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Review Article

2, 5-DIHYDROXY-3-UNDECYL-1, 4-BENZOQUINONE (EMBELIN)-A SECOND SOLID GOLD OF INDIA- A REVIEW

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ABSTRACT

Embelia ribes Burm f. (Myrsinaceae), an important traditional medicinal plant of Indian origin reported to be available in the Western Ghats of Tamil Nadu, Karnataka, Northern- eastern and Kerala state. *E. ribes* fruits contain a quinone derivative, embelin, an alkaloid christembine, a volatile oil and vilangin. Among them, embelin is the major bioactive constituents and marker compound in *E. ribes* berries. Embelin (2, 5-dihydroxy-3-undecyl-1, 4-benzoquinone) has a wide spectrum of biological activities, including antioxidant, antitumor, anti-inflammatory, analgesic, anthelmintic, antifertility and antimicrobial. The present review exemplifies the collective knowledge on therapeutic, pharmacological and medicinal applications of embelin. The development of this knowledge with perspectives of conservation, efficacy, safety and quality this will help not only to preserve this traditional heritage but also to rationalize the use of active compound in health care without any side effects. Our research on UVB protective effect of embelin using cell lines suggests, the antioxidant property prevents the irradiation damages. Considering the recent scientific bandwagon that multi-targeted is better than mono-targeted therapy for most curable diseases, embelin can be considered as an ideal life-saver drug. It can be considered as second solid gold of India next to curcumin with respect to wide spectrum of biological activities.

Keywords: Embelia ribes, Embelin, Biological activities, Zinc & Copper (II) embelin complexes.

INTRODUCTION

In India, berries of the *Embelia ribes* are used for numerous traditional medicinal remedies. The Government of India has set up a National Medicinal Plants Board (under the Ministry of Indian System of Medicine and Homeopathy) for over all enhancements of medicinal plants and its knowledge in the country. The Board has identified and prioritized 32 medicinal plants and *E. ribes* is one of plant which has gained national importance owing to it's therapeutically and commercial need [1]. *E. ribes* is also one among the top 20 ayurvedic drugs of the country as reported by Patwardhan [2]. Recently Stasiuk and Kozubek [3] reviewed and highlighted the antimicrobial, contraceptive and pro-apoptotic properties of embelin. Nevertheless, the present review summarizes the state of the art and highlights the most significant advances of 2, 5-dihydroxy-3-undecyl-1, 4-benzoquinone (Embelin) till date.

Botanical identity

Embelia ribes Burm. f., a plant of climber in nature, which belongs to the family of Myrsinaceae.

Distribution

It is found throughout India up to an altitude of 1600 m, from Central Himalaya to Konkan, Deccan, Western Ghats and South India.

Classical names

Following are the some classical names of *E.ribes*. Vidanga, Krimighna, Chitratandula, Jantunashana, Vella, Amogha, Kitashatru, Kitari,Krimijit, Krimiripu, Krimihara, Krimihrit, Jantughna and Jantuhrit.

Vernacular names

Following are the some vernacular names of *E.ribes* locally used by herb healer of different regions in India

English : *False pepper;* Hindi : *Vayavidanga;* Bengali : *Vidang;* Gujrati : *Vavading.*

Kannada : *Vayuvilanga;* Malayalam : *Vizhalari;* Marathi : *Vavding;* Punjabi : *Babrung,* Tamil : *Vayuvilangam;* Telugu : *Vayuvidangalu;* Assam : *Vidang;* Kashmiri : *Babading.* Oriya : *Bidanga.*

Botanical description

A large, scandant climber with long slender, flexible, terete branches; bark studded with lenticels. Leaves are simple (Figure.1a), alternate, elliptic-lanceolate, gland dotted, short and obtusely acuminate, entire, shiny above. Flowers are small, white or greenish, in both terminal and axillary panicles. Fruits are globose, wrinkled or warty, dull red to nearly black, a short pedicel often present (Figure 1b), usually one seeded and globose.

