A Review on Therapeutic Potential of Amla

By

Syeda Sazia Tahsin

16346002

Department of Pharmacy
Brac University
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

SYEDA SAZIA TAHSIN

Syeda Sazia Tahsin
16346002

Approval

A project titled “A Review on Therapeutic Potential of Amla” submitted by Syeda Sazia Tahsin (16346002) of Summer, 2016 been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on Summer 2020.

Examining Committee:

Supervisor:
(Member)

raushan

Dr. Raushanara Akhter
Associate Professor, Department of Pharmacy
Brac University

Program Coordinator:
(Member)

Dr. Hasina Yasmin
Associate Professor, Department of Pharmacy
Brac University

Departmental Head:
(Chair)

Professor Dr. Eva Rahman Kabir
Chairperson, Department of Pharmacy
Brac University

Ethics Statement

The study does not involve any kind of animal trial and human trial.

Abstract

Amla (*Emblica officinalis* or *Phyllanthus emblica Linn.*) is one of the vital medicinal plants belong to Euphorbiaceae family and it is used as an important herbal drug. Abundance and easy availability make this plant a promising source for potential therapeutic agents. The main purpose of this review was to compile information on therapeutic potential of the crude extracts and the phytochemicals isolated from Amla by the researchers. The compounds that are found in Amla include Vitamin-C, tannoids, ellagic acid, tannins, phyllembelic acid, phyllembelin, rutin, curcum-inoids, emblicol, some phenolic compounds etc. These compounds are found to show significant activity as an anti-oxidant, anti-cancer, anti-diabetic, cardioprotective, anti-inflammatory, analgesic, anti-pyretic, anti-microbial, hepatoprotective, nephoprotective, anti-diarrheal and antitussive agents. This plant is enriched with vitamin C, amino acid and thus, it is highly nutritious. The information was collected from various authentic scientific journals and renowned databases.

Keywords: Amla, antioxidant, therapeutic potential, phytochemicals, bioactivity.

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Chapter 1

Introduction

General information of Amla

Amla (Amalaki) which is also known as Indian gooseberry is a familiar and major medicinal plants and is very common in the traditional and Ayurvedic medicinal system (Baliga & Dsouza, 2011). Scientific name of Amla is *Emblica officinalis* or *Phyllanthus emblica Linn.* under the family of Phyllanthaceae (Yadav, Singh, Singh, & Kumar, 2017). Fruits and leaves of amla have widespread usage in the traditional and folklore medical system because of its numerous benefits. In India, Amla is commonly used as an Ayurvedic medicine. It is one of the main constituents of a polyherbal formulation known as Chyavanprash which is familiar for its health beneficial activity including various respiratory and cardiac disease treatments (S. K. Bhattacharya, Bhattacharya, Sairam, & Ghosal, 2002). According to the World Health Organization (WHO), many developing countries are still depending on the traditional medicine system and rely on phytotherapy which is because of their faith in medicinal plants (Yadav et al., 2017). Besides, the therapeutic effectiveness, safety and economical advantages of using these medicinal plants are the reasons behind dependence on herbal medicines by huge populations which is almost 70 percent of the world's people (Jain, Das, Pandey, & Jain, 2016).

Amla possess high therapeutic efficacies and immense medicinal value. For instance, they are commonly used as an astringent and for treating hair fall and PGH (premature graying of hair). Moreover, they are also used in treatment of ophthalmic disease, anemia, diabetes, asthma, cough, constipation, colitis for increasing anti-coagulant, blood fluidity and antiplatelet functions and leads to a warming sensation. Furthermore, they act as an natural immunity booster and improve digestion (Kapoor, Suzuki, Derek, Ozeki, & Okubo, 2020).

Leaves extract of amla provides therapeutic response against diabetes mellitus. Besides, they are also used to prepare bactericidal mouthwash which is helpful to cure aphthae (Nadkarni, 2014). The milky juice of amla has a great response in the treatment of sores (Nain, Saini, Sharma, & Nain, 2012). However, both leaves and fruits are utilized in treatment of inflammation and to reduce fever (James B. Perianayagam, Sharma, Joseph, & Christina, 2004).

Amla trees are usually located in several tropical and subtropical areas of Asia particularly, in the tropical southeastern part. They are commonly grown in Indonesia, China, Malaysia and India, Bhutan, Bangladesh, Sri-lanka, Nepal and Pakistan (A. Bhattacharya, Kumar, Ghosal, & Bhattacharya, 2000).

Amla trees have small to moderate size. A mature Amla tree has height of around 8 to 18 meters. It has a crooked trunk with light gray bark. The flower of Amla is greenish yellow in color and they appear in axillary clusters. The shape of the leaves of amla is round base and acute apex. They have feathery and non-oblong features grown closely from the bracelets. The leaves are very short in size and around 7 to 10 cm long. The shapes of fruits are spherical and have six vertical bands and greenish yellow in color. The fruits are around 1.8 and 2.5 cm in diameter (Gaire & Subedi, 2014). The taste of fruits is sour, bitter and acidic (Variya, Bakrania, & Patel, 2016). Fruits of Amla is the most important part and have numerous medicinal values. The main constituent of Amla is vitamin C or Ascorbic acid which provides natural immunity. According to a study, 100g of edible amla fruits can provide vitamin - C around 470 to 680 mg (Yadav et al., 2017). They are also rich in amino acids, fatty acids, oils and minerals as well as glycosides (Gaire & Subedi, 2014). The fruit extracts of Amla shows many therapeutic responses in - vitro as well as in animal studies including antidiabetic, antimicrobial, anti-inflammatory and also many immune-regulating actions(B. Yang & Liu, 2014). The leaves extract of Amla containing active constituents have

shown effectiveness as anti-inflammatory, antioxidant and anti-bacterial substances (Purena, Seth, & Bhatt, 2018). Studies show that the mechanism of alkaloids, phenols, carbohydrates, amino acids and tannoids is responsible for Amla's analgesic and anti-inflammatory activities (Variya et al., 2016).

Compounds identified and isolated from Amla

Figure 1: Fresh amla or Emblica officinalis fruits (Jain et al., 2016*)*

Vitamin-C or Ascorbic acid is the most abundant compound found in Amla. Additionally, other phytochemicals that are identified and isolated from the fruit extracts are rutin, tannins, phyllembelic acid, curcuminoides, emblicol, phyllemblin and many other phenolic compounds. Fatty acids that are found in Amla fruits include stearic, linolenic, palmitic, oleic, linoleic and myristic acids. The sugars are D-glucose, D-xylosyI, D-fructose, D-myo-inositol, D-rhamnosyl, D-galacturonic acid, D-mannosyl, D-arabinosyl, D-glucosyl and D-galactosyl residues (Gaire & Subedi, 2014). Amla contains complex tannins and ellagitannins which are the most active compounds. Most common hydrolyzable tannins that are found in the amla fruits are mucic acid gallate, monogalloylglucose, mucicacidlactone gallate, digalloylglucose, chebulagic acid putranjivain A, galloyl-HHDP-glucose, gallic acid, and elaeocarpusin(B. Yang & Liu, 2014).

Major tannins that are identified in Amla extracts are punigluconin, pedunculagin, Emblicanin A and B. The ellagitannins include geraniin, corilagin, chebulagic acid and elaeocarpusin. These substances have antioxidant property (Kapoor et al., 2020).

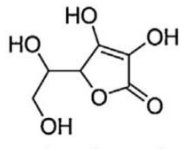
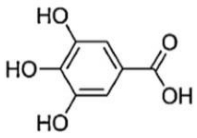
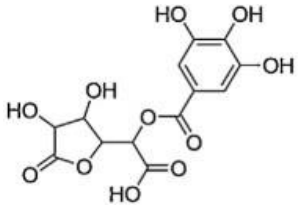
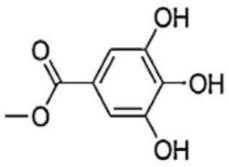
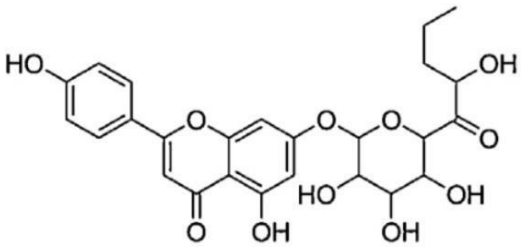
The compounds that are identified and isolated from the leaves extract of Amla are gallic acid which is also known as Glucogallin (3,4,5-trihydroxy benzoic acid), methyl gallate, ellagic acid (2,3,7,8-tetrahydroxy-chromeno[5,4,3-cde]chromene-5,10-dione), Apigenin-7-O-(6-butyryl-glucopyranoside), 5-hydroxymethylfurfural or 2-furancarboxaldehyde-5-(hydroxymethyl), pyrogallol (1,2,3-benzenetriol), flavanone glycosides, luteolin-4-O-neohesperidoside, 2-acetyl-5-methyl furan (5-methyl-2-furyl methyl ketone), 5,6,7-acetoxysitosterol, 1,2,3,4,6 penta-O-galloylglucose, and trihydroxysitosterol,. These active constituents have shown effectiveness as anti-inflammatory, antioxidant and anti-bacterial substances (Purena et al., 2018). Two sterols are identified from the leaves and branches of amla - trihydroxysitosterol and 5α,6β,7α-acetoxysitosterol(El-Desouky, Ryu, & Kim, 2008). Along with these compounds there are some other constituents isolated and identified that are, malic acid, histidine, arginine, thiamin, aspartic acid, astragalin, β-carotene, gibberellins, β-sitosterol, leucodelphinidin, chebulic acid, rutin, chebulagic acid, glutamic acid, riboflavin, chebulinic acid,quercetin, phyllemblin acid, isoleucine, corilagin, methionine, cysteine, ellagic acid, chebulaginic acid, emblicol, glycine, kaempferol, phyllantidine, phenylalanine, corilagic acid, valine, threonine, tyrosine, zeatin and tryptophan (Gaire & Subedi, 2014).

