REVIEW ARTICLE

Emblica officinalis (*Amla*): A review of potential therapeutic applications

Prasan R. Bhandari, Mohammad Ameeruddin Kamdod
Department of Pharmacology, SDM College of Medical Sciences and Hospital, Sattur, Dharwad, Karnataka, India

Emblica officinalis Gaertn. or *Phyllanthus emblica* Linn, commonly known as Indian gooseberry or *Amla*, is perhaps the most important medicinal plant in the Indian traditional system of medicine, the Ayurveda. Several parts of the plant are used to treat a variety of diseases, but the most important is the fruit. Many ailments are treated by the fruit which is used either alone or in combination with other plants. These include common cold and fever; as a diuretic, laxative, liver tonic, refrigerant, stomachic, restorative, alterative, antipyretic, anti-inflammatory, hair tonic; to prevent peptic ulcer and dyspepsia, and as a digestive. *E. officinalis* possesses antipyretic, analgesic, antitussive, antiatherogenic, adaptogenic, cardioprotective, gastroprotective, antianemic, antihypercholesterolemic, wound healing, antidiarrheal, antiatherosclerotic, hepatoprotective, nephroprotective, and neuroprotective properties as demonstrated in numerous preclinical studies. Furthermore, experimental studies have reported that *E. officinalis* and some of its phytochemicals also exhibit anticarcinogenic properties. *E. officinalis* is also reported to possess radiomodulatory, chemomodulatory, chemopreventive, free radical scavenging, antioxidant, anti-inflammatory, antimutagenic and immunomodulatory activities. These properties are efficacious in the treatment and prevention of cancer. This review summarizes the results related to these properties and also emphasizes the aspects that warrant future research establishing its activity and utility as a cancer preventive and therapeutic drug in humans.

Key words: *Amla*, *Emblica officinalis*, *Phyllanthus emblica*, therapeutic applications

INTRODUCTION

To encourage a disease free healthy life Mother Nature has gifted mankind medicinal plants. Numerous medicinal plants are present in a collection of herbal preparations of the Indian traditional health care system (Ayurveda) named *Rasayana*, recommended for their interesting antioxidant activities. *Phyllanthus emblica* Linn. (syn. *Emblica officinalis*), commonly known as Indian gooseberry or *Amla*, family Euphorbiaceae, is a main herbal drug utilized in unani (Graceo-arab) and ayurvedic systems of medicine. It is used equally as a medicine and as a tonic to build up lost energy and vigor. *E. officinalis* is extremely nutritious and might be a chief dietary source of vitamin C, amino acids, and minerals. Entire parts of the plant are used for medicinal purposes, particularly the fruit, which has been used in Ayurveda as a powerful *rasayana* and in customary medicine for the treatment of diarrhea, jaundice, and inflammation. The fruit is used either alone or in combination with other plants to treat many ailments such as common cold and fever; as a diuretic, laxative, liver tonic, refrigerant, stomachic, restorative, alterative, antipyretic, anti-inflammatory, hair tonic; to prevent peptic ulcer and dyspepsia, and as a digestive. Moreover, plant parts show antidiabetic, hypolipidemic, antibacterial, antioxidant, antiulcerogenic, hepatoprotective, gastroprotective, and chemopreventive properties.[1]

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PHYTOCHEMISTRY

E. officinalis is one of the most extensively studied plants and reports suggest that it contains tannins, alkaloids, and phenolic compounds. It has been reported that fruits of *E. officinalis* contains higher amount of vitamin C and considerably higher concentrations of most minerals, protein and amino acids like glutamic acid, proline, aspartic acid, alanine, cystine and lysine. vitamin C levels are more than those in oranges, tangerines, or lemons. Fresh pericarp of *E. officinalis* contains higher amount of hydrolysable tannins like emblicanin A and B, punigluconin, pedunculagin. Activity-directed fractionation and purification process identified phytochemicals present in *E. officinalis*. They have identified gallic acid, methyl gallate, corilagin, furosin and geraniin in *E. officinalis* by a chromatographic and spectroscopic method. Phytochemical investigations revealed that *E. officinalis* contains higher amount of flavonoid like quercetin. Fruits were also analyzed for their alkaloidal

Address for correspondence: Dr. Prasan R. Bhandari, Department of Pharmacology, SDM College of Medical Sciences and Hospital, Sattur, Dharwad - 580 009, Karnataka, India. E-mail: prasangeeta2012@gmail.com
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content. Alkaloids like phyllantine and phyllantidine were confirmed by chromatography and IR spectral studies. The fruit also contains gallic acid, ellagic acid, chebulinic acid, chebulagic acid, emblicanin A, emblicanin B, punigluconin, pedunculagin, citric acid, ellagotannin, trigallayl glucose, pectin, 1-*O*-galloyl-*β*-D-glucose, 3,6-di-*O*-galloyl-D-glucose, chebulagic acid, corilagin, 1,6-di-*O*-galloyl-*β*-D-glucose, 3 ethylgallic acid (3 ethoxy 4,5 dihydroxy benzoic acid), and isostrictiniin. It also contains flavonoids such as quercetin, kaempferol 3 *O*-*α*-L (6″ methyl) rhamnopyranoside and kaempferol 3 *O*-*α*-L (6″ ethyl) rhamnopyranoside.[2]

TRADITIONAL USES

Siddha, Unani Tibetan, Sri Lankan, and Chinese systems of medicine utilize *E. officinalis*. *E. officinalis* is considered to be a powerful *rasayana* (rejuvenator) and to be useful in delaying the degenerative as well as a senescence process. It helps to increase longevity, improve digestion and to treat constipation. It also diminishes fever, cleanses the blood, decreases cough, eases asthma, strengthens the heart, benefits the eyes, encourages hair growth, invigorates the body, and augments the intellect, as per the ayurvedic system of medicine.

