE2, and MMPs production, and suppression of immune cell activation [55]. Studies have shown that emodin at 200 μg/mL exhibited antioxidant activity of 92.1±1.0%, similar to that of butylated hydroxytoluene at 20 μg/mL [56]. Emodin exhibited antioxidant action via activation of the Nrf2/HO-1 pathway, which strengthens cellular antioxidant defenses and lowers oxidative stress. It reduces oxidative damage from inflammation and protects tissues by inhibiting NF-κB signaling, upregulating antioxidant enzymes, and reducing reactive oxygen species and lipid peroxidation [57].

2.8. Immunosuppressive activity.

Immunosuppressive cells, i.e., tumor-associated neutrophils, tumor-associated dendritic cells, regulatory T-cells (Treg), tumor-associated macrophages, and myeloid-derived suppressive cells, are significant factors linked to immunological resistance [58]. In Swiss mice, emodin altered t-helper cells and had antiproliferative effects on lymphocytes, which may have led to immunomodulatory effects [59]. Emodin showed a significant increase in skin transplant survival and averted CD^{3+} T-cell infiltration in male BALB/c and C57BL/6 allograft mice [60].

2.9. Antiallergy activity.

Allergens cause allergic reactions by attaching themselves to the mast cells' high-affinity IgE receptor. Allergic reactions such as hay fever, food allergies, asthma, and type I hypersensitivity are examples of IgE-mediated immune responses. Emodin reduces mast cell degranulation, suggesting that it could be explored as a therapeutic intervention in acute as well as chronic allergy disorders [61]. Emodin treatment significantly increased immunoglobulin E and IgG1/IgG2a levels compared with the BALB/c model group. Emodin inhibited inflammatory cell infiltration and reduced serum and BALF levels of inflammatory cytokines, IL-5, IL-17, and interferon-g [45]. In an *in vitro* study in mouse bone marrow-derived mast cells, emodin inhibited the receptor-proximal Syk-dependent signaling cascade, leading to reduced phosphorylation of Syk and downstream signaling pathways such as Ca^{2+} mobilization, MAPK, PI3K, and NF-κB, thereby suppressing IgE-mediated anaphylaxis and mast cell activation. In passive anaphylaxis IgE-sensitized mice, emodin (p.o) showed mast cell-dependent passive anaphylactic reaction via inhibition of mast cell activation and suppression of receptor-proximal Syk-dependent signaling pathways [62].

2.10. Antiosteoporotic activity.

Osteoporosis is the most prevalent primary health danger in recent years, along with decreased bone mass and microarchitecture degeneration of bone structures. It increases bone fragility, increasing the risk of fracture with minimal impact, and affects more than 2000 million people globally [63]. Emodin has the potential to accelerate osteoblast growth by inducing MC3T3-E1 cells to produce the gene for bone morphogenetic protein-2. Additionally, it has been shown that emodin inhibits synovial inflammation and joint degeneration. Emodin may offer protection against bone loss since it prevents the formation of osteoclasts [64]. Emodin prevents osteoporosis in ovariectomized rats by promoting osteogenesis in MC3T3-E1 cells through the BMP-9/Smad pathway. The study demonstrated that emodin promotes osteoblast differentiation by activating phosphatidylinositol 3-kinase and increasing expression of the bone morphogenetic protein-2 gene [65].

2.11. Antiarthritic activity.

Osteoarthritis is widely regarded as a prevalent chronic joint condition, and its increasing incidence can be attributed to the dual factors of the obesity epidemic and the aging population [66]. Emodin may mitigate osteoarthritis by attenuating IL-1β-induced cytotoxicity, inhibiting MMP-3 and MMP-13 expression, and suppressing Wnt/β-catenin signalling [67]. Intra-articular injection of emodin in Sprague-Dawley rats has shown antiarthritic effects by blocking Wnt/β-catenin and NF-κB signaling, resulting in reduced cartilage breakdown, MMP,

and ADAMTS enzyme production. By activating the Nrf2/NQO1/HO-1 antioxidant system, emodin reduced oxidative stress and reactive oxygen species, inhibited inflammation, apoptosis, and extracellular matrix degradation, preserving cartilage and slowing the development of osteoarthritis [68].

2.12. Psoriasis therapy.

The phenomenon of T-cell-mediated hyperproliferation of keratinocytes manifests as a common autoimmune dermatological disorder known as psoriasis. The activation of the cellular immune system leads to psoriasis, an organ-specific autoimmune condition that has similarities to multiple sclerosis, rheumatoid arthritis, Crohn's disease, and juvenile-onset diabetes [69,70]. A notable susceptibility locus for psoriasis, designated psoriasis susceptibility 1, is located within a 220 kb segment of the major histocompatibility complex on chromosome 6p21 [71]. The incorporation of aloe emodin into a topical hydrogel applied to the psoriatic skin of mice has resulted in decreased epidermal thickness, scaling, and ear size, with a significant reduction in tissue necrosis factor. The test and commercial formulation exhibited no apparent difference regarding the percentage reduction in ear thickness. These findings suggested that aloe emodin-loaded hydrogel exhibited potential for plaque-like psoriasis therapy while maintaining a safety profile regarding skin toxicity [72].

