A Comprehensive study of Vidanga: Phytochemical and Pharmacological Activitiesand Novel formulation an overview

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Abstract-
Embeliaribes is a woody shrub distributed throughout India belongs to Myrsinaceae family. It is commonly known as false black pepper and Vidanga as per Ayurvedic system of medicine.It is of great demand in Ayurveda and pharmaceutical industries. It has been used traditionally since many centuries as medicinal remedy for several diseases.Embelia species was first identified by Sushruta, Father of surgery and was mainly known for anthelmintic property. Later, Dr. Harris found it effective in tapeworm infection through an ancient Arabic writing named birang-I-kabuli. It is known for its digestive, carminative, laxative and anthelminticproperties since time immemorial. Due to over exploitation of this plant for therapeutic and research purpose, it has been reported in red data book as vulnerable. Several naturally occurring bioactive molecules present in Embeliaribesare used for their diverse range of pharmacological activities such as anti-inflammatory, antiviral, antimicrobial. antioxidant, antidiabetic, anticancer, wound healing, cardioprotective, neuroprotective and hepatoprotective activities. Embelin is a hydroxyl benzoquinone with alkyl substitution in its structure and is considered one of its main phytoconstituent. This review provides a comprehensive overview of several phytoconstituents present in Embeliaribesand various pharmacological activities exhibited by embelin that will help in exploring the unexplored areas of pharmacology attributable to this plant. This review highlights the areas of research where this endangered plant species has been extensively studied and also focuses on the current status of this medicinal plant.

Keywords-Embelin; Antidiabetic; Anticancer; Wound healing; Antiviral; Antioxidant.

I. INTRODUCTION

Embeliaribes, also known as Vidanga in Ayurveda belongs to Myrsinaceae family. E. ribes is also known as false black pepper, baobarang and white flowered Embelia. It is a woody shrub mainly found in South China, India, Cambodia, Malaysia, Thailand, Sri Lanka etc. In India, E. ribes is found in hilly areas mainly from outer Himalayas to Western Ghats, other than this it is mainly found in Arunachal Pradesh, Assam, Orissa, Madhya Pradesh and Andhra Pradesh[1,2]. It has been narrated in ancient literature of Charaka, Sushruta and Vagbhatta and is mainly recommended as krimighna. It has been used in traditional medicine since past several years because of several effects including analgesic, antibacterial, antidiabetic, anticancer and wound healing property. Various herbal or ayurveda based formulations include Guduchilauha, Ardakakhandavaleha, Erandapaka, Vidangadichurna, Vidangataila and many more. This plant is considered to be vulnerable as it has been extensively exploited for therapeutic and research purpose. Several phytochemicals are found in E. ribes including embelin, emebeliaflavosides, vilangin and embelialkylresorcinols, quercitol, an alkaloid, christembine, a resinoid and volatile oils, among all these phytocompounds, embelin has the greatest therapeutic potential[3,4].Natural regeneration of E. ribes is difficult due to overexploitation that results in

development of abortive embryos and slow germination leading to small size[5]. Artificial regeneration also seems difficult because of various factors such as poor seed viability and low germination rate. It is one of the 32 medicinal plant species identified by Medicinal Board, Government of India identified for large scale production because of its commercial value but traditional methods of propagation are not suitable for its large scale production. The active constituent of Embeliaribes, embelin was first isolated more than a decade ago[6, 7]. Figure 1 illustrates the Embeliaribes twig with fruits.

Taxonomical classification

Kingdom: Plantae;

Phylum: Angiosperm;

Order: Ericales;

Family: Myrsinaceae;

Figure 1: Embeliaribes twig with fruits

Genus: Embelia;

Species: ribes.

Embelin is mainly isolated from the fruit and leaves of E. ribes. Embelin is 2, 5 dihydroxy-3-undecyl-1,4 benzoquinone according to IUPAC nomenclature, a benzoquinone derivate with alkyl substitution. Embelin is phenolic lipid in nature which is a secondary metabolite found in fungi, bacteria and animals apart from plants and is formed in both normal and stress conditions[8-10].It possesses various pharmacological activities including anticancer, antiviral, antimicrobial, antioxidant, neuroprotective, cardioprotective and hepatoprotective action. This review provides comprehensive information about various pharmacological properties elicited by embelin along with several nanotechnology-based formulations.

II. PHYTOCHEMICAL CONSTITUENTS OF EMBELIA RIBES

Embeliaribes contains a range of phytoconstituents such as embeliol, embelinol, quercitol, vilangin and many more. The most important phytoconstituents present in Embeliaribes are illustrated in Figure 2.

Fig 2: Phytochemical constituents of Embeliaribes

III. PHARMACOLOGICAL ACTIVITIES OF EMBELIN

Embelin exhibits a wide range of pharmacological activities such as antiviral, antimalarial, cardioprotective, antidiabetic and many more. Various pharmacological activities elicited by embelin are illustrated in Figure 3.

