



**A REVIEW ON THE PHARMACOLOGY OF *EMBELIA RIBES* BURM.F.-A  
THREATENED MEDICINAL PLANT**

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**ABSTRACT**

*Embelia ribes* Burm.f. commonly known as false black pepper, is being used since the ancient times, in the form of the drug 'Vidanga'. It has been attributed to contain numerous medicinal properties and is of very high commercial value. The root, berries and leaves of *E.ribes* is used in herbal formulas. It contains the benzoquinone compound embelin (2, 5-dihydroxy-3-undecyl-2, 5-cyclohexadiene-1, 4-benzo-quinone) which has been studied for its various medicinal activities such as antitumor, antidiabetic, antimicrobial, antifungal and antifertility. This review is a comprehensive overview about the existing pharmacology of *E.ribes*, helping to fuel further research in the various unexplored activities that are attributable to this plant.

**KEYWORDS:** *Embelia ribes*, *Vidanga*, Embelin, Threatened, Antifertility, Anticancer, Antidiabetic



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## INTRODUCTION

The plant world is a Pandora of active chemical compounds. Nearly half the medicines that we use today are of herbal origin, and a quarter contains plant extracts or active chemicals taken directly from plants. Though the new era has seen advances in chemistry, which have paved the way to reproduce the active ingredients found in plants, but plants still will continue to have the medicinal importance in their own right. Their active components may be slightly modified to improve their efficacy or to reduce undesirable side effects, but they are still the basis of drugs that are vital for treatment of disorders such as cancer or diabetes, one such classical example is the modified form of the compound acetylsalicylic acid more commonly known as aspirin was the first modern drug that was born from the nature's medicine, the bark of the willow tree. It is no accident that plants play an important role in contemporary pharmacological research: the compounds that have the medicinal applicability are those that the plant itself uses to survive. There are more than 100,000 of these active compounds have been found in the plant world, because of their complex and diverse chemical structures, they are the basis of many medicines. Scientists have always targeted plants known to contain the active compounds such as the morphine from opium poppy or the caffeine from coffee beans, their research is normally backed with the information provided by the so-called ethnobotanists, who collect the traditional knowledge from the traditional healers among native populations, a classical example of which is the *Trichopus zeylanicus* ssp. *travancoricus* that was identified by a team of scientists with the help of the Kani tribesmen. Detailed chemical and pharmacological investigations showed that the leaf of the plant contained various glycolipids and some other non-steroidal compounds with profound adaptogenic and immuno-enhancing properties. Yet another holistic approach is with the help of the ancient Vedas and sacred texts Charka Samhita, which describes 582 herbs (Majno, 1975) or the main book on surgery, the Sushruta Samhita, which lists some 600 herbal remedies. This approach is proving

particularly successful in the discovery of new and more effective drugs as such plants were already used medicinally and documented for their medicinal properties and are therefore much more likely to contain active chemical compounds. One such medicinal plant is the *Embelia ribes*, whose mention has been found since the ancient times, in the form of the drug 'Vidanga' or 'Baibidanga' which has been an important ingredient in a number of ayurvedic formulations. *E. ribes* yields embelin, and other highly valued secondary metabolites, which have a wide range of clinical applications such as anticancer, antitumor, antifertility, antimicrobial, antidiabetic activity etc<sup>1</sup>. The main active medicinal component in dried fruits of *E. ribes* is embelin (2, 5-dihydroxy-3-undecyl-2,5-cyclohexadiene-1,4-benzo-quinone), which is being commercialized in the name of the drug, Vidanga, is produced and used in high volumes, estimated to be at a demand of ~500 tons/yr. It was also estimated that the annual trade growth rate of Vidanga is about 23%<sup>2</sup>.

### PHYTOCHEMISTRY

The ripe fruits of *E. ribes* was studied to contain the active compound namely Embelin<sup>3</sup>. Further investigation resulted in three new compounds: embelinol, embeliaribyl ester and embeliol<sup>4</sup>. Also another compound namely Vilangin was also identified<sup>5</sup>.

