

ANTIOXIDANT, IMMUNOMODULATORY AND ANTICANCER ACTIVITIES OF *EMBLICA OFFICINALIS*: AN OVERVIEW

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Article Received on: 13/06/11 Revised on: 16/07/11 Approved for publication: 12/08/11

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ABSTRACT

Emblica officinalis (Amla) is traditionally used for several diseases, and it is believed to increase the defense against diseases. It is particularly used for the treatment of cancer, diabetes, liver disorders, heart disease, ulcer, snake venom, haemorrhage, diarrhea, dysentery, anaemia and ophthalmic disorders. The antioxidant, immunomodulatory, anticancer, cytoprotective, analgesic, antimicrobial, antipyretic, antitussive and gastroprotective are the important properties of amla. Vitamin C, tannins and flavanoids present in amla have very powerful antioxidant activities. Due to rich vitamin C, amla is successfully used in the treatment of human scurvy.

KEYWORDS: *Emblica officinalis* (Amla), activities as antioxidant, immunomodulatory and anticancer.

INTRODUCTION

Emblica officinalis Gaertn. (*Phyllanthus emblica* Linn., Amla, Indian Gooseberry) belongs to Euphorbiaceae family. Amla fruits are acrid, cooling, refrigerant, astringent, diuretic and laxative. The raw fruits are aperient; while the dried fruits are useful in inflammation, haemorrhage, cough, diarrhoea and dysentery, and in combination with iron, used for anaemia, jaundice and dyspepsia. The flowers of *E. officinalis* are cooling, refrigerant and aperient; while the root and bark are astringent. The fermented liquor prepared from the fruits is used in jaundice, dyspepsia and cough. Exudation from incision on the fruit is used as external application for the inflammation of eye. *E. officinalis* seeds are used for asthma, bronchitis and biliousness. *E. officinalis* fruit contains ellagic acid, gallic acid, quercetin, kaempferol, emblicanin, flavonoids, glycosides and proanthocyanidins. Vitamin C (ascorbic acid or ascorbate), tannins (e.g., emblicanins A and B) and flavonoids present in amla have very powerful immunomodulatory, antioxidant and anticancer activities. Due to rich vitamin C, amla is successfully used in the treatment of human scurvy. Quercetin present in amla has hepatoprotective effect. Fruit has also been reported to contain phyllemblic acid, gallic acid, lipid, emblicol, colloidal complexes, micic acid, amino acids and minerals. Phyllembin, from fruit pulp identified as

ethyl gallate; tannin from bark and leaves; fixed oil, essential oil and phosphatides from seeds; and leucodelphinidin from bark of *E. officinalis* have also been isolated. Phyllembin potentiates the pharmacologic action of adrenaline *in vitro* and *in vivo*¹⁻³.

E. officinalis is also used as antipyretic, analgesic, cytoprotective, antitussive and gastroprotective. Additionally, it is useful in memory enhancing, ophthalmic disorders and lowering cholesterol level. It is also helpful in neutralizing snake venom and used as an antimicrobial agent. A number of medicinal plants, traditionally used for thousands of years, are present in a group of herbal preparations of the Indian traditional health care system (Ayurveda) named "Rasayana", identified for their interesting antioxidant activities, indicating that *E. officinalis* also has antioxidant activity. *E. officinalis* is often incorporated in the herbal formulation called "Triphla", which contains the equal proportions of the fruits of *E. officinalis*, *Terminalia chebula* and *Terminalia bellerica*. Triphla, due to its strong antioxidant activity, restores the noise-stress induced changes. Albino rats were used to assess the immunomodulatory activities of Triphla on various neutrophil functions like adherence, phagocytic index, avidity index and nitro blue tetrazolium. Oral administration of Triphla appeared to stimulate the neutrophil functions in the immunized rats, and stress