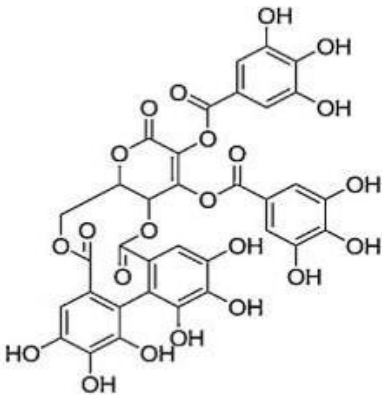
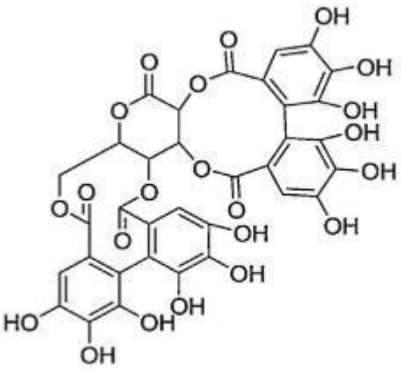
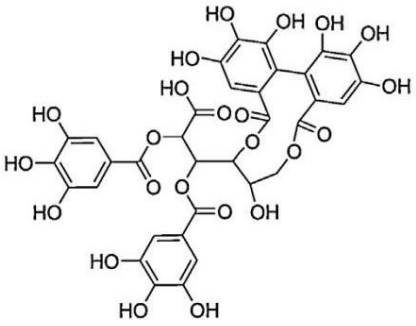
The root of Amla contains three norsesquiter- penoids which are phyllaemblicin-A, B and C. Beside these compounds other isolated compounds are, phyllaemblic acid (methyl ester of highly oxygenated norbisabolane), 2-carboxylmethylphenol 1-O-β-D-glucopyranoside and 2,6-dimethoxy-4-(2-hydroxyethyl)phenol 1-O-β-D-glucopyranoside (Zhang, Tanaka, Iwamoto, Yang, & Kouno, 2000).

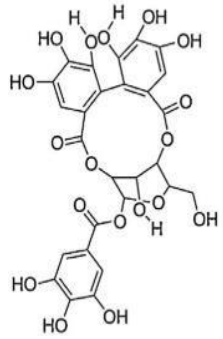
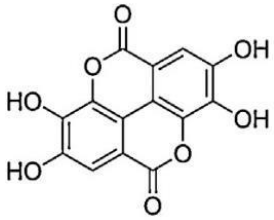
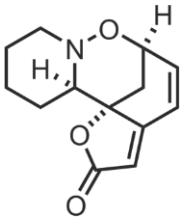
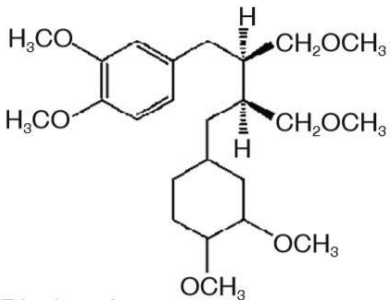
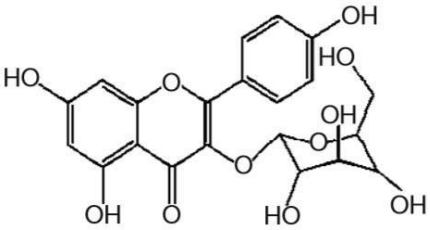
The pulp of Amla is rich in phenolic content along with gallic acid and quercetin. Tannins are identified in abundant quantities in the seeds of amla. However, caffeic acid, coumaric acid, myricetin along with synergic acid are identified and isolated from both pulp and seeds of Amla (Variya et al., 2016).

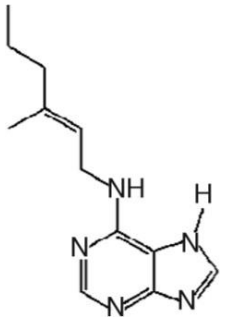
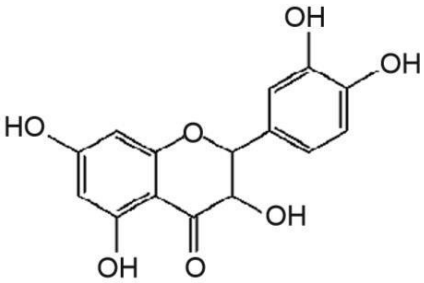
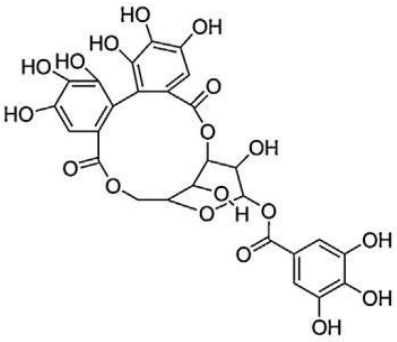
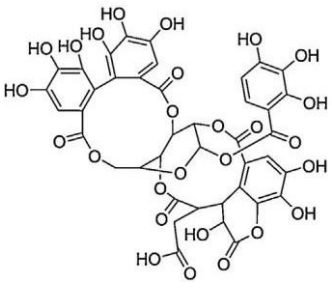
Table 1: Some phytochemical constituents of Amla

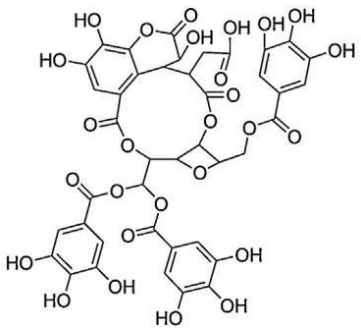
(Variya et al., 2016, Gaire & Subedi, 2014, Kapoor et al., 2020)

Isolated compound	Figure
Ascorbic acid (Vitamin - C)	
Gallic acid	
Mucic acid gallate	
Methyl gallate	
Apigenin-7-O-(6-butyryl-glucopyranoside)	

Emblicanin A	
Emblicanin B	
Punigluconin	

Pedunculagin	
Ellagic acid	
Phyllantidine	
Phenylalanine	
Astragalin	

Zeatin	
Quercetin	
Corilagin	
Chebulagic acid	

Chebulinic acid	

Rationale of the study

Amla has been considered as a safe and economical medicinal plant which shows a number of effective bioactivities (Jain et al., 2016). It has been commonly used in traditional medicinal system (Baliga & Dsouza, 2011). Amla trees are generally familiar in different parts of Asia (A. Bhattacharya et al., 2000). The main reason of this study is to overview and compiles information on the phytochemicals and the therapeutic potential of Amla. In addition to that the study would help in finding out new scopes for future researches.

Aim of the study

The aim of the study is to overview and compiles information on the therapeutic potential of various parts of Amla.

Objective of the study

The principal objectives of this project work are-

a) To overview on general information of Amla and it's the chemical constituents.

b) To compile information on characteristic features and traditional use of Amla.

c) To gather information on therapeutic potential of Amla.

d) To find out scopes for future researches.

Chapter 2

Methodology

The study has been carried out by scheming and screening a number of renowned journals and research articles. Along with that, various research databases have been used such as, Science Direct, Pub Med, Google Scholar, Academic journals, Wiley Online Library etc. The relevant data and information associated with features, isolated phytochemicals and bioactivities of Amla have been extracted and collaborated to write this literature review. In addition, Mendeley by Elsevier has been utilized for citation of the employed articles.

Chapter 3

Therapeutic Potential of Amla

3.1 Antioxidant activity of Amla:

Various compounds and phytoconstituents that are isolated from Amla have been reported as antioxidant agents. These antioxidants show their effectiveness against various free radicals including 5, 5-dimethyl-1-pyrroline-N-oxide, iron (III) reduction, 1, 1-Diphenyl-2-picrylhydrazyl radical (DPPH) free radicals, nitric oxide and superoxide. Some isolated compounds are claimed to be metal ion chelators since they have the properties to block oxidative cascade (Gaire & Subedi, 2014). The active constituents of Amla typically includes vitamin - C, complex tannoids and ellagitannins. The ellagitannins are corilagin, chebulagic acid, geraniin and elaeocarpusin. These phytochemical possess high antioxidant properties (Kapoor et al., 2020). Tannoids exhibit antioxidant action three times greater than vitamin-C (Justin Thenmozhi, Dhivyabharathi, Manivasagam, & Essa, 2016). Amla fruits contain significant amount of Vitamin C or ascorbic acid and also some other antioxidants e.g. Vitamin E or alpha-tocopherol and beta carotene, they work as a chronic cough inhibitor (Nosál'Ováx, Mokrý, & Hassan, 2003). Gallic acid and tannic acid found in the phenolic fraction of the fruit extracts of Amla which are two major antioxidant compounds (B. Yang & Liu, 2014). Amla fruits also exhibit synergistic activity with vitamin A, C, E and green tea and show good antioxidant properties (Yadav et al., 2017). According to a study, the pulp of Amla has more antioxidant properties than seeds (Variya et al., 2016).

Amla has been reported to increase memory function in rats that can be due to its antioxidant properties through which vulnerable brain cells are exposed towards lesser oxidative stress leading to decreased neuronal damage as well as enhanced neuronal activity. The ethanolic extract of amla aided numerous enzymatic parameters and improved liver antioxidants which

helped in vivo against intoxicated mice by DMBA (7, 12-dimethylbenz (a) anthracene). This protecting measures may be because of the antioxidant potential of Amla and the regulatory function on hepatic detoxifying enzymes activation (Yadav et al., 2017).Besides, the antioxidant and antiapoptotic potential of the amla fruits showed protective response in case of hepatotoxicity caused by arsenic (M. Singh et al., 2014).