In several folk medicines the fruits, which are astringent, are beneficial in treating ophthalmic problems, dyspepsia, gastritis, hyperacidity, constipation, colitis, hemorrhoids, hematuria, menorrhagia, anemia, diabetes, cough, asthma, osteoporosis, premature graying of hair, weakness and fatigue. *E. officinalis* is also stated to have hepatoprotective, cardioprotective, diuretic, laxative, refrigerant, stomachic, restorative, alterative, antipyretic, and anti-inflammatory properties. Besides being a hair tonic, *E. officinalis* also prevents peptic ulcer dyspepsia, and is a digestive medicine.[3]

POTENTIAL THERAPEUTIC APPLICATIONS

Antioxidant

Nature has gifted us with defensive antioxidant mechanisms-superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), GSH peroxidases, reductase, vitamin E (tocopherols and tocotrienols), vitamin C, etc., along with several dietary components. Higher consumption of components/nutrients with antioxidant capabilities has been associated with lower frequency of numerous human morbidities or mortalities are per many epidemiological studies. Diverse potential applications of antioxidant/free radical manipulations in prevention or control of disease has been revealed by ongoing research. Natural products from dietary components such as Indian spices and medicinal plants are known to possess antioxidant activity.[4] The study by Poltanov *et al*., investigated the chemistry and antioxidant properties of *E. officinalis* fruit extracts. Extracts produced positive responses in the total phenol, total flavonoid and total tannin assays.[5]

Reddy *et al*., suggested that the amelioration of alcohol-induced oxidative stress might be due to the combined effect of phytophenols such as tannins, flavonoid compounds and vitamin C.[6] Shivananjappa *et al*., demonstrated that *E. officinalis* aqueous extracts have potency to modulate basal oxidative markers and enhance endogenous antioxidant defenses using a hepatocyte cell line (HepG2). Substantial reduction in the levels of lipid hydroperoxide and reactive oxygen species (ROS) was observed in the study that incubated *E. officinalis* for 24 h. Moreover, *E. officinalis* increased the levels of GSH, antioxidant capacity and activities of antioxidant enzymes (SOD; CAT; GSH peroxidase; GSH reductase; and GSH S-transferase).[7] Additionally, when administered once daily for 7 days the active tannoids of *E. officinalis* induced a rise in both frontal cortical as well as striatal SOD, CAT and GSH peroxidase (GPX) activity, with associated reduction in lipid peroxidation in these brain areas. The results also specify that the antioxidant activity of *E. officinalis* may reside in the tannoids of the fruits of the plant, which have vitamin C-like properties, rather than vitamin C itself.[8]

Hepatoprotective

The utilization of natural remedies for the treatment of liver diseases has a long history, beginning with the Ayurvedic treatment, and spreading to the Chinese, European as well as other systems of traditional medicines.[9] These phytochemicals cannot only be isolated but also be developed as single-ingredient drugs, with quality and standards of modern medicine. Pharmacological validation of each hepatoprotective plant should include efficacy evaluation against liver diseases induced by various agents.[10]

Inflammation and oxidative stress contribute to liver injury. *E. officinalis* which is rich in vitamin C, gallic acid, flavonoids, and tannins, protects against hepatoxicity-induced liver injury. *E. officinalis* supplementation offsets N-nitrosodiethylamine (NDEA) -induced liver injury via its antioxidant, anti-inflammation, anti-apoptosis, and anti-autophagy properties.[11] A profound pathological protection to liver cell as described by univacuolated hepatocytes was exhibited by the pretreatment of *E. officinalis* for seven consecutive days. Pretreatment with *E. officinalis* prior to CCl_4 (Carbon tetrachloride) intoxication exhibited major decrease in the levels of serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, lactate dehydrogenase (LDH), GSH-S-transferase, lipid peroxidation (LPO) and DNA synthesis. There was also enhanced levels of reduced GSH, GSH peroxidase and GSH reductase. The results suggest that *E. officinalis* inhibits hepatic toxicity in Wistar rats.[12] Tasduq *et al*., demonstrated

the hepatoprotective property of a 50% hydroalcoholic extract of the fruits of *E. officinalis* (fruit) (EO-50) against anti-tuberculosis drugs-induced hepatic injury. The hepatoprotective activity of EO-50 was found to be due to its membrane stabilizing, antioxidative and Cytochrome (CYP) 2E1 inhibitory effects.[13] Oxidative stress and ROS-mediated toxicity are considered two of the vital fundamental mechanisms responsible for alcohol-induced liver injury and mitochondrial dysfunction. The effect of *E. officinalis* fruit extract (EFE) against alcohol-induced hepatic damage in rats was explored. EFE possesses antioxidant as well nitric oxide (NO) scavenging activity as per *in vitro* studies. *In vivo* administration of EFE to alcoholic rats significantly brought the plasma enzymes towards near normal level and also significantly reduced the levels of lipid peroxidation, protein carbonyls besides restoring both the enzymatic as well as non-enzymatic antioxidants level. This observation was supported by histopathological examination in liver. Thus, this data suggests that the tannoid, flavonoid and NO scavenging compounds present in EFE may offer protection against free radical mediated oxidative stress in rat hepatocytes of animals with alcohol-induced liver injury.[14,15] Chronic treatment of CCl_4 and thioacetamide revealed abnormal histopathology suggestive of pre-fibrogenic events. EO reversed such modifications with substantial regenerative changes indicative of its preventive role in pre-fibrogenesis of liver. The reversal of pre-fibrogenic events could probably be due to its favorable antioxidative activity.[16-18]

Arsenic, a significant human toxin, is naturally present in groundwater. The protective role of the fruits of *E. officinalis* was investigated in adult Swiss albino mice against arsenic-induced hepatopathy. Pre- and post-supplementation of EFE considerably reduced arsenic-induced oxidative stress in liver. Combined treatment of *E. officinalis* and arsenic (pre and post) decreased the serum transaminases and LPO content in liver. *E. officinalis* caused a significant increase in SOD, CAT, GST and serum alkaline phosphatase activities. EFE had ameliorated karyolysis, karyorrhexis, necrosis and cytoplasmic vacuolization induced by NaAsO (2) intoxication as demonstrated in liver histopathology.[19]

