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EMBLICA OFFICINALIS: A MERITOCRATIC DRUG FOR TREATING VARIOUS DISORDERS

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ABSTRACT

Phytogenic agents have traditionally been used by herbalists and indigenous healers for the prevention and treatment of various diseases. Emblica officinalis (Amla) is a deciduous tree belonging to family Euphorbiacea. Growing body of evidences have shown that amla possess anti diabetic activity and have been used to treat diabetes-induced complications. Amla is a potent antioxidant. Wide array of studies such as hepatoprotective, anticancer, anti inflammatory, analgesic, anti hyperlipidemic etc are associated with this plant. The present review demonstrates the pleiotropic actions of amla in various disorders. Moreover, the underlying mechanisms of amla-induced protection in various diseases have been delineated.

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INTRODUCTION

Emblica officinalis/Phyllanthus emblica is a small to medium sized deciduous tree commonly known as Amla from sanskrit Amalika or Indian gooseberry belonging to family Euphorbiaceae. It is found in tropical and subtropical areas of various countries like Malaysia, China, Pakistan, India, Indonesia, Zubekistan, Sri lanka and Malay Peninsula [1]. The height of the plant is about 8-18 m and has spreading branches. The branchlets of the branches are 10-20 cm long and have simple, subsessile leaves which are light green in colour and set closely to the branchlets. Fruits of amla bearing pale yellow colour, have smooth surface and spherical shape with six vertical furrows on them [2]. Propagation of amla plant is done through seeds and it requires light and tropical conditions to grow. For cultivation heavy soils, calcareous soil with rocky substratum, moderately alkaline soils are good but well drained loamy soil increases the yield of the plant. Young plants of amla easily die so they are protected from hot winds during May-June and from frost during winter, require proper sunlight and irrigated during monsoon season [3]. Fruits are ripen in autumn season and are harvested by hand. Amla fruit has sour, bitter, acrid, sweet and astringent taste. Fruit is rich in vitamin C (200-900 mg per 100 gm of edible portion), gallic acid, quercetin and pectin, root contains ellagic acid and lupeol and seeds contain fixed oils [4]. Amla is a source of amino acids like alanine, arginine, aspartic acid etc. and of invaluable minerals such as potassium, magnesium, calcium, iron etc. Polyphenols like tannins, flavonoids (like rutin) and kaempferol are the other bioactive compounds present in *E.officinalis.* It also contains ellagitannins like emblicanin A and B, punigluconin, pedunculagin, curcuminoids [5]. Seed oil of amla is rich in fatty acids like saturated fatty acids (palmitic, myristic and stearic acids) and unsaturated fatty acids (oleic and linoleic acids) but the physico-chemical and fatty acid analysis study found that linoleic acid was present in high quantity in amla fruit [2]. By high performance liquid chromatography (HPLC) it was found that ethanolic extract of fruit of *E.officinalis* contains 34% of quercetin [1,6]. From the roots of amla new norsesquiterpenoids like phyllaemblicins A, B, C and phyllaemblic acid were isolated [5]. Various studies with the help of different spectral methods like NMR spectroscopy, UV-Visible spectrophotometry, Mass spectroscopy showed that phenolic compounds like geraniin, isocorilagin, quercetin `3-β-D-glucopyranoside, kaempferol 3-β-D-glucopyranoside etc were found in ethyl-acetate fraction of amla fruit [7].

All parts of the plant like seed, fruit, leaf, root, bark, flowers are used in folk medicine, in Ayurvedic and Sidha systems for the treatment of various diseases [8]. It is an ingredient of several preprations like Brahma Rasayan, Chyavanaprash, Triphla, Septilin etc. which are marketed products [9]. Raw fruit of amla is eaten as it is or cooked into variety of dishes, used for making pickle, preservatives and murabbha (a sweet dish) which is taken after meals [10]. Preclinical studies found that extract of amla shows anti-diabetic action by increased release of insulin and through improving the activities of enzymes like glicose-6-phosphatase, α-amylase and hexokinase, and have preventive action against various diabetic complications like cataract via its inhibitory action on aldose reductase (AR) and advanced glycation end products (AGEs) [11,12]. Various *in vivo* and *in vitro* studies revealed that tannins and ellagic acid present in amla have anti-oxidant potential and free radical scavenging activity [13,14]. It was found that different extract of amla shows hepatoprotective activity by regulating the expressions of beclin-1, inducible nitric oxide synthase (iNOS), cytochrome P450 2E1 protein, Bax and Bcl-2 [15,16]. Amla extracts were also evaluated for anti-tumour activity and showed that amla has potential to inhibit cell growth and cell cycle, induce apoptosis and alter the regulation of various proteins (Bax and Bcl-2) and enzymes (cdc 25 phosphatase) [17,18]. Some studies evaluated that alcoholic and aqueous extract of amla possess anti-ulcer activity via inhibiting the activity of *H.pylori* and by ameliorating the levels of offensive and defensive factors [19,20]. Experimental studies has been revealed that flavonoids, tannic acid, gallic acid and vitamin C found in amla were responsible for regulating the levels of acid phosphatase, alkaline phosphatase, acetyl cholinesterase, monoamine oxidase-B (MAO-B) and GABA in brain and showed protective effect against CNS disorders [21,22]. Various *in vitro* studies showed anti-microbial potential of amla extract in different solvents [23]. It was found that amla juice and amla extracts inhibited various inflammatory mediators and pro-inflammatory cytokines involved in inflammation and thus possess anti-inflammatory activity [24]. Aqueous and alcoholic extract of amla shows analgesic action by inhibiting pain mediators like substance P and PGs [25]. Further amla possess radio protective effect due to its antioxidant potential [26]. Flavanoids from

E.officinalis have the potential to reduce the lipid concentration in serum and in different tissues and therefore used in dyslipidemia [27]. *P.emblica* acts as a body coolant, due to which it is widely used in the treatments for burning sensation and fever [28]. Fresh and dry fruits of *E.officinalis* are used in the treatment of jaundice and diarrhoea. It is also used in the treatment of leprosy, anemia, skin diseases, dysentery, leucorrhoea, hyperacidity, dyspepsia, flatulence, anorexia, indigestion etc. [9]. In this review, we will critcally discuss the role of amla in various pathophysiological disorders. Further, the mechanisms responsible for its therapeutic potential are explored.

MEDICINAL VALUES OF AMLA

Amla and Diabetes mellitus

Treatment of alloxan-induced diabetic rats with amrithadi churnam (consisit of *Emblica Officinalis, Tinospora cordifolia, Salacia prenoides, Curcuma long and Tribulus terrestris*) at a dose of 100 mg/kg p.o/day decreased the blood glucose levels and subsequently increased insulin levels [29]. Further, administration of methanolic extract of *E.officinalis* at a dose of 100 mg/kg *p..o* in alloxan-induced diabetic rats lowered blood glucose level and showed antioxidant effect by scavenging of free radicals [30]. Moreover, administration of methanolic seed extract of amla for 45 days in STZ-induced type-2 diabetic rats showed increase in insulin level which may be exhibited by restoration of β-cells of pancreas [31]. A recent study showed that the hydro-methanolic extract of leaves of amla at different doses (i.e 100, 200, 300 and 400 mg/kg bw) in STZ-induced diabetes in rats decreased fasting blood glucose level by increasing insulin levels and decrease oxidative stress by maintaining the impaired antioxidant status and decreasing lipid peroxidation [32]. In addition, amla fruit powder at a dose of 2g or 3g daily for 21 days in diabetc patients decreased fasting and post-prandial glucose level and altered lipid profile by decreasing the levels of low density lipoprotein and subsequently increasing the levels of high density lipoprotein [33]. It has been noted that administration of methanolic fruit extract of amla (200 mg/kg bw for 45 days) in STZ-induced type-2 diabetes lowered the blood glucose level via increased insulin release and normalized lipid profile in plasma and tissues by reducing the activity of cholesterol synthesizing enzymes and lipolysis [34]. Administration of *E.officinalis* fruit powder (2.5, 5 and 10 g %) in flouride-induced toxicity in rats decreased blood glucose level by decreasing glucose-6-phophatase (G-6-phase) activity and enhancing hexokinase activity and level of hepatic glycogen and decreased oxidative stress by increasing levels of anti-oxidant enzymes [12].