Regular Amla consumption results in enhanced antioxidant potential in plasma as well as reduced oxidative stress. These phenomena assist in developing oxidative homeostasis (Kapoor et al., 2020). the strong antioxidant property also helps to minimize oxidative stress originated from arsenic toxicity (Rao, Sakaguchi, Juneja, Wada, & Yokozawa, 2005). The antioxidant activity and cyto-protective mechanism of Amla allow them to fight against gastric lesions induced by the adverse reaction of non-steroidal anti-inflammatory drugs (Yadav et al., 2017). Amla extracts exhibit potential activity to regulate basal markers of oxidative stress. Besides, they showed prominent effect by elevating endogenous antioxidant defensive measures against hepatocyte cell lines (HepG2) (Kapoor et al., 2020). Studies reveal that when the noise stressed animals are treated with E. officinalis, they show progress and are relieved from the stress situation. The observation implies that the antioxidant property of amla exhibits these anti-stressor activity which helps to reduce behavioral changes due to noise stress (Wankhar, Sheela Devi, & Ashok, 2014). Amla fruit extracts has potential to improve the level of some kidney and liver antioxidant enzymes to fight against oxidative stress induced by cyclophosphamide.

Studies also claimed that Amla has protective activity against metal induced oxidative stress as well as oxidative damage caused by arsenic, necrosis along with apoptosis in the hepatocyte in experimental mice (Yadav et al., 2017). Amla contains ellagitannins and polyphenols and metabolites of these compounds can be absorbed readily by the cell tissues. Regular administration of amla thus helps to increase the protective measures to prevent

DNA damage and mutation induced by oxidation (Kapoor et al., 2020). Alma showed significant reduction in cyclophosphamide associated DNA damage and a decrease in micronuclei as well as in chromosomal abnormality in mice bone marrow cells (N. Sharma, Trikha, Athar, & Raisuddin, 2000). Amla decreases the cytochrome P450 level and raises antioxidant glutathione and antioxidant enzymes (glutathione reductase and glutathione peroxidase) level. These result in a protective mechanism against DNA damage induced by gamma radiation. The experiment was observed in vitro in human peripheral blood lymphocytes and plasmid DNA. This protective action was introduced by the antioxidant activity of amla along with inhibiting action of lipid peroxidase and increasing the detoxification effect of glutathione-S-transferase (Baliga & Dsouza, 2011). Aqueous fraction of Amla fruits demonstrated defensive response against 3, 4-benzo (a) pyrene which is a genotoxic carcinogen and this resulting in chromosomal damage through formation of free radicals of oxygen. Studies suggest that this protective effect of amla was possibly because of its isolated constituents' combined antioxidant properties. These phytochemicals are mostly vitamin C alongside gallic acid, tannoids and ellagic acid. Amla exerts potential antioxidant activity in brain cells. Similarly, it also shows beneficial effects against age related kidney disease as well as improving the urinalysis parameters because of its high concentration of various antioxidants containing compounds (Kapoor et al., 2020).

A number of studies claimed that the antioxidants exhibit a defensive measure in case of cardiac ischemia-reperfusion injury (Haramaki, Packer, Assadnazari, & Zimmer, 1993). Long term administration of Amla fruit helps to enhance myocardial adaptation by increasing the endogenous antioxidants. This result in a protective mechanism in the heart against oxidative stress induced from ischemia-reperfusion injury. Studies on antioxidant effect of Amla extracts claims that amla fruits have cardioprotective properties (Gaire & Subedi, 2014). A study with hepatocyte cell line (Hep G2) demonstrated the function of Amla’s aqueous

extract as it alters the basal oxidative markers as well as elevate endogenous antioxidant activity (Yadav et al., 2017). Isolated compounds of amla that have significant antioxidant properties have been reported to maintain vascular homeostasis as well as regulate various physiological activities. They help to maintain vascular permeability along with antithrombotic activity which helps in preventing arterial thrombosis (Kapoor et al., 2020).

The antioxidant potentiality of Amla leaves extract has demonstrated hypoglycemic property (Nain et. al., 2012). According to several studies, in diabetes, oxidative stress is correlated with a decline in the function of antioxidant defense mechanism and results in a long-term complexity. Amla is responsible for elevating the antioxidant enzyme level e.g. GSH S-transferase, GSH reductase, GSH peroxidase, superoxide dismutase and catalase (Yadav et al., 2017). Factors that cause the alteration of oxidative stress in diabetic patients activate protein glycation, increased lipid peroxidation; deactivate antioxidant enzymes and alter the structural function of collagen and basement membranes. Since vitamin C has shown great efficacy in diabetes by decreasing the oxidative stress, the antioxidant activity of amla and ethyl acetate extract is possibly a potential source of decreasing oxidative stress in diabetic sample (Rao et al., 2005). Studies suggest that Amla can possibly be used in treatment of obesity and some metabolic syndrome as a preventive measure. This is because amla showed improved production of adiponectin in the adipocytes of HFD (high fat diet) caused by NAFLD (Non Alcoholic Fatty Liver Disease) in the rat model (Yadav et al., 2017).

3. 2 Anti-cancer activity of Amla

Various studies claimed Amla is a promising candidate to develop anticancer agents. Researchers identified and isolated numerous phytochemicals from amla which demonstrated anticancer properties (Yadav et al., 2017). Numerous studies on amla demonstrated that they

have potential to stop the initiation, development and spread of cancer along with the capability to exert potential chemopreventive effect (Baliga & Dsouza, 2011). Abundant amounts of vitamin C presence in Amla helps to increase the potential of natural killer cells along with the antibody-dependent cell-mediated cytotoxicity (Variya et al., 2016). Amla showed an anti-carcinogenic reaction in animal models on mammary tumors as well as adenocarcinoma of the prostate. The ellagic acid present in the amla extracts is responsible for this action. Another constituent gallic acid showed defensive effect against osteosarcoma in tumor cells by causing apoptosis. The main constituent of amla is vitamin C and has been claimed to have anticancer effect since it possesses strong anticancer properties (Yadav et al., 2017). Yang et al. demonstrated pyrogallol's function against lung cancer cell lines of human such as, H441 (lung adenocarcinoma) and H520 (lung squamous cell carcinoma). Investigation was conducted on both in vitro and in vivo system and the observations indicated that the pyrogallol is a potential candidate as anti-lung cancer agent, particularly in case of non-small cell lung cancer (Bhandari & Kamdod, 2012). This anticancer activity of fruits of Amla has been observed by Baliga and Dsouza (Baliga & Dsouza, 2011). According to their observations, fruits and extracts of Amla can be utilized as antineoplastic agents (Pinmai, Chunlaratthanabhorn, Ngamkitidechakul, Soonthornchareon, & Hahnvajanawong, 2008), (Pinma et al., 2010), radio-protective agents (Kumar K. B., Sabu, Lima, & Kuttan, 2004), (I. Singh, Sharma, Nunia, & Goyal, 2005) and chemopreventive and chemomodulatory agents (Ghosh, Sharma, & Talukder, 1992), (Dhir, Agarwal, Sharma, & Talukder, 1991), (Jeena, Joy, & Kuttan, 1999) to decrease the risk of cancer.

Experiments have been indicated that the Amla has the potential to prevent the attack of MDAMB-231 cells in the invasion assay with matrigel matrix in-vitro (Ngamkitidechakul, Jaijoy, Hansakul, Soonthornchareonnon, & Sireeratawong, 2010). Kaempferol a phytochemical isolated from Amla showed inhibitory action in case of stromelysin 1 (MMP-

3) expression against breast cancer cell line (MDA-MB-231) (Phromnoi, Yodkeeree, Anuchapreeda, & Limtrakul, 2009). Moreover, polyphenolic gallic acid showed inhibition against migration of gastric adenocarcinoma cell, reduced MMP2/9 expression in-vitro (Ho et al., 2010) and P815 mastocytoma tumor model in sample DBA/2 mice liver (Ohno, Inoue, &Ogihara, 2001). Furthermore, flavan-3-ols and quercetin, another two isolated compound from Amla have been exhibited reduction in the gelatinases A and B (MMP-2 and MMP-9) expression in the PC-3 cells which is a human prostate cancer cell line (Vijayababu et al., 2006) and stromelysin 1 (matrix metalloproteinase-3) in the breast cancer cell line (MDA-MB-231) (Phromnoi et al., 2009) as well as expressed inhibitory response against murine colon 26-L5 carcinoma cells on the lung metastasis (Ogasawara, Matsunaga, & Suzuki, 2007) along with B16-BL6 melanoma which is a murine tumor cell line in the model mice (Piantelli et al., 2006).

The mechanism of the anticancer effects of amla extracts are the potential of decreasing the amount of hepatic phase I enzymes, the ability to improve phase II enzyme called glutathione S-transferase (GST) level, scavenging activity of free radicals as well as reduce the oxidation of lipids along with other biomolecules, having antimutagenic effects, possessing immunomodulatory effects, modulating the proteins levels that are vital for the cell cycle progression, preventing metastasis, inducing apoptosis of neoplastic cells, dropping the ornithine decarboxylase level and improve the antioxidant enzymes levels (Baliga & Dsouza, 2011). However, the inhibitory action of amla fruit extracts possibly vary among various cancer cell lines (Pinmai et al., 2008). Again, the Amla fruit extract can work in synergy with several cytotoxic agents (doxorubicin and cisplatin) that have therapeutic properties to suppress the progression of neoplastic cells (Pinma et al., 2010). Furthermore, Amla showed short term inhibitory action against the non-cancer cells growth in vitro (B. Yang & Liu, 2014). To evaluate the potential of hydrolyzable tannins isolated from *P. emblica* were

observed using mouse models of cancer in-vitro.

