Super Fruit Amla (*Emblica officinalis*, Gaertn) in Diabetes Management and Ensuing Complications: A Concise Review

Muhammed Majeed 1,2, Narayanan K. Narayanan 2, Lakshmi Mundkur 1, Priji Prakasan 1 and Kalyanam Nagabhushanam 2,*

1 Sami-Sabinsa Group Limited, 19/1&19/2, I Main, II Phase, Peenya Industrial Area, Bengaluru 560058, Karnataka, India; mail1@sami-sabinsagroup.com (M.M.); lakshmi@sami-sabinsagroup.com (L.M.); priji@sami-sabinsagroup.com (P.P.)

2 Sabinsa Corporation, 20 Lake Drive, East Windsor, NJ 08520, USA; narayanan@sabinsa.com

* Correspondence: kalyanam@sabinsa.com; Tel.: +1-(732)-777-1111

Abstract: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease showing an exponential increase in its prevalence all over the world. High blood glucose level is one of the main clinical signs of the disease. Although several classes of drugs are available for treatment, their prolonged use and adverse effects behoove the use of alternative medicine. Plant-derived natural products have multifaceted beneficial roles in human pathophysiology. Plant metabolites like tannins, organic acids, polyphenols, terpenes, and flavonoids show multiple mechanisms of action against diabetes. The fruits of *Emblica officinalis* (EOF), also known as Indian gooseberry (amla), contain several phytochemicals, potentially having anti-diabetic activity. Hydrolyzable tannins are the major bioactive components of the amla fruit, the most abundant hydrolyzable tannin being β-glucogallin. The present review summarizes the mechanism of action and clinical evidence for the beneficial effects of EOF on T2DM and its associated complications.

Keywords: diabetes mellitus; *Emblica officinalis*; amla; β-glucogallin; hydrolyzable tannins; diabetic complications

1. Introduction

Diabetes is a chronic metabolic disease affecting millions of people all over the world. Type 2 diabetes mellitus (T2DM) is considered one of the fastest-growing global health emergencies of the 21st century [1]. According to the 2021 International Diabetes Federation, 537 million (10.5%) adults aged between 20 and 79 years have T2DM worldwide, and this is expected to increase to 643 million by 2030 and 783 million by 2045 [2]. In the USA, the age-adjusted death rates directly attributable to T2DM increased by 14.8% from 2019 to 2020 [3]. More than 80% of diabetic cases (three in four adults with diabetes) reside in low- and middle-income countries. Interestingly, diabetes is reported as one of the world’s oldest diseases, as it is described in several historical records of ancient civilizations found in Egypt, Persia, and India, and is considered a major epidemic of this century [4,5].

T2DM is characterized by high blood glucose levels due to insulin resistance or insulin inadequacy. Generally, insulin production is impaired due to obesity, diet, sedentary life, and aging, resulting in hyperglycemia. Persistent hyperglycemia generates excess reactive oxygen species (ROS) and mitochondrial dysfunction in various tissues [6]. It remains undiagnosed in its early stages, while chronic hyperglycemia may lead to several associated complications leading to increased morbidity and reduced life expectancy for an individual [7].


Usually, diabetic treatment involves the use of hypoglycemic drugs, many of them associated with side effects such as anorexia, nausea, dyspeptic episodes, and diarrhea [8].

As diabetes is a global burden, its management consumes a significant share of the world economy. There exists a persistent demand to explore alternative natural remedies with efficacy, limited side effects, and relatively low-cost intervention. Phytoconstituents from food sources with multiple health benefits and reduced toxicity may be the prospective candidates for T2DM intervention [9,10].

The fruits of *Emblica officinalis* (EOF), also known as Indian gooseberry in English and amla or amalaki in most Indian languages, is an important medicinal plant in the traditional Indian systems of medicine Ayurveda, Siddha, and Unani; homeopathy; and Sri Lankan, Tibetan, and Chinese medicine [11,12]. They have myriad medicinal benefits and are traditionally used for the treatment of various chronic diseases, like cerebral and intestinal ailments, diabetes mellitus, coronary heart diseases, and cancers [12]. They are considered a potent rejuvenator and immunomodulator with beneficial effects on digestion, cough, asthma, heart diseases, hair growth, eye health, and overall body and intellect [13]. Several studies have reported their application in the management of diabetes, dyslipidemia, obesity, cancer, liver disorders, arthritis, gingivitis, and wound healing [14,15].