It has been demonstrated in an *in vitro* study that aqueous extract of *E.officinalis* in clonal pancreatic beta cell line (BRIN-BD11) (*in vitro)* increased the insulin level by promoting the glucose-stimulated insulin secretion. Futher, the same extract of amla at a concentration of 1 mg/ml mimiced like insulin and enhanced insulin action by insulin-stimulated glucose transport in 3T3 L1 adipocytes, whereas, at higher concentration i.e 5-50 mg/ml and 1-50 mg/ml extract inhibited both protein glycation and starch digestion [35]. It has been revealed in a recent study that hydro-alcoholic extract of *E.officinalis* in 3T3L1 adepocyte cell culture (*in vitro*) at concentration of 200 µg/ml stimulated glucose uptake in adipocyte cells which showed that amla possess insulin sensitizing and glucose stimulatory activity [36].

Oral administration of herbal product hyponidd (composed of various medicinal plants out of which *E.officinalis* is one of the component) at a dose of 100 and 200 mg/kg (for 45 days) in STZ-induced diabetic rats decreased blood glucose level by stimulating the release of insulin and glycogen synthase and lowered oxidative stress by elevating glutathione level [37]. Polyherbal drug i.e Glyoherb on oral administration (200, 400 and 600 mg/kg) for 28 days in STZ-induced diabetic rats reduces blood glucose level, cholesterol, triglyceride (TG), creatinine and urea levels in serum and reduce oxidative stress by increasing levels of antioxidant enzymes, thus, ameliorates kidney and liver dysfunction in diabetic rats [38]. Sun amla (commercial product) at a dose of 20 or 40 mg/kg and ethyl-acetate extract of amla at a dose of 10 or 20 mg/kg on oral administration for 20 days in STZ-induced diabetic rats prevented oxidative stress by inhibiting advanced glycation end products and ameliorated glucose metabolism [39]. Various mechanisms responsible for therapeutic effect of amla in diabetes have been shown in Fig 1.

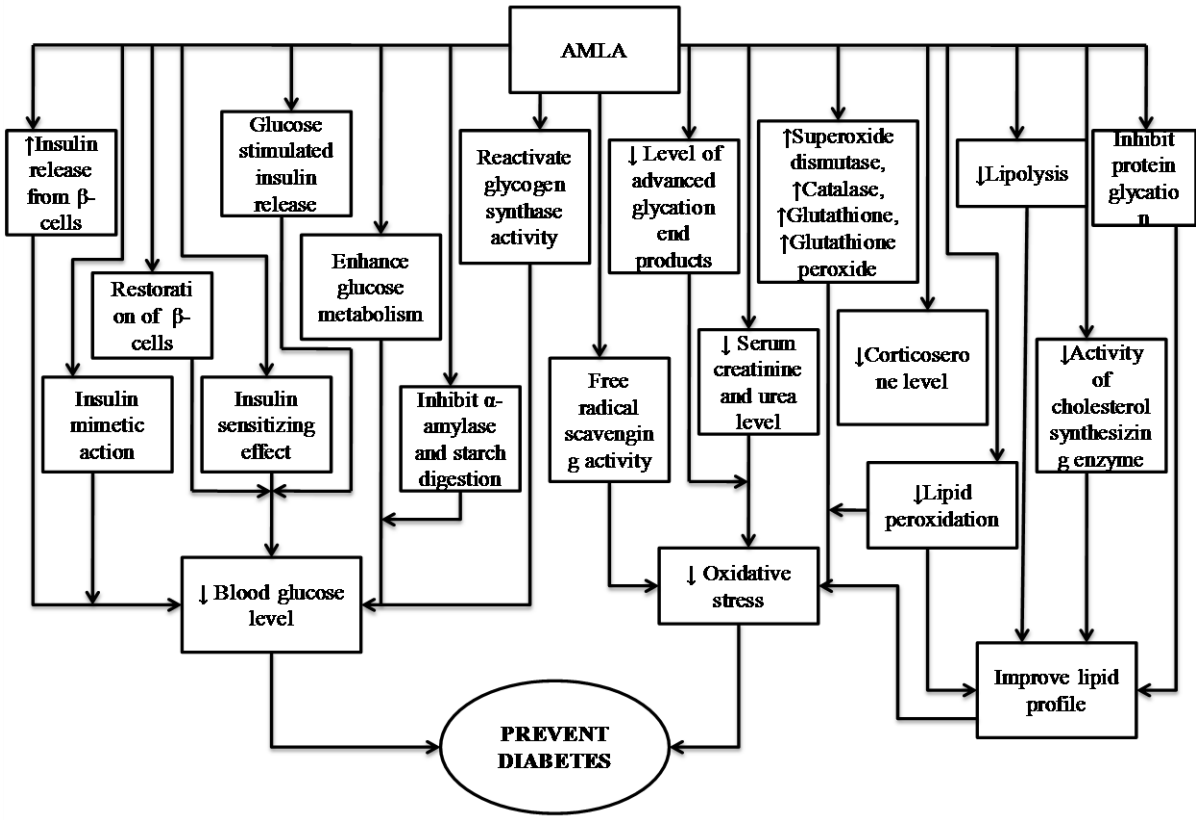

Figure 1: Mechanism of Amla as anti-diabetic agent.

Amla and Diabets-induced complications

It has been noted that tannoid principles present in *E.officinalis* prevented cataract in STZ-induced diabetic cataract in rats (*in vitro and in vivo*) by inhibiting the Aldose reductase (AR) (rate limiting enzyme in polyol pathway) and polyol pathway-induced oxidative stress [11,40]. Another study revealed that natural flavonoids in amla ameliorates cataractogenesis via inhibiting AR, advanced glycation and its antioxidant action [41]. Further, a recent study has reported that β-glucogallin a novel compound found in amla showed selective inhibitory activity against AKR_1B_1 *in vitro* and *ex-vivo* organ culture of lenses excised from transgenic mice inhibited sorbitol accumulation thereby preventing cataract [42]. Moreover, β-glucogallin treatment attenuated catarct in mice exposed to lipopolysaccharide endotoxins by inhibiting infiltration of inflammatory cells and morphological changes in retinal layers and down regulating pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α) and interleukin-1b (IL-1b) [43]. It has been documented that ethyl acetate and methanol fraction of amla at a dose of 10 mg/kg *p.o.* in STZ-induced diabetic rats was found to be useful in diabetes–induced neuropathy by reducing level of sciatic nerve malondialdehyde (MDA) and elevating pain threshhold level [44]. Administration of fruit juice of amla in diabetes-induced myocardial dysfunction in rats decreased glucose level by enhancing insulin sensitivity and prevented cardiac muscular damage by lowering levels of lactate dehydrogenase (LDH) and CK-MB in serum, inhibiting the production of reactive oxygen species (ROS) by elevating the levels of anti-oxidant enzymes in diabetic heart [45].