A number of isolated compounds from the extract of Amla showed remarkable anticancer by utilizing xenograft models. The ellagic acid isolated from Amla exhibited significant activity against pancreatic and triple-negative breast cancers in Xenograft models (Suresh & Vasudevan, 1994), (Duan, Yu, & Zhang, 2005). Pyrogallol, another components found in *Phyllanthus emblica* ablates the development of the lung adenocarcinoma xenografts (I. Singh et al., 2005). Again, gallotannins showed remarkable anti-tumor reaction in case of both triple-negative breast cancers and cholangiocarcinoma (Mehta, Singh, Jaiswal, Rai, & Watal, 2009), (Sai Ram et al., 2003). The ellagic acid isolated from *P. emblica* may act as a prophylactic agent and showed potential protective action against development of prostate and breast cancer cells in experimental animal models (Ganju et al., 2003), (Sidhu, Pandhi, Malhotra, Vaiphei, & Khanduja, 2011). Corilagin showed potential antitumor action in hepatocellular carcinoma in xenograft models (Muthuraman, Sood, & Singla, 2011). The quercetin which is a flavonoid showed inhibitory response against development of tumor in several animal models including xenograft model of pancreatic and leukemic cancer cells (Tiwari, Kuhad, & Chopra, 2011). Quercetin was tested in murine models in-vivo based well-defined mechanism of action and substantial data was collected from phase I clinical trial and the result showed antityrosine kinase properties(Nain et al., 2012).

Aqueous extract of Amla demonstrated anticancer properties against tumorigenesis of mouse skin by decreasing the amount and volume of the tumor. Moreover, they also showed effectiveness against breast cancer. Amla aqueous extracts showed significant inhibition of cytotoxic L929 growth in culture (Gaire & Subedi, 2014). A number of studies claimed that Amla can be a potential agent for chemotherapy and radiotherapy due to their protective activity (Variya et al., 2016). Along with that, the fresh fruit extract was also reported to decrease Dalton lymphoma ascites (DLA) cells induced solid tumors and showed moderate

impact on ascites tumors (Gaire & Subedi, 2014). Another study on amla showed that the aqueous extracts help to expand the life span of experimental animals by decreasing the number of solid tumors through the mechanism of cell cycle control process. Researchers confirmed that the effect of anti-proliferation of amla fruit extract developed by apoptotic cascade activation. The anticancer properties of crude amla extracts along with its purified compounds is mainly by inhibiting NF- kappaB which is responsible for controlling DNA transcription, cytokine production and survival of cells (Yadav et al., 2017).

The anti-tumoral properties of Amla were observed by using six kinds of human cancer cell lines in vitro. Those six types are - HeLa (cervical), A549 (lung), SK-OV3 (ovarian), SW620 (colorectal), HepG2 (Hepatocytes) and MDA-MB-231 (breast, triple negative). Beside these human cell lines substantial antitumor properties were also observed in vitro in skin tumors of mice caused by DMBA/TPL (Variya et al., 2016). The ellagic acid in amla has the potential to improve the cytotoxic activity of radiation in the tumor cells e.g. HeLa and Ehrlich ascites carcinoma by developing free radical, decreasing antioxidant enzymes along with modifying the mitochondrial potency against experimental mice that were bearing tumor induced by radiation damage. However, the normal cells (splenic lymphocytes) were being protected (Bhosle, Huilgol, & Mishra, 2005). In the HeLa cell line, Amla introduce apoptosis in vitro. The observation demonstrates fragmentation of DNA, elevated function of caspase- 3, 7 and 8, and up-regulating the Fas protein which results in apoptosis through stimulating the death receptor pathway. However, caspase-9 remained unchanged (Variya et al., 2016). The isolated phytochemicals of amla including nor-sesquiterphenoids, phenolic compounds, and proanthocyanidin polymers showed anti-proliferative effects against HeLa, MK-1, and B16F10 cells in the in-vitro system. The phenolic compounds exhibit inhibitory potential in these three cell lines. However, their activity was more efficient in case of B16F10 rather than HeLa and MK-1 cell lines (Haque et al., 2001).

Additionally, Amla extract also exhibited chemopreventive activity. Study was done using methanolic extract of amla fruits in experimental rat models that have hepatocarcinogenicity induced by chemicals. The results showed a suppressive effect of amla fruits (Sultana, Ahmed, & Jahangir, 2008). A number of interconnected mechanisms in in-vivo systems provide combined activity to prevent any substance's carcinogenic effect. Amla works on several pathways involving oxidative stress inhibition, blocking the production of pro-inflammatory molecules, aids apoptosis, preventing DNA damage and hampers the inflammatory pathway (Yadav et al., 2017). A study on Amla in combination with Tibetan traditional medicinal system known as 'YukyunkKarne' against SKOV6 which is an ovarian cancer cell line showed remarkable anti-metastatic activity (Variya et al., 2016). According to a research, in combination with chemotherapy, Amla can enhance the efficacy of the treatment. The result was evaluated based on the defensive response of Amla's aqueous extract against toxicity caused by cyclophosphamide in experimental mice. Amla improves the function of natural killer cells along with the antibody-dependent cell-mediated cytotoxicity against Dalton's lymphoma ascites tumor in albino (BALB/c) mice. These improved properties resulted in increased life span of the experimental mice (Baliga & Dsouza, 2011). Amla extract contains a catechin compound known as pyrogallol which has anti-proliferation properties against several human cancer cell lines. In both in vivo and in vitro processes, studies demonstrated pyrogallol's possible activity against lung cancer cell lines of human such as, H441 (lung adenocarcinoma) and H520 (lung squamous cell carcinoma). The observation indicated potentiality of pyrogallol as a candidate to treat lung cancer, especially beneficial in case of non-small cell lung carcinoma (C. J. Yang et al., 2009). The study showed that Amla fruit extracts have promising effectiveness as an anti invasive agent as well as contribute to suppress carcinogenesis.

Anti-diabetic activity of Amla

Amla has been proved as a potential and promising agent for lowering the level of blood glucose in diabetic patients as well as in healthy people by numerous experiments and investigations (Kapoor et al., 2020). Researchers claimed that studies and experiments suggested the potential of Amla fruits asantihyperglycemic along with the potential to lower the lipid level and can be effectively use as an ideal plant source to develop safe and effective alternative therapeutic agent for preventing and treatingdyslipidemia, cancers, diabetes and obesity in patients as well as in general population (Akhtar, Ramzan, Ali, & Ahmad, 2011). Experiments in rats model with diabetic induced by streptozotocin showed that the administration of Amla in oral route helps to increase adiponectin levels in serum which results in enhanced metabolism of glucose in diabetes mellitus (Rao et al., 2005). Antioxidants found in Amla particularly vitamin C and E possess potential action by decreasing oxidative stress in model diabetic rats. Along with that, antioxidants of Amla have also been claimed to improve renal efficiency though lowering the creatinine production in the serum of diabetics. Amla leaf extract have normoglycaemic activity. The leaves extract of Amla were administered in experimental rats with diabetic and the result demonstrated a decline in glycosylation of hemoglobin and results in enhanced hemoglobin level in the model rats (Nain et al., 2012). Several clinical and non-clinical experiments Amla on have been established to observe the hyperglycemic activity (Grover, Yadav, & Vats, 2002).

A clinical study was conducted with Amla to observe the hyperglycemic properties. Amla was administered for 21 days in human volunteers with diabetic and the result indicated a significant reduction in both fasting and two-hours post-prandial blood glucose level alongside a decline in total amount of cholesterol and triglyceride (TG) level (Variya et al., 2016). Experiment on both healthy and diabetic human volunteers demonstrate significant escalation in case of high density lipoprotein (HDL) and decrease in low density lipoprotein

(LDL) levels (Akhtar et al., 2011). The inhibitory role of Amla was observed in a three-month clinical trial on diabetic patients. The result was a major increase in the antioxidant protection mechanism, along with a decline in patients' diabetic and atherogenic indexes. In addition, the unchanged state of function including liver function, renal and inflammatory reaction suggests that no adverse drug reactions are triggered by Amla administration. (T. S. Chen et al., 2011). A study was conducted on rat model with diabetic induced by streptozotocin (STZ) to observe the preventive role of Amla in case of diabetes and other associated complications (Goyal, Jadav, Patel, Shah, & Tirgar, 2013). The result suggested that *E. officinalis* are effective to improve glucose metabolism in diabetic condition (Rao et al., 2005). According to the researchers the anti-diabetic properties of *E. officinalis* is probably because of the phytoconstituents such as ellagic acid, gallotannins, gallic acid and corilagin (D'Souza et al., 2014). Gallic acid, found in *E. officinalis* showed anti-diabetic properties in animal models (Patel & Goyal, 2011a). Flavonoids derived from Amla have shown hypoglycemic and hypolipidemic properties (Anila & Vijayalakshmi, 2000).

Amla fruit extract have been found to improve insulin sensitivity as well as decrease blood sugar level in streptozotocin mediated experimental diabetic mice (Variya, Bakrania, & Patel, 2019). Significant dropping in the level of serum glucose and triglyceride as well as modified glutathione were observed when freeze-dried aqueous extract of Amla was administered in male Long-Evans rats with STZ-induced diabetic (Ansari et al., 2014). A clinical study on diabetic patient demonstrated that Amla is effective to enhance endothelial activity along with oxidative stress reduction and decrease inflammatory markers with no significant change in any safety parameters (Usharani, Fatima, & Muralidhar, 2013). Administration of Amla for 8 weeks in sample rats indicated remarkable decrease in plasma glucose and AUC glucose levels (Patel & Goyal, 2011b). Moreover, creatinine kinase, cardiac marker enzymes and lactate dehydrogenase have been preserved in case of myocardial dysfunction caused by

diabetes (Dwivedi & Aggarwal, 2009). Amla fruit has been reported to have preventive action against hyperglycemia induced aggregation and precipitation of the lens proteins (Suryanarayana, Saraswat, Petrash, & Reddy, 2007). According to the researchers, these protective effect is probably because of polyphenols e.g. gallic acids that are found in fruit extracts of Amla (Patel & Goyal, 2011a).The ethanol extract of Amla fruits were orally administered streptozotocin (STZ) mediated type-2 diabetic rats. The result demonstrated a major decline in the level of plasma glucose and a substantial rise in blood insulin level (Krishnaveni, Mirunalini, Karthishwaran, & Dhamodharan, 2010).

