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Original Review Article

Assessment of therapeutic potential of *Phyllanthus emblica* (Amla): A natural Godsend

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Abstract

These days, the use of herbal products has become the foremost option for human all over the cosmos because of curing treatment without any side effect. The pharmacological role of Phyllanthus emblica (L) is discussed in various medical literatures from ancient time and is a common ingredient of many traditional and herbal medicines. contains high concentrations of acorbic acid, gallic acid, and mixture of phenolic compounds. Active extracts of PE have been shown to possess antimicrobial, anticancer, radioprotection, anti-inflammatory and antioxidant properties etc in several models. In this review, we discussed the core therapeutic significance proved through various in vitro and/or in vivo studies along with the possible mechanism of action. This review will encourage readers to elaborate the biosynthetic pathways present in this plant as well as use of present knowledge to produce genetically modied crops containg these valuable metabolites through transgenic approach.

Keywords: *Amla, Therapeutics*

1. Introduction

Phyllanthus emblica (L.) or *Emblica officinalis* Gaertn. commonly known as "amla" (family-Euphorbiaceae) is one of the medicinal plant that has been used in ayurvedic medicines for over 2,000 years. In Hinduism, amla is regarded as a sacred tree worshipped as "Mother Earth". Tree is normally reaching a height of 60 feet (18 meter) and in rare instances, 100 feet (30 meter) (J.F. Morton, 1987). Its branchlets are glabrous and the plant is often cited as an evergreen. *P. emblica* flowers are small, usually monoeicious, inconspicuous, greenish-yellow flowers, born in compact clusters in the axils of lower leaves. It has the widest variety of pollen types of any plant genus (P.P. Joy *et al*, 2001). Fruits are hard, nearly stemless, round or oblate, indented at the base and smooth on surface.

The plant is indigenous to tropical South-East Asia and occurs mainly in dry or moist deciduous forests of Central and Southern India, Nepal, Sri Lanka, Malaysia, Mayanmar etc (L.Z. Zhang *et al*, 2003; K.H. Khan, 2009) and is widely cultivated for its fruits throughout India, Mascareme Islands (Reunion and Mauritius), West Indies (Cuba, Trinidad), central America (Honduras, Costa Rica) and Japan etc. *P. emblica* mainly grows in tropical and subtropical areas near sea level to 1,500 meter altitude. However, it grows equally well in arid and wet or humid conditions. It has been reported to thrive in dry areas and on soil poor for most other fruit crops. It is a light dependent plant found common in grassy areas, brush and village groves. Also being a photosensitive plant, it produces flowers at a day length between 12 to 13.5 hours. The plant can grow on a wide range of soil type (ranging from sandy loam to clay), and pH (slight acidic to slightly alkaline) (V. Brun and T. Schumacher, 1987). It flourishes in deep, fertile soil. Usually it is moderately drought resistant but some cultivers may be sensitive to drought and frost. It is fire tolerant and can recover well after a fire.

2. Phytochemicals

The dynamic ingredients that have significant pharmacological action in *P. Emblica* are vitamin C, phenolic compounds, including hydrolyzable tannins, proanthocyanidins, flavanols, flavonols, and compounds belonging to other phenolic groups etc. (E. Singh *et al*, 2011). The edible fruit of amla is an adaptogen, nontoxic herb that normalizes body functions. The main constituents of the plant are listed in table table 1.

Tannins are found in fruits, leaves and bark at higher concentration. Ellagic acid and lupeol found in roots while bark is known for rich source of leucodelphinidin. The seed oil contains various fatty acids as linolenic acid (8.8%), linoleic acid (44.0%), oleic acid (28.4%), palmitic acid (3.0%), stearic acid (2.15%) and myristic acid (1.0%) (Thakur et al., 1989). The plant also have various hydrolyzable tannins, i.e., Emblicanin A, Emblicanin B, punigluconin, pedunculagin (S. Ghosal *et al*, 1996), flavonoids such as Kaempferol 3 O alpha L (6" methyl)

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Table 1 Main constituents found in different tissue of *Phyllanthus emblica* (L)

Sr. No.	Plant part	Active constiuents
1	**Root**	Ellagic acid, Glycosides and Lupeol.
2	**Shoot**	3-6-di-o-galloyl-glucose, β-sitosterol, Chebulagic acid, Chibulinic acid, Corilagin, Ellagic acid, Gallic acid, Glucogallin and Lupeol
3	**Bark**	β-sitosterol, Lupeol, Leucodelphinidin, Betulin, β-Humulene, Friedelan-3-one and Tannins.
4	**Leaf**	Amlaic acid, Astrgalin, Benzenoid, β-sitosteerol, Chebulagic acid, Chibulinic acid, Corilagin, Ellagic acid, Gallo-tannin, Gibberellin, Kaempferol, Kaempferol-3-o-glucoside, Lupeol, 3,4,8,9,10-Pentahydroxydibenzo[b,d]pyran-6-one, 3,4,3'-Tri-O-methylellagic Acid, lup-20,29-en-3β,30-diol and betulin Phyllantidine, Phyllantine, Rutin and Tannins.
5	**Fruit**	3-6-di-o-galloyl-glucose, Alanine (5.4%), Arginine, Ascorbic-acid, Aspartic-acid, β-carotene, Boron, Calcium, Carbohydrates, Chebulagic acid, Chebulaginic acid, Chebulic acid, Chibulinic acid, Chloride, Chromium (2.5ppm), Copper (3ppm), Corilagic acid, Corilagin, Cystine, Ellagic acid, Emblicanins, Emblicol, Ethyl gallate, Fibre, Flavonoids, Furosin, Gallic acid, Gallic acid ethyl ester, Gallotanins, Geraniin, Gibberellin-a-1, Gibberellin-a-3, Gibberellin-a-4, Gibberellin-a-7, Gibberellin-a-9, Glucogallin, Glucose, Glutamic acid, Glycine, Histidine, Iron, Isoleucine, Kaempferol, Leucine, Lysine, Magnesium, Manganese, Methionine, Myo-inositol, Myristic acid, Niacin, Nitrogen, Pectin, Phenylalanine, Phosphorus, Phyllantidine, Phyllantine, Phyllemblic acid, Phyllemblin, Phyllemblinic acid, Potassium, Proanthocyanidins, Proline, Proteins, Putranjivin A, Riboflavin, Rutin, Selenium, Serine, Silica, Sodium, Starch, Sucrose, Sulfur, Terchebin, Thiamin, Threonine, Trigalloyl glucose, Tryptophan, Tyrosine, Valine, Zeatin, Zeatin nucleotide, Zeatin riboside and Zinc
6	**Fruit Pulp**	Constitutes 90.97% of the whole fruit, Ascorbic acid, Albumin, Calcium, Crude cellulose, Gallic acid, Gum, Iron, Magnesium, Mineral matter, Pectin, Phosphorus, Potassium, Protein, Reducing sugars, Tannins
7	**Pericarp**	Ellagic acid, Emblicol, Gallic acid and Phyllemblic acid.
8	**Seeds**	Fat, fixed oil, Linolenic acid, Myristic acid, Oleic acid, Palmitic acid, Phosphatides and Stearic acid
9	**Seed oil**	Arachidic acid, Behenic acid, β-sitosterol, Linoleic acid, Linolenic acid, Myristic acid, Oleic acid, Palmitic acid and Stearic acid