Numerous bioactive phytochemicals present in the EOF, including polyphenols like tannins, gallic acid, ellagic acid, amino acids, vitamins, minerals, fixed oils, and flavonoids, have been reported to play a major role in the management of diabetes and related metabolic complications [16]. The bioactive polyphenols of EOF, especially tannins and flavonoids, appear to play a key role in the management of diabetes, particularly in the restoration of glucose and insulin levels [14,17,18]. In this mini-review, for the first-time, we have highlighted the hydrolyzable tannins, the major bioactive components of the Amla fruit, and the most abundant hydrolyzable tannin—β-glucogallin—and we endeavored to outline the beneficial effects of EOF on T2DM and its associated complications with an emphasis on the mechanism of action.

3. Pathophysiology of Diabetes and Drugs Used for Treatment

The etiology of diabetes is complex including genetic, environmental and metabolic predispositions. However, a sedentary lifestyle, unhealthy diet, age, obesity, and family history are strongly associated with the development of diabetes (Figure 1). Epidemiological evidence suggests that T2DM can be prevented or controlled by improving the status of some modifiable risk factors, such as obesity, physical activity, and diet.

![Figure 1. The major risk factors of type 2 diabetes.](image-url)
T2DM is also known as non-insulin-dependent diabetes mellitus (NIDDM), which constitutes most diabetes cases. Insulin plays an important role in glucose homeostasis. Generally, high insulin promotes glucose uptake, glycolysis, as well as the uptake and synthesis of amino acids, proteins, and fats. Low insulin level is associated with gluconeogenesis, glycogenolysis, lipolysis, and free fatty acid (FFA) liberation and proteolysis. Diabetes is caused by the imbalance between insulin function and insulin secretion, which eventually leads to abnormally high glucose levels in the blood and consequent complications [19]. It is characterized by β-cell inefficiency coupled with peripheral insulin resistance. In the early stages of disease development, due to insulin resistance, blood sugar level remains high even in the presence of high blood insulin levels, and the peripheral tissues like muscle, liver, and adipose tissue fail to respond to persisting hyperinsulinemia. Reduced insulin sensitivity induces a compensatory increase in the β-cell function to produce more insulin to maintain normoglycemia. However, gradually, β-cells fail to compensate for the reduced insulin sensitivity which leads to degeneration. Accumulation of glycogen and sorbitol within the β-cell due to sustained hyperglycemia and nonenzymatic glycation of β-cell proteins are attributed to dysfunction [20].

Pharmacological agents used in diabetes treatment act through different mechanisms and may be synergistic in their activity. Most of the oral antihyperglycemic drugs used for diabetic treatment either enhance the pancreatic insulin secretion (sulfonylureas such as glyburide, glipizide, glimepiride, and meglitinide) or reduce the insulin resistance of peripheral tissues (thiazolidinediones such as pioglitazone and rosiglitazone) [21,22]. Biguanides like metformin reduce hepatic glucose production via gluconeogenesis and glycogenolysis. Biguanides also lower lipid levels and may also decrease gastrointestinal nutrient absorption and increase beta cell sensitivity to circulating glucose [23]. Some drugs regulate incretins, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino-tropic polypeptide/gastric inhibitory peptide (GIP), which act on both β- and α-cells to enhance insulin production and suppress glucagon secretion, respectively. GLP-1 receptor agonists (GLP-1 RAs) (exenatide, an incretin hormone), lixisenatide, liraglutide, dulaglutide, albiglutide, and semaglutide) bind and activate the GLP-1 receptor, enhancing insulin secretion. The use of GLP-1 RAs is a well-established approach in the treatment of T2DM [24].

Dipeptidyl peptidase-4 (DPP-4) degrades the incretin hormones, mainly GLP-1 and GIP. DPP-4 inhibitors increase the levels of both GLP-1 and GIP, which in turn increase β-cell insulin secretion in the pancreas and decrease glucagon secretion, respectively, thereby maintaining glucose homeostasis by reducing postprandial and fasting hyperglycemia. DPP-4 inhibitors (e.g., alogliptin, linagliptin, saxagliptin, sitagliptin) are a class of oral antihyperglycemic FDA-approved medications used for the management of T2DM [25].

Inhibitors of the sodium-glucose cotransporter-2, SGLT2 (e.g., canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. SGLT2 inhibitors act on the SGLT-2 proteins expressed in the renal proximal convoluted tubules reducing the renal reabsorption of glucose while increasing urinary glucose excretion [26,27].