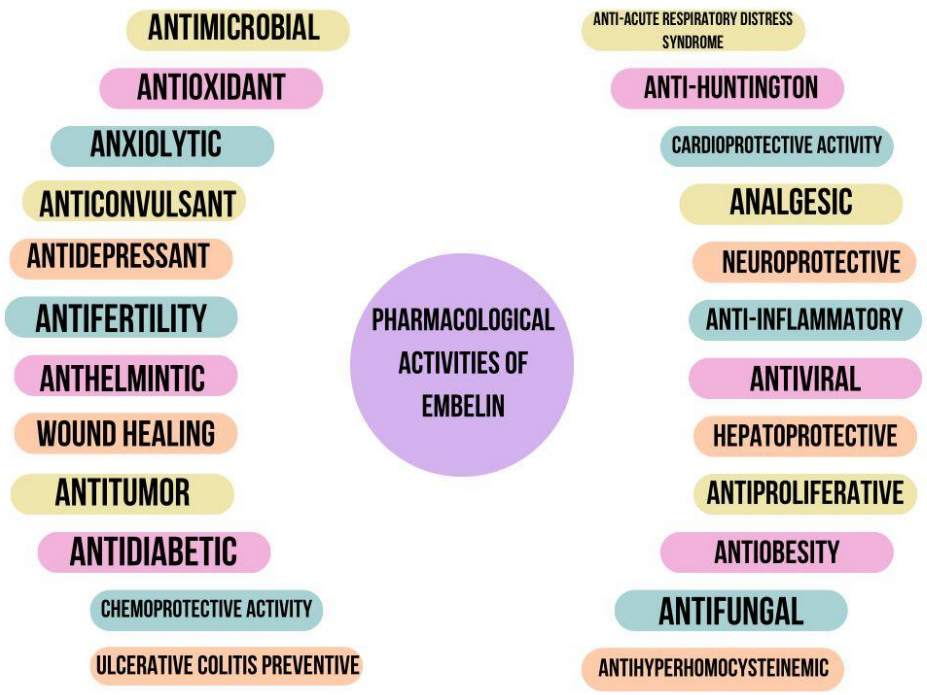

Fig 3: Pharmacological activities of embelin

A. Wound healing property

A study done by Swami*et al*in 2007 showed that ethanolic extract of embelin extract from leaves showed significant wound healing activity on Swiss albino rats. The wound healing activity was compared with Framycetin skin ointment, embelin extract showed comparatively better results [11]. Embelin loaded hydrogels showed faster healing process as compared to marketed formulations [12]. Another study demonstrated the wound healing property of embelin by impairing the angiogenic activity of proliferating endothelial cells by depleting the energy reserves [13].

B. Antidiabetic effect

A study conducted by Mahendran *et al* in 2011 in demonstrated the antidiabetic effect of embelin in rats. Embelin showed antihyperglycemic activity in alloxan induced diabetes in rats. It caused significant reduction in fasting serum glucose level and also showed significant improvement in body weight [14]. Another study suggested that embelin had significant effect in lowering plasma glucose level in streptozotocin (STZ) diabetic rats. This study suggested that embelin has diabetes modulating activity and can be effective in the treatment of Type-2 diabetes mellitus but needs further evaluation on human subjects [15]. One more study revealed that embelin reduces plasma insulin levels in diabetic rats via translocation and activation of GLUT4[16]. Another work on embelin by Bhandari *et al*in 2013 demonstrated the antidiabetic activity of embelin. This study concluded that embelin reduces sugar levels in High fat diet (HFD) and low dose streptozotocin induced type 2 diabetes in male wistarrats [17].Another study demonstrated the antidiabetic activity of embelin in glucose induced hyperglycemic albino rabbits. The results of this experiment were comparable to gliclazide [18].

Embelin attenuates the real injury in type 2 diabetes via improvement in glucose and lipid metabolism and hence shows significant antidiabetic effect [19]. In another study, embelin was able to decrease heart rate, systolic blood pressure, LDH and CKlevels in the blood serum when evaluated for antidiabetic action in STZ induced diabetic rats [20]. A study suggested the antidiabetic activity of embelin as it was able to reduce blood glucose level; glycated hemoglobin in STZ induced diabetes in rats [21]. Another study demonstrates the antidiabetic effect of embelin mainly via its direct action on tissue or by increase in insulin secretion [22,23].

C. Anti-depressant action

A study performed by Wang *et al* suggested that embelin can effectively suppress depressive behavior that occurs due to chronic unpredictable stress (CUS) by increasing the concentration of brain-derived neurotrophic factor (BDNF) and also preventing oxidative stress [24]. Another study demonstrated the potential antidepressant action of embelin upon intraperitoneal administration on mice using two experimental models- Forced Swimming Test (FST) and Mice Tail Suspension Test (MST)[25,26].