Sources: (R. S. Thakur *et al*, 1989; M. Bajpai *et al*, 2005; A. Kumaran and R. J. Karunakaran, 2006; Habib-ur-Rehman *et al*, 2007; Y.J. Zhang *et al*, 2000; Y.J. Zhang et al., 2001; L.Z. Zhang et al.., 2003; Y.Z. Zhang *et al*., 2004; Bhattacharya et al., 2002; Y.Z. Zhang *et al*, 2013; Deepak and Gopal, 2014 etc).

rhamnopyranoside, Kaempferol 3 O alpha L (6" ethyl) amnopyranoside (Rahman, 2007), alkaloids such as Phyllantidine and phyllantine (P. Khanna *et al*, 1975). The fruit of *Phyllanthus emblica* also known for quercetin, Gallic acid, ellagic acid, 1-Ogalloyl-beta-D-glucose, 3,6-di-O-galloyl-D-glucose, chebulinic acid, chebulagic acid, corilagin and isostrictinnin (L.Z. Zhang *et al*, 2003). A new acylated glucoside, isolated from the methanolic extract of the leaves of *P. emblica*, was named as apigenin7-O-(6"-butyryl-beta)-glucopyranoside by S.K. El-Desouky *et al*,, 2008.

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* (Y.J. Zhang *et al*, 2000). Roots of *P.emblica* are also a rich source of Ellagic acid and lupeol (L.D. Kapoor 1990; R.P. Rastogi, B.N. Mehrotra, 1993). In a recentl study, ten chemical ingredients with four new of the *P. emblica* leaves were isolated and elucidated. 3,4,8,9,10-Pentahydroxydibenzo[b,d]pyran-6-one, 3,4,3'-Tri-O-methylellagic Acid, lup-20,29-en-3β,30-diol and betulin were isolated first time from the *P. emblica* (L) while compounds 3,4,8,9,10-Pentahydroxydibenzo [b,d]pyran-6-one, and lup-20,29-en-3β,30-diol were the first isolated from the genus *Phyllanthus* (Y.J. Zhang *et al*, 2013).

3. Health benefits of *P. emblica*

3.1 Traditional importance

According to Ayurveda, fruit of P. emblica has five GUNA (5 properties); Rasa (Taste), Veerya (Nature), Vipaka (Taste developed through digestion), Guna (Qualities), Doshas (Effect on humors). The fruit of P. emblica has been used as a medical and food material in traditional Asian medicines (E.A. Poltanov et al, 2009). In traditional Indian medicine (Ayurveda), a number of medicinal properties have been ascribed to P. emblica. It is called Sarvadosha hara (remover of all diseases). It is also referred to as "Nurse" in Ayurvedic medicine, since it has strong antioxidant and hepatoprotective properties. The fruit of P. emblica is a necessary constituent of many ayurvedic multiherbal formulations which are still commonly used to treat various ailments including diarrhoea, jaundice, inflammation, cerebral and intestinal disorders, diabetes mellitus, coronary heart disease, cancer, rheumatic pain, diseases of the eye and genitalia, gonorrhoea, constipation, asthma, biliousness and as a tonic for hair (M.R.R. Rao & H.H. Siddiqui, 1964; L.M. Perry, 1980; L.V. Aslokar et al, 1992; P. Scartezzini and E. Speroni, 2000; M.S. Baliga and J.J. Dsouza, 2011). Since amla fruit has a highly stable vitamin C content, it is

considered to be effective even when dried, powdered or prepared in the form of candies or tablets. Combination of P. emblica fruits with haritaki (Terminalia chebula) and bahera (Terminalia billerica), known as Triphala, is an ancient ayurvedic remedy revered for its many therapeutic actions (H. Dhir, 1993). It stimulates the brain to rebalance three main components of all physiological functions, the water, fire and air elements within the body (J.F. Morton, 1987). The present scenario worldwide rates cardiovascular disease as number one killer, closely followed by cancer anticipates that the fruit extract will be named as modern day protector ensuring to its multi beneficial properties (M. Vasudevan and M. Parle, 2007).