### PHARMACOLOGY

#### ANALGESIC ACTIVITY

*E.ribes* was studied as a potent centrally acting analgesic. In vivo studies were carried out in the rat brain for characterization of binding sites for potassium embelate, an active compound obtained from *E.ribes*. The results indicated that the mixed mu and kappa binding sites in the brain may be involved in the analgesic action<sup>6</sup>. Embelin was condensed with different primary amines, to give 10 disalts and 14 diamines. Embelin and all its disalts showed analgesic activity whereas all the diamines derivatives were inactive. The disalt, 2:5 disobutyl amine embelin showed the maximum action. Analgesic effect was noticed only after intraperitoneal administration but no other

forms of administration were effective. Embelin and its disalt, 2:5 isobutyl amine embelin also exhibited antipyretic and anti-inflammatory activities<sup>7</sup>. Potassium embelate was studied for its analgesic activity in rats and mice. Administration was from oral, Intramuscular and I.C.V routes, and it was seen that Potassium embelate acted centrally and not peripherally. In comparison to the standard drug Morphine, it was found to be non-necrotic, with high oral efficacy, high therapeutic index<sup>8</sup>. High analgesic activity was seen in visceral evoked responses when compared to thermal evoked responses and suggested that potassium embelate has a strong affinity for kappa type of opine receptors<sup>9</sup>.

### ANTHELMINTIC ACTIVITY

*Gynandropsis gynandra*, *Impatiens balsamina*, *Celastrus paniculata*, *Embelia ribes* and *Mucuna pruriens* were studied for their anthelmintic property. A bioassay was undertaken wherein the seed oils of the species was studied along with standard drug piperazine citrate, to determine the time of paralysis and time of death of the worm *Pheritima posthuma*. *E. ribes* showed the best anthelmintic activity in both the parameters<sup>10</sup>. The antinematodal activity of a mixed prescription of *Veronica antheilmintica* seed (Kali zeeri) and *E.ribes* fruit (Babrang) was evaluated in goats. The EPG (Egg per gram) counts were made in the faeces before and on different days of treatment. The evaluation showed that the two plants are equally effective and safe in treating natural gastrointestinal nematode infection of the local goats<sup>11</sup>. *E.ribes* and *Butea fondosa* (Palaasha) seeds were studied to have definite ascaricidal properties with doses of 6g or more, administration modes were either single or in combination, and they were compared with the standard drug santonin. They showed increased anthelmintic property against *Taenia* and hookworm<sup>12</sup>. Both alcoholic as well as the aqueous extracts of the ripe fruits of *E.ribes* were studied to present significant anthelmintic property, when they showed motility of earthworms. It was also seen that the alcoholic extract was more potent<sup>13</sup>. The anthelmintic activity of Vidangadi churna- Ayurvedic formulation containing traditionally used herbs viz., *E.ribes*, *Hordeum vulgare*, *Mallotus*

*philippinensis*, *Terminalia chebula* was studied. It was tested against adult earthworm *Pheritima posthuma*, taking Piperazine citrate (15 mg/ml) and albendazole (20 mg/ml) as standard references and normal saline as control. The time to achieve paralysis of the worms was determined. And it was seen that Vidangadi churna produced a potent activity against the *P. posthuma*<sup>14</sup>. Extracts of six different plant species namely Bromelain, the enzyme complex of the stem of *Ananas comosus*, the ethanolic extracts of seeds of *Azadirachta indica*, *Caesalpinia crista* and *Vernonia antheilmintica*, the ethanolic extracts of the whole plant of *Fumaria parviflora* and of the fruits of *Embelia ribes* were tested against *Haemonchus contortus* using a modified (MTT) reduction assay. Pyrantel tartrate was used as reference. All the six showed an anthelmintic efficacy of up to 93%<sup>15</sup>. Invitro anthelmintic activity of aqueous and alcoholic extracts of *Melia azedarach*, *Ananas comosus*, *E.ribes* and *Mucuna prurita* were evaluated against *Taenia canina* and *Phamphistomum cervi*. All of them were found to be anthelmintic in nature<sup>16</sup>. A comparative anthelmintic activity study was done between *E. ribes* and substitutes, *E. tsjeriam-cottam* (Roem. & Schult.) A. DC., *Myrsine africana* L. and *Maesa indica* (Roxb.) DC. On the eggs, L1 larvae and adults of *Caenorhabditis elegans*. Bioactivity of *E. tsjeriam-cottam* was found to be comparable to *E. ribes*, followed by *M. africana* and *M. indica* all of them showed good anthelmintic activity<sup>17</sup>.

### ANTI-ANXIETY ACTIVITY

The effect of embelin compound against anxiety was investigated by using Elevated zero-maze test and Novelty induced suppressed feeding latency test in rat models. They were tested in a dose dependent manner in comparison with the standard drug diazepam. The anxiolytic activity was found at 20mg/kg. And it was observed that the anxiolytic effect of the compound was regulated through the monoaminergic system in the brain<sup>18</sup>. In the elevated plus maze test, *E.ribes* (100 and 300 mg/kg p.o.) significantly ( $P<0.01$ ) increased the number of entries and time spent in open arm, in the hole board test, it (100 and 300 mg/kg p.o.), showed

significant increase ( $P < 0.01$ ) in the number of head dips, in the mirrored chamber apparatus, it showed significant increase in the number of entries and time spent in mirrored chamber, along with significant decrease in the latency to enter the mirrored chamber also it showed significant ( $P < 0.01$ ) increase in the brain GABA level. The results indicate that *E.ribes* possesses anxiolytic activity probably by increasing the GABA concentration in the brain<sup>19</sup>. In light and dark model, embelin produced a significant increase in time spent, number of crossing and decrease in the duration of immobility in light box. In open field test, embelin showed a significant increase in number of rearing, assisted rearing and number of square crossed. On the basis of result, embelin showed its anxiolytic effect in a dose-dependent manner<sup>20</sup>.