Unfortunately, clinical studies are lacking. The future is to carry out controlled prospective double-blind multi-center studies with the newly discovered drugs with proven beneficial effects on animals. Fundamental hepatobiology should also be encouraged.[20]

Nephroprotective

Yokozawa *et al.*, investigated the effects of *E. officinalis* on renal dysfunction involved in oxidative stress during the aging process. The raised level of serum creatinine and urea nitrogen in the aged rats was decreased following the administration of *E. officinalis* extract. Furthermore, the tail arterial blood pressure was significantly diminished. Thiobarbituric acid-reactive substance levels of serum, renal homogenate, and mitochondria in aged rats too were considerably reduced by the extract, suggesting that *E. officinalis* would ameliorate oxidative stress due to aging. The increases of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 expressions in the aorta of aging rats were also significantly suppressed. The expressions of renal nuclear factor-kappaB, inhibitory kappaB in cytoplasm, iNOS, and COX-2 protein levels were also increased with aging. These results indicate that *E. officinalis* would be a very useful antioxidant for the prevention of age-related renal disease.[21] Chen *et al.*, assessed whether supplementation with *E. officinalis* extract could diminish oxidative stress in patients with uremia. The outcomes indicate that supplementation with *E. officinalis* extract for 4 months reduced the plasma oxidative marker, 8-iso-prostaglandin, and increased plasma total antioxidant status in uremic patients.[22]

Hypolipidemic

The silent epidemic of ischemic heart disease, type 2 diabetes mellitus (T2DM), hypertension, and stroke is been currently faced in India. Indian people develop both diabetes and ischemic heart disease a decade earlier compared to whites. A scientific scrutiny should be undertaken to corroborate the recent evidence that certain medicinal plants possess hypoglycemic, lipid-lowering, and immunomodulating properties on account of their rich flavonoid and/or other glucose-lowering active constituents.[23]

The lipid levels, such as cholesterol and triacylglyceride, in serum as well as liver were markedly elevated in aged control rats, while they were significantly decreased by the administration of *E. officinalis*. Peroxisome proliferator-activated receptors (PPARalpha) is known to regulate the transcription of genes involved in lipid and cholesterol metabolism. The PPARalpha protein level in liver was reduced in aged control rats. However, the oral administration of *E. officinalis* significantly increased the hepatic PPARalpha protein level. In addition, oral administration of *E. officinalis* significantly inhibited the serum and hepatic mitochondrial thiobarbituric acid-reactive substance levels in aged rats. These results indicate that *E. officinalis* may prevent age-related hyperlipidaemia through attenuating oxidative stress in the ageing process.[24] Treatment with *E. officinalis* produced significant reduction of total cholesterol (TC), low-density lipoprotein (LDL), triglyceride (TG), very LDL, and a significant increase in high-density lipoprotein levels. In view of the above results, it is recommended that addition of *E. officinalis* to the currently available

hypolipidemic therapy would offer significant protection against atherosclerosis and coronary artery disease. This could benefit by a reduction in the dose and adverse effects of the hypolipidemic agents.[25] These results suggest that *E. officinalis* may be effective for hypercholesterolemia and prevention of atherosclerosis.[26]

Metabolic Syndrome

The Ethyl acetate extract of *E. officinalis* ameliorated the high fructose-induced metabolic syndrome, including hypertriacylglycerolaemia and hypercholesterolaemia. These findings suggests that fructose-induced metabolic syndrome is attenuated by the polyphenol-rich fraction of *E. officinalis*.[27]

Cardioprotective

The main etiologic factor in atherogenesis is ox-LDL, and antioxidants are accepted as effective treatment of atherosclerosis. Results suggest that *Phyllanthus emblica* is effective in inhibiting the progress of atherosclerosis by alleviating oxidation injury or by inhibiting ox-LDL-induced vascular smooth muscle cell proliferation, which may be promising mechanisms for treating atherosclerosis.[28]

Regularization of hyperglycemia, hyperlipidemia and oxidative stress are important objectives in averting diabetes-induced cardiac dysfunction. The effects of the fruit juice obtained from *E. officinalis* on myocardial dysfunction in diabetic rats were explored by Patel *et al*., Treatment with the fruit juice not only prevented the streptozotocin-induced loss of body weight, increases in water and food intake, increases in serum glucose levels and disturbed lipid profile, but also an increase in serum LDH and creatinine kinase-MB levels, and increased myocardial hypertrophy and cardiomyopathy. There was a decrease in antioxidant enzyme levels (in SOD, reduced GSH and CAT) in diabetic hearts, which could be improved by treatment with fruit juice. Hence, *E. officinalis* fruit juice may be beneficial for the treatment of myocardial damage associated with type 1 diabetes mellitus. The activity of *E. officinalis* fruit juice can be attributed to the concentration of the polyphenol present.[29]

The hemodynamic and left ventricular functions were restored by pretreatment with *E. officinalis*. Significant preservation of antioxidants, myocytes-injury-specific marker enzymes and significant inhibition of lipid peroxidation was also observed. Furthermore, histopathological salvage of the myocardium reconfirmed the protective effects of *E. officinalis*. Results demonstrate the cardioprotective potential of *E. officinalis* attributed to its potent antioxidant and free radical scavenging activity as evidenced by favorable improvement in hemodynamic, contractile function as well as tissue antioxidant status.[30]

Diabetes and Related Complications

Diet has been recognized as a corner stone in the management of diabetes mellitus. Fenugreek seeds (*Trigonella foenumgraecum*), garlic (*Allium sativum*), onion (*Allium cepa*), and turmeric (*Curcuma longa*) have been experimentally documented to possess antidiabetic potential. Cumin seeds (*Cuminum cyminum*), ginger (*Zingiber officinale*), mustard (*Brassica nigra*), curry leaves (*Murraya koenigii*) and coriander (*Coriandrum sativum*) have been reported to be hypoglycaemic in a limited number of studies.[31]