3.2 Therapeutic importance

Antioxidant and radical scavenging properties

The generation of free radicals in excess is linked to many human diseases e.g. chronic inflammation, cancer, cardiovascular diseases, ischaemia/reperfusion injury, rheumatoid arthritis, diabetes and neurological disorders. Reactive oxygen species [ROS, superoxide anion radicals ($O^{2\bullet-}$), hydroxyl radicals ($OH^{\bullet}$) and hydrogen peroxide (H_2O_2)] and reactive nitrogen species [RNS, nitric oxide (NO) and peroxynitrite (ONOO–)], respectively, cause oxidative and nitrosative stress. Free radicals generated by the actions of these species are highly reactive and cause damage to membrane lipids, proteins and DNA (T.P. Devasagayam *et al,* 2004).

The free radical-scavenging activity of plants extract and individual compounds in the extracts of *P. emblica* were evaluated in several *in vitro* studies **(**A. Kumaran and R.J. Karunakaran, 2006; G.S. Kumar *et al,* 2006; O.N. Pozharitskaya *et al,* 2007; S.V. Nampoothiri *et al,* 2011). Methanol extract of *P. emblica* exhibited the highest scavenging activity against DPPH, $O^{2\bullet-}$, $OH^{\bullet}$ and NO radicals and also significantly inhibited the oxidation of low density lipoprotein (LDL) *in vitro* (S.V. Nampoothiri *et al,* (2011). A. Kumaran and R.J. Karunakaran (2006) found that the ethyl acetate fraction of a methanolic extract of *P. emblica* fruits showed strong NO scavenging activity *in vitro.* Further, the extracts of *P. emblica* also exhibited significant protection to DNA against oxidative damage as evidenced by migration of DNA on an agarose gel (G.S. Kumar *et al,* 2006). The beneficial effects of *P. emblica* fruit extract on alcohol-induced brain mitochondrial dysfunction in rats was also reported (V.D. Reddy *et al,* 2011). Administration of the *P. emblica* fruit extract to alcohol-treated rats lowered the levels of NO, protein carbonyls and lipid peroxide levels and elevated the activities of the antioxidant enzymes succinate dehydrogenase (SDH), nicotinamide adenine dinucleotide (NADH) dehydrogenase and cytochrome *c* oxidase as well as the content of cytochromes in the brain (V.D. Reddy *et al,* 2011). Recently, In a new study it was evident that intake of *Curcuma longa* (turmeric) and *P. emblica* increases life span in *D. melanogaster* due to their high antioxidant properties as evidenced from both SOD and catalase enzymatic assay. Interestigly, in this observation ROS scavenging activities of *P. emblica* was found lower than *C. longa* (S. Rawal *et al,* 2014).

Effects on cardiovascular problems

It has been shown that *P. emblica* and its extracts have beneficial effects on different cardiovascular diseases. Myocardial cellular injury occurring during reperfusion of ischaemic cells, known as ischaemia-reperfusion injury (IRI), is primarily due to oxidative stress.

Studies have shown that *P. emblica* fruit can ameliorate the oxidative stress induced by IRI. Oral administration of a *P. emblica* fruit extract enriched with emblicanin A and B (50 mg and 100 mg kg^{-1} BW twice per day for 14 days) significantly reversed the effects of IRI on super-oxide dismutase (SOD), catalase (CAT), Glutathione peroxidase (GPx) and lipid peroxidise (LPO) activities (S.K. Bhattacharya *et al,* 2002). Similar results were found in a study by S. Rajak *et al,* (2004), in which fresh *P. emblica* fruit homogenate (250–750 mg kg^{-1} per day) and saline were administered orally to Wistar albino rats for 30 days. There was a reduction in basal myocardial lipid peroxidation (LPO), as evidenced by decreased thiobarbituric acid reactive substances **(**TBARS) levels, and an augmentation of myocardial endogenous antioxidants in the *P. emblica* treated rats compared to those in the saline group. The results indicated that chronic *P. emblica* administration improves myocardial adaptation by augmenting endogenous antioxidants and protects the rat heart from oxidative stress associated with IRI (S. Rajak, *et al,* 2004). Hypercholesterolaemia is one of the major risk factors for coronary artery disease. S. Saravanan et al. (2006) demonstrated the hypolipidaemic effects of Triphala (a polyherbal formulation containing *P. emblica*) on experimentally-induced hypercholesterolaemia in rats. J. Bhatia *et al,* (2011) investigated the anti-hypertensive effect of *P. emblica* in a deoxycorticosterone acetate/1% NaCl high salt (DOCA/HS)-induced hypertension model rat. Hypertension was induced in rats by the DOCA salt (20 mg kg^{-1}, s.c.) and at the same time, these rats received co-treatment with different doses of an extract of *P. emblica* (75-300 mg kg^{-1} BW per day) for 5 weeks. The *P. emblica* extract significantly decreased arterial blood pressure and heart rate as well as cardiac and renal hypertrophy in a dose-dependent fashion as compared to DOCA control rats. Increased TBARS and decreased endogenous antioxidants activity in serum, heart and kidney tissues of hypertensive rats were also normalized.