Plant parts

Commonly used parts of plants include fruits (berries), roots and leaf, to cure various diseases as described in the following paragraphs.

Biotechnology approach in conservation of E. *ribes*

In vitro conservation of E. ribes has already been initiated and made available in Botanical Garden, Institute of ayurveda and Integrative medicine (I-AIM, formerly known as FRLHT), Bengaluru. However, necessary conservation through biotechnological approach is need of hour to meet the growing market potential. Recently, Shankarmurthy and Krishna [4] reported, rapid regeneration of plantlets from the immature ovary calli attached to inflorescence segments of E.ribes. Raghu et al [5] reported direct shoot organogenesis from leaf explants of E. ribes.Annapurna and Rathore [6] reported rapid micropropagation of E. ribes through auxiliary shoot proliferation from mature plants. Balakrishna Gowda et al [7] reported AFLP as robust tool in identifying the degree of similarity and variation between E. ribes and Embelia tsjeriam-cottam.

Traditional uses

In olden days, dried fruits were considered for anthelmintic, astringent, carminative and used as an alternative and stimulant and usually administered as powder along with milk, followed by a purgative. It was also effective for the treatment of ascariasis better than Santonin and as good as Oil of Chenopodium [8].

Active constituents

Isolation of active constituent namely embelin started from the year 1900 onwards [9-10]. In addition, the plant also contains quercitol and fatty ingredients; an alkaloid, christembine, a resinoid, tannins and minute quantities of a volatile oil [8, 11]. Followed by its potential use, chemical synthesis was attempted [12-14]. All these publications exemplify the numerous biological/pharmaceutical studies and deliberately confirmed the potential value of the natural products for the treatment of various diseases Scenario on research publications related to embelin - 1914 up to September-2013

Fig. 1a: *E.ribes*

Fig. 1b: Berries of *E.ribes*

The following

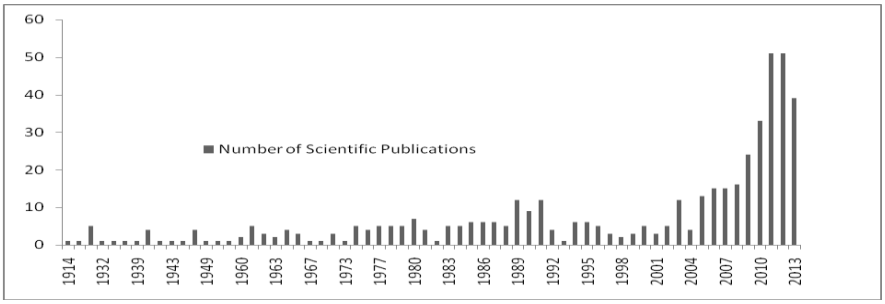
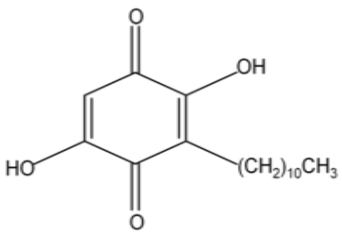
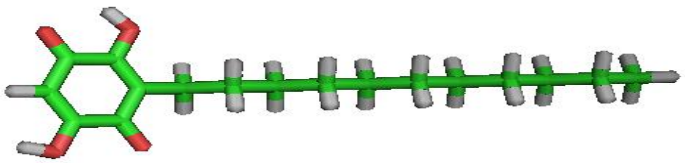


Fig. 2: illustrate the state of art of research publications made on embelin for the last 99 years.

Physicochemical properties of embelin

Table 1: summarizes the physicochemical characteristics of embelin for better understanding.