D. Antifertility activity

A study suggested that embelin has significant antiandrogenic activity when tested in male rats. It significantly altered the histology of testicles and gametogenic counts upon subcutaneous administration in male rats for 45 days at the dose of 0.3, 0.4 and 0.5 mg/kg body weight of male rats [27]. Another study demonstrated the contraceptive nature of embelin by showing remarkable anti-implantation activity at 50 and 100 mg/kg doses [28]. Subcutaneous administration of embelin in male rats for 20 days at a dose of 20 mg/kg revealed the inhibition of epididymal motile sperm count and other fertility parameters. Light and scanning electron electroscopic images revealed about the morphological changes in spermatozoa [29]. Another study conducted to evaluate the antifertility activity of embelin suggested that embelin disrupts the production of testosterone hormone at testicular level when injected through intramuscular route in sexually mature white New Zealand rabbits at a dose of 30 mg/kg of body weight on alternate days for 14 days [30]. A study conducted by Wango *et al* 2005 revealed that embelin interferes with female reproductive system by suppressing the production of sex steroid hormones from ovary [31].

E. Anxiolytic activity

A study done by Afzal *et al*2012 demonstrated anxiolytic activity of embelin isolated from Embeliaribes. It was significantly able to increase percentage of time spent and number of entries in open arm in elevated plusmaze apparatus [32]. In another study, embelin was evaluated for its anxiolytic activity using standard tests such as elevated zero maze test and novelty induced suppressed feeding latency test in a dose dependent manner and it showed anxiolytic activity at 20 mg/kg, its activity was comparable to diazepam in terms of reduction of anxiety [33].One more study suggested the anxiolytic activity of embelin via increase in GABA concentration in the brain [34].

F. *Anticonvulsant activity*

A study conducted on extract of embelin showed potential anticonvulsant activity against grand mal and petit mal epilepsy. Its activity was comparable to phenytoin and

diazepam[35].Embelinshows anticonvulsant action by decreasing dopaminergic level and increasing GABAergic transmission in the brain [36].

G. Antimicrobial activity

A study conducted by Chitra*et al*2003 demonstrated the antibacterial activity of embelin at 100 µg concentration. It was able to exhibit a potential inhibitory effect against five strains and moderate activity another five strains of bacteria [37].Other study suggested the potential antimicrobial effect of embelin against 21 bacteria and 4 fungal pathogens when tested using the disc diffusion method [38]. In another study, the antimicrobial activity of embelin was evaluated against several pathogens using the disc diffusion method. Embelin showed significant action against *Bacillus subtilis* and *Streptococcus mitis*[39]. A study done by Radhakrishnan *et al* demonstrated that embelin shows bactericidal activity against gram-positive bacteria and bacteriostatic activity against gram-negative bacteria [40]. A study conducted to determine the antimicrobial efficacy of embelin showed that it is able to inhibit bacterial growth at all concentrations while the maximum activity was seen at 2000 µg concentration [41].

H. Anti-inflammatory activity

An experimental study conducted by Bansal *et al* in 2020 demonstrated that embelin can significantly prevent inflammatory changes in high fat diet feed mice[42]. In another study, embelin was measured for the anti-inflammatory activity using carrageenin-induced hind paw edema method in mice. Embelin was successfully able to reduce the inflammation caused due to carrageenin as compared to the control group [43]. Embelin suppresses the biosynthesis of eicosanoids by selectively inhibiting 5-lipooxygenase [44].

I. Antioxidant activity

Various types of studies have been conducted over several years to evaluate the antioxidant activity of embelin, a study conducted in which embelin was tested in THP-1 human leukemic monocytes and BV-2 mice microglia. It showed a good antioxidant effect when measured using a fluorescent probe. It suggests that embelin can be an interesting tool to decrease the damage associated with neurodegenerative disorders [45]. Another study also indicates a good antioxidant effect of embelin [46]. In one more study, it was found that embelin shows structural resemblance to ubiquinone which exhibits mitochondrial uncoupling and antioxidant effect [47]. A study conducted by Sreeharsha*et al*2020, it was found that embelin can significantly reduce the concentration of oxidative stress marker, malondialdehyde [48]. X-ray crystal structural determination shows strong $\pi - \pi$ interactions and was found to scavenge superoxide radical [49]. A study conducted by Joshi *et al*2007demonstrated the antioxidant mechanism of embelin via scavenging DDPH radical and inhibit hydroxyl radical induced deoxyribose degradation [50].

J. Analgesic activity

A study conducted by Mahendran *et al* in 2011 suggested the potent analgesic activity of embelin. Its analgesic potential was found to be more than standard pentazocine [51]. In another study, analgesic activity of embelin was evaluated in mice by using acetic acid-induced writhing method. The dose of 50 and 100 mg/kg of embelin was able to prevent writhings in acetic acid-induced mice [52].