Akhtar *et al*., evaluated the anti-hyperglycemic and lipid-lowering properties of *E. officinalis* fruit in normal as well as diabetic human volunteers. The results indicated a significant decrease in fasting and 2 h post-prandial blood glucose levels on the 21st day in both normal and diabetic subjects receiving 1, 2 or 3 g *E. officinalis* powder per day as compared with their baseline values. Significant decreases were also observed in TC and triglycerides in both normal and diabetic volunteers on day 21 that were given either 2 or 3 g *E. officinalis* powder per day. Both normal and diabetic volunteers receiving 2 or 3 g *E. officinalis* powder significantly improved high-density lipoprotein-cholesterol and lowered low-density lipoprotein-cholesterol levels.[32]

Diabetic neuropathy is one of the most common microvascular complications of diabetes mellitus, which distresses more than 50% of diabetic patients. The study conducted by Tiwari *et al*., demonstrated that *E. officinalis* extracts not only attenuated the diabetic condition but also reversed neuropathic pain through modulation of oxidative-nitrosative stress in diabetic rats.[33] Even Kumar *et al*., investigated flavonoid rich fruit extract of *E. officinalis* in type II diabetes induced diabetic neuropathy in male Sprague-Dawley rats. Treatment with *E. officinalis* extract (EOE) in diabetic rats displayed a significant increase in tail flick latency in hot immersion test and pain threshold level in hot plate test compared to control rats. *E. officinalis* extract significantly restored the changes in lipid peroxidation status and anti-oxidant enzymes (SOD and CAT) levels observed in diabetic rats. Diabetic-induced axonal degeneration too was attenuated by *E. officinalis* extract. The study provides experimental evidence of the preventive and curative effect of *E. officinalis* on nerve function and oxidative stress in the animal model of diabetic neuropathy. Since, *E. officinalis* fruit is already in clinical use for diabetic patients it may be evaluated for preventive therapy in diabetic patients at risk of developing neuropathy.[34]

Uremic patients with diabetes suffer from high-levels of oxidative stress due to regular hemodialysis therapy (neutrophil activation induced by hemo-incompatibility between the hemodialyser and blood) and complications associated

with diabetes. It was observed that oral administration of a 1:1 mixture of Epigallocatechin gallate (EGCG) and Amla extract (AE) (EOE) for 3 months significantly improved antioxidant defense as well as diabetic and atherogenic indices in uremic patients with diabetes. Furthermore, no significant changes in hepatic function, renal function, or inflammatory responses were observed. These results suggest that a 1:1 combination of EGCG with AE is a safe and effective treatment for uremic patients with diabetes.[35]

Immunostimulant

There are many plants having immunostimulatory activity.[36] *E. officinalis*, an excellent source of vitamin C (ascorbate), has been found to improve natural killer (NK) cell activity and antibody dependent cellular cytotoxicity. *E. officinalis* stimulated a 2-fold proliferation in splenic NK cell activity. An increase in life span of 35% was recorded in tumor bearing mice treated with *E. officinalis*.[37] Additionally, Sai Ram *et al*., investigated the anti-oxidant and immunomodulatory properties of *E. officinalis* using chromium (VI) as an immunosuppressive agent. Cytotoxicity, free radical production, lipid peroxidation, decreased GPx activity and diminished GSH levels is caused by chromium. Both lipopolysaccharide and concanavalin-A-stimulated lymphocyte proliferation were also significantly inhibited. Chromium also inhibited concanavalin-A stimulated interleukin-2 and gamma-interferon production. Presence of Cr enhanced apoptosis and DNA fragmentation. *E. officinalis* significantly inhibited Cr-induced free radical production, and restored the anti-oxidant status back to control level. *E. officinalis* also inhibited apoptosis and DNA fragmentation induced by Cr. Interestingly *E. officinalis* relieved the immunosuppressive effects of Cr on lymphocyte proliferation and even restored the IL^{-2} and gamma-IFN production considerably.[38]

Antimicrobial

Infectious diseases are a major reason of morbidity and mortality globally. It accounts for roughly 50% of all deaths in tropical countries and as much as 20% of deaths in the America. Notwithstanding the noteworthy advancement made in microbiology in addition to the control of microorganisms, intermittent occurrences of epidemics due to drug resistant microorganisms and previously unknown disease-causing microbes pose a huge risk to public health. These adverse health developments demand a universal initiative for the development of novel approaches for the prevention and treatment of infectious disease. For over 100 years chemical compounds isolated from medicinal plants have served as the models for many clinically proven drugs, and are now being re-assessed as antimicrobial agents. The explanations for this revival include a decrease in the new antibacterial drugs in the pharmaceutical pipeline, a proliferation in antimicrobial resistance, and the necessity of treatments for new evolving pathogens. Factually, thousands of plant species have been tried against hundreds of bacterial strains *in vitro* and many medicinal plants are active against a wide range of gram positive as well as gram-negative bacteria.[39]

The chloroform soluble fraction of the methanolic extract of *E. officinalis* displayed significant antimicrobial activity against some gram-positive and gram-negative pathogenic bacteria with a strong cytotoxicity having a LC50 (lethal concentration) of 10.257 ± 0.770 microg mL (-1).[40] The aqueous extracts of the fruit pulp of *E. officinalis* were evaluated by Vijayalakshmi *et al*., for antimicrobial activity against gram-positive bacteria *Staphylococcus aureus*, gram-negative bacteria *Escherichia coli* and fungal strains of Candida species by using agar cup plate method. The extracts showed a different degree of activity against pathogenic microbes.[41] Aqueous infusion and decoction of *E. officinalis* exhibited potent antibacterial activity against *E. coli, Klebsiella pneumoniae, K. ozaenae, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella typhi, S. paratyphi A, S. paratyphi B* and *Serratia marcescens*.[42]

