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## IMPORTANCE OF *EMBELIA RIBES*: AN UPDATE

Bharat Lal and Neeraj Mishra\*

Department of Pharmaceutics, ISF College of Pharmacy, Ferozepur Road, Ghal Kalan, Moga, Punjab, India

### Keywords:

*Embelia ribes*, Antibacterial, Antioxidant, Antifertility, Vidangadi Churna, Vidanga taila

### Correspondence to Author:

**Dr. Neeraj Mishra**

Department of Pharmaceutics, ISF College of Pharmacy, Ferozepur Road, Ghal Kalan, Moga, and Punjab, India


E-mail: neerajdops@rediffmail.com

**ABSTRACT:** *Embelia ribes* Burm F. is large scandent shrub, disturbed throughout India and belongs to the family Myrsinaceae. It is commonly known as false black pepper or Vidanga. *E. ribes* grows in semi-evergreen and deciduous forests at an altitude of 1,500m found in central and lower Himalayas, Arunachal Pradesh, Assam, Bengal, Orissa, Andhra Pradesh and Madhya Pradesh throughout India. *Embelia ribes* has been proven to have great pharmacological potential with a great utility and usage as folklore medicine. The root, berries and leaves of *Embelia ribes* is used in herbal formulas. It is used as antibacterial, antifertility activities, antiprotozoal, abdominal disorders, lung diseases, constipation, indigestion, fungus infections, mouth ulcer, sore throat, pneumonia, heart disease and obesity, analgesic, anti-inflammatory, antioxidant and formulations of *Embelia ribes* are Ardrakakhandavaleha, Eranda paka, Krimighna kashaya churna, Vidangadi churna, Taramandura guda, Guduchi lauha, Abhayarishta, Kumari asava, Manibhadra yoga, Pippalyasava, Kaishore guggulu, Vyoshadi guggulu, Saptavishantika guggulu, Eladi ghrita, Kasisadi ghrita, Chandraprabha vati, Wdangadi lauha, Vidanga taila.

**INTRODUCTION:** *Embelia ribes* Burm F a medicinal woody climber belongs to the Myrsinaceae family. It is also commonly known as false black pepper or vidanga. *E. ribes* is one of the 32 medicinal plant species identified by the Medicinal Board, Govt. of India, New Delhi, as being important for large-scale cultivation because of its commercial use<sup>1</sup>. *E. ribes* grows in semi-evergreen and deciduous forests at an altitude of 1,500m found in central and lower Himalayas, Arunachal Pradesh, Assam, Bengal, Orissa, Andhra Pradesh and Madhya Pradesh<sup>2</sup> throughout India.

It is considered to be vulnerable due to excessive harvesting; because of it is used in about 75 Ayurvedic preparations. Natural regeneration of *E. ribes* is poor due to overharvesting and exploitation, more fragmented populations resulting in inbreeding, development of abortive embryos, and the slow germination of fertile seeds that are small in size<sup>3</sup>. On the other hand, artificial regeneration of this species is difficult due to its poor seed viability, low rate of germination, and poor rooting from stem cuttings<sup>4</sup>.

The fruits, leaves and roots are used to cure various diseases Embelin reported as aqueous extract of the fruits showed antibacterial<sup>5</sup> and antifertility<sup>6</sup> activities. It has the anti-bacterial and antiprotozoal properties<sup>7</sup>. Also in abdominal disorders, lung diseases, constipation, indigestion, fungus infections, mouth ulcer, sore throat, pneumonia, heart disease and obesity<sup>8</sup>, antifertility<sup>9</sup>, analgesic, anti-inflammatory, antioxidant<sup>10</sup>.

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As embelia possess non-steroidal & non hormonal moiety will have a hope to nullify the health hazardous system & eliminates unwanted physiological symptoms & expectation of new molecule & to prove its hormonal activity is still under controversy. The main active component is Embelin, chemically 2, 5-dihydroxy-3-undecyl-1, 4- benzoquinone. Embelin is occur in golden yellow needles and is insoluble in water but soluble in alcohol, chloroform and benzene. Other components are christembine, qesrcitol, vilangin and resinoid <sup>11</sup>. *Embelia ribes* have a long history of use in ayurvedic system of medicine in various forms like churna, asava, aristha, lauha and taila. Notes on the drug under the names of Birang-I-kabuli and Biranj-I-kabuli were found in Arabian writing. Dr. Harris had directed attention to the value of this drug as a remedy for tapeworm. He stated that he had administered it for several years with good results to natives of India and Europe.

### Taxonomical classification

Kingdom	:	Plantae
Phylum	:	Angiosperms
Order	:	Ericales
Family	:	Myrsinaceae
Genus	:	Embelia
Species	:	ribes

### Synonyms of *Embelia ribes*:

Sanskrit	:	Jantughna, Krmighna, Vella, Krmihara, Krmiripu
Assamese	:	Vidang
Bengali	:	Vidang
Gujrati	:	Vavding, Vavading, Vayavadang
Hindi	:	Vayavidanga, Bhabhiranga, Baberang
Kannada	:	Vayuvilanga, Vayuvidanga
Kashmiri	:	Babading

Malayalam	:	Vizhalari, Vizalari
Marathi	:	Vavading, Vavding
Oriya	:	Bidanga, Vidanga
Punjabi	:	Babrung, Vavaring
Tamil	:	Vayuvilangam,
Vayuvidangam	:	
Telugu	:	Vayuvidangalu
Urdu	:	Baobarang, Babrang

**Habitat:** These climbers are found in the hilly parts of India from the central and lower Himalayas down. It is commonly seen in places up to the height of 1500 m, it is generally seen in areas of eastern India to Ceylon (Sri Lanka) and Singapore. & Ranges from India to Southern China, south to Indonesia, East Africa & identified on Malayan estates etc

**Description:** A straggling shrub, almost a climber (**Figure 1**). The roots are brownish gray, with hairy reddish rootlets. The stem is whitish gray, studded with lenticels, with a mature girth of 45-72 cm. Leaves are coriaceous, elliptic. Lancelate 6-14cm long and 2-4cm broad, alternating, acuminate entire, perfectly glabrous and petiole 1.0 cm -0.8 cm margined.



