**ABSTRACT**

*Embelia ribes* Burm. f. belongs to the family Myrsinaceae found in hilly parts of India up to 1500 m. elevation from outer Himalayans to Western Ghats. It is an endangered medicinal plant valued for its digestive, carminative, anthelmintic and laxative property since time immemorial. It is also used in diabetes, heart related problems, nervous disorders, cancerous tumors and liver disorders. The seeds are also used for wound healing antioxidant, anti-inflammatory, analgesic and contraceptive activity. Due to over exploitation of this plant it is reported in red list data book as vulnerable [Ravikumar & Ved 2000]. Therefore an overview of this plant on pharmacognosy, pharmacology, safety and toxicity is presented below along with HPLC details of Embelin the active constituent of the seeds.

**Key words:***Embelia ribes*, Myrsinaceae, Pharmacognosy, Pharmacology

**INTRODUCTION**

*Embelia ribes* Burm. (Myrsinaceae) is a large woody tropical forest scandent shrub with slender branches and gland-dotted leaves[9]. It is distributed in moist deciduous forests of the Western Ghats of South India, Jammu & Kashmir, Himachal Pradesh, Uttar Pradesh, Assam and Maharashtra, Sri Lanka, Malaya, Singapore and South China[2,3,4]. In historical purview it is narrated in ancient classical texts of Charaka, Sushruta, and Vagbhatta where it is recommended mainly as a krimighna. It is also considered digestive, carminative, laxative and useful in dropsy and pneumonia[4]. It is a popular adjuvant in most of the herbal formulas. The plant contains quinone derivative embelin (3-Undecyl 2, 5-dihydroxy, 1, 4-benzoquinone), quercitol, and fatty ingredients; an alkaloid, christembine, a resinoid, tannins and minute quantities of a volatile oil[2,4,9]. The dried fruits are being used for preparation of medicine. It is widely used as anti-helminthic, anti-carminative, antibacterial, anti-inflammatory, anti-diuretic and anti-astringent[9,9]. Embelin has been also reported as a potent inhibitor of NF-κB activation, which makes it a potentially effective suppressor of tumor cell survival, proliferation, invasion, angiogenesis, and inflammation and has great potential as a therapeutic agent for osteoporosis and cancer-linked bone loss[7,8]. Recent findings also suggest embelin as a novel adjuvant therapeutic candidate for the treatment of hormone-refractory prostate cancer that is resistant to radiation therapy[9].

**Morphology**

*Embelia ribes* Burm. f., is a large scandent shrub; branches long, slender, flexible, terete with long internodes, the bark studded with lenticels. Leaves coriaceous, 5-9 by 2-3.8 cm., elliptic or elliptic lanceolate, shortly and obtusely acuminate, entire, glabrous on both sides, shining above, paler and somewhat silvery beneath, the whole surface covered with scattered minute reddish sunken gland (conspicuous in the young leaves), base rounded or acute; main nerves numerous, slender; petioles 6-16 mm. long, more or less margined, glabrous. Flowers penta-merous, numerous, small, in lax panicked racemes which are terminal and from the upper axils; branches of the panicle often 7.5-10 cm long with more or less glandular pubescent; bracts minute, setaceous, deciduous. Calyx is about 1.25 mm. long; sepals connate about 1/3rd of the way up, the teeth 5, broadly triangular-ovate, ciliate. Petals 5, greenish yellow, free, 4 mm. long, elliptic, subobtuse, and pubescent on both sides. Stamens 5, shorter than the petals, erect; filaments inserted a little below the middle of the petals. Fruit is globose, 3-4 mm. diam., smooth, succulent, black when ripe, like a peppercorn when dried, tipped with the persistent style[10]. **Fig 1.**
**Distribution**

*E. ribes* is highly restricted to hilly parts of India up to 1500 m, elevation from outer Himalayas to Western Ghats. It is also found in Sri Lanka, Singapore, South China and Malayan archipelago. It is distributed in moist deciduous forests of the Western Ghats of South India, Jammu & Kashmir, Arunachal Pradesh, Himachal Pradesh, Madhya Pradesh, Uttar Pradesh, Assam and Maharashtra[2,3,4,11].

**Threat Status**

*Embelia ribes* is considered as Vulnerable (A1c, d) in Karnataka and Tamil Nadu. It is of Lower Risk Near Threatened in Kerala[12].

**Pharmacognosy**

*Physicochemical and Organoleptic Parameters Stem*

<table>
<thead>
<tr>
<th>Physicochemical Constants</th>
<th>Organoleptic Characters</th>
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</thead>
<tbody>
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<td>Parameters</td>
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<td>WSE</td>
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(TA - Total Ash; AIA - Acid Insoluble Ash; ASE - Alcohol Soluble Extractive; WSE - Water Soluble Extractive)

**TLC Finger Printing Profile**

Prominent bands were observed with anisaldehyde spray and sulphuric acid spray at the Rf values 0.13, 0.33, 0.54, 0.97 and 0.37, 0.55, 0.98, respectively. All the other Rf values were given in Table. Fig. 2.

**Anatomy of Stem**

Fig. 3. T.S. of mature stem is somewhat circular in outline. The epidermis is single layered and is provided with unicellular glandular trichomes. Periderm is 5 to 6 layered which is followed by distinguishable cortical region of parenchymatous and schlerenchymatous tissues. Tannin cells are very prominent in parenchymatous region. Schizogenous cavities are also characteristic. Schlerenchymatous strand arches into the secondary phloem tissue. The secondary xylem and secondary phloem are produced by the cambium, as usual. Tannin cells are very common in the phloem tissue. Vessels are characteristically of large lumen. Medullary rays are thin walled and biseriate. Pith cells are parenchymatous[3].