2.13. Atopic dermatitis treatment.

Atopic dermatitis is a persistent inflammatory skin condition characterized by scaly, red, and itchy lesions, typically localized to flexural regions of the body. Atopic dermatitis is a medical condition that affects the epidermis, resulting in highly irritating skin lesions [73]. A variety of immunologic and inflammatory mechanisms are engaged in the intricate etiology of atopic dermatitis. The interaction of susceptibility genes, environmental factors, dysfunctional skin barrier mechanisms, and both systemic and localized immune responses resulted in clinical manifestations that define atopic dermatitis. Atopic dermatitis is characterized by a personal or familial history of asthma, allergic rhinitis, and conjunctivitis, as well as a tendency toward excessive production of immunoglobulin E antibodies, which affects the majority of patients [74]. The prior investigation demonstrated that oral administration of rhubarb in an animal model inhibited mast cell synthesis of leukotrienes mediated by 5-lipoxygenase. The inhibitory effect of rhubarb on atopic dermatitis can be attributed to the 5-lipoxygenase inhibitory effect of emodin [75]. Table 1 provides an exploration of the pharmacological applications of emodin investigated over recent decades. Table 2 summarizes the mechanism of action and molecular targets for various pharmacological activities.

Table 1. The exploration of the pharmacological applications of emodin has been examined over the past few decades.

Route (dose and duration)	Disease (animal model)	Outcomes	Ref.
Oral (1, 2, 3 g/kg/day for 2 days)	Laxative (Mice)	It augmented the functionality of cyclic adenosine monophosphate-dependent protein kinase. cAMP response element-binding protein in HT-29 cells led to phosphorylation by α-catalytic subunits.	[76]
Intraperitoneal (25 or 50 mg/kg for two weeks)	Anticancer (hepatocellular carcinoma) (Mice)	Showed concentration-dependent cell death and suppressed the growth of SMMC-7721 after 24-hour treatment. This induced phosphorylation of p38 and extracellular signal-regulated kinase while slightly restricting p-c-Jun-N-terminal kinase expression.	[77]
Intragastric (1.25 mg/kg for two months)	Alzheimer's disease (Mice)	Cognitive impairment was diminished by 60–70% after administration of emodin. The findings showed that high dosages of emodin had 50–70% less Aβ accumulation in the brains of animal models.	[78]

Route (dose and duration)	Disease (animal model)	Outcomes	Ref.
Intraperitoneal (20 mg/kg)	Asthma (Mice)	Levels of activated AAM Ym-1, Fizz-1, and arginase-1 in lung tissues were reduced significantly. Process of alternatively activated macrophage polarization and STAT-6 phosphorylation induced by IL-4 was suppressed dose-dependently.	[79]
Intragastric (12.5 mg/kg and 50 mg/kg, for 8 weeks)	Diabetes (Mice)	The research demonstrated a boost in insulin sensitivity in KKAy diabetic mice by stimulating the expression of IRS-1, PI3K, and Akt-ser473 while suppressing FoxO1.	[80]
Oral (3.3, 6.7, 11.3 g/kg/day for 7 days)	Antiviral (herpes simplex virus) (Mice)	The research revealed that emodin administration suppressed HSV-1 and HSV-2 multiplication in cell culture, raised the survival rate of mice infected with HSV, extended their survival period, and exhibited more efficiency in eradicating HSV from the brain, heart, liver, and ganglia than the viral controls.	[81]
Intragastric (25mg/kg, 50mg/kg, 100 mg/kg per day)	Immunosuppression (Mice)	The serum IL-2 production was diminished, the MST of skin grafts was extended, IL-4 secretion was increased, and IL-2 production was decreased.	[82]
Intraperitoneal (100 mg/kg/day emodin for 12 weeks)	Osteoporosis (Rats)	Emodin resulted in an increased quantity of mineralized nodules and heightened alkaline phosphatase activity, which suggests a promotion of MC3T3-E1 cell differentiation and mineralization. In contrast to low-dose oestrogen alone, its combination with emodin improved the trabecular bone microarchitecture in the lumbar vertebra and augmented the strength of the vertebral mass.	[83]
Intraperitoneal (50 mg/kg for 2 weeks	Hepatoprotection (Rats)	The administration of emodin decreased liver enzyme levels, suggesting possible therapeutic advantages for hepatic function. The concurrent administration of emodin and CCl4 resulted in a downregulation of TGFβ/Smad4 while simultaneously promoting the expression of anti-inflammatory markers IL-1β and IL-10.	[84]
Intra-articular cartilage (20, 50, 80 mg/kg for 2 weeks)	Osteoarthritis (Rats)	COL2A1 content was reversed, and tissue expression of MMP-13, MMP-3, ADAMTS-4, and iNOS declined substantially in chondrocytes and cartilage treated with varying dosages of emodin.	[85]

Table 2. An overview of the mechanism of action and molecular targets for various pharmacological activities.

