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A Review on Plant Derived Multitarget Therapeutic Phytomolecule - Embelin

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ABSTRACT

Embelin is a multi targeted therapeutic agent extracted from fruits of Embelia ribes. It exhibits various bioactivities making it a vital molecule of future research. This article focuses on various pharmacological activities involved by Embelin. The plant exhibit extensive pharmacological activities such as wound healing, hypoglycemic, cardiovascular, antioxidant, antimicrobial, antidiabetic and anti fertility.

Key words:
Multi-Targeted, Therapeutic Agent,Fruits of Embelia Ribes, Embelin, Plant Derived,Phytomolecule.

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INTRODUCTION

Embelin is chemically known as 2, 5-dihydroxy-3-undecyl-1,4-benzoquinone, which is the major active constituent of the fruits from *Embeliaribes* Burm (Family: Myrsinaceae), commonly known as "False Black Pepper". It has a wide spectrum of biological activities and is not toxic at low dose[1]. Embeliaribes has extensive propertises making it a subject of research and studies. The plant exhibit extensive pharmacological activities such as wound healing, hypoglycemic, cardiovascular, antioxidant, Antimicrobial, anti diabetic and ant ifertility[2].

CHEMISTRY

Embelin belongs to class of dihydroxy-1, 4-benzoquinones that is 2,5-dihydroxy-1,4-benzoquinone which is substituted by an undecyl group at position[3].It is isolated from Lysimachiapunctata and Embeliaribes, it displays antimicrobial, anti neoplastic and inhibitory activity towards hepatitis C protease. It finds it's as hepatitis C protease inhibitor, an antimicrobial agent, an antineoplastic agent and a plant metabolite. Embelin is a phytochemical component of tropical plants that have a long medicinalhistory of being used in ethnic pharmacology across the globe, including Ayurdvedic and Chinese medicinal texts. Many modern studies authenticate it as a medicinal compound. The X-ray crystal structure determination of embelin displays a remarkably ordered alkyl chain and particularly strong pi–pi interactions for a nonaromatic system. Embelin when entrenched in the plasminogen activator inhibitor1 (PAI1) binding site shows 10° torsion angle(almost planar) where as torsion angle of molecule is 67° between the ring and the alkyl chain of the molecule e). This establishes thatembelin's flexible structural skeleton can be useful in biological environment. Besides this, Embelin's hydrophobic nonpolar tail allows a variety of interactions and responsible for its biological activities. Embelin executes this reaction towards superoxide radical. embelin prefers to accept an electron from the superoxide radical, which then transforms into molecular oxygen, instead of releasing a H atom to the superoxide radical to form the anionic species O_2H [3].

VARIOUS PHARMACOLOGICAL ACTIVITIES

1. COMBATS CANCER

- Inhibits apoptosis

The study was conducted to suggest that X linked inhibitor of apoptosis is an important molecular target for anticancer drugs that overcome apoptosis resistance of malignant cells. XIAP associate with BIR3 domain of capase9 and thereby act as inhibitor of apoptosis. Embelin which is isolated from Embeliaribes plant exhibited chemo preventive, anti-inflammatory and apoptotic activities by inhibiting XIAP activity. They found that embelin causes a dose dependent suppression of proliferation in leukemic cell lines K562 and U937.They also inferred that embelin treatment cause loss of mitochondrial membrane potential and release of cytochrome which AKTse-polymerase(PARP) cleavage.Embelin treatment also lowered constitutive phosphorylation/activated level of AKT& down regulation of XIAP.Gene silencing of XIAP and AKT expression displayed a link b/w XIAP expression and activated AKT in leukemic cells.Also,targeting of XIAP & P13 kinase / AKT signaling augmented inhibition of proliferation and induction of apoptosis in leukemic cells.They concluded that embelin or its combination with inhibitors ofP13 kinase /AKT pathway are beneficial in therapeutic treatment of leukemia and possibly other malignancies with upregulated XIAP pathway[4].

- Cytotoxic effect

The study was conducted to isolate embelin from underground parts of Lysimachia punctate and they found that it showed significant cytotoxic activity invitro against B16 and XC cell lines with ED50 values of 13microg/ml &8 microg/ml respectively[5].