Amla and Anti-oxidant activity

It has been documented from various studies that amla is a powerful antioxidant. Aqueous extracted carbohydrate polymers of *E.officinalis* reduced the oxidative stress by its free radical scavenging property [46]. This antioxidant potential has been attributed to flavonoid contents of *E.offficinalis* at a dose of 10 mg/kg p.o. in cholesterol-fed rats [47]. Further, treatment with fresh fruits of amla at dose of 250, 500 and 750 mg/kg for 30 days against ischemic reperfusion (IR) injury in rats prevented oxidative stress and myocyte injury by inhibiting lipid peroxidation and increased levels of myocardial antioxidants like catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH) and SOD [48]. Moreover, administration of aqueous extract of seeds of amla (300 mg/kg for 30 days) in STZ-induced diabetic rats reduced oxidative stress by enhancing antioxidant enzymes and reducing lipid preoxidation in erythrocytes [49]. In an *in vitro* study it was revealed that an aqueous extract of amla fruit in hepatocyte cell line (HepG2) reduced oxidative stress by attenuating level of lipid hydroperoxide, ROS, increasing the levels of antioxidant enzymes such as GSH, glutathione reductase, glutathione S-transferase, glutathione peroxidase etc. [50]. In addition, tannoid principles (emblicanin A and B) of *E.officinalis* at a dose of 5 and 10 mg/kg i.p once daily for 7 days on frontal cortical and striatal rat brain areas normalised the reduced levels of anti-oxidant enzymes like SOD, CAT and GPx [13]. Furthermore, administration of amla juice (0.01 ml/day) in radiation and cadmium induced-rats prevented brain cell damage by its antioxidant potential by various mechanisms such as decrease in peroxidation of lipids and proteins, free radical scavenging mediated by polyphenols, increase in the levels of GSH, reducing activities of acid phosphatase and alkaline phosphatase (these are lysosomal enzymes which cause cell damage) [51]. It has been noted that phenolic content in ethanolic extract of amla has shown antioxidant potential in β-carotene bleaching method inhibiting auto-oxidation via free radical scavenging, singlet oxygen quenching and hydrogen donating mechanisms [52]. Ellagic acid and ascorbic acid in methanolic extract of amla were found to possess in vitro antioxidant property evaluated in terms of reduction in nitric oxide and hydroxyl radicals through its free radical scavenging property and preventing LDL oxidation [14]. Various mechanisms responsible for role of amla in combating oxidative stress have been shown in Fig 2.

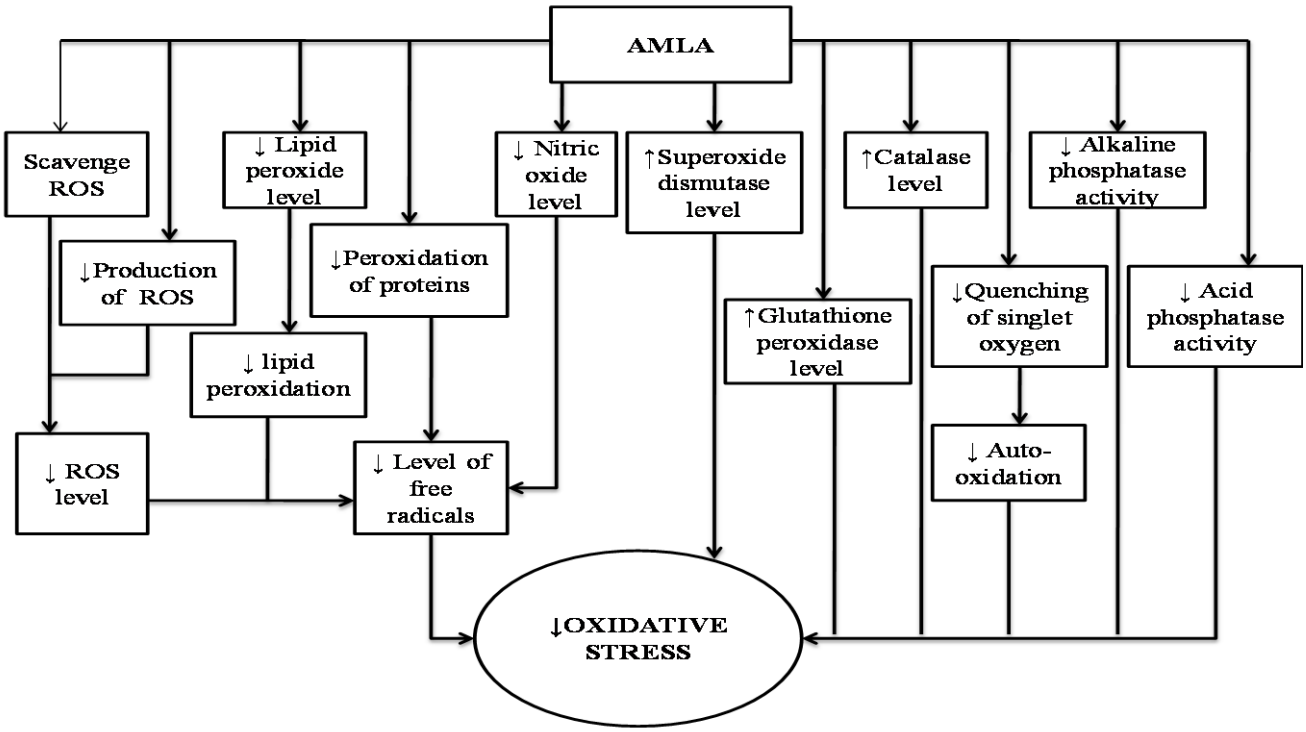

Figure 2: Mechanism of Amla as antioxidant agent. ROS indicates Reactive oxygen species

Amla and Hepatoprotective activity

Hepatoprotective action of 50% hydroalcoholic extract of fruits of *E.officinalis* was evaluated in suspension culture of rat hepatocytes against anti-tuberculosis drugs which was exhibited by its antioxidative action and inhibition of Cytochrom P450 2E1 (CYP 2E1) (protein which produces oxidative stress and cause hepatic injury) [53,54,15]. Amla at adose of 100 mg/kg b.w in N-nitrosodimethylamine-treated rat liver decreases the expression of iNOS and CYP2E1 protein, improve manganese superxide dismutase (Mn SOD) and CAT expression as well as, amla reduces hepatic apoptosis and autophagy by down-regulating the expression of beclin-1 and Bax/Bcl-2 ratio [16]. Further, preadministration of *E.officinalis* in carbon tetrachloride (CCl_4)-induced hepatic injury in rat prevented the hepatotoxicity by reducing the levels of Serum Glutamate Pyruvate Transaminase (SGPT), Serum Glutamate Oxaloacetate Transaminase (SGOT), LDH, lipid peroxidation and increasing the levels of GSH, glutathione reductase and peroxidase [55]. Moreover, the administration of aqueous extract of amla at the dose of 2 mg/day *p.o.* for 45 days in ochratoxin-induced lipid peroxidation in liver and kidney of mice decreased the lipid peroxidation through its free radical scavenging activity and thus reduced the production of hydroxyl, peroxides and superoxide radicals and subsequently increased the concentration of GSH [56]. In addition, a study demonstrated that flavonoids and tannins in amla showed its protective effect in alcohol-induced hepatic injury in rat by combating oxidative stress via decreasing lipid peroxidation and scavenging reactive nitrogen species [57]. Another study on amla revealed that alcoholic extract of amla at a dose of 100 mg/kg p.o in CCl_4-induced liver injury in rats prevented the fibrosis and pre-fibrogenic process by reducing the elevated levels of collagen-hydroxyproline and by enhancing the regenerative activities like anisocytosis and anisonucleosis and therefore, prevented the abnormal histopathology of liver [58,59]. Various mechanisms responsible for protective effect of amla in hepatotoxicity have been shown in Fig 3.

