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Phytochemistry and ethnomedicinal qualities of metabolites from *Phyllanthus emblica* L.: A review

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Abstract: *Phyllanthus emblica* or Indian gooseberry is an integrated part of Ayurvedic and Traditional Chinese Medicines. For several decades, the well-known ancient herb has been extensively utilized in traditional medicine to cure diseases like fever, diabetes, constipation, jaundice, ulcers, biliousness, anemia, anorexia, and dyspepsia. In the traditional system, Indian gooseberry has various ethnomedicinal applications. In the Ayurvedic system, different methods of administration (anupan) have shown different ethnomedicinal properties of Indian gooseberry. Seventy well-known chemical components in Indian gooseberry have been identified through phytochemical evaluation, among which the flavonoids and phenols are most prominent. From the toxicity perspective, it is considered a safe herb in India, and is taken as a food supplement in European countries. The wide-spectrum pharmacological activities of the crude extracts and isolates of Indian gooseberry are attributed to the predominance of phenols and flavonoids. Thus, it is important to study the exact mechanism of the activity of the phytochemicals in Indian gooseberry, especially in anti-cancer activities. Extract of Indian gooseberry enhances proliferation in several cancer cells *in vitro*, including stem cells like ovarian cancer (OC) cells, and also has been observed to possess anti-proliferative characteristics *in vivo*. This review intends to explore the therapeutic potential of Indian gooseberry based on scientific reports and attempts to find the gaps for future research.

Introduction

Medicinal plants have been known for their healing properties for decades. Plants have been a major source of medicines since ancient or Vedic times (Dehghan et al., 2016; Chakraborty, 2018; Kumar *et al.*, 2018a). Plants and their secondary molecules are a divine blessing to mankind. Even in the 21st century, traditional medicine is still used in most underdeveloped and developing nations (Newman and Cragg, 2016; Kota *et al.*, 2017; Khan *et al.*, 2018b; Kumar *et al.*, 2018b). Secondary metabolites synthesized by the plants are considered of great therapeutic value owing to their ability to cure diverse diseases (Chakraborty, 2018; Kumar *et al.*, 2018a; Sridevi *et al.*, 2018). In spite of the progressive development in the field of synthetic chemistry, medicines derived from plants or plant products, such as morphine, taxol, atropine, ephedrine, etc, are still in the developing stage (Newman and Cragg, 2016; Sridevi *et al.*, 2018). The majority of the plant-derived drugs are of therapeutic importance and are enriched with nutrients (Newman and Cragg, 2016; Chakraborty, 2018).

The unique nutritional, antioxidant, and therapeutic properties of *Phyllanthus emblica* can be attributed to the predominance of multiclass secondary biomolecules, especially flavonoids and polyphenols (Dehghan *et al.*, 2016; Kumar *et al.*, 2018a; Sridevi *et al.*, 2018; Choudhary and

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Grover, 2019; Sriwatcharakul, 2020). Almost all Indian gooseberry based products can replace synthetic supplements or antioxidants (Newman and Cragg, 2016).

Antioxidants are crucial constituents of drugs that aid in treating a particular disease and help in capturing free radicals and cease the free radical-associated redox reactions (Chakraborty, 2018; Kumar *et al*., 2018b).

The current sedentary lifestyles make the sour immune system weak. To restore and heal our system Ayurveda plays a vital role (Govindarajan *et al*., 2005; Khan *et al*., 2018b). Each herb and shrub have specific medicinal qualities to cure ailments and restore health. Herbs like *Ocimum basilicum*, *Anethum graveolens*, *Origanum vulgare*, *Rosmarinus officinalis*, *Crocus sativus*, *Mentha spicata*, and *Thymus vulgaris* are non-toxic if taken fresh or in dried form (Vázquez-Fresno *et al*., 2019). These herbs can have a higher therapeutic effect in their fresh form (Govindarajan *et al*., 2005; Khan *et al*., 2018b; Mukherjee *et al*., 2018; Srinivasan *et al*., 2018). The extraordinary nutritional value of these herbs and medicinal plants is a treasure to society. Many yet undetermined nutritional elements need further study. These herbs rejuvenate our whole system and are not specific to certain organs or bodies (Variya *et al*., 2016; Yadav *et al*., 2017; Khan *et al*., 2018b; Mukherjee *et al*., 2018; Srinivasan *et al*., 2018).

According to Ritucharya, an ayurvedic practice, if medicinal plants are consumed in their season of availability, it revitalizes one's health. The role of 'rasayana' drugs comes to our rescue. Among the rasayana drugs, *P. emblica*, commonly called Indian gooseberry, is the drug of choice as it helps in restoring strength and energy (Govindarajan *et al*., 2005; Khan *et al*., 2018a; Srinivasan et al., 2018). Indian gooseberry belongs to the family Euphorbiaceae. It is enriched with vitamin C and known to possess different activities like anti-inflammatory, anti-diabetic, hepatoprotective, immunomodulatory, radiomodulatory, and antioxidant properties (Govindarajan *et al*., 2005; Khan *et al*., 2018a; Mukherjee *et al*., 2018; Srinivasan *et al*., 2018; Kaur *et al*., 2021). Owing to the above-mentioned properties, more exploration has become the primary target to gain better insight into the *P. emblica*. Therefore, the current review aims to provide critical information about *P. emblica* related to its cultural significance, phytochemical constituents, and pharmacological activities.

Data Extraction

Ayurvedic literature about Indian gooseberry

The information on Indian gooseberry regarding its toxicological effects, phytochemistry, pharmaceutical application, and ethnomedicinal usage was obtained from library and online sources like ScienceDirect, Google Scholar, SciFinder, PubMed, etc., for the period 2000 to 2020.

Literature about Indian gooseberry

Amalaki consists of fresh fruit pulp of medium-sized *P. emblica* tree, a native of deciduous forests, at altitudes up to 1300 m and cultivated in home-yards and gardens (Krishnaveni and Mirunalini, 2010; Poltanov *et al*., 2009; Variya *et al*., 2016; Yadav *et al*., 2017). *P. emblica*is known by various other names like Sanskrit: Amitaphala, Amalaka; Assamese: Amlaku Amlakhi, Bengali: Dhatri, Amla, English: *Emblic myrobalan, Phyllanthus emblica* Gujrati: Amala, Ambala; Hindi: Aonla, Amla; Kashmiri: Embali, Kannada: Nellikayi; Amli; Marathi: Avalkathi, Anvala; Malayalam: Nellikka; Oriya: Anala; Ainla, Punjabi: Amla, Aula; Tamil: Nellikkai; Nelli, Telugu: Usirika; and in Urdu: Amlaj, Amla (API, 2010; Variya *et al*., 2016; Yadav *et al*., 2017). The main properties and actions of *P. emblica* in Ayurveda are rasa (taste): madhura (sweet), amla (sour),tikta (bitter); guna (properties): laghu (light), ruksa (rough); virya (potency): sita (cold); vipaka (final transformation): madhura (sweet). Itstherapeutic uses include raktapitta (haemorrage), amlapitta (gastric trouble), and prameha (diabetes mellitus) (API, 2010; Variya *et al*., 2016; Yadav *et al*., 2017).