- Inhibitory effect on colon carcinogenesis Certain studies evaluated the impact of embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone), associated degree antagonist of XIAP, on carcinoma, and targeted on whether or not PPAR gamma is crucial for embelin to exert its impact. A dominant-negative PPAR gamma was wont to antagonize endogenous PPAR gamma in HCT116 cells. Cells

were treated either with or without embelin.Then cell proliferation, apoptosis, and nuclear factor-kappaB (NF-kappaB) activities were determined. 1, 2-dimethylhydrazine dihydrochloride (DMH) was s.c. injected to inicite colon carcinoma in PPARgamma(+/+) and PPAR gamma(+/-) mice. Mice were nourished with embelin daily for ten days before DMH injection, and prolonged for thirty a lot of weeks. Embelin inhibited proliferation and elicited cell death in HCT116 cells with marked up-regulation of PPAR gamma. Additionally, embelin considerably inhibited the expressions of survivin, cyclin D1, and c-Myc. These effects were part hooked in to PPAR gamma. PPAR gamma(+/-) mice were a lot of vulnerable to DMH-induced colon carcinogenesis than PPAR gamma(+/+) mice, and embelin considerably reduced the incidence of carcinoma in PPAR gamma(+/+) mice however not in PPAR gamma(+/-) mice. Embelin inhibited NF-kappaB activity in PPARgamma (+/+) mice however marginally thus in PPARgamma (+/-) mice. Thus, reduced expression of PPAR gamma considerably sensitizes colonic tissues to the cancer impact of DMH. Embelin inhibits chemical carcinogen-induced colon carcinogenesis, however this impact is part hooked in to the presence of useful PPARgamma, indicating that PPAR gamma may be a necessary sign pathway concerned within the anti neoplastic activity of traditional organisms[5].

2. SUPPRESSES INFLAMMATORY REACTION

- Fights sepsis

The study was conducted to show the capability of embelin to fight sepsis. Their studies probed the upshot of embelin on cecal and ligation and puncture (CLP)-induced rat sepsis. Their studies unveiled that single-dose administration of embelin 1 h after surgery significantly ameliorates survival of rats with CLP-induced sepsis. Besides, embelin treatment also reduced the serum levels of pro-inflammatory cytokines including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 and dropped organ inflammation and injuries. Furthermore, embelin suppressed the activation of p65 subunit of nuclear factor-kappa B (NF-κB) and signal transducers and activators of transcription 3 (STAT3). They finally concluded that embelin ameliorates sepsis in rats through suppressing STAT3 and NF-κBpathways[6].

- Fights autoimmune disorders

The study was performed to show the potential effect of embelin on autoimmune inflammatory disorders. Their studies indicated that EB suppressed human CD14 (+) monocyte-derived dendritic cell (DC) differentiation, maturation, and endocytosis and further hindered the stimulatory function of mature DCs on allogeneic T cell proliferation in vitro. Furthermore studies demonstrated that, embelin blocked the DC-derived expression of the Th1 cell-polarizing cytokines interferon-γ and interleukin (IL)-12 and the Th17 cell-polarizing cytokines IL-6 and IL-23.There was a reduction of EAE clinical score after in vivo administration of embelin in central nervous system inflammation, and in demyelination., Through the promotion of transforming growth factor-beta and β-catenin expression and obstruction of signal transducer and activator of transcription 3 signaling pathways in DCs, embelin also subdued inflammatory Th1 and Th17 cells in EAE. Their researches authenticate that embelin has potent anti-inflammatory and immunosuppressive properties and is therefore a potential therapeutic drug for MS and other autoimmune inflammatory diseases[7].

Research was conducted to investigate the effect of embelin isolated from EmbeliaribesBurm in lipopolysaccharide (LPS)-induced sickness behaviour in mice. In the experiment they pretreat an adult male Swiss albino mice with embelin (10 and 20 mg/kg, p.o.) or dexamethasone (1 mg/kg, i.p.) for 3 days and then challenged with LPS (400 µg/kg, i.p). Sickness behaviour was assesed in the animals by behavioural tests.) At different time intervals of post-LPS challenge. Oxidative stress makers (reduced glutathione and lipid peroxidation) levels in mice brain were also examined. Behavioural alterations, anhedonia and anorexia, were induced by LPS in mice. Behavioural changes induced by LPS was attenuated by pre-treatment with embelin . Also, embelin averted anhedonia, anorexia and ameliorated brain oxidative stress markers.Their studies concluded that embelin has protective effect in LPS induced sickness behaviour in mice[8].

