Emblica officinalis for the Treatment of Hyperlipidemia

Subjects: Food Science & Technology

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The ayurvedic herb *Emblica officinalis* (*E. officinalis*) is a gift to mankind to acquire a healthy lifestyle. It has great therapeutic and nutritional importance. *Emblica officinalis*, also known as Indian gooseberry or Amla, is a member of the Euphorbiaceae family. Amla is beneficial for treating illnesses in all its forms. The most crucial component is a fruit, which is also the most common. It is used frequently in Indian medicine as a restorative, diuretic, liver tonic, refrigerant, stomachic, laxative, antipyretic, hair tonic, ulcer preventive, and for the common cold and fever. Hyperlipidemia is also known as high cholesterol or an increase in one or more lipid-containing blood proteins. Various phytocompounds, including polyphenols, vitamins, amino acids, fixed oils, and flavonoids, are present in the various parts of *E. officinalis*. *E. officinalis* has been linked to a variety of pharmacological effects in earlier studies, including hepatoprotective, immunomodulatory, antimicrobial, radioprotective, and hyperlipidemic effects.

Keywords: Emblica officinalis ; hyperlipidemia ; phytochemicals

1. Introduction

The most prevalent type of dyslipidemia, hyperlipidemia, is caused by increased blood lipid levels, including triglycerides and cholesterol. The early onset of atherosclerosis and its cardiovascular complications are predicted to continue to be significantly influenced by hyperlipidemia. Globally available cholesterol-lowering drugs may be expensive and have side effects, making herbal medicines an alternative in cases where cardiovascular diseases are the primary cause of death [1][2].

In the ancient Indian medical system known as Ayurveda, *Emblica officinalis* (*E. officinalis*) holds a revered place. It is the first tree ever made in the history of the universe. It belongs to the Euphorbiaceae family, according to ancient Indian mythology. commonly known as *Phyllanthus emblica*, Amla, or Indian gooseberry [3]. In Ayurveda, the fruit of the *E. officinalis* plant is frequently used to boost immunity. Cancer, diabetes, liver disease, ulcers, heart problems, anemia, and a number of other diseases can all be helped by the chemical constituents of *P. emblica*. Additionally, it helps with lowering cholesterol levels, ophthalmic disorders, and improving memory [4][5].

The hypoglycemic medications on the market all have one or more side effects. According to WHO recommendations, it can be difficult to find new cholesterol-lowering drugs made from herbal plants that have negligible or no side effects [6]. Interestingly, there is a paucity of information on the effectiveness of EO in lowering cholesterol. Nanocoatings made from Amla essential oil appear to extend the shelf life of fruits [7]. In addition, nanoencapsulated amla provides nutraceuticals and functional foods to improve human health. The therapeutic and traditional potential of amla can be fully utilized by nanoencapsulation of the active components of amla for target delivery, enhanced bioavailability, and increased bioactivity [8].

2. Pharmacological Activity of Amla

In light of the medicinal and pharmaceutical qualities of *E. officinalis*, every part is beneficial. According to research by Krishnaveni and Mirunalini [3], *E. officinalis* has antioxidant, antimicrobial, anti-inflammatory, anticancer, antiulcer, antidiabetic, memory enhancer, cardioprotective, neuroprotective, neuroprotective, antidiarrheal, renoprotective, and immunomodulatory potential, as shown in **Figure 1**, and major phytoconsituents present in *E. officinalis* and its pharmaceutical effects point toward anti-hyperlipidemia properties [5][9]. It also has positive effects on hyperlipidemia, osteoporosis, and a number of reactive oxygen species that can lead to oxidative stress and fundamental cell damage in the body.