In addition, in normal along with sub-diabetic and mildly diabetic rats, consumption of Amla seed aqueous extract has been reported to decline the level of fasting glucose and improve glucose tolerance (Mehta et al., 2009). The juice of Amla were administered for twelve weeks (Mand et al., 1991) in experimental rabbit models. Amla is enriched with vitamin C, polyphenols and dietary fibers (Scartezzini, Antognoni, Raggi, Poli, & Sabbioni, 2006) (Muthuraman et al., 2011)**.** These phytochemical lowered the cholesterol level in both normal as well as diabetic sample. High consumption of dietary fiber helped to lower the level of serum cholesterol and triglyceride in the sample diabetic model (Akhtar et al., 2011). Various complications in diabetes can arise from prolonged exposure to uncontrolled chronic hyperglycemia which may leads on microvascular and macrovascular diseases. Numerous observations showed the beneficial action possessed by Amla fruits and its phytochemical tannins against many complications associated with diabetes e.g.neuropathy (Tiwari et al., 2011), cataracts (Suryanarayana, Anil Kumar, Saraswat, Petrash, & Reddy, 2004) and uremia (T. S. Chen et al., 2011). Diabetic patients associated with uremia often havehigh level oxidative stress since they have to regularly undergo hemodialysis and other diabetes related complications. Investigations showed that a mixture of Amla extract (AE), (EOE) and Epigallocatechin gallate (EGCG) in 1:1 ratio if administered orally for consecutive three

months raised the antioxidant defensive measures significantly and also demonstrated an effective treatment for diabetic and atherogenic index in diabetic patients with uremia (Bhandari & Kamdod, 2012). Tannins isolated from Amlafruits showed effectiveness in slow down the migration of cataract associated diabetic in sample model (Suryanarayana et al., 2007).

Studies suggested that Amla fruits showed hypoglycemic principles probably because of its potential to stimulate the release of insulin from beta cells of the normal as well as type 2 diabetics. This activity of Amla fruits may be act indirectly while initiate the insulin release as well as provide a specific insulin-like response observed in alloxan-mediated diabetic models since their beta cells cannot synthesize any insulin. The results of this investigation supported the theory of effectiveness of Amla fruits to control blood glucose level when administered orally in diabetes and in appropriate dose (Akhtar et al., 2011). A study was conducted in both type 2 diabetic human patients and normal subject to evaluate the antidiabetic properties of Amla. Powder of Amla fruits was administered to both groups to determine the level of blood glucose and lipid profile. The result demonstrated that Powder of Amla fruits can lower the amount of blood glucose and lipid profile in a dose-dependent and time-dependent manner in both normal population and type 2 diabetic patients (Akhtar et al., 2011). The aqueous fraction of Amla fruits are enriched with tannins and have been reported to prevent the activation of aldose reductase (AR) as well as to inhibit the sosmotic alteration mediated by sugar in the cultured lens of rats (Suryanarayana et al., 2004). Again, polyphenol found in the ethyl acetate extract of Amla fruit have been reported to improve the hypertriacylglycerolemia and hypercholesterolemia caused by high amount of fructose consumption in rats (B. Yang & Liu, 2014). Around 50% of diabetic patients suffer from diabetic neuropathy which is a common microvascular complication of diabetes mellitus.

Moreover, a study on Amla demonstrated that the extracts are potential agent to attenuate the

diabetes and also altered the neuropathic pain by modulating oxidative-nitrosative stress in the sample diabetic rats(Tiwari et al., 2011). Numerous studies have shown experimental evidences of effectiveness of Amla as a curative and preventive agent on oxidative stress and function of nervous system in the experimental animal model in case of diabetic neuropathy (Bhandari & Kamdod, 2012). However, more comprehensive phytochemical studies of Amla along with pharmacological evaluations need to be done to evaluate and determine precisely the hypoglycemic principle, action and mechanism in animal models as well as in human subjects (Akhtar et al., 2011).

Cardio-protective activity of Amla

The Amla demonstrated substantial protective measures against modifications in myocardial system. Results showed cardio-protective effect because of the strong antioxidant along with free radical scavenging activity of Amla (Ojha, Golechha, Kumari, & Arya, 2012). According to animal research, Amla has the properties to improve cardiovascular health by decreasing triglycerides and increasing cholesterol profile (Kapoor et al., 2020). The observation indicates that oral supplementation of Amla for four weeks helps to modify the lipid level by reducing almost 90% LDL cholesterol (S. K. Bhattacharya et al., 2002). Again, it also showed a decrease in total triglyceride level well as total cholesterol level. Furthermore, it helps to improve the HDL cholesterol level (Kapoor et al., 2020). An experiment carried out on beetal kids and the observations claimed that administration of Amla for ninety days showed remarkable decline in blood sugar level, cholesterol and LDL level (Variya et al., 2016). Amla has been reported to have cardio-protective effect against LAD ligation following reperfusion in experimental rats. An experiment was carried out where pretreatment of Amla was observed to restore the cardiac function, endogenous antioxidants

and related hemodynamic parameters against isoproterenol-intoxicated myocardial damages (Thirunavukkarasu et al., 2015).

The oral consumption of Amla has been reported to possess remarkable increase in contractile and hemodynamic functions. The administration dose was ranged between 100 to 500 mg/kg. The cardio protection activity of Amla against isoproterenol-induced cardio toxicity is because of its antioxidant activity (Yadav et al., 2017). Fruit juice of Amla has the potential to restore heart rate and force of contraction. The polyphenols, especially gallic acid which was isolated from fruit juice of Amla was reported effective in cardiac impairment treatment by decreasing mean arterial blood pressure caused by diabetes, cardiac hypertrophy and oxidative stress (Patel & Goyal, 2011b), (Patel & Goyal, 2011a). A study showed the antihypertensive properties of Amla in rat models. The hydro-alcoholic extract of Amla was administered into a rat model having hypertension caused by DOCA- salt. A significant drop in arterial blood pressure and heart rate in a dose-dependent manner was recorded in the observation. These activity of Amla was modulated by activating endogenous antioxidant system, serum electrolytes, serum NO and eNOS (Bhatia et al., 2011). The tannins (emblicanin-A and emblicanin -B), gallic acids, ellagic acid and corilagin isolated from Amla are responsible for the protective action (Variya et al., 2016).

Investigations claim that fruit extract of Amla work in a dose dependent manner and can lower the arterial blood pressure alongside the cardiac and renal hypertrophy in experimental rats treated with DOCA alone. The result of the experiment showed that extract of Amla can be potential in inhibiting the initiation and development of hypertension and cardiac and renal hypertrophy in DOCA/HS-mediated hypertension (B. Yang & Liu, 2014). Oxidized low density lipoprotein-cholesterol is one of the major causes behind atherosclerosis. Antioxidants can be used as an effective measure to treat atherogenesis. The tannoids in Amla extracts had shown significant antioxidant properties. Studies claimed that Amla has

anti-atherogenic potential in vitro on rat vascular smooth muscle cells as well as in human umbilical vein endothelial cells. Amla showed potential effectiveness by reducing oxidative stress and preventing oxidative LDL cholesterol mediated vascular smooth muscle proliferation (Variya et al., 2016). The principal etiological factor in atherogenesis is Oxidative LDL and for treating atherosclerosis antioxidants are important. Results showed that Amla was successful in inhibiting atherosclerosis progression by ameliorating oxidation damage or by restricting oxidative LDL-mediated proliferation of vascular smooth muscle cells, which probably a potential measure in treatment of atherosclerosis (Bhandari & Kamdod, 2012). Maintaining hyperglycemia, hyperlipidemia along with oxidative stress are important factors in avoiding myocardial dysfunction caused by diabetes. The fresh extract of Amla was examined on myocardial dysfunction in experimental diabetic rats. The result showed that these fruit extracts stopped the streptozotocin mediated weight loss, improved consumption of water, enhanced serum glucose levels and distributed lipid profile. Moreover, the serum LDL and creatinine kinase levels increased as well as the myocardial hypertrophy and cardiomyopathy improved. The amount of antioxidant enzyme has decreased (in case of SOD, decreased GSH and CAT) in diabetic hearts. However, Amla fruit extracts has the potential to raise these levels. Thus, Amla can be a potential agent to treat myocardial dysfunction accompanied by type 1 diabetes mellitus (Patel & Goyal, 2011b).

Oxygen derived free radicals provides a significant contribution in introduction and development of ischemic heart diseases. Myocardial cell damage that occurs during ischemic cell reperfusion, called ischemia-reperfusion damage, is largely due to oxidative stress (B. Yang & Liu, 2014). Studies claimed that the fruits of Amla have antioxidant properties which are beneficial in case of cardiac ischemia-reperfusion injury (IRI) because of their cardio protective effect (S. K. Bhattacharya et al., 2002). The study was carried out by extracting the fresh juice of Amla which were rich in emblicanin A and emblicanin B with aqueous

methanol fraction. This extract was orally administered twice daily for fourteen days (Gaire & Subedi, 2014).The experiment was conducted on rat model and the result showed prominent modification in ischemia- reperfusion induced oxidative injury along with significant decrease in myocardial lipid per-oxidation (Variya et al., 2016).Study demonstrated that administration of Amla fruits for long term can enhance myocardial adaptation through increasing endogenous antioxidants. The experiment was conducted on wistar albino rats and fresh Amla fruits were consumed orally for continuous 30 days. The observation exhibited a reduction in basal myocardial LPO and increase myocardial endogenous antioxidants as well as protects the rat heart from oxidative stress related to ischemia-reperfusion injury (B. Yang & Liu, 2014). Maintaining hyperglycemia, hyperlipidemia along with oxidative stress are important factors in avoiding myocardial dysfunction caused by diabetes.