Structure	
CAS Registry number	550-24-3
Molecular formula	$C_{17}H_{26}O_4$
Molecular weight	294.391 g/mol
Chemical name	2,5-Dihydroxy-3-undecyl-1,4-benzoquinone
Synonyms	Embeline, emberine, embelic acid
Melting point	142.5^{0}C
Log p (octanol-water)	4.34
Solubility	Insoluble in water, but soluble in organic solvents such as DMSO and Ether.
Appearance	Orange solid
3DMET number	B03757
3D structure	

Derivatives of embelin

Other than embelin, research on derivatives of embelin has been initiated globally. Dhar and Onkar Singh [15] reported various metal complexes of embelin. Synthesis and characterization of copper (II) complexes of embelin in the cavities of zeolite Y attempted by Abraham and Yusuff [16] displayed catalytic activity. Similarly, Cherutoi et al [17] prepared copper (II) embelin and zinc (II) embelin. Pyrano embelin derivatives were also available in the literature [18]. Further, the following complexes, viz., Potassium embelate, 5-Methyl embelin, Embelin-5-O-Alkyl Ethers[2-hydroxy-5-methoxy-3-undecylcyclohexa-2,5-diene-1,4-dione, 5-ethoxy-2-hydroxy-3-undecylcyclohexa-2,5-diene-1,4-dione, 2-hydroxy-5-propoxy-3-undecylcyclohexa-2,5-diene-1,4- dione, 5-butoxy-2-hydroxy-3-undecyl benzo-1,4-quinone, 5-allyloxy-2- hydroxy-3-undecyl benzo-1,4-quinone, 5-benzyloxy-2- hydroxy-3-undecyl benzo-1,4-quinone were prepared by Kantham srinivas [19]. Recently, Viault et al [20] reported, synthesis of new derivatives of embelin by following the strategy on functionalization of aromatics by Suzuki–Miyaura reaction, which offered an embelin derivatives of second generation.

Biological activities

The most important aspect of biological activities of embelin is discussed in detail in the following paragraphs. The pie chart given below illustrates the overall biological activities of embelin. The maximum studies were on the antioxidant profile of embelin followed by anti-inflammatory and anti-helmintic activities. The percentage of other related activities are more or less similar.

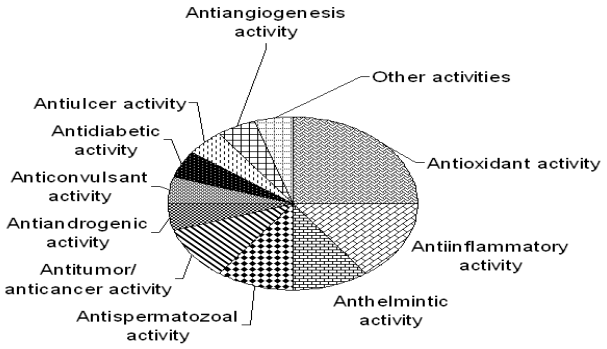


Fig. 3

Antioxidant activity

In general, an antioxidant is a molecule or agent capable of inhibiting the oxidation of other molecules. Oxidation reactions generate free radicals and these radicals triggered the biochemical chain reactions, which finally damage cells. Antioxidants terminate these chain reactions by neutralizing free radical intermediates and inhibit other oxidation reactions. In general, both plants and animals owns complex systems of multiple types of antioxidants defense systems endogenously, such as glutathione, vitamin C, and vitamin E (classical examples of non-enzymatic antioxidants) and catalase, superoxide dismutase and various peroxidases (enzymatic antioxidants). With regard to antioxidant activity of embelin few reports are available in public domain. Sumino et al [21] reported, embelin exhibited free radical scavenging activities towards diphenyl-picrylhydrazyl (DPPH) radicals with 50% inhibitory concentration (IC_{50}) of 23.3 ± 0.5 µM. Joshi et al [22] reported embelin inhibits lipid peroxidation and restore impaired Mn-superoxide dismutase in rat liver mitochondria. Siddharthan Surveswaran et al [23] reported crude *E.ribes* displayed free radical scavenging activities when tested using diphenyl-2-picrylhydrazyl ($DPPH^{\bullet}$). Uma et al [24] reported aqueous extract of *E.ribes* administered orally (100 and 200 mg/kg body weight) showed antioxidant activity against streptozotocin induced diabetic rats and Venkateshwar rao et al [25] substantiates the antioxidant activity of embelin. Dharmendra Singh et al [26] reported embelin exhibited a natural antioxidant activity against hepatotoxicity induced rats (at concentration of 25 mg/kg body weight). Radhakrishnan et al [27-28] observed embelin inhibits lipid peroxidation and restore impaired Superoxide dismutase in UVB-induced lymphocytes and fibroblasts.