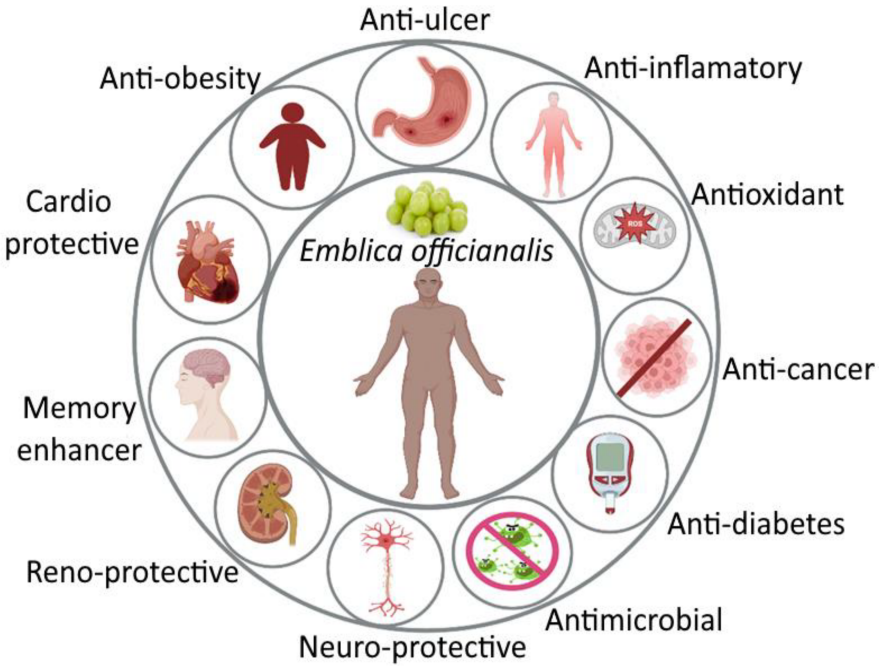

Figure 1. Different pharmaceutical activities of *E. officinalis*.

Large quantities of polyphenols, tannins, and other phytochemicals found in *E. officinalis* can lessen oxidative damage to cells. The natural antioxidants of *E. officinalis* play a significant role in the activity of free radical scavengers, and methanolic seed extract and pulp extract of *E. officinalis* show promising 1,1, diphenyl-2-picryl-hydrazil (DPPH) free radical scavenging activity in a concentration-dependent manner [10][11]. There is strong considerable potential for ferric reduction, free radical scavenging, and ROS (reactive oxygen species) inhibition in the water extract of *E. officinalis* fruit [12].

Different solvent systems were used to test *E. officinalis*' antimicrobial activity, and it was found to have antifungal properties against *Aspergillus* sps. [13]. Fruit ethanolic and acetone extract demonstrated activity against *Candida albicans* and *Fusarium equiseti*. The antibacterial activity against *Staphylococcus* was demonstrated using the zone inhibition method, and the tube dilution method significantly reduced the colony counts of *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Pasteurella multocida* [14][15][16]. The phytochemical in *E. officinalis* called pentagalloyl glucose has anti-influenza properties. WST-1 assay, plaque-forming unit assay, time of-addition assay, and hemagglutination inhibition (HI) assay were used to evaluate a virus replication with a dual mode of action [17].

In Sprague-Dawley rats exposed to both acute and chronic inflammation caused by carrageenan and cotton pellets, the water extract of *E. officinalis* was discovered to exhibit anti-inflammatory effects by minimizing paw volume in the case of acute inflammation and myeloperoxidase activity, granulomatous tissue mass, and plasma extravasation in the case of chronic inflammation [18]. Histopathological studies were used to investigate the hepatoprotective activity of *E. officinalis*. Liver-protective behavior HepG2 cells were used to test the efficacy of *E. officinalis* against tert-butyl hydroperoxide (t-BH)-induced toxicity, and rats were used to test the efficacy of a 50% hydroalcoholic extract of fresh *E. officinalis* fruit against chronic toxicity brought on by carbon tetrachloride and thioacetamide. Nephroprotective properties reduced the elevated levels of thiobarbituric acid-reactive substance in the serum, renal homogenate, and creatinine and urea nitrogen in aged rats [19][20]. The forced swim test (FST) and tail suspension test (TST) with Swiss albino mice were used to test the aqueous extract of fruits from *E. officinalis* for its antidepressant activity. The results revealed a significant decrease in depression. The result was that aged mice with improved memory (elevated plus maze and passive avoidance apparatus) had lower total serum cholesterol levels and higher brain cholinesterase activity [21]. In albino rats, *E. officinalis* was found to have immunomodulatory activity as evidenced by increases in hemagglutination antibody titer, macrophage migration index, hypersensitivity reaction, respiratory burst activity of the peritoneal macrophages, total leukocyte count, percentage lymphocyte distribution, serum globulin, and relative lymphoid organ weight. It is also able to stimulate humoral and cell mediated immunity as well as macrophage phagocyte [22]. On type II diabetes, triglycerides (TG), and the liver-specific enzyme alanine transaminase, the aqueous fruit extract of *E. officinalis* was assessed (ALT). According to this research, alloxan-induced diabetic rats could significantly lower their blood glucose levels when given an aqueous fruit extract dose of 200 mg/kg body weight [23]. Compared to control and extract-treated diabetic rats, oral administration of the aqueous extract (350 mg/kg body weight) significantly decreased serum glucose levels, glycosylated hemoglobin, insulin, cholesterol, triglycerides, HDL-cholesterol, protein, urea, and creatinine [24].