Effects on diabetes

The anti-diabetic activities of *P. Emblica* and its extract have been studied in animal models and in humans. A combined methanolic extract of 'Triphala' significantly reduced blood sugar levels in normal rats and in alloxan-induced type 1 diabetic rats within 4 h of oral administration with a dose of 100 mg kg^{-1} body weight. Continuous, daily administration of the drug produced a sustained effect (M.C. Sabu and R. Kuttan, 2002). In a separate study by S. Mehta *et al,* (2009), a maximum reduction of 27.3% in the blood glucose level was observed at the 6 h time point in fasting blood glucose studies in normal rats after the administration of 300 mg

kg^{-1} BW of an aqueous extract of *P. emblica* seeds. The same dose produced a maximum reduction of 34.1% and 41.6% compared to the control group in sub and mildly diabetic animals, respectively. M.S. Akhtar *et al*, (2011) studied the hypoglycaemic properties of *P. emblica* in normal and diabetic human volunteers. The results indicated a significant decrease ($P < 0.05$) in fasting and 2 h post-prandial blood glucose levels on day 21 in both normal and diabetic subjects receiving 1, 2 or 3 g *P. emblica* powder per day compared with their baseline values. A study on "Type 2" diabetes by S.V. Nampoothiri *et al*, (2011) revealed that an extract of *P. emblica* fruit was able to inhibit both enzymes α-amylase and α-glucosidase significantly more efficiently than that of a reference compound, acarbose. Diabetes can cause different types of complications in patients. Studies have shown that *P. emblica* and its tannins have beneficial effects on diabetic cataracts (P. Suryanarayana *et al*, 2004; P. Suryanarayana *et al*, 2007), diabetic neuropathy (V. Tiwari *et al*, 2011) and diabetic uraemia (T.S. Chen *et al*, 2011b). In a recent *in vitro* study, S.A. Kalekar *et al*, (2013) showed that amla possess insulin sensitizing and glucose stimulatory activity. A hyro-alcoholic extract of *P. emblica* (200 µg/ml) was found effective to stimulate glucose uptake in adipocyte cells in 3T3L1 adepocyte cell culture (S.A. Kalekar *et al*, 2013).

Cytotoxic and anticancer activities

The anticancer effects of *P. emblica* fruit were reviewed in detail by M.S. Baliga and J.J. Dsouza (2011). They summarised that *P. emblica* fruit and its extracts can be used 1) as antineoplastic agents, 2) as radioprotective agents and 3) as chemopreventive and chemomodulatory agents. The mechanism of the anti-cancer effects includes the following aspects: *P. emblica* fruit or its extracts 1) are free radical scavengers; 2) can decrease the hepatic levels of phase I enzymes; 3) can increase levels of GST, a phase II enzyme; 4) can decrease levels of ornithine decarboxylase; 5) can increase levels of antioxidant enzymes; 6) can decrease LPO; 7) have antimutagenic effects; 8) possess immunomodulatory effects; 9) can modulate the levels of proteins important in cell cycle progression; 10) can cause apoptosis and cytotoxicity in neoplastic cells; 11) can prevent metastasis.

A study at University of Ferrara (Province of Ferrara, Italy), showed that its extract inhibited the growth of *in vitro* human breast cancer cells (E. Lambertini *et al*, 2004). Solid tumours induced by Dalton's lymphoma ascites (DLA) were reduced significantly and life span of tumour bearing animals increased to up to 60%.

P. emblica extracts have been shown to have cytotoxic effects on cancer cells *in vitro* and *in vivo* without a clear influence on normal cells. K. Pinmai *et al*, (2008) studied the synergistic inhibitory effects of a *P. emblica* extract with conventional cytotoxic agents (doxorubicin and cisplatin) against human hepatocellular carcinoma (HepG2) and lung cancer cells (A549). The *P. emblica* extract demonstrated growth inhibitory activity, with a certain degree of selectivity between the two cancer cell lines tested. Synergistic effects (CI < 1) between *P. emblica* and doxorubicin as well as between *P. emblica* and cisplatin were demonstrated on A549 and HepG2 cells at different dose levels (K. Pinmai *et al*, 2008). In a separate study, K. Pinmai *et al*, (2010) reported that an aqueous extract of *P. emblica* exhibited cytotoxic activity on Vero cells with an IC50 value of 157.9 3 µg ml^{-1} and with a selectivity index (SI) of 11. V.N. Sumantran *et al*, (2007) investigated the short- and long-term growth inhibitory effects of an aqueous extract *P. emblica* fruit on Chinese hamster ovary (CHO) cells. An aqueous extract of *P. emblica* fruit (50 µg ml^{-1}) caused 42% growth inhibition in CHO cells. In another in vitro study, *P. emblica* fruit extract (PE) showed anticancer activity in cervical cancer cells. The extract resulted in a dose-and time-dependent inhibition of DNA binding activity of constitutively active activator protein-1 (AP-1) in both HPV16-positive (SiHa) and HPV18-positive (HeLa) cervical cancer cells. PE-induced AP-1 inhibition was found mediated through downregulation of constituent AP-1 proteins, c-Jun, JunB, JunD, and c-Fos (S. Mahata *et al*, 2013).

Protective effects against chemical-induced carcinogenesis

Several researches have been covered to show that *P. emblica* is effective against carcinogenesis caused by different chemicals. An extract of *P. emblica* fruit was found significantly effective to inhibit hepatocarcinogenesis induced by *N*-nitrosodiethylamine (NDEA) in a dose-dependent manner. The anticarcinogenic activity of the extract was evaluated by its effects on tumor incidence, levels of carcinogen metabolizing enzymes, levels of cancer markers and injury markers in the liver. The morphology of liver tissue and levels of marker enzymes indicated that the *P. emblica* extract offered protection against chemical carcinogenesis (K.J. Jeena *et al*, 1999). K. Veena et al. (2006a; 2006b; 2007) studied the potency of Kalpaamruthaa (a preparation contains *Semecarpus anacardium* L., *P. emblica* and honey) against breast cancer induced by 7,12-dimethylbenz(a)anthracene (DMBA) in rats and noticed positive changes in the levels of glycoprotein components, marker enzymes [lactate dehydrogenase (LDH) and 5′ nucleotidase (5′ ND)], lysosomal enzymes, plasma lipids, lipid-metabolising enzymes, lipid peroxides and antioxidants in the blood and vital organs (liver, kidney and breast tissue) were investigated in mammary carcinoma-bearing rats. Changes in body weight and the volume of cancer were also determined. The results provided evidence for the therapeutic effects of Kalpaamruthaa against mammary carcinoma (K. Veena et al., 2007). A. Sharma and K.K. Sharma (2011) showed the protective potential of Triphala against DMH induced early neoplastic alterations coupled to ER stress in mouse liver. The protective effect of Triphala could result due to stimulation of hepatic regeneration by preventing damage by alkyl free radicals. In a different study, 7,12-dimethylbenz(a)anthracene (DMBA) induced buccal pouch carcinoma in hamsters was treated with methnolic extract (ascorbic acid-24.13%, gallic acid-10.45%), ellagic acid-1.74% quercetin -0.009%) of *P. emblica* fruit