Saini *et al*., evaluated the effect of *E. officinalis* administration on the vulnerability of experimental mice to respiratory tract infection induced by *K. pneumoniae*. These results suggest that dietary supplementation with *E. officinalis* protects against bacterial colonization of lungs on long-term feeding in an experimental model. Further studies need to be conducted to understand the actual mechanism.[43] Thaweboon *et al*., demonstrated that *E. officinalis* ethanolic extract interferes with the adhesion of *C. albicans* to BECs (human buccal epithelial cells) and denture acrylic surfaces *in vitro*.[44]

Promising antiplasmodial activity was found in the extracts from *E. officinalis* leaf. They were also found to be active against Chloroquine-resistant strains. These results demonstrate that extracts of *E. officinalis* may serve as antimalarial agents even in their crude form.[45] Pinmai *et al*. revealed that *in vivo* antiplasmodial activity with good suppression activity ranged from 53.40% to 69.46%.[46]

It is suggested that the polyphenolic compound isolated from *E. officinalis* might exert anti-herpes simplex virus (HSV) activity both by inactivating extracellular viral particles and by inhibiting the viral biosynthesis in host cells. These results warrant further studies on its antiviral mechanisms and suggest that it might be a candidate for HSV therapy.[47]

E. officinalis definitely possesses potent antimicrobial activities, thus serving as an important platform for the development of inexpensive, safe and effective medicines.[48]

However, very few of these medicinal plant extracts have been tested in animal or human studies to determine safety and efficacy. The studies provided indicate that *emblica* plant offers significant potential for the development of novel antibacterial therapies and adjunct treatments. It is imperative for pharmaceutical chemists, microbiologists, practitioners of traditional as well as allopathic medicine to come together and expedite discovery of what would be vital drugs for the treatment of infections in the coming decades.[49]

Anticancer

Natural products of plant origin currently constitute a considerable proportion of commercially available antineoplastic drugs.[50] Polyphenols act on multiple targets in pathways and mechanisms related to carcinogenesis, tumor cell proliferation and death, inflammation, metastatic spread, angiogenesis, or drug and radiation resistance.[51] Chemoprevention with food phytochemicals is meanwhile regarded as one of the most important strategies for cancer control. *E. officinalis* indigenous to India is valued for its unique tannins and flavanoids, which contain very powerful antioxidant properties. *E. officinalis* is a medicinal fruit used in many Asian traditional medicine systems for the treatment of various diseases, including cancer.

Ngamkitidechakul *et al*., tested the potential anticancer effects of aqueous extract of *E. officinalis* in four ways:[1] against cancer cell lines,[2] *in vitro* apoptosis,[3] mouse skin tumourigenesis and[4] *in vitro* invasiveness. The *E. officinalis* extract at 50-100 microg/mL significantly inhibited cell growth of six human cancer cell lines, A549 (lung), HepG2 (liver), HeLa (cervical), MDA-MB-231 (breast), SK-OV3 (ovarian) and SW620 (colorectal). However, the extract was not toxic against MRC 5 (normal lung fibroblast). These results suggest *E. officinalis* exhibits anticancer activity against selected cancer cells, thus warrants further study as a possible chemopreventive and antiinvasive agent.[52]

The inhibition of tumor incidences by fruit extract of this plant has been evaluated on the two-stage process of skin carcinogenesis in Swiss albino mice, induced by a single application of 7, 12-dimethyabenz(a)anthrecene, and 2 weeks later, promoted by repeated application of croton oil till the end of the experiment (16 weeks). The tumor incidence, tumor yield, tumor burden and cumulative number of papillomas were found to be higher in the control (without *E. officinalis* treatment) as compared to experimental animals (*E. officinalis* treated).[53]

The mechanism of human hepatoma BEL-7404 cells apoptosis induced by Galic acid from leaves of *Phyllanthus emblica* may be blocking G2/M period in cell life cycle, up-regulating the expression of Bax and down-regulating the expression of Bcl-2 (B-cell lymphoma 2). This can decrease membrane potential of mitochondria, trigger the caspases of activation cascade and induce cell death.[54]

Pyrogallol, a catechin compound, is an active component of *E. officinalis* extracts and has an anti-proliferative effect on some human cancer cell lines. Yang *et al*., investigated the beneficial effect of pyrogallol on human lung cancer cell lines-H441 (lung adenocarcinoma) and H520 (lung squamous cell carcinoma). Results from both *in vitro* and *in vivo* studies together indicate that pyrogallol can be developed as a likely anti-lung cancer drug, particular for the non-small cell lung cancer.[55]

Ethanolic extracts of EO fruit extract was investigated for protection against genotoxicity induced by the rodent carcinogen, 7,12-dimethylbenz(a)anthracene (DMBA). Oral administration of EO fruit extract in various concentrations for seven consecutive days prior to a single intraperitoneal injection of DMBA reduced the occurrence of bone marrow micronuclei induced in Swiss albino mice. The protection provided by EO may be related with its antioxidant capacity and through its modulatory effect on hepatic activation and detoxifying enzymes.[56]

Rajeshkumar *et al*., investigated the efficacy of *E. officinalis* polyphenol fraction (EOP) on the induction of apoptosis in mouse and human carcinoma cell lines along with its modulatory effect on NDEA induced liver tumors in rats. The results suggest that EOP treatment might induce apoptosis in Dalton's Lymphoma Ascites and CeHa cell lines. The results also suggested that EOP treatment could decrease the liver tumour development induced by NDEA.[57] All the phenolic compounds from the fruit juice, the branches, leaves, and the roots showed stronger inhibition against B16F10 cell growth than against HeLa and MK-1 cell growth.[58]

Cyclophosphamide (CP) is one of the most standard alkylating anticancer drugs despite its toxic side effects, including immunotoxicity, hematotoxicity, mutagenicity and a host of others. Haque *et al*., assessed the protective effects of total aqueous extract of a medicinal plant *E. officinalis* in mice treated with CP. Plant extracts, in particular, was very effective in reducing CP-induced suppression of humoral immunity. In CP-exposed animals, plant pretreatment provided protection to antioxidants of kidney. Not only were the reduced GSH levels significantly increased but the plant extract treatment resulted in restoration of antioxidant enzymes in CP-treated animals. It is suggested that *E. officinalis* or its medicinal preparations may prove to be useful as a component of combination therapy in cancer patients under the CP treatment regimen.[59]

