



## AMLA – THE ROLE OF AYURVEDIC THERAPEUTIC HERB IN CANCER

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### ABSTRACT

Medicinal plants are part of human society to combat diseases, from the dawn of civilization. *Phyllanthus emblica* (Amla) possesses a vast ethnomedical history and represents a phytochemical reservoir of heuristic medicinal value. It is one of the oldest oriental medicines mentioned in Ayurveda as potential remedy for various ailments. The fruit is rich in quercetin, phyllaemblic compounds, gallic acid, tannins, flavonoids, pectin, and vitamin C and also contains various polyphenolic compounds. A wide range of phytochemical components including terpenoids, alkaloids, flavonoids, and tannins have been shown to possess useful biological activities. Many pharmacological studies have demonstrated the ability of the fruit shows antioxidant, anticarcinogenic, antitumor, antigenotoxic, antiinflammatory activities, supporting its traditional uses. In this review, we have focused our interest on phytochemistry, traditional uses, cancer chemopreventive activity of *Phyllanthus emblica* both in vivo and in vitro. In view of its reported pharmacological properties and relative safety, *P.emblica* could be a source of therapeutically useful products.

**Keywords:** *Phyllanthus emblica*, Medicinal herb, anticarcinogenic, antitumor activity, chemoprevention.

### INTRODUCTION

Cancer is a multifactorial, multifaceted and multimechanistic disease requiring a multidimensional approach for its treatment, control and prevention. Cancer remains a major public health burden in the United States and in other developed as well as developing countries<sup>[1]</sup>. World Health Organization (WHO) reported that there are now more than 11 million are diagnosed with cancer every year and it is estimated that there will be 16 million new cases per year by 2020<sup>[2]</sup>. Epidemiological studies indicate that exposure of chemical carcinogens such as tobacco smoke, diet, workplace is a major cause of human cancer<sup>[3,4]</sup>.

Chemoprevention is a rapidly growing area of oncology which focuses towards the cancer preventive strategy of natural or synthetic interventions<sup>[5,6,7,8]</sup>. Chemoprevention also deals with the chemotherapy of pre-cancerous lesions, which are called pre-invasive neoplasia, dysplasia or intra-epithelial neoplasia depending on the organ system<sup>[9]</sup>. Chemoprevention by synthetic agents can produce toxic side effects, which have limited their extensive use<sup>[10]</sup>. Renewed scientific interest in herbs and herbal products for health care has started in the last two decades. This shift from synthetic chemical agents to plant based products is primarily due to more frequent untoward effects seen with the former.

Medicinal plant derived drug research has made significant progress in anticancer therapies. Nature has bestowed our country with an enormous number of medicinal plants therefore India has often referred to as the medicinal garden of the world. In the armory of modern medicine, the components of synthetic drugs or the medicinally accepted plants are evaluated for their efficacy against certain diseases thus forming a valuable source of therapeutic agents<sup>[11,12]</sup>.

Many components of medicinal plants or dietary plants have been identified as possessing potential chemopreventive properties capable of inhibiting, retarding or reversing the multistage process<sup>[13,14]</sup>. The important advantages claimed for therapeutic use of medicinal plants in various ailments due to their safety besides being economical, effective and their easy availability<sup>[15,16]</sup>. Therefore, scientific validation of such medicinal plants is needed in order to find out their possible use in cancer prevention.

*Phyllanthus emblica* (Family: Euphorbiaceae, Syn: *Emblca officinalis*), commonly known as amla, is one of the foremost plants utilized from antiquity till to date. Amla is regarded as "one of the best rejuvenating herbs" in the Ayurveda, an Indian traditional medicinal system. It is distributed in tropical and subtropical areas of china, India, Indonesia and the Malay Peninsula. It is highly regarded due to its magnificent vitamin C content<sup>[17]</sup>. Traditionally, the fruit is useful as an astringent, cardiac tonic, diuretic, laxative,

liver tonic, diuretic, refrigerant, stomachic, restorative, antipyretic, anti-inflammatory, hair tonic and digestive medicine<sup>[18,19]</sup>. The fruits of amla contain a wide variety of phenolic compounds, such as tannins, phyllembelic acid, phyllembin, rutin, curcuminoides and emblicol<sup>[20]</sup>. The fruit is reputed to have a broad range of therapeutic effects including anticarcinogenesis and antimutagenic<sup>[21]</sup>, antitumor<sup>[22]</sup> and induction of apoptosis<sup>[23]</sup>.