In Ayurvedic terminology, amla is known as "Amalaki", which means "Dhatri or Nurse", as it possesses the ability to reinstate health like a caring mother (Caldecott, 2006; Mir *et al*., 2005). It is the only plant to control all three doshas (fault or disease) (Vata, Pitta, and Kapa), which shows its Ayurvedic significance (Caldecott, 2006). The Indian gooseberry tree is revered and adored by many Hindus since it is believed that the god Vishnu resides on the plant. Indian gooseberry is a part of almost all Ayurvedic formulations. The main application and mode of administration of Indian gooseberry are described in Fig. 1.

The well-known formulations of Indian gooseberry are amla churn, triphala churn, trikattu churn, amalaki rasayan, etc. (API, 2010; Caldecott, 2006). Unripe Indian gooseberry fruit can control the inflammation of the conjunctiva (Kirtikar and Basu, 1935). Consumption of Indian gooseberry fruit pickles before meals can stimulate the appetite (Nadkarni, 1954; Priya and Islam, 2019). The colon functions and intestinal flow can be improved when fresh Indian gooseberry juice is administrated with ghee (ghrta). The decoction process using the dry Indian gooseberry powder can treat ophthalmia and is hemostatic and antidiarrheal (Nadkarni, 1954; Caldecott, 2006). The combination of jaggery (guda) with dried powder of Indian gooseberry fruits is useful in jaundice, biliousness, anemia, anorexia, and dyspepsia (Sharma, 2002). Indian gooseberry has shown its wide applications in hair fall, fever, diabetes, and heart ailments. It is known for its immune-boosting applications through the actions of its antioxidant. As per Sarangadhara Samhita, the combination of amla, citraka, haritaki, pippli, and saindhava can cure all types of fevers (Srikantha Murthy, 1984). When Indian gooseberry is administrated in a combination of draksa, sugar, and honey, it can cure nausea and vomiting (Caldecott, 2006). Rasayana of Indian gooseberry is effective against chronic lung and heart diseases, strength, intelligence, vigor resembling an elephant, wisdom, infertility, and mental disorders (Srikantha Murthy, 1984; Sharma, 2002).

Cultural and Religious Significance

From ancient times, in India, Indian gooseberry has been worshipped as Mother Earth as it is believed to nurture mankind (Mir *et al*., 2005; Ur-Rehman *et al*., 2007). Various parts of the Indian gooseberry plant are used in worship

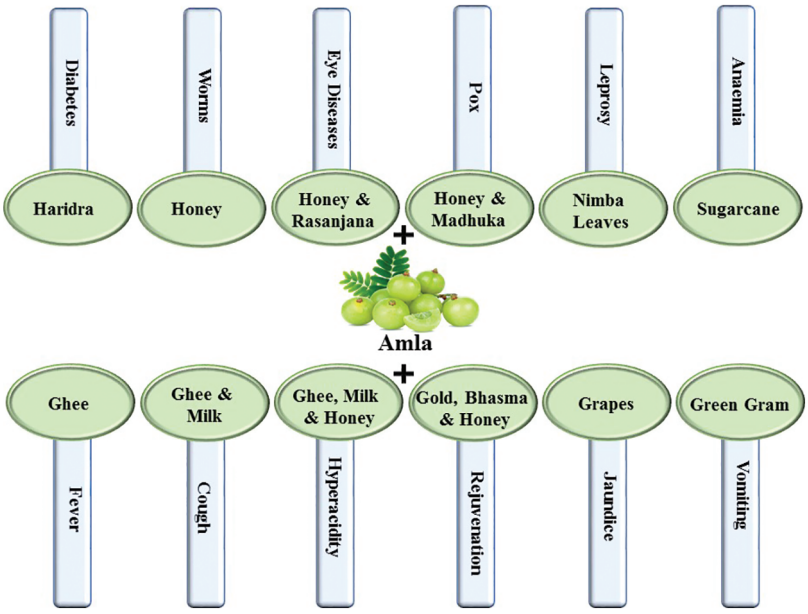


FIGURE 1. Therapeutic applications of *Phyllanthus embelica* in Ayurveda.

rituals across India. VratKaumudi and Kartik Mahatma (Goddess of Hindus) order to worship this tree, and the leaves of this tree are offered to deities on auspicious days (Yadav *et al.*, 2017). In Indian states like Himachal Pradesh, Indian gooseberry is worshipped mostly in the month of Kartik as chaste and propitious (Ur-Rehman *et al.*, 2007; Variya *et al.*, 2016). Moreover, it is utilized in Ayurveda, Unani, and Siddha systems in India, China, Tibet, and Sri Lanka to treat different ailments.

Phytochemical Constituents

The main phyto-elements (per 100 g) present in the Indian gooseberry are listed in Table 1 and Fig. 2. It contains a variety of various chemical components such as carbohydrates, mucic acid, tannins, glycosides, amino acids, flavonol glycosides, alkaloids, phenolic acids, flavones, glycosides, and sesquiterpenoids (Ur-Rehman *et al.*, 2007; Poltanov *et al.*, 2009; Yang and Liu, 2014; Variya *et al.*, 2016; Yadav *et al.*, 2017; Rose *et al.*, 2018). Liquid extract of *P. emblica* encompasses high vitamin C content (478.56 mg/100 mL) compared to various fruits like grape, lime, apple, and pomegranate. Vitamin C is present in abundant amounts in *P. emblica* (Zhang *et al.*, 2003; Bansal *et al.*, 2014).

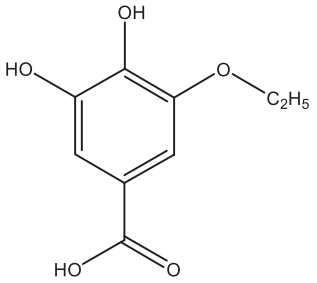
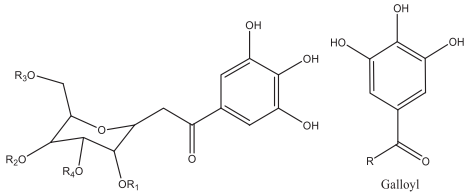
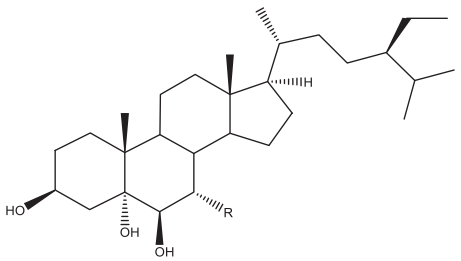
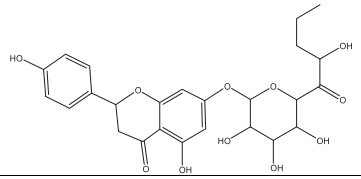
The phytochemical composition of *P. emblica* has been investigated by various researchers in various solvents, including acetone-water (Zhang *et al.*, 2001a, 2001b; Liu *et al.*, 2008a), water (Majeed *et al.*, 2009; Khan *et al.*, 2018a; Tung *et al.*, 2018), fresh juice (Yang and Liu, 2014), enzyme-water (Yokozawa *et al.*, 2007), hydro-alcoholic (Liu *et al.*, 2008b), ethyl acetate (Zhang *et al.*, 2003; Yokozawa *et al.*, 2007), ethanolic (Iqbal *et al.*, 2017), methanol (Ur-Rehman *et al.*, 2007; Liu *et al.*, 2009; Yang *et al.*, 2012), and freeze-dried juice (Majeed *et al.*, 2009). Various other phyto-constituents (in mg/100 mL) of Indian gooseberry juice, including chlorogenic acid (17.43 mg), ellagic acid (71.20 mg), quercetin (2.01 mg), and gallic acid (37.95 mg) from the extract of *P. emblica* were also reported (Bansal *et al.*, 2014).