K. Antihuntington activity

A study conducted by Dhadde*et al*2016suggested the neuroprotective action of embelin. In this study, the neuroprotective effect of embelin was evaluated against 3-Nitropropionic acid-inducedHuntington's disease in rats, embelin caused behavioral and status alterations and also reversed the neuronal damage caused by 3-NP which suggests the neuroprotective action of embelin against HD[53]. An in situ gel was prepared to enhance the concentration of embelin in brain to prevent HD. This formulation easily crosses the blood brain barrier by decreasing oxidative stress in brain [54].

L. Ulcerative colitis preventive activity

A study conducted by Thippeswamy *et al* demonstrated the colitis preventive action of embelin. To evaluate the colitis preventive action of embelin, acetic acid is used to induce colitis in rats and thenwas treated with embelin and sulfasalazine for five consecutive days. Embelin was able to reduce myeloperoxidase activity, serum lactate dehydrogenase, and increased the serum glutathione level which is suggestive of the colitis preventive effect of embelin [55]. Embelin-loaded lipid nanospheres made of soyabean oil/ coconut oil as liquid lipid carriers have been produced to enhance the colitis preventive activity [56]. Embelin-loadedenteric-coated microspheres have been formulated to sustain the action of embelin. This formulation significantly reduces the ulcer activity score and oxidative stress and thus attenuates the inflammatory changes [57]. Embelin-loaded guar gum microparticles have also been formulated and have been found to show lesser side effects as compared to conventional dosage forms [58]. Another study conducted by Kumar *et al*2011suggested the colitis preventive effect of embelin when it was able to suppress edema and mucosal damage [59].

M. Cardioprotective activity

A study conducted by Sahu *etal*2014suggested the cardioprotective effect of embelin in isoproterenol induced myocardial infarction in rats. Embelin was found to reduce the elevated levels of cardiac injury biomarkers such as LDH and AST. The underlying mechanism behind prevention of myocardial infarction was that embelin restored the myocardial mitochondrial respiratory enzymes [60]. Another study also suggested the cardioprotective effect of embelin in myocardial injury due to anti-inflammatory and antioxidant properties [61]. In another study, several derivatives of embelin such as 4i, 6a, 6d, 6k and 6m were found to have cardioprotective effect as they can attenuate DOX induced cardiotoxicity effect on oxidative stress [62]. Experimental study conducted by Qian *et al*2017 demonstrated the cardioprotective effect of embelin via upregulation of PPAR protein and reduction ofTNF-α level [63]. Another study was conducted to evaluate protection against isoproterenol induced myocardial infarction in albino rats. Embelin significantly reduced the increased heart beat and systolic blood pressure and elevated levels of LDH and CK in serum which is suggestive of cardioprotective effect of embelin [64]. A study conducted to evaluate the ISO induced cardiomyopathy in STZ induced diabetic rats and the results obtained suggested the cardioprotective effect of embelin [65].

N. Anti acute respiratory distress syndrome

A study was conducted to evaluate the activity of embelin on lipopolysaccharide induced respiratory distress syndrome in murine models. Embelin was able to reduce respiratory distress syndrome by reducing nitrosative stress and mononucleated cellular infiltration which is suggestive of its potential activity against acute respiratory distress syndrome [66]. Another study demonstrated the acute respiratory distress syndrome preventive activity against ovalbumin

lipopolysaccharide induced airway inflammation in rats via suppression of Th2- mediated immune response [67].

O. Neuroprotective activity

Embelin can cross blood brain barrier easily and hence its neuroprotective effects have been studied in the past using in vitro models of neuronal disorders such as convulsions and epilepsy [68]. A study was designed to evaluate the neuroprotective effects of embelin on global ischemia/reperfusion-induced brain injury in rats. It was found that embelin increased locomotor activity, hanging latency time and thus found to have neuroprotective activity [69]. Another study suggested that embelin has the capability to treat several chronic neuronal disorders via upregulation of antioxidant enzymes such as SOD, CAT and GSH [70].A study conducted to check the anti-alzheimer's activity demonstrated that embelin was able to reverse amnesia produced by diazepam and shows neuroprotective effect in dose dependent manner in rats [71]. Another study conducted to evaluate the neuroprotective effect of ethanolic extract of Embeliaribes on middle cerebral artery occlusion-induced focal cerebral ischemia in rats suggested that chronic treatment with ethanolic extract enhance antioxidant against MCAO induced focal cerebral ischemia and thus exhibits neuroprotective effect [72].

P. Antiviral activity

A study conducted by Hossan*et al* in 2018 suggested the antiviral activity of embelin against influenza virus *in vitro*. It was found that embelin has the capability of antiviral action when added at the early stages of viral lifecycle [73]. In another study, it was found that embelin is capable of reducing oxidative damage caused by HSV-1 virus and thus can be a potential antiviral molecule, although more studies need to be conducted to evaluate the potential of embelin as an antiviral agent [74]. Embelin is also known to exhibit antiviral activity against influenza and Hepatitis B [75]. Another study demonstrated that embelin can effectively inhibit HSV-1 virus at the binding stage of viral lifecycle. Study conducted by Elias et *al*2021suggested that embelin is capable to produce significant antiviral action to prevent HSV-1 infection [76].