E. officinalis has the potential to lower cholesterol because it naturally contains flavonoids and other phytochemicals. Several clinical studies showed significant drops in C-reaction protein (CRP), low-density lipoprotein, and total cholesterol [25]. Variya et al. [26] assessed the hypolipidemic effect of *E. officinalis* and compared it to the standard simvastatin in patients with type-II hyperlipidemia. Treatment with *E. officinalis* resulted in significantly lower levels of total cholesterol, LDL cholesterol, and triglycerides as well as noticeably higher levels of the common medication simvastatin [27].

Polyphenols from *E. officinalis* have also been shown to protect gastrointestinal organs. Because *Helicobacter pylori* is a pathogen, one of the potential effects of amla's bioactive compounds is the competitive inhibitor of clarithromycin-resistant strains in vitro [28]. Studies using animals reported relevant results as well. In order to induce gastrointestinal ulcers in mice, Al-Rehaily et al. [29] used a variety of techniques, including ligating the pylorus, administering indomethacin and necrotizing agents (25% NaCl, 0.2 M NaOH, and 80% ethanol), and inducing hypothermia. These techniques included studying the antisecretory and antiulcer activities of *E. officinalis* extract. Using the pylorus-ligated and necrotizing agent-intoxicated ulcer methods, both doses (250 and 500 mg/kg) decreased gastric secretion, intraluminal bleeding, ulcer index, and gastric lesions. Only the animals receiving treatment with 500 mg/kg for the indomethacin-induced ulcer method had a significantly lower ulcer index than animals in the control group (treated only with indomethacin).

3. Antihyperlipidemic Activity of Emblica officinalis

According to reports, *E. officinalis* fruit has significant anti-hyperlipidemic, hypolipidemic, and antiatherogenic effects [30]. In patients with type II hyperlipidemia, treatment with *E. officinalis* resulted in a significantly lower level of total cholesterol (TC), low-density lipoprotein (LDL), triglyceride (TG), and very-low-density lipoprotein (VLDL), as well as a significantly higher level of high-density lipoprotein (HDL) (**Figure 2**). Studies conducted in vitro and in vivo using cholesterol-fed rats and Cu^{2+}-induced LDL-oxidation established the anti-hyperlipidemic activity of extract from *E. officinalis* and demonstrated a significant reduction in total and free cholesterol levels in a dose-dependent manner [31]. Given that oxidized LDL is a key enzyme in atherosclerosis, administration of *E. officinalis*' potential antioxidant property resulted in a decrease in oxidized LDL levels in cholesterol-fed subjects, as shown in **Figure 2** [32].