Other reported data show the presence of corilagin, 3-ethylgallic acid, chebulagic acid, Glucogallin, iso-strictiniin, quercetin, kaempfero-l,3-O-l-(6-ethyl)-rhamnopyranoside, and various other phenolic compounds like mucic acid 1,4-lactone 3,5-di-O-gallate, mucic acid 2- O-gallate, 1,4-lactone 3-O-gallate, 1,4-lactone 2-O-gallate,mucic acid 1,4-lactone 5-O-gallate, mucic acid, and L-malic acid 2-O-gallate have been extracted from *P. emblica* (Zhang *et al.*, 2001b; Zhang *et al.*, 2003; Bansal *et al.*, 2014; Yang and Liu, 2014; Variya *et al.*, 2016; Yadav *et al.*, 2017). Two flavonoids, namely Kaempferol-3-O-α-L-(5″-ethyl)-rhamno-pyranoside and Kaempferol-3-O-α-L-(6″-Methyl)-rhamno-pyranoside were isolated and differentiated on the basis of the presence of ethyl (–CH2CH3) and methyl (–CH3) groups (Ur-Rehman *et al.*, 2007). Here both the compounds were extracted from the shoots and leaves of *P. emblica* using methanol as solvent (Ur-Rehman *et al.*, 2007).Various terpenoid molecules have been reported by researchers; 15 terpenoids with antioxidant and cytotoxic properties were reported by Qi *et al.* (2013), which were obtained from the stems and leaves of *P. emblica* (Qi *et al.*, 2013). Recently, two terpenoids, namely ursophyllemblicoside and secofriedelanophyllemblicine were extracted from the roots of *P. emblica* (Nguyen *et al.*, 2018).

The most common and important chemical constituents of *P. emblica* with their source and biological activities are presented in Table 1. The phenolic compounds of *P. emblica* are well known and have well-established biological activities (Nisar *et al.*, 2018). Phytochemical components of *P. emblica* like ellagic acid, corilagin, chebulagic acid, gallic acid, pyrogallol, and quercetin have been identified by liquid chromatography-mass spectrometryand high-performance liquid chromatography techniques in various extracts of *P. emblica* (Yang and Liu, 2014; Zhao *et al.*, 2015; Variya *et al.*, 2016). Significant antioxidant and antitumor effects of these phytochemicals have been observed in *in-vitro* and *in-vivo*

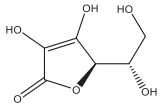
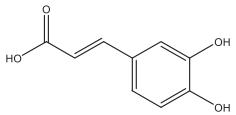
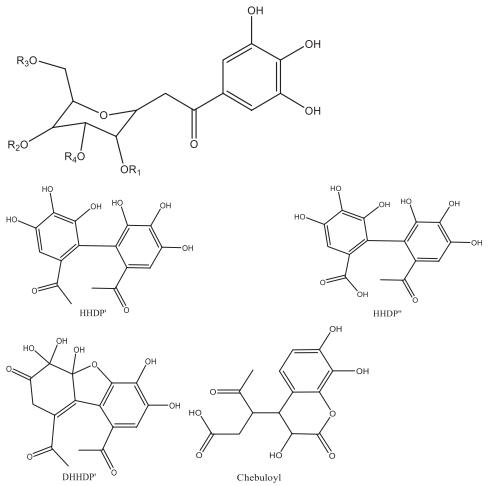
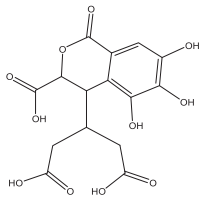
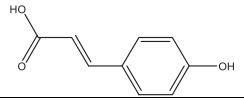
TABLE 1

Main phytochemicals of *Phyllanthus emblica* (Indian gooseberry) and their biological activities

Molecule	Chemical structure	Biological activities	Source	Class	Reference
3-ethygallic acid		Antioxidant	Fruits	Phenol	(Variya *et al.*, 2016; Yang and Liu, 2014)
1(β)-O-galloylglucose $R_1 = R_2 = R_3 = R_4 = H$ 1(β),6-di-O-galloylglucose $R_1 = R_2 = R_4 = H$ and R_3 = Galloyl 1,2,3,6-tetra-O-galloylglucose $R_1 = R_3 = R_4$ = Galloyl and $R_2 = H$ 1,2,3,4,6-penta-O-galloylglucose $R_1 = R_2 = R_3 = R_4$ = Galloyl		Antioxidant, anti-inflammatory, aldose reductase, neuroprotective, and anti-microbial	Fruits	Phenol and sugar	(Bansod, 2012; Bhattacharya *et al.*, 1999; Chang *et al.*, 1995; Chansriniyom *et al.*, 2018; Dhale and Mogle, 2011; Goyal and Bhadauria, 2008; Gupta *et al.*, 2012; Hazra *et al.*, 2010; Liu *et al.*, 2008a, 2008b; Poltanov *et al.*, 2009)
5α,6β-dihydroxysitosterol R = H Trihydroxysitosterol R = OH		Antioxidant and cytotoxic	Leaves and stem	Terpenoids and sterols	(Qi *et al.*, 2013; Variya *et al.*, 2016)
Apigenin-7-O-(6-butyryl-β-glucopyranoside)		Antioxidant and cytotoxic	Leave	Flavonoids	(Jyothi and Rao, 2011; Pinmai *et al.*, 2008; Rahman *et al.*, 2009)

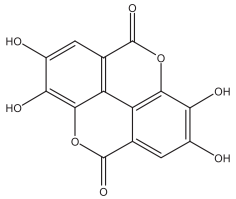
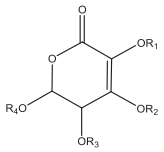
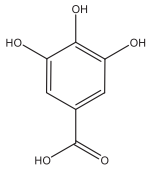
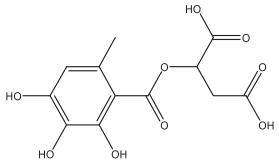
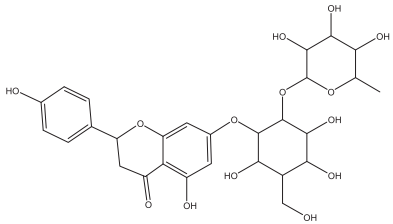
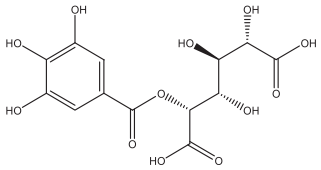
(Continued)

TABLE 1 (continued)