3. INHIBIT ANTIOXIDANT ACTIVITY

The study was conducted to show the free radical scavenging and antioxidant activity of embelin. They found that embelin has capability to scavenge DPPH radical and prevent hydroxyl radical induced deoxyribose degradation. They also discovered that embelin has abilityI to restrain lipid peroxidation and revive impaired Mn-superoxide dismutase in rat liver mitochondria. Nanosecond pulse radiolysis technique was used to study kinetics and mechanism of the reactions of embelin with hydroxyl, one-electron oxidizing, organo-haloperoxyl and thiyl radicals' .Cyclic voltammetry was used to estimate its redox potential. Their studies proved that embelin is a combative antioxidant in physiological conditions[9].

4. FIGHTS ALZHEIMERS DISEASE

The study was carried out to know about the therapeutical potential of embelin against intra cerebro ventricular streptozotocin (ICV-STZ)-induced experimental sporadic dementia in rats. In the experiment STZ was suffused bilaterally at the dose of (3 mg/kg/1 µl/1 min) ICV on first and third day. By employing morris water maze and object recognition task in rat's spatial and non-spatial memory was assessed. From the seventh day after ICV-STZ infusion in rats embelin (2.5, 5, and 10 mg/kg, i.p.) was taken. Rats were immolated on 22nd day and hippocampal brain regions were used to identify biochemical, neurochemical, and neuro inflammatory alterations. Due to escalated oxidative stress (lipid peroxidation and nitrite), compromised antioxidant defense (reduced glutathione), neurotransmitter alterations (AChE, dopamine, noradrenaline, 5-hydroxytryptamine, gama amino butyric acid, and glutamate), and upsurgedneuroinflammatory cytokine (IL-1 β, IL-6, and TNF-α) levels STZ-infused rats showed significant learning and memory deficit. Embelin dose dependently diminished STZ-induced cognitive deficit and biochemical alterations and revived hippocampal neurochemical levels.The studies surmised the therapeutic potential of embelin to defend Alzheimer's disease (SAD) [10].

5. FIGHTS HYPOXIA

The study was performed to estimate capability of embelin to combat hypoxia, which is a common cause of neurological injury in premature/low-birth-weight infants and term infants with birth complications. The clinical evidence shows that male infants with HI exhibit more severe cognitive deficits compared to females with equivalent injury. Experiment makes use of neonatal injections of vehicle or embelin (a small molecule inhibitor of XIAP) in male and female rats with or without induced HI injury on postnatal day 7 (P7). Behavioral testing was performed using a clinically relevant task and which unveils that the inhibition of XIAP enraged HI-induced persistent behavioral deficits in females, with no effect on HI males. These experiment suggest that development of sex-specific neuro protectants for the treatment of HI offers a potential clinical benefit[11].

6. FIGHTS EPILEPSY

Certain studies was conducted for the anticonvulsant drug activity of embelin.The anticonvulsant drug activity of embelin (2.5, five and 10mg/kg, i.p.) was studied. It showed a big inhibition of the seizures evoked by shock therapy and pentylenetetrazole during a dose dependent manner and also the activity was resembling diphenylhydantoin and Valium. Vital decrease in locomotion revealing its central nervous system depressant activity was discovered. The findings recommend that embelin possess anticonvulsant drug activity against each generalized seizure and epilepsia minor brain disease[12].

7. FIGHT HUNTINGTON'S DISEASE

3-Nitropropionic acid (3-NP) causes severe neurotoxicity in animals, that depicts monogenic disease (HD) in humans.The study was conducted to explore neuroprotective effect of embelin against 3-NP induced experimental HD in rats. The adult Wistar rats were pretreated with vehicle/embelin (10 and 20mg/kg p.o.) for 7 days.From 8th day onwards, embelin was co-treated with 3-NP (15mg/kg, i.p.) for 7 days. Animals wereevaluated for activity alterations and brain homogenates were used for estimation of aerobic stress parameters (lipid peroxidation, reduced glutathione, catalase and glutathione-S-transferase)at the tip of the treatment schedule.2,3,5-Triphenyl tetrazolium chloride (TTC) stained brain slices were used for lesion size activity .During the experiment, it was observed thatadministration of 3-NP considerably altered the activity and vegetative cell inhibitor standing and caused important vegetative cell harm in striatal region.Embelin, at each the tested doses, caused a significant reversal of behavioral and antioxidant status alterations and reversed the striatal neuronal damage induced by 3-NP.Their findings recommend the neuroprotective impact of embelin against HD. and it ascertained protecting impact may be attributed to the inhibitor properties of embelin[13].