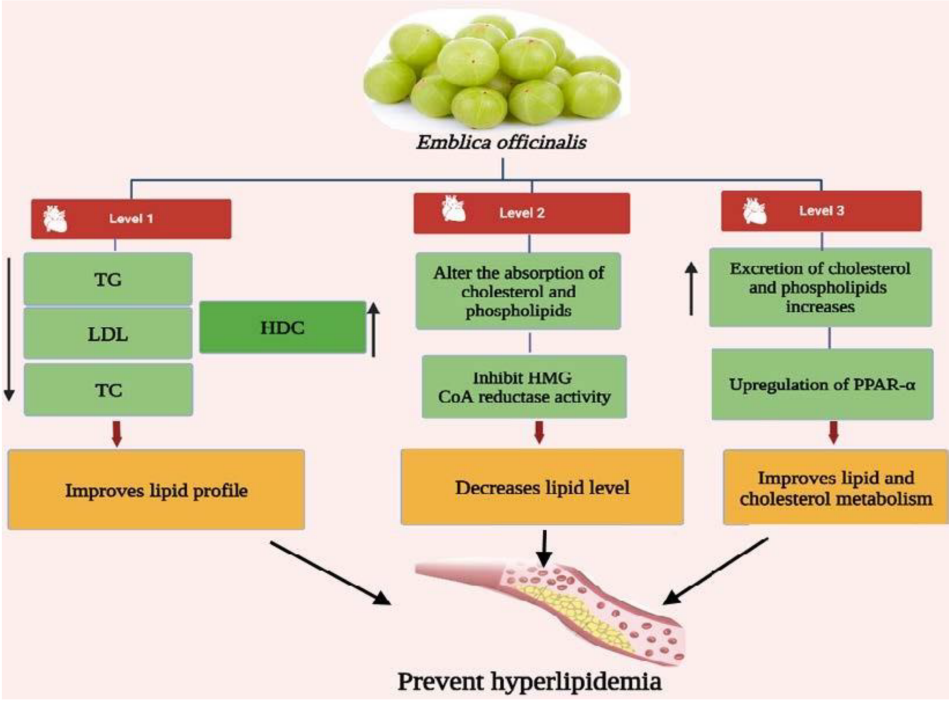

Figure 2. Anti-hyperlipidemia activity of amla bioactive compounds. **Figure 2** is adapted from Gul et al. [32] (Copyright © 2022 by authors), which is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license. TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; PPAR-α, peroxisome proliferator-activated receptors-α.

Another study revealed elevated lecithin-cholesterol acyltransferase and hepatic 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibition as anti-hyperlipidemic effects (LCAT). Flavonoids, which prevent the synthesis and deterioration of lipids, are responsible for this effect [33]. Oral administration of *E. officinalis* extracts in a dose of 500 mg twice daily for 12 weeks significantly lowered total cholesterol, LDL cholesterol, and high-sensitive creatine kinase (hr-CRP) levels, according to a study on animals that used class one obese subjects with body weights between 250 and 350 g. *E. officinalis* showed significant antiatherosclerotic action through a decrease in serum and hepatic cholesterol content,

serum triglyceride, phospholipids, and LDL cholesterol in a high-cholesterol-fed rabbit model. Platelet aggregation induced by ADP and collagen was also decreased, and diabeto-cardiac malaise was eventually reduced [25]. Growing fructose consumption in the diet has been linked to a higher risk of obesity and related metabolic syndromes in Western countries. Increased intake of fructose alters several signaling cascades, including NF-, TNF-, JNK-1, PTP-1B, PTEN, LXR, FXR, and SREBP-1c [34]. The SREBP-1 expression, total cholesterol, TG level, and metabolic issues associated with high fructose levels are all improved by the supplement's high polyphenol content from *E. officinalis*. According to reports, *E. officinalis* inhibits the level of MDA in the liver and controls the expression of the COX-2, bax, NF-, and bcl-2 markers [35]. Previous findings have shown that *E. officinalis* therapies increase lipid metabolism and regulate the expression of proteins such as PPAR-α, which is involved in fatty acid-oxidation, FXR, and LXR involved in lipid metabolism, as well as insulin-induced gene-2 to reduce fructose-induced metabolic syndrome and prevent the maturation of steroyl CoA desaturase-1 and SREBP-1, which are involved in the synthesis of TG. Additionally, RAW 264.7 cell lines' expression of CD36 scavenger receptor was markedly reduced to prevent foam cell formation by these mechanisms [36]. The major contributors to *E. officinali's* antihyperlipidemic activity are its polyphenols and functional products. Gallic acid, Vitamin C, Emblicanin A and B, apigenin, ellagic acid, and 3-hydroxy-3-methylglutaryl-CoA myricitine, among other antioxidants, polyphenols, and phenolic acids, play a significant role in lowering hyperlipidemia [37][38][39][40]. As these molecules are less stable with different environmental conditions or pH and less soluble in water, they are reported to have less bioavailability or poor assimilation of major constituents. This is the main drawback of these polyphenols and functional products [40][41]. Consequently, nanoformulation strategies can increase the bioavailability of phenolic acids and functional products.

4. Nanoparticulate Carrier System for the Treatment of Hyperlipidemia

Nanotechnology is one of the emerging technologies that influence human life in different approaches that assist in overcoming the multiple limitations of various diseases, especially hyperlipidemia. Nanoformulations have become a novel profitable approach for increasing the bioavailability of poor soluble drugs [37][42]. These nanoformulations have several unique qualities that make them more valuable for the drug delivery system. Diverse nanostructures include solid lipid nanoparticles (SLNs), nanoliposomes, phytosomes, noisome polymer nanoparticles, nanomicelles, and carbon nanotubes, which are used in drug delivery systems, significantly increase the effectiveness, and improve the pharmacokinetics of drugs with reduced side effects [43]. Many reports revealed that several nanoformulations from a number of natural products, such as emblicanin-A and emblicanin-B, quercetin, curcumin, piperine, nigella, etc., have become a promising technology for the use of nanoformulation from natural products, as shown in **Figure 3** [41][44].