FIGURE 1: *EMBELIA RIBE* PLANT

Flowers pentamerous, minute, white or yellow, fruit a berry, 2, 4-4 mm obovate to sub globular tipped with style, smooth, succulent, in dry condition with wrinkles with loss of calyx (**Figure 2**).



**FIGURE 2: EMBELIA RIBE FRUITS**

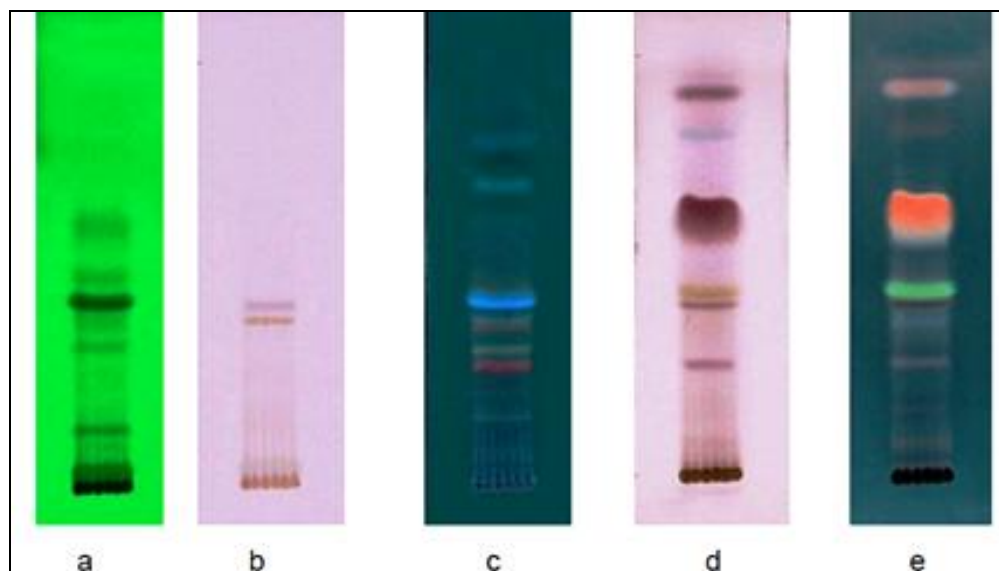
The reddish seed, enclosed in a brittle pericarp, is covered by a thin membrane; when this is taken off; the seed is seen covered with light spots which disappear after immersion in water. The seed is horny, depressed at the base and has a ruminated endosperm. Taste, aromatic and astringent, with a slightly pungency, owing to a resinous substance present in them<sup>12</sup>. The Ayurvedic properties of *Embelia ribes* is discussed in **Table 1**.

**TABLE 1: AYURVEDIC PROPERTIES OF EMBELIA RIBES<sup>14</sup>**

GUNA (Quality)	Laghu, Ruksha, Tikshan
RASA (Taste)	Katu, Kashay
VIPAK (Metabolism)	Katu
VIRYA (Potency)	Ushan
PRABHAV (Impact)	Krimighan

**TLC of *Embelia ribes*:** The methanol and chloroform extracts of fruits of *E. ribes* were prepared. A large number of solvent systems were tried to achieve a good resolution. Finally, the solvent system toluene: acetone: acetic acid (9: 1: 0.5) (**Figure 3**) was selected for methanol extract.

The band at Rf 0.13 was observed only under 254 nm. The band at Rf 0.27 appeared orange under 366 nm and violet under 366 nm after spray with anisaldehyde-sulphuric acid reagent. A light-green band at Rf 0.32 was seen only under 366 nm. An orange band was observed at Rf 0.60 under 366 nm and violet under visible light after derivatization<sup>13</sup>.



**FIGURE 3: TLC FINGERPRINT PROFILE OF FRUITS OF *E. RIBES* UNDER 254 nm (a), under visible light before spray (b), under 366 nm after spray with anisaldehyde-sulphuric acid reagent (c), under visible light after spray, (d) and under 366 nm after spray**

#### **Organoleptic evaluation of *Embelia ribes* fruits:**

The macroscopic character was useful in quick identification of plant material and also serves as an important standardization parameter. The *Embelia ribes* fruits are blackish brown colored with 2.4-

4mm size, sub globular shape, distinct odour, astringent taste and wrinkled textured. Organoleptic evaluation of *Embelia ribes* is discussed in **Table 2**.

**TABLE 2: ORGANOLEPTIC EVALUATION OF *EMBELIA RIBES* FRUITS**<sup>15</sup>

Size	2.4-4 mm
Color	Blackish brown
Shape	Sub globular
Odour	Distinct
Texture	Wrinkled
Taste	Astringent

The determination of physicochemical parameters is important in determination of adulterants and improper handling of drugs. **Table 3** shows the results of various physicochemical parameters of powdered drug carried out using standard methods.

**TABLE 3: PHYSICOCHEMICAL PARAMETERS OF *EMBELIA RIBES* FRUIT POWDER**<sup>15</sup>

Physicochemical parameters	Mean (mg/gm)	SD (Standard Deviation)	SE (Standard Error)	%RSD (Relative Standard Deviation)
Total ash	48.6	0.07	0.085	0.144
Water soluble ash	13.88	0.151	0.13	1.09
Acid insoluble ash	12.49	0.546	0.355	4.37
Water extractable matter	91.45	0.94	1.122	1.02
Ethanol Extractable matter	111.15	1.434	1.432	1.29
Loss on drying (100-105 <sup>0</sup> C)	25.3	0.0036	0.004	1.42
Swelling Index	2.95	0.0057	0.0081	0.195
Foaming Index	<100	0	0	0

Ash values used to determine quality and purity of crude drugs. It indicates the presence of various impurities like carbonate, oxalate and silicate. The acid insoluble ash consist mainly silica and indicate contamination with earthy material. The water soluble ash is used to estimate the amount of inorganic elements present in drugs.