8. IMPROVES OSTEOPOROSIS

Osteoclast is amenable for the osteolysis seen in bone metastases of the tumor. The major mediator of bone loss is the receptor activator of NF-κB ligand (RANKL), a member of the tumor necrosis factor superfamily and an activator of the NF-κB signaling pathway commonly associated with cancer and other chronic inflammatory diseases. Embelin (2, 5-dihydroxy-3-undecyl-1,4-benzoquinone), derived from the Ayurvedic medicinal plant EmbeliaRibes, exhibited the ability to bind and inhibit X-linked inhibitor of apoptosis protein and inhibit inflammatory pathways. The study was conducted to research whether embelin could inhibit osteo clastogenesis-associated bone loss induced by RANKL and by tumor cells in vitro. They found that embelin suppressed the RANKL-induced differentiation of monocytes into osteoclasts. This chemical compound conjointly suppressed the osteoclastogenesis elicited by myeloma and by carcinoma cells. This impact of embelin correlative with the suppression of NF-κB activation and inhibition of IκBα phosphorylation and IκBα degradation. Inhibition of IκBα phosphorylation was thanks to the inhibition of IκBα enzyme (IKK) activation. Furthermore, by using an inhibitor of the IKKγ or NF-κB essential modulator (NEMO), the regulatory component of the IKK complex, they showed that the NF-κB signaling pathway is mandatory for RAW 264.7 cell differentiation into osteoclasts. The experiment summarized that embelin, AN substance of RANKL-induced NF-κB activation has nice potential as a therapeutic agent for pathology and cancer-linked bone loss[14].

9. ANALGESIC PROPERTY

Certain studies investigated analgesic property of embelin.Acetic acid induced writhing method (18) was carried out in mice(n=4) to evaluate the analgesic activity of embelin.The animals were given acetic acid(0.6%,10 ml/kg I.P),30 min after intake of embelin(50&100mg/kg) or the vehichle(DMSO) SC. Embelin prevented writhing in embelin treated rats in the dosage study for analgesic activity(50 &100mg/kg)[15].

10. IMPROVES DIABETES

Studies were performed to evaluate embelin for its potential to control hypoglycemic agent resistance, alter β-cell pathology and modulate key markers concerned in hypoglycemic agent sensitivity and aldohexose transport victimization high-fat diet (HFD)fed-streptozotocin (STZ) (40mg/kg)-induced rats infected withtype 2 diabetes. Molecular-dockings were performed to research the binding modes of embelin into PPARγ, PI3K, p-Akt and GLUT4 active sites. Embelin (50mg/kg b wt.) reduced weight gain, blood sugar and plasma hormone in treated diabetic rats. It any modulated the altered supermolecule profiles and inhibitor enzymes with cytoprotective action on β-cell. Embelin considerably multiplied the PPARγ expression in epididymal fatty tissue compared to diabetic management group; it conjointly smothered adipogenic activity; it gently activated PPARγ levels within the liver and muscle. It conjointly regulated hormone mediate aldohexose uptake in epididymal fatty tissue through translocation and activation of GLUT4 in PI3K/p-Akt sign cascade. Embelin guaranteed toPPARγ; it disclosed stable binding affinities to the active sites of PI3K, p-Akt and GLUT4[16].

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11. ANTIMICROBIAL ACTIVITY

The study was performed to examine the restrictive activity of embelin against β-lactamase NDM-1. Embelin was tested against NDM-1 carbapenemase the IC50 of embelin was found to be 2.1 ± 0.2 μM The hydroxyl of embelin interacted directly with the metallic ion Zn2+ as most regions of the embelin molecule were buried in NDM-1's active site. Systematic analysis of the medicine activities of embelin and antibiotics, incontestable that embelin improved meropenem activity against a panel of NDM-positive pathogens, like escherichia, entero bacteria pneumoniae, and Acineto bacterbaumannii. Based on these results, they concluded that embelin may be a promising carbapenem adjuvant candidate against NDM-1-producing microorganism strains[17].

