International Journal of Scientific Research in Chemistry (IJSRCH)
© 2020 IJSRCH | Volume 5 | Issue 5 | ISSN : 2456-8457

# Phytochemical and Pharmacological Review of *Embelia ribes*

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**Article Info**
Volume 5, Issue 5
Page Number: 57-62
Publication Issue :
September-October-2020

**Article History**
Accepted : 18 Oct 2020
Published : 30 Oct 2020

## ABSTRACT

*Embelia ribes* Burm. f. is a large, scandent, struggling, medicinal climbing shrub belongs to the family *Myrsinaceae*. The plant is highly esteemed in Unani system of medicine as a powerful anthelmintic and it has been described as "Krimighna" in Ayurveda Classical text, Charaka Samhita. A thorough review of its priorly determined activities will give an overview on the existing activities and gives an inspiration to explore the unexplored activities. Many activities are yet to be explored to determine the complete pharmacological profile of the plant. The reported activities so far are anthelmintic, amylase inhibitory activity, antibacterial activity, antioxidant activity, anti diabetic activity, anticonvulsant activity, anti cancer activity, anti hyperlipidemic activity and anti fungal activity etc.

**Keywords:** *Embelia ribes*, Embelin, Embelic acid, Phytochemistry, pharmacological profile

## I. INTRODUCTION

*Embelia ribes* is popularly known as Vidanga' or 'Vavding' (in Sanskrit) and Baberung (in Hindi), is highly esteemed in Unani system of medicine as a powerful anthelmintic and it has also been described as "Krimighna" in Ayurveda Classical text of Charaka Samhita[1]. However, the dried fruits of *E. ribes* Burm. f. was officially declared as the botanical source of the drug 'vidanga' by the Government of Indian in 1966 and was included in Indian Pharmacopeia. *E. ribes* is one of the 32 medicinal plant species identified and earmarked in the 'Priority Species List' for cultivation by the National Medicinal Plant Board, Govt. of India, New Delhi[2]. Among the many species in demand, *E. ribes* occupies a prime position as it constitutes major ingredients in many preparations of Indian System of Medicine and Homoeopathy (ISM&H) and traditional herbal medicine. According to Poojari, the vidanga is being used as an ingredient in about 75 different ayurvedic formulations. They include Vidangadi churna (antihelminthic, flatulence), Vidangadi yoga (anti-fertility), Pippalyadi yoga (contraceptive) Vidangsaravaleha (urinary diseases, leprosy and skin diseases) Kumariasava (seminal disorders, dementia, debility and liver disorders) Madhukasava (leprosy, leucoderma, blood disorders, dyspepsia) and Krmimudgar rasa (worm infestations, dyspepsia)[3].

Most of the biological actions of *Embelia ribes* have been ascribed to the active principle Embelin, a dihydroxy benzoquinone (2,5-dihydroxy-3-undecyl-p-benzoquinone) and reported to have the potentials of the anthelmintic, antifertility, antidiabetic, antidyslipidemic, antioxidant and anticancer activities. Because of high demand for the fruit of *E. ribes*, in domestic as well as international markets, coupled with the restricted geographic distribution of taxon and IUCN threatened status, inherent sterility of the seed, less yielding capacity, crude drug traders are subjected to the menace of the fruits of 26 species are currently being traded under the name of vidanga[4-7].

## PHYTOCHEMICAL CONSTITUENTS

*Embelia ribes* berries contain several chemical constituents like embelic acid, volatile oil, fixed oil, resin, tannin, christembine (alkaloid), phenolic acids like caffeic acid, vanillic acid, chrorogenic acid, cinnamic acid, ocumaric acid[8]. 4.33% of the embelin content is observed in the berries of *Embelia ribes*17. embelin is water insoluble, but forms a water soluble, violet colored complex, in alkaline medium18. Plant contains potassium embelate, 2, 5-dihydroxy,3-undecyl-1,4-benzoquinone, embelin, quercitol, fatty ingredients, vilangin16. Phytochemical investigation of the seeds revealed 3 new compounds identified as 3–(4"-hydroxyoctadecanyloxy)–p-quinonyl-5-methylene-8-(10-pentanyloxy)-p-quinine (embelinol), n-pentacosanyl-nnonadeca- 71-en-91–alpha–ol-11-oate (embeliaribyl ester), 1,2,4,5-tetrahydroxy 3-undecanyl benzene (embeliol) and a known compound embelin[9].