(PFMet) for 14 weeks and was found most effective at a dose of 200mg/kg BW. PFMet supplementation significantly restored the levels of TBARS and antioxidants status in pouch and plasma of tumor groups (M. Krishnaveni and S. Mirunalini, 2012).

Protective effects against metal-induced clastogenicity

The protective effects of *P. emblica* against chromosome aberrations (CA) induced by metal salts has also been reported. These metal salts included caesium chloride (CsCl) (A. Ghosh *et al*, 1992), nickel chloride (H. Dhir *et al*, 1990), lead nitrate (H. Dhir *et al*, 1991), aluminium sulphate (A.K. Roy et al., 1992) and chromium (M. Sai Ram *et al*, 2003). Ghosh et al. (1992) reported that the oral administration of an aqueous extract of *P. emblica* fruit (685 mg kg^{-1} BW) for 7 days significantly reduced the frequency of CA on bone marrow cells induced by CsCl (125, 250 and 500 mg kg^{-1} BW) in Swiss albino mice (A. Ghosh *et al*, 1992). An aqueous extract dried *P. emblica* fruit was fed to *Mus musculus* prior to treatment with nickel chloride (10–40 mg kg^{-1} BW), lead nitrate (10–40 mg kg^{-1} BW) or aluminium sulphate (250–1000 mg kg^{-1} BW). The fruit extract significantly reduced the frequency of CA per cell, the percentage of aberrant cells and the frequency of micronuclei induced by all metal salts in the bone marrow cells of treated mice (H. Dhir *et al*, 1990; H. Dhir *et al*, 1991; A.K. Roy *et al*, 1992).

Radioprotective effects

The radioprotective effects of *P. emblica* have been investigated in animal models. I. Singh *et al*, (2005) studied the radioprotective properties of an aqueous extract of *P. emblica* fruit against sublethal gamma radiation (9 Gy) in Swiss albino mice. The dose of the fruit pulp extract found to be most effective against radiation was 100 mg kg^{-1} BW with 87.5% survival after 30 days (Singh et al., 2005). K.B. Hari Kumar *et al*, (2004) found that the fruit pulp of *P. emblica* significantly reduced the effects of radiation on Swiss albino mice, and suggested that *P. emblica* extract may be useful in reducing the side effects produced during radiation therapy. G.C. Jagetia *et al*, (2002) demonstrated that Triphala is also a good radioprotective agent in mice exposed to γ-radiation.

Protective effects against the toxicity of anti-cancer medicine

Cyclophosphamide (CP) is one of the most commonly used alkylating anticancer drugs, but has toxic side effects including immunotoxicity, hematotoxicity and mutagenicity. Haque et al. (2001) found that oral administration of an extract of *P. emblica* to rats at a dose of 100 mg kg^{-1} body weight (BW) per day for 10 days resulted in the modulation of immunological parameters and antioxidants in the kidney and liver in normal as well as cyclophosphamide (50 mg kg^{-1})-treated animals. The *P. emblica* extract, in particular, was very effective in reducing the cyclophosphamide-induced suppression of humoral immunity. Pretreatment with an extract of *P. emblica* also preserved antioxidant levels in the kidneys of cyclophosphamide-treated rats. GSH levels were significantly ($P<0.001$) increased and antioxidant enzymes were restored by the *P. emblica* extract compared with cyclophosphamide treatment alone (R. Haque *et al*, 2001). The preventive effects of Immu-21 (a polyherbal formulation containing extracts of *Ocimum sanctum, Withania somnifera, P. emblica* and *Tinospora cordiafolia*) against genotoxicity induced by cyclophosphamide were also found in mice (G.B. Jena *et al*, 2003).

Immunomodulating effects

Immune activation is an effective as well as protective approach against emerging infectious diseases. Studies have shown that *P. emblica* and its extracts have immunomodulating effects. R. Srikumar *et al*, (2005; 2006) studied the immunomodulatory activities of Triphala by testing various functions of neutrophils such as adherence, the phagocytic index (P.I.) and the avidity index (A.I.), as well as nitro blue tetrazolium (NBT) reduction on noise-induced stress in albino rats. They found that supplementation with Triphala prevented the noise-stress induced changes in the antioxidant as well as cell-mediated immune response in rats.