Pharmacological activity	Mechanism of action and molecular targets	Ref.
Laxative activity	By stimulating the expression of aquaporin 3 in the colon through stimulation of cAMP/PKA/p-CREB signalling pathway, emodin showed improvement in water secretion and produced laxative effects.	[76]
Anticancer activity	Emodin showed restriction of cancer cells from growing, invading, and forming new blood vessels by causing apoptosis and stopping the cell cycle by downregulation of Bcl-2, upregulation of p53, production of ROS, mitochondrial cytochrome c release, caspase-3/8/9 activation, and NF-κB, MMP-2/9, and survivin suppression.	[30,32]
Alzheimer's disease	Emodin protected neurons from neurodegenerative diseases by mitochondrial dysfunction and minimised oxidative stress, restricting Aβ42 accumulation, stimulating the Bcl-2 pathway, blocking PI3K/AKT/mTOR to improve autophagic clearance, and influencing kinase activity.	[38]
Asthma	Emodin reduced airway inflammation, Th2 cytokines (IL-4, IL-5, IgE), and activated macrophages by suppressing IL-4-induced STAT6 phosphorylation and downregulating AAM markers (Ym-1, arginase-1, Fizz-1).	[79]
Diabetes	Emodin showed efficacy in diabetic nephropathy by preventing the p38 MAPK pathway from causing high-glucose-induced podocyte epithelial-mesenchymal transition by raising GLUTs expression, improving insulin sensitivity, boosting glucose tolerance, triggering PPARγ, and regulating IRS/PI3K/Akt/FoxO1 signaling.	[46-48]
Antiviral	Emodin reduced HSV-1 and HSV-2 replication, decreased HSV-1's UL12 alkaline nuclease activity, and inhibited host cell casein kinase 2 (CK2), necessary for phosphorylation of viral proteins, also extended the survival time and rate.	[51, 81]
Antiosteoporotic activity	Emodin showed accelerated osteoblast development and enhanced anti-osteoporotic action by stimulation of PI3K and rise of bone morphogenetic protein-2 gene expression. By triggering the bone morphogenetic protein receptor-Smad signaling pathway, which includes activation of p38 MAPK and Smad1/5/8, it increases the production of osteogenic markers and mineralization.	[65]
Antioxidant activity	Emodin showed improvement in cellular antioxidant defences and decreased oxidative stress by Nrf2/HO-1 pathway activation. It showed an increase in antioxidant enzymes, a reduction in reactive oxygen species, and lipid peroxidation levels. Emodin suppressed NF-κB signalling, which decreases oxidative damage by inflammation.	[57]

3. Nanotechnology-based Approaches for Emodin Delivery

Emodin is a bioactive anthraquinone with a broad range of pharmacological activities, but it has significant physicochemical limitations that can be effectively addressed with nanocarriers. Emodin's low systemic bioavailability, low permeability, rapid metabolism, and poor water solubility limit its therapeutic potential. Emodin's solubility and stability can be improved by encapsulation in nano-systems such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanoemulsions. Nanocarriers can improve emodin absorption, enable targeted drug release to specific tissues, reduce off-target side effects, and prolong plasma circulation time, thereby improving pharmacokinetics and therapeutic outcomes [86-88].

3.1. Liposomes.

Liposomal formulations serve as effective carriers for emodin administration, including high entrapment efficiency, controlled release, structural stability, and the capacity to integrate various lipid components [89]. Advancements in liposome technology have facilitated the advancement and approval of several liposomal medications in clinical trials, owing to improved biodistribution and enhanced therapeutic indices. Lipids, stabilizers, or surface modifiers may exhibit potential toxicity, and liposomes might provoke immunological responses or prompt fast clearance. Scalability is another issue with liposomes, as large-scale production requires consistent size, stability, and encapsulation efficiency. Physicochemical characterisation, long-term stability data, and rigorous safety assessments are required for regulatory clearance. Liposomes are still a cutting-edge therapeutic nanocarrier for enhancing medication delivery [90-92]. The combination of emodin and daunorubicin in liposomes enabled chemotherapeutic agents to target the tumor site selectively, hence displaying a pronounced antitumor effect, and offers a viable therapeutic approach for invasive breast cancer [93]. To inhibit tumor growth and migration, high-performance ferromagnetic iron oxide nano-cubes were simultaneously encapsulated in a hydrophilic bilayer and loaded with emodin using liposomes. *In vivo* studies on magnetic liposomal emodin's anti-tumor therapeutic effects indicated that tumors in the treatment group were significantly reduced, suggesting that magnetic liposomal emodin may serve as a promising magnetically guided nano-theranostic agent [94].