For preliminary phytochemical screening, the aqueous and alcoholic extracts were subjected to qualitative chemical test to determine the presence of various phytoconstituents like alkaloids, carbohydrate, saponins, phenolic compounds and tannins, proteins, oil and fats and mucilage. The qualitative photochemical screening of *Embelia ribes* fruit powder is discussed in **Table 4**.

**TABLE 4: PHYTOCHEMICAL SCREENING OF *EMBELIA RIBES***<sup>15</sup>

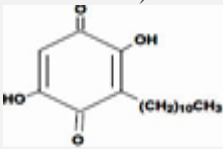
Test For	Observation
Reducing sugars	+ve
Non-reducing polysaccharides	-ve
Gums	-ve
Mucilage	+ve
Proteins	+ve

Amino acids	+ve
Fats and oils	+ve
Steroids	-ve
Glycosides	-ve
Saponin	+ve
Flavonoids	-ve
Alkaloids	+ve
Tannins	+ve
Volatile oil	-ve

**Phytochemical Constituents of *Embelia ribes*:** *Embelia ribes* berries contain several chemical constituents like embelin, volatile oil, fixed oil, resin, tannin, christembine (alkaloid), phenolic acids like caffeic acid, vanillic acid, chlorogenic acid, cinnamic acid, o-cumaric acid. 4.33% of the embelin content is observed in the berries of *Embelia ribes* Burm F.

Plant also contain contains potassium embelate, 2, 5-dihydroxy, 3-undecyl-1,4-benzoquinone, embelin, quercitol, fatty ingredients, vilangin, which are shown in the **Table 5**.

**TABLE 5: PHYTOCHEMICAL CONSTITUENTS OF EMBELIA RIBES**<sup>14, 16, 17</sup>

S. No.	Active ingredients	Character
1.	Embelin (2,5-dihydroxy-3-undecyl-2,5-cyclohexadiene-1,4-dione) 	(Golden yellow needle like insoluble in water, soluble in alcohol/chloroform /benzene)dyes with silk & wool with alcoholic solution.
2.	Christembine	Crystalline compounds of embolic acid with soda, potash and ammonia
3.	Embelin dimer	-
4.	Embelin disalts	-
5.	Embelinol	-
6.	Embeliaribyl ester	-
7.	Embeliol	-
8.	Gomphilactone derivative	-
9.	Homoembelin	-
10.	Homorapanone	-
11.	Monopotassium embelate	-
12.	New compounds	-
13.	A nitrogen containing alkyl 1,4-benzoquinone	-
14.	An unusual nitrogen-containing 3-alkyl-1,4-benzoquinone derivative	-
15.	N-(3-carboxylpropyl)-5-amino-2-hydroxy-	-

	3-tridecyl-1,4-benzoquinone	
16.	Quarvital-1%	-
17.	Quercitol,	-
18.	Rapanone	-
19.	Resins	-
20.	Oleic	-
21.	linoleum acid	-
22.	Sitosterol	-
23.	Stable oil	-
24.	Tannins	-
25.	Daucosterol	-
26.	Vidangin	colorless & crystalline k
27.	Vilangine,	-

**Reported extracts of *Embelia ribes* and its use:**

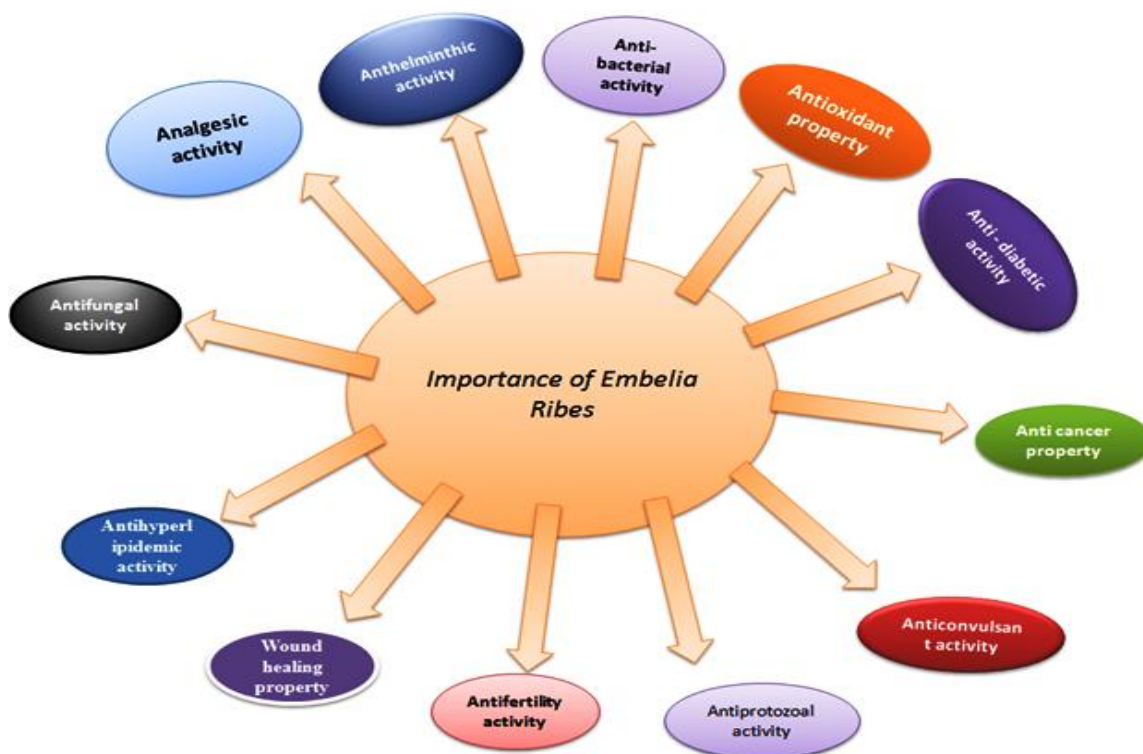
Extraction, as the term is used pharmaceutically, involves the separation of medicinally active portions of plant or animal tissues from the inactive or inert components by using selective solvents in standard extraction procedures. The products so obtained from plants are relatively impure liquids, semisolids or powders intended only for oral or external use. General methods of extraction are maceration, infusion, digestion, decoction, percolation, hot continuous extraction (Soxhlet), aqueous alcoholic extraction by fermentation, counter current extraction, ultrasound extraction (sonication). For *Embelia ribes* used hot continuous extraction and we get various activity in different solvent system are shown in **Table 6**.