Additionally, the radioprotective effect of EOE was demonstrated from different studies in mice.[60-63]

Analgesic, Antipyretic and Antiinflammatory

It has been extensively shown that many plant-derived compounds present substantial anti-inflammatory effects. Hence, they signify prospective molecules for the development of new drugs, particularly designed for the treatment and/or control of chronic inflammatory states such as rheumatism, asthma, inflammatory bowel diseases, atherosclerosis, etc.[64]

Asmawi *et al*., examined the effects of *E. officinalis* extracts on carrageenan- and dextran-induced rat hind paw oedema. The water fraction of methanol extract of the plant leaves demonstrated anti-inflammatory activity. This suggests that the mechanism of the anti-inflammatory action found in the rat paw model does not involve inhibition of the synthesis of the measured lipid mediators.[65] Perianayagam *et al*., investigated the anti-pyretic and analgesic activity of ethanol (EEO) and aqueous (AEO) extracts of *E. officinalis* fruits in numerous experimental models. Brewer's yeast induced hyperthermia in rats was significantly reduced by a single oral dose of EEO and AEO. Both the extracts also elicited pronounced inhibitory effect on acetic acid-induced writhing response in mice in the analgesic test. These findings suggest that extracts of *E. officinalis* fruits possessed potent anti-pyretic and analgesic activity.[66] Thus, phenolic compounds of *E. officinalis* possibly be a potential herbal candidate for amelioration of acute and chronic inflammation due to their modulatory action of free radicals.[67,68]

Osteoporosis

Osteoclasts (OCs) are involved in rheumatoid arthritis and in numerous pathologies associated with bone loss. Current results support the notion that certain medicinal plants as well as derived natural products are of great interest for developing therapeutic approaches against bone disorders, including rheumatoid arthritis and osteoporosis.

Penolazzi *et al*. determined whether extracts of *E. officinalis* fruits exhibit activity of probable interest for the treatment of rheumatoid arthritis and osteoporosis by triggering programmed cell death of human primary osteoclasts. Extracts of *E. officinalis* were able to induce programmed cell death of mature OCs, without modifying the process of osteoclastogenesis. Induction of apoptosis of osteoclasts could be an important strategy both in interfering with rheumatoid arthritis complications of the bone skeleton leading to joint destruction, as well as preventing and reducing osteoporosis. Accordingly, Penolazzi *et al*. suggest the application of *E. officinalis* extracts as an alternative tool for therapy applied to bone diseases.[69] Furthermore, there is a need for effective nutraceuticals for osteoarthritis care. Hence, Sumantran *et al*. measured the chondroprotective potential of *P. emblica* fruits *in vitro*. Aqueous extracts of both fruit powders significantly inhibited the activities of hyaluronidase and collagenase type 2 *in vitro*. These data provide pilot pre-clinical evidence for the use of *P. emblica* fruits as a chondroprotective agent in osteoarthritis therapy.[70]

Gastroprotective

Although the major emphasis of phytochemical research has been on cancer prevention, several products of plant origin are being used and/or under study for a variety of gastrointestinal problems.[71]

Phyllanthus emblica, besides its food value, can be used as a gastroprotective agent in non-steroidal anti-inflammatory drug-induced gastropathy. It has been suggested that the antioxidative property of *Phyllanthus emblica* is the key to its therapeutic effect.[72] Additionally, pretreatment with the butanol extract of the water fraction of *Phyllanthus emblica* fruits exhibited increased secretion of gastric mucus and hexosamine in the indomethacin-induced ulceration of rats.[73] The ulcer protective potential of methanolic extract of *E. officinalis* was also assessed in different acute gastric ulcer models in rats. Ulcers were induced by aspirin, ethanol, cold restraint stress and pyloric ligation and chronic gastric ulcers induced by acetic acid in rats. *E. officinalis*, showed dose-dependent ulcer protective effects in the entire above acute ulcer models besides a significant ulcer healing effect after 5 to 10 days treatment. The results showed that *E. officinalis* had a significant ulcer protective as well as healing effects which might be due to its effects both on offensive and defensive mucosal factors.[74] Mehmood *et al*. conducted a study intended at providing the probable mechanisms for the medicinal use of *Phyllanthus emblica* in diarrhea. The results indicate that the *Phyllanthus emblica* fruit extract possesses antidiarrheal and spasmolytic activities, mediated possibly through the dual blockade of muscarinic receptors and $Ca(2^+)$ channels, thus explaining its medicinal use in diarrhea.[75]

Acute necrotizing pancreatitis is characterized by focal macroscopic or diffuse necrosis, hemorrhage, and vascular thrombosis of the pancreas. It is associated with an excessively high mortality for which no adequate therapy exists. Existing treatment alternatives are restricted to supportive and symptomatic interventions. A large amount of experimental work is ongoing to identify novel therapeutic agents for acute pancreatitis. The present study was conducted to assess the favorable effects of *E. officinalis*, a medicinal plant of India, on acute pancreatitis. *E. officinalis* treatment was found to be beneficial for treating acute pancreatitis. Serum

levels of lipase and interleukin-10 were significantly lower. Nucleic acid content, rate of DNA synthesis, pancreatic proteins, and pancreatic amylase content were significantly improved. On light microscopic examination, acinar cell damage was less and the total inflammatory score was significantly lower in the *E. officinalis* treated group. Electron microscopy confirmed this by showing an increased amount of smooth endoplasmic reticulum and small, condensed granules embedded in a vacuole. Histopathological examination showed significantly lower total scores. Thus, *E. officinalis* treatment was found to be beneficial in acute necrotizing pancreatitis. More studies are needed to explore the clinical potential of *E. officinalis* and its mechanism of action.[76,77]