12. ANTIFERTILITY ACTIVITY

Certain studies investigated anti fertility property of embelin.31 mature male Swiss albino rats weiglung 180-200 g, were selected and maintained on a standard diet .Water ad libitum, were dispensed into 4 groups. Different doses of embelin were prepared by dis- solving a weighed quantity of embelin in a weak solution of ammonia. The solution was boiled to evaporate ammonia, cooled and administered subcutaneously to various treat- ment groups. Control rats were given vehicle only by the same route. The animals were sacrificed 24 hr after the last treatment using light ether anesthesia. Testes, accessory reproductive organs, adrenal gland and levatorani muscle were excised, blotted free of blood and weighed on 'Polar' monopan balance. Diameter of Leydig cell nuclei was measured at X 675 from many sections. Germ cells were counted following Leblond and Clermont (1952) and corrected by Abercrombie's formula (1946). Diameter of germ cells was meas- ured at X 1000 from many sections. The results were statistically assesed using student test. Embelin, extracted from Embeliaribes Burm. Berries, altered the testicular histology and glycogen, gametogenic counts and accessory sex gland fructose at the dose levels 0.3, 0.4 and 0.5 mg/kg body weight administered subcutaneously for 35 days. The experiment suggested embelin possess antiandrogenic activity[18].

13. FIGHT PSORIASIS

The study was conducted to analyze the consequences of embelin on lipo polysaccharide induced TNF-α production in mice and in human keratinocytes in vitro and conjointly check the effect of embelin on acute and chronic skin inflammation in mice. Production of pro-inflammatory cytokines (TNF-α and IL-1β), activation of myeloperoxidase and microscopic anatomy assessment were examined in acute and chronic skin 12-O-tetradecanoyl-phorbol-13-acetate (TPA)-induced mouse ear lump..It was seen that embelin suppressed topical lump inside the mouse ear, leading to substantial reductions in skin thickness and tissue weight, inflammatory protein production, neutrophil-mediated myeloperoxidase activity, and various histopathologicalindicators. Furthermore, embelin was potent at reducing inflammatory injury induced by chronic TPA exposure. Their studies indicate that embelin has anti-inflammatory activities in both acute and chronic irritant contact dermatitis in vivo and this effect of embelin could also be due, a minimum of partly, to the inhibition of IL-1β and TNF-α and to the following blockade of blood cell accumulation[19].

15. COSMETIC AGENT

Certain studies proved the use of embelin as a cosmetic agent to cure skin disorders. E.ribes is employed particularly for coloring hairs, sensible symptom remover, trea-ting acne, treating carbuncle infections, treating skin problem and leucoderma. E. Ribes berries contain aquinone by-product embelin (2, 5-dihydroxy -3-undecyl,l ,4- benzoquinone), incorporates a wide spectrum of biological activities like inhibitor, antitumor, medicine and analgesic ,anti helmintic, anti fertility and antimicrobial. benzoquinone derivatives andalso the analogs; coenzyme (Coenzyme Q10), ldebenone, Arbutin and Hydroquinone square measure well-known for cosmetic applications. Within the giftstudy, embelin from E.ribes berries of Indian origin was extracted and characterised by ultraviolet radiation and Ff-IR analyses. Hemolytic, tyrosinase and dihydroxy phenylalanine auto-oxidation assays were additionally dole out. About 1.9± 0.1 gramof pure embelin was obtained from one hundred gram of small-grained berries (E.ribes). The characteristics stu-dies reveal the properties square measure on par with the quality embelin received from letter of the alphabet (USA). The half-maximal effective concentration (ED50) of embelin to cause haematolysis was found as 109± O.I μg/ml. Thetyrosinase restrictive activity of embelin was nit and also the dihydroxyphenylalanine auto-oxidation activity was observed up to 350 μg/ml concentration. So the embelin finds doubtless application in cosmetic industries[24].

16. FIGHT LIVER DISEASE

The study was conducted to evaluate hepatic antioxidant activity of embelin in albino rats. Rats were subjected to carbon tetrachloride treatment making it susceptible to peroxide damage. On comparing to vehichle controls the concentration of lipid peroxidation was significantly ($P \leq 0.001$) higher in liver and serum.The serum of CCl-treated rats displayed variation in the activities of marker enzymes--transaminases (AST, ALT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH)--along with the total bilirubin and total protein levels significantly ($P \leq 0.001$).The rats were orally administered with embelin(25 mg/kg) from day 1 today 15.The peroxide damage was found less in serum and liver along with effectively inducing the antioxidant potential in CCl -treated rats. They compared biochemical results with standard drug Silymarin a combination of flavonolignans of Silybummarianum and histology of liver sections and concluded that embelin is a potential antioxidant against hepatotoxicity elicited in rats[22].