**TABLE 6: REPORTED EXTRACTS OF *EMBELIA RIBES***<sup>14, 18, 19, 42</sup>

S. No.	Extracts	Uses	Dosology
1	Methanolic extract	Acetylcholinesterase inhibitory activity	Root
2	Aqueous- Ethanol extract	Anthelmintic	(fruits-berries)
3	Methanol extract	Prevent pregnancy 75%	(fruits-berries)
4	Ethanol extract	Hepatoprotective, Antifertility,	(fruits-berries)
		Uterine weight levels	
5	Butanol extract	Antifertility	-
	Benzene extract	Antifertility 51%	-
6	Benzene extract	Antifertility 51%	-
	n-Hexane extract	Anthelmintic	-
7	Petroleum ether extract	Tapeworm, (but not round/hook) Prevent pregnancy 75%	-
8	Aqueous- Ethanol extract	No Antifertility, 37% Anthelmintic	-
9	Aqueous- Ethanol extract Fresh juice	No Antifertility, 37% Anthelmintic Cooling, diuretic and laxative	-
10	Fresh juice	Cooling, diuretic and laxative	-
	Butanol extract	No Antifertility, 37% Anthelmintic	-
11	Butanol extract	Insecticidal activity	-
	Ethyl acetate extract		-
12	Hexane extract	Antifertility	-
13	Fresh juice	Cooling, diuretic and laxative	Leaves/fruit/root
14	Powdered fruit	Antifertility	Fruit
15	Milk extract	Digestive & upper respiratory infection	Leaves/fruit/root
16	Aqueous extract	Hypolipodemic Anthelmintic	Leaves

**Pharmacological activity of *Embelia ribes*:** *Embelia ribes* Burm F. is having antibacterial, antifertility, antiprotozoal, abdominal disorders, lung diseases, constipation, indigestion, fungus infections, mouth ulcer, sore throat, pneumonia,

heart disease and obesity, analgesic, anti-inflammatory, antioxidant, anthelmintic, anti-diabetic, anticonvulsant, anticancer, anti-hyperlipidemic, wound healing and molluscicidal activity which are depicted in **Figure 4**.

**FIGURE 4: PHARMACOLOGICAL ACTIVITY OF *EMBELIA RIBES***

1. **Analgesic activity:** Embelin has non-narcotic orally effective analgesic property which acts centrally. It has a different central site of action and is not antagonized by naloxone. It is more acceptable than morphine due to high oral efficacy, high therapeutic index and absence of abstinence syndrome<sup>51</sup>. Naloxone is known to antagonize mu ( $\mu$ )-receptor mediated activity associated with narcotic analgesics<sup>50</sup>.

The mixed mu ( $\mu$ ) and kappa ( $\kappa$ ) agonists (such as EKC and bremazocine) and pure kappa( $\kappa$ ) agonist like U50, 488H caused significant displacement of potassium embelate. This indicates that potassium embelate has high affinity for mu ( $\mu$ ) and kappa ( $\kappa$ ) binding sites which may be involved in the modulation of potassium embelate induced analgesia in the rat brain<sup>20</sup>.

2. **Anthelmintic 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)<sup>21</sup>. *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<sup>22</sup>.

3. **Anti-bacterial 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*. *Embelia ribes* did not produce any inhibitory /anti-microbial activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escheresia coli*<sup>23</sup>.

Ethanol extract of *Embelia ribes* seeds show mild antibacterial property against *Staphylococcus aureus*, *Enterobacter aerogenes* and *Klebsiella pneumoniae*. Acetone fraction of *Embelia ribes* seeds show mild antibacterial property against *Enterobacter aerogenes*,

*Klebsiella pneumoniae* and the standard used is Amoxicillin<sup>22</sup>. 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 *Klebsiella pneumoniae*. 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*<sup>24</sup>.

4. **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  $\beta$ -cells against loss in streptozotocin induced diabetic rats<sup>25</sup>.

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<sup>26</sup>. In experimental diabetes, *E. ribes* displays its antioxidant potential and protection of pancreatic cells. Total glutathione activity was reduced by 69.13% in pancreatic tissue of diabetic rats as compared to normal control animals. The levels were significantly ( $P < 0.01$ ) increased with ethanolic extract of *E. ribes* (in a dose of 200 mg/kg)<sup>27</sup>.

5. **Anti - diabetic 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.

Administration of ethanolic extract of *Embelia ribes* berries orally for 6 weeks at a dose of 100 mg/kg and 200 mg/kg significantly ( $p < 0.01$ ) reduced the levels of blood glucose, heart rate (HR) and systolic blood pressure (SBP) in streptozotocin induced diabetic Wistar albino rats. Gliclazide at a dose 25 mg/day is the standard used in this study<sup>28</sup>. Further studies revealed that ethanolic extract of *Embelia ribes* fruits significantly ( $p < 0.01$ ) reduced the pancreatic thiobarbituric acid-reactive substances (TBARS) in pancreatic tissue of diabetic rats<sup>27</sup>.