Q. Hepatoprotective activity

A study conducted by Poojari *et al* in 2010 evaluated the hepatoprotective activity of embelin on N-nitrosodiethylamine and carbon tetrachloride induced toxicity in rat liver. Embelin actively prevents the NDEA or CCl4 induced increase in the biomarker enzymes such as SGOT, SGPT and ALT [77]. Another review states that embelin is able to reduce the damage caused due to liver toxicity and exhibits significant hepatoprotective action [78].A study conducted to evaluate the protective effect of embelin on acute liver injury in mice demonstrated the hepatoprotective effect of embelin via reduction in hepatic necrosis [79].

R. Antiproliferative activity

A study conducted by Martin-Acosta *et al*2021demonstrated the antiproliferative activities of synthetic derivatives of embelin in three hematologic cell lines, HEL, K-562 and HL-60 [80]. In another study, embelin derivatives were investigated for antiproliferative activity against tumor cells; these derivatives arrested HL-60 cells in the G_0/G_1 phase in a dose dependent manner and thus can be potential antimitotic agents targeting microtubular proteins [81]. Another study

suggested the antiproliferative activity of embelin against phenobarbital induced hepatocarcinogenesis in wistar rats via exhibiting cytotoxicity against K562 and Dalton's Lymphoma ascite cells [82]. In another study, the anti-cancer activity of embelin was evaluated in breast cancer, embelin significantly affected the viability of cells and also showed potent action against MCF-7 breast cancer cells in dose dependent manner [83].There are several mechanisms by which embelin exerts its antitumor action, most of these mechanisms induce apoptotic cell death via modulating various characteristic markers of tumor cells [84]. A study suggested that embelin exerts its anticancer effect by molecular changes associated during early apoptotic phase [85].

S. Antiobesity activity

The antiobesity potential of embelin in rats was studied in Murine ST2 stromal cells and C3H10T1/2 mesenchymal cells. Embelin suppressed proliferation and differentiation of these cells into mature adipocytes. In vivo studies demonstrated that embelin treatment significantly reduced total body weight and serum triglycerides and also blocked induction of adipogenic and lipogenic factor that contributes to weight gain [86]. A study conducted to evaluate the anti-obesity effect of ethanolic extract of Embeliaribes in murine model of high fat diet-induced obesity showed significant reduction in serum glyceride level and increase in HDL-C level, also embelin decreased the myocardial lipid peroxidation which suggests the potential anti-obesity effect of embelin [87,88]. The aim of another study was to evaluate the preventive effect of embelin against hyperlipidemia and oxidative stress in high fat diet- induced obesity in rats, embelin significantly reduced serum glucose level and increased SOD, CAT and GSH levels in obesity induced rats [89]. Another study demonstrated that anti-obesity action of embelin is mainly attributed to down regulation of leptin, TNF-α expression [90].

T. Antifungal activity

A study conducted by Rathi *et al* evaluated the antifungal potential of embelin using in vitro antifungal susceptibility test and it was found to possess significant antifungal effect [91]. Another study suggested that embelin and ketoconazole can be promising therapeutic moiety for antifungal action [92]. Several semisynthetic derivatives of embelin are also available that also possess significant antifungal activity against fungal pathogen [93]. Another study conducted to evaluate the in vitro antifungal activity of embelin on eight different fungal species suggests that embelin can significantly inhibit the fungal growth, maximum antifungal activity was observed at 2 mg concentration [94].

U. Antihyperhomocysteinemic activity

Embelin was evaluated for its antihyperhomocysteinemic and lipid lowering potential in methionine- induced hyperhomocysteinemia in rats. It significantly increased the levels of homocysteine, LDH and triglycerides with concomitant decrease in serum high density lipoprotein [95]. Another study demonstrated the antihyperhomocysteinemicactivity of embelin in male wistar rats by inducing methionine. Embelin was able to significantly reduce LDH, LDL-C, VDL-C and total glycerides levels in blood serum [96,97].

V. Anthelmintic activity

A study was done to evaluate the in vitro anthelmintic activity of embelin in earthworms, various concentrations of embelin were used and albendazole was used as standard to compare with embelin. The results were suggestive of potential anthelmintic activity of embelin [98]. Another study also suggests the potential anthelmintic activity of embelin [99]. Another study conducted to evaluate the anthelmintic activity of embelin demonstrated that disalts obtained from embelin were active while diimines were inactive [100].