17. CARDIOPROTECTIVE EFFECT

The study was performed to ensure the cardioprotective impact of liquid extract of fruits of EmbeliaRibesBurm (ER) in a rat model having acute MI, evoked by isoproterenol (5.25 and 8.5 mg/kg, sc, for 2 consecutive days. The isoproterenol treated rats were pretreated orally aqeous extract (100mg) for 40 days. Rats displayed decreased the heart rate, systolic blood pressure, exaggerated levels of serum lactate dehydrogenase, serum creatine kinase and myocardial lipid peroxides and significantly attenuated the myocardial endogenous

antioxidants (glutathione, superoxide dismutase and catalase) levels.. The results of biochemical observations in bodily fluid and heart tissues were supplemented by histopathological examination of rat's heart sections to verify the heart muscle injury. The results were akin to that of gliclazide treated cluster. The research offer proof for the primary time, that aqeous ER extract pretreatment ameliorated heart muscle injury and increased the inhibitor defense againstnst ISO-induced MI in rats and exhibited cardio protective property[23].

18. FIGHT OBESITY

The study was conducted to show the effect of embelinon adipocyte differentiation and lipogenesis in murine ST2 stromal cells and C3H10T1/2 mesenchymal cells. Their experiment investigated mechanisms through which Embelin regulates adipogenic differentiation and lipogenesis. The *in vivo* anti-obesity effects of Embelin in high-fat diet (HFD)-induced obesity mice and transcriptional impact were explored. The studies revealed that Embelin treatment restrained the proliferation of ST2 and C3H10T1/2 cells, and differentiate into mature adipocytes, along with the inhibition of adipogenic factors peroxisome proliferator-activated receptor γ, CCAAT/enhancer binding protein-α, adipocyte protein 2 and adipsin. . Embelin treatment also hindered the expression levels of lipogenic factors sterol regulatory element-binding protein 1, fatty acid synthase, acetyl-CoA carboxylase 1 and stearoyl-Coenzyme A desaturase. The translocation of β-catenin from the cytoplasm into the nucleus in C3H10T1/2 were attenuated by embelin. . Moreover, embelin down regulated Dickkopf-1 (Dkk1) .The over expression of Dkk1 in C3H10T1/2 .reversed the inhibition of adipogenesis and lipogenesis. Embelin also that induction of adipogenic and lipogenic factors and Dkk1 in adipose tissue in HFD-fed mice. Hinderd. The work concluded that embelin has ability to intercept weight gain and to refute obesity related problem[24].

19. AMELIORATE RESPIRATORY DISTRESS SYNDROME

Studies estimated the effectiveness of Embelin isolated from Embeliaribes seeds on attenuation of LPS-induced acute respiratory distress syndrome in murine models. Rats were administered with embelin (5, 10 and 20 mg/kg/day, i.p.) and roflumilast (1 mg/kg/day, p.o.) for four days prior to LPS. Animals were anesthesized and bronchoalveolar lavage was done with ice-cold phosphate buffer afer four days of LPS challenge. Albumin, total protein, total cell and neutrophil count, TNF-α levels, nitrosoative stress were assessed. Superior lobe of right lung was used for histopathologic examination where as Inferior lobe of right lung was used to obtain lung edema. . Arterial blood was collected and pH, pO2 and pCO2 were evaluated. It was found that pretreatment with embelin (5, 10 and 20 mg/kg, i.p.) reduced lung edema, mononucleated cellular infiltration, nitrate/nitrite andtotal protein. Albumin concentrations, TNF-α in the bronchoalveolar lavage fluid and myeloperoxidase activity in lung homogenate WERE ALSO REDUCED. Embelinhindered pO2 down-regulation and pCO2 augmentation. Moreover it increased lung histopathological changes in acute respiratory distress syndrome model. Their studies indicate that embelin is a potential therapeutic agent for acute respiratory distress syndrome[25].