6. **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<sup>29</sup>.

7. **Anti-cancer activity:** Embelin is reported to decrease tumor size and inhibit the increase in activity of serum enzymes, viz. acid phosphatase,  $\tau$ -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<sup>30</sup>. The osteoclasts are responsible for the osteolysis observed in bone metastases of the tumor. RANKL (receptor activator for nuclear factor  $\kappa$ B ligand), a member of the TNF superfamily 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.

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- $\kappa$ B activation have great potential as therapeutic agents for osteoporosis and cancer -linked bone loss<sup>31</sup>.

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-kappa B activation. Both inducible and constitutive NF-kappa B activation were abolished by embelin. In addition, NF-kappa B 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 TNFalpha-induced activation of the inhibitory subunit of NF-kappa B (Ikappa B) kinase,



Ikappa Balpha phosphorylation, Ikappa Balpha degradation, and P65 phosphorylation and nuclear translocation. Embelin also suppressed NF-kappa B-dependent reporter gene transcription induced by TNF alpha, TNF receptor-1 (TNFR1), TNFR1-associated death domain protein, TNFR-associated factor-2, NF-kappa B-inducing kinase, and Ikappa Balpha 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<sup>32</sup>.

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 glutathione levels for regular intervals. A dose-dependent decrease in labeled thymidine uptake, lipid peroxide and glutathione levels were observed on embelin administration<sup>33</sup>.

8. **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 HDL-cholesterol 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<sup>18</sup>.
9. **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 MIC<sub>50</sub> range of 120 mg/L against *Candida albican* (MTCC no. 183) and among four *Candida* species tested embelin had reported MIC<sub>50</sub> values below 700 mg/L. Solvent ether extract, petroleum ether extract, methanol extract and embelin reported to have MIC<sub>50</sub> in range of 300-700 mg/L against *Candida albica* (MTCCno.227) and *Candida parapsilosis* (MTCCno.1744).

Petroleum ether extract shows lowest MIC<sub>50</sub> range of 250 mg/L against *Candida parapsilosis* (MTCC no. 1744) and 360 mg/L against *Candida laurintis* (MTCC no. 2898) while water extract required higher MIC<sub>50</sub> 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<sup>34</sup>.

10. **Antihyperhomocysteinemic activity:** Anti-hyperhomocysteinemic activity of *Embelia ribes* was evaluated in hyperhomo-cysteinemia induced adult male Wistar rats. Hyperhomocysteinemia was induced by methionine treatment (1 g/kg p.o) for 30 days. Administration of aqueous extract of *Embelia ribes* (100 and 200 mg/kg p.o) for 30 days to hyperhomocysteinemic rats significantly ( $p < 0.01$ ) decreased the levels of homocysteine, LDH, total cholesterol, triglycerides, LDL-C and VDL-C and increased the HDL-C levels in serum. The results are comparable to the standard anti-hyperhomocysteinemic drug folic acid<sup>35</sup>.
11. **Molluscicidal 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 molluscicides with synergists were more toxic with respect to the single treatment of the plant-derived molluscicides<sup>36</sup>. 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 combination (1:1:1) of *Lawsonia inermis* seed powder with *Cedrus deodora* oil and *Embelia ribes* fruit powder against *Lymnaea acuminata* was highest (24 hr LC<sub>50</sub> 14.80 mg/l) when compared to other combinations in this study<sup>37</sup>.

12. **Wound healing property:** Ethanolic extract of *Embelia ribes* (30 mg/ml) and embelin both reported significant wound healing activity. In embelin treated groups (4 mg/ml of 0.2% sodium alginate gel), epithelialization of the incision wound was faster with a high rate of wound contraction. The tensile strength of the incision wound was significantly increased than the ethanol extract. Also in deed space model the weight of the granulation was increased indicating increase in collagenation. The histological examination of the granulation tissue of embelin treated group reported increased cross-linking of collagen fibres and absence of monocytes. The results are comparatively evaluated with standard skin ointment framycetin<sup>38</sup>.

13. **Antifertility activity:** Embelin extracted from *Embelia ribes* Burm. Berries altered the testicular histology and glycogen, gametogenic counts and accessory sex gland fructose at the dose levels 0.3, 0.4 and 0.5mg/kg body weight administered subcutaneously for 35 days. The compound is suggested to possess anti-androgenic activity. An oral herbal contraceptive would allow couples control their fertility without consulting a health worker, which in turn would likely markedly increase the number of couples practicing family planning.

Other advantages of such a contraceptive would include the familiarity rural people have with herbal medicines, the fewer side effects associated with herbal preparations, their ready availability from local sources, and protection of privacy. There are many references to plants in India with antifertility properties.

Since 1966, the Indian Council of medical Research (ICMR) has been conducting research to identify an herbal contraceptive, as have other organization. Plants that have exhibited antifertility activity in clinical trials include *Hibiscus roasinensis* (benzene extract of the flower petals suppresses implantation); Rudrapusphaka (extract of the flower petals prevents pregnancy); *Embelia ribes* (pregnancy prevention); *Daucus carota*, *Butea monosperma*, and anti-implantation effect); and *Mentha arvensis* (leaves have anti-implantation effect).

Effect of embelia on oestrous cycle, plasma levels of progesterone and oestradiol, and in vitro production of oestradiol and progesterone by mixed ovarian cells was studied. Forty adult (4 months old), regularly cycling female Spargur-rats each. Groups I and II (controls) were given 1 ml/kg body weight of physiological saline or com oil (vehicle). Groups III and IV animals, and there was significant depression in plasma oestrediol ( $p < 0.05$ ) 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.