3.2. Microsphere.

Microspheres have the potential to provide prolonged release and enhanced drug stability by protecting the drug from enzymatic degradation prior to absorption. Nonetheless, constraints include possible toxicity from polymer remnants, difficulties in scaling uniform particle manufacturing, and rigorous regulatory requirements for uniformity, biocompatibility, and long-term safety [95]. A novel embolic agent, identified as drug-loaded microspheres, has effectively obstructed the arterial blood supply to tumors, leading to subsequent necrosis and ischemia within the tumor itself. It can sustain higher drug concentrations at the tumor site, deliver chemotherapeutic agents, and facilitate their gradual, continuous release within the tumor, ultimately leading to the destruction of tumor cells [96]. A nano-in-micro system was formed by incorporating emodin microcapsules in nanoparticles loaded with Tan IIA. Microcapsules with high encapsulation efficiency, uniform spherical morphology, and substantial drug loading were synthesized, leading to a substantial improvement in oral bioavailability [97].

3.3. Micelles.

Micelles enhance the transport of a highly hydrophobic drug through self-assembling block copolymers. Cytotoxicity, long-term safety, regulatory demands for stability, lack of reproducibility, and challenges in scalability and biocompatibility are major limitations of micelles [98,99]. Aloe emodin-loaded micelles were formed by the thin-film hydration method, which, in turn, improved bioavailability, anti-hyperuricemic effects, and the drug's solubility. It was observed in the pharmacokinetic study of aloe-emodin micelles that relative oral bioavailability was increased by 3.09-fold as compared to free aloe-emodin, which demonstrated that mixed micelles help in gastrointestinal absorption. It suppressed xanthine oxidase and, hence, reduced the levels of uric acid in a rat model [100]. For anticancer action, ultrasonication-dialysis was employed to form emodin-loaded stearic acid-g-chitosan oligosaccharide nanomicelles. It was observed that these nanomicelles significantly enhanced anticancer activity against BGC823 and MGC803 cells compared with free emodin [101].

3.4. Carbon nanotubes.

Carbon nanotubes are formed with nanometer-sized diameters and axial symmetry. These tubular structures have unique characteristics offering targeted delivery of medicines directly to specific cells and tissues intended for treatment [102]. Functionalized carbon nanotube systems hold significant promise in nanobiotechnology and nanomedicine due to their non-immunogenic properties and low toxicity [103]. Carbon nanotubes have potential roles as drug delivery carriers, including the ability to reduce adverse effects, provide targeted drug transport to specific cells/organs, enhance specificity, and achieve high efficacy. Carbon nanotubes have wide applications in drug delivery, cancer treatment, biological signal sensing, and imaging [104]. The research study examined the electrochemical properties of emodin using multi-wall carbon nanotube-modified glassy carbon electrodes, which indicated that multi-walled carbon nanotubes exhibited significant electrocatalytic activity toward emodin and therefore offer a novel methodology for its detection [105].

3.5. Nanoemulsion.

Nanoemulsions are heterogeneous colloidal systems comprised of two immiscible liquids. The methodologies for nanoemulsion manufacturing include spontaneous emulsion, emulsion phase inversion, high-energy approaches, and rotor-stator emulsification. Nanoemulsions offer certain advantages, such as precise, controlled, and targeted drug administration, and they resist creaming or sedimentation due to their small droplet sizes [106-108]. An emodin-loaded nanoemulsion was prepared using ultrasonic emulsification, aiming to investigate the effects of various ultrasonic operating configurations and primary formulation variables on the nanoemulsion's characteristics. The enhancement of emodin nano-emulsion zeta potential can be achieved with relative ease by incorporating oleic acid and adjusting pH. An *in vitro* study revealed that emodin nanoemulsion exhibited release of 80.79±1.11% emodin within 120 hours [109].

3.6. Magnetic nanoparticles.

Recent advancements in technology have been significantly enhanced by the application of magnetic materials derived from metals such as iron, cobalt, and nickel, as well as various metal oxides, across a diverse range of contexts [110]. For more than three decades,

magnetic nanoparticles have been the subject of rigorous investigation as a promising platform for targeted drug delivery, owing to their unique physical properties and ability to operate at molecular and cellular sites of biological interactions [111]. Due to their diminutive dimensions, significant specific surface area, magnetic responsiveness, and super-paramagnetism, magnetic nanoparticles represent a sophisticated category of nanomagnetic materials. Magnetic nanoparticles can be assembled and subsequently subjected to an alternating magnetic field, wherein they absorb heat from the electromagnetic wave. The superparamagnetic state is exhibited by magnetic nanoparticles. Iron oxide nanoparticles, including magnetite and maghemite, represent the most extensively employed category of nanomaterials [112]. Superparamagnetic nanoparticles exhibit nontoxic properties and possess surface coatings that are specifically functionalized for the targeting of ligands or proteins. These applications encompass delivery of pharmaceuticals, transfection processes, magnetic resonance imaging, and the separation of cellular components, proteins, and DNA. Consequently, to enhance their thermal stability and prolong release, it is essential for drugs to be conjugated with magnetic nanoparticles [113]. Despite their remarkable attributes, including diminutive dimensions, high magnetic saturation, and lack of coercivity, iron oxide nanoparticles are currently attracting considerable scholarly attention [114]. The creation of emodin-loaded Cy7-functionalized PEG-coated Fe3O4 nanoparticles for the dual purposes of diagnosis and therapy in pancreatic cancer, utilizing ultrasonication alongside the organic solvent evaporation method. An *in vivo* study in pancreatic tumor xenografted mice revealed that iron oxide nanoparticles enabled targeted therapy and dual-modal FI/MRI imaging [115].