W. Antitumor activity

A study was done to evaluate the antitumor activity of embelin in gastric cancer cells. Gastric cancer cells were treated with embelin and 5-FU for reference. Embelin induced cell cycle arrest at S and G2/M phases and caused downregulation of cell cycle-regulatory proteins and modulated several other pathways responsible for apoptosis and this mechanism is suggestive of significant anti-tumor activity of embelin [101]. Embelin exhibits anti-tumor activity via blocking the activity of X-linked inhibitor of apoptosis protein. Nanomicellar carrier of PEG-derivatized embelin were able to release paclitaxel for the treatment of breast and prostate cancer in a sustained manner [102]. Colitis associated cancer (CAC) model was used to demonstrate the antitumor properties of embelin, embelin attenuated M2- like polarization of macrophages and eliminated tumor promoting functions [103]. Another study conducted to understand the underlying mechanism by which embelin inhibit pancreatic cancer growth was done in mice by modulating the tumor immune microenvironment. Embelin significantly inhibited PANC-1 tumor growth, angiogenesis and inhibited the expression of Bcl-2, CDK2, CDK6 and also reversed the epithelial mesenchymal transitions [104]. A study conducted to evaluate the effect of embelin, an antagonist of XIAP, on colon cancer, it was found that Peroxisome Proliferator-activated receptor significantly contributes to the inhibition of colon carcinogenesis by embelin [105]. Another study investigation the antitumor action of embelin and celastrol in combination, this study concluded that both shows synergistic effect and majorly acts via XIAP and NF-κB pathways and can be further investigated as a combination therapy in acute myeloid leukemia [106].

X. Chemopreventive activity

A study conducted to demonstrate the chemopreventive effect of embelin against N-nitrosodiethylamine/phenobarbital- induced hepatocarcinogenesis in wistar rats suggests that embelin was able to prevent the induction of hepatic hyper plastic nodules and thus show significant chemopreventive effect [107]. The underlying mechanism of chemopreventive activity of embelin is not clear because nuclear factor κB regulates various genes associated with inflammation, proliferation and apoptosis [108].

Y. Antimalarial activity

A study was conducted to evaluate the in vivo antimalarial activity of embelin and its semisynthetic derivatives. This study demonstrates embelin and its semisynthetic derivatives show antimalarial activity in a dose dependent manner [109]. Another study done to evaluate the antimalarial activity of embelin suggests the potential antimalarial activity which is not attributed to β-hematin formation inhibition [110]. Chloroquine resistance is very common and thus the need to identify other molecules to augment antiplasmodium is required. This study suggests that embelin has significant antiplasmodium effect and does not synergism with chloroquine [111].

The key molecular biomarkers involved in the protective effects of embelin on various body system have been illustrated in figure3 and In -vivo and In -vitro effects of embelin in the treatment of various disorders have been summarized in Table 1.

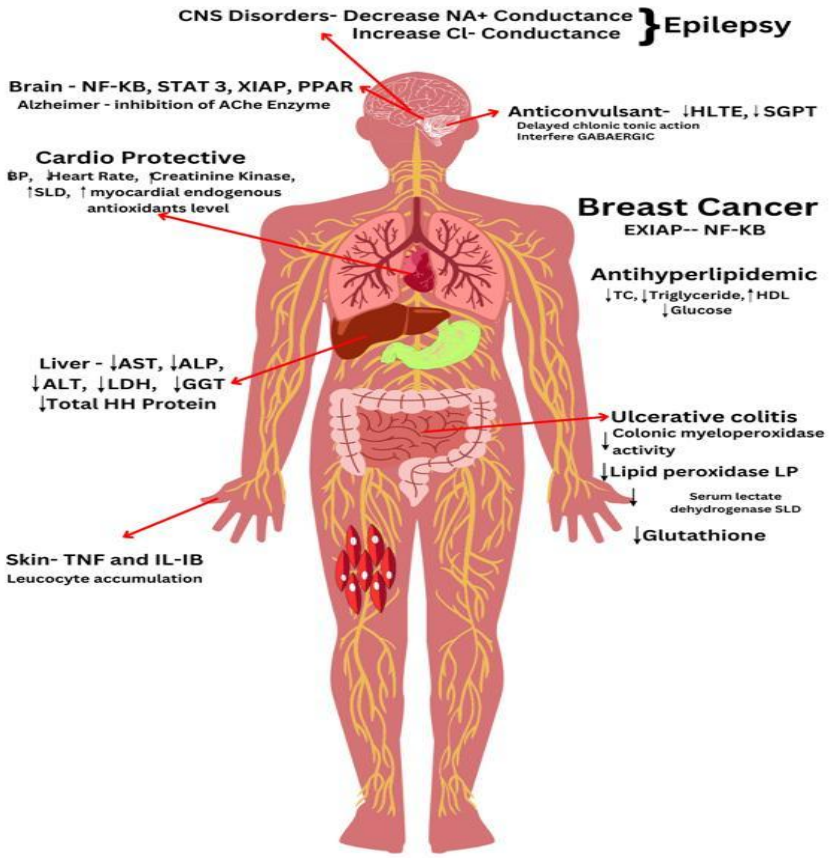

Figure 3: The key molecular biomarkers involved in the protective effects of embelin on various body system.