Dermoprotective

Clinical and laboratory studies have identified the benefits of an array of natural ingredients for skin care over the last 20 years. Consequently, a number of these ingredients and compounds are today being developed, used or considered not only for anti-aging effects, but also for use in dermatologic disorders.[78,79]

E. officinalis extract is known to provide protection for human dermal fibroblasts against oxidative stress due to its potent antioxidant properties. Hence it is supposed to be beneficial for natural skin care. Fujii *et al*. demonstrated that *E. officinalis* extract stimulated proliferation of fibroblasts in a concentration-dependent manner. Besides it also induced production of procollagen in a concentration- and time-dependent manner. Conversely, matrix metalloproteinases (MMP)-1 production from fibroblasts was dramatically decreased, but there was no evident effect on MMP-2. From these results, it appears that *E. officinalis* extract works effectively in mitigative, therapeutic and cosmetic applications through control of collagen metabolism.[80] As a part of ongoing research for novel natural cosmeceutical actives from plant extracts, Majeed *et al*., demonstrated that EFE has shown its efficacy in protection against ultraviolet-B irradiation-induced ROS and collagen damage in normal human dermal fibroblasts. Thus, *emblica* extract is a significantly better natural active to ascorbic acid, with promising cosmeceutical benefits against photoaging.[81,82]

Draelos *et al*., in a double-blind study examined the skin lightening ability of a topical formulation containing kojic acid, *E. officinalis* extract, and glycolic acid compared with prescription generic hydroquinone cream 4%. Study results demonstrated efficacy parity between the study product and hydroquinone 4%. Thus, this novel skin lightening preparation is an alternative to hydroquinone 4% for participants with mild to moderate facial dyschromia.[83]

Throughout wound healing, the wound site is rich in oxidants, such as hydrogen peroxide, typically contributed by neutrophils and macrophages. Ascorbic acid along with tannins of low molecular weight, namely emblicanin A and emblicanin B present in *E. officinalis*, have demonstrated a very strong antioxidant action. Sumitra *et al*. observed that topical application of *E. officinalis* accelerated wound contraction and closure of the full-thickness excision wounds that were created on the back of the rat. *E. officinalis* increased cellular proliferation as well as cross-linking of collagen at the wound site. Thus, this study provides firm evidence to support that topical application of *E. officinalis* represents a feasible and productive approach to support dermal wound healing.[84]

In summary, *E. officinalis* helps protect the skin from the damaging effects of free radicals, non-radicals and transition metal-induced oxidative stress. Hence *E. officinalis* is suitable for use in anti-aging, sunscreen and general purpose skin care products.[85]

Cerebroprotective/Antiaging

There are very limited therapeutic options for treating multi-factorial ailments and disorders of cognition such as Alzheimer's disease. However, certain plant-derived agents, including, for example, galantamine and rivastigmine are finding an application in modern medicine. These plants are used both in herbal as well as conventional medicine and offer benefits that pharmaceutical drugs lack.[86]

The upregulated complement system plays a damaging role in disorders of the central nervous system (CNS). The classical along with the alternate pathways are two major pathways activated in neuroinflammatory disorders such as Alzheimer's disease, multiple sclerosis, traumatic brain injury, spinal cord injury, HIV-associated dementia, and Parkinson's disease. Numerous active ingredients of herbal origin are found to have complement-inhibitory activity. These herbal ingredients along with other anti-inflammatory roles might be useful in treating neuroinflammation associated with CNS disorders.[87]

Several stress-induced diseases, including the process of aging, may be related to accumulation of oxidative free radicals in different tissues.[88] Additionally, *E. officinalis* tannoids exerts a protective effect against neuroleptic-induced Tardive Dyskinesia which is likely to be due to its earlier reported antioxidant effects in rat brain areas, including striatum.[89] Aqueous extract of *E. officinalis* showed antidepressant-like activity possibly by inhibiting Monoamine oxidase-A (MAO-A) and Gamma Amino Butyric Acid (GABA), along with its antioxidant activity.[90]

The active tannoid principles present in *E. officinalis* with its antioxidant as well as NO scavenging properties might

have contributed to the observed protection against alcohol-induced brain mitochondrial dysfunction.[91]

The cognitive impairment observed in epileptics may be a consequence of either the underlying epileptogenic process alone or it could manifest on account of the use of antiepileptic drugs that cause cognitive impairment as an adverse effect or both. Thus, there is a requirement for drugs that can subdue epileptogenesis without contributing to or, if possible, by acting to prevent the development of cognitive impairment. Hydroalcoholic extract of *E. officinalis* (HAEEO) completely abolished the generalized tonic seizures and also improved the retention latency in passive avoidance task. Further, HAEEO dose-dependently ameliorated the oxidative stress induced by Pentylenetetrazol (PTZ). These findings suggest the potential of HAEEO to be used as an adjuvant to treatment with antiepileptic drugs.[92]

A dose-dependent enhancement in memory scores of young and aged rats was produced by *Anwala churna*. The amnesia induced by scopolamine and diazepam too was reversed. Based on these results, *Anwala churna* may prove to be a useful remedy for the management of Alzheimer's disease due to its multifarious beneficial effects such as memory improvement, reversal of memory deficits and anticholinesterase activity.[93-95]

Thus, *emblica* extract has a promising pharmacological effect that benefits collagen synthesis and protects against its degradation, thus, could be used as a natural anti-aging ingredient.[96]

Eye Disorders

Deficient GSH levels contributing to a faulty antioxidant defense system within the lens of the eye are some of the pathophysiological mechanisms of cataract formation. Diabetic cataracts are caused by an elevation of polyols within the lens of the eye catalyzed by the enzyme aldose reductase (AR).[97]