3.7. Silica nanoparticles.

The use of the water-in-oil microemulsion technique facilitates the formation of homogeneous core/shell nanoparticles, characterized by a silica layer enveloping a core composed of either color or magnetite. The dimensions of the highly luminous and photostable nanoparticles span from 5 nm to 400 nm. Upon bioconjugation with diverse molecules, particularly deoxyribonucleic acid, antibodies, and enzymes, these silica nanoparticles exhibit unique biofunctional properties [116,117]. The use of mesoporous silica nanoparticles in biomedicine and drug delivery has attracted significant interest, owing to their substantial pore volume and extensive surface area [118]. Mesoporous silica nanoparticles serve as biodegradable carriers for medications, effectively reducing side effects while enhancing therapeutic efficacy. Mesoporous silica nanoparticles meet the criteria for nanoparticulate carriers due to their exceptional structure, which enables substantial loading capacity and a diverse array of surface modifications [119]. Within the realm of biomedicine, mesoporous silica, amorphous silica, microporous crystalline titano-silicates, and zeolites have been used extensively. Mesoporous silica nanoparticles can interact with a diverse array of functional groups, facilitating targeted delivery to the site of action [120].

3.8. PLGA nanoparticles.

PLGA is a biodegradable and biocompatible polymer, and PLGA-based nanoparticles have been investigated for emodin to impart stability and sustained release. These nanoparticles may enhance cellular uptake and prolong circulation, thereby increasing bioavailability [121]. Residual solvents, surfactants, or acidic breakdown products of PLGA may cause toxicity, inducing local inflammation. Their scalability is also a hurdle, as laboratory-scale

nanoprecipitation or emulsification techniques often struggle to achieve uniform particle size, drug loading, and batch-to-batch repeatability in industrial production. Obtaining regulatory compliance for PLGA nanoparticles requires comprehensive characterisation, rigorous safety evaluations, and standardized manufacturing procedures, which may extend development times and increase costs [122].

3.9. Solid lipid nanoparticles.

A solid lipid core that enables controlled release and protection against degradation makes solid lipid nanoparticles a viable delivery vehicle for emodin, thereby improving its solubility, stability, and bioavailability. Higher drug loading, the use of physiologically acceptable lipids, and reduced manufacturing costs are advantages of SLNs over PLGA nanoparticles. Nonetheless, constraints include potential toxicity from surfactants, the likelihood that polymorphic transitions will affect stability, and difficulties in achieving uniform large-scale production. Regulatory obstacles persist, as SLN formulations require comprehensive assessments of lipid purity, long-term stability, and repeatability. SLNs provide a straightforward and cost-effective alternative to polymeric and other types of nanoparticles [123,124]. Table 3 presents a detailed overview of research outcomes on the nanotechnological aspects of emodin that have been explored in previous years.

Table 3. Illustration of the research outcomes related to the nanotechnological aspects of emodin investigated in previous years.

Technique	Excipients	Research Outcome	Ref.
Solid lipid nanoparticles (SLNs) [High-pressure homogenization]	Glycerol monostearate, stearic acid, Tween 80, Poloxamer 188	Emodin-loaded solid lipid nanoparticles demonstrated a sustained release (~80% in 24 hours, continuing up to 72 hours), a good encapsulation efficiency, and a particle size of around 28.6 nm. In MCF-7 and MDA-MB-231 cells, SLNs produced greater cell cycle arrest and apoptosis rates than bulk emodin. This increased anticancer effectiveness was achieved by cellular absorption and extended drug release.	[125]
Solid lipid nanoparticles loaded with aloe emodin [High-pressure homogenization technique]	Tween 20, Glycerol monostearate, Poloxamer 188, glyceryl tri-stearate, glyceryl tri-myristate, and Ethylenediamine tetraacetic acid, Poloxamer 407	Solid lipid nanoparticles loaded with aloe-emodin showed a sustained drug release of 48 hours, a particle size of about 89 nm, and encapsulation effectiveness of around 97.7%. It was shown that free aloe emodin only marginally caused cell apoptosis because up to 70% of aloe emodin-SLNs had apoptotic cells. In contrast to aloe emodin solution, aloe emodin-SLNs exhibited greater in-vitro cytotoxicity against human hepatoma HepG2 cells as well as human breast cancer MCF-7 cells and increased anticancer activity.	[126]
Protein nanoparticles functionalized with folic acid [Gamma irradiation]	Bovine serum albumin, Tween 80%	The nanoparticles were of particle size (70 nm), and controlled cumulative release was shown by the bioconjugate of bovine serum albumin nanoparticles with emodin. By lowering metabolic rates by 30% as compared to 15% with folic acid-modified BSA nanoparticles alone, it dramatically increased anticancer activity on MCF-7 and PC-3 cell lines, exhibiting better transport and effectiveness with less damage.	[127]
Phenyl-boronic acid functionalized nanoparticles [Solvent displacement technique]	3-(acrylamido) methyl phenyl boronic acid homopolymer	The release of emodin was significantly enhanced at pH 5 and reached 90% after 7 hours, suggesting that the drug release profile from nanoparticles is pH-dependent. It exhibited a significantly higher degree of cytotoxicity towards HepG2 cancer cells in comparison to MC-3T3-E1 cells or normal cells.	[128]
Polymeric nanoparticles encapsulated with polybutylcyanoacrylate [Anionic emulsion polymerization]	PEGMA, DMAEMA	Emodin encapsulated in nanoparticles (particle size ~100-200 nm) exhibited great entrapment efficiency and sustained cumulative release, enhanced bioavailability. Treatment with nano-emodin in rats at a 1 mg/ml dosage alleviated diabetic neuropathic pain in dorsal root ganglia primary sensory neurons that is mediated by P2X3 receptor. Transfection of HEK293 cells with the P2X3 receptor resulted in a significant reduction of currents generated by P2X3 agonist α, β-meATP upon administration with	[129]