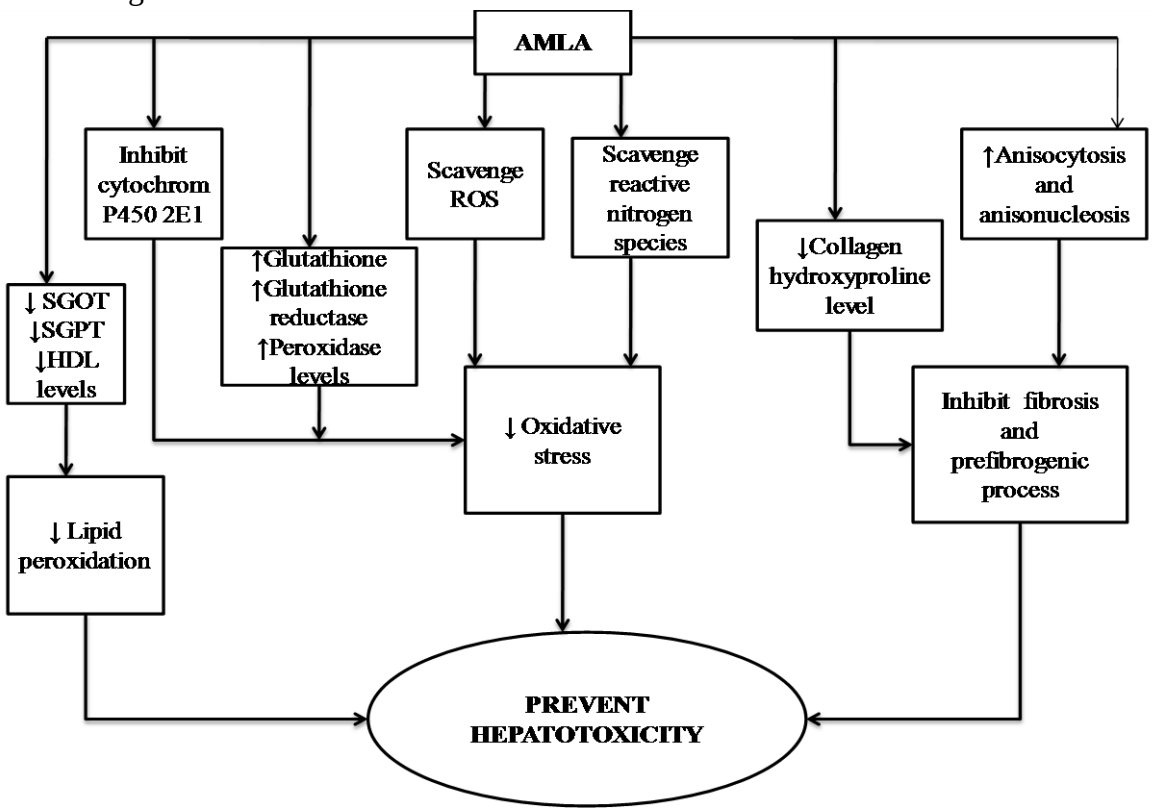

Figure 3: Mechanism of Amla as hepatoprotective agent.

SGPT indicates Serum glutamate pyruvate transaminase, SGOT indicates Serum glutamate oxaloacetate transaminase, HDL indicates High density lipids, ROS indicates Reactive oxygen species.

Amla and Cancer

Aqueous extract of *E.officinalis* showed anticancer activity in L929 cell culture by inhibiting cell cycle regulating enzymes such as cdc 25 phophatase and cdc 2 kinase [17]. Further, aqueous extract of amla inhibited the induction and progression of cancer in human cancer cell lines like HepG2 (liver), A549 (lung), HeLa (cervical), MDA-MB-231 (breast), SK-OV3 (ovarian), SW620 (colorectal) by arresting cell growth through its selective antiprolifeative action [60]. Pyragallol and phenolic contents found in amla have been found to be responsible for the antiprolifeartive action of amla [61,62]. Experimental studies have shown the ability of polyphenols present in amla to be effective against Dalton's Lymphoma Ascites (DLA) and human cervical cancer cell by inducing the process of apoptosis by various mechnism such as condensation of chromatin, membrane blebbing and intenucleosomal breaking [63]. Moreover, aqueous extract of amla in HeLa cells have been found to induce apoptosis by causing DNA fragmentation and upregulating the activities of caspase 3/7, caspase 8 and Fas protein. Furthermore, it has been demonstrated in an *in vitro* study aqueous extract of amla showed protective effect by inducing apoptosis in MDA-MB-231 cells (human breast cancer cells) via downreglating the expression and activity of matrix metalloproteinases-1,2 and 9 (MMP-1,2,9) [60]. Further a fruit extract of amla in human primary osteoclast cell culture induced apoptosis by opposes the binding of Nf-κB and by altered expression of Fas receptor and interleukin-6 [64]. It has been found that amla leaves exert apoptotic effect in hepatocellular carcinoma cell (BEL-7404 cell) via down-regulating the expression of Bcl-2 and by up-regulation of Bax expression. Therefore, it was observed that progallin A present in amla shows apoptotic effect of amla in prevention of cancer [18].

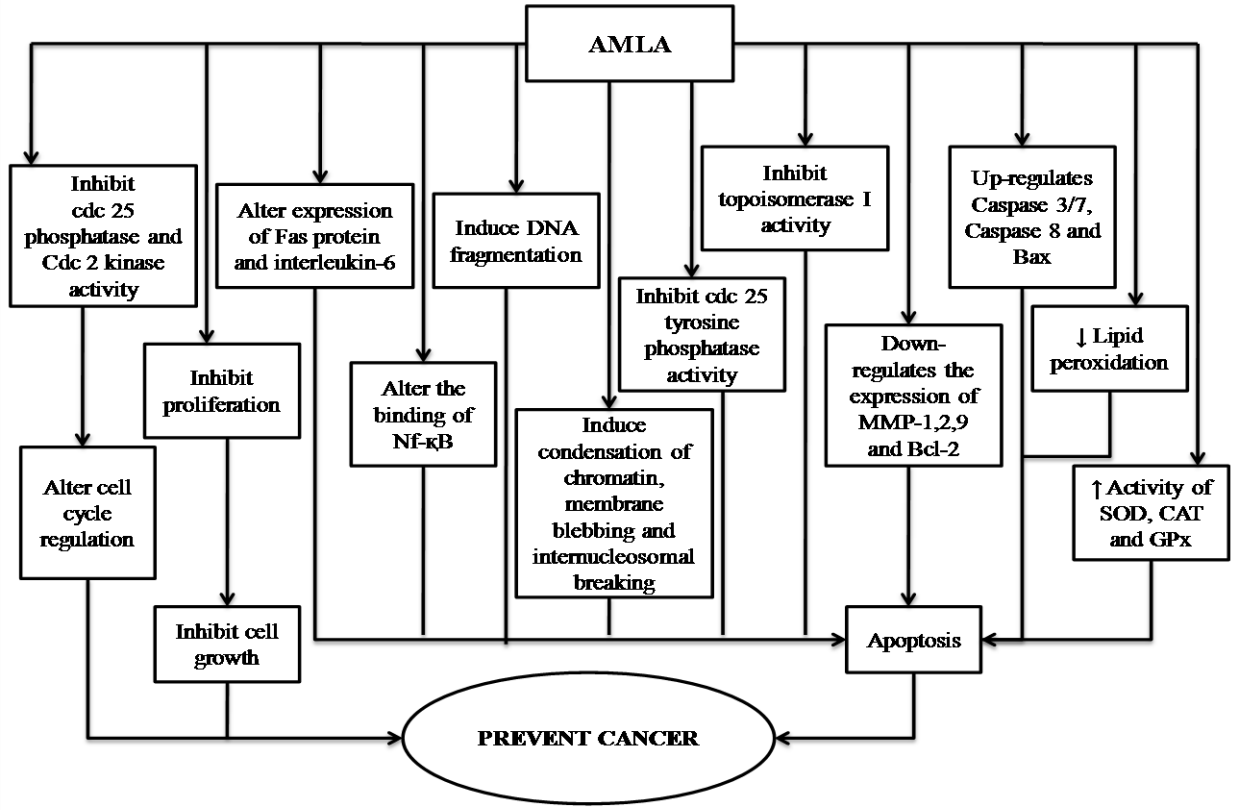

Figure 4: Mechanism of Amla as anti-cancer agent.

MMP-1,2,9 indicates Matrix metalloproteinases-1,2 and 9, SOD indicates Superoxide dismutase, CAT indicates Catalase, GPx indicates Glutathione peroxidase, NF- κB indicates Nuclear factor-κB.

In addition, treatment of aqueous and methanolic fruit extract of amla in DNBA/TPA-induced tumours, in 7,12-dimethyabenz(a)anthrecene skin carcenogenesis in mice and buccal pouch carcinogenesis in hamster ameliorated cancer by decreasing tumour number and volume via its antioxidant potential by decreased lipid peroxidation and ameliorating anti- oxidant enzyme activities like SOD, CAT and GPx [65,60,66]. Further, an *in vitro* study showed that polyphenols in *Saccharomyces cervisiae* mutant cell cultures prevented the

activity of topoisomerase I and cdc25 tyrosine phosphatase [63]. The signalling pathways involved in anticancer effect of amla have been delineated in Fig 4.