Some other medications act on the central nervous system and reduce food intake and body weight. Dopamine agonists like bromocriptine reduce glycohemoglobin via an unknown mechanism [28]. Although current anti-diabetic drugs provide improved glycemic control, adverse effects are also reported [21,29] (Figure 2).
Figure 2. Pathophysiology and therapeutics of T2DM. (AGEs: advanced glycation end products; AGIs: α-glucosidase inhibitors; DPP4: dipeptidyl peptidase-4; FFA: free fatty acid; IR: insulin resistance; SGLT2: sodium–glucose cotransporter-2; TZDs: thiazolidinediones).

4. Major Phytochemicals (Bioactive Components) in EOF

*E. officinalis* fruit has been extensively studied for its chemical constituents [10,12,16,17,30]. EOF accumulates around 28% of the total tannins present in the whole plant. Hydrolyzable tannins are the major bioactive components of the EOF and the most abundant hydrolyzable tannin is β-glucogallin (Figure 3A) [31,32]. The other important bioactives reported in EOF include galloyl glucoses, gallic acids and its esters, mucic acid and their gallates, gallloylated mucic acid lactones, various acids, flavonols and related compounds, and other tannins [18,33–38] (Figure 3A–C). Furthermore, some earlier studies claimed that the fruits of *E. officinalis* contain two more hydrolyzable tannins, emblicanin A and emblicanin B [39]. However, subsequent independent studies were not able to confirm the structures, and it is likely that, either they are not present, or they are artifacts [31,32,37]. Similarly, few early investigations claimed the extensive presence of vitamin C in amla fruits, but they were later proven to be erroneous [31,39]. In addition, amla fruit extracts contain copious amounts of mucic acid gallates (2), representative of hydrolyzable tannins, which strongly resemble vitamin C (3) in their structural characteristics [31,32]. However, the standardized aqueous extract of EOF was found to contain good amounts of β-glucogallin, which was proven beyond doubt by spectral means [31]. EOF contains considerable amounts of amino acids (glutamic acid, proline, aspartic acid, alanine, cysteine, lysine) and minerals (chromium, zinc and copper) [40] which augment EOF’s nutritive value.

Although EOF is reported for its anti-diabetic activity, the biological properties of extracts may differ based on the extraction methods and the biomarkers standardized in the final product [41,42].
Figure 3. Cont.
Figure 3. Cont.
Figure 3. Bioactive components of EOF: (A) Galloyl glucoses, gallic acid and esters, mucic acid and gallates. (B) Mucic acid lactone gallates and acids. (C) Flavonols and related, and condensed tannins.
5. Anti-Diabetic Activities of *E. officinalis*: Mechanism of Anti-Diabetic Action

*E. officinalis* is an important traditionally used medicinal plant well-known for its anti-diabetic activities. At present, increasing shreds of evidence show that EOF can alleviate the symptoms of diabetes with obvious hypoglycemic and hypolipidemic effects. Moreover, EOF is efficacious in managing the course of diabetic complications that are mostly unresponsive to anti-diabetic drugs [14,42,43]. The anti-diabetic activities of EOF appear to be achieved by multidirectional mechanisms including antioxidant activities, inhibition of poly(ADP-ribose) polymerase/ poly(ADP-ribose) glycohydrolase (PARP/PARG) activation, inhibition of carbohydrate-metabolizing enzymes, regulation of glucose homeostasis, alleviation of mitochondrial dysfunction, inhibition of polyol pathway, inhibition of advanced glycation end products (AGES) formation, and regeneration and rejuvenation of β-cells.

5.1. Antioxidant Activities of EOF

Several studies have shown that EOF exerts anti-diabetic activity via its free-radical-scavenging and antioxidant activities. Diabetes is characterized by the augmented generation of free radicals and diminished antioxidant capacity leading to oxidative stress [44]. The elevated level of blood glucose induces the reduction of molecular oxygen to superoxide and hydroxyl free radicals that are capable of damaging cellular molecules, DNA, proteins, and lipids, leading to altered cellular functions. Oxidative stress decreases the levels of insulin mRNA and cellular apoptosis, resulting in β-cell dysfunction and insulin resistance, which may be responsible for the genesis of later complications of diabetes like renal failure, retinopathy, neuropathy, hepatopathy, and heart disease [45]. Several in vitro cell-free assays have shown that *E. officinalis* is a potent free radical scavenger and efficient antioxidant suggesting that EOF may be beneficial for the management of diabetes [46,47]. The cellular damage induced by glucose at the pathological concentration (50 mM) was studied in red blood cells (RBCs) preincubated with different concentrations of EOF extract. The study highlighted that EOF effectively protected the RBCs from oxidative damage by decreasing the malondialdehyde (MDA) levels in RBC and increasing glutathione (GSH) [48].