#### **ANTIBACTERIAL ACTIVITY**

The antibacterial activity of aqueous and ethanolic extracts of *E.ribes* was determined by disc diffusion and broth dilution techniques against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*<sup>21</sup>. Among the embelin derivatives, the aryl substituted benzoxadiazine produced, significant zones of inhibition against *Bacillus subtilis*, *Bacillus Polymyxa* and *Proteus vulgaris* but excluding *Escherichia coli*. Methyl substituted benzoxadiazine didn't possess any activity due to inductive effect, while the compounds -CONHNHCOCH<sub>3</sub> and P-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> are active against only *B.subtilis* and *P.vulgaries*. The phenyl and Para-nitro phenyl substituted benzoxadiazines had maximum antibacterial activity against *B. subtilis*<sup>22</sup>. Embelin showed bactericidal activity against Gram +ve organisms, and bacteriostatic against Gram -ve organisms. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of embelin against both Gram +ve and Gram -ve bacteria were studied using micro dilution method and agar plate method. Thus, the study proved that embelin finds application as potent antibacterial agent<sup>23</sup>.

#### **ANTICANCER ACTIVITY**

A fibrosarcoma cell line was exposed to increasing concentrations of embelin, and simultaneously inoculated with [<sup>3</sup>H]-thymidine.

Using a rapid technique to assess drug-induced cell toxicity, a dose-dependent decrease in labelled thymidine uptake, lipid peroxide and glutathione levels was observed giving an insight into the anticancer property of embelin<sup>24</sup>. Biological activities of two embelin derivatives namely 5-*O*-ethylembelin and 5-*O*-methylembelin were investigated showing antiproliferative activity in HeLa cell line in comparison to PtK2 cell line. They arrested HL-60 cells in the G<sub>0</sub>/G<sub>1</sub> phase of the cell cycle in a dose- and time-dependent manner. This evidence suggests that both the derivatives of embelin are promising novel antimetabolic and anticancer molecules targeting microtubular proteins<sup>25,26</sup>. The sensitizing potential of embelin on ionizing radiation (IR) in a human prostate cancer model was researched. *In vitro*, it was seen that embelin combined with radiation suppressed prostate cancer PC-3 cell proliferation that was associated with S and G<sub>2</sub>/M arrest in the cell cycle. Moreover, the combination treatment promoted caspase-independent apoptosis, but not autophagy. *In vivo*, embelin significantly improved tumor response to X-ray radiation in the PC-3 xenograft model. Combination therapy showed decreased tumor growth, decreased cell proliferation, induced apoptosis, compared with either treatment alone, suggesting combinatory inhibition on tumor suppression and angiogenesis. This finding warrants embelin as a novel adjuvant therapeutic candidate for the treatment of hormone-refractory prostate cancer that is resistant to radiation therapy<sup>27</sup>. Embelin was studied to inhibit the X-linked inhibitor of apoptosis protein (XIAP) in induced HepG2 human hepatocellular carcinoma cells. After treatment with different dosages of embelin, the MTT method was used to determine cell viability revealing embelin induced the apoptosis. Flow cytometric analysis demonstrated that embelin caused blockade of the HepG2 cells in the G<sub>2</sub>/M phase of the cell cycle. Western blot analysis was performed to determine the expression levels of the apoptosis-associated proteins Bax, Bcl-2 and the caspase family. The results revealed that embelin induced the apoptosis of the HepG2 cells in a dose- and time-dependent manner<sup>28</sup>.