**Root**

T.S. of mature root is somewhat circular in outline with single layered epidermis. Epidermis possesses multicellular

| Table 2: Showing Rf values of bands with different detective reagents and UV light |
|-------------------------------|-----------------|---|---|---|---|---|---|---|---|
| **Under Visible Light**       |                 |   |   |   |   |   |   |   |   |
| Rf Values                     | 0.04            | 0.08 | - | - | - | - | - | - | - |
| **Sprayed with 10% H₂SO₄**   |                 |   |   |   |   |   |   |   |   |
| Rf Values                     | 0.37            | 0.55 | 0.98 | - | - | - | - | - | - |
| **Sprayed with Anisaldehyde**|                 |   |   |   |   |   |   |   |   |
| Rf Values                     | 0.13            | 0.33 | 0.54 | 0.97 | - | - | - | - | - |
| **Under Short UV (254 nm)**  |                 |   |   |   |   |   |   |   |   |
| Rf Values                     | -               | -   | -   | -   | -   | -   | -   | -   |
| **Under Long UV (366 nm)**   |                 |   |   |   |   |   |   |   |   |
| Rf Values                     | 0.59            | -   | -   | -   | -   | -   | -   | -   |

**Figure 2:** TLC fingerprinting profile of *Embelia ribes* stem (a) under visible light (b) sprayed with 10% H₂SO₄ (c) sprayed with anisaldehyde (d) observed under short UV 254nm (e) observed under long UV 366nm.
and unicellular glandular trichomes. In mature root cork is about 15-17 layered having schizogenous cavities. Cork is followed by a wavy sclerenchymatous ring. Beneath this, secondary vascular tissues are seen. Biseriate medullary rays with tannin cells are very conspicuous[3].

**Petiole**

T.S. of petiole is somewhat shield shaped in outline; vascular bundle is crescent shaped; epidermis is single layered with thin cuticle. Cortical region is parenchymatous. Schizogenous cavities are few when compared to that of stem. Tannin cells are very common[3].

**Physicochemical and Organoleptic Parameters of Leaf**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
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<tbody>
<tr>
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<td>ASE</td>
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<tr>
<td>WSE</td>
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<th>Parameters</th>
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</thead>
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<td>Color</td>
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<tr>
<td>Odour</td>
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</tr>
<tr>
<td>Texture</td>
<td>Fibrous</td>
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</table>

**TLC Finger Printing Profile**

Several bands were observed with anisaldehyde spray and long UV and Chlorophyll content is major contributor for the banding pattern. Rf values of bands were given in Table. **Fig.4.** After Sprayed with anisaldehyde total of eight distinct bands were observed.

**Anatomy of Leaf**

**Fig. 5.** T.S. of leaf shows common dicotyledonous characters. Epidermis is single layered without any trichomes. Mesophyll consists of a single layered palisade, and spongy tissue with abundant intercellular spaces. Most of these cells are rich in tannin. Characteristic oil glands are very common in mesophyll especially near the midrib. Vascular bundle is broad ‘C’ shaped. Phloem fibers are very prominent. Stomata are of Ranunculaceous type[3].

**Fruit (Macroscopic)**

**Fig. 6.** Fruit brownish-black, globular 2-4 mm in diameter, warty surface with a beak like projection at apex, often short, thin pedicel and persistent calyx with usually 3 or 5 sepals present, pericarp brittle enclosing a single seed.

**Physicochemical and Organoleptic Parameters of Leaf**

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</thead>
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<tr>
<td>TA 6.75%</td>
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</tr>
<tr>
<td>AIA 0.1%</td>
<td>Color Green</td>
</tr>
<tr>
<td>ASE 9.2%</td>
<td>Odour Mild</td>
</tr>
<tr>
<td>WSE 28.8%</td>
<td>Texture Fibrous</td>
</tr>
</tbody>
</table>

Table 3: Physicochemical and Organoleptic Parameters of Leaf

<table>
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</tr>
<tr>
<td>Odour</td>
<td>Mild</td>
</tr>
<tr>
<td>Texture</td>
<td>Fibrous</td>
</tr>
</tbody>
</table>

Table 4: Showing Rf values of bands with different detective reagents and UV light after Sprayed with anisaldehyde for leaf

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
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<tbody>
<tr>
<td>Under Visible Light</td>
<td>0.08 0.39 0.78 - - - - -</td>
</tr>
<tr>
<td>Sprayed with 10% H₂SO₄</td>
<td>0.09 0.38 0.54 0.97 - - - - -</td>
</tr>
<tr>
<td>Sprayed with Anisaldehyde</td>
<td>0.12 0.38 0.54 0.61 0.7 0.76 0.9 0.98</td>
</tr>
<tr>
<td>Under Short UV (254 nm)</td>
<td>0.05 0.22 0.95 - - - - -</td>
</tr>
<tr>
<td>Under Long UV (366 nm)</td>
<td>0.03 0.19 0.34 0.44 0.59 - - -</td>
</tr>
</tbody>
</table>

Figure 3: T. S. of *Embelia ribes* stem (a) whole view (b) cortex and cork (c) secondary xylem and tannin cells (d) schizogenous cavity (e) Medullary rays and secondary phloem (f) pith region

Figure 4: TLC fingerprinting profile *Embelia ribes* leaf (a) under visible light (b) sprayed with 10% H₂SO₄ (c) sprayed with anisaldehyde (d) observed under short UV 254nm (e) observed under long UV 366nm
covered by a thin membrane, entire seed, reddish and covered with yellowish spots (chitra tandula), odour slightly aromatic, taste, astringent.[13]

**Physicochemical and Organoleptic Parameters Fruit**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Limit</th>
<th>Physicochemical Constants</th>
<th>Organoleptic Characters</th>
</tr>
</thead>
<tbody>
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<td>TA</td>
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<td></td>
<td>Taste Bitter</td>
</tr>
<tr>
<td>AIA</td>
<td>0.55%</td>
<td>NA</td>
<td></td>
<td>Color Brown</td>
</tr>
<tr>
<td>ASE</td>
<td>1.0%</td>
<td>NA</td>
<td></td>
<td>Odour Mild</td>
</tr>
<tr>
<td>WSE</td>
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<td>NA</td>
<td></td>
<td>Texture Fibrous</td>
</tr>
</tbody>
</table>

(TA - Total Ash; AIA - Acid Insoluble Ash; ASE - Alcohol Soluble Extractive; WSE - Water Soluble Extractive)

**TLC Finger Printing Profile Fruit**

Prominent bands were observed with anisaldehyde spray and sulphuric acid spray at the Rf values 0.27, 0.91 and 0.32, 0.51, 0.56 respectively. One band is visible under long UV and short UV. **Fig. 7.**

**Anatomy of Fruit**

Fig. 8. Transverse section of fruit shows epicarp consisting of single row of tabular cells of epidermis, usually obliterated, (Fig 8b). In surface view cells rounded with wrinkled cuticle, Mesocarp consists of a number of layers of reddish-brown coloured cells and numerous (Fig 8c). Fibrovascular bundles and rarely a few prismatic crystals of calcium oxalate (Fig 8f, 8g & 8h). Inner part of mesocarp and endodermis composed of stone cells, endodermis consisting of single layered (Fig 8d). Thick-walled, large, palisade-like stone cells, seed coat composed of 2-3 layered reddish-brown coloured cells, (Fig 8e & 8f). Endosperm cells irregular in shape, thick-walled, containing fixed oil and proteinous mass.