Triphala is a traditional Ayurvedic herbal formulation, consisting of equal parts of three medicinal plants namely *Emblca officinalis*, *Terminalia chebula* and *Terminalia bellerica*. Triphala strengthens the different tissues of the body, prevents ageing, promote health and Immunity<sup>[24]</sup>. The goals of this review is to provide a critical insight on the cancer preventive potential of *Phyllanthus emblica*, covering its phytochemistry, traditional medicinal uses, experimental and laboratory investigations and toxicological properties.

### DESCRIPTION

*Phyllanthus emblica* is a medium to large deciduous tree. Leaves are simple, linear-oblong blunt, small, 8-10mm or more long. Flowers are greenish yellow, in axillary fascicles, 0.5-1.5cm long, fruits are nearly spherical or globular, about 18-25mm wide and 15-20mm long<sup>[25]</sup>. The bark is shining greyish brown or greyish green.

### TRADITIONAL MEDICINAL USES

Over the past few decades scientific investigations have laid a credible basis for some of the traditional ethnomedical uses of the *Phyllanthus emblica*. The history of *Phyllanthus emblica* with respect to development of mankind is impressive. *P.emblica* has a long history as a medicinal remedy to treat a wide range of complaints.

According to Ayurveda, the fruits are sweet, sour, astringent, bitter and pungent. The dried fruits are used for hemorrhages, diarrhea, dysentery. A fruit mixed with lemon juice were used to treat acute bacillary, dysentery, fruit juice for inflamed eyes. A fruit with seeds used for asthma, bronchitis and biliousness<sup>[26,27]</sup>. A decoction of the fruit with stems of *Tinospora cordifolia* is a well known remedy for urinary diseases.

It is also part of multicomponent drugs for hemorrhage, anemia, colic, acute leprosy, jaundice, and cough, indigestion, asthma. The juice of the bark mixed with honey and turmeric used for gonorrhoea. An infusion of leaves with fenugreek seed is given for chronic diarrhea<sup>[28]</sup>. The Barks have been reputed to exert antidiarrheic effects and for treatment of leucorrhoea (vaginal infection)<sup>[29]</sup>.

The fresh fruit are eaten for general fatigue, weakness, poor appetite, as a purgative. The dried and ground barks were used orally for a number of mouth diseases and gastrointestinal disorders<sup>[30]</sup>. The fruits have been reputed as a tonic to favor long

life, health and young appearance. The fruits are used as an expectorant, an antidote to "mineral" poisons, particularly vermilion and sulfur. The crushed fruits have a good effect on hair growth and prevent hair graying<sup>[31]</sup>. In Tibetan medicine, the fruit have been described as having a sour taste with cooling potency. It is used as a febrifuge, as an anti-inflammatory and unusually as an anti-diuretic<sup>[32]</sup>. Indonesians used the fruits for the treatment of dysentery, diarrhea, cholera and biliary disorders<sup>[33]</sup>. The pulp of the fruit is smeared on the head to dispel headache and dizziness caused by excessive heat<sup>[34]</sup>.

#### PHYTOCHEMICAL CONSTITUENTS

The phytochemicals of this plant include hydrolysable tannins (Emblcanin A, Emblcanin B, punigluconin, pedunculagin)<sup>[35]</sup>, flavonoids (Kaempferol 3 O alpha L (6" methyl) rhamnopyranoside, Kaempferol 3 O alpha L (6" ethyl) rhamnopyranoside)<sup>[36]</sup>, alkaloids (Phyllantidine and phyllantine)<sup>[37]</sup>. Gallic acid, ellagic acid, 1-O-galloyl-beta-D-glucose, 3,6-di-O-galloyl-D-glucose, chebulinic acid, quercetin, chebulagic acid, corilagin together with isostrictinnin, were isolated from the fruit of *Phyllanthus emblica*<sup>[38]</sup>.