Amla and Anti-hyperlipidemic activity

Elevated levels of lipids like LDL, total cholesterol (TC), TG are considered as major contributing factors for the induction of atherosclerosis. Oral administration of ethyl acetate extract of amla in cholesterol-fed rats decreased LDL-cholesterol levels [67]. Further, treatment with amla fruit pulp powder in birds normalized blood lipid profile via regulating the altered levels of LDL, TG and HDL [68]. Moreover, a clinical study found that aqueous extract of amla fruits at the dose of 500 and 1000 mg/day for 6 months in hypercholesterolemic humans attenuates the level of TC and lipid profile by inhibiting HMG CoA reductase and squalene epoxidase [69]. In addition, it has been observed that flavonoids obtained from *E.officinalis* lowered the lipid levels by inhibiting HMG CoA reductase and increased degradation of cholesterol in hyperlipidemic rats [70,71]. Furthermore, fresh juice of amla at a dose of 5 ml/kg for 60 days in cholesterol-fed rabbits reduced lipid levels by altering the absorbtion of cholesterol and phospholipids and by increasing their excretion [72]. Ethyl acetate extract of amla has been reported to show its hypolidemic potential in age-related hyperlipidaemia at the dose of 40 or 10 mg/kg for 100 days in rats by upregulating the levels of PPAR α (protein which regulates the transcription of genes involved in lipid and cholesterol metabolism) [73]. Various mechanisms responsible for therapeutic effect of amla in hyperlipidemia have been shown in Fig 5.

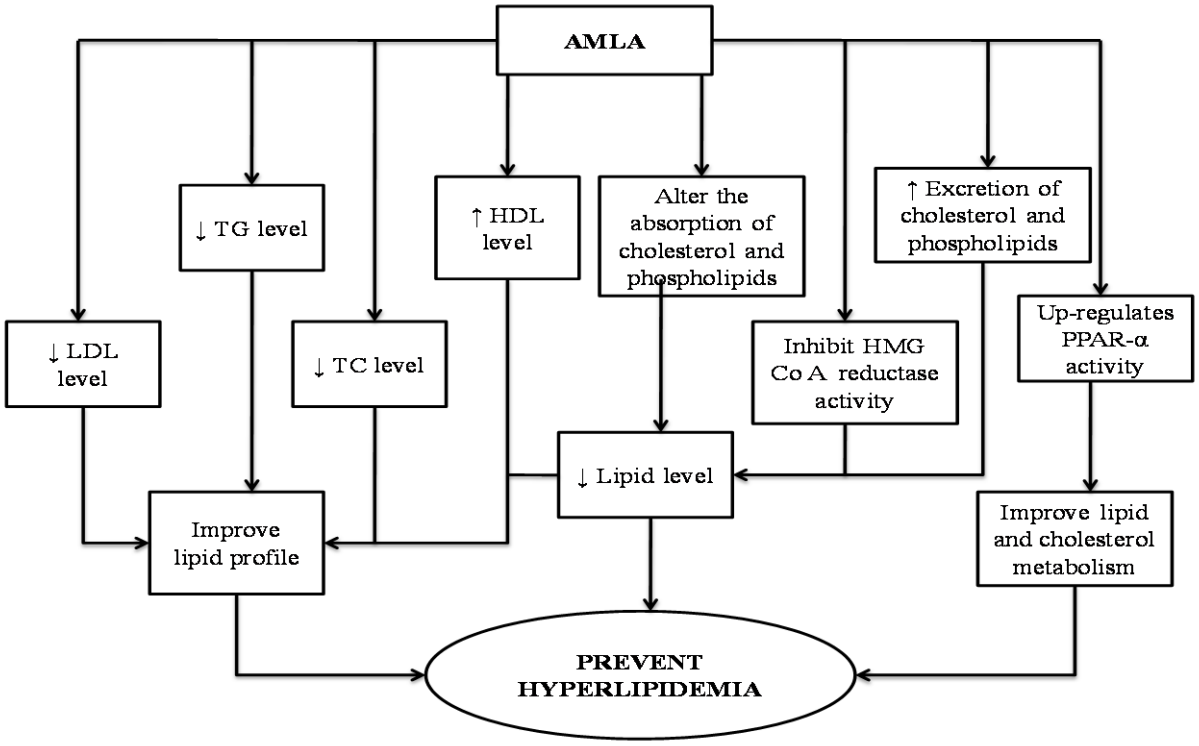

Figure 5: Mechanism of Amla as anti-hyperlipidemic agent.

TG indicates Triglycerides, TC indicates Total cholesterol, LDL indicates Low density lipids, HDL indicates High density lipids.

Amla and Gastric ulcer

Fresh fruit juice and methanolic extract of amla at a dose of 25-100 mg/kg in histamine-induced ulcer in rats showed cytoprotective effect against gastric mucosal cells via its antioxidant potential [74-76]. Further, ethanolic extract of amla fruit at a dose of 60 mg/kg in an indomethacin-induced ulcer in mice protects ulcer by increasing the levels of mucin, PGE_2 and IL-10 and decreasing an indomethacin-induced elevated levels of TNF-α and IL-1β [77]. It has been noted that gallic acid present in amla fruit extract has been found responsible for ulcer healing protective potential [78]. Moreover, it has been reported that ethanolic and butanol fruit extract

of amla showed protective effect on gastric lessions and mucosal depletion in indomethacin-induced and hypothermic restraint stress-induced gastric ulcer in rats by increasing the secretion of gastric mucus, hexosamine and prostaglandins (PGs) [79,80]. In addition, the protective effect of amla has been demonstrated in aspirin and acetic acid-induced gastric ulcer in rats by decreasing the offensive factors such as pepsin and acid and subsequently increasing the defensive factors such as mucin and mucus [19]. It is intriguing to note that phenols, carotenoids and flavonoids present in ethanolic and aqueous extract of amla possess anti *H. pylori* activity mediated by inhibition of cell division and by damaging its cell wall [20,81].

Tannins found in aqueous extract of amla at the dose of 150, 300 and 600 mg/kg shows anti-ulcerogenic activity in stress-induced gastric lesions by inhibiting the COX-2 enzymes [82]. Studies revealed that a herbomineral formulation like Pepticare (consist of *Glycyrrhiza glabra*, *Emblica officinalis* and *Tinospora cordifolia*) and polyherbal formulation like DHC-1 on oral administration in pylorus ligation ethanol-induced ulcer in rats reduces the ulcer index by raising the pH and by altering microbial flora through elevating the levels of Ca^{2+}ATPase, Mg^{2+} ATPase and Na^{+} K^{+} ATPase enzymes and by ameliorating the antioxidant status [83,84]. Various mechanisms responsible for therapeutic effect of amla in gastric ulcer have been shown in Fig 6.