**Table 5:** Physicochemical and Organoleptic Parameters Fruit

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Limit</th>
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</tbody>
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(TA - Total Ash; AIA - Acid Insoluble Ash; ASE - Alcohol Soluble Extractive; WSE - Water Soluble Extractive)

**Table 6**: Showing Rf values of bands with different detective reagents and UV light Fruit

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Limit</th>
<th>Under Visible Light</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sprayed with 10% $\text{H}_2\text{SO}_4$</td>
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<tr>
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<td></td>
<td></td>
<td>Sprayed with Anisaldehyde</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Under Short UV (254 nm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Under Long UV (366 nm)</td>
</tr>
</tbody>
</table>

**Table 6**: Showing Rf values of bands with different detective reagents and UV light Fruit

Under Visible Light

Sprayed with 10% $\text{H}_2\text{SO}_4$

Sprayed with Anisaldehyde

Under Short UV (254 nm)

Under Long UV (366 nm)

**Figure 5**: T. S. of *Embelia ribes* leaf (a) whole view (b) single layered epidermis (c) oil glands (d) C shaped vascular bundle

**Figure 6**: Fruits of *Embelia ribes*

**Figure 7**: TLC fingerprinting profile *Embelia ribes* fruit (a) under visible light (b) sprayed with 10% H$_2$SO$_4$ (c) sprayed with anisaldehyde (d) observed under short UV 254nm (e) observed under long UV 366nm
tridecyl-1, 4-benzoquinone, and a gomphilate derivative, 5,6-dihydroxy-7-tridecyl-3-[4-tridecyl-3-hydroxy-5-oxo-2(5H)-furylidene]-2-oxo-3(2H)-benzofuran were isolated from the roots of *E. ribes* using ethanolic extract[17].

Latha proposed an alternate way of extraction of embelin from *E. ribes*. Aromatic hydrodrotropes such as sodium n butyl benzene sulfonate (NaNBS), and sodium cumene sulfonate (NaCS) were effective for selective extraction with a recovery of 95% from aqueous solution of hydrodrotropes with high purity[18]. Further a microwave assisted extraction procedure was developed where solvent selection, microwave energy input and solid loading were optimized. Maximum extraction was achieved in acetone and non-polar solvents such as hexane and dichloromethane were not effective for extraction of embelin[19].

Another unusual nitrogen-containing 3-alkyl-1, 4-benzoquinone, N-(3-carboxylpropyl)-5-amino-2-hydroxy-3-tridecyl-1, 4-benzoquinone was isolated from *E. ribes*. The steps involved for isolation were a microwave-assisted combined Mitsunobu reaction-Claisen rearrangement to introduce the alkyl side chain into 2, 5-dimethoxyphenol, followed by alkene reduction, oxidation to the quinone, and sequential displacement of the methoxy groups with hydroxide and GABA tert-butyl ester[20].

High Performance Liquid Chromatography method was developed for determination of embelin in *Embelia ribes*. The Embelin content of 4.33% w/w was observed in *Embelia ribes*. The proposed method can be used for quantitative determination of embelin in Embelia plants[21].

**Table 7: Microbial Limit Test Fruit**

<table>
<thead>
<tr>
<th>Raw herb sample</th>
<th>Total Aerobic Bacterial Count (TABC) (Cfu/gm)</th>
<th>Total Yeast And Mould Count (TYMC) (Cfu/gm)</th>
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</thead>
<tbody>
<tr>
<td><em>Embelia</em> ribes -Fruit</td>
<td>$7.5 \times 10^4$</td>
<td>$1.5 \times 10^3$</td>
</tr>
</tbody>
</table>

**Microbial Limit Test Fruit**

Results of microbial assay of *Embelia ribes* -fruit showed 75000 colonies for aerobic bacteria and 1500 colonies for yeast and moulds which is below the limits (TABC ≤ $1 \times 10^7$; TYMC ≤ $1 \times 10^5$) of international guidelines (Table 7).

**Fruit Powder**

Powder-Reddish, under microscope shows reddish parenchyma and stone cells[13].

**Phytochemistry**

Vilangin was isolated from the dry ripe berries of *E. ribes*. The structure was assigned as methylenebis (2, 5-dihydroxy-4-undecyl-3-6-benzoquinone)[14]. 3 new compounds identified as embelinol, embeliaribyl ester and embeliol were isolated from the seeds of *Embelia ribes* along with embelin[15]. Seeds of *Embelia ribes* showed the presence of Cr, K, Ca, Cu, Zn and Mn to be enough, with high carbohydrates but low position along with higher nutritive value[16].

An unusual nitrogen-containing 3-alkyl-1, 4-benzoquinone derivative, N- (3-carboxylpropyl)-5-amino-2-hydroxy-3-tridecyl-1, 4-benzoquinone, and a gomphilate derivative, 5,6-dihydroxy-7-tridecyl-3-[4-tridecyl-3-hydroxy-5-oxo-2(5H)-furylidene]-2-oxo-3(2H)-benzofuran were isolated from the roots of *E. ribes* using ethanolic extract[17].