AR has been a drug target because of its involvement in the development of secondary complications of diabetes, including cataract. Clinically, synthetic AR inhibitors (ARIs) have not been very successful, although numerous synthetic ARI's have been tested and shown to inhibit the enzyme. Therefore, evaluating natural sources for ARI potential may lead to the development of safer and more effective agents against diabetic complications. Suryanarayana *et al*. assessed the inhibition of AR by constituents of *E. officinalis* both *in vitro* and in lens organ culture. *E. officinalis* extract inhibited rat lens as well as recombinant human AR with IC50 values 0.72 and 0.88 mg/ml respectively. Furthermore, the isolated tannoids not only prevented the AR activation in rat lens organ culture but also sugar-induced osmotic changes. These results indicate that tannoids of *E. officinalis* are potent inhibitors of AR and suggest that exploring the therapeutic value of natural ingredients that people can incorporate into everyday life may be an effective approach in the management of diabetic complications.[98]

The results also point out that *E. officinalis* and its tannoids might counter the polyol pathway-induced oxidative stress as there was a reversal of changes with respect to lipid peroxidation, protein carbonyl content, and activities of antioxidant enzymes. *E. officinalis* also prevented aggregation and insolubilization of lens proteins caused by hyperglycemia. The results provide evidence that *E. officinalis* and an enriched fraction of *emblica* tannoids are effective in delaying development of diabetic cataract in rats.[99]

Miscellaneous

Chakraborty *et al*., evaluated the spermatotoxic effect of ochratoxin and its amelioration by *E. officinalis* aqueous extract.[100] Madhavi *et al*., evaluated the protective effect of *E. officinalis* against clastogenicity induced by lead nitrate on the incidence of sperm head abnormalities in the germ cells of mice.[101] Antitussive activity of the dry extract of *E. officinalis* is due not only to antiphlogistic, antispasmolytic and antioxidant efficacy effects, but also to its effect on mucus secretion in the airways.[102]

Lung pathology characterized by chronic infection and inflammation, sustained mainly by *Pseudomonas aeruginosa* (*P. aeruginosa*), is the most relevant cause of morbidity and mortality in cystic fibrosis patients. Extracts from EO strongly inhibited the *P. aeruginosa* laboratory strain PAO1-dependent expression of the neutrophil chemokines IL-8 (Interleukin-8), growth regulated oncogene (GRO-alpha), GRO-gamma, intercellular adhesion molecule (ICAM-1) and the pro-inflammatory cytokine IL-6.[103]

Oral administration *E. officinalis* extract for 30 days in hyperthyroid mice reduced T_3 and T_4 concentrations by 64% and 70% respectively, as compared to a standard antithyroid drug propyl thiouracil that decreased the levels of the thyroid hormones by 59% and 40% respectively. Thus, findings suggest that the test material may potentially ameliorate the hyperthyroidism.[104]

DISCUSSION AND CONCLUSION

About 80% of the world's people depend largely on traditional plant-derived drugs for their primary health care. Additionally, several of our existing medicines are derived directly or indirectly from higher plants. Some essential plant-derived drugs are atropine, codeine,

morphine, digitoxin/digoxin, and quinine/artemisinin. Medicinal plants serve as sources of direct therapeutic agents and raw materials for the manufacture of more complex compounds, as models for new synthetic products, and as taxonomic markers. While several classic plant drugs have lost much ground to synthetic competitors, others have gained a new investigational or therapeutical status in recent years. Moreover, a number of novel plant-derived substances have entered into Western drug markets. Clinical plant-based research has made particularly rewarding progress in the important fields of anticancer (e.g., taxoids and camptothecins) and antimalarial (e.g., artemisinin compounds) therapies. In addition to purified plant-derived drugs, there is an enormous market for crude herbal medicines. Furthermore, use of indigenous medicinal plants reduces developing countries' reliance on drug imports. Natural product research can often be guided by ethnopharmacological knowledge, and it can make substantial contributions to drug innovation by providing novel chemical structures and/or mechanisms of action. Thus, however, both plant-derived drugs and crude herbal medicines have to take the same pharmacoeconomic hurdle that has become important for new synthetic pharmaceuticals.[105,106]

Plant-derived drugs have an important place in both traditional and modern medicine. For this reason, a special effort to maintain the great diversity of plant species would undoubtedly help to alleviate human suffering in the long term. Medicinal plants constitute the base of health care systems in many societies. The recovery of the knowledge and practices associated with these plant resources are part of an important strategy linked to the conservation of biodiversity, discovery of new medicines, and the bettering of the quality of life of poor rural communities. Research in phytosciences, an emerging multidisciplinary science, is almost unlimited, with several aspects to be discussed. However, problems related to the efficacy, of the isolation techniques and stability of bioactive compounds too needs to be addressed. Emphasis should be laid to investigate plant species that have not been the subject of pharmacological studies, although their popular uses have been reported.

The antioxidant properties of *E. officinalis* are of particular interest in view of the impact of oxidative modification of low-density lipoprotein cholesterol in the development of atherosclerosis. As several metabolic diseases and age-related degenerative disorders are closely associated with oxidative processes in the body, the use of *E. officinalis* as a source of antioxidants to combat oxidation warrants further attention. Immediate studies should focus on validating the antioxidant capacity of *E. officinalis*, as well as testing their effects on markers of oxidation. This will work in parallel with clinical trials that are aiming to establish antioxidants as mediators of disease prevention. Though *E. officinalis* has been studied for anticarcinogenic properties in animals, the challenge lies in integrating this knowledge to ascertain whether any effects can be observed in humans, and within defined cuisines. Research on the effects of *E. officinalis* on mental health should distinguish between cognitive decline associated with ageing and the acute effects of psychological and cognitive function. There is very limited scientific evidence for the effects of *E. officinalis* on T2DM. More research is required, particularly examining the effects of chronic consumption patterns. With increasing interest in alternatives to non-steroidal anti-inflammatory agents in the management of chronic inflammation, research is emerging on the use of food extracts such as *E. officinalis*. With time, we can expect to see a greater body of scientific evidence supporting the benefits of *E. officinalis* in the overall maintenance of health and protection from disease.

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