induced suppression in the neutrophil functions was significantly prevented by Triphla. This formulation has been reported to exhibit the chemopreventive potential. The presence of Triphla in diet had significantly lowered the benzo(a)pyrene induced forestomach papillomagenesis in mice. Triphla also significantly increased the antioxidant status of animals which might have contributed to the chemoprevention. The cytotoxic effects of aqueous extract of Triphla were investigated on a transplantable mouse thymic lymphoma (barcl-95) and human breast cancer cell line (MCF-7). The differential response of normal cells and tumour cells to Triphala *in vitro* and the substantial regression of transplanted tumour in mice fed with Triphla indicate its potential use as an anticancer drug for clinical treatment⁴. Suppression of the growth of cancer cells due to gallic acid- a major polyphenol as observed in Triphala has also been reported⁵. "EuMil" is another polyherbal formulation composed of the standardized extracts of *O. sanctum*, *W. somnifera*, *Asparagus racemosus* and *E. officinalis*. This drug is used as an anti-stress agent to attenuate the various aspects of stress related disorders. It shows the significant anti-stress and adaptogenic activities against a number of behavioural, biochemical and physiological perturbations, induced by unpredictable stress, which has been proposed to be a better indicator of clinical stress than acute stress. The contribution of the individual constituents of EuMil in the adaptogenic action has also been reported⁴. Another herbal formulation, "ProImmu" which also contains *E. officinalis* including *Ocimum sanctum* (Tulsi), *Tinospora cordifolia* (Giloe) and *Withania somnifera*, has been reported as anticancer and immunomodulatory drug. The immunomodulatory activity of Immu-21 (a research name of ProImmu) containing the extract of was studied on proliferative response of splenic leukocytes to T cell mitogens, concanavalin-A and phytohemagglutinin, and B cell mitogen, lipopolysaccharide (LPS) *in vitro* by [3H]-thymidine uptake assay in mice. Pretreatment with Immu-21 selectively elevated the proliferation of splenic leukocyte to B cell mitogen, LPS and cytotoxic activity against K 562 cells in mice⁶⁻⁷.

In view of the above facts, the present article has been put forth to discuss the antioxidant, immunomodulatory and anticancer activities of *E. officinalis* as reported by various authors.

ANTIOXIDANT ACTIVITY OF *E. OFFICINALIS*

It is increasingly being realized now that majorities of the diseases are mainly due to the imbalance between pro-oxidant and anti-oxidant homeostatic phenomenon in the body. Pro-oxidant condition dominates either due to increased generation of free radicals and/or their poor

quenching/scavenging into the body. Free radicals are the fundamental to any biochemical process, and represent an essential part of the aerobic life and our metabolism. They are continuously produced by body, such as respiration and some cell mediated immune functions. There is a dynamic balance between the amount of free radicals generated in the body and anti-oxidant to quench and or/scavenge them and protect the body against the deleterious effects. Thus, the oxidant status in human reflects the dynamic balance between the antioxidant defense and pro-oxidant conditions and has been suggested as a useful tool in estimating the risk of oxidative damage⁴.