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**Uses**

**Traditional Uses**

Fig. 7. The fruit is hot, dry, with a sharp bitter taste; it’s a good appetite; carminative, anthelmintic, alexiteric, laxative, alterative, cures tumor, ascites, bronchitis, mental diseases, dyspnoea, diseases of the heart, urinary discharges, jaundice, hemicrania, and worms in wounds[10]. Sushruta recommends the use along with liquorice for strengthening the body and to prevent the effect of age. The berries are used in the preparation of several compositions for ringworm and other skin diseases. The seeds are of high repute as anthelmintic particularly for tapeworms[10]. Pulp of the fruit is purgative. Fresh juice is cooling, diuretic and laxative[11].

Berries prevent flatulence and useful in dyspepsia. A paste of the seed is used against ringworm and other skin diseases.
Leaves along with ginger are used as a gargle for sore throat, aphthae and indolent ulcers of mouth\textsuperscript{[11]}. Decoction of the root two or three times daily is effective against influenza\textsuperscript{[10]}. Powder of dried root bark is a reputed remedy for toothache. For lung diseases like pneumonia paste of the bark is a valuable application for the chest. In headache paste is applied to the forehead made from berries of the plant and butter\textsuperscript{[80]}. Vidanga taila made of Croton tiglium, E. ribes and carbonate of sodium is used for relieving headache or hemicranias\textsuperscript{[11]}.

The fruit is good for plethoric constitutions; analgesic, pungative, vulnerary, anthelmintic, cures bronchitis by thickening phlegm and drying; dries discharges from wounds, reddens the urine and removes bad humors from the body. It is considered to be attenuant and pungative of phlegmatic humors. Few berries are given to children with milk for children against flatulence\textsuperscript{[10]}.

**Ayurvedic formulations**

*E. ribes* is used in about 75 formulations where fruits are used in Ayurvedic preparations like Vidangarista, Vidanga Lauha, Vidangadi Lauha\textsuperscript{[13]}, Abhayarishtam, Ayaskrithi, Pippallyasavam, Anuthailam, Kachuradithailam\textsuperscript{[3]}.

**Ethnobotanical Uses**

According to Duke’s ethnobotanical data *E. ribes* ethnobotanical properties are for vermifuge, alterative, anthelmintic, astringent, carminative, diuretic, stimulant, stomachic, taenifuge, tonic and tumor (Abdomen). It is also used in cough, diarrhea, chest disorders, fever, ringworm and other skin disorders\textsuperscript{[23]}.

**Carbuncle**

According to Siakia et al., berries of *E. ribes* along with Emblica officinalis, Piper longum, Terminalia bellerica are mixed in equal amounts and the crushed form (powder) is added to honey and the concentrated honey is then applied on the infected carbuncle for relief\textsuperscript{[23]}.

**Wound healing**

According to Chopda and Mahajan fruits of *E. ribes* are used for wound healing in Jalgaon District of Maharashtra State\textsuperscript{[24]}.

**Stomach Disorder**

Tagin people of Arunachal Pradesh for stomach disorder use leaves and fruits of *E. ribes*\textsuperscript{[25]}.

**Age related Cognitive disorders**

Brahmarasayana one of the ayurvedic preparations used to treat age related cognitive disorders. Emblica officinalis is the main ingredient in the preparation along *E. ribes* and 16 others, which are also added to the mixture. This preparation is for a disease-free life with long lasting youth, great vigor and no dementia\textsuperscript{[26]}.

**Cough & Cold**

The roots of *E. ribes* grounded with lemon juice or buttermilk and 1-3 teaspoonful of juice is taken orally with sugar/jaggery, twice daily for 2 days to cure cough and cold in eastern region of Shimoga district\textsuperscript{[27]}.

**Paralysis**

For Paralysis the leaves of *E. ribes* along with roots of Withania somnifera (L.) Dun. and Asparagus racemosus Wild. and made into paste, which is taken orally with a cup of hot water, twice daily for 1 month\textsuperscript{[27]}.

**Leucoderma**

For leucoderma the mixture of Withania somnifera root, bark of *E. ribes*, leaves of Plumbago zeylanica, seeds of Croton tiglium and fruit pulp of Cassia fistula with cow’s urine was applied on white patches for 2-3 months\textsuperscript{[28]}.

**Anthelmintic**

Powder of Embelia ribes fruits alone or mixed with powder of Butea monosperma with water or honey orally is used in traditional medicine as anthelmintic\textsuperscript{[29]}.

**Pharmacological Uses**

**Lipid peroxidation**

Hepatic antioxidant capacity of embelin (*Embelia ribes*) was tested in CCl\textsubscript{4}-treated rats using different antioxidant tests where peroxidative damage was minimal in both liver and serum along with effectively inducing the antioxidant potential suggesting that that embelin acts as a natural antioxidant against hepatotoxicity induced in rats\textsuperscript{[29]}. The aqueous extract of *Embelia ribes* fruit enhances the antioxidant defense against methionine induced hyperhomocysteinemia, hyperlipidaemia and oxidative stress in brain by decreasing the level of homocysteine, lactate dehydrogenase, total cholesterol, triglycerides, low density lipoprotein (LDL-C) and very low density lipoprotein (VLDL-C) and increased the high density lipoprotein (HDL-C) levels in serum. The extract also decreased lipid peroxides (LPO) levels with increase in glutathione (GSH) content in hyperhomocysteinimic rats\textsuperscript{[31]}.

Ethanol extract of *Embelia ribes* fruit significantly reversed the methionine increased homocysteine, lactate dehydrogenase, total cholesterol, triglycerides, and low-density lipoprotein levels in serum and lipid peroxides levels in heart homogenates with decrease in serum high-density lipoprotein and myocardial glutathione levels in pathogenic control rats. Thus indicating the effect of Embelia on...
antihyperhomocysteinemic and lipid-lowering potential in hyperhomocysteinemic rats\[32\].

Lipid lowering and antioxidant potential of ethanolic extract of \textit{E. ribes} Burm fruits was investigated in streptozotocin induced diabetes in rats. Twenty days of oral feeding of the extract resulted in significant 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 (TBARs) values providing the biochemical evidence for diabetic dyslipidemia of \textit{E. ribes}\[33\].