Oral administration of embelin (75 mg/kg per day, daily for 15 and 30 days) to male rats caused significant elevation in the uptake of D-glucose, L-alanine, L-leucine and calcium in small intestinal segments. Embelin also produced significant increases in intestinal brush border membrane-associated enzymes (sucrose, lactase, maltase, alkaline phosphatase and leucine amino-peptidase) in both intestinal homogenates and partially purified brush border membrane preparations.

Significant increase was also noted for microsomal glucose-6-phosphatase and cytosolic lactate dehydrogenase. Increase in brush border membrane-associated total lipids, phospholipids, cholesterol, triacylglycerol, unestrified fatty acids and ganglioside sialic

acid were seen but not in the cholesterol/phospholipids molar ratio. All these changes returned to control or near control levels following withdrawal of the drug<sup>9</sup>.

14. **Antihyperglycemic activity:** Diabetic mellitus has been treated orally with herbal remedies based on folk medicine *Embelia ribes burm* (Myrsinaceae), known commonly as vidanga, was used in Ayurveda for its antheminitic activity. Ayurveda describes vidanga as pungent. Causes increase in digestive fire and cures flatulence and colic. A single study reported the antihyperglycemic activity of decoction of *E. ribes* in glucose-induced the lipid-lowering and antioxidant potential of ethanolic extract of *E. ribes* Burm was investigated in streptozotocin (40 mg/kg, IV, single injection) - induced diabetes in rats.

Twenty days of orally feeding the extract (200mg/kg) to diabetic rats 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 TBARS diabetic rats. The results of test drug were comparable to gliclazide (25 mg/kg, orally), a standard antihyperglycemic agent. This is the first pilot study to provide biochemical evidence of potential of *E. ribes* in diabetic dyslipidemia<sup>28</sup>.

15. **Antinematodal activity:** The antinematodal activity of a mixed prescription of *Veronia anthemintica* seed (Kali zeeri) and *Embelia ribes* fruit (Babrang) was evaluated in goats. The EPG (Egg per gram) counts were made in the faeces before and on the 3rd, 10th and 15th days of the treatment with the powder in 0.5, 1 and 2 g/kg body weight doses and with the water and methanol extracts equivalent to 2g/kg of the original powder. The evaluation of data on 15th day of the administration showed that 2 extract and 0.01 g/kg of morantel tartrate are equally effective and safe in treating

natural gastrointestinal nematode of the local goats<sup>39</sup>.

16. **Antiproliferative activity:** Biological activities of the 1, 4-benzoquinone derivatives 5-O-ethylumbelliferone (1) and 5-O-methylumbelliferone (2) were investigated. Both of them showed antiproliferative activity against a panel of human tumor cell lines upon comparison to normal marsupial kidney cells (Ptk2). They arrested HL-60 cells in the G (0)/G(1) phase of the cell cycle in dose- and time-dependent manner. In HeLa cells, exposure to 100 microM of 1 or 2 for 6h induced a complete disassembly of the microtubule network and an increased number of cells blocked in mitotic stages. Treatment with 10 microM of 1 and 2 for 24h induced apoptosis in HL-60 cells. This evidence suggest that both 1 and 2 are promising novel antimitotic and anticancer molecules targeting microtubular proteins<sup>40</sup>.

17. **Antispermatozoic activity:** *Embelia*, the active principle of the seeds of *Embelia ribes* Burm, has been isolated and the purity established. Daily subcutaneous administration of the 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.

Light and scanning electron microscopy showed that both *in vivo* and *in vitro* treatment with the drug causes profound morphological changes in spermatozoal head, a) decapitation of the spermatozoal head, b) discontinuity of the outer membranous sheath in the mid-piece and the tail region, and c) alteration in the shape of the cytoplasmic droplet in the tail. Embelin from *Embelia ribes* significantly reduced the sperm count and motility and also the weight of the testes, in albino rats<sup>41</sup>.

**18. Antitumor and anti-inflammatory activities:**

Embelin, a plant-based benzoquinone derivative, has been found to exhibit significant antitumor activity in methylcholanthrene-induced fibrosarcoma in albino rats besides enhancing their survival time. The drug also has an appreciable action on pain and inflammation. The changes in DNA, RNA and RNA and protein levels in various organs in the tumor-treated animals were also studied<sup>10</sup>.

**19. Chemotherapeutic activity:** Identifying the active chemical ingredients of ancient medicines and the molecular targets of those ingredients is an attractive therapeutic objective. Embelin, identified primarily from the *Embelia ribes* plant, is one such compound shown to exhibit chemopreventive, anti-inflammatory, and apoptotic activities through an unknown mechanism. Because nuclear factor-kappaB (NF-kappaB) regulates several genes associated with apoptosis, postulated the embelin might mediate its activity through modulation of NF-kappaB activation.

Found that embelin inhibited tumor necrosis factor (TNF) alpha-induced NF-kappaB activation was abrogated by embelin. In addition, NF-kappaB activated by diverse stimuli such as interleukin-1 beta, lipopolysaccharide, phorbol myristate acetate, okadaic acid, hydrogen peroxide, and cigarette smoke condensate also was suppressed. Found that embelin inhibited sequentially the TNF alpha-induced activation of the inhibited subunit of NF-kappaB alpha (IkappaBalpha) kinase, IkappaBalpha phosphorylation, IkappaBalpha degradation, and p65 phosphorylation and nuclear translocation. Embelia also suppressed NF-kappaB-dependent reporter gene transcription induced by TNFalpha, TNF receptor-1 (TNFR1), TNFR1-associated death domain protein, TNFR-associated factor-2, NF-kappaB-inducing kinase, and IkappaBalpha kinase but not by p65.

Furthermore, found that 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<sup>30</sup>.

**20. Contraceptive activity:** In a search for traditionally medicinal plants having contraceptive efficacy, plants were identified and collected throughout India, generally by purchase from seller of Ayurvedic remedies. The plants were air dried, cut and processed using different organic solvents. The contraceptive properties of the plants were studied in rats, mice, and hamster's. Doses of 100-200 mg/kg of 137 plants was given orally to 5-6 animals for each plant. 27 appeared promising enough for further testing in which 2-3 extracts of each plants were administered to adult rats. The contraceptive action of 14 plants was confirmed.