Anti-inflammatory activity

Anti-inflammatory drug is a medication or pharmaceutical preparation used to treat or reduce inflammation. Most of commercially available anti-inflammatory drugs are steroids in chemical nature, and the adverse side effects are well known. Embelin finds use as anti-inflammatory drug in traditional medicine. Kapoor et al [29] reported the whole *E.ribes* plant as anti-inflammatory drug to relieve rheumatism and fever. Embelin and its 2, 5-isobutylmine salts have been reported to possess anti-inflammatory activity in carrageenan-induced paw edema and cotton pellet granuloma formation in rats [30]. Chitra et al [31] reported embelin as anti-inflammatory agent using albino rat model. Quinn et al [32] reported embelin inhibits (IC_{50} 2.4 µM) binding of MIP-1α to HEK cell membranes expressing human CCR1 receptor.

Anthelmintic activity

By definition, anthelmintics are drugs that eradicate/expel parasitic worms (helminths) from the body, by either inhibiting or killing them. They may also be called as vermifuges (inhibiting) or vermicides (killing).

Honiberger [33] reported *Embelia ribes as* a vermifuge, and after him, almost each publications on Indian indigenous medicines described the use of herb. Watt [34] reported addition of powdered seeds (*E. ribes*) in curdled milk in combination with castor oil was effective in the eradication/expel of tapeworms. According to Ved Prakash and Mehrotra [35], among the fifty-two Indian traditional herbs identified for anthelmintic activity, *E. ribes* is one among them. Further, herbal monographs (of M/s Himalayan Drugs Company, Bengaluru) suggested Embelin is effective against tapeworm but not against roundworm or hookworm [36]. The nematicidal activity of embelin has been reported by Mojumder and Mishra [37] against root-knot nematode (*Meloidogyne incognita*) with 90% mortality after 48 h exposure (at 100 ppm concentration level). Jalalpure et al [38] reported, *E.ribes* seed oil demonstrated effective against *Pheretima posthuma* compared to standard piperazine citrate (10 mg/ml).

Antimicrobial activity

Anti-microbial is a substance/compound that kills or inhibits the growth of microbes such as bacteria, fungi, or protozoans. These drugs either kill microbes (microbiocidal) or prevent the growth of microbes (microbiostatic). With regard to antimicrobial property of embelin, Chitra et al [39] studied antimicrobial activity of embelin against 12 pathogenic bacteria using disk diffusion method. At a concentration of 100 microgram/disk, inhibition was observed for all the twelve, but two of the bacterium namely *E.coli* and *K.pneumoniae* showed significant level of inhibition. Feresin et al

[40] reported embelin inhibited methicillin-sensitive and methicillin-resistant strains of *Staphylococcus aureus* with minimal inhibitory concentration (MIC) value of 250, 62 µg/ml respectively. Against *E.coli* they observed MIC value of 50 µg/ml. They also reported that embelin inhibits the dermatophytes namely *Epidermophyton floccosum*, *Microsporum canis*, *Trichophyton mentagrophytes* and *Trichophyton rubrum* with MIC of 50 µg/ml, however 100 µg/ml against *Microsporum gypseum.* Rani and Khullar [41] reported moderate antibacterial activity of aqueous and methanol extracts of *E.ribes*. Tambekar et al [42] reported acetone fraction of *E.ribes* berries showed mild antibacterial property against *Enterobacter aerogenes, Klebsiella pnemoniae*, compared to the standard drug Amoxicillin. Rathi et al [43] reported petroleum ether extract of *E.ribes* showed lowest MIC value of 250 µg/ml against *Candida parapsilosis* (MTCC 1744) and 360 µg/ml against *Candida laurintis* (MTCC 2898) while water extract of *E.ribes* showed higher MIC value for all organisms. Suthar et al [44] reported embelin exhibited antifungal activity with MIC_{50} values of 470, 1015 mg/L against *Aspergillus flavus* 871 and *Aspergillus* fumigates 2550 respectively. In our study, we observed bactericidal activity of embelin against Gram +ve organisms and bacteriostatic activity against Gram –ve organism [45].