In a comparative study between aqueous extract of \textit{Tinospora cordifolia}, \textit{Cyperus rotundus} and \textit{Embelia ribes} on hyperlipidaemic rats the order of curative effects of \textit{E. ribes} stood last when compared to \textit{Tinospora cordifolia} and \textit{Cyperus rotundus}\[34\].

**Antihyperglycemic activity**

Oral feeding of aqueous \textit{E. ribes} extract to streptozotocin induced diabetic rats produced significant decrease in heart rate, systolic blood pressure, blood glucose, blood glycyslated hemoglobin, serum lactate dehydrogenase, creatine kinase and increase in blood glutathione levels. Further, significantly decreased the levels of pancreatic lipid peroxide and increased the levels of pancreatic superoxide dismutase, catalase and glutathione. Suggesting a significant blood glucose and blood pressure lowering potential by \textit{E. ribes} along with enhancing endogenous antioxidant defense against free radicals produced under hyperglycemic conditions, thereby, seemingly protects the pancreatic beta cells against loss\[35\].

In another study Bhandari et.al., investigated the modulatory effect of chronic oral administration of \textit{E. ribes} ethanolic extract on diabetes mellitus induced by a diabetogen, streptozotocin. Oral administration of the extract significantly reduced levels of blood glucose, glycated haemoglobin, heart rate and systolic blood pressure in rats\[36\].

Ethanolic extract of \textit{Embelia ribes} enhances antioxidant defense against reactive oxygen species produced under hyperglycemic condition and thus protects beta-cells against loss, and exhibit antidiabetic property by decreasing blood glucose, blood glycyslated haemoglobin, serum lactate dehydrogenase, creatine kinase, pancreatic thiobarbituric acid-reactive substances (TBARs) levels and increase in blood superoxide dismutase, catalase and glutathione levels. There was expansion of islets when treated with test drug in diabetic rats\[37\].

**Cardioprotective activity**

Bhandari & Ansari demonstrated that ethanolic extract of \textit{Embelia ribes} fruit attenuates isoproterenol induced oxidative stress in diabetic rats by enhancing cellular antioxidant defense through significant increase in heart rate, blood glutathione, serum lactate dehydrogenase, and myocardial endogenous antioxidant levels along with decrease in systolic blood pressure, blood glucose, HbA1C, serum creatine kinase, and myocardial thiobarbituric acid reactive substances levels\[38\].

In another trial with the same ethanol extract decreased the elevated levels of lactate dehydrogenase and creatine kinase in serum and myocardial thiobarbituric acid reactive substances and increased reduced levels of glutathione, superoxide dismutase and catalase in heart homogenates in isoproterenol induced myocardial infarction in albino rats. Histopathological studies observed a marked protection by the extract in myocardial necrotic damage\[39\].

In another study aqueous extract of fruits of \textit{Embelia ribes} decreased significantly the heart rate, systolic blood pressure, increased levels of serum lactate dehydrogenase, serum creatine kinase and myocardial lipid peroxides and increased significantly the myocardial endogenous antioxidants like glutathione, superoxide dismutase and catalase levels in isoproterenol treated rats. The results were supplemented with histopathological examination of rat’s heart sections to confirm the myocardial injury\[40\].

**Neuroprotective activity**

Aqueous extract of \textit{Embelia ribes} pretreatment ameliorates cerebral ischemia/reperfusion injury and enhances the antioxidant defense against middle cerebral artery occlusion-induced cerebral infarction in rats by significant increase in the post stroke grip strength activity. Further reversed the levels/activities of thiobarbituric acid reactive substances; enhanced glutathione; glutathione peroxidase; glutathione reductase; and, glutathione-S-transferase and also resulted in decreased cerebral infarct area, as compared to the ischemic group, thus exhibits neuroprotective property\[41\].

Administration of ethanolic \textit{E. ribes} extract orally to methionine induced hyperhomocysteinemic rats produced a significant decrease in the levels of homocysteine, LDH, total cholesterol, triglycerides, in serum and LPO levels in brain homogenates with significant increase in serum HDL-C levels and GSH content in brain homogenates, when compared with pathogenic control rats. Degenerative changes of neuronal cells in methionine treated rats were minimized to near normal morphology as evident by histopathological examination\[42\].

Chronic pretreatment with ethanolic \textit{E. ribes} extract enhances the antioxidant defense against middle cerebral artery occlusion induced focal cerebral ischemia in rats and exhibits neuroprotective activity by significant increase in the grip
strength activity, and glutathione, glutathione peroxidase, glutathione reductase and glutathione-S-transferase levels in hippocampus and frontal cortex with significant decrease in lactate dehydrogenase levels in serum and thiobarbituric acid reactive substance levels in hippocampus and frontal cortex[43].

**Antioxidant Activity**

Embelin (from *Embelia ribes*) is a component of herbal drugs and possess wide range of medicinal properties. It has been found to scavenge DPPH radical and inhibit hydroxyl radical induced deoxyribose degradation. It was also found to inhibit lipid peroxidation and restore impaired Manganese-superoxide dismutase in rat liver mitochondria. Further, kinetics and mechanism of the reactions of embelin with hydroxyl, one-electron oxidizing, and organohaloperoxyl and thyl radicals were studied using nanosecond pulse radiolysis technique[44].

**Hepatoprotective Activity**

*Embelia ribes* commonly known as vidanga has been reported to be useful in jaundice. It is a constituent of various formulations marketed for liver ailments. In a hepatoprotective study the ethanolic extract of *Embelia ribes* on paracetamol induced liver cell damage was studied using mice as experimental animals. The mice treated with *Embelia ribes* extract showed a dose dependent fall in the serum glutamate pyruvate transaminase (SGPT) levels. Histopathology of liver revealed normal livers in a dose dependant manner[45].

**Antitumor activity**

Embelin was found to exhibit significant antitumor activity in methylcholangan-threne-induced fibrosarcoma in albino rats along with enhancing their survival time. It also had an appreciable action on pain and inflammation. The changes in DNA, RNA and protein levels in tumor bearing control and drug treated animals were also studied[46].

Chitra et.al. In an in vitro study assessed drug induced cell toxicity using a rapid technique in a fibrosarcoma cell line where the cells were inoculated with increasing concentrations of embelin along with [3H]-thymidine, where thymidine uptake was decreased by embelin in lipid peroxidation, and glutathione levels dose dependently[47].