Technique	Excipients	Research Outcome	Ref.
		nanoemodin, showing enhanced effects in diabetic neuropathic pain.	
Polymeric Lipid Hybrid Nanoparticles [Nano-precipitation]	Polylactic acid-glycolic acid copolymer, Poloxamer 188, soybean lecithin, di-lauroyl lecithin, PEG	Tumor proliferation was greatly suppressed by nanoparticles by more than 60%, which may be attributable to the passive targeting of nanoparticles at the tumor site. Emodin-PLNs exhibited delayed release characteristics with a cumulative release of over 90% after 36 hours. The nanoparticles exhibited heightened toxicity towards MCF-7 cells and were capable of inducing early apoptosis in these cells, thereby demonstrating improved anticancer efficacy.	[130]
Shuttle shape polymeric nanoparticles [Rotary vacuum evaporation]	Cyclodextrin, gelatin A	In comparison to emodin solution, the nanoparticles had a greater impact on biofilm inhibition and showed eradication of *S. suis* biofilm during an *in vitro* study, which showed antibacterial activity.	[131]
Polymeric nanoparticles [Ultrasonic emulsification solvent evaporation method]	D-α-tocopherol polyethylene glycol-1000 succinate, PLGA	With an encapsulation effectiveness of >70% and a particle size of around 150-180 nm, emodin was gradually released into mice's liver over 24 hours, reaching maximum quantities EGPTN displayed stronger effects on HepG2 cell growth in vitro and in vivo in PLC mice as compared to free EMO demonstrating EGPTN had a more effective active targeting mechanism and a stronger inhibitory effect on liver cancer cells.	[132]
Polymeric aptamer-functionalized PEG-PLGA nanoparticles [Emulsion solvent evaporation technique]	PLGA, PEG	Approximately 38.7±2.3% and 36.3±3.1% drug was released from emodin nanoparticles and aptamer emodin nanoparticles. In a sustained-release and dosage-dependent way, aptamer-emodin nanoparticles showed a reduction in lipid stacking in 3T3-L1 adipocytes. In comparison to EMO-NP functionalized with a nonspecific aptamer, Ap-EMO-NP showed significantly differentiated 3T3-L1 cells, which increased the internalization of efficiently treating obesity.	[133]
Polymeric microgel films (borate nanoparticles [Simple solvent exchange method]	Sodium carboxymethyl cellulose, sodium borohydride	The polymeric microgel film loaded with emodin borate nanoparticles showed good loading capacity, encapsulation efficiency, average hydrodynamic diameter of 38.9± 2.3 nm and zeta potential of 8.9± 3.0 mV. Emodin borate was released quickly in 1 hour, and the remaining emodin was released gradually.	[134]
Monoolein-based lyotropic liquid crystalline nanoparticles [Emulsification method and Film hydration method]	Glyceryl monooleate, Poloxamer-407	Exhibited controlled release of aloe emodin of 80.5%±2.2% and 85.4%±3.6%, respectively, in 48 hours. It demonstrated a particle size of 190 nm. In comparison to free AE, AE-PEG-LCNPs showed a 5.4-fold increase in half-life. Formulation displayed greater cytotoxic effects and cellular uptake in MCF-7 cells, in addition to enhanced serum stability and hemocompatibility in comparison to the free drug.	[135]
Mesoscale nanoparticles [Nanoprecipitation method]	PLGA, PEG, poloxamer 188	Emodin showed a high release profile from emodin mesoscale nanoparticles with increasing time. When compared to free mesoscale nanoparticles, Emodin-mesoscale nanoparticles treatment might considerably decrease extracellular matrix deposition and kidney tubule damage.	[136]
[Polymeric nanoparticle] Emulsion-solvent evaporation technique	PLGA, Eudragit S100	Emodin nanoparticles showed drug loading and entrapment efficiency of 6.1% and 84.3%, respectively. About 75% of the medicine had been released cumulatively after 48 hours. Emodin nanoparticle successfully increased the anti-colitis benefits of emodin in the context of improvement of the intestinal barrier.	[137]
Polymeric nanoparticle [Modified solvent-emulsion-diffusion-evaporation method]	PLGA, Tween 20	These nanoparticles showed a mean diameter of 267.66±17.78 nm. The total drug depletion from diosgenin and emodin nanoparticles was 40% and 70%, respectively. The study, executed both in vitro and *in vivo*, showed that polymeric nanoparticles had prospective therapeutic benefits against liver cancer.	[138]
Emodin liposomes conjugated with D-α-tocopherol polyethylene glycol-1000 succinate (TPGS) [Thin-film hydration technique and polycarbonate	Cholesterol, hydrogenated soy phosphatidylcholine, egg phosphatidylcholine	With an encapsulation efficiency of 95.2% and a particle size of 121 nm, TPGS liposomal emodin demonstrated sustained release of approximately 22% in 24 hours. TPGS liposomes showed higher cytotoxicity of emodin on leukemia cells in comparison to mPEG2000–DSPE liposomes. Compared to mPEG2000-DSPE liposomes, TPGS liposomes had a larger bioavailability for emodin in the kidney and lung. The liposomes released approximately 22% of emodin within 24 hours.	[139]