Table1: In -vivo and In -vitro effects of embelin in the treatment of various disorders.

Bioactive effects	Models	Dose (mM)	Duration (hrs)	Effects	Suggested mechanisms	References
Antiapoptotic	Cytokine	50mg/ml	12h	down-regulation of NF-B-dependent gene products, inhibit tumor cell survival proliferation, invasion, and angiogenesis.	NF-B activation, inhibiting IKK activation, p65 phosphorylation, p65 acetylation, nuclear translocation,	Ahn et al.
Wound healing activity	excision wound model, incision wound model, and dead space wound model	4 mg/ml	6h	increased collagen deposition and tensile strength of the incision wound	release enhancePGE1 and PGE2, wound contraction, epithelialization, and granulation tissue formation	H.M. Kumara Swamy et al.
antidiabetic	alloxan induced diabetes	25 and 50 mg/kg b.wt	21 days	reduction in fasting serum blood glucose levels, improved body weights in rats	↓TGL, ↓TC, ↓TB, ↓CR, ↓LDH,↓ ALP and VLD↓	S. Mahendran et al.
Anticonvulsant activity	MES-induced seizure in rats, PTZ induced seizure model	2.5, 5 and 10 mg/kg, i.p	72h	reduction in the duration of Hind Limb Tonic Extension (HLTE)	GABAergic mechanism	S. Mahendran et al.
ANTIOXIDANT	DPPH radical scavenging method.	10 and 20 mg/(kg	18:00 h	Decrease lipid, AST, ALT.	-	S. Mahendran et al.
ANALGESIC	Eddy's hot-plate test,	10 and 20	6h	complete abolition of	-	S. Mahendran

	Tail immersion, Acetic acid induced writhing	mg/(kg		writhing		et al.
Antihyperglyce-mic, lipid lowering, and antioxidant activities	-	50 mg/kg	21 days	↓levels of glucose,↓ insulin, leptin, ↓serum lipid levels,↓ Heart rate	↓TBARS, ↑GSH, ↑SOD, ↑CAT	Chaudhari HS et al
Apoptosis	MTTAssay, Western Blot Analysis	100 µM	-	down-regulation of NF-B-dependent gene products	-Akt/mTOR/S6K 1, -NF-kB, STAT3	Kim et al.
Antidepressant	Tail suspension test (TST), Forced swimming test (FST)	2.5 and 5 mg/kg	1h	↓immobility	-	Gupta et al.
anti-carcinogenic	dextrane sulfate sodium-induced colitis in mice	1 mM		Lower myeloperoxidase activities and nitric oxide (NO), reduced expression of inducible NO synthase, tumor necrosis factor (TNF)a, interleukin (IL)-1b, and IL-6	XIAPs, NFkB, STAT-3, Akt and mTOR, inhibition of 5-LO and mPGES-1	A.M. Schaible et al

Apoptosis	MTT assays, Transient transfection and luciferase assays, Western blot analysis, Cell viability assays,	50 μM	6 days	↓proliferation of human glioma cells,	inactivating NF-κB, XIAP inhibitor, inhibition of NF-κB, XIAP, STAT3, and PPARγ , reducing c-FLIP expression. Bcl-XL and Bcl-2, ↓CDK2, ↓CDK4, ↓Cyclin D1, and ↓Cyclin E, ↑CASPs, ↑CASP8, 9 and ↑T98G cells, ↑PARP.	S-Y Park et al
antidiabetic	Streptozotocin-induced diabetes	15, 25, and 30 mg/kg/ day,	21 days	scavenge free radicals and inhibit lipid peroxidation	increase the activity of superoxide dismutase, catalase, and glutathione peroxidase	GUPTA et al.
ulcerative colitis	myeloperoxidase activity (MPO), lipid peroxidation and reduced glutathione (GSH), serum lactate dehydro-genase (LDH) ERBA diagnostics kit	25 and 50 mg/kg,	7 DAYS	↓MPO levels, (-)Lipid peroxides activity	↓TNF-α level	B.S. Thippeswamy et a
Liver Damage	carbon tetrachloride (CCl4) induce lever damage	25 mg/kg	15 days	↓AST,↓ ALT, ↓ALP,↓ GGT,↓ LDH,	inhibiting CYP2E1 activity,increasing free radical scavenging activity	DHARMENDRA SINGH ET AL.

skin edema	lipopolysaccharide induced, TPA)-induced mouse ear edema.	50 mg/kg,	10 days	reducing inflammatory damage, blockade of leukocyte accumulation	inhibition of kappa B (NF-κB, ↓TNF-α, ↓(IL-6)	G. Kalyan Kumar et al.
Antidiabetic	streptozotocin-induced diabetes.	15,25, and 30 mg/kg /day	21 days	↓Serum glucose, ↓Serum urea, Serum insulin,↓ Serum nitric oxide, ↓Blood glycated hemoglobin %	↑SOD↑ CAT ↑ GPx, ↑GSH, ↑GST,↓ LPO,	R. GUPTA et al.
anxiolytic activity	Open field test, Light and dark test	2.5 and 5 mg/kg	5 min	↓number of entries and time spent in closed arm	agonistic effect on GABA/benzodiazepine receptor complex.	M. Afzal et al.