Chemopreventive effects of embelin against N-nitrosodiethylamine/Phenobarbital-induced hepatocarcinogenesis in Wistar rats were studied where embelin prevented the induction of hepatic hyper plastic nodules, body weight loss, increase in the levels of hepatic diagnostic markers, and hypoproteinemia[48].

In a trial on carbohydrate moieties of glycoprotein in plasma, liver and kidney of tumor bearing rats continuous administration of embelin lowered the values of total hexose, hexosamine and sialic acid to near normal indicating an antitumor activity[49].

1, 4-benzoquinone derivatives 5- O-ethylembelin and 5-O-methylembelin showed antiproliferative activity against a panel of human tumor cell lines upon comparison to normal marsupial kidney cells (PtK2). They inhibited multiplication of HL-60 cells in the G (0)/G (1) phase of the cell cycle. When HeLa cells, were exposed to 100 μM of 1, 4-benzoquinone derivatives 5- O-ethylembelin and 5-O-methylembelin for 6 h complete disassembly of the microtubule network and an increased number of cells blocked in mitotic stages were observed. Apoptosis in HL-60 cells was observed when treated with 10 μM of 1, 4-benzoquinone derivatives 5- O-ethylembelin and 5-O-methylembelin for 24 h. Suggesting both 1, 4-benzoquinone derivatives 5- O-ethylembelin and 5- O-methylembelin are promising novel antimitotic and anticancer molecules targeting microtubular proteins[50].

Chen et.al., had previously identified that embelin as an inhibitor of XIAP through computational structure-based database screening. Further efforts led to the identification of new and more potent inhibitors like compound 6g has Ki value of 180 nM binding to XIAP BIR3, in competitive binding assay and represents a promising lead compound for further optimization[51].

Embelin, identified primarily from the *Embelia ribes* plant, is a compound shown to exhibit chemopreventive, anti-inflammatory, and apoptotic activities through an unknown mechanism which was demonstrated when it inhibited tumor necrosis factor, alpha-induced NF-kappaB activation, the TNF α-induced activation of the inhibitory subunit of NF-kappaBz kinase, IkappaBz phosphorylation, IkappaBz degradation, p65 phosphorylation, nuclear translocation. It also suppressed NF-kappaB-dependent reporter gene transcription, TNF receptor-1, TNFR1-associated death domain protein, TNFR-associated factor-2, NF-kappaB-inducing kinase, and IkappaBalpha kinase. 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. In addition, NF-kappaB activated by diverse stimuli was suppressed[52].

Embelin inhibits chemical carcinogen-induced colon carcinogenesis, which is partially dependent on presence of functional PPARgamma, was proved by Dai et.al., where it inhibited proliferation and induced apoptosis in HCT116 cells with marked up-regulation of PPARgamma. In addition, it significantly inhibited expressions of survivin, cyclin D1, and c-Myc, which were partially dependent on...
PPARgamma. Embelin significantly reduced incidence of colon cancer in PPARgamma (+/+) mice but not in PPARgamma (+/-) mice. Embelin inhibited NF-kappaB activity in PPARgamma (+/+ ) mice but marginally in PPARgamma (+/-) mice. Thus, reduced expression of PPARgamma significantly which sensitizes colonic tissues to the carcinogenic effect of 1, 2-dimethylhydrazine dihydrochloride.[53]

Effect of bicalutamide and embelin on growth of prostate cancer cells in vitro and in vivo was carried out. Embelin induced caspase 3 and 9 activation in LNCaP and C4-2 cells by decreasing XIAP expression and was more potent than bicalutamide in killing prostate tumor cells irrespective of their androgen status. According to isobologram analysis combination of bicalutamide and embelin was synergistic for C4-2 but additive and slightly antagonistic for LNCaP cells. Increase in aqueous solubility of drugs resulted in Micellar formulation. Tumor growth was effectively regressed upon treatment with bicalutamide, but tumor response stopped after prolonged treatment of bicalutamide and began to grow. Sequential treatment with XIAP inhibitor embelin resulted in regression of these hormone refractory tumors.[54]

Embelin has been used as an anticancer agent in therapeutic studies. In one of the study embelin along with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) or the combination of both were tried against glioblastoma cells and human astrocytes. It broadly sensitized malignant glioma cells to TRAIL-mediated apoptosis. Combined treatment augmented activation of initiator caspases-8/-9 and effector caspases-3/-7. Further Embelin alone down-regulated expression of long- and short-isoform of c-FLIP and forced expression of short isoform of c-FLIP attenuated apoptosis. It did not modulate mRNA levels of c-FLIP (S), suggesting that Embelin modulates expression of c-FLIP in a posttranscriptional manner.[55]

Wound healing activity
Wound healing activity by excision, incision and dead space wound models on Swiss Albino Rats was carried out where ethanol extract of the leaves of Embelia ribes Burm. and its isolated quinone compound embelin were screened. Significant wound healing activity was observed in both ethanol crude extract and embelin treated groups. In embelin treated groups, 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. In dead space wound model also the weight of the granulation was increased indicating increase in collagenation. The histological examination of the granulation tissue of embelin treated group showed increased cross-linking of collagen fibers and absence of monocytes.[56]

Acetylcholinesterase activity
Dysfunction of cholinergic neurotransmission in the brain contributes to the salient cognitive decline in Alzheimer’s disease. Loss of cholinergic cells, particularly in the basal forebrain, is accompanied by loss of the neurotransmitter acetylcholine. One of the most accepted strategies in Alzheimer’s disease treatment is the use of cholinesterase inhibitors. Their clinical efficacy is thought to result from prolonging the half-life of acetylcholine through inhibition of AChE. The half-life of acetylcholine inhibition of methanolic extract of E. ribes root was 23.04 µg/ml, which partially substantiates the traditional use of E. ribes for improvement of cognition.[57]

Antifertility activity
Altered metabolic function was observed along with significant rise in levels of acid and alkaline phosphatases of testis and prostate when embelin was administered along with Vinca rosea to male albino rats.[58]