Molecule	Chemical structure	Biological activities	Source	Class	Reference
Ascorbic acid		Antioxidant and anti-diabetic	Fruits	Hydroxyls and ketones	(Variya *et al.*, 2016; Yang and Liu, 2014)
Caffeic acid		Antioxidant, ant-cancer and anti-hyperlipidemic	Fruits	Phenolic acids	(Baliga and Dsouza, 2011; Mahata *et al.*, 2013)
Chebulanin $R_1 = R_2$ = Chebuloyl and $R_3 = R_4 = H$ Chebulagic acid $R_1 = R_2$ = Chebuloyl and $R_3 = R_4$ = HHDP Corilagin $R_1 = R_2 = H$ and $R_3 = R_4$ = HHDP Furosin $R_1 = R_2$ = DHHDP and $R_3 = R_4 = H$ Geraniin $R_1 = R_2$ = DHHDP and $R_3 = R_4$ = HHDP Geraniin Acid $R_1 = H$, R_2 = HHDP' and $R_3 = R_4$ = HHDP Isostrictinin $R_1 = R_4 = H$, and $R_2 = R_3$ = HHDP Tercatain $R_1 = H$, R_2 = Galloyl, and $R_3 = R_4$ = HHDP Punicafolin $R_1 = R_2$ = Galloyl, and $R_3 = R_4$ = HHDP		Antioxidant, anti-inflammatory, anti-diabetic, anti-cancer and anti-proliferative	Fruits	Phenols and tannins	(Bansod, 2012; Bhattacharya *et al.*, 1999; Chang *et al.*, 1995; Dhale and Mogle, 2011; Gupta *et al.*, 2012; Liu *et al.*, 2008a, 2008b; Poltanov *et al.*, 2009; Zhao *et al.*, 2015)
Chebulic acid		Anti-secretory, anti-ulcer, anti-cancer, and cyto-protective	Fruits	Phenolic acids	(Mishra *et al.*, 2013; Variya *et al.*, 2016; Zhao *et al.*, 2015)
Coumaric acid		Antioxidant and anti-hyperlipidemic	Fruits	Phenolic acids	(Variya *et al.*, 2016; Yang and Liu, 2014)

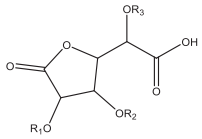
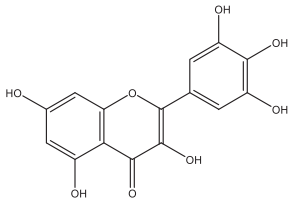
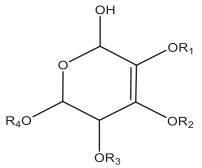
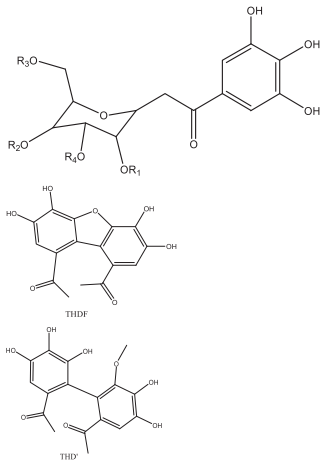
(Continued)

TABLE 1 (continued)

Molecule	Chemical structure	Biological activities	Source	Class	Reference
Ellagic acid		Antioxidant, ant-proliferative, chemo-protective, radio-protective, anti-cancer, estrogenic/anti-estrogenic, and anti-diabetic	Whole plant	Phenolic acids	(Chen and Li, 2006; Jagetia *et al.*, 2002; Papoutsi *et al.*, 2005; Sumitra *et al.*, 2009; Zhao *et al.*, 2015)
Emblicanin-A $R_1 = R_4$ = Galloyl, and $R_2 = R_3$ = HHDP Emblicanin-B $R_1 = R_4$ = HHDP, and $R_2 = R_3$ =HHDP'		Antioxidant and anti-diabetic	Fruits	Phenols and tannins	(Deep *et al.*, 2012; Qureshi *et al.*, 2009)
Gallic acid		Antioxidant, chemo-protective, radio-protective, anti-inflammatory, anti-cancer anti-diabetic, and anti-proliferative	Whole plant	Phenolic acid	(Variya *et al.*, 2016; Yang and Liu, 2014; Zhao *et al.*, 2015)
L-malic acid 2-O-gallate		Antioxidant and anti-atherosclerotic	Fruits	Phenolic acid	(Variya *et al.*, 2016; Yang and Liu, 2014)
Luteolin-7-O-neohesperidoside		Anti-inflammatory and anti-diabetic	Leave	Phenols and tannins	(Deep *et al.*, 2012; Jaijoy *et al.*, 2010; Qureshi *et al.*, 2009; Zhang *et al.*, 2004)
Mucic acid 2-O-gallate		Anti-proliferative	Fruits	Phenolic acids	(Goyal and Bhadauria, 2008; Zhang *et al.*, 2004)

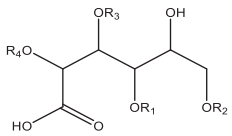
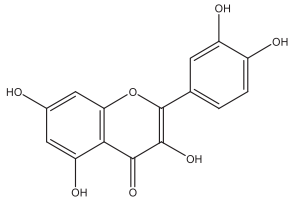
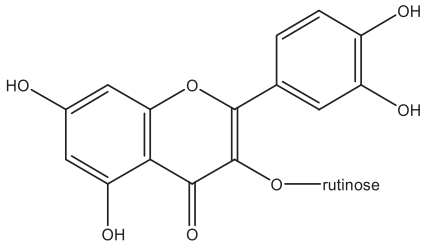
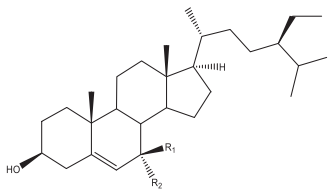
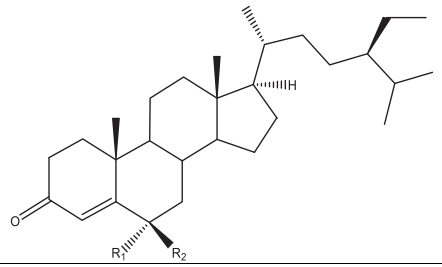
(Continued)

TABLE 1 (continued)

Molecule	Chemical structure	Biological activities	Source	Class	Reference
Mucic acid 1,4-lactone 2-O-gallate R_1 = Galloyl, and R_2 = R_3 = H Mucic acid 1,4-lactone 3-O-gallate R_1 = R_3 = H, and R_2 = Galloyl. Mucic acid 1,4-lactone 5-O-gallate R_1 = R_2 = H, and R_3 = Galloyl. Mucic acid 1,4-lactone 3,5 di-O-gallate R_1 = H, and R_2 = R_3 = Galloyl.		Antioxidant and anti-proliferative	Fruits	Phenolic acids	(Chang *et al.*, 1995; Dhale and Mogle, 2011; Goyal and Bhadauria, 2008; Zhang *et al.*, 2004)
Myricetin		Antioxidant, anti-inflammatory, anti-diabetic, and anti-proliferative	Fruits	Flavonoids	(Variya *et al.*, 2016; Yang and Liu, 2014)
Pedunculagin R_1 = R_2 = HHDP', and R_3 = R_4 = HHDP		Antioxidant, anti-tumor and anti-inflammatory	Fruits	Tannins and phenolic acids	(Baliga and Dsouza, 2011; Mahata *et al.*, 2013; Verma *et al.*, 2012)
Phyllaemblic acid R_1 = R_2 = R_3 = H, and R_4 = THDF Phyllaemblicin-A R_1 = R_2 = THDF, and R_3 = R_4 = H Phyllaemblicin-B R_1 = R_2 = THD, and R_3 = R_4 = H Phyllaemblicin-C R_1 = R_2 = THD', and R_3 = R_4 = H		Antioxidant, protein kinase inhibitor, anti-microbial, anti-cancer; anti-viral, and anti-inflammatory	Roots	Phenols and sugar	(Gopa *et al.*, 2012; Modilal and Pitchai, 2011; Qureshi *et al.*, 2009; Variya *et al.*, 2016; Yang and Liu, 2014; Zhang *et al.*, 2004; Zhao *et al.*, 2015)