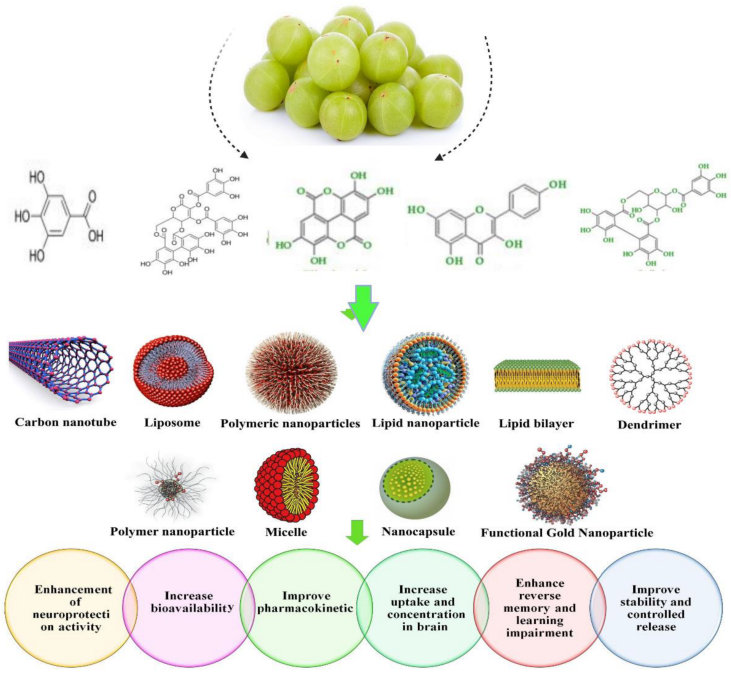

Figure 3. Nanoformulations from natural products and their advantages at a target delivery site. **Figure 3** is adapted from Moradi et al. [44] (Copyright © 2020 by authors), which is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

5. Nanoformulation of Emblica officinalis and Its Applications

Nanomedicine has developed into a successful platform that incorporates various modalities, including therapeutics and diagnostics. It might provide individualized medical treatment to manage fatal illnesses such as cancer and diabetes. Indeed, nanocarriers act as precise delivery mechanisms for desired phytochemicals to the target site and are biocompatible, biodegradable, and less toxic. The site-specific, controlled, slow, and sustained delivery of phyto-based drugs by nanoparticles (NPs) with exceptional entrapment efficiency may enhance both their pharmacokinetics and bioavailability, while also increasing membrane permeability and preventing drug efflux through gastrointestinal mucosa [44]. Recently, there has been an increase in interest in using nanotechnology to boost phytochemical effectiveness. In the healthcare industry, the advent of nanotechnology in medical therapeutic strategies has raised hopes for the delivery of better treatments with greater efficacy and precision [45][46][47]. Nanoformulation of *E. offficinalis* is the major research area of interest due to its synergistic and improved bioavailability efficacy. The study by Omran et al. [48] focused on the synthesis of nanoemulgel by adding Carbopol 940 along with *E. officinalis* and other extracts to improve the synergistic efficacy of the extract for their antimicrobial property. Silver nanoformulation amla were studied for their antiproliferative and cytotoxic activity by Rosario et al. [49] and Abitha et al. [50]. Biosynthesis of nanocomposites using silver and graphene oxide and *E. officinalis* were characterized and studied for their antibacterial and cytotoxicity activities [51]. A recent study by Ranjani et al. [52] shows the significant cytotoxicity and antibacterial activity of amla-mediated graphene oxide and silver nanocomposites against oral pathogens. Another survey by Naik et al. [53] exhibits the anticancer and antidiabetic activity of phytofabricated silver and zinc-oxide conjugated *E. officinalis*. Considering its eco-friendly and safe aspects, the study recommends its use for pharmaceutical applications. In addition, green synthesized amla with magnesium oxide exhibited photocatalysis activity (Evans blue degradation) and antibacterial activity, thereby confirming amla's efficacy in the removal of water contaminants.