M. Sai Ram et al. (2003) investigated the cytoprotective and immunomodulating properties of a 90% ethanol extract of dry *P. emblica* fruit on lymphocytes using an *in vitro* method. Chromium (VI) was used as an immunosuppressive agent. The *P. emblica* extract significantly inhibited chromium (Cr) induced free radical production and restored the antioxidant status back to the control level. The *P. emblica* extract also inhibited apoptosis and DNA fragmentation induced by chromium, relieved the immunosuppressive effects of Cr on lymphocyte proliferation, and returned IL-2 and γ-interferon (γ-IFN) production to control levels. The presences of the *P. emblica* extract enhanced cell survival, decreased free radical production and maintained antioxidant levels close to those of the control cells. Further, chromium (VI) treatment resulted in decreased phagocytosis and γ-IFN production which were restored by the *P. emblica* extract (M. Sai Ram *et al*, 2003). K. Suresh and D.M. Vasudevan (1994) found that *P. emblica* could enhance natural killer (NK) cell activity and antibody-dependent cellular cytotoxicity (ADCC) in syngeneic BALB/c mice bearing Dalton's lymphoma ascites (DLA) tumors. The immunomodulatory effects of *P. emblica* were evaluated in an adjuvant-induced arthritic (AIA) rat model and the results showed *P. emblica* extract can cause immunosuppression in AIA rats (L. Ganju *et al*, 2003).

Antimicrobial activity

The antimicrobial properties of *P. emblica* were studied by R. Srikumar *et al*, (2007), S. Saeed and P. Tariq (2007), A. Saini et al. (2008) and H. Rahman et al. (2009). R. Srikumar *et al*, (2007) showed that aqueous and ethanol

extracts of *Triphala* and its individual herbal components had antibacterial activity against several bacterial isolates (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Shigella sonnei*, *S. flexneri*, *Staphylococcus aureus*, *Vibrio cholerae*, *Salmonella paratyphi-B*, *Escherichia coli*, *Enterococcus faecalis* and *Salmonella typhi*) obtained from HIV-infected patients using the Kirby-Bauer disk diffusion and minimum inhibitory concentration (MIC) methods. In a separate study, aqueous infusion and decoction of *P. emblica* exhibited potent antibacterial activity against *E. coli*, *K. pneumoniae*, *K. ozaenae*, *Proteus mirabilis*, *P. aeruginosa*, *S. typhi*, *S. paratyphi* A & B, and *Serratia marcescens*, but did not show any antibacterial activity against some Gram-negative urinary pathogens (S. Saeed and P. Tariq, 2007). A. Saini *et al*, (2008) studied the protective efficacy of *P. emblica* against *Klebsiella pneumoniae*-induced pneumonia in mice. The results in the long-term feeding (30 days) experimental model suggested that supplementation with *P. emblica* reduce bacterial colonisation in the lung (A. Saini *et al*, 2008).

H. Rahman *et al*, (2009) found that *P. emblica* and its extracts had antimicrobial and cytotoxic activities. The chloroform extract of the fresh ripe fruit of *P. emblica* showed the strongest inhibitory effect against *Bacillus subtilis* and moderate inhibitory activity against *S. typhi*, *Bacillus cereus*, *P. aeruginosa,*, *Shigella boydii*, *Shigella dysenteriai*, *S. aureus*, *Sternbergia lutea*, *E. coli*, *S. paratyphi*, *Vibrio parahaemolyticus* and *V. mimicus* (Rahman et al., 2009). S. M. Moazzem Hossen *et al*, (2014) demonastrated antimicrobial activities against various gram positive, gram negative bacteria and fungal strains and suggested fruit of *P. emblica* as a remedy for different bacterial diseases.

Hepatoprotective effects

P. emblica fruit and its extract were found to have beneficial effects on hepatic injury induced by chemical agents (S.A. Tasduq *et al*, 2005; P. Pramyothin *et al*, 2006; R. Verma and D. Chakraborty, 2008; K.H. Chen *et al*, 2011a; M.K. Singh *et al*, 2014). Moreover, it was found that the fruit of *P. emblica* could reverse fibrosis in the liver (S.A. Tasduq *et al*, 2005; A.I. Mir *et al*, 2007).

The protective effect of the hydroalcoholic (50%) extract of *P. emblica* fruit used by S.A. Tasduq *et al*, (2005) against anti-tuberculosis (anti-TB) drug-induced liver toxicity was studied. The *P. emblica* extract was found to be hepatoprotective, due to its membrane stabilising, antioxidant and CYP 2E1 inhibitory properties (SA. Tasduq *et al*, 2005). Treatment of rats with *P. emblica* extract (75 mg kg-1 per day) also enhanced liver cell recovery by bringing the levels of AST, ALT and IL-1β back to normal (P. Pramyothin *et al*, 2006). In study by R. Verma and D. Chakraborty (2008), administration of a *P. emblica* aqueous extract (2 mg/animal/day) for 45 days along with ochratoxin caused significant amelioration in the ochratoxin-induced reduction in DNA, RNA and protein contents in the livers and kidneys of mice.

The effects of *P. emblica* fruit supplementation (100 mg ml^{-1} BW) was elucidated on NDEA-induced injury in rats by evaluating ROS responses in the liver and bile. They found that *P. emblica* fruit significantly preserved the expression of MnSOD and CAT and decreased the expression of iNOS and cytochrome P450 2E1 (CYP2E1) protein in the livers of NDEA-treated rats. *P. emblica* fruit also decreased NDEA-enhanced hepatic apoptosis and autophagy *via* downregulation of the bax/bcl-2 ratio and beclin-1 expression (K.H. Chen *et al*, 2011a).

In another study, M.K. Singh *et al*, (2014) demonstrated antioxidant property of *P. emblica* responsible for its protective efficacy in arsenic induced hepatic toxicity. Arsenic exposures (3 mg/kg body weight/day for 30 days) in mice exhibited enhanced oxidative stress in hepatocytes with increase in the lipid peroxidation and decrease in the levels of reduced glutathione and activity of superoxide dismutase, catalase, and glutathione peroxidise along with significant chages in SGOT, SGPT and creatinine. Administration of fruit extract of *P. emblica* (500 mg/kg body weight/day for 30 days) with arsenic resulted into a significant reduction of arsenic transference associated with significant decreases hepatic arsenic levels and balanced the antioxidant enzyme and levels of serum hepatic enzymes like SGOT and SGPT (M.K. Singh *et al*, 2014).