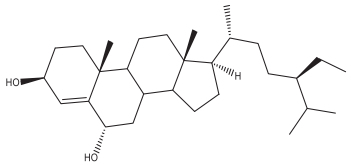
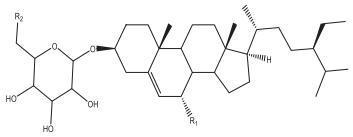
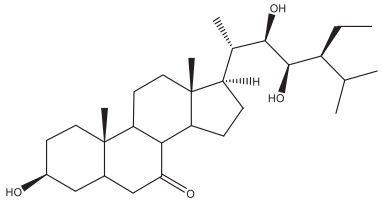
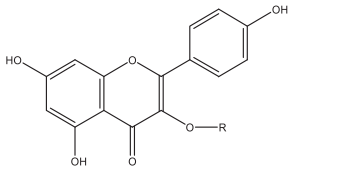
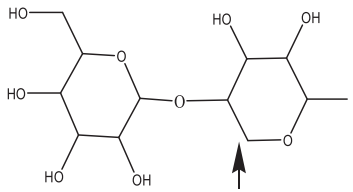
(Continued)

TABLE 1 (continued)

Molecule	Chemical structure	Biological activities	Source	Class	Reference
Punigluconin $R_1 = R_2$ = HHDP, and $R_3 = R_4$ = Galloyl		Antioxidant	Fruits	Phenols and tannins	(Variya *et al.*, 2016; Yang and Liu, 2014)
Quercetin		Antioxidant, anti-inflammatory, anti-cancer, hemo-protective, radio-protective, anti-diabetic, and anti-proliferative	Whole plant	Flavonoids	(Estari *et al.*, 2012; Hazra *et al.*, 2010; Liu *et al.*, 2008a, 2008b; Pinmai *et al.*, 2008; Rahman *et al.*, 2009; Zhao *et al.*, 2015)
Rutin		Antioxidant, anti-inflammatory, anti-cancer, hemo-protective, radio-protective, anti-diabetic, and anti-proliferative	Whole plant	Flavonoids	(Estari *et al.*, 2012; Hazra *et al.*, 2010; Liu *et al.*, 2008a, 2008b; Zhao *et al.*, 2015)
5α,6β,7α-7α- acetoxysitosterol R_1 = H and $R_2 = CH_3COO$ β-sitosterol R_1 = H and R_2 = H 7α-hydroxysitosterol R_1 = H and R_2 = OH 7β-ethoxysiterol R1 = CH_3CH_2O and R_2 = H 7-ketositosterol $R_1 = R_2$ = O		Antioxidant and cytotoxic	Leaves and stem	Terpenoids and sterols	(Qi *et al.*, 2013; Variya *et al.*, 2016)
Stigmast-4-en-3-one $R_1 = R_2$ = H Stigmast-4-en-3,6-dione $R_1 = R_2$ = O Stigmast-4-en- 6β-ol-3-one R_1 = H and R_2 = OH		Antioxidant and cytotoxic	Leaves and stem	Terpenoids and sterols	(Qi *et al.*, 2013; Variya *et al.*, 2016)

(Continued)

TABLE 1 (continued)

Molecule	Chemical structure	Biological activities	Source	Class	Reference
Stigmast-4-ene-3β,6α-diol		Antioxidant and cytotoxic	Leaves and stem	Terpenoids and sterols	(Qi *et al.*, 2013; Variya *et al.*, 2016)
Daucosterol R_1 = H and R_2 = OH 6′-(stigmast-5-en-3-O-β-D-glucopyranosidyl) hexadecanoate R_1 = H and R_2 = OOC-$(CH_2)_{14}$-CH_3 6′-(stigmast-5-en-7-one-3-O-β-D-glucopyranosidyl) hexadecanoate R_1 = OH and R_2 = OOC-$(CH_2)_{14}$-CH_3		Antioxidant and cytotoxic	Leaves and stem	Terpenoids and sterols	(Qi *et al.*, 2013; Variya *et al.*, 2016)
(3S,10S,13R,17R)-17-((2S,3R,4R,5S)-5-ethyl-3,4-dihydroxy-6-methylheptan-2-yl)-3-hydroxy-10,13-dimethyl-dodecahydro-2H-cyclopenta[a] phenanthren-7(8H,9H,14H)-one		Antioxidant and cytotoxic	Leaves and stem	Terpenoids and sterols	(Qi *et al.*, 2013; Variya *et al.*, 2016)
Kaempferol R = H Kaempferol-3-O-α-L-rhamnopyranosyl-(1-6)-β-D-galactopyranoside R = APP (bonding from the position of arrow head) Kaempferol-3-O-glucosyl (1-2) rhamnoside R = DPP (bonding from the position of arrow head)	  DPP	Antioxidant, anti-inflammatory, anti-cancer, hemo-protective, radio-protective, anti-diabetic, and anti-proliferative	Whole plant	Flavonoids	(Estari *et al.*, 2012; Hazra *et al.*, 2010; Liu *et al.*, 2008a, 2008b; Pinmai *et al.*, 2008; Rahman *et al.*, 2009; Zhao *et al.*, 2015)

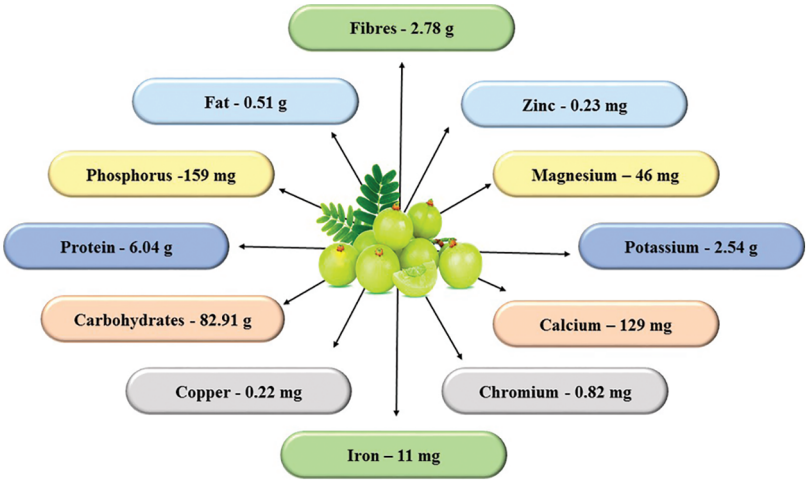


FIGURE 2. Main phyto-elements present in *Phyllanthus emblica* (per 100 g).