The fresh extract of Amla was examined on myocardial dysfunction in experimental diabetic rats. The result showed that these fruit extracts stopped the streptozotocin mediated weight loss, improved consumption of water, enhanced serum glucose levels and distributed lipid profile. Moreover, the serum LDL and creatinine kinase levels increased as well as the myocardial hypertrophy and cardiomyopathy improved. Pretreatment with Amla have been observed to recover the hemodynamic and left ventricular functions. The investigations also showed remarkable sustainability of myocytes-injury-specific marker enzymes, antioxidants as well as blocking of lipid per-oxidation. This beneficial effect of Amla has been confirmed by histopathology of myocardium. Results indicated that, Amla's cardio-protective mechanism is due to the strong antioxidant along with free radical scavenging activity as demonstrated by improved performance in tissue antioxidant, hemodynamic and contractile function (Bhandari & Kamdod, 2012).

Anti-inflammatory, Analgesic and Anti-pyretic properties of Amla

Ethanolic and aqueous extract of Amla have been claimed to have analgesic properties. This mode of action could be because of peripheral mechanism. The studies support the traditional phenomena of curing fever, pain and inflammatory illness by using Amla. However, further study is require to explore the precise mechanism of these responses (James B. Perianayagam et al., 2004). Many studies revealed that *P. emblica* fruits have potential to exhibit antipyretic and analgesic properties, skin protection and wound-healing activity (Golechha, Bhatia, Ojha, & Arya, 2011). Another study demonstrated that the phenolic compounds of Amla have anti-inflammatory response in case of both acute and chronic inflammatory response mediated by carrageenan along with cotton pellet in animal model of research (Muthuraman et al., 2011). The result showed more effectiveness at higher doses (Baliga & Dsouza, 2011). Numerous studies proved that extract of Amla and the phytochemical pyrogallol which is isolated from the plants, also have anti-inflammatory properties and can inhibit the laboratory strain of *Pseudomonas aeruginosa* PAO1-dependent expression of the neutrophil chemokines IL-8, GRO-a, GROg, of both of the intercellular adhesion molecule (ICAM-1) and the pro-inflammatory cytokine(IL-6) (Nicolis et al., 2008). The experiments on carrageenan mediated oedema in the anti-inflammatory study revealed that, the water fraction of the methanolic extract of Amla and phenylbutazone has the property to inhibit the formation of oedema significantly which proves the phenomena of anti-inflammatory activity of Amla. The studies support the traditional phenomena of curing fever, pain and inflammatory illness by using Amla. However, further study is require to explore the precise mechanism of these responses (James B. Perianayagam et al., 2004).

The aqueous fraction of fruits was found to exhibit dose dependent anti-inflammation and analgesic action in experimental rat (Jaijoy, Soonthornchareonnon, Panthong, & Sireeratawong, 2010). Again, another study showed that the phenolic compounds of Amla

can exhibit anti-inflammatory reaction to both acute and chronic inflammatory disease in two oral doses (Muthuraman et al., 2011). Similarly, a study was carried out with Amla fruits in experimental rat models to determine the anti-pyretic and analgesic properties of ethanolic as well as aqueous extracts. The result showed a significant reduction in hyperthermia and exhibit inhibitory activity against writhing response (James B. Perianayagam et al., 2004). Moreover, Amla showed healing response against indomethacin induced gastropathy in experimental mice in a dose dependent process and restore the level of inflammatory cytokines in a biphasic manner (Chatterjee, Chattopadhyay, & Bandyopadhyay, 2010). Furthermore, the ethanolic extract of Amla showed anti-ulcerogenic properties along with healing effect against a number of acute ulcer models (Sairam et al., 2002). Likewise, another experiment was conducted to understand the anti-inflammatory response of hydroalchoholic extracts of Amla against acute inflammation mediated by carrageenan and chronic inflammation induced by cotton pellet granuloma on rodent models (Golechha, Sarangal, Ojha, Bhatia, & Arya, 2014).

Fruit extract of Amla showed apoptosis in primary osteoclasts cells in human through enhancing the expression of Fas as well as by inhibiting the expression of IL-6 possibly because of modified action of NF-kB (Penolazzi et al., 2008). Observations indicated that the fruits of Amla have dual action as an antioxidant agent as well as an anti- inflammatory agent and probably they work synergistically. In the inflammatory site, the response of tissue damage generates nitric oxide synthase (iNOS). These produce a huge amount of nitric oxide (NO) which leads to lipid per-oxidation and finally damage the cells. The infiltrate inflammatory cells cause the formation of reactive oxygen species (ROS) and produce free radicals that eventually cause oxidative stress. Fruit extracts of Amla can regulate inflammatory reactions by reducing the production of a number of chemokines, restricting immune cell infiltration into the affected area and encouraging the production of

immunoprotective cytokines to speed up the recovery procedure (M. K. Singh et al., 2015). Phytoconstituents such as emblicanins, ellagic acids and gallic acid showed free radical scavenging activity while methyl gallate, gallic acid, geraniin, corilagin, and furosin have been reported to have nitric oxide (NO) scavenging activity (Kumaran & Karunakaran, 2006). Extract of Amla has the potential to inhibit the activity of NF-kB which regulate the inflammatory and immune responses (Kim, Okubo, Juneja, & Yokozawa, 2010). Thus, Amla can be effective to reduce the level of pro-inflammatory cytokines in several inflammatory diseases.

In both postoperative and neuropathic pain models, ethanolic extract of Amla showed promising analgesic efficacy in vivo (Lim, Kim, & Kim, 2016). Another experiment showed the anti-pyretic function of Amla on prostaglandin biosynthesis. Again, studies suggested that the analgesic and anti-inflammatory action of Amla is mainly because of tannoids, amino acids, phenolates, carbohydrates and alkaloids (James B. Perianayagam et al., 2004). According to the observation, Amla extract exhibit analgesic properties in a dose of 600 mg/kg against abdominal writhing caused by 6% NaCl and result in significant reduction (Goel et al., 2014). Moreover, a number of models and different fractions of Amla have been utilized to determine the acute and chronic inflammation and the results indicated that Amla have an inhibitory action on production and secretion of pain and inflammatory mediators that function similarly to NSAIDs rather than steroidal substances (Variya et al., 2016). Another investigation demonstrated that the ethanol and aqueous extracts Amla fruits have the potential to significantly decrease the rectal temperature when administered at a single dose of 500 mg/kg in hyperthermic rats and inhibit writhing production caused by intraperitoneally introduced acetic acid in experimental mice (Sairam et al., 2002). The aqueous portion of the butanol extract of *P. emblica* fruits has been observed to have

significant anti-inflammatory efficacy against indomethacin-induced gastric ulcer (Gaire & Subedi, 2014).

Study showed when 90% ethanolic extract of dried Amla fruit powder applied topically, it speeded wound healing process by up-regulating collagen expression and also extracellular signal regulated kinase (ERK1/2) signaling (B. Yang & Liu, 2014). Hyperthermia induced by Brewer's yeast in experimental rats was decreased by administrating EEO and AEO in a single oral dose. Both of these extracts exhibited protective reaction on writhing response is caused by acetic acid in mice model in the analgesic experiment. The observations suggested that Amla fruits extract have significant anti-pyretic and analgesic properties (James B. Perianayagam et al., 2004). Thereby, because of the regulatory function of free radicals, phenolic compounds of Amla can be a promising herbal candidate in treatment of acute and chronic inflammatory diseases (Bhandari & Kamdod, 2012). Studies indicated that fruits of *P. emblica* and its extracts possess immune-modulatory and anti-inflammatory properties. The extract have the potential to reduce the apoptosis and fragmentation of DNA caused by chromium and altered the inhibiting action of chromium on cell proliferation and generation of IL-2 and γ-interferon (γ-IFN) of lymphocytes (B. Yang & Liu, 2014).Treatment with *P. emblica* fruit powder showed improved activity of natural killer (NK) cells as well as antibody-dependent cellular cytotoxicity (ADCC) in syngeneic BALB/c mice bearing Dalton 's lymphoma ascites (DLA) tumors (Suresh & Vasudevan, 1994). As a model of rheumatoid arthritis (RA) and reactive arthritis, generally adjuvant-induced arthritis (AIA) sample has been utilized. Crude aqueous extracts of fruits of *P. emblica* showed immune response suppressing action in the AIA model in sample rats (Ganju et al., 2003). Acute pancreatitis is one of the fast-growing inflammatory diseases of the pancreas. *P. emblica* fruit extract has been examined in treatment of acute pancreatitis caused arginine in rats and showed significant effectiveness (Sidhu et al., 2011). The levels of lipase and interleukin10 in serum

decreased with the administration of *P. emblica* extract in the experimental rats treated with arginine. The amount of nucleic acid and DNA synthesis rate in pancreatic tissue, pancreatic proteins, and amount of pancreatic amylase have been remarkably enhanced (B. Yang & Liu, 2014).