Technique	Excipients	Research Outcome	Ref.
membrane extrusion technique]			
Emodin encapsulated in liposomes [Rotary vacuum evaporation]	Phospholipids dipalmitoyl phosphatidyl glycerol, polyethyleneimine	A comparison of the emodin release profile from films with and without liposomes revealed that liposome-based films were capable of showing drug release for a prolonged period.	[140]
Silk-fibroin-coated liposomes [Lyophilization technique]	Silk fibroin, sericin	Applying silk fibroin-coated emodin-loaded liposomes to tumor-like cells from keloids increased the drug's efficacy and specificity. SF coating reduced the release rate of emodin and improved adhesion to keloid fibroblasts. This slow drug release may be attributable to steric hindrance and to hindrance caused by the silk fibroin coating.	[141]
Polylactic Acid Microspheres [Solvent diffusion method]	Polylactic acid, gelatine	Intravenous administration of microspheres demonstrated predominant distribution of emodin to the lungs, which showed the potential of emodin nanoparticles in the treatment of lung diseases. The release of emodin from microspheres was 23.46% during the initial 12 hours, 48.19% after 5 days, and 67.06% after 8 days.	[142]
Aloe emodin-loaded micelles [Thin-film hydration method]	Soluplus, glycyrrhizic acid	Micelles showed particle size and encapsulation efficiency of 30.13±1.34 nm and 90.3±1.08%, respectively. An *in vitro* study showed that micelles exhibited cumulative release of 60% while plain aloe emodin showed 40% emodin over 10 hours. A pharmacokinetic study showed that mixed micelles of aloe emodin showed a relative oral bioavailability of 3.09 times compared to plain aloe emodin. It showed enhanced anti-hyperuricemia and anti-inflammatory activity in rats by inhibiting xanthine oxidase activity, lowering uric acid levels, and inflammation markers IL-1 and IL-6.	[143]
Multi-wall carbon nanotubes [Surface imprinting technique]	Ethylene glycol dimethacrylate	High encapsulation efficiency and selective recognition were shown by multiwalled carbon nanotubes for emodin extraction. These had a particle size that allowed for quick adsorption equilibrium in less than 60 minutes. This method improved extraction efficiency by offering high recovery rates of 89.2–93.8% and great site accessibility.	[144]
Silica nanoparticle [Standard sol-gel procedure]	Pluronic P123, silica SBA-15	*In vitro* studies on mouse melanoma B16 and B16F10 cells and human melanoma A375 cells revealed a dose-dependent decrease in cell viability. Tumor cell growth was hindered, and apoptosis was induced by emodin nanoparticles, which may be linked to the activation of caspase, overexpression of Bax, suppression of Bcl-2 and Bim, and amplification of the poly-(ADP-ribose)-polymerase cleavage fragment.	[145]
Magnesium Silicate Hollow Nanocarriers [Stober method]	Silica	Magnesium silicate hollow nanocarriers loaded with emodin demonstrated prolonged cumulative drug release and a high encapsulation efficiency. These nanocarriers showed significant inhibition of VEGF, which revealed their efficacy in antiangiogenic treatment.	[146]
Nano-emulsion [Traditional aqueous titration method]	Polyethylene glycol 400, Tween 80, PEG 600, Gelucire 44/14, Solutol HS15, Tween 20	Zeta potential of emodin-loaded nanoemulsions was −25.2 ± 0.5 mV, and the mean diameter was in the range of 10–30 nm. Emodin-loaded nanoemulsions showed drug release of 80.79±1.11% within 120 hours and exhibited drug release by Fickian diffusion mechanism.	[147]
Nano-emulsion [Modified emulsification technique]	Cremophor EL, glucuronic acid	Exhibited improved apparent permeability by 2.3 times with 5.3×10^{-6} cm/s for nano-emulsion and 1.2×10^{-5} cm/s for solution, exhibited lesser glucuronidation because of the inhibition of cellular metabolism by Cremophor EL, proved to be a potentially effective method for enhancing transcellular permeation and raising the oral bioavailability.	[148]
Cy-7-functionalized Polymeric iron oxide nanoparticles [Ultrasonication]	N-(3-dimethylaminopropyl)- N-ethyl-carbodiimide hydrochloride; N-hydroxy succinimide	The hydrodynamic diameter of Fe3O4-PEG and Fe3O4-PEG-Cy7-emodin were 9.1+1.7 nm and 9.9+1.2 nm, respectively, demonstrating a disposition to cluster on the tumor site.	[149]