In contrast, phytoconstituents of *E. officinalis* such as ellagic acid, gallic acid, quercetine, and chebulagic acid were nanoformulated for the amelioration of oral bioavailability and biocompatibility properties. Harakeh et al. [54] studied the antidiabetic property of novel nanoformulated ellagic acid. Another study conducted by Hosny et al. [55] developed the sustained release of ellagic acid nanotransferosomes for its antiproliferative activity. The amla fruit's active ingredient, gallic acid, is abundant naturally and has a variety of health benefits that makes it appealing for use in clinical settings. To increase amla's aqueous solubility and subsequently bioactivity, gallic acid was extracted and separated from it. Using a probe sonicator and a high-pressure homogenization method, glyceryl monooleate (GMO), chitosan, and poloxamer 407 were combined to create gallic acid nanoparticles. According to the study's findings, nanoparticles can be designed and manufactured to facilitate the extraction, manufacture, and sustained release of gallic acid, particularly in the colonic region [56]. Dendrimer nanodevices coated with gallic acid were developed to fight against chemoresistance in neuroblastoma cells [57]. Gallic acid and quercetine nanopolymers were synthesized to improve its bioavailability. Ongoing studies have concentrated on the pharmacological properties of gallic acid and its derivatives, as well as their biological effects on skin, with a particular focus on their use in (nano-)cosmetic formulations. Because the field of study is still developing, emphasis has been given to its advantages of various nanoformulations [58]. *E. officinalis* (leaves, stem, root, fruit, seeds) and its active compounds nanoformulation and delivery system are shown in **Figure 4**.

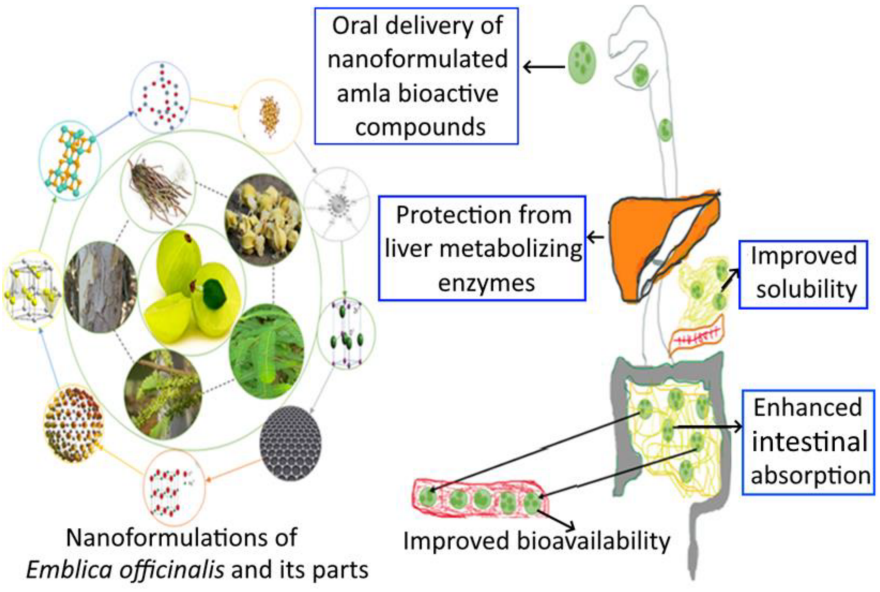

Figure 4. Nanoformulations of amla and its health benefits.

6. Health Care Application for Emblicanin-A and Emblicanin-B Nanoformulation

The fruit stands out from the competition due to its natural composition, which is thought to help the body fight off various illnesses and strengthen the immune system. With adequate amounts of fiber, carbohydrates, and iron, this is the best source of vitamin C. The herb *E. officinalis* is a powerful antioxidant. The fruit contains Emblicanin-A and Emblicanin-B, two hydrolyzable tannins. Ellagic acid (EA), gallic acid (GA), glucose, and EA glucose are produced during the hydrolysis of emblicanin-A and emblicanin-B [59].