Antispermatazoal activity

Antispermatazoal compounds are drug or compounds, which interfere with spermatogenesis process. Purandare et al [46] reported powdered berries of *E.ribes* administered orally three months at a dose of 100 mg /day to male bonnet monkeys, which results reduction in both the quantity and quality of semen. And added that reduction in testosterone levels in circulation may be responsible for the reduced of secretary activity of the accessory glands and which in turn decrease in volume of semen. Seth et al [47] reported embelin significantly reduced the sperm count and motility and also the weight of the testes, in albino rats at all the three tested concentration of 50,100 and 200 mg/kg body weight respectively. Gupta et al [48] reported significantly reduction in the percentage motile sperm count and also observed strong dose dependent reductions for all of the carbohydrate metabolism enzymes, when determined in spermatazoal suspensions with embelin concentrations from 1 to 5 mg/ (50×10^6) sperm cells with reductions of 29-73%.

Antiandrogenic activity

An anti-androgen, is a group of hormone receptor antagonist substances or compounds that are capable of preventing or inhibiting the biologic effects of androgens, male sex hormones, on normally responsive tissues in the body. Antiandrogens agents are used to treat severe male sexual disorders such as benign prostatic hyperplasia (prostate enlargement), *acne vulgaris*, androgenetic alopecia (male pattern baldness), and hirsutism (excessive hairiness). Agrawal and co-workers [49] reported antiandrogenic property of embelin during the year 1986 and after this report; no reports were available to till date.

Wound healing activity

Wound healing, is an intricate process in which skin repairs itself after injury. Upon injury to the skin, a set of complex biochemical events takes place in a closely orchestrated cascade to repair the damage. Wound healing is divided into four sequential, yet overlapping phases: (1) hemostasis , (2) inflammatory, (3) proliferative and (4) remodeling. The three phase (proliferate phase) is very important phase, which is characterized by angiogenesis, collagen deposition, granulation tissue formation, epithelialization, and wound contraction. Re-epithelialization or remodeling of the epidermis occurs, in which epithelial cells proliferate and crawl atop the wound bed, providing cover for the new tissue (wound closer).

Kumara swamy et al [50] reported wound healing activity of ethanolic extract of *E.ribes (*30 mg/ml) and further the authors also demonstrated, amongst the three wound models significant wound healing in embelin treated rats (4 mg/ml of 0.2% sodium alginate gel). Alam Khan and Naidu [51] reported significant improvement in burn wound contraction in the experimental group treated with the combination of embelin and silver sulphadiazine formulation respectively. In contradict to the above observations; Radhakrishnan & co-workers [52] observed inhibitory effect of wound healing in *in-vitro* wound healing model studies using fibroblast as well as endothelial cells. However, the reasons for inhibitory effect are yet to be explored (Results are not yet published).

Enzyme inhibitory activity

An enzyme inhibitor is a substance or molecule that binds to enzymes and decreases their activity. The binding of an inhibitor can arrest a substrate from entering the enzyme's active site and/or hinder the enzyme from catalyzing its reaction. Inhibitor binding is either reversible or irreversible. Most of the drugs are identified as enzyme inhibitors. Eventually, not all substances or molecules that bind to enzymes are inhibitors; enzyme activators also bind to enzymes and increase their enzymatic activity. In general, blocking an enzyme's activity can even kill a pathogen in case of microbes or cure disease/ diseases or correct a metabolic imbalance.