20. ANTIPSYCHOTIC ACTIVITY

The study was conducted to assess the antipsychotic activity of embelin against apomorphine-induced climbing behaviour in mice and stereotyped behaviour in rats. Rats were administered with two doses of embelin (5 and 10mg/kg) once daily for 15days before exposure to apomorphine. The climbing and stereotyped behaviors of rodents were evaluated on the last day of pretreatment after apomorphine-injection. Results showed that embelin pre-treatment hindered apomorphine-induced climb and stereotypical behaviours in mice and rats. .Moreover, embelin reversed raised levels of dopamine, noradrenaline and serotonin neurotransmitters in the brain of rats and mice. Embelin exhibited more important results at high dose (10mg/kg) than low dose (5mg/kg) in both the tested models. Their research suggested that embelin possesses antipsychotic activity in the treatment of psychotic disorders[26].

21. PROTECTS NEPHROTOXICITY

The study was carried out to examine the nephroprotective effects of ethanol extract of Embeliaribes fruits alone and in combination with vitamin E (tocopherol) in cisplatin (12mg/kg i.p)-induced nephro toxicity in mice.36 mice. Group I treated with (vehicle) distilled water and taken as normal.Group II injected with one dose of cisplatin (12 mg/kg weight, i.p.) was kept as control. Group III and IV were treated with ethanolic extract of Embeliaribes fruits (200 and 400 mg/kg body weight), and group V received vitamin E 200 mg/kg body weight, while group VI received combination of extract and vitamin E (200 mg/kg body weight each) The extract and vitamin E were administrated orally 1 h before and 24 and 48 h 72 hr after cisplatin injection, animals were anaesthetized with ether and sacrificed.The blood was collected via retro-orbital puncture from each animal and serums were rapidly separated and processed for the determination of serum urea, serum creatinine and blood urea. The serum urea, creatinine and blood urea nitrogen levels in cisplatin alone treated groups were significantly elevated ($P < 0.01$) with respect to control group. The serum urea, creatinine and blood urea nitrogen levels were reduced in the Embeliaribes fruits extract treated (200 and 400 mg/kg, p.o), vitamin E (200 mg/kg, p.o), andEmbelia genus Ribes fruits (200 mg/kg) with vitamin E (200 mg/kg, p.o) treated groups.The renal levels of reduced glutathione (GSH) were declined in cisplatin alone treated groups.The level of GSH was elevated considerably ($P < 0.01$) in the Embeliaribes fruits (200 and 400 mg/kg) and Embeliaribes fruits (200 mg/kg) with vitamin E (200)[27].

22. USEFUL AS TOOTH PASTE ALTERNATIVE

The study was conducted to evaluate a novel herbal dental cream in plaque formation via double-blind, randomized, controlled clinical trial. E. ribes (in combination with Ajamodasatva, Vaikrantabhasma, Azadirachtaindica, Zanthoxylumalatum, Punicagranatum, Acacia arabica, Vitexnegundo, and Triphala) in a cream has been shown to be a secure way to remove dental plaque.One hundred and two patients with established plaque were assigned to either seasoning dental cluster or flouride dental cluster for 6 weeks in an exceedingly double-blind style. Oral hygiene status, bleeding index, and gingival index improvement in plaque index, was assessed in these patients along with microbiological study. Results depicted a significant decrease in plaque index, gingival index, oral hygiene index, and

microbial growth in both groups. Their study indicates that herbal dental cream is as safe and effective as fluoride dental cream, but not superior to it[28].

23. ANTIDEPRESSANT ACTIVITY

The study was performed to evaluate Embeliaribes for antidepre-ssantactivity. Embelin was extracted by fractionation of the methanolic extract of dried powdered fruits. Using column chromatography over silica gel. Mice were induced experimental depression by exposing mice to tail suspension test (TST) and compelled swimming test (FST) experimental models. Intra peritoneal administration of embelin (2.5 and 5 mg/kg) 30 min prior to induction of experimental depression ended in dose-dependent reduction of paralysis under both test conditions. The efficacy of embelin at the dose of 5 mg/kg in both experimental models was comparable withthe standard antidepressant drug, imipramine administered at the dose of 15 mg/kg. The studies concluded that embelinhasve therapeutic potential for managing depression[29].