*Embelia ribes* Burm and *Artabotrya odoratissimus* Linn were found to have interesting biologic properties but string toxic effects. *P. tuberosa* had strong estrogenic and progestational effects but was not toxic in a dose of 500 mg/kg for 30 days in adult rats<sup>9</sup>. The combination of some plants products i.e. *Embelia ribes*, Borax and *Piper longum* has been found to be safe and effective as a female contraceptive and the results of phase-I clinical trials are encouraging. Research work is going on reference to hormonal contraceptive, immuno-contraceptives, antiprogestins, etc.

**21. Inhibitory activity:** Seventy-six plant extracts including methanolic and successive water extracts from 37 India medicinal plants were investigated for acetylcholinesterase (AChE) inhibitory activity (*in vitro*). Results indicated that methanolic extracts to be more active than water extracts. The potent AChE inhibiting methanolic plant extracts included *Withania somnifera* (root), *Semecarpus anacardium* (stem bark), *Embelia ribes* (root), *Tinospora cordifoila* (stem), *Ficus religiosa* (stem bark) and *Nardostachys jatamansi* (rhizome). The IC<sub>50</sub> values of *Embelia ribes* (Root) obtained for the extract was 23.04 mug/ml<sup>42</sup>.

**Toxicology profile:** Administration of embelin in female cyclic rats at 120 mg/kg body weight has reported no change in weight of liver, kidney and spleen but the net weight of adrenals increased considerably. Several pathological changes are observed by administration of embelin for 6 weeks. Adrenals showed hypertrophy, but spleen histological features remained unchanged<sup>20</sup>. Anatomical evidence of ganglion cells degeneration in retinae of chicks administered orally with 1.25 g/kg dose of *Embelia ribes* has been reported. But at low dose of 0.25 g/kg visual deficit and retinotoxicity are not observed<sup>45</sup>.

Potassium embelate toxicology studies reported an ED<sub>50</sub> of 8.2 mg/kg. A very high dose of 2 g/kg administered in rats and mice has reported no mortality. The administration of potassium embelate for 10 weeks in mice and 24 weeks in monkeys did not produce significant toxicity symptoms. There is no effect on fertility. The drug and the F1 animals revealed no change in their reproductive capacities. Necropsy examination, histopathological studies indicated that there is no effect on major organs proving it to be a safer drug. The naturally occurring anthelmintics, *E. ribes* have been reported to possibly cause optic atrophy among the Ethiopian population. In this study, we found retinal pathology and defects in visual behavior in chicks treated with *E. ribes* or embelin, a crystalline extract of *E. ribes*<sup>45</sup>.

An Ayurvedic contraceptive-pippalyadi vati, containing equal parts of powdered seeds or fruit berries of *Embelia ribes*, fruit of *Piper longum* and borax powder was fed orally to two groups of pregnant rats : 2.5 times to one and five times to the other, the recommended dose for humans. The fetuses of mothers fed with pippalyadi had low birth weights and were smaller in length. The Development defects of soft tissues and of herniation of the intestines into the umbilical cord in foetuses of mothers who were administered pippalyadi. The control and the gum acacia groups did not show such herniation<sup>49</sup>.

Pippalyadi yoga or pippalyadi vati is an Ayurvedic contraceptive used in India since ancient times. It is a combination of powdered fruit berries of *Embelia ribes* Burm. F. (Myrsinaceae), *Piper longum* L. (piperaceae) and borax in equal proportion. Though the contraceptive potential is

known since ancient times, no systematic development toxicity studies have been carried out to evaluate the postnatal development toxicity and the reproductive performance of the progeny exposed in uterus to pippalyadi yoga was obtained from National Institute for Pharmaceutical Education and Research (NIPER). India and the developmental toxicity was studied by administering three doses, viz. 140, 300 and 700mg/(kg day) to gravid females from day 6 to day 16 of gestation. Pippalyadi did not have any development effects with low doses, however, with five times higher dose, a decrease in body weight of the pups was observed.

The reproductive performance of the pregnancy born to mothers treated with pippalyadi was not significantly affected. The study suggests than in utero exposure to pippalyadi does not have any adverse effect on the postnatal development and reproductive performance of the F(1) progeny. Potassium embelate, 2-5-dihydroxy, 3-undecyl-1,4-benzoquinone, from *Embelia ribes* Burm, was subjected toxicity evaluation which included subacute, chronic, reproductive toxicity testing and teratological investigations in laboratory animals (mice, rats and monkeys). The results did not indicate adverse effects suggesting that potassium embelate is a safe compound<sup>20</sup>.

**Therapeutic evaluation:** Clinical studies were conducted with alcoholic and aqueous extracts of *E. ribes* fruits on 40 children infected by ascarides<sup>45</sup>. Alcoholic extract was found effective in 80 percent cases, while aqueous extract cured 55 percent cases, rendering stools free from ova. No toxic effects were observed during and after treatment. Fruits of *Embelia ribes*, when administered in doses of 200 mg/kg to patients of worm infestation, produced good results. Marked improvement was observed in cases of tape worm, giardia and nana. A single dose upto a maximum of 8 gm was sufficient. Worms were expelled within 6 to 24 hours of taking the drug. The drug was well tolerated and safe for use<sup>45</sup>.

School children (5-12 years) suffering from various helminth diseases were treated with the Ayurvedic preparation, Kuberakshadi yoga, in a dose of 200 mg per kg body wt. in two divided doses<sup>46</sup>. The drug was found effective against *Enterobium vermicularis* and *Ascaris lumbricoides*.

Kuberakshadi yoga contained *Caesalpinia bonducella*, *Embelia ribes*, *Ptychotis* sp., *Myristica fragrans*, *Caryophyllum aromaticum* and *Curcuma cyminum*.