Embelin and curcumin were studied against *N*-nitrosodiethylamine (DENA)-initiated and phenobarbital (PB) to prevent the induction of hepatic hyperplastic nodules, body weight loss, increase in the levels of hepatic diagnostic markers, and hypoproteinemia induced by DENA/PB treatment. Hence the study suggested the possible chemopreventive effects of embelin (EMB) and curcumin (CUR) against DENA/PB-induced hepatocarcinogenesis in Wistar rats<sup>29</sup>. Receptor activator of NF- $\kappa$ B ligand (RANKL), a member of the tumor necrosis factor super family and an activator of the NF- $\kappa$ B signaling pathway, has emerged as a major mediator of bone loss, commonly associated with cancer and other chronic inflammatory diseases. In the study it was found that embelin suppressed the RANKL-induced differentiation of monocytes into osteoclasts. Embelin also suppressed the osteoclastogenesis induced by multiple myeloma and by breast cancer cells. This led to the suppression of NF- $\kappa$ B activation, inhibition of I $\kappa$ B $\alpha$  phosphorylation and I $\kappa$ B $\alpha$  degradation.. Furthermore, by using an inhibitor of the IKK $\gamma$  or NF- $\kappa$ B essential modulator (NEMO), the regulatory component of the IKK complex, it was shown that the NF- $\kappa$ B signaling pathway is mandatory for RAW 264.7 cell differentiation into osteoclasts. Thus, the study summarized that embelin, an inhibitor of RANKL-induced NF- $\kappa$ B activation has great potential as a therapeutic agent for osteoporosis and cancer-linked bone loss<sup>30</sup>. The study summarized that embelin inhibited both inducible and constitutive tumor necrosis factor (TNF) -induced NF- $\kappa$ B, interleukin-1, lipopolysaccharide, phorbol myristate acetate, okadaic acid, hydrogen peroxide, and cigarette smoke condensate activation. It was found that embelin inhibited sequentially the TNF-induced activation of the inhibitory subunit of NF- $\kappa$ B(I $\kappa$ B) kinase, I $\kappa$ B phosphorylation, I $\kappa$ B degradation, and p65 phosphorylation and nuclear translocation. Embelin also suppressed NF- $\kappa$ B-dependent reporter gene transcription induced by TNF, TNF receptor-1 (TNFR1), TNFR1-associated death domain protein, TNFR-associated factor-2, NF- $\kappa$ B-inducing kinase, and I $\kappa$ B kinase but not by p65. Furthermore, embelin down-regulated gene products involved in cell

survival, proliferation, invasion, and metastasis of the tumor. This down-regulation was associated with enhanced apoptosis by cytokine and chemotherapeutic agents<sup>31</sup>. Embelin was able to induce apoptosis of MCF-7 breast cancer cells in a dose-and time-dependent manner. There were changes in the MCF-7 cell mitochondrial membrane potential and the cell cycle of MCF-7 cells in the G2/M phase was blocked. Embelin was studied to promote mitochondrial release of cytochrome C via regulation of Bax and Bcl-2, resulting in the activation of caspase-3 and -9. The results demonstrated that embelin-induced apoptosis of MCF-7 involves the mitochondrial pathway<sup>32</sup>. Studies on cancer cell lines revealed that the crude hexane extract of the fruits of *E. ribes* exhibited cytotoxicity against Human leukaemic cells (K562) and Dalton's Lymphoma ascites cells (DLA)<sup>33</sup>.

#### **ANTICONVULSANT ACTIVITY**

The anticonvulsant activity of embelin was studied at different dosages namely 2.5, 5 and 10mg/kg. It showed a significant inhibition of the seizures induced by electroshock and the drug pentylenetetrazole in a dose dependent manner. This activity was compared to the market standard drugs phenytoin and diazepam. Significant decrease in locomotion revealing its CNS depressant activity was observed. The findings suggest that embelin possess anticonvulsant activity against both grand mal and petit mal epilepsy<sup>34</sup>.

#### **ANTIDEPRESSANT ACTIVITY**

Experimental depression was induced by subjecting mice to tail suspension test (TST) and forced swimming test (FST) experimental models. Intraperitoneal administration of embelin (2.5 and 5 mg/kg), 30 min prior to induction of experimental depression resulted in a dose-dependent reduction of immobility under both test conditions. The effect of embelin at the dose of 5 mg/kg in both experimental models was compared with the standard antidepressant drug, imipramine administered at the dose of 15 mg/kg. It is concluded that *Embelia ribes* and its major bioactive compound, embelin, have therapeutic potential for managing depression<sup>35</sup>.