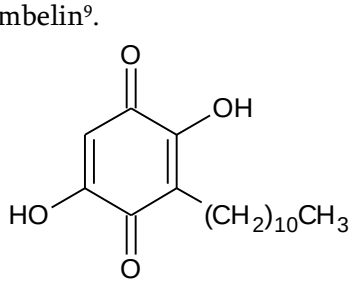


**Figure 1.** Structure of Embelin

## PHARMACOLOGICAL STUDIES

### *Anthelminthic activity*

*Embelia ribes* seed oil when administered at different doses like 10 mg/ml, 50 mg/ml and 100 mg/ml reported death of the worms (*Pheretima posthuma*). But response of worms to different doses altered in the time of paralysis parameter. Increase in dose reported a decreased time of paralysis. And the values are significant when compared with standard piperazine citrate (10 mg/ml). *Embelia ribes* fruit extract in combination with *Veronica anthelmintica* seed extract administered at 1g/kg exerted a considerable decrease in the fecal eggs per gram (EPG) count in goats suffering from mixed gastrointestinal nematode infections[10-11].

### *Antifungal activity*

Antifungal activity evaluation of *Embelia ribes* using standard in vitro antifungal susceptibility was studied by test method NCCLS (The national committee for clinical laboratory standard M27-A2 Protocol). NCCLS method revealed that methanol extract of *Embelia ribes* and embelin had lowest MIC50 range of 120 mg/L against *Candida albican* (MTCCno.183) and among four *Candida* species tested embelin had reported MIC50 values below 700 mg/L. Solvent ether extract, petroleum ether extract, methanol extract and embelin reported to have MIC50 in range of 300-700 mg/L against *Candida albica* (MTCCno.227) and *Candida parapsilosis* (MTCCno.1744)[12]. Petroleum ether extract shows lowest MIC50 range of 250 mg/L against *Candida parapsilosis* (MTCCno.1744) and 360 mg/L against *Candida laurintis* (MTCC no. 2898) while water extract required higher $MIC_{50}$ value for all species. Thus the result shows that the percentage growth was increased with the decrease in the concentration of the plant extracts, except for the water extract[13].

### *Antihyperlipidemic activity*

Ethanolic extract of *Embelia ribes* administered orally at a dose of 200 mg/kg for 20 days reported significant

($p$<0.01) decrease in blood glucose level, serum total cholesterol and triglycerides and increase in HDLcholesterol levels when compared to pathogenic diabetic rats which are induced by streptozotocin (at a dose of 40 mg/kg intravenously). The extract further lowered the liver and pancreas thiobarbituric acid-reactive substances (TBARS) values ($p$<0.01) when compared to TBARS values of liver and pancreas of the pathogenic diabetic rats[14].

### *Anticancer property*

Embelin is reported to decrease tumor size and inhibit the increase in activity of serum enzymes, viz. acid phosphatase, τ-glutamyl transferase, lactate dehydrogenase, aldose, etc in rats with experimental fibrosarcoma. Embelin interferes with carbohydrate and amino acid metabolism in tumor bearing animals. Embelin 50 mg/kg/day in combination with curcumin 100 mg/kg/day prevented the induction of hepatic hyper plastic nodules, body weight loss, increase in the levels of hepatic diagnostic markers, and hypoproteinemia induced by N-nitrosodiethylamine in adult male Wistar rats[15]. The osteoclasts are responsible for the osteolysis observed in bone metastases of the tumor. RANKL(receptor activator for nuclear factor κB ligand), a member of the TNF superfamily and an activator of the NF-kB signaling pathway, has emerged as a major mediator of bone loss, commonly associated with cancer and other chronic inflammatory diseases. Embelin has been reported to bind and inhibit XIAP protein and inhibit inflammatory pathways. The investigations whether embelin could inhibit osteoclastogenesis-associated bone loss induced by RANKL and by tumor cells in vitro reported that embelin suppressed the RANKL-induced differentiation of monocytes into osteoclasts. Thus, inhibitions of RANKL-induced NF-kB activation have great potential as therapeutic agents for osteoporosis and cancer-linked bone loss Nuclear factor-kappaB (NF-kappaB) regulates several genes associated with inflammation, proliferation, carcinogenesis, and apoptosis. It was found that embelin inhibited tumor necrosis factor (TNF) alpha-induced NF-kappaB activation. Both inducible and constitutive NF-kappaB activation were abrogated by embelin. In addition, NF-kappaB activated by diverse stimuli such as interleukin-1beta, lipopolysaccharide, phorbol myristate acetate, okadaic acid, hydrogen peroxide, and cigarette smoke condensate also was suppressed. Embelin inhibited sequentially the TNF alpha-induced activation of the inhibitory subunit of NF-kappaBalpha (IkappaBalpha) kinase, IkappaBalpha phosphorylation, IkappaBalpha degradation, and P65 phosphorylation and nuclear translocation. Embelin also suppressed NF-kappaB-dependent reporter gene transcription induced by TNFalpha, TNF receptor-1 (TNFR1), TNFR1-associated death domain protein, TNFR-associated factor-2, NFkappaB- inducing kinase, and IkappaBalpha 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. Together, the results indicate that embelin is a novel NF-kappaB blocker and potential suppressor of tumorigenesis. In assessing the drug-induced cell toxicity, a fibrosarcoma cell line was exposed in vitro to increasing concentrations of embelin and simultaneously inoculated with[3H]-thymidine. The cells were examined for incorporation of the labeled thymidine in DNA, lipid peroxide and gluthathione levels for regular intervals. A dose-dependent decrease in labeled thymidine uptake, lipid peroxide and glutathione levels was observed on embelin administration[16].