IV. PHARMACOKINETICS OF EMBELIN

A. Oral administration

A study conducted by Zhen *et al* in 2019 demonstrated that the oral bioavailability of embelin in rats was found to be 30.2 ± 11.9%. The value of T_{max} was found to be 0.31 ± 0.18h which suggests that embelin easily quickly reach the maximum plasma concentration, elimination half-life suggested rapid elimination from the body. All these results indicate towards poor aqueous solubility of embelin [112].

B. Intravenous administration

Intravenous administration of embelin in rats showed quick elimination [112].

V. NANOTECHNOLOGY BASED FORMULATIONS OF EMBELIN

Embelin has been used over several years for the formulation of various nanotechnology-based formulations for variety of diseases. Nanotechnology based formulations of Embelin have been summarized in Table 2.

Table 2: Nanotechnology-based formulations of embelin

S. No.	Formulation	Disease	MOA	Year	Reference
1	Silver nanoparticles	Breast cancer	Apoptosis	2023	[113]
2	Nanoparticles	Cervical cancer	Inhibition of SLC16A1/3	2023	[114]
3	Nanoparticles	Diabetes	Reduction of plasma glucose levels	2022	[115]
4	Nanoliposomes	Depression	Prevention of oxidative stress and neuronal inflammation	2022	[116]
5	Silver nanoparticles	Lung cancer	Dose dependent inhibition of cell proliferation	2022	[117]
6	Nanoparticles	Cancer	Induction of apoptosis	2022	[118]
7	Gold nanoparticles	Bacterial infection	Inhibition of efflux pumps	2021	[119]
8	Nanoparticles	Alcohol induced hepatotoxicity	Increase in the level of liver enzymes	2020	[120]
9	Silver nanoparticles	Cancer	Reduction in cancerous cell growth	2019	[121]
10	Niosomes	Diabetes	Increase in SOD, CAT and GSH along with decrease in lipid peroxidation level	2018	[122]
11	Microparticles	Ulcerative colitis	Antioxidant and anti-inflammatory actions	2018	[123]
12	Nanoemulsion	Diabetes	Reduction in serum glucose level	2018	[124]
13	Microspheres	Ulcerative colitis	Reduction of ulcer activity score and oxidative stress	2017	[125]
14	Nanospheres	Ulcerative colitis	Reduction of MPO, LDH and LPO levels and increase GSH level	2015	[126]

VI. CONCLUSION

It can be concluded from the literature review that embelin is an effective biological molecule withthe potential to act against different diseases, but it needs to be further exploredin order to gain a better understanding of its therapeutic potential. It has widespread pharmacological activities such as antioxidant, antiviral. antimicrobial, antidiabetic, anti-inflammatory, and anticancer and found to have minimum side effects. Embelin is abundantly found in Embeliaribes (Myrsinaceae) and thus this plant can be a good source of embelin. Poor aqueous solubility has limited the clinical applications of embelin. Various synthetic analogs have been formulated in order to increase its aqueous solubility, further in vivo investigations and clinical trials are needed to validate the clinical validation of embelin.

LIST OF ABBREVIATIONS

STZ: Streptozocin

HFD: High fat diet

CK: Creatine kinase

LDH: Lactate dehydrogenase

THP-1: Tamm-Horsfall protein-1

CUS: chronic unpredictable stress

BDNF: Brain derived neurotrophic factor

FST: Forced swimming test

MST: Mice tail suspension test

HD: Huntington disease

SOD: Superoxide dismutase

CAT: Catalase

GSH: Glutathione

MCF: Macrophage chemotactic factor

NDEA: N-nitrosodiethylamine

HSV-1: Herpes simplex virus-1

MCAO: Middle cerebral artery occlusion

AST: Aspartate aminotransferase

TNF: Tumor necrosis factor

DOX: Doxycycline

ISO: Isoproterenol

PPAR: Peroxisome proliferator-activated receptors

DDPH: 2,2-Diphenyl-1-picrylhydrazyl

SGOT: Serum Glutamic-oxaloacetic transaminase

SGPT: Serum glutamic-pyruvic transaminase

ALT: Alanine aminotransferase

XIAP: X-linked inhibitor of apoptosis

CDK: Cyclin dependent kinase

Bcl-2: B-cell lymphoma 2

PANC-1: Pancreatic cell

FU: Fluorouracil

3-NP: 3-Nitropropionic acid

LDL-C: Low-density lipoprotein-cholesterol

VLDL-C: Very Low-density lipoprotein-cholesterol

CONFLICT OF INTEREST

None

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