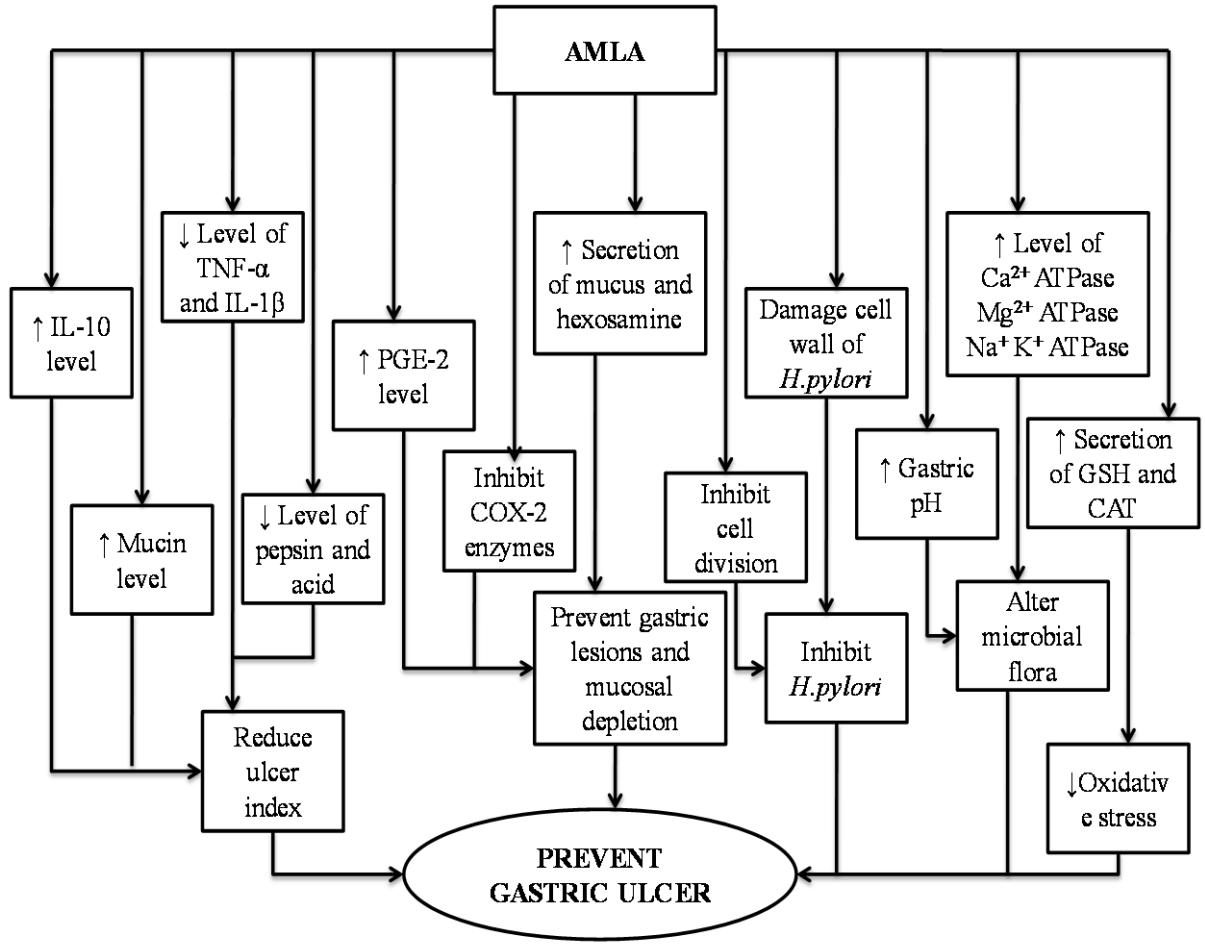

Figure 6: Mechanism of Amla as anti-ulcer agent.

TNF-α indicates Tumor necrosis factor-α, IL-1β indicates Interleukin-1β, IL-10 indicates Interleukin-10, PGE-2 indicates Prostaglandin E-2, COX-2 indicates Cycloxygenase-2, GSH indicates Glutathione, CAT indicates Catalase.

Amla and Inflammation

An *in vitro* study of leaf extract of *E.officinalis* in tetrahydrofurane, 1,4-dioxane and methanol against human polymorphonuclear leukocyte (PMN) showed the inhibition of receptor-mediated migration and degranulation of human PMNs [85]. Methanolic leaf extract of *E.officinalis* in carrageenan and dextron-induced hind paw oedema in rats showed the inhibition of leukotriene B4 (LTB_4), thromboxane B2 (TXB2), platelet activating factor (PAF) [86]. Another *in vitro* study revealed that diethyl ether extract of amla leaves in human PMNs inhibits the adrenalin-induced platelet aggregation and blood clotting by preventing the production of TXB2 in platelets [85]. An aqueous extract of amla fruits at a dose of 1 mg/ear in ethyl phenylpropiolate (EPP)-induced and arachidonic acid (AA)-induced ear oedema in rats inhibits the inflammatory mediators like serotonin (5-HT), kinins, histamine, pro-inflammatory cytokines and prostaglandins [24]. It was evaluated that pretreatment with methanolic extract of amla fruit in an indomethacin and acetic acid-induced ulcerative colitis in rats prevented the infiltration of inflammatory cells, oedema and declines the level of serum LDH [87,88]. Study showed that treatment with amla in L-arginine-induced pancreatitis in rats prevented hemorrhage and vascular thrombosis of pancreas via ameliorating the synthesis of DNA, pancreatic proteins and amylase content and by decreasing the levels of lipase and IL-10 in serum [89]. Aqueous extract of amla fruit in explant culture of articular knee cartilage showed chondroprotective potential by inhibiting the activities of hyaluronidase and collagenase type 2 enzymes [90]. Ethyl acetate and n-butyl alcohol extract of amla in sodium urate –induced gouty arthritis in rats prevented inflammation by preventing the release of TNF-α and PGE2 in local tissue and serum [91]. It was evaluated that pyrogallol found in amla extract showed anti-inflammatory action against PAO1 (*Pseudomonas aeruginosa* laboratory strain) in IB3-1 cystic fibrosis (CF) bronchial epithelial cells via preventing the expression of adhesion molecule ICAM-1, chemokines IL-8, neutrophil and pro-inflammatory cytokine IL-6 [92]. Various mechanisms responsible for therapeutic effect of amla in inflammation have been shown in Fig 7.

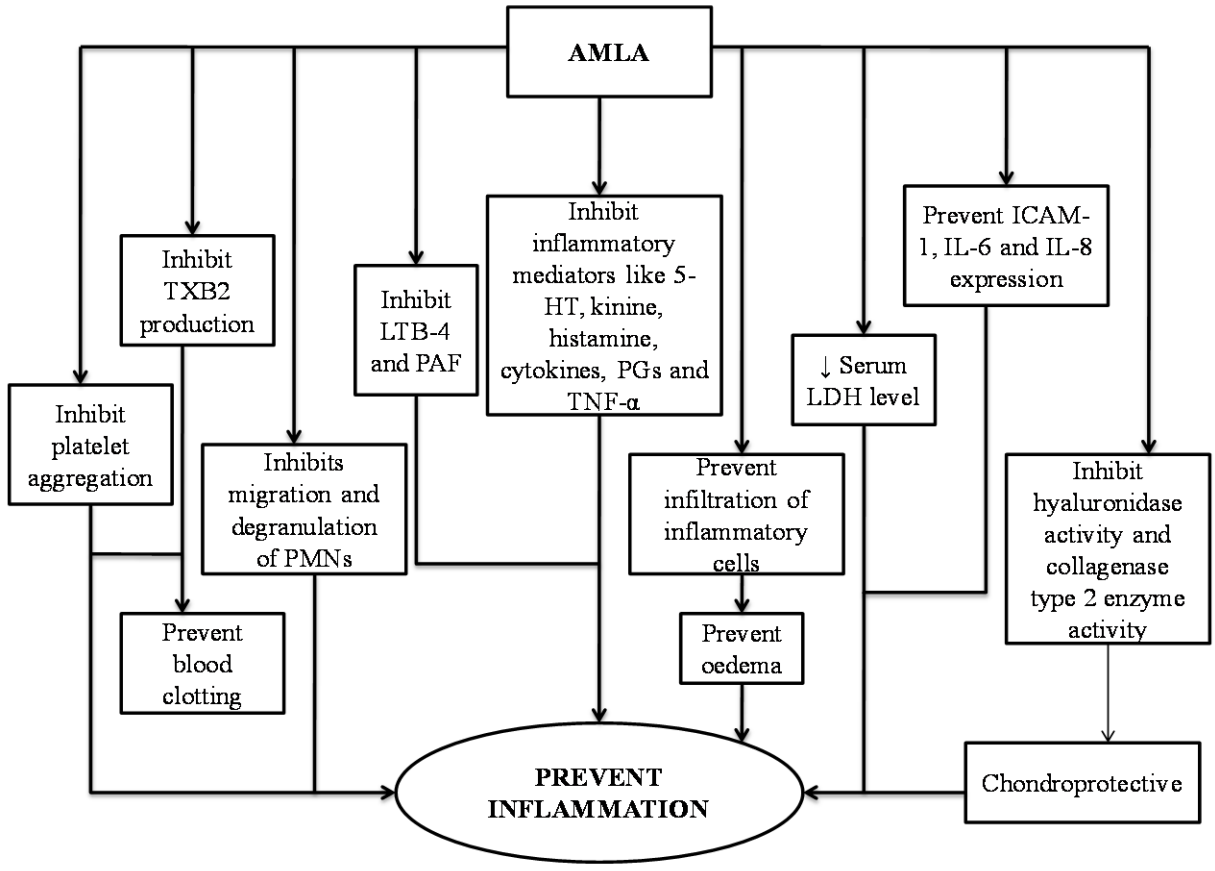

Figure 7: Mechanism of Amla as anti-inflammatory agent.