4. Current Challenges

The therapeutic utility of emodin is substantially hindered by several translational obstacles. Poor absorption, significant glucuronidation, and rapid metabolism are certain drawbacks resulting from low oral bioavailability [150]. The toxicity concerns also complicate its medical use as emodin is reported to cause toxicity through hepatotoxicity, nephrotoxicity, cytotoxicity, reproductive, and genetic effects when employed at a high dose [151]. The transition from preclinical to clinical utility is also affected by inadequate clinical studies and pharmacokinetic and safety issues. Although solubility and bioavailability have been improved by nanoformulations such as solid lipid nanoparticles and other targeted delivery vehicles, much of the available information is based on in *vitro* or preliminary preclinical studies. In turn, the major obstacles to the successful implementation of emodin in clinical practice are overcoming its low bioavailability, reducing its toxicity profile, and conducting comprehensive clinical studies [152,153].

Regarding nanoemodin formulations, regulatory viewpoints emphasize thorough quality, safety, and efficacy assessments tailored to their distinct nanoscale characteristics. FDA and EMA authorities have guidelines that require an exhaustive assessment of physicochemical properties, stability, biodistribution, and toxicology. Pharmacovigilance and ecotoxicological assessment are also part of safety evaluation. Existing pharmacological frameworks apply despite the lack of specialized rules for nanomedicine, requiring thorough clinical data and case-by-case evaluation to ensure regulatory approval and translational success [154].

5. Conclusion and Future Perspectives

The mechanistic and clinical research strategies for emodin nanoformulations seek to elucidate and manage the intricate, multi-targeted mechanisms of emodin, to better understand and control its complex, multi-targeted mechanisms, and to enhance its bioavailability and targeted distribution to maximize its therapeutic value while reducing its intrinsic toxicity. The nanoformulations of emodin may enable precise characterization of molecular targets, enabling targeted distribution that helps researchers recognize and verify specific molecular targets across many disorders. Nanoformulations have the potential to enhance the pharmacokinetics and bioavailability of emodin, thereby addressing issues such as its poor water solubility, lower bioavailability upon oral administration, and increased metabolism. SLNs and polymeric lipid hybrid nanoparticles are promising nanocarriers for enhancing absorption, stability, and therapeutic efficacy.

The forthcoming advances in emodin nanoformulations aim to enhance aqueous solubility, overcome permeability issues, improve metabolic stability, and enable tissue-specific drug targeting. Upcoming investigations focus on the development of ‘smart nanoparticles’ for active targeting to cancer cells by surface coating with specialized ligands or biomimetics. These smart nanocarriers enhance drug accumulation in tumor tissues and reduce systemic toxicity in non-target tissues. The use of emodin nanoformulations in combination with conventional chemotherapeutic agents, such as doxorubicin or cisplatin, demonstrates synergistic effects and can overcome multidrug resistance in cancer cells. The innovative carriers, such as magnetic nanoparticles, injectable hydrogels, and polymer-lipid hybrid systems, are expected to facilitate controlled drug release accompanied by improved drug infiltration into solid tumors. Future research aims to study emodin nanoformulations for

other diseases, such as acute pancreatitis, neurodegenerative disorders, and inflammatory disorders. The future perspective for neuroprotective-based nanoformulation aims to develop synergistic therapies to explore the delivery of emodin with other neurotherapeutic agents and to understand specific molecular signalling pathways underlying neurological disorders, thereby enabling the design of effective, tailored therapy. The key objective is to convert preclinical insights into human clinical trials for clinical translation. The rapidly developing field of artificial intelligence in nanoparticle design and drug delivery system improvement has the potential to yield more customized, effective therapies.

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Conflict of Interest

The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
IL	Interleukin
TNF-α	Tumour Necrosis Factor-alpha
MMP	Matrix Metalloproteinase
VEGF	Vascular Endothelial Growth Factor
AMPK	AMP-activated Protein Kinase
MAPK	Mitogen-activated Protein Kinase
PLGA	Poly(lactic-co-glycolic acid)

Abbreviation	Definition
PEG	Polyethylene Glycol
PPARγ	Peroxisome Proliferator-Activated Receptor Gamma
IFN-γ	Interferon Gamma
BALF	Bronchoalveolar Lavage Fluid
BMP	Bone Morphogenetic Protein
ERK	Extracellular Signal-Regulated Kinase
PEGMA	Poly(ethylene glycol monomethacrulate)
DMAEMA	N, N-dimethylaminoethylmethacrylate

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