Ethyl acetate extract of amla has been reported to reduce the elevated levels of urea nitrogen and serum creatinine in aged rats. Oral administration of this extract significantly reduced the thiobarbituric acid-reactive substance levels of serum, renal homogenate and mitochondria in aged rats, suggesting that amla would ameliorate the oxidative stress under aging. Increased inducible nitric oxide synthase and cyclooxygenase (COX)-2 expression in the aorta of aging rats were also significantly suppressed by ethyl acetate extract of amla. This extract reduced the COX-2 and nitric oxide synthase expression levels by inhibiting NF-kappaB activation in the aged rats. Thus, amla would be a very useful antioxidant for the prevention of age-related renal disease⁸. Pre-feeding of amla appeared to reduce the hexachlorocyclohexane (HCH)-induced raise in renal gamma-glutamyl transpeptidase (GGT) activity. This shows the elevation of hepatic antioxidant system and lowering of cytotoxic products as which were otherwise affected by the administration of HCH⁹. Rats were examined for the antioxidant properties of amla extracts and its effect on the oxidative stress in streptozotocin-induced diabetes was also reported. The extracts showed strong free radical scavenging activity. Amla extracts orally administered to the diabetic rats slightly improved body weight gain and also significantly increased various oxidative stress indices of the serum of the diabetic rats. Moreover the decreased levels of albumin in the diabetic rats were significantly improved with this drug. It also significantly improved the serum adiponectin levels. Thus, amla can be used for relieving the oxidative stress and improving glucose metabolism in diabetes¹⁰. *E. officinalis* is used to protect the skin from the devastating effects of free radicals, non-radicals and transition metal-induced oxidative stress. It is suitable for use in anti-aging, general purpose skin care products and as sunscreen¹¹. *E. officinalis* fruits contain tannoid principles that have been reported to exhibit antioxidant activity *in vitro* and *in vivo*. Emblicanin-A (37%) and -B

(33%) enriched fractions of fresh juice of *E. officinalis* fruits were investigated for antioxidant activity against ischemia-reperfusion-induced oxidative stress in rat heart. The study confirmed the antioxidant effect of *E. officinalis* and also indicated that the fruits of plant may exhibit a cardioprotective effect¹². The antioxidant activity of *E. officinalis* extract associated with the presence of hydrolyzable tannins having ascorbic acid-like action have been also reported¹³. *E. officinalis* contains tannoid principles comprising of emblicanin A, emblicanin B, punigluconin and pedunculagin, which have been reported to possess antioxidant activity *in vitro* and *in vivo*¹⁴. Ellagic acid, as a powerful antioxidant present in *E. officinalis*, has the ability to inhibit mutations in genes and repairs the chromosomal abnormalities¹.

IMMUNOMODULATORY ACTIVITY OF *E. OFFICINALIS*

Immune activation is an effective as well as protective approach against emerging infectious diseases. *E. officinalis* has been reported to inhibit chromium-induced free radical production, and it restored the antioxidant status back to control level. It also inhibited the apoptosis and DNA fragmentation induced by chromium. It relieved the immunosuppressive effect of chromium on lymphocyte proliferation, and even restored the IL-2 and gamma-IFN production¹⁵. *E. officinalis* and *Evolvulus alsinoides* (Shankhpushpi) were assessed for immunomodulatory activity in adjuvant induced arthritic (AIA) rat model. Complete Freund's Adjuvant (CFA) was injected in right hind paw of the animals induced inflammation. Lymphocyte proliferation activity and histopathological severity of synovial hyperplasia were used to study the antiinflammatory response of both the extracts, which showed a marked reduction in inflammation and oedema, and caused immunosuppression in AIA rats, indicating that these drugs may provide an alternative approach for the treatment of arthritis¹⁶. The immunomodulatory activity of the combined extracts of *O. sanctum*, *W. somnifera* and *E. officinalis* was noticed¹⁷.

ANTICANCER ACTIVITY OF *E. OFFICINALIS*

E. officinalis inhibits the growth and spread of various cancers, including breast, uterus, pancreas, stomach and liver cancers, and malignant ascites. It reduces the side effects of chemotherapy and radiotherapy¹. *E. officinalis* reduced the cytotoxic effects in mice dosed with carcinogens¹⁸. *E. officinalis* has been reported to possess many medicinal properties, including immune-stimulator and antitumour activities¹⁹. Amla fruit contains 18 compounds that inhibit the growth of tumour cells such as gastric and uterine cancer cells²⁰. It enhances natural

killer (NK) cell activity in various tumours. Its extract reduced the ascites and solid tumours induced by Dalton's lymphoma ascites cells in mice. The extract also increased the life span of tumour bearing animals^{1,6}. Emblicanins A and B (tannins) present in *E. officinalis*, have been reported to possess strong antioxidant and anticancer properties¹.