Pippalyadi yoga, a composite drug containing *Piper longum*, *Embelia ribes* and borax in equal amount, was investigated in 254 women covering 4694 cycles for contraceptive property. Oral administration of drug in a dose of 1 gm/day gave very good results. Drug failure was observed only in 4 women. Pregnancy due to drug omission was found in 26 women. Minor side effects were observed in 17 cases. Fertility appeared normal after discontinuation of the drug<sup>47</sup>.

Clinical trials were conducted with Vidangdi yoga (an herbal preparation containing *Embelia ribes* seeds, *Hibiscus rosa-sinensis* flowers and *Ferula foetida* oleo-gum resin) for its antifertility activity<sup>48</sup>. The drug was found to be very effective and showed no toxic effects. AC-4, a composite drug containing *Embelia ribes*, *Laccardia lacca*, *Areca catechu* and *Saraca asoca* in equal parts, when administered orally (1 gm/day in two divided doses) to 281 women for 15 days (4th day of menstrual cycle to 18th day) exhibited good contraceptive activity.

There was no pregnancy due to drug failure after 10th cycle. No toxic symptoms or severe side effects were noticed.

Solid extract prepared from the decoction of *Holarrhena antidysenterica* (bark and seeds), *Berberis aristata* (wood), *Embelia ribes* (fruit), *Cyperus rotundus* (tuber), *Aegle marmelos* (fruit pulp) and *Butea monosperma* (seeds), in a clinical trial on 25 patients of diarrhoea and dysentery, showed cure rate of 80 percent with an average 3.3 days treatment, without any toxic effect.

Gasozyme syrup (indigenous herbal drug, containing *Carica papaya*, *Carum copticum*, *Coriandrum sativum*, *Peucedanum graveolens*, *Atropa belladonna*, *Aegle marmelos*, *Piper nigrum* and *Embelia ribes* seeds) was administered orally (2 teaspoonful twice a day after meals for months) to 40 patients of gastritis. Eight cases (20 %) were completely relieved of symptoms, 16 cases showed marked improvement and 10 showed satisfactory improvements.

### Ancient Uses:

1. Paste: It is being used for mouth wash and avoiding cavities. It is being also used in skin related problems.
2. Powder: It is being used in wormal infestation, infections in body, indigestion, constipation, paralysis, convulsions, epilepsy etc. it also helps in purifying the blood.
3. Oil: It is used in skin related problems and wound infections.
4. Decoction: Decoction of the roots is given in insanity and heart diseases

### Formulation List (List of marketed products):

*Embelia ribes* used in various formulations like Ardrakakhandavaleha, Eranda paka, Krimighna kashaya churna, Vidangadi churna, Taramandura guda, Guduchi lauha, Abhayarishta, Kumari asava, Manibhadra yoga, Pippalyasava, Kaishore guggulu, Vyoshadi guggulu, Saptavishantika guggulu, Eladi ghrita, Kasisadi ghrita, Chandraprabha vati, Wdangadi lauha, Vidanga taila (Table 7).

TABLE 7: LIST OF MARKETED FORMULATIONS

Vidanga taila	Vyoshadi guggulu
Saptavishantika guggulu	Kasisadi ghrita
Chandraprabha vati	Wdangadi lauha
Pippalyasava	Kaishore guggulu
Kumari asava	Manibhadra yoga
Taramandura guda	Guduchi lauha
Krimighna kashaya churna	Vidangadi churna
Ardrakakhandavaleha	Eranda paka
Abhyarista	Agnitundi vati
Amarsundari vati	Ardrak khanda avaleha
Ayaskriti	Bhallatak rasayana
Brhacchagaladya ghrita	Brhanmanjisthadi kvath churna
Brihat guduchi taila	Brihat phal ghrita
Chandanadi lauha	Chandraprabha vati
Dashmularishta	Devadarvarishta
Draksharishta	Eladi ghrita
Guduchi lauha	Haridra khanda
Kalyanaka guda	Kasisadi ghrita
Krimi kuthar rasa	Krimighan kashay churna
Kumaryasava	Kutajavaleha

Lohasava	Madhukasava
Mahayogaraj guggulu	Manibhadra yoga
Narayana churna	Navayas churna
Nimbadi churna	Nityanand rasa
Panchanimb churna	Panhatiktaguggulu ghrita
Pippaladyasava	Pippalyadi lauha
Ajamodadi churna	Gudapippali
Avipatkar churna	Jatiphaladya churna
Brahma rasayan	Kasisadi taila
Brihanmarichadya taila	Krmimudgar rasa
Brihat vidyadharabhra rasa	Laghu cinkadik lehya
Dantodbhed gadantak rasa	Madhus nuhi rasayana
Dhanvantara ghrita	Nagarjunanjan
Pathyadi lepa	Navayas lauha
Pradarantak lauha	Palashbijadi churna

**CONCLUSION:** *Embelia ribes* Burm F a medicinal woody climber belongs to the Myrsinaceae family. *Embelia ribes* contain embelin as an active constituent so it show its activity like antibacterial, antifertility, antiprotozoal, constipation, antifungal, mouth ulcer, sore throat, pneumonia, obesity, analgesic, anti-inflammatory, antioxidant, anthelmintic, antidiabetic, anticonvulsant, anticancer, antihyperlipidemic, wound healing and molluscicidal and its formulation in the market are Ardrakakhandavaleha, Eranda paka, Krimighna kashaya churna, Vidangadi churna, Taramandura guda, Guduchi lauha, Abhayarishta, Kumari asava, Manibhadra yoga, Pippalyasava, Kaishore guggulu, Vyoshadi guggulu, Saptavishantika guggulu, Eladi ghrita, Kasisadi ghrita, Chandraprabha vati, Wdangadi lauha, Vidanga taila etc.

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