### *Anticonvulsant activity*

Embelin i.p (intraperitoneal) administration at doses 2.5, 5 and 10 mg/kg body weight significantly inhibited seizures induced by electroshock and pentylenetetrazole in a dose dependent manner and the activity was comparable to phenytoin and diazepam. C.N.S depressant activity was revealed by significant decrease in locomotion .The observation

suggests that embelin possess anticonvulsant activity against both grand mal and petit mal epilepsy[17].

### *Antioxidant property*

Aqueous extract of *Embelia ribes* administered orally at doses 100 mg/kg and 200 mg/kg body weight significantly decreased the levels of pancreatic superoxide dismutase, catalase and glutathione in the streptozotocin (at a dose of 40 mg/kg, intravenously as a single dose) induced diabetic rats. This antioxidant activity further protects the pancreatic β-cells against loss in streptozotocin induced diabetic rats[18]. Free radical scavenging activity of embelin was studied and found that embelin scavenges DPPH radical and inhibits hydroxyl radical induced lipid peroxidation and restores impaired Mn-superoxide dismutase in liver mitochondria of rat. Further studies on the kinetics and mechanism of reactions of embelin with hydroxyl, one electron oxidizing, organo-haloperoxyl and thiyl radicals using nano second pulse radiolysis technique suggests that embelin can act as a competitive antioxidant in physiological conditions[19].

### *Antibacterial activity*

*Embelia ribes* at a concentration of 500 mg/50ml reported 12 mm diameter of zone of inhibition when compared to the standard drug nitrofurazone which has 22 mm diameter of zone of inhibition against test organism *Bacillus subtilis*[20]. *Embelia ribes* did not produce any inhibitory/anti microbial activity against *Pseudomonos aeruginosa, Staphylococcus aureus* and *Escheresia coli*. Ethanolic extract of *Embelia ribes* seeds show mild antibacterial property against *Staphylococcus aureus, Enterobacter aerogenes, klebsiella pneumoniae*. Acetone fraction of *Embelia ribes* seeds show mild antibacterial property against *Enterobacter aerogenes, Klebsiella pnemoniae*, the standard used is Amoxicillin. Embelin, the principal constituent of the fruit of *Embelia ribes* is proved to have antibacterial property against both gram +ve and gram –ve bacteria, depending on the dose and bacteria test for the response alters. Even at very high doses (100 mg/disc) embelin did not exhibit any antibacterial property on *Escherichia coli* and *Klebsielia pneumoniae*[21]. At 25 mg/disc dose the zone of inhibition is not observed when experimented on *Streptococcus faegalis, Salmonella typhi* and *Vibrio cholarae* but, at high doses (50 mg/disc and 100 mg/disc) mild antibacterial property is observed on these organisms. At 100 mg/disc dose embelin reported more diameter of zone of inhibition than standard (kanamycin) used at 39 mg/disc when tested against *Staphylococcus aureus, Shigella flexneri and Shigella sonnei*. Same kind of response greater than standard (ciprofloxacin 5 mg/disc) is observed in *Pseudomonas aeruginosa* when embelin is used at high dose of 100 mg/disc considerable antibacterial property is shown against test organisms like *Streptococcus pyogenes, Salmonella typhi, Shigella boydii, Proteus mirabilis*. And very mild antibacterial activity has been reported. When tested against *Streptococcus faecalis* and *Vibrio cholera*[22].