TXB2 indicates Thromboxane B2, PMNs indicates Polymorphonuclear leukocytes, 5-HT indicates Serotonin, TNF-α indicates Tumor necrosis factor-α, PGs indicates Prostaglandins, ICAM-1 indicates Intracellular adhesion molecule-1, IL-6 indicates Interleukin-6, IL-8 indicates Interleukin-8.

Amla and CNS protective activity

Pretreatment with hydroacoholic extract of fruits of *E.officinalis* in kainic acid (KA)- induced seizures in rats showed neuroprotective effect by improving the levels of GSH and TNF-α in brain [93]. Further treatment with hydroalcoholic extract of amla at dose of 300, 500 and 700 mg/kg i.p in pentylenetetrazole (PTZ)-induced seizures prevented cognitive impairment via ameliorating oxidative stress markers like MDA and GSH [94]. Another study showed radioprotective effect on pretreatment with aqueous fruit extract of amla in radiation-induced biochemical lesions in the brain of mice prevented peroxidation of membrane lipids by decreasing lipid peroxidation and via increasing the levels of GSH, protein and cholesterol in brain [26]. It was observed that flavonoids and vitamin C present in amla were responsible for antioxidant potential [95]. Moreover hydroalcoholic extract of amla fruits when administered intraperitoneally in scopolamine-induced amnesia in mice showed memory enhancer and antioxidant potential by ameliorating the levels of GSH, MDA and by decreasing the acetyl cholinestrase level in brain [96]. Amla churna on oral administration at the dose of 50, 100 and 200 mg/kg in diazepam and scopolamine-induced amnesia in rats reversed the memory deficits by promoting cholinergic transmission and by improving antioxidant status in brain [21]. Pretreatment of ischemic reperfusion injury in rats for 15 days with alcoholic extract of amla at dose of 250-500 mg/kg improved the levels of MDA, CAT, SOD and vitamin C by ameliorating the levels of protective oxydative enzymes [97]. Oral administration of juice of *E.officinalis* prevented biochemical changes induced by radiations and cadmium in mice brain by preventing the release of hydrolytic enzymes, by increasing the protein and DNA contents and by decreasing the elevated levels of acid phosphatase, alkaline phosphatase, RNA and glycogen in brain [55]. It was found that oral administration of aqueous extract of amla (at 200 and 400 mg/kg) in tail suspension and forced swim test in mice showed anti-depressant effect by decreasing the levels of monoamine oxidase-A (MAO-A) and GABA. Experimental study has been revealed that polyphenols, tannic acid and gallic acid found amla were responsible for monoamine oxidase inhibition [22].

Amla and Anti-microbial activity

Tannins, flavonoids, saponims and phenols present in methanolic and aqueous extract of fruit and leaf of *E.officinalis* were responsible for preventing respiratory diseases by showing inhibitory action against respiratory pathogens like *Staphylococcus aureus, Klebsiella pneumoniae* and *Streptococcus pyogenes* in agar ditch plate method [98]. Alkaloids found in chloroform extract of fruits of *E.officinalis* at a concentrattion of 400 µg/disc showed anti-bacterial activity against some gram positive bacteria like *Bacillus subtilis*, *Bacillus cereus* and *Bacillus megaterium* and gram negetive bacteria like *Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa* and *Shigella boydii* [99]. An *in vitro* study showed that aqueous extract of amla fruit possesed anti-fungal activity against test dermatophytes [100]. An aqueous infusion and decoction of *E.officinalis* showed an anti-microbial potential in well diffusion method against gram negetive bacilli like *Staphylococcus haemolytics, Micrococcus varians, M;lylae, M.roseus* and *Candida albicans* isolated from urine specimens [101]. Another *in vitro* study revealed that aqueous and methanolic extract of amla fruit showed preventive action against various pathogenic bacteria like *Staphylococcs aureus, Staphylococcus saprophyticus, Escherichia coli, Enterococcus faecalis, Enterococcus cloacae, Proteus vulgaris and Klebsiella pneumoniae* [102]. Further in an *in vitro* study it was found that volatile components like beta-caryophyllene, beta-bourbonene, 1-octen-3-ol, thymol, and methyleugenol present in amla showed anti-microbial action against various gram positive and gram negetive bacteria [103]. It was found that Triphal (mixture of *E.officinalis, Terminalia chebula* and *Terminalia belerica*) showed anti-bacterial activity against multi-drug resistant *Salmonella typhi* [23].

Amla and Cardioprotective activity

Treatment with hydroalcoholic extract of *E.officinalis* at dose of 75, 150 and 300 mg/kg in deoxycorticisterone acetate/NaCl high salt (DOCA/HS)-induced hypertension in rats for 5 weeks showed reduction in hypertension and oxidative stress by increasing the expression of eNOS, by ameliorating the levels of nitric oxide (NO), SOD, GSHPx and electrolytes like Na^+ and K^+ [104]. Another study revealed that aqueous extract of amla lowers the mean arterial blood pressure, heart rate and respiratory rate by showing synergistic histaminergic and cholinergic effect [105]. On administration of amla (100, 250 and 500 mg/kg) for 30 days showed cardioprotective potential in isoproterenol-induced cardiotoxicity in rats through ameliorating the levels of antioxidant enzymes and creatinine phosphokinase-MB and LDH by its antoxidant free radical scavenging activity [106]. Study revealed that amla fruit juice at dose of 1 ml/kg p.o for 8 weeks in diabetes-induced myocardial dysfunction showed preventive action in myocardial hypertrophy, cardiomyopathy and hypertension by increasing heart rate, lowering blood pressure through its anti oxidant potential and by maintaining the lipid profile and enzyme levels [45]. Homogenate of amla fruit on oral administration in IR-injury in rats causes myocardial adaption and prevented against oxidative stress by elevating levels of endogenous antioxidant enzymes [48]. Methanolic extract and fruit powder of amla has been known to attenuate the induction and progression of atherosclerosis in hypercholesterolemic rabbits by preventing the formation of plaque in blood vessels and aorta via inhibiting HMG CoA reductase and LDL oxidation; and by reducing LDL cholesterol levels and subsequently increasing HDL levels [107-109]. It is interesting to note that cardipro, a polyherbal drug (contains *Terminalia arjuna, Ocimum sanctum, Boerhaavia diffusa, Emblica officinalis and withania somnifera*) on oral administration at a dose of 25 mg/kg for 30 days in cholesterol fed rats prevents the progrssion of atherosclerosis by modulating the lipid profile, retarding the process of calcification via diminishing the deposition of calcium salt and preventing fat accumulation in aorta [110]. Various mechanisms responsible for cardioprotective action of amla have been shown in Fig 8.