**ANTIFERTILITY ACTIVITY**

According to the study, daily administration of *Vinca rosea* extract and embelin to male albino rats caused significant rise in levels of acid and alkaline phosphatases of testis and prostate indicating altered metabolic function, giving rise to study further about their probable role in causing antifertility<sup>36</sup>. Embelin altered the testicular histology and glycogen, gametogenic counts and accessory sex gland fructose at the dose levels 0.3, 0.4 and 0.5 mg/kg body weight when administered subcutaneously for 35 days. Hence the compound is suggested to possess antiandrogenic activity<sup>37</sup>. Subcutaneous administration of the embelin compound at a dose of 20 mg/kg body weight to male albino rats for 15 or 30 days revealed an inhibition of: a) epididymal motile sperm count, b) fertility parameters such as pregnancy attainment and litter size, and c) the activities of the enzymes of glycolysis and energy metabolism. These changes were reversible, as seen after 15 and 30 days of recovery. Addition of embelin to epididymal sperm suspensions caused a dose- and duration-dependent inhibition of spermatozoal motility and the activities of the enzymes of carbohydrate metabolism<sup>38</sup>. Berries of *E.ribes* showed spermicidal activity, affecting the sperm motility, the quality and quantity of semen and lowered the hormonal levels Male bonnet monkeys (*Macaca radiata*)<sup>39</sup>. Carbohydrate metabolism impairment of the primary and secondary reproductive tissues of male rats caused by subcutaneous embelin injection was studied and was reversed when drug therapy was withdrawn, thus showing the role of Embelin in antifertility<sup>40</sup>. According to a recent review article, it was seen that the berries of the *E.ribes* has been commonly used on rat models to study various activities such as reduced testosterone levels, antifertility, antispermatogenic, antiandrogenic, and spermicidal activity<sup>41</sup>. To further investigate antifertility effect varying doses of embelin was administered in sexually mature male white New Zealand rabbits. An intramuscular injection of 5 mg/kg body weight of embelin caused a 54% decline in testosterone. Oral administration as a suspension of 10 mg/kg body weight embelin caused a significant ( $p < 0.001$ ) lowering in the hormone levels

from  $12.2 \pm 0.70$  nmol/L (pre-treatment) to  $4.55 \pm 0.35$  nmol/L after treatment. But when administered orally as a 50 mg base tablet, a decline of 40% in testosterone levels was observed. Subcutaneous administration of 20 mg/kg body weight of embelin caused a 12.4% decline in the hormone levels<sup>42</sup>.

The effects of embelin on the evolution of estrous cycles, progesterone and estradiol profiles and ovarian histopathology were examined. Subcutaneous injections of embelin in this animal model resulted in the disruption of the regular oestrous cycle patterns. Significant depression of plasma estradiol and progesterone. Histopathological evaluation of the ovaries from the embelin treated rats revealed the presence of abnormal follicles. There were no significant changes in the liver and pituitary glands. In a separate experiment, mixed ovarian cells were isolated from another set of normally cycling rats and directly challenged with embelin *in vitro*. These data demonstrate that embelin suppresses plasma estradiol and progesterone levels; disrupts the evolution of the regular oestrous cycles and also affecting the ovarian morphology in rats<sup>43</sup>. Forty adult (4 months old) regularly cycling female Sprague-Dawley rats were divided into four groups of 10 rats each. Groups I and II (controls) were given 1 ml/kg body weight of physiological saline or corn oil (vehicle). Groups III and IV received 10 mg/kg and 20 mg/kg body weight embelin in corn oil, respectively. Embelin disrupted the oestrous cycles in Groups III and IV animals, and there was a significant depression in plasma oestradiol ( $p < 0.05$ ) and progesterone ( $p < 0.02$ ) at both 10 and 20 mg/kg body weights, respectively. Isolated mixed ovarian cells from embelin treated rats produced significantly less progesterone and estradiol than controls *in vitro*. It is concluded that embelin probably interferes with reproductive functions in female rats by suppressing ovarian production of sex steroid hormones<sup>44</sup>.

**ANTIFUNGAL ACTIVITY**

Antifungal activity of *E.ribes* was evaluated on eight different fungal species namely *Colletotricum crassipes*, *Cladosporium*, *Armillaria mellea*, *Colletotricum capsici*, *Aspergillus niger*, *Rhizopus oryzae*, *Aspergillus terreus* and *Candida* by

employing various concentrations of the seed extract (0.5-2.0 mg). All the concentrations of seed extract inhibited the fungal growth, whereas maximum activity was observed at 2.0 mg concentration of seed extract<sup>45</sup>. NCCLS method revealed that methanol extract and Embelin had lowest MIC50 range of 120mg/L against *Candida albican* and among four *Candida* species tested Embelin had reported MIC50 values below 700mg/L. Solvent ether extract, petroleum ether extract, methanol extract and embelin reported to have MIC50 in range of 300-700mg/L against *Candida albican* and *Candida parapsilosis*. Petroleum ether extract shows lowest MIC50 range of 250mg/L against *Candida parapsilosis* and 360mg/L against *Candida laurintis* showing effective antifungal activity<sup>46,47,48</sup>.