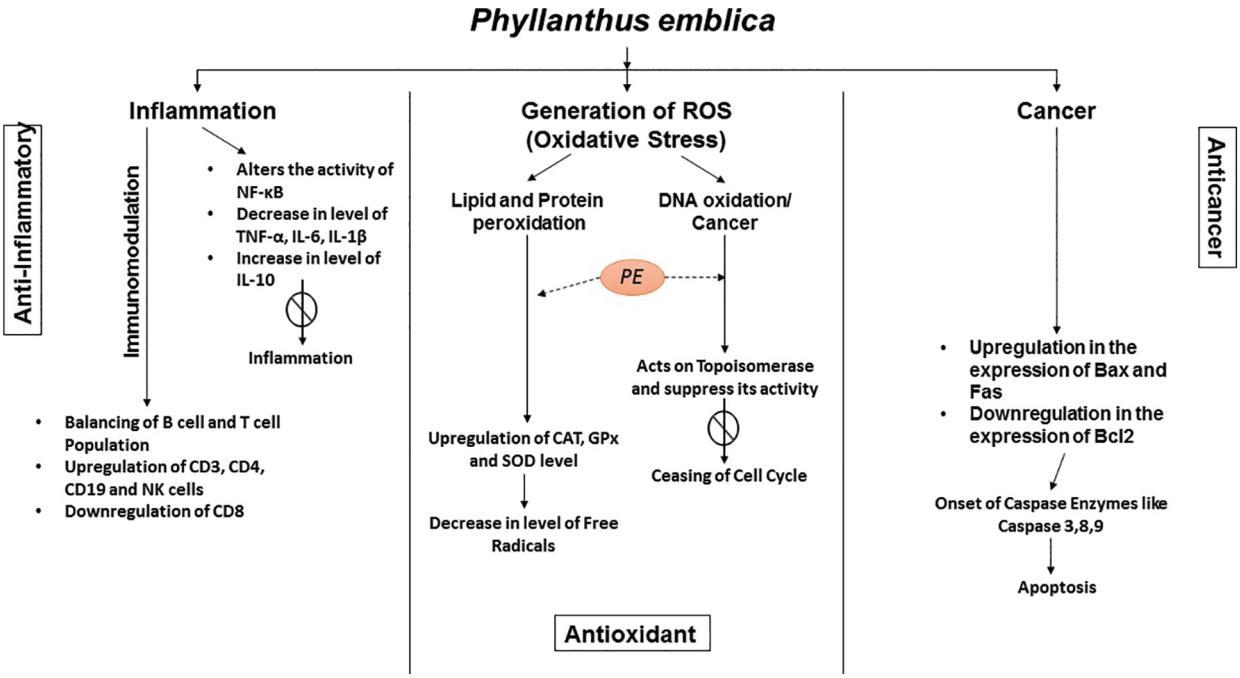


FIGURE 3. Mode of action of *Phyllanthus emblica* against various oxidative stresses, cancer, and inflammations.

models (Yang and Liu, 2014; Zhao *et al.*, 2015; Variya *et al.*, 2016).

Pharmacological Activities

Various reports suggest that Indian gooseberry has immune-modulatory, anti-cancer, anti-inflammatory, anti-microbial, anti-diabetic, adaptogenic, and antioxidant properties (Kumar *et al.*, 2018a). The mode of action of *P. emblica* against various oxidative stresses, cancer, and inflammations is represented in Fig. 3.

P. emblica also prevents various other ailments, such as osteoporosis and hyperlipidemia (Mirunalini and Krishnaveni, 2010). Extracts of dried *P. emblica* fruits are beneficial for a wide range of ailments, including anemia, digestive problems, asthma, cough, leprosy, and liver disorders, as mentioned in Ayurvedic literature (API, 2010; Patel and Goyal, 2012; Khan *et al.*, 2018b). In Tibetan medical literature, *P. emblica* is recommended as a diuretic, anti-inflammatory, and antipyretic (Kletter and Kriechbaum, 2001; Yadav *et al.*, 2017; Jantan *et al.*, 2019). The fruiting body of *P. emblica* has good medicinal and nutritive value. The fruit shows major pharmacological activities (Variya *et al.*, 2016; Yadav *et al.*, 2017; Khan *et al.*, 2018b; Yang *et al.*, 2020).

Cure against diabetes

A proper and balanced diet is of utmost importance in the management of diabetes (type 1 and type 2) and various other metabolic complications (Musman *et al.*, 2019; Sharma *et al.*, 2020). Diabetes is mediated through the stimulation of pancreatic cells, which interferes with the adsorption of dietary glucose (Grover *et al.*, 2002; Platel and Srinivasan, 1997; Srinivasan, 2005). Many non-clinical and clinical studies have been conducted against the anti-hyperglycemic activity of *P. emblica* (Grover *et al.*, 2002)

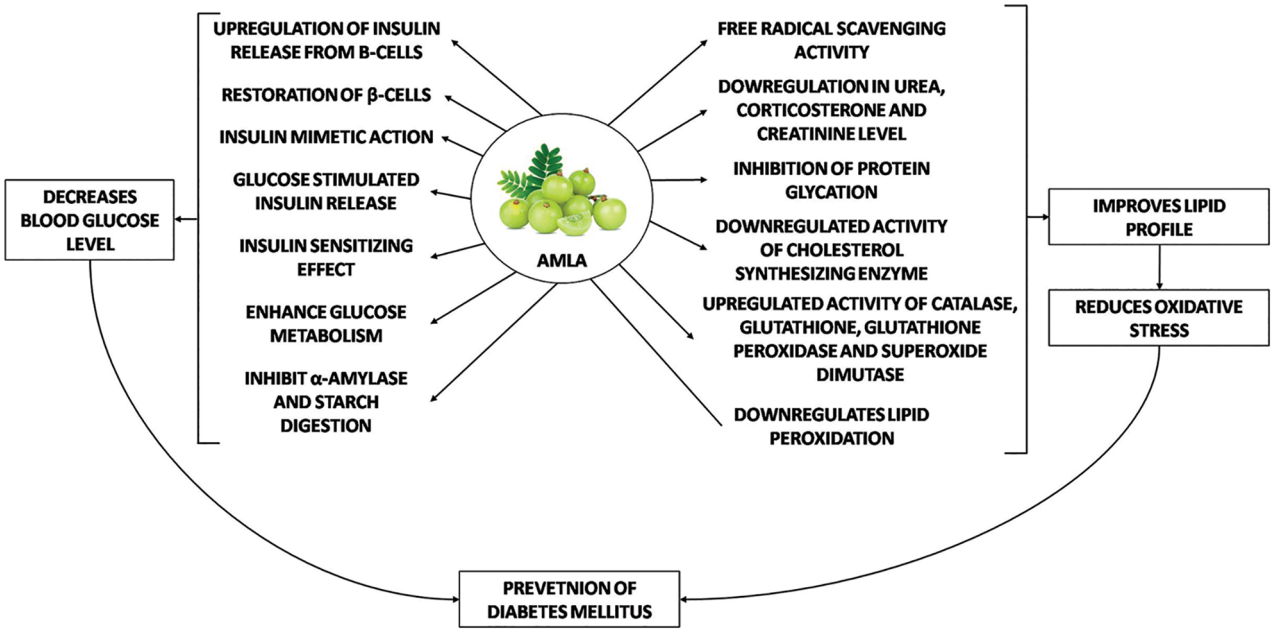


FIGURE 4. Various activities and mechanism of action of *Phyllanthus emblica* fruit extracts in the cure of diabetes.