Chemoprevention with food phytochemicals is presently considered as one of the most important strategies to control cancer. Chemopreventive potential of amla extract on 7,12-dimethylbenz(a)anthracene (DMBA) induced skin tumorigenesis in Swiss albino mice have been found²¹. *E. officinalis* fruit administered orally at different concentrations (100, 250, 500 mg/kg) for 7 consecutive days in Swiss albino mice prior to a single intraperitoneal injection of DMBA, decreased the frequency of bone marrow micronuclei. The protection provided by *E. officinalis* fruit may be due to its antioxidant capacity and through its immunomodulatory effect on hepatic activation and detoxifying enzymes²². Phenolic compounds derived from amla exhibit a number of beneficial effects and can potentially inhibit several stages of carcinogenesis. Efficacy of the polyphenol fraction of *E. officinalis* on the induction of apoptosis in mouse and human carcinoma cell lines, and its immunomodulatory effect on N-nitrosodiethylamine (NDEA) induced liver tumours in rats was also investigated. The polyphenol fraction of *E. officinalis* could induce the apoptosis in Dalton's lymphoma ascites (DLA) and CeHa cell lines. The polyphenol fraction also inhibited the DNA topoisomerase I in *Saccharomyces cerevisiae*, mutant cell cultures and the activity of cdc25 tyrosine phosphatase²³. Amla extract was found most active in inhibiting *in vitro* cell proliferation towards human tumour cell lines, including human erythromyeloid K562, T-lymphoid Jurkat, B-lymphoid Raji, erythroleukemic HEL cell lines²⁴.

Cyclophosphamide is one of the most famous alkylating anticancer drugs in spite of its toxic side effects, including hematotoxicity, immunotoxicity and mutagenicity. *E. officinalis* may be the beneficial as a component of combination therapy in cancer patients under cyclophosphamide treatment²⁵. Phenolic compounds and the major components from the fruit juice of *E. officinalis* and from the branches, leaves and roots showed stronger inhibition against B16F10 cell growth than against HeLa and MK-1 cell growth. Norsesquiterpenoid glycosides from the roots showed significant antiproliferative activities²⁰. The cytoprotective and immunomodulating properties of *E. officinalis* against chromium (VI) induced oxidative damage have been reported²⁶. These workers observed

that the chromium (VI) at 1 µg/ml was highly cytotoxic; it enhanced the free radical production and decreased the reduced glutathione (GSH) levels and glutathione peroxidase (GPx) activity in macrophages. However, the presence of amla resulted in an enhanced cell survival, decreased free radical production and higher antioxidant levels similar to that of control cells. Further, chromium (VI) treatment resulted in decreased phagocytosis and gamma-interferon production, while amla inhibited the chromium induced immunosuppression and restored both phagocytosis and gamma-interferon production by macrophages significantly.

CONCLUSION

E. officinalis fruit (Amla) has been said to be useful against many severe diseases, including cancer, diabetes, hepatic disorders and heart diseases. Different biological activities of amla include antioxidant, immunomodulatory, anticancer, cytoprotective, analgesic, antimicrobial, antipyretic, antitussive and hepatoprotective, etc. The present article emphasizes particularly on the antioxidant, immunomodulatory and anticancer activities of amla. It is now realized that majorities of the diseases are chiefly due to the imbalance between pro-oxidant and anti-oxidant homeostatic phenomenon in the body, and the amla balances this because of its antioxidant activity. Amla also has immunostimulatory as well as protective effects against many emerging infectious diseases. *E. officinalis* inhibits the growth and spread of many cancers, including breast, uterus, pancreas, stomach and liver cancers. It also reduces the side effects of chemotherapy and radiotherapy. Therefore, the detailed research must be done on amla so as to get a new natural anticancer drug which will be a miracle in the field of pharmaceutical sciences.

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