The creation of a nanosized formulation has as its goal the achievement of high therapeutic efficacy with minimal toxicity. As it has better efficacy and fewer side effects, herbal medicine has long been accepted as a form of treatment by doctors for their patients. The scientific method for sustained drug delivery to the target site helps avoid repeated dosing and causes less harm to the other healthy cells or tissues. For herbal constituents, novel drug delivery systems reduce the need for repeated administration. The development of formulations with the aid of nanotechnology is one potential application. The development of herbal constituent nanoformulations relies heavily on nanocarriers [60]. The involved EA microdispersion was prepared to improve the EA's poor water solubility and low bioavailability. The content improved nearly 30 times the water solubility and 22% (*w*/*w*) drug loading by using only water and low methoxylated pectin as a food-compatible excipient (DL). Later, non-PAMAM was used. Researchers were successful in creating two EA nanodispersions using hydrophilic and amphiphilic (polyamidoamine) dendrimers as nanocontainers, obtaining water-solubility 300–1000 times at (60–70 nm) with 46 and 53% (*w*/*w*) DL higher than the free EA's. Suitable for food and biomedical applications, this bioactive compound is a very effective antioxidant that is also nontoxic [61].

GA's nanoformulation was fabricated and measured. The GA units for peripheral esterification and a delivery system that is GA-enriched (GAD) with exceptional antioxidant capacity and significant potential were successful in preventing diseases from oxidative stress (OS). GA is highly efficient against the illness that OS causes [47]. It has very few clinical applications due to inadequate gastrointestinal absorption and pharmacokinetic drawbacks, fast metabolism, and strong backs. The ready dendrimer made of polyester GA has been manufactured with an absorbable carrier to protect and deliver it. The stability in solution with a tendency to form was indicated by a ZP of 25 mV low polydispersity index and megamers. It has been on display to demonstrate GAD has four times more intrinsic antioxidant power than the GA [62].

Ellagic acid-nanosponges (EA-NS) utilized cyclodextrin and cross-linked by dimethyl carbonate is a nanoformulation that improved the solubilization efficiency of EA and controlled its release to achieve better oral absorption bioavailability. The polyphenolic compound EA, which is naturally present in many fruits, has demonstrated antioxidant, anticancer, and antimutagenic properties; however, its disadvantage is that it has a low oral bioavailability by creating a nanoformulation [62]. The use of natural product-based nanoformulations in treating various metabolic syndromes has grown in popularity among researchers. The compounds' solubility, bioavailability, and efficacy were all improved through nanosizing. The effectiveness of a number of natural constituent nanoformulations in the treatment of numerous diseases has been observed. The molecular targets were pertinent to the way these compounds affect metabolic disorders. The natural bioactive substances emblicanin-A and emblicanin-B have high therapeutic potential and can be incorporated into systems for treating various diseases using nanotechnology [63].

The primary use of lipid-lowering medications such as statins and/or derivatives of fibric acid has been to treat elevated lipid levels and the negative effects that go along with them. It is likely that the modern medical system works to treat disease on the one hand while having negative side effects on the other [64]. The creation of lipid-lowering medications or formulations derived from natural sources has become more significant in recent years. As a result, there has been a lot of interest in using natural products with minimal side effects; *E. officinalis* is one such ingredient thought to have medicinal benefits. Recent research on nanoformulated gallic acid in in vitro models shows great lipid lowering activities [64]. Ellagic acid and 3-hydroxy-3-methylglutaryl-CoA nanoemulsion attenuates fat in in vivo models investigated by Harakeh et al. [65], and Dayar and Pechanova [66]. Because of its multimode cardio protective properties, *E. officinalis* has recently attracted new attention. It is also a powerful antioxidant that has been shown to affect how lipid metabolism is regulated.

7. Adversity and Toxicity of Nanoformulations

In recent years, the use of nanotechnology in medicine has significantly increased. When long-term or ongoing treatment is necessary for the management of metabolic diseases compliance has been regarded as a crucial factor. By providing a variety of administration methods, controlling release, enhancing biological stability, achieving target specificity, and reducing toxicity, nanoformulations have been found to increase patient compliance [67]. Accordingly, interest in creating nanoformulations to treat metabolic diseases has been dramatically increasing. Nevertheless, the majority of these

studies have been limited by a lack of long-term exploratory statistics and insufficient data, particularly when it comes to the sustained resilience profiling, long-term therapeutic efficacy, and toxicological properties of the developed nanoformulations of plant-derived molecules to treat metabolic disorders. As a result, the majority of the findings are limited to the laboratory scale. Therefore, finding a solution to this problem requires considerable attention [68][69]. The toxicity evaluation of nanoscale materials and with their multiple delivery methods for active principles and nutritional supplements is of utmost priority. The use of novel functional materials could be accompanied by a number of safety concerns and require the implementation of speculative practices that consider human health and safety [70].

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