Treatment with 50% ethanol and benzene extracts of Embelia ribes Burm. increased the glycogen, protein and non-protein nitrogen contents in the uterus of normal and ovariectomized rats. The effect is statistically significant at low dose level but decreases as the dose is increased. Higher dose of benzene extract is toxic.[59]

Long-term metabolic effect of embelin on the testes of adult male dogs was evaluated by feeding them with embelin for 100 days. A three tiered finding containing histology, tissue biochemistry and blood/serum profile of dogs treated with embelin showed that 100 days therapy inhibits spermatogenesis, loss in weights of testes and spermatogenic elements and epididymides was devoid of spermatozoa but functional morphology remained unaltered. The 250 days of recovery period brought about normal spermiogenesis with all 1-8-cell stages and epididymal milieu showed functional physiology. This proved that 250 days recovery period restored all contraception like activity of embelin. Sexual potency and libido of the animals were not altered. Therefore a reversible male contraception with the help of embelin looks promising.[60]

Traditional medicinal plants having contraceptive efficacy were searched, identified and collected throughout India. Contraceptive properties were studied in rats, mice, and hamsters. Significant contraceptive effects were seen after administration of Crotalaria juncea Linn, Verbena bonariensis Linn, Verbena hybrida Linn, Verbena bonariensis Linn, and Embelia ribes Burm, Artabotrys odoratissimus Linn., and Pueraria tuberosa. Biological property of Embelia ribes Burm and Artabotrys odoratissimus Linn were interesting but had strong toxic effects.[61]
Antifertility effects of *E. ribes* berries, its petroleum ether, methanol, chloroform and benzene extracts, embelin and the putative active principal were reported. The berries showed 62% antifertility effect when incorporated into the diet at 10 & 20% dose levels, which was due to prolonged diestrous phase within 2 weeks of treatment. In serially hot-extracted petroleum ether and methanol extract cyclicity was affected and prevented pregnancy in 75% of treated rats. Benzene extract showed 51%, whereas chloroform extracts showed 37% antifertility activity. These doses were all administered post-coitally, from Day 1-7 of pregnancy. Antifertility effect was assessed by number of implantation sites post treatment.

Semen analysis and hormonal levels in Bonnet macaques after three months of administration of *E. ribes* berries did not affect spermatogenesis but reduced circulating testosterone level.

Antiandrogenic activity of Embelin extracted from *Embelia ribes* Burm. berries was observed where the berries, altered the testicular histology and glycogen, gametogenic counts and accessory sex gland fructose at different dosage levels.

Estrogenic mode of action of *E. ribes* was observed when the 50% ethanolic and benzene extract of dried berries increased the intensity of reaction for alkaline phosphatase in luminal and glandular epithelium.

Daily subcutaneous administration of embelin, the active principle of the seeds of *Embelia ribes* Burm, revealed inhibition of epididymal motile sperm count, fertility parameters such as pregnancy attainment and litter size, and the activities of the enzymes of glycolysis and energy metabolism. Further addition of embelin to epididymal sperm suspension caused inhibition of spermatozoal motility and the activities of the enzymes of carbohydrate metabolism. Histological observations showed that both invivo and Invitro treatment caused morphological changes in spermatozoa such as, decapitation of the spermatozoal head, discontinuity of the outer membranous sheath in the mid-piece and the tail region, and alteration in the shape of the cytoplasmic droplet in the tail, displaying the antispermatic effect of embelin on male albino rats.

It is suggested that uterine peroxidase assay can be utilized as a biochemical parameter in the screening of new antifertility agents for their estrogenic/antiestrogenic properties. In one of the trial uterotrophic and uterine peroxidase activities in ovariectomized rats were highly correlated in response to treatment with embelin.

Male fertility regulating potential of embelin was investigated in rabbits. There was a marked reduction of testosterone concentrations within two days of administration and up to 90% reduction by the 6th day. Luteinising hormone showed a corresponding rise with the falling testosterone levels and also there was rapid increase in progesterone levels. The concentrations of progesterone and luteinising hormone declined when dosage was stopped. This suggests that embelin disrupts production of testosterone at the testicular level.

In a trial on most effective and convenient route of delivery of embelin was carried out on plasma testosterone levels of sexually mature male white New Zealand rabbits. In which oral administration offered the best and effective method of drug delivery system.

Embelin has a role to play in reproductive functions in female rats as it disrupted oestrous cycles and there was significant depression in plasma oestradiol and progesterone. In vitro studies isolated mixed ovarian cells from embelin treated rats produced significantly less progesterone and oestradiol than controls. Thus confirming that embelin interferes with reproductive functions in female rats by suppressing ovarian production of sex steroid hormones.

The developmental toxicity of in utero exposure to pippaliyadi yoga or pippaliyadi vati an ayurvedic contraceptive used in India since ancient times was studied by administering low and very high doses to gravid females from day 6 to day 16 of gestation. Pippaliyadi vati did not have any adverse developmental effects with low doses; however, with higher dose decrease in body weight of the pups was observed. The reproductive performance of the progeny born to mothers treated with pippaliyadi vati was not significantly affected. The present study suggests that in utero exposure to pippaliyadi does not have any adverse effect on the postnatal development and reproductive performance of the F1 progeny.

**Analgesic activity**

Embelin and all its disalts showed analgesic activity in which 2:5 disobutyl amine embelin showed maximum action. The effect was observed after intraperitoneal administration but not after subcutaneous, intramuscular or oral administration. Analgesic effect was seen in dogs and cats after intravenous injection also. Embelin and 2:5 isobutyl amine embelin showed maximum action. The analgesic activity of embelin and all its disalts showed analgesic activity in which 2:5 disobutyl amine embelin showed maximum action. The effect was observed after intraperitoneal administration but not after subcutaneous, intramuscular or oral administration. Analgesic effect was seen in dogs and cats after intravenous injection also. Embelin and 2:5 isobutyl amine embelin also exhibited antipyretic and anti-inflammatory activities.