Hattori et al [53] studied various ayurvedic medicines for the inhibitory activities on the reverse transcriptase enzyme and reported that arecatanins and embelin are the two major potent inhibitory substances from *Areca catechu* and *E. ribes* respectively. Vijaya and Vasudevan [54] reported embelin as a weak, non-competitive and reversible inhibitor of trypsin. Embelin from *E.ribes* has been reported as a potent inhibitor of hepatitis C virus protease with IC_{50} value of 21 µM [55]. Gowadia and Vasudevan [56] reported a 10% (w/v) aqueous extract of *E. ribes* berries inhibited pancreatic lipase by 62%. Prashanth et al [57] reported ethanolic extract of the *E.ribes* seeds has shown α-amylase inhibitory activity (i.e. 59.3% inhibition) at concentration of 1mg / ml level. And further added α – amylase inhibitory activity of any plant material can be proven as an excellent tool for the treatment of obesity and diabetes. Acetyl choline esterase inhibitory activity of *E.ribes* root extract has been reported by Vinutha et al [58] with IC_{50} value of 23.04 µg/ml. Recently, Biradar [59] reported embelin inhibits histidine rich protein (HRP2) or heme polymerases with IC_{50} of 24.48 µM. And added embelin also inhibits Plasmepsins II & IV (10 Aspartic protease) in range of 5-25 µM level.

Antihyperlipidemic activity

Antihyperlipidemic agents are a diverse group of pharmaceuticals that are used in the treatment of hyperlipidemias. They are also called as lipid-lowering drugs (LLD) or agents. Uma et al [24] reported antihyperlipidemic activity of aqueous *E.ribes* extract in albino rats. Similarly, Jagadeesh et al [60] reported embelin protects and exhibits antihyperlipidemic activity towards chemically-induced (DENA/PB) hepatocarcinogenesis in wistar rats.

Anticonvulsant activity

Anticonvulsants are a diverse group of pharmaceuticals used in the treatment of epileptic seizures. Anticonvulsants are more exactly called antiepileptic drugs (AEDs), sometimes referred to as antiseizure drugs. Till date no drug has been shown to prevent epileptogenesis (the development of epilepsy after an injury such as a head injury) in Clinical trials [61]. Mahendran et al [62] reported embelin significantly inhibited seizures induced by electroshock and pentylenetetrazole in a dose dependent manner (2.5, 5 and 10 mg/kg, i.p) and added that embelin exhibits anticonvulsant activity against both grand mal and petit mal epilepsy.

Antitumor/anticancer activity

Antitumor /anticancer activity compounds are drug or agent that inhibit or delay or reverse tumor or carcinogenesis. Chitra et al [31] reported antitumor activity of embelin in methylcholanthrene-induced fibrosarcoma in albino rats and in addition enhancing their survival time. Nikolovska-Coleska et al [63] reported embelin as a fairly potent, nonpeptidic, cell-permeable, small-molecule inhibitor of XIAP and represents a promising lead compound for entirely new class of anticancer agents that target the BIR3 domain of XIAP. Dai et al [64] reported embelin inhibits chemical carcinogen-induced colon carcinogenesis.

Chemopreventive activity

The use of a drug or compound that interfere with a disease process, for instance, cancer chemopreventive agents are agents used to inhibit or delay or reverse carcinogenesis. Sreepriya and Bali [65] reported embelin prevents the induction of hepatic hyper plastic nodules, bodyweight loss, increase in the levels of hepatic diagnostic markers and hypoproteinemia against DENA/PB-induced hepatocarcinogenesis in wistar rats.

Antidiabetic activity

Anti-diabetic medications are used to treat diabetes mellitus by lowering glucose levels in the blood. They also called as hypoglycemic agents or antihyperglycemic agents. There are different classes of anti-diabetic drugs are available, and their selection depends on the nature of the diabetes, age and physical condition of the subjects/patients, as well as other factors. Diabetes mellitus type 2 is a disease of insulin resistance by cells. Treatments for these includes; (1) agents which increase the amount of insulin secreted by the pancreas; (2) agents which increase the sensitivity of target organs to insulin, and (3) agents which decrease the rate at which glucose is absorbed from the gastrointestinal tract.