#### **ANTIGENOTOXICITY ACTIVITY**

Cyclophosphamide (CP) produced a significant increase in chromosomal aberrations (CA), and micronuclei (MN) in polychromatic erythrocytes (PCEs), produced cytotoxicity in mouse bone marrow cells and induced abnormal sperms in male germ line, markedly inhibited the activities of superoxide dismutase (SOD), glutathione (GSH), Catalase (CAT) and increased the malondialdehyde (MDA) content. *Embelin* significantly inhibited the CAs, micronuclei formation and cytotoxicity in mouse bone marrow cells induced by CP, also produced significant reduction of abnormal sperm and antagonized the reduction of CP-induced SOD, CAT and GSH activities, and inhibited the increase in MDA content in liver. In conclusion, Embelin have a protective effect against mutagenicity induced by CP<sup>49</sup>.

#### **ANTI-HISTAMIC ACTIVITY**

The ethanolic extract of *E.ribes* was tested on histamine induced contraction in goat tracheal chain preparation and in histamine induced bronchospasm in guinea pigs. It was seen that *E.ribes* inhibited contraction in goat tracheal chain and also showed significant protection in induced bronchospasm by prolonging the Preconvulsion dyspnoea time. Hence *E.ribes* possesses potential role in the treatment of asthma<sup>50</sup>.

#### **ANTIMITOTIC ACTIVITY**

Series of Embelin derivatives, 2-hydroxy-5-substituted-3-undecylcyclohexa-2,5-diene-1,4-diones were synthesized by treating alkyl and aryl halides in dichloromethane, sodium hydroxide and tetrabutyl ammonium bromide. These synthesized compounds along with Embelin were evaluated for antimitotic activity, using germinating Bengal gram seeds and germinating Onions, *Allium cepa*. All the Embelin derivatives demonstrated antimitotic activity, among all the derivatives, benzyl derivative showed significant activity<sup>51</sup>.

#### **ANTIOXIDANT AND NEUROPROTECTIVE ACTIVITY**

Free radical scavenging reactions and antioxidant activity of embelin has been studied and found that embelin scavenge DPPH radical and inhibit hydroxyl radical induced deoxyribose degradation, lipid peroxidation and restore impaired Mn-superoxide dismutase in rat liver mitochondria<sup>52</sup>. Neuroprotective effect of ethanolic extract of *E.ribes* on middle cerebral artery occlusion (MCAO)-induced focal cerebral ischemia in rats was investigated. Male Wistar albino rats were fed ethanolic *E.ribes* extract for 30 days. The right middle cerebral artery was occluded with a 4-0 suture for 2 h. Ischemia followed by reperfusion in ischemic group rats significantly ( $P < 0.001$ ) reduced the grip strength activity and non-enzymatic (reduced glutathione, GSH) and enzymatic [glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione-S-transferase (GST)] antioxidant levels in hippocampus and frontal cortex compared to sham-operated rats. Further, serum lactate dehydrogenase (LDH) and thiobarbituric acid reactive substance (TBARS) levels in hippocampus and frontal cortex were significantly increased in ischemic group compared to sham-operated rats. Whereas, ethanolic *E.ribes* extract pretreatment gave the opposite results<sup>53,54</sup>. Inhibition of Ultraviolet B (UVB, 290-320 nm) radiation-induced oxidative damage in peripheral blood human lymphocytes by embelin was studied. Lymphocytes ( $1 \times 10^6$  cells) were pre-treated with embelin for a period of 60 min and then exposed to UVB for 30 min. Pre-treatment of lymphocytes with embelin prevented UVB-induced oxidative

damage. It was formulated that Embelin prevents oxidative stress induced by UVB irradiation via its antioxidant property<sup>55</sup>. Transient global ischemia was induced by occluding bilateral common carotid arteries for 30 min followed by 24-h reperfusion. Pretreatment of embelin increased locomotor activity, hanging latency time and decreased beam walking latency. The treatment also reduced significantly the lipid peroxidation and increased the total thiol content and glutathione-S-transferase activity in brain homogenates. These observations suggested that embelin is a neuroprotective agent and may prove to be a useful adjunct in the treatment of stroke<sup>56</sup>.