(Fig. 4). In one clinical trial study, *P. emblica* was also reported to reduce 2 h post-prandial and fasting blood sugar levels in diabetic patients (Akhtar *et al.*, 2011).

For elucidation of the significant role of *P. emblica* against diabetes and related complications, various studies have been performed on a rat model involving the induction of diabetes by streptozotocin in rats with or without a high-fat diet. The administration of *P. emblica* incurs significant protection against 5-hydroxyfurfural and low antioxidant levels. The serum adiponectin levels were found to improve, and simultaneously glycosylated proteins were reduced. The study reported the role of *P. emblica* in improving the metabolism of glucose in diabetes hyperglycemic conditions (Rao *et al.*, 2005).

Cytoprotective and anti-cancer activity

P. emblica is rich in hydrolysable tannin and polyphenols-derived compounds, which prevent lipid peroxidation and mutagenesis induced by carcinogens (Yang and Liu, 2014; Zhao *et al.*, 2015; Variya *et al.*, 2016). Ellagic acid tannins, and chebulagic acid, extracted from *P. emblica*, have anti-proliferative and pro-apoptotic activity against cancer cells (Thoidingjam and Tiku, 2019; Balusamy *et al.*, 2020; Fig. 5). They help in scavenging free radicals, therefore, preventing the formation and accumulation of ROS and protecting DNA from damage (Makena and Chung, 2007). *P. emblica* is also reported to act against carcinogen 3, 4-benzo (a) pyrene in mice,which helps in preventing the negative effects of chromosomal damage (Nandi *et al.*, 1997). Aqueous extract of the fruit of *P. emblica* also reduces the effect of benzopyrene, which has cytotoxic effects as reported in murine models (Nandi *et al.*, 1997).

Anti-inflammatory properties

It has been reported that aqueous extract of *P. emblica* has the ability to cure several inflammatory disorders, including psoriasis, inflammatory bowel syndrome, atherosclerosis, osteoarthritis, rheumatoid arthritis, etc. Asmawi *et al.* (1993) reported that the hydro-methanolic extract of leaves of *P. emblica* possesses excellent anti-inflammatory action against dextran and carrageenan-induced rat paw models (Asmawi *et al.*, 1993). It modulates inflammatory responses by decreasing the synthesis of various chemokines, which inhibit the localization of immune cells to the target area and promotes the synthesis of T cells to overcome the damaging effects (Li *et al.*, 2020; Singh *et al.*, 2015).

Immuno-modulatory activity

P. emblica also has a unique property of acting as an immuno-modulator which attenuates acquired and innate immunity (Fig. 6). They strengthen the immune system by improving the host defense mechanism (Patil *et al.*, 2012). Products of *P. emblica*, like dried extract, tonic, syrups, medicines, etc, act as disease-preventing or energy boosting agents that directly work on various immuno-pathogens and support the immune system. Reports also suggest that they are rich in vitamin C, which helps in improving cellular cytotoxicity and natural killer cell activity (NK). The fruits of *P. emblica* increase the life expectancy (35%) of tumor-affected mice by stimulating proliferation in the splenic activity of a natural killer cell (Suresh and Vasudevan, 1994). It also acts as an immune modulator by inducing DNA fragmentation, decreasing apoptosis and cytoprotection against various pathogenic cells and chromium-induced immunosuppressive and cellular stresses. A dosage of 100 mg/mL of *P. emblica* also restores the decreased level of gamma interferon and interleukin (IL)-2 of lymphocyte proliferation by chromium-induced immunosuppressive and cellular stress (Ram *et al.*, 2002; Nair *et al.*, 2018; Li *et al.*, 2020). A study by Singh *et al.* (2013) showed that the aqueous extract of *P. emblica* serves as an immune-modulatory agent in thymocyte cells of mice against oxidative stress and cytotoxicity caused by arsenic (Singh *et al.*, 2013).

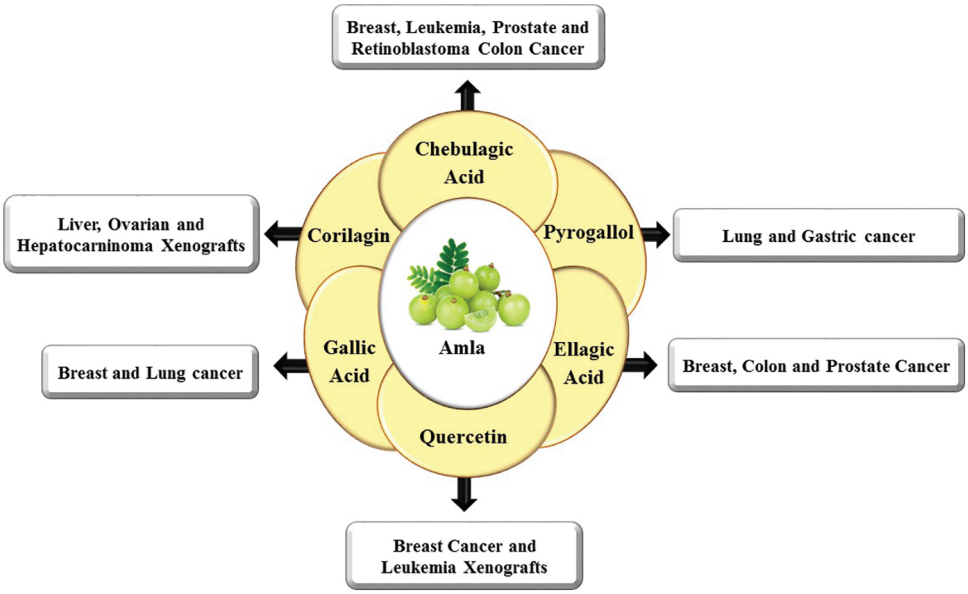


FIGURE 5. Depiction of various components of *Phyllanthus emblica* fruit extracts possessing anti-cancer properties.