Effects on gastric ulceration

The healing properties of *P. emblica* fruit and its extracts against gastric ulceration have been studied. Most of these studies were carried out in animal models (S.K. Bandyopadhyay *et al*, 2000; M. Sairam *et al*, 2003; S.K. Bhattacharya *et al*, 2007).

S.K. Bandyopadhyay *et al*, (2000) found that pretreatment with the butanol fraction of the aqueous extract of *P. emblica* fruit at a dose of 100 mg kg^{-1} BW per day, orally administered to rats for 10 consecutive days, enhanced the secretion of gastric mucus and hexosamine ($P< 0.001$) in the context of indomethacin-induced ulceration in rats. P.A. Bafna and R. Balaraman (2005) suggested that Pepticare (a herbomineral formulation, consisting of *Glycyrrhiza glabra*, *P. emblica* and *Tinospora cordifolia*) could ameliorate gastric ulcers in rats. S.K. Bhattacharya *et al*, (2007) suggested that a 95% ethanol extract of sun-dried *P. emblica* fruit (100 mg kg^{-1} per day) accelerated the healing process of ulcers.

A. Chatterjee *et al*, (2011) suggested that the ethanolic extract of *P. emblica* showed biphasic activity in non-steroidal anti-inflammatory drug (NSAID)-induced ulcers in mice, with the healing effect observed at 60 mg kg^{-1} and an adverse effect at 120 mg kg^{-1}. In a separate study A. Chatterjee *et al*, (2012) found ethanolic amla extract endorse healing of indomethacin-induced gastric ulcers in mice by reducing neutrophils infiltration and increase mucosal PGE_2 as well as NO levels.

Effects on the nervous system

P. emblica is traditionally used to treat disorders of the central nervous system (CNS). M. Vasudevan and M. Parle (2007) investigated the memory-enhancing activity of *P. emblica*. *P. emblica* produced a dose-dependent improvement in memory scores in young and aged mice. Furthermore, it reversed the amnesia induced by

scopolamine (0.4 mg kg^{-1} BW) and diazepam (1 mg kg^{-1} BW). Brain cholinesterase activity and total cholesterol levels were also reduced by *P. emblica* when administered orally. Authors suggested that the plant may be a useful remedy for the management of Alzheimer's disease on account of its multiple beneficial effects such as its memory improving, cholesterol lowering and anti-cholinesterase activities.

The effects of a standardized hydroalcoholic extract of *P. emblica* fruits against kainic acid-induced seizures, cognitive deficits and on markers of oxidative stress in rats were studied by M. Golechha *et al*, (2011). The results showed that pretreatment with an extract of *P. emblica* fruit (500 and 700 mg kg^{-1} i.p.) significantly ($P<0.001$) increased the latency of seizures compared with the vehicle-treated kainic acid group. The *P. emblica* fruit extract significantly prevented the increase in TBARS levels and ameliorated the fall in GSH. Furthermore, the *P. emblica* fruit extract dose-dependently attenuated the kainic acid-induced increase in TNF-α levels in the brain. The *P. emblica* extract also significantly improved the cognitive deficits induced by kainic acid (M. Golechha *et al*, 2011).

Antiinflammatory effects

A. Ihantola-Vormisto *et al*, (1997) found that leaf extracts of *P. emblica* have antiinflammatory effects. The leaves of *P. emblica* were extracted with different solvents and inhibitory activity of the extracts on human polymorphonuclear leukocyte (PMN) and platelet function were studied. These results showed that the leaves of *P. emblica* had inhibitory activity on PMNs and platelets, which confirm their anti-inflammatory and antipyretic properties (A. Ihantola-Vormisto *et al*, 1997). The anti-inflammatory activities of *P. emblica* fruit or fruit extracts were also studied in animal models. Acute pancreatitis is a rapidly developing inflammation of the pancreas and causes high mortality. *P. emblica* has been reported to have beneficial effects in the treatment of acute pancreatitis in rats (S. Sidhu *et al*, 2011). Serum levels of lipase and interleukin-10 were significantly lower in the *P. emblica* treated group than in the arginine and placebo-treated group. The nucleic acid content, rate of DNA synthesis, pancreatic proteins and pancreatic amylase content were significantly improved (S. Sidhu *et al*, 2011). A. Muthuraman *et al*, (2010) studied the anti-inflammatory effects of free and bound phenolic compounds from *P. emblica* in carrageenan-and cotton pellet-induced acute and chronic inflammatory animal models at dose levels of 20 and 40 mg kg^{-1}. In acute and chronic inflammation, both the free and bound phenolics of *P. emblica* reduced inflammation; at high doses, the effects of both fractions were comparable to treatment with diclofenac. In a recent research, ethanolic extraction of *P. emblica* branch significantly inhibited the mRNA expressions of tyrosinase and related proteins (TRP-1 and TRP-2) in B16 murine melanoma cells as well as suppressed the LPS-induced pro-inflammatory genes (COX-2, iNOS, TNF-α, IL-16 and IL-6) expression in RAW 264.7 murine macrophage cells (B. Sripanidkulchai & J. Junlatat, 2014).