Tripathi [66] reported, antihyper -glycemic activity of decoction of *E.ribes* berries in glucose-fed albino rabbits. Uma et al [67] reported the hypoglycemic effects of ethanolic extract of *E. ribes* berries in streptozotocin- induced diabetic rats. And added that *E. ribes* treated rats showed 68% reduced blood glucose level versus untreated group (control group). Mahendran et al [68] reported antidiabetic activity/antihyperglycemic activity of embelin against alloxan induced diabetic rats at concentration of 25 and 50 mg/kg body weight administered orally, reduces significantly fasting blood (serum) glucose levels and also added embelin treated rats improved significantly in body weights.

Antiulcer activity

Antiulcer activity compounds are drug or agent that inhibit or delay or reverse ulcer. Vyawahare et al [69] reported *E.ribes* one of the active ingredients of amlant (capsule), which cures ulcer. Similarly, Thippeswamy et al [70] reported protective effect of embelin against acetic acid- induced ulcerative colitis in rats and added that the protective effect may be due to its antioxidant and anti-inflammatory activities.

Anti-angiogenesis activity

Anti-angiogenesis compounds are drugs or agents that inhibit or delay or reverse angiogenesis process. Thangapazham et al [71] reported *E.ribes* one among herb of brahma rasayana, inhibits angiogenesis. And added that brahma rasayana treated animals showed significant reductions in Factor VIII, pro-angiogenic factors like VEGF, MMP-9 and MMP-2, suggesting that the rasayana may also have anti-angiogenic properties.

Zhengfang et al [72] reported embelin as a potent drug for inhibiting angiogenesis. Radhakrishnan and co-workers observed anti-angiogenic activity of embelin and its dimer (Vilangin) when tested using chick chorioallantoic membrane (CAM) and human endothelial cells models(data under communication).

Cytotoxicity activity

Cytotoxicity agents are substances or compounds being toxic to any cells at given concentration. Cytotoxicity assays are widely used by the pharmaceutical industry to screen for cytotoxicity in compound libraries or to ensure product safety under *in vitro* condition or model. Researchers are interested in discovering newer cytotoxic compound and developing as therapeutic agent, which targets rapidly dividing cancer cells with affecting normal cells.

Feresin et al [40] observed embelin at 217 µg /ml was toxic to lung fibroblasts. Podolak et al [73] reported cytotoxicity of embelin (ED_{50} value) using B16, Human fibroblast and XC cell lines at respective concentrations of 13, >20 and 8 µg /ml.

Krishnaraju et al [74] reported cytotoxicity of *E.ribes* berries against brine shrimp at LC_{50} (24 hour) 463 µg /ml. Sreepriya et al [75] reported cytotoxicity of embelin (IC_{50} value) at concentrations of 16.85 µM, 27.52 µM against mouse lymphocytes and mouse macrophages respectively.

Toxicity

This paragraph highlights about toxicological profile of embelin, which is more relevant in the current era that assures safety to one and all and also the need of the hour. According to OSHA 29 CFR 1910.1200 as reported in (M/S Santa Cruz Company, USA) material safety data sheet [76] embelin is not a hazardous agent. Despite this information, number of experimental studies have been undertaken to understand the nature of embelin using animal models and the results substantiate with the material safety date sheet. Gupta et al [77] observed no change in food intake, behavior, appearance and clinical signs in the experimental animals (Rats) administered with embelin (subcutaneous) at a dose of 20 mg/kg body weight/day for 30 days. Similarly, Prakash [78] also observed no significant physical and morphological changes after the administration embelin at a dose of 120 mg/kg body weight, except an increase in weight of the adrenals.

Radiosensitization activity

Radiosensitization activity compounds are drugs or agents that make tumor cells more sensitive to radiation therapy, for example Ferulic acid (FA) and 2-Deoxy glucose (2DG). Dai et al reported embelin enhances the anti-tumor activity of conventional radiation therapy under *in vitro* and *in vivo* conditions, representing a promising new adjuvant regime for the treatment of hormone refractory prostate cancer. However, *E. ribes* one of the active ingredient of abana, a polyherbal drug, which reported to protect total body gamma radiation in experimental mice [79].