### **CARDIOPROTECTIVE ACTIVITY**

Cardioprotective effect of aqueous extract of *E.ribes* was evaluated in a rat model having acute myocardial infarction, induced by isoproterenol. *E.ribes* significantly decreased the heart rate, systolic blood pressure, increased levels of serum lactate dehydrogenase, serum creatine kinase and myocardial lipid peroxides and significantly increased the myocardial endogenous antioxidants levels<sup>57</sup>. Pretreatment with ethanol *E.ribes* extract against isoproterenol (ISO)-induced myocardial infarction in albino rats significantly ( $P < 0.01$ ) decreased the elevated levels of LDH and CK in serum and myocardial TBARS and increased the reduced levels of GSH, SOD and CAT in heart homogenates. Histopathological observation revealed a marked protection by the extract in myocardial necrotic damage. The results of this study provide evidence that ethanol *E.ribes* extract treatment enhances the antioxidant defence against ISO-induced myocardial infarction in rats and exhibits cardioprotective properties<sup>58</sup>. The protective effect of *E.ribes* on isoproterenol (ISO)-induced cardiomyopathy in streptozotocin (STZ)-induced diabetic rats was studied by treatment of *E.ribes* ethanol extract (200 mg/kg) on pathogenic (STZ + ISO treated) rats resulted in a significant ( $p < 0.01$ ) increase in HR, blood glutathione, serum LDH, and myocardial endogenous antioxidant levels with a significant ( $p < 0.01$ ) decrease in SBP, blood glucose, HbA<sub>1C</sub>, serum CK, and myocardial TBARS levels<sup>59</sup>.

### **COSMETIC AGENT**

Quinone derivatives and the analogs; Ubiquinone (Coenzyme Q10), Idebenone, Arbutin and Hydroquinone are well-known for cosmetic applications. In the present study, embelin from *E.ribes* berries was analyzed. Hemolytic, tyrosinase and DOPA auto-oxidation assays were also carried out. The half maximal effective concentration (ED50) of embelin to cause hemolysis was found as  $109 \pm 0.1$  g/ml. The tyrosinase inhibitory activity of embelin was nil and the DOPA auto-oxidation activity was observed up to 350 g/ml concentration. Thus the embelin finds, potential application in cosmetic industries<sup>60</sup>.

### **WOUND HEALING ACTIVITY**

Ethanol extract of the leaves of *E.ribes* and its isolated quinone compound embelin were screened for wound healing activity by excision, incision and dead space wound models on Swiss Albino Rats. After treatment epithelialization of the incision wound was faster with a high rate of wound contraction and increase in collagenation and the tensile strength of the incision wound. The histological examination of the granulation tissue of embelin treated group showed increased cross-linking of collagen fibers and absence of monocytes. The wound healing effect was evaluated with the standard skin ointment Framycetin<sup>61</sup>. The burn wound healing property of ethanolic extract of *E.ribes* in comparison to combination of *E.ribes* extract and silver sulphadiazine and silver sulphadiazine alone was studied. Partial thickness burn wounds were inflicted upon four groups of six rats each. Different groups were treated with different combinations. Significant results were seen in the group treated with the combination of *E.ribes* and silver sulphadiazine<sup>62</sup>.

### **NEPHROPROTECTIVE ACTIVITY**

Nephroprotective effects of ethanol extract of *E.ribes* alone and in combination with vitamin E (tocopherol) in cisplatin induced nephrotoxicity in mice was studied. The results indicated that *E.ribes* significantly and dose dependently protected the cisplatin-induced nephrotoxicity. The serum urea, creatinine and blood urea nitrogen levels in cisplatin alone treated groups were



significantly elevated ( $P < 0.01$ ) with respect to control group. This was otherwise reduced in the groups treated with *E. ribes*. The renal levels of reduced glutathione (GSH) were declined in cisplatin alone treated groups. The level of GSH was elevated significantly ( $P < 0.01$ ) in the *E.ribes* treated groups<sup>63</sup>. The nephroprotective and anti-polyuric role of embelin on lithium induced nephrogenic diabetes insipidus (NDI) was studied in albino rats. Embelin 50 and 100 mg/kg showed an increase in the body weight and decrease in plasma and urine creatinine, blood urea nitrogen levels, and urine protein level. Histopathological examination of the kidney indicated that embelin reduced the vascular degeneration of tubules as well as slight degeneration and dilatation of renal tubules, however N-acetyl cysteine standard drug treated rats showed normal glomeruli and renal tubule with slight degeneration. Embelin seemed to be effective in NDI by its predominant effect on promoting antioxidant status and decrease the urine excretion may be due to the blocking of sodium channels<sup>64</sup>.