A new acylated glucoside was isolated from the methanolic extract of the leaves of *P.emblica*. Their structures were named as apigenin 7-O-(6"-butyryl-beta)-glucopyranoside, along with four known compounds gallic acid, methyl gallate, 1,2,3,4,6-penta-O-galloylglucose and luteolin-4'-Oneohesperidoside<sup>[39]</sup>. The seeds of *P. emblica* contain fixed oil, phosphatides and a small quantity of essential oil. In addition, the leaves contain gallic acid, ellagic acid, chebulagic acid and chebulinic acid. Phyllaemblic acid, a novel highly oxygenated norbisabolane were isolated from the roots of *P.emblica* and its structure was fully characterized by spectroscopic and chemical means<sup>[18]</sup>. Ellagic acid and lupeol are present in roots of *P.emblica*<sup>[40,41]</sup>. Structures of chemical constituents are found in figure 1.

#### NUTRITIONAL VALUE

Amla is well known for its nutritional qualities. It is rich in polyphenols, minerals and is regarded as one of the richest source of vitamin C (200-900 mg per 100 g of edible portion) <sup>[42,43]</sup>. Major components of nutritional importance are reported in table 1.

#### CANCER PREVENTIVE EFFECTS

*Phyllanthus emblica* has been prescribed in the traditional ayurvedic medicine for the treatment of various ailments. To the best of our knowledge, there is some little scientific investigation that deals with the chemopreventive activity of *Phyllanthus emblica* in laboratory and experimental studies. A summary of the findings of these studies is presented below.

#### IN VITRO

##### ANTICANCER/ANTITUMOUR EFFECTS

The potential anticancer effects of aqueous fruit extract of *P. emblica* was tested in several different human cancer cell lines such as A549 (lung), HepG2 (liver), HeLa (cervical), MDA-MB-231 (breast), SK-OV3 (ovarian) and SW620 (Colorectal). *P.emblica* extract significantly inhibited the growth of several human cancer cell lines at doses of 50-100µg/ml. *P. emblica* extract inhibited invasion of MDA-MB-232 cells in vitro matri gel invasion assay at doses of 25 and 50 µg/ml<sup>[44]</sup>. Aqueous extracts of *P.emblica* can inhibit L929 cells growth in a dose dependent manner. Its IC<sub>50</sub> value was 16.5 µg/ml<sup>[22]</sup> and it was most active in inhibiting *in vitro* cell proliferation<sup>[45]</sup>.

Apoptosis (programmed cell death), is a useful marker for predicting tumour response after anticancer treatment. The increased activity of caspase-3, caspase-7 and caspase-8 but not caspase-9, upregulation of FAS protein via a death receptor mechanism and apoptotic DNA fragmentation in HeLa cells treated with *P.emblica* extract<sup>[44]</sup>.

The efficacy of *Emblca officinalis* Polyphenols (EOP) on the induction of apoptosis in mouse and human carcinoma cell lines. EOP was reported to induce apoptosis in DLA and CeHa cell lines. In

addition, it also inhibited DNA topoisomerase I in *Saccharomyces cerevisiae*, mutant cell cultures and the activity of cdc-25 tyrosine phosphatase<sup>[23]</sup>. *P.emblica* extract was found to inhibit cell cycle regulating enzymes cdc 25 phosphatase in a dose dependent manner. The IC<sub>50</sub> dose of extract was found to be 5 µg/ml<sup>[22]</sup>. *In vitro* biological activities are reported in table 2.

The modulatory effect of EOP fractions was evaluated on liver tumours induced by Nitrosodiethylamine (NDEA) in rats 5 days a week for 20 weeks followed by NDEA administration. Alkaline phosphatase (ALP), glutamate pyruvate transaminase (GPT), liver glutathione S-transferase (GST) was evaluated in the treated animals. The level of above mentioned enzymes was increased, whereas the treatment of EOP reduced the activities of all enzymes<sup>[23]</sup>.