Embelin derived from *E. ribes* was studied for its analgesic effects in rats and mice. It was effective by oral, Intramuscular and ICV routes and could be compared with morphine. The potassium embellate acts centrally to produce analgesia; its effect is not antagonized by naloxone indicating a different central site of action. High oral efficacy and
non-narcotic properties of the test drug make it more acceptable than morphine. In addition, lack of any adverse effects, high therapeutic index and absence of abstinence syndrome confers a long-term safety on potassium embelate for use as an analgesic[73]. In another study Zutshi et.al., observed that the analgesic property of potassium embelate may be due to the involvement of mu and kappa binding site in the brain[74].

In a study on analgesic activity of embelin it was revealed that there are naloxone resistant specific binding sites for potassium embelate in the spinal cord through which the antinociceptive response is modulated. Mono and dipotassium salts of embelin, displayed higher analgesic activity in visceral evoked responses when compared with thermal evoked responses. It is suggested that potassium embelate has strong affinity for kappa type of opiate receptors[75].

The effect of potassium embelate on neurotransmitter content in cerebrospinal fluid of dog was observed where the drug significantly affected levels of noradrenaline and acetylcholinesterase activity[76].

In a pharmacokinetic study by Zushi et.al., revealed that biexponential kinetic pattern was followed by the compound. Bioavailability was complete and fast. The disposition half-life is 9.5 h on intravenous and 11 h on oral administration. High concentrations of the drug were found in brain between 0.25 and 2 h, which is in agreement with its pharmacological action. The kidney plays a major role in the excretion of the drug[77].

**Anthelmintic activity**

Seed oil of *Embelia ribes* was investigated for its anthelmintic property against *Pheritima posthuma*. Three concentrations of oil were studied in the bioassay, which involved determination of time of paralysis and time of death of the worm. The oil exhibited moderate to significant anthelmintic activity. When compared with other plants like *Gynandropsis gynandra*, *Impatiens balsamina*, *Celastrus paniculata* and *Mucuna pruriens* *E. ribes* had the best anthelmintic activity[78].

Ethanolic extract of *E. ribes* fruits showed an anthelmintic efficacy of up to 93% against gastrointestinal nematodal larvae *Haemonchus contortus*[79].

Antinematodal activity of mixed preparation of *Vernonia anthelmintica* seed and *Embelia ribes* fruit was studied in goats with water, methanol extract and powder, which was compared with morantel tartarate. Egg per gram (EPG) counts was made in the faeces before and on the 3rd, 10th and 15th days of treatment. The data of 15th day of administration showed that 2 g/kg of powder, its equivalent amount of methanol extract and 0.01 g/kg of morantel tartarate are equally effective and safe in treating natural gastrointestinal nematode infection of the local goats[80].

**Antibacterial activity**

Embelin, isolated from *E. ribes*, exhibited significant inhibition against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Shigella flexneri*, *S. sonnei* and *Pseudomonas aeruginosa* and moderate activity against *Salmonella typhi*, *S. boydii* and *Proteus mirabilis*[81].

Moderate antibacterial activity was shown by methanol and aqueous extract of *Embelia ribes* against multi-drug resistant *Salmonella typhi*[82].

**Clinical trial on contraceptive activity**

A clinical trial was conducted on 48 fertile women (age 26-42 yrs) for 1 year covering 536 menstrual cycles with indigenous oral contraceptive Maswin (*Embelia ribes*). I tablet (400 mg extract) was taken each morning for 10 days beginning on the fifth day of menstruation; total dosage was 10 tablets for 1 menstrual cycle. No pregnancies, side effects, or toxic symptoms occurred. All expressed a sense of well-being and were eager to continue usage of Maswin. *Embelia ribes* antagonizes the effects of estrogen on the uterus so the uterus is not in the necessary condition to accept fertilized ovum, so pregnancy does not take place even though ovulation and fertilization have occurred[83].

**Safety**

Potassium embelate, from *Embelia ribes* Burm. was subjected to sub-acute, chronic, reproductive toxicity testing and teratological investigations in laboratory animals (mice, rats and monkeys). Adverse effects were not observed in the animals indicating that potassium embelate is a safe compound[84].

**Toxicity studies**

The alcoholic and aqueous extracts of the berries of *E. ribes* on rats did not reveal any toxic effect on male reproductive organs[85].

In a study conducted by Low et.al., retinal pathology and defects in visual behavior in chicks treated with *Embelia ribes* (Enkoko), *Hagenia abyssinica* (Kosso), or embelin, a crystalline extract of *E. ribes* was observed. The chicks fed with high doses of the anthelmintics significantly reduced the ability of chicks to detect a moving bead introduced into peripheral field of vision. Degree of constriction of the visual field for detection was dose dependent. Performance on a visual discrimination task, which required discrimination of feed grains from pebbles, was also impaired. The visual deficits observed in Enkoko-treated...
animals were mimicked by embelin, which suggests embelin may be responsible for visual defects. Anatomical evidence of degeneration of ganglion cells was found in retinæ exposed to high doses. However, no retinal lesions were detected in animals following treatment with low doses[80].

In a short-term toxicity study wet weight and biochemical constituents of the adrenals and activity of acid and alkaline phosphatase in kidney and adrenal showed a remarkable increase, whereas no changes were observed in weight of liver, kidney and spleen and in biochemical constituents such as protein and glycogen. Embelin intake for 6 weeks caused severe pathological changes in liver and kidney like disintegration, necrotic changes and perinuclear vacuolation[87]..

In an embryotoxicity and teratogenicity studies of an ayurvedic contraceptive—pippaliyadi vati, containing equal parts of powdered seeds or fruit berries of Embelia ribes, fruit of Piper longum and borax powder foetuses of mothers fed with pippaliyadi vati had low birth weights and were smaller in length. The mothers gained less weight during gestation. When developmental defects of soft tissues and skeletons were analyzed there were instances of herniation of the intestines into the umbilical cord in foetuses of mothers[88].

Miscellaneous
In a study to develop tablet formulation of embelin co-crystallized lactose-microcrystalline cellulose was the best diluent and alcoholic polyvinyl pyrrolidone proved to be the best binder. Solubility study revealed that it has optimum solubility in phosphate buffer of pH 8 and in 2% aqueous sodium lauryl sulfate solution and incorporation of 10% v/v ethanol to phosphate buffer of 7.4 pH enhanced the solubility of embelin[89].

REFERENCES