#### **ANTIDIABETIC ACTIVITY**

Oral feeding of the *E.ribes* extract to diabetic Wistar rats resulted in significant decrease in blood glucose, blood glycosylated haemoglobin, serum lactate dehydrogenase, creatine kinase, pancreatic thiobarbituric acid-reactive substances (TBARS) levels and increase in blood glutathione levels as compared to pathogenic diabetic rats. Islets were found to be shrunken in diabetic rats where as in extract treated rats, there was an expansion of islets. The study concluded that *Embelia ribes* enhances the antioxidant defense against reactive oxygen species produced under hyperglycaemic condition and protects  $\beta$ -cells against loss, and exhibits antidiabetic property<sup>65</sup>. Oral feeding of *E.ribes* berries extracts reduced blood glucose level in by 13.1% and 20.3% normoglycaemic rats and 28.1% and 34.5% in alloxan induced diabetic rats. Thus it was postulated that *E. ribes* berries possesses active hypoglycaemic constituents, and its action may be due to its direct action on tissue or due to increase in insulin secretion<sup>66</sup>. Embelin was evaluated for its potential to regulate insulin resistance, alter  $\beta$ -cell dysfunction and modulate key markers

involved in insulin sensitivity and glucose transport using high-fat diet (HFD) fed-streptozotocin (STZ) induced type 2 diabetic rats. Embelin reduced body weight gain, blood glucose and plasma insulin in treated diabetic rats. It also regulated insulin mediated glucose uptake in epididymal adipose tissue through translocation and activation of GLUT4 in PI3K/p-Akt signaling cascade. Thus embelin can be used in the prevention and treatment of type 2 diabetes mellitus caused due to obesity<sup>67</sup>.

Lipid-lowering and antioxidant potential of ethanolic extract of *E. ribes* was investigated in streptozotocin induced diabetic rats. Twenty days of orally feeding the extract (200 mg/kg) resulted in significant ( $P < 0.01$ ) decrease in blood glucose, serum total cholesterol, and triglycerides, and increase in HDL cholesterol levels when compared to pathogenic diabetic rats. Further, the extract also lowered the liver and pancreas thiobarbituric acid-reactive substances (TBARSs) values ( $P < 0.01$ ) when compared to pathogenic diabetic rats<sup>68</sup>. The biochemical effects of embelin and curcumin against hepatocarcinogenic regimen comprising of N-nitrosodiethylamine (DENA)/phenobarbital (PB) was studied in wistar strain male albino rats. Rats administered with DENA/PB showed hyper cholesterolaemia, hyper triglyceridaemia, elevated low-density lipoproteins (LDL), free fatty acids (FFA), very-low-density lipoproteins (VLDL) levels and decreased urea levels. Pre- and co-treatment with embelin and curcumin for 14 weeks significantly prevented the biochemical alterations induced by DENA/PB<sup>69</sup>.

#### **TOXICITY STUDIES**

Alcoholic and aqueous extracts of the ripe fruits of *E. ribes* were concentrated in the form of capsules (500mg). Two capsules per day cured 50%-80% of nematode infected patients. The capsules were found to be free from toxicity and no purgative was required during treatment<sup>70</sup>. In a study on cancer cell lines *E.ribes* exhibited cytotoxicity against Human leukaemic cells (K562) and Dalton's Lymphoma ascites cells (DLA), *invitro* studies on Embelin suggests the potential of the compound on these two cell lines however the compound did not exhibit toxicity on normal

lymphocytes isolated from human blood preferentially attacking the tumour cells<sup>71</sup>. In study on naturally occurring anthelmintics, *E.ribes* (Enkoko) and *Hagenia abyssinica* (Kosso), have been reported to possibly cause optic atrophy among the Ethiopian population. Treatment with Enkoko or Kosso significantly reduced the ability of chicks to detect a moving bead introduced into the peripheral field of vision. The degree of constriction of the visual field for detection was dependent upon the total amount of drug administered. Performance on a visual discrimination task, which required discrimination of feed grains from pebbles, was also impaired in chicks treated with total doses of 0.200 and 0.250 g of Enkoko or Kosso. The visual deficits observed in Enkoko-treated chicks were mimicked by embelin, which suggests that embelin may be responsible for the visual defects. However, no retinal lesions were detected in chicks following treatment with cumulative doses of less than 0.25 g of Enkoko or Kosso. Similarly, retinal pathology was not observed in embelin-exposed retinae<sup>73</sup>.

#### **NANOMEDICINE**

Nanoparticles of embelin were prepared by emulsification cross linking method using chitosan, cross linked with glutaraldehyde.

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Embelin- chitosan nanoparticle was used to extend the release so as to reduce the adverse effects using chitosan<sup>74</sup>.

#### **CONCLUSION**

This review is a collection of exhaustive literature on the pharmacology of *Embelia ribes*, a species that has attracted a lot of attention globally for being a promising candidate in various traditional, complementary and alternative systems. To understand the mechanism of action, the researchers have worked at molecular levels and significant phytochemicals have been isolated. Also it can be noted that a lot of these promising phytochemicals have been tested in various disease models using modern scientific methodologies and tools<sup>74</sup>. Significant research in the form of integrated Ayurvedic formulations and lab to land products are still awaited.

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