#### IN VIVO

##### LIVER CANCER

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and also existing as a leading cause of death<sup>[46]</sup>. The major occurrence of HCC in Africa and Asia are linked to chronic infection with hepatitis B (HBV) and/or hepatitis C (HCV) virus and perhaps to aflatoxins exposure<sup>[47,48]</sup>. More and more efforts have been made in search of natural materials and foods as a means of chemical prevention of liver cancer<sup>[49]</sup>.

Only a few studies have speculated the chemopreventive effects of *P.emblica* against liver cancer. It was tested *in vivo* in wistar rats treated with carcinogen Diethylnitrosamine (DEN) (200mg/kg b.wt. i.p) to induce liver cancer. The results showed that pretreatment of methanolic fruit extract (100 and 200 mg/kg b.w) exhibited significant pathological manifestations at both the doses. *Emblca officinalis* (EO) has the potential to be useful in ameliorating the carcinogen-induced response in rat<sup>[50]</sup>.

##### SKIN CANCER

Skin cancer is the most common type of cancer in the United States<sup>[51]</sup>, with more than a million reported cases<sup>[52]</sup> and 9,000 deaths per year<sup>[53]</sup>. According to the World Cancer Report, it constitutes ~30% of all newly diagnosed cancers in the world, and solar ultraviolet (UV) radiation (particularly, its UVB component; 290-320 nm) is an established cause of ~90% of skin cancers<sup>[54,55]</sup>.

The cancer preventive effect of EO was investigated on two stage process of skin cancer induced by 7, 12-dimethylbenz (a) anthracene (DMBA) in swiss albino mice. It showed significant chemopreventive effects on DMBA-initiated and croton oil (1% in 100µl of acetone) promoted skin cancer development. *P.emblica* exhibited a significant reduction in tumour incidence, tumour yield, tumour burden and cumulative number of papillomas. These finding were indicative of chemopreventive potential of *P. emblica* against skin carcinogenesis<sup>[56]</sup>.

##### ANTIGENOTOXICITY

The protective effect of *P. emblica* fruit extract against clastogenicity induced by lead nitrate on the incidence of sperm head abnormalities in the germ cells of mice. The results clearly indicate that extract exhibited significant reduction in the frequency of sperm head abnormalities. The finding of the above study shows that *P. emblica* plays a key role in inhibition of heavy metal mutagenesis in mammals<sup>[57]</sup>.

The ethanolic extract of *Emblca officinalis* (EO) fruit extract was evaluated for protection against genotoxicity induced by the rodent carcinogen, 7,12-dimethylbenz(a)anthracene (DMBA). The results showed that extract significantly increases glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase (GR) and detoxifying enzyme glutathione-S-transferase (GST). The extract also reduced the hepatic levels of the activating enzymes cytochrome (CYT) P<sub>450</sub> and Cyt bs.

The protection afforded by EO may be associated with its antioxidant capacity and through its modulatory effect on hepatic activation and detoxifying enzymes<sup>[58]</sup>. An aqueous extract of

Emblica officinalis fruit protected mice against the chromosome damaging effects of the well known carcinogen 3,4-benzopyrene<sup>[59]</sup>.

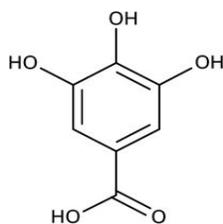
**Table 1: Nutritional Value of fruit of *Phyllanthus emblica* (% or per 100g)**

| Chemical components               | Percentage  |
|-----------------------------------|-------------|
| Fruits: Moisture                  | 81.2%       |
| Protein                           | 0.5%        |
| Fat                               | 0.1%        |
| Mineral matter                    | 0.7%        |
| Fibre                             | 3.4%        |
| Carbohydrate                      | 14.1%       |
| Bulk elements Mg/100g, net weight |             |
| Calcium                           | 0.05%       |
| Phosphorous                       | 0.02%       |
| Iron                              | 1.2 mg/100g |
| Vitamin C                         | 600mg/100g  |
| Nicotinic acid                    | 0.2mg/100g  |