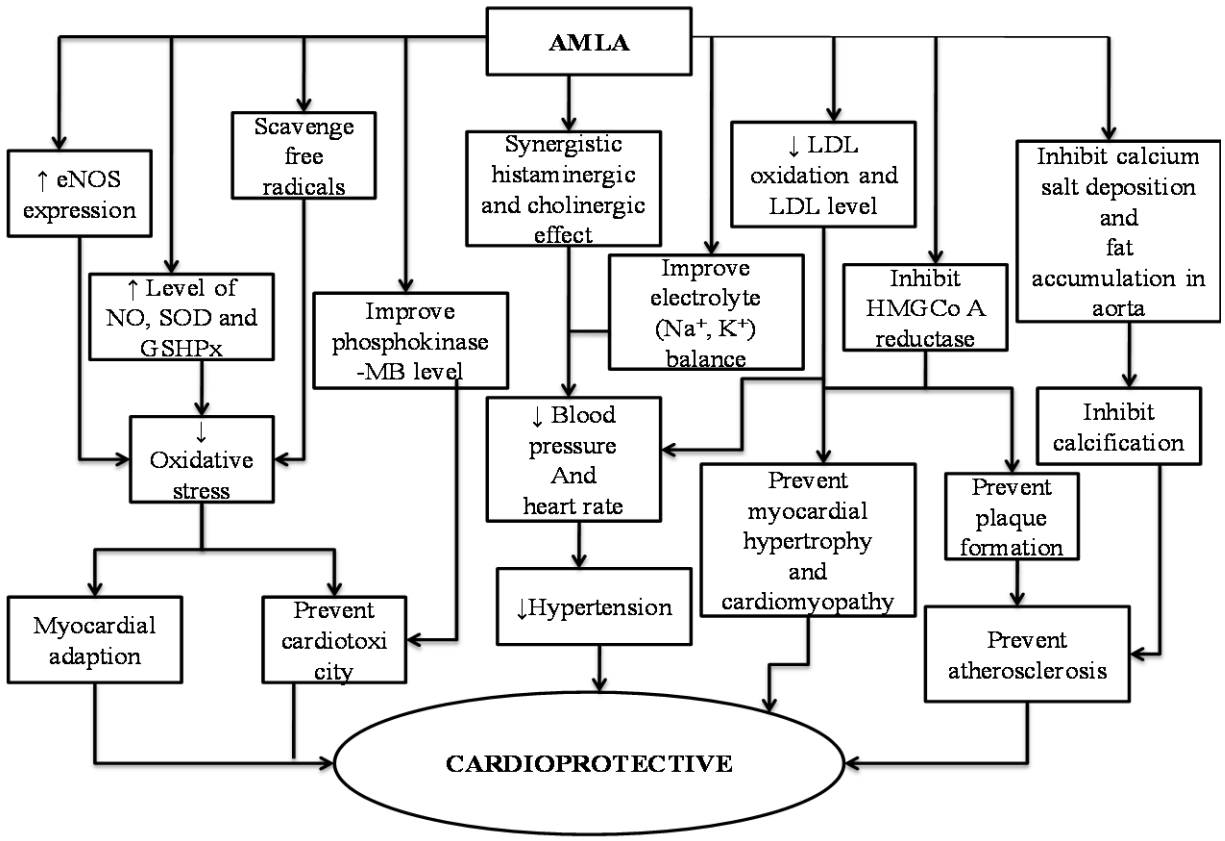

Figure 8: Mechanism of Amla as cardioprotective agent.

NO indicates Nitric oxide, SOD indicates Superoxide dismutase, GSHPx indicates Glutathione peroxidase.

Amla and Analgesic Activity

Ethanolic and aqueous extract of amla fruit have analgesic potential at a dose of 500 mg/kg i.p in acetic acid-induced writhing in mice [25]. On the other hand, preadministration of aqueous extract of amla in formalin test in rats at a dose of 600 mg/kg showed analgesic activity by inhibiting nociceptors and synthesis of pain mediators like substance P and PGs [24].

Amla and Miscellaneous uses

It was found that amla extract in chromium (Cr)-induced immunosuppression (*in vitro*) has been responsible for immunomudulatory effect via enhancing the proliferation of lymphocytes and by restoration of IL-2 and gamma-IFN production [111]. Treatment with polyherbal formulation Immu-21 consist of extracts of *Ocimum sanctum, Withania somnifera, Emblica officinalis* and *Tinospora cordifolia* showed immunomodulatory activity through increased leukocyte proliferation by lipopolysaccharide (in vitro) and by increasing the activity of natural killer cells (NK cells) in mice [112]. Further *E. officinalis* at a dose of 100 mg/kg for 15 days showed immunomodulatory action in BALB/c mice (infected with *Leishmania donovani*) by reduced parasite load through mediating immune response via increasing levels of IgG2a and by lowering the level of IgG1 [113]. Another study showed that triphla a herbal formulation at a dose of 1 g/kg p.o in noise stressed-immunized mice enhanced the immunity by stimulating the function of neutrophils [114].

Methanolic extract of amla fruit in castor oil and magnesium sulfate-induced diarrhea in rats reduced gastrointestinal motility via inhibiting PGE-2 [115]. Crude extract of amla in castor oil-induced diarrhea in mice at a dose of 500-700 mg/kg and in carbachol and K^+-induced contractions in rabbit jejunum (*in vitro)* showed anti-diarrheal and spasmolytic action by blocking the muscarinic receptors and Ca^{2+}-channel [116]. Decoction of amla fruit with sour milk is given in the cases of dysentry and infusion of leaves with fenugreek seeds is used for the treatment of chronic diarrhoea [117].

Administration of bark juice of *E.officinalis* with honey and turmeric is used for the treatment of gonorrhoea and leucorrhoea [118,9]. Fresh fruits of amla are used to prepare sharbat with raisins and honey which is used as effective diuretic. Amla berry has been shown to reduce burning sensation while urination. Paste of amla fruit with or without *Nelumbium speciosum* (Egyptian lotus), saffron and rose water is applied over pubic region in irritability of bladder, in retention of urine. Amla fruits are widely used as an ingredient of shampoo and hair oil. Fruits of *E.officinalis* enhance the absorption of calcium which creats healthier hair, nails, bones and teeth. Fixed oil obtained fron the amla fruits used to strengthen and promote the hair growth. Dried fruits boiled in coconut oil prevents the graying of hair [119]. Juice of *E.officinalis* leaves is used to get releif from toothache. Mixture of amla node and water is passed through cloth and then put into the right ear if the pain is on left hand side in teeth and vice versa [9].

An active compound phthalate isolated from root extract of *E.officinalis* used to neutralize the viper venom. It antagonized the myotoxicity induced by viper venom in experimental animals [120]. Coagulation, defibrinogenating, haemorrhage and inflammation induced by *Vipera russellii* snake were neutralized by extract of *E.officinalis* [121].

Fresh fruits of amla and decoction of leaves are used for the treatment of fever. Infusion of amla seeds act as a body coolant and effective in fever. Amla also act as a skin protecting agent in UV-induced erythema by quenching free radicals, by chelating ability to copper and iron as well as by inhibiting the activities of MMP-1 and MMP-3 [122,9]. Another study revealed that amla extract possessed dermoprotective action by stimulating proliferation of fibroblasts, by inducing production of procollagen and by decreasing the synthesis of MMP-1 (Fujji et al., 2008) [123].

Tannins and ascorbic acid present in amla have been found to responsible for wound healing in rats through increased cellular proliferation and cross-linking of collagen by enhancing the activity of extracellular signal-regulated kinase ½ and type III collagen [124]. Another study revealed that application of suspension of

amla fruit (1 ml) accelerated the wound healing in surgical wound in dogs by its antioxidant and anti-microbial potential [125]. Amla extract at a dose of 500 mg/kg showed wound healing activity on skin of mice by formation of epithelial and connective tissues [126].

Pretreatment with *E. officinalis* extract showed radioprotective action in radiation-induced damage in mice by increased levels of crypt cells and mitotic figures by decreasing lipid peroxidation and ameliorating the levels of anti-oxidant enzymes [127].

CONCLUSION

Several pharmacological studies of amla have been reported such as anti diabetic, anticancer, antioxidant and cardioprotective activity. But the mechanistic studies and application in clinical studies are still lacking. Further studies to explore the optimization of extraction conditions, isolation and characterization of the active constituents of amla are warranted. In nut shell, the broad spectrum activities of plant concluded in this review can be used as a benchmark to further explore its therapeutic potential.

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Conflict of interest

The Author(s) declare(s) that he has no conflicts of interest to disclose.

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