Antimicrobial activity of Amla

Infectious diseases are significantly responsible for most morbidity and mortality events in the world. Almost 50% of total deaths in the tropical countries and 20% of deaths in the America is causing because of microbial diseases. The incidents of antimicrobial resistance is increasing in an alarming rate and demand of novel entities to prevent emerging pathogens, scientists are trying to utilize plant derived antimicrobial agents. Various researches and studies are conducted to evaluate medicinal plants and explore their activity to develop new antimicrobial entities against evolving pathogens. Several studies in-vivo and in-vitro conducted to prove the substantial antimicrobial activity of traditional medicinal plants (Mahady, 2005). The active constituents isolated from the leaves of *E. officinalis* have been showed antibacterial and antioxidant properties (Purena et al., 2018). Researchers claimed that Amla has potential anti-microbial activity which can be effective to develop novel, safe and effective treatment system at reasonable costs (Kumar, Tantry, Rahiman, & Gupta, 2011). Amla been investigated by numerous research groups to explore the anti-microbial property and cytotoxic actions (Srikumar et al., 2007). Alkaloids isolated from methanol extract of *Emblica officinalis* demonstrated strong anti-microbial action against several gram positive bacteria e.g. *Staphylococcusaureus, Bacillus subtilis, Sarcinaluteasome* and *Bacillus cereus* as well as some gram negative pathogenic bacteria such as *Escherichia coli, Shigella boydii, Pseudomonas aeruginosa, Salmonella paratyphi* and *Salmonella typhi* along with

some fungi such as *Candida albicans, Aspergillus niger* and *Sacharomyces cerevisiae* (Rahman, Akbor, Howlader, & Jabbar, 2009). Aqueous extracts of Amla was investigated on some gram positive and gram negative pathogens along with some fungal strains of Candida species by utilizing agar plate technique and showed potential antimicrobial activity (Vijayalakshmi et al., 2007) . Another study was conducted against 345 specific bacteria including *Klebsiella ozaenae, Pseudomonas, Serratia marcescens Salmonella typhi, Proteus mirabilis, Klebsiella pneumonia, Escherichia coli, Salmonella paratyphi-A* and *Salmonella paratyphi –B* collected from human urine specimen to determine the potential anti-microbial response. The findings did not, however, indicate any noticeable impact against gram negative pathogenic urinary bacteria (Saeed & Tariq, 2007). Again, another experiment was carried out with different Amla leaves extracts to demonstrate antifungal activity against *Furasiumoxysporum* and *Rhizonctoniasolani*. The whole extract exhibited more inhibitory response in compare to individual phytoconstituents from the respective segments and indicated synergistic activity of isolated phytochemical (Chugh & Bharti, 2014).

An investigation by Kumar et al. demonstrated the anti-microbial properties of both aqueous and methanol extract of Amla against several pathogenic entities e.g. *Klebsiella pneumonia, E. cloacae* and *E. coli.* The result showed effective action because of the presence of flavonoids, saponins, phenolates, terpenoids and tannoids in the extract of Amla (Kumar et al., 2011). It has been observed that, the polyphenols found in Amla exhibited significant inhibitory response on herpes virus. 1,2,4,6-Tetra-O-galloyl-β-D-glucoseidentified in Amla extract and showed anti-herpes action (Xiang et al., 2011). Furthermore, a research on Amla showed significant inhibition of attachment of *Candida albicans* to the human buccal epithelia cells and denture acrylic surface (Thaweboon & Thaweboon, 2011). Another study on pneumonia in mice model induced by *K. pneumonia* demonstrated the protective action of

Amla and observations indicated that, with an increase in phagocytosis and nitrite levels in broncheoalveolar fluid, Amla reduced bacterial load (Saini, Sharma, & Chhibber, 2008).

Extracts from different sections of Amla have been recorded to have different antibacterial response against Gram-positive and Gram-negative pathogenic bacterial species. Silver nano-particles produced from green synthesis by utilizing fruits and leaves of Amla demonstrated significant anti-microbial potential against several pathogenic bacteria such as, *Bacillus subtilis, Staphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa* (Ramesh, Kokila, & Geetha, 2015). Ramanuj et al. carried out an experiment with different fractions from *Emblica officinalis* seed and the result showed bacteriostatic action against *Acinetobacter baumannii* (Ramanuj, Kothari, & Kothari, 2014). Several in-vivo and in-vitro model was used for evaluating the anti-plasmodial action of Amla. Bahavan et al. showed the anti-malarial activity of Amla leaves with ethyl acetate along with methanol extract against both chloroquine-resistant and chloroquine-sensitive strains *of P. falciparum*. The observation showed prominent and significant anti-malarial action against both plasmodium species e.g. chloroquine-sensitive and chloroquine-resistant (Bagavan, Rahuman, Kaushik, & Sahal, 2011).

Another experiment was conducted for determining the anti-plasmodial action of aqueous extract of Amla in vitro and in vivo against multiple drug resistant strain of *P. falciparum.* The observation showed potential anti-malarial action in a range of 53–70% by blocking the absorption of hypoxanthine into the malarial parasite (Pinma et al., 2010). The promising anti-microbial action of ethanolic, chloroform, acetone and aqueous portions of fruits of Amla was demonstrated against several bacterial species such as, *Escherichia coli, Proteus sp., Salmonella paratyphi, Pseudomonas sp, Staphylococcus aureus, Klebsiella sp. Bacillus sp., and Salmonella typhi*. However, among all these isolated extracts, ethanolic, acetone and aqueous extracts showed microbicidal activity but the chloroform extract exhibited minimal

or no antimicrobial properties (Varghese, Ninan, Alex, Soman, & Jacob, 2014). The ethanolic fraction of Amla demonstrated promising inhibitory activity against *Candida galbrata* and *Cryptococcus neoformans* with no cytotoxic activity on vero cell line (Variya et al., 2016). The chloroform soluble portion of methanol extract of Amla demonstrated major and promising antimicrobial action along with a significant cytotoxicity against various gram positive and gram negative pathogenic bacteria (Rahman et al., 2009). Aqueous infusion extract of Amla demonstrated promising anti-microbial response against *Escherichia coli,Enterobacter cloacae*and *Klebsiella pneumoniae* (Kumar et al., 2011). Amla's aqueous infusion and decoction demostrated good antibacterial action against *Serratia marcescens , K. pneumoniae, E. coli,K. ozaenae, Pseudomonas aeruginosa, S. paratyphi A,S. paratyphi B Salmonella typhi* and *Proteus mirabilis* (Saeed & Tariq, 2007). 1,2,4,6-tetra-O-galloyl-β-D-glucose that is found in Amla has been reported to have anti-viral property in vitro against anti-herpes simplex virus (Xiang et al., 2011).

Leaves extract of Amla has been demonstrated anti-malarial activity with the 50% inhibitory concentration (IC50) in *Plasmodium falciparum* parasite sample (Bagavan et al., 2011). Saini et al. demonstrated the defensive function of Amla fruit in pneumonia in mice model induced by *Klebsiella pneumonia.* Fruit powder of Amla were administered in experimental mice with lungs infection caused by *K. pneumoniae* ATCC43816 to investigate short term effect (for 15 days) and long term effect (for 30 days) for evaluating bacterial colonization, formation of nitrite, malondialdehyde and macrophage activity in the broncho-alveolar lavage (Saini et al., 2008). The data proposed that dietary supplementation of Amla helped to protect against colonization of bacteria in lungs when administrated for long term in the experimental model. However, to clarify the exact mechanism, further research must be carried out (Saini et al., 2008).

Potential anti-plasmodial activity was exhibited in the Amla leaves extracts. Researches also observed that Amla extract possess potential response against Chloroquine-resistant strains as well. The observations indicated that Amla extracts can also be used in its crude form in the treatment of malaria (Bagavan et al., 2011). Researchers found that in-vivo anti-plasmodial response with adequate suppressive action ranged from 53.40% to 69.46% (Pinma et al., 2010). Moreover, scientists claimed that the polyphenolic compounds found in Amla could exhibit promising anti-herpes simplex virus (HSV) properties through inhibiting the function of extracellular viral particles as well as by preventing the viral metabolism in host cells. The observation suggested that further investigations need to be done to explore the opportunities of Amla as a candidate in treatment of HSV (Xiang et al., 2011).

Hepatoprotective activity of Amla

Inflammation and oxidative stress are responsible for liver diseases. Vitamin C, flavonoid, tannins and gallic acid which are isolated from Amla have been reported to have protective action against hepatoxicity-induced liver injury. Administration of Amla inhibited liver injury induced by N-nitrosodiethylamine (NDEA) since it possess anti-inflammation, antioxidant, anti-apoptosis along with anti-autophagy properties (K. H. Chen, Lin, Chien, & Ho, 2011). Researchers observed that pretreatment with Amla for consecutive seven days exhibited significant protective action to liver cell as described by univacuolated hepatocytes. Moreover, pretreatment with Amla prior to Carbon tetrachloride (CCl4) intoxication resulted in substantial decline in DNA synthesis, GSH-S-transferase, lactate dehydrogenase (LDH), lipid peroxidation (LPO), serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels. Furthermore, the observation indicated improved level of GSH peroxidase, GSH reductase and reduced GSH. Researchers claimed that all these data

suggested the inhibitory action of Amla against hepatic toxicity in experimental Wistar rats (Sultana, Ahmad, Khan, & Jahangir, 2005).

Tasduq et al. carried out an experiment with 50% hydroalchoholic extract of the fruits of Amla to determine the hepatoprotective action against hepatic injury caused by anti-tuberculosis drugs. The observation showed that the activity of membrane stabilizing, antioxidative and Cytochrome (CYP) 2E1 inhibitory effects are responsible for the hepatoprotective activity of 50% hydroalchoholic Amla fruits extracts (S. A. Tasduq et al., 2005). Reactive oxygen species along with Oxidative stress induced toxicity are the major two vital fundamental mechanisms is possibly the reason of alcohol-induced liver impairment and mitochondrial dysfunction. An experiment was conducted to observe the effectiveness of Amla fruits against alcohol-mediated hepatic damage in experimental rats. The fruit extracts of Amla exhibited anti-oxidant effect along with nitric oxide (NO) scavenging action in-vitro. Similarly, using fruit extracts of Amla in-vitro demonstrated that the plasma enzymes level significantly reduce towards the normal level as well as decrease the lipid peroxidation levels and protein carbonyls in alcoholic rats. Along with these, it also reported to restore the level of both enzymatic and non-enzymatic antioxidants. This result of the study was confirmed by a liver histopathological investigation. Thereby, this results indicates that the flavonoid, tannoids and NO scavenging compounds isolated from fruits of Amla possibly have promising protective action in case of free radical induced oxidative stress in rat hepatocytes of liver injury mediated by alcohol (Suryanarayana et al., 2004) (Damodara Reddy, Padmavathi, & Varadacharyulu, 2009).