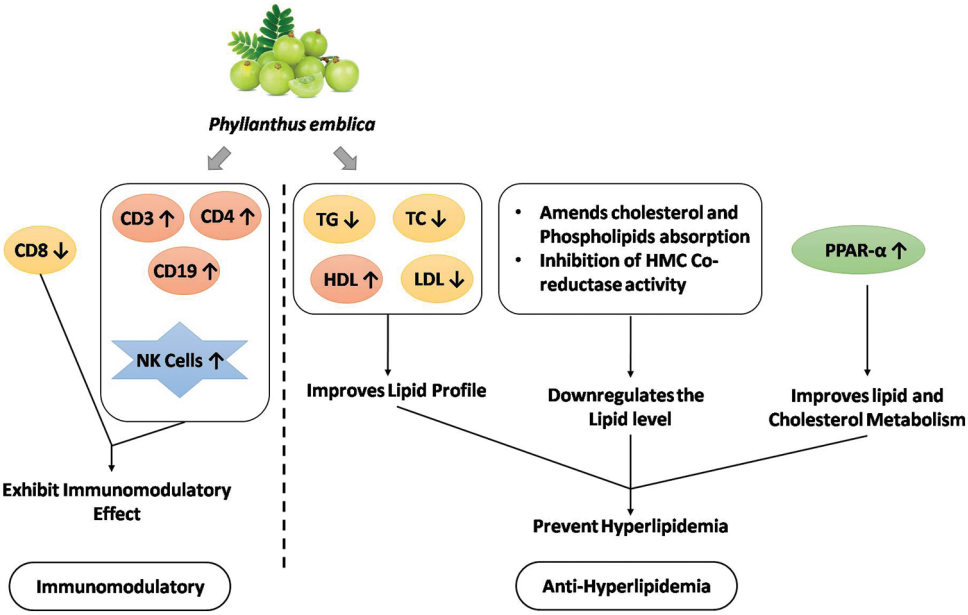


FIGURE 6. Regulation of immuno-modulatory and anti-hyperlipidemic properties by *Phyllanthus emblica* fruit extracts.

Anti-hyperlipidemia and related metabolic syndrome

Phyto-constituents and flavonoids obtained from the extract of *P. emblica* are also reported to possess hypolipidemic potential (Dwivedi and Aggarwal, 2009; Hakimi *et al.*, 2019). Kim *et al.* (2005) proposed the anti-hyperlipidemic effects of *P. emblica* on rats supplemented with cholesterol under copper-induced stresses. A decrease in the concentration level of oxidized LDL was observed, which prevents atherosclerosis in model organisms (Kim *et al.*, 2005; Usharani *et al.*, 2019).

Anti-mutagenic activity

Other secondary metabolites, such as terpenoids, phenolates, flavonoids glycosides, etc, are also reported in *P. emblica*, which have high anti-mutagenic properties. It inhibits mutagenicity and activation of 4-nitro-O-phenylenediamine, 2-acetamidofluorene, and 20-methylcholanthrene, which induces sarcoma (Jose *et al.*, 1997). It works by inhibiting the phase I enzymes, establishing an important role against mutagenicity in various model organisms (Haque *et al.*, 2001; Bhattacharjee *et al.*, 2020).

Uses in Ophthalmology

Retinal disorders including glaucoma, retrolental fibroplasia, diabetic retinopathy, retinitis pigmentosa, cataract, and macular degeneration are the major conditions that cause blindness worldwide. Antioxidant property and free radical scavenging potential of *P. emblica* are reported to manage ophthalmic issues such as redness, itching, burning, lacrimation, eyesight, etc. (Head, 2001, 1999; Rizvi *et al.*, 2013; Nashine *et al.*, 2019; Prasad and Srivastava, 2020).

Other uses

Earlier findings indicate that the fruit extracts of *P. emblica* possess wide-spectrum pharmacological activities and show

synergistic activity in combination with vitamins (A, C, E) and green tea (Jain *et al*., 2011; Kamal *et al*., 2012). The potential role of *P. emblica* in cardioprotection has also been well-comprehended in the literature highlighting its high antioxidant activity against isoproterenol, and the corresponding results indicate substantial enhancement in contractile and hemodynamic functions when the dose range of 100–500 mg/kg of body weight was administrated orally (Ojha *et al*., 2012). The presence of phytophenols like flavonoids and tannins in *P. emblica* fruits acts against oxidative stress in alcohol-induced hepatic injury (Reddy *et al*., 2010). *P. emblica* also has a protective effect against its related toxicity during metal-induced stresses. Singh *et al.* (2014) concluded that the protective effects of *P. emblica* against necrosis, apoptosis, DNA damage, and oxidative damage aredue to arsenic (As) in liver cells of mice at a dosage of 500 mg/kg of body weight per day for 30 days (Singh *et al*., 2014).

Earlier findings indicate that the fruit extracts of *P. emblica* possess wide-spectrum pharmacological activities and show synergistic activity in combination with vitamins (A, C, E) and green tea (Jain *et al*., 2011; Kamal *et al*., 2012). The potential role of *P. emblica* in cardioprotection has also been well-comprehended in the literature highlighting its high antioxidant activity against isoproterenol, and the corresponding results indicate substantial enhancement in contractile and hemodynamic functions when the dose range of 100–500 mg/kg of body weight was administrated orally (Ojha *et al*., 2012). The presence of phytophenols like flavonoids and tannins in *P. emblica* fruits acts against oxidative stress in alcohol-induced hepatic injury (Reddy *et al*., 2010). *P. emblica* also has a protective effect against its related toxicity during metal-induced stresses. Singh *et al.* (2014) concluded that the protective effects of *P. emblica* against necrosis, apoptosis, DNA damage, and oxidative damage aredue to arsenic (As) in liver cells of mice at a dosage of 500 mg/kg of body weight per day for 30 days (Singh *et al*., 2014).

Extract of *P. emblica* showed anti-resorptive and anti-osteoclastic activity by showing changes in Interleukin 6 (IL-6), nuclear factor (NF-) and FS-7-associated surface antigen (Fas) expression by activating apoptosis of osteoclasts cells without changes in osteoclastogenesis (Penolazzi *et al*., 2008; Pompo *et al*., 2014). It regulates glucose 6-phosphate dehydrogenase activity and has a good aphrodisiac effect (Panda and Kar, 2003). A polyherbal formulation of *P. emblica*, i.e., Chayavanprasha, is used as a tonic for sexual vitality (Dweck et al., 2002).

Conclusion and Future Research

Recent studies concluded that *P. emblica* is a miracle tree. Every part (i.e., leaf, stem, heartwood, and roots) of this plant is very beneficial. Maximum research has been performed on the fruit, and there are a few reports on the leaves and roots. Thus, there is a need to explore the therapeutic properties of leaves and stem because while the fruits are seasonal, their medicine is required throughout the year. *P. emblica* contains more than 100 phytochemicals of different classes with the dominancy of phenols and tannins. However, many compounds are unidentified, which is an important aspect of future research. Further, detailed investigations of their biological activities in individual or mixed forms are other important aspects of future research. Until now, most experiments have been performed on animal and *in-vitro* models, highlighting the need for clinical studies with well-established facts. We rarely found ant published clinical studies on the therapeutic effects of *P. emblica*. Many reports claim that pharmacological activities like anti-cancer, anti-hyperlipidemia, and anti-hyperthyroidism are attributed to the antioxidant activities of *P. emblica*. Detailed research is required for the characterization and isolation of these compounds. After a detailed review, we found that few compounds have proven safety efficacy and medicinal properties. For example, ellagic acid, corilagin, chebulagic acid, gallic acid, and quercetin have proven anti-cancer and anti-proliferative activities. So, it has become essential to unravel the bio-molecular mechanism of the action of these both compounds as well as their physiological effects.

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Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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