Application of embelin.

The above-summarized paragraphs explicitly demonstrated the multifaceted function of embelin evaluated scientifically. Further, embelin and *E.ribes* has also been reported other applications as summarized below: (a) Harish chander and Ahmed [80] reported grain protectant activity of embelin against pests in wheat storage. (b) Paranjpe et al [81] reported one of Ayurvedic formulation namely; Sunder Vati (contains *E.ribes* as one of key ingredient) showed a significant improvement in inflammatory and non-inflammatory lesions compared with baseline or placebo in Indian patients with *Acne vulgaris*. Samatha and Vasudevan [82] reported embelic acid (synonym of embelin) isolated from *E.ribes* for dyeing hair. However, retention of the color is inferior to *Pterocarpus santalinus* extract studied. Anand Kumar and Sachidanand [83] conducted a clinical trial studies with new polyherbal formulations namelly CLARINA cream and PURIM tablet. *E.ribes* is one of ingredients of CLARINA cream and added that CLARINA cream along with PURIM tablet was useful in treating patients with various degrees of acne. Prashant et al [84] reported various Indian medicinal plants, which have been used in cosmetic preparations and added that *E. ribes* one among the plant has been used as a cosmetic agent to cure skin disorders for centuries. Recently in our laboratory we observed enhancing pigmentation of human skin/hair by embelin via promoting tyrosinase activity [85]; (c) Renuka et al [86] prepared polymer material in the presence of embelin and studied the biodegradable nature of the resultant polymer; (d) Embelin has also been used as an analytical agent according to Bheemasankara rao et al [87-88] for the estimation of uranium and thorium, copper and cadmium; (e) Kalaselvi and Renuka [89] reported embelin as a cathode electrode agent in a zinc based secondary battery using $ZnCl_2$-NH_4Cl electrolyte.

Patents pertaining to embelin

This paragraph highlights about intellectual wealth of embelin, which is more appropriate in knowing intellectual rights and in the perspective of intellectual wealth makers. In European patent search (worldwide) database only '5' direct hits are available among this one patent filed by Indian inventors [90] related to preparation of salts of embelin with primary amines. One patent filed by Japanese inventors [91] related to tooth decay prevention by embelin as an active ingredient. One patent filed by Taiwan

inventors [92] related to multiple specific inhibitors of cytochrome P450 isozyme (CYP2C9) that contains embelin as an active ingredient. One patent filed by Chinese inventors [72] related to application of embellin in preparation of medicament for inhibiting angiogenesis. One patent filed by Americans inventors [93] related to naturally occurring and chemically synthesized small molecule antagonists of XIAP family proteins that contain embelin as one of active ingredient.

Miscellaneous

Embelin isolation has been reported from other natural or botanical sources (alternative to *Embelia ribes*) such as *Embelia tsjersium-cottam*, *Embelia barbeyana*, *Embelia robusta*, *Embelia kilimandscharica*, *Ardisia humilis*, *Rapanea umbellata*, *Connarus ritchiei*, *Myrsine africana*, *Myrsine semiserrata* & *Myrsine capitellata*. Recently, a stress degradation study of embelin provides additional information about its stability and storage conditions required for modern therapeutically use [94]. Similarly, embelin reported to have Interleukin-1 beta (IL-1β), Tumor necrosis factor-alpha (TNF-α), human 5-Lipoxygenase (5-LO) and microsomal prostaglandin E_2 synthase-1 (mPGES-1) inhibitory activity respectively [95-96]. Furthermore, biological properties of Zinc and Copper (II) embelin complexes has been evaluated and reported by us [97-98]. Recently, embelin has been reported to bind with collagen [99], tyrosinase [100] and human neutrophil elastase [101] using molecular docking studies.

CONCLUSION

All the above said descriptions exemplify the varied roles of embelin and all the studies evidently accepted the fact embelin has enormous potential for treatment of several diseases. The overall biological efficacy, safety and the continuous usage from the past century justify calling embelin" Second solid gold of India".

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