24. ANTIMITOTIC ACTIVITY

The study was conducted to ensure the anti mitotic effect of Embelin, isolated from berries of embeliaribes using hexane and crystallized from benzene. Embelin derivatives, 2-hydroxy-5-substituted-3-undecylcyclohexa-2, 5-diene-1,4-diones (IIa-f) were prepared from Embelin by treating alkyl and aryl halides in dichloromethane, sodium hydroxide and tetrabutyl ammonium bromide to give corresponding ethers. Germinating Bengal gram seeds and germinating Onions, Allium cepa were used to evaluate antimitotic activity of embelin. New Embelin derivatives exhibited antimitotic activity in the order of IIf, IIa, IIb, IIe, IId, IIc. Benzyl derivative (IIf) has shown significant activity when compared to rest of the compounds[30].

25. USEFUL AS SUNSCREEN ALTERNATIVE

Certain studies investigated the inhibition of Ultraviolet B (UVB, 290–320 nm) radiation-induced oxidative damage in peripheral blood human lymphocytes by embelin. Six experimental groups, as well as several controls were created to assess the restrictive impact of embelin for the chosen concentrations of ten and twenty µg/ml. lymphocytes (1 × 106 cells) were pre-treated with the chosen concentration of embelin for a period of 60 min and then exposed to UVB for thirty min. UVB radiation restrictive impact of embelin assessed by estimating antioxidant and peroxidation levels, deoxyribonucleic acid (DNA) damage, reactive oxygen species (ROS) and mitochondrial membrane potential (MMP) at scheduled time points after irradiation. Their experiment resulted that pre-treatment of lymphocytes with embelin prevents UVB-induced oxidative damage[31].

TOXICITY

The toxicity study of emblin has been performed in feminine cyclic rats. Its administration at a dose of a hundred and twenty mg/kg weight failed to cause any changes within the weight of liver, excretory organ and spleen, however, the wet weight of the adrenals showed a stimulating increase. The constituents like glycogen and protein failed to show any amendment within these organs except in the adrenal where a major increase was determined. The activity of acid and basic enzyme was inflated within the excretory organ and adrenal. Administration of embelin for six weeks caused severe pathological changes within the liver and excretory organ that primarily comprises disintegration, necrotic changes and perinuclear vacuolisation. Marked tubular damage was determined within the kidneys. The adrenals showed hypertrophy and also the histological features of the spleen remained unchanged[32]. Certain studies showed that treatment with Curcumin (100 mg kg(-1)body wt) and Embelin (50 mg kg(-1)body wt) prevented the decrease in liver glutathione antioxidant defense, diminished lipide peroxidation, shrivelled thehistological alterations induced by DENA/PB, but exhibited toxic effects on the hematopoietic cells[33].

In another studies rats were received NDEA, 1 ppm/g b.w. in drinking water for six weeks or CCl4, 0.7 ml/kg i.p. once a week for four weeks and embelin 50 mg, and 100 mg/kg b.w. orally, during and after exposure to NDEA/CCl4 for 20 or 5 weeks, respectively. NDEA or CCl4 induced increase in biochemical marker enzymes: glutamate pyruvate transaminase, oxaloacetate transaminase, , gamma-glutamyltranspeptidase, glutathione-S-transferase, lipid peroxide, alkaline phosphatase was decreased by embelin treatment . Embelin treatment depleted hypo proteinemia, hypo albuminuria and glutathione depletion. Acute toxicity studies were performed in mice where they had been administered oral doses of 50 and 100 mg/kg of embelin revealed no significant change in mortality and body weight[34].

Another toxicity studies used pancreatic-cancer xenograft mice. Mice spent on a 450 mg/kg diet for six weeks. Normal liver and kidney functioning was shown in blood analyses by embelin dietary group, suggesting that embelin was well tolerated and did not induce apparent toxicity[35].

The pharmacokinetics of oral and intravenous potassium embelate (20 mg/kg) was studied in rats. The results discovered that this compound follows a biexponential kinetic pattern. Absorption was complete (bioavailability 97%) and fast. The disposition half-life is 9.5 h on intravenous and 11 h on oral administration. Brain has high concentrations of the drug 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[36].

Potassium embelate, 2,5-dihydroxy, 3-undecyl-1, 4-benzoquinone, from Embeliaribes Burm was subjected to toxicity analysis including acute, chronic, generative 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[37].

CONCLUSION

It is evident from the literature that Embelin is a potential drug molecule. It has immense pharmacological activities such as antimitotic, antioxidant, anticancer, anti-inflammatory etc. They can cure many ailments making it a versatile molecule for future research. Thus, future studies can unmask the unexplored activities of embelin.

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