Antidiarrhoeal effects

J.B. Perianayagam *et al*, (2005) found that the methanol extract of *P. emblica* fruit showed a significant inhibitory effect on diarrhoea in Wistar albino rats induced by castor oil and magnesium sulphate. Oral administration of the extract (50–150 mg kg^{-1} BW) produced a significant dose-related reduction i in gastrointestinal motility in charcoal meal tests in rats. It also significantly inhibited the production of prostaglandin E2 (PGE2)-induced enteropooling as compared to control animals (J.B. Perianayagam *et al*, 2005). M.H. Mehmood *et al*, (2011) studied the possible medicinal use of *P. emblica* in diarrhoea *in vivo* (mice) and *in vitro* (rabbit jejunum and guinea pig ileum). The results showed that the crude extract of *P. emblica* caused an inhibition in castor oil-induced diarrhoea and intestinal fluid accumulation in mice at 500–700 mg kg^{-1} BW. The results of the *in vitro* studies indicated that the *P. emblica* fruit extract possesses antidiarrhoeal and spasmolytic activities, possibly mediated through dual blockade of muscarinic receptors and Ca2+ channels (M.H. Mehmood *et al*, 2011).

Antiviral activity

Methanolic extract of fruits showed significant inhibitory activity on HIV reverse transcriptase with an IC50 of about 50 µg/ml. Puttranjivin A, di-o- galloyl, β-D glucose and digallic acid isolated from fruit also showed antiviral activity (S. El-Mekkawys *et al*, 1995). It has ability to block DNA polymerase, the enzyme needed for hepatitis B virus to reproduce. *P. emblica* has ability to inhibit replication of variety of RT inhibitor resistant HIV-1 strains. It has been found that aqueous extracts of *P. emblica* inhibited viral DNA polymerase of HepaDNA viruses *in vitro* (including Hepatitis B virus and several Hepatitis viruses) (D.W. Unander, 1995). In an *in vitro* study, 1,2,4,6-tetra-*O*-galloyl-β-d-glucose (1246TGG), a polyphenolic compound isolated from *P. emblica*, was found to inhibit herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) infection by inhibiting HSV-1 E and L gene expressions as well as viral DNA replication (Y. Xiang *et al*, 2011). In another study, the sesquiterpenoid glycoside isolated from *P. emblica* displayed potential anti-hepatitis B virus (HBV) activities with IC50 of 8.53 ± 0.97 and 5.68 ± 1.75 µM respectively towards the HBV surface antigen (HBsAg) and HBV excreted antigen (HBeAg) secretion (Lv Jun-Jiang *et al*, 2014).

Other functions

Beyond the health effects mentioned above, some studies also suggest that extracts of *P. emblica* may possess antipyretic and analgesic activity, skin protective effects and wound-healing effects (J.B. Perianayagam *et al*, 2004; M.S. Kumar *et al*, 2008; M. Sumitra *et al*, 2009; M.D. Adil *et al*, 2010). J.B. Perianayagam *et al*, (2004) found that a single oral dose of the ethanol and aqueous extracts of *P. emblica* fruit (500 mg kg^{-1} BW, i.p.) led to a significant reduction in brewer's yeast-induced hyperthermia in rats. Ethanol and aqueous extracts of *P.*

emblica fruit also elicited pronounced inhibitory effects on the acetic acid-induced writhing response in mice in a test for analgesic activity. Allergic rhinitis, a state of hypersensitivity occurs when the body overreacts to a substance such as pollens or dust. Allen-7 developed from 7 medicinal plants (*P. emblica* being one of them) proved to be a potent anti-inflammatory agent that can ameriolate symptoms of allergic rhinitis. Extracts of leaves inhibited Polymorphonuclear leucocyte (PMN) and platelet activity, supporting their anti-inflammatory and antipyretic activity (V.N. Sumantran *et al*, 2007).

Effect of *P. emblica* fruit against UVB-induced photo-aging in human skin fibroblasts was studied by M.D. Adil *et al*, (2010). The results suggested that *P. emblica* fruit effectively inhibits UVB-induced photo-aging in human skin fibroblasts *via* its strong ROS scavenging ability.

M.S. Kumar *et al*, (2008) found that an alcoholic extract of *Triphala* promoted the healing of infected full-thickness dermal wounds. M. Sumitra *et al*, (2009) proved that the topical application of a 90% ethanol extract of dry *P. emblica* fruit powder exerted wound healing action through the upregulation of collagen expression and extracellular signal-regulated kinase (ERK1/2) signalling. Recent *in vivo* studies suggested emblica as one of the herbs that acclaimed with hair growth promoting activity as it is composed in the herbal formulations that effectively enlarge size and prolong the anagen phase of hair follicles (L. Purwal *et al*, 2008; V.M. Jadhav *et al*, 2009).

P. emblica toxicities and challenges

P. emblica has hypoglycemic effect, hence it may interact with diabetic medications therefore should be used with extreme caution in these individuals. A dosage of 100 mg/kg body weight of *P. emblica*, administered orally for 30 days was investigated in cyclic adult female mice. No significant changes in absolute body and organ weights, and also no effect on hematological and clinical biochemical tests were observed suggesting that *P. emblica* is non toxic. Interestingly, contraceptive effect was seen in cohabited females with normal male mice as they were unable to become pregnant since their cyclicity was affected. This effect was reversed upon discontinuation of the extract.

Conclusion and future prospects

More than 80% of the world's population depending largely on traditional plant derived formulas/drugs for their health maintenance. Furthermore, several of our existing medicines are derived directly or indirectly from higher plants. 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. A number of novel plant derived substances have entered into Western drug markets. A variety of phytochemical such as tannins, flavonoids and alkaloids have reported to indicate several pharmacological properties. These compounds are considered to be a safe herbal medicine without any adverse effects. So it can conclude that Indian gooseberry is traditionally and clinically proven fruit for both its application and efficacy. A plant having such clinically proved medicinal properties is still waiting to be explored at the molecular level. Understanding of metabolic pathways responsible for biosynthesis of these compounds in *P. emblica* is very important. In this direction, we have standardized a protocol for the RNA isolation from different tissues of the plant (A. Kumar and K. Singh, 2012) which will encourage researchers to dig out the hidden secrets in *P. emblica* genome.

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