### *Effect on CNS*

Embelia ribes has shown a pronounced effect on CNS with anticonvulsant and adaptogenic activities[23].

### *Antidiabetic activity*

Aqueous extract of *Embelia ribes* fruits at doses 100 and 200 mg/kg orally fed for forty days produced significant ($p$<0.01) decrease in heart rate, systolic blood pressure, blood glucose, blood glycosylated haemoglobin, serum lactate dehydrogenase, creatine kinase and increase in blood glutathione levels in streptozotocin (administered at a dose of 40 mg/kg, intravenously single dose) induced diabetic rats. Gliclazide is used as standard in this study[24].

### *α-amylase inhibitor activity*

Ethanolic extract of the *Embelia ribes* seeds has shown pronounced % of α-amylase inhibitory activity in-vitro i.e. 59.3% inhibition is observed when tested at concentration of 1mg / ml of the reaction mixture where as the active reference

standard (α-amylase inhibitor from *Phaseolus vulgaris*) has shown 59.4% inhibition. α – amylase inhibitory activity of any plant material can be proven as an excellent tool for the treatment of obesity and diabetes[25].

### *Mollusicidal activity*

Fruit powder of *Embelia ribes* in combination with *Azadirachta indica* and *Cedrus deodara* oil with synergists MGK-264, piperonyl butoxide (PB) in binary and tertiary combinations were used against the *Lymnea acuminata*. It was observed that the toxic effects of these mixtures were time and dose-dependent. The binary and tertiary mixtures of plant-derived mollusicides with synergists were more toxic with respect to the single treatment of the plant-dervied molluscides62. The order of toxicity of various tertiary combinations against *Lymnaea acuminata* was *Lawsonia inermis* seed + *Cedrus deodara* + *Embelia ribes* > *Lawsonia inermis* seed + *Azadirachta indica* + *Embelia ribes* > *Lawsonia inermis* seed + *Polianthes tuberosa* + *Embelia ribes* > *Lawsonia inermis* seed + *Allium sativum* + *Embelia ribes*. The toxicity of tertiary combnination (1:1:1) of *Lawsonia inermis* seed powder with *Cedrus deodora* oil and *Embelia ribes* fruit powder against *Lymnaea acuminata* was highest (24 hr LC50 14.80 mg/l) when compared to other combinations in this study[26].

### *Cardio protective effect*

Aqueous extract of *Embelia ribes* (100 mg/kg) pre-treatment orally for 40 days in isopretenolol (5.25 and 8.5 mg/kg: subcutaneously, for two consecutive days) induced acute myocardial infraction in albino rats significantly ($p$<0.01) decreased the heart rate, systemic blood pressure, increased levels of serum lactate dehydeogenase, serum creatinine kinase and myocardial lipid peroxides and significantly increased the myocardial endogenous antioxidants (glutathione, superoxide dismutase and catalase) levels. These results are supported by the histopathological examination of rat's heart sections[27-28].

## II. CONCLUSION

India has a great wealth of various naturally occurring plant drugs which have great potential pharmacological activities. *Embelia ribes* is one amongst them. *Embelia ribes* has been proven to have great pharmacological potential with a great utility and usage as folklore medicine. Many activities are yet to be explored to determine the complete pharmacological profile of the plant like anthelmintic, amylase inhibitory activity, antibacterial activity, antioxidant activity, anti diabetic activity, anticonvulsant activity, anti cancer activity, anti hyperlipidemic activity and anti fungal activity etc.

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**Cite this article as :**

Akshay R. Yadav, Dr. Shrinivas K. Mohite , "Phytochemical and Pharmacological Review of Embelia ribes", International Journal of Scientific Research in Chemistry (IJSRCH), ISSN : 2456-8457, Volume 5 Issue 5, pp. 57-62, September-October 2020.
URL : http://ijsrch.com/IJSRCH20566