Chronic treatment of CCl4 and thioacetamide showed abnormality in the histopathology indicating pre-fibrogenic incidents. Study showed Amla has the potential to alter such modifications with significant regenerative improvements indicative of its protective function in pre-fibrogenesis of liver. This alteration of pre-fibrogenic incidents is possibly because of

its favorable antioxidative activity (Mir et al., 2007), (Sultana, Ahmed, Sharma, & Jahangir, 2004), (Sheikh Abdullah Tasduq, Mondhe, Gupta, Baleshwar, & Johri, 2005). Arsenic which is a natural human toxin is found in the groundwater. Fruits of Amla showed major role in prevention of arsenic induced hepatopathy in adult Swiss albino mice. Pre- and post supplementation of fruits of Amla showed significant reduction in arsenic induced liver oxidative stress. A combination therapeutic system of Amla and arsenic (pre and post) showed considerable decline in the liver serum transaminase and LPO level. Again, treatment with Amla showed substantial improvement in serum alkaline phosphatase SOD, GST and CAT activities. Investigations showed that Amla has the potential to improve necrosis, karyorrhexis, karyolysis and cytoplasmic vacuolization mediated by NaAsO intoxication which are observed in histopathology of liver(A. Sharma, Sharma, & Kumar, 2009). However, there are not adequate clinical studies in these measures. In order to determine the beneficial effect of Amla further hepatobiology should be encouraged (Bhandari & Kamdod, 2012).

Nephroprotective activity of Amla

Yokozawa et al., demonstrated that Amla have promising effectiveness on kidney diseases associated with oxidative stress during the process of aging. Studies showed that, introduction of Amla extract reduced the level of blood urea nitrogen and improved serum creatinine level in the old rat. Along with that, the arterial blood pressure of tail of the rats was reduced significantly. Moreover, observation suggested Amla may have the potential to that ameliorate oxidative stress due to aging since thiobarbituric acid reactive substance levels of serum, renal homogenate along with mitochondria were decreased substantially in those old rats. Again, the expressions of renal nuclear factor-kappaB, inhibitory kappaB in cytoplasm, iNOS, and COX-2 protein levels were also enhanced with aging process. Investigations demonstrated that Amla is a effective and promising antioxidant agent in treatment of kidney

disease that are associated with ageing (Yokozawa et al., 2007). Furthermore, Chen et al., showed that administration of Amla for consecutive four months decreased the 8-iso-prostaglandin, plasma oxidative marker and improved the total plasma antioxidant levels in the uremic patients (Bhandari & Kamdod, 2012).

Anti-diarrheal activity of Amla

In Ayurvedic medicinal system, fruit decoction of Amla was combined with sour milk and administered in treatment of dysentery. Again, Amla leaves were infused with fenugreek seed in case of chronic diarrhea. However, present studies claimed that the dry fruit extract of Amla have antidiarrheal and spasmolytic properties which explain its medicinal use in diarrhea (Gaire & Subedi, 2014). Studies showed that the crude extract and the fruits of Amla have the property to exhibit antidiarrheal and spasmolytic activities. The experiment was conducted with a sound mechanistic assistance to evaluate the therapeutic use of Amla at slightly higher concentrations in hyperactive gastrointestinal conditions e.g. diarrhea and provided evidence-based support to evaluate the relaxant activity of the plant extract which is influenced by muscarinic receptors along with Ca2+ channel blocking activity (Bolton, 1979). Consequently, an agent that inhibits high K+-induced contractions is regarded as a blocker of Ca2 + influx (Godfraind, Miller, & Wibo, 1986). The phenomena of Ca2+ antagonistic action of the Amla extract was further established in Jejunum where it migrated the Ca2+ CRCs to the right with suppression of the maximum activity at the two tested concentrations. The spasmolytic effect of Amla is conducted through dual inhibition activity of both muscarinic receptors and Ca2+ channels (Lee, Sarna, Singaram, & Casper, 1997). Thus, the potential of dually acting spasmolytic action in the Amla plant extract could be promising because of its effecacy in treatment of diarrhea and abdominal spasm (J. B.

Perianayagam et al., 2005).

Antitussive activity of Amla

Amla has been investigated to explore the antitussive property in the laryngopharyngeal along with tracheobronchial mucous areas of airways by using mechanical stimulation. The observation indicated that, Amla has more potential effect than dropropizine which is a narcotic agent used as a cough suppressant but less effective than codeine which is a lassical narcotic antitussive drug (Bhide & Nitave, 2014). The action of Amla was compared to widely applied medications in the medicinal practice in different doses to suppress cough parameters. The excellent effectiveness of codeine as a cough-suppressing agent which is also a centrally active antitussive narcotic medication is popular and common but followed by numerous side effects that may restrict its application. Another common non-narcotic antitussive drug, dropropizine at a dosage of 100 mg / kg body weight lower the action remarkably, but exhibited less unwanted results than codeine. Amla at a dosage of 50 mg / kg body wt showed comparable antitussive properties to dropropizine. The dosage was preferred for better compare with the anti-tussive properties of other plant extracts since most of those plants are tested at this particular dosage. The dry extract of Amla is expected to exhibit the anti-causing activity not only because of antioxidant, antispasmolytic and antiphlogical properties, but also because of the action on mucus secretion in the airways (Nosál'Ováx et al., 2003). Amla when administered perorally at a dose of 50 mg/kg cough frequency is reduced from both of the irritated areas in airways. According to the statistics, more significant decrease was observed in the laryngo-pharyngeal area for this parameter. The outcome showed major effects of Amla on attack severity at both expiration and inspiration. However, only 1 h after administration of Amla at 50 mg/kg body wt., a significant change in

cough attack intensity was recorded for both irritated areas during inspiration. On the other hand, there was no significant alteration has been reported altering the intensity of maximal cough attack during expiration.

Narcotic antitussive drugs for instance, codeine's group has been known as developing various complex side effects for instance, the depletion of respiratory center activity, reduction of secretion and enhance sputum viscosity and elasticity, reduction of expectoration, dependence (mostly in children as well as bronchoconstriction. Amla was administered in an amount of 200 mg/kg body wt. which demonstrated a prominent reduction of unwanted and complicated side effects. The goal of the experiment was to establish a novel entity or mechanism to treat cough reflux without developing any side effects or to minimize them as much as possible. Investigations showed that, in terms of synthetic agents comprising the category of non-narcotic cough suppressants, Amla may be a possible agent for developing such substances specifically. (Kardošová, Malovíková, Pätoprstý, Nosál'ová, & Matáková, 2002), (Nosal'ova, Kardosova, & Franova, 2000). Scientists claimed that the abundant amounts of vitamin-C or ascorbic acid isolated from the fruits of Amla are possibly responsible for antitussive action of Amla. The vitamin C is probably the factor behind the chronic cough inhibitory response along with other antioxidants e.g. alpha-tocopherol (vitamin E) and beta-carotene (Grievink, Smit, Ocké, Van 'T Veer, & Kromhout, 1998), (Rautalahti et al., 1997). The activity of smooth muscle contractility in the airways possibly another factor influencing coughs, particularly due to an inhibitory action on prostanoid synthesis (Ihantola-Vormisto et al., 1997). The study indicated that pharmacological properties particularly antioxidant, spasmolytic along with antibacterial activities are probably partly responsible in the antitussive action of the dry extract of fresh Amla fruits.

Amla's antitussive action is due to the gastrointestinal tract's reflex expectorant action induced by vagal neuronal fibers connecting the mucous membranes of the gastrointestinal

tract and the respiratory tract. The Amla extract is likely to have an intrusive action on the neural vagal ends of the gastrointestinal mucous membranes and induces mucus production from the respiratory tract. As a result, airways are coated with mucus and therefore cough receptors (irritant receptors) are seldom available for discomfort, causing a reduction in cough reflex, as demonstrated by antitussive activity measurement. This phenomenon is supported by an enhanced salivation which was observed during the experiment. The experiment was conducted in experimental cats by using mechanical stimulation of both laryngopharyngeal as well as tracheobronchial mucous areas of airways although, most of the antitussive experiments were carried out with mice and rats model (Mandal et al., 2000), (Saha, Mukherjee, Murugesan, Saha, & Pal, 1997), (Mukherjee et al., 1997). Amla only at higher doses appeared to be quite capable of inhibiting mechanically induced cough which is 200 mg/kg body wt. These effects have been observed, in particular, in the declining amount of attempts and the intensity of incidents while expiration, that are recognized to be the most significant predictors of any substance's anti-tussive behavior. The intensity of maximal effort was not affected significantly. From the viewpoint of expectoration, this result is beneficial. Moreover, this phenomenon is supported by a peripheral mechanism of suppression of cough incidents (Nosál'Ováx et al., 2003).

Chapter 4

Conclusion

Amla is a common and popular medicinal plant used form ancient time in traditional and Ayurvedic medicine system. Amla is safe for human use and possess immunomodulatory and other pharmacological activities and so it can be a potential source to develop therapeutic agents. This gives the researchers additional benefits to investigate the properties, pharmacological action and function of individual phytochemicals present in Amla. Various investigations and clinical trials have been carried out to determine the therapeutic potency of Amla against several pathological conditions. However, the number of validated clinical and systemic research is still not enough.

Future recommendations

According to a number of studies, Amla is a potential source to develop nontoxic anticancer, an adjuvant in chemotherapy and radiotherapy as well as a chemopreventive agent. Further investigations can help to explore the basic mechanism of action of the individual phytochemicals isolated from Amla. Therefore, rationally and systemically designed clinical trials can be helpful to determine the maximum acceptable dose as well as adverse effects. Observations suggest that Amla could become a new approach to mitigate arsenic induced immunotoxicity. Moreover, further comprehensive evaluation needs to be one to determine the phytochemical and pharmacological properties and to acknowledge its potential immunoprotective properties and the mechanism of hypoglycemic activity of Amla. Furthermore, investigating the probability of using amla in the treatment of Alzheimer patients could be a potential scope since herbal preparation of amla helped to decrease the serum cholesterol level in experimental mice and increased the level of acetylcholine in the brain which eventually resulted in modifying the memory of mice.

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