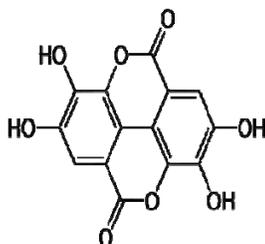
**Table 2: *In vitro* biological activities of *P.emblica*:**

|                                   | IN VITRO CELL LINES  | BIOLOGICAL ACTIVITY   |
|-----------------------------------|--|---|
| Aqueous fruit of <i>P.emblica</i> | A549 (LUNG)<br>HepG2 (liver)<br>HeLa (cervical)<br>MDA-MB-231 (Breast)<br>SK-OV3 (Ovarian)<br>SW620 (Colorectal)<br>L929 cells | Inhibition of cell growth in human cancer cell lines<br><br><br><br><br><br>Inhibition of cell growth |
| Emblica officinalis polyphenols   | Dalton's Lymphoma Ascites (DLA) and CeHA cell lines  | Induction of apoptosis  |
| <i>P.emblica</i> extract          | MDA-MB-232 cells   | Inhibition of invasion  |
| Pyrogallol (Active compound)      | Human Erythromyeloid, K562, T-Lymphoid Jurkat, B-Lymphoid Raji, Erythroleukemic HEL cell lines                                 | Inhibition of cell proliferation  |

**Structure of gallic acid**



**Structure of ellagic acid**



**Fig. 1: Structure of chemical constituents found in *Phyllanthus emblica*:**

#### ANTIMUTAGENICITY

The activation and mutagenicity of 2-Acetamidofluorene (2-AAF) was inhibited by *P.emblica*. It also inhibits the cytochrome P-450, aniline hydroxylase<sup>[21]</sup>. The antimutagenic potential of water, acetone and chloroform extracts of Emblica officinalis has been evaluated on sodium azide and 4-nitro-o-phenylenediamine induced his+ revertants in TA100 and TA97 tester strains of Salmonella

typhimurium. The study revealed that chloroform extract was less active compared with water and acetone extracts<sup>[60]</sup>.

#### TRIPHALA

The cancer chemopreventive potential of Triphala was established on benzopyrene induced fore stomach papillomagenesis in mice. The results reported that Triphala significantly increased the antioxidant status which might have contributed to the chemoprevention<sup>[61]</sup>. The *in vitro* cytotoxic effect of Triphala was tested on Shionogi 115 (S115) and MCF-7 breast cancer cells and PC-3 and DU-145 prostate cancer cell lines.

It was found that acetone extracts showed significant cytotoxic effect on cancer cells, which may be due to the presence of polyphenols gallic acid present in Triphala<sup>[62]</sup>. Triphala was administered orally to nude mice implanted with Capan-2 xenograft. Further, oral administration of 50 mg/kg or 100 mg/kg Triphala in PBS, 5days/week significantly suppressed the growth of Capan-2 pancreatic tumor-xenograft. Reduced tumor-growth in Triphala fed mice was due to increased apoptosis in the tumors cells, which was associated with increased activation of p53 and ERK<sup>[63]</sup>.

#### TOXICOLOGY

*Phyllanthus emblica* has been widely consumed by persons for thousands of years, largely without untoward incident, and thus is considered generally safe. It was found to be non-toxic to human and experimental animals<sup>[64]</sup>. No toxicity or mutagenicity was observed in the toxicological results of the experimental models in the highest dose range<sup>[65]</sup>. Toxicological studies in animals stated that LD50 for orally administered extract in rats was reported to be about 1 g/kg body weight<sup>[66,67]</sup>.

#### CONCLUSION

*Phyllanthus emblica* L. the versatile medicinal plant deserves a special attention of the scientific fraternity to emerge as a milestone for medical science of this millennium due to its various medicinal uses. In this review, we have presented information on the botanical description, traditional uses, phytochemistry, anticancer effects, and toxicity studies of *Phyllanthus emblica*.

A variety of phytochemicals such as tannins, flavonoids, terpenoids, alkaloids are reported to indicate several pharmacological properties such as antioxidant, anticancer, antitumor, antigenotoxic, and anticarcinogenic effects. It is considered to be a safe herbal medicine without any adverse effects. Future research should focus on how genetic variability and daily environmental factors influence the anticancer benefits attributed to emblica, which can be used for the welfare of the mankind.

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