β-glucogallin has many phytopharmaceutical activities, mainly due to its antioxidant properties. β-glucogallin has been reported to upregulate antioxidant enzymes such as GSH, catalase, and SOD. Its free-radical-scavenging property was shown to offer protection in several diseases including diabetes [49]. β-glucogallin is a potent and selective inhibitor of the enzyme aldose reductase, which is responsible for developing oxidative stress and secondary complications in diabetes. Inhibitory efficacy of β-glucogallin was demonstrated in vitro and in lens tissues in an ex vivo model [50].

β-glucogallin, a gallotannin present in EOF, has been shown to exert a protective effect against arsenic-induced oxidative stress in RAW 264.7 macrophage cells without side effects in vitro [51]. The aqueous extract of amla fruits invariably contains β-glucogallin, and this extract improved the oxidative parameters MDA and GSH as well as PPBS in the T2DM rats [44]. Similar effects were also observed in in vivo studies. Supplementation of EOF powder (2.5% w/w) significantly reduced the levels of various oxidative stress indicators, such as MDA, nitric oxide (NO), and advanced protein oxidation product (APOP) in plasma, heart, and kidney tissues in 2K1C rats [52]. Similarly, supplementation of EOF extract at a dosage of 20 or 40 mg/kg of body weight/day significantly reduced oxidative stress indices, such as AGES, creatinine, and thiobarbituric-acid-reactive substance levels in the serum of streptozotocin (STZ)-induced diabetic rats. Additionally, EOF significantly improved the serum adiponectin levels in diabetic rats [53].

Oxidative stress associated with T2DM can impair platelet function [54]. In a randomized open-label crossover study with T2DM patients (n = 10), administration of *E. officinalis* (500 mg containing 160.4 mg of low molecular weight hydrolyzable tannins) twice daily for 10 days produced a significant reduction in platelet aggregation. The results show that *E. officinalis* may be responsible in producing antiplatelet action by reducing oxidative-
stress-induced aggregation in diabetic patients [55]. All these results scientifically support the efficacy of EOF extract in reducing oxidative stress and improving overall glucose metabolism.

5.2. Inhibition of PARP/PARG Activation by EOF

ROS-induced DNA damage triggers a cascade of cellular events leading to cell death via the activation of the nuclear enzyme poly (ADP-ribose) polymerase (PARP). PARP activation represents a key pathway involved in β-cell injury and pathophysiological conditions associated with diabetes. Hence, PARP inhibitors are considered a future option in the clinical management of diabetes and its complications [56]. Gallotannin, an important component of hydrolyzable tannins in EOF, prevents PARP cleavage and thereby plays a significant role in cell death signaling, a hallmark for apoptotic cell death, and could be used to ameliorate the development of diabetic complications [57]. However, some studies have shown that PARP inhibitors may have undesirable metabolic side effects as they increase mutation rates and cancer risk and hinder DNA repair. Hence, inhibition of poly (ADP-ribose) glycohydrolase (PARG) is considered an effective mechanism for suppressing the obstruction of DNA repair [58]. Chandak et al. showed that inhibition of PARG instead of PARP by gallotannins could be an alternative approach for reducing insulin-dependent diabetic complications in STZ-induced diabetic mice [59]. Another study showed that two mono-galloyl glucose derivatives (3-galloyl-glucose and 3-galloyl-O-methyl-glucose) present in EOF inhibit PARG activation, with activities similar to that of ADP-(hydroxymethyl) pyrrolidinediol, a very potent standard inhibitor of PARG [60].

5.3. EOF Regulates Carbohydrate Metabolizing Enzymes

Inhibition of carbohydrate-digesting enzymes like α-amylase and α-glucosidase enzymes is used as a therapeutic measure in diabetic patients to slow down the digestion of dietary carbohydrates into glucose and subsequent absorption in the gut [61]. An in vitro study showed that the methanol extract of *E. officinalis* exhibited anti-diabetic activity by reducing α-amylase, α-glucosidase, and antiglycation activity [62]. Similarly, Majeed et al. showed that standardized EOF extract inhibited the activities of α-amylase from porcine pancreas and human saliva in a concentration-dependent manner with IC₅₀ values of 135.7 µg/mL and 106.7 µg/mL, respectively [63]. In addition, it also inhibited the enzyme activities of α-glucosidase (IC₅₀ = 562.9 µg/mL) and DPP-4 (IC₅₀ = 3770 µg/mL). Recently, ethyl acetate extract of *E. officinalis* also has been found to have inhibitory effects on α-amylase and α-glucosidase in vitro [63].

5.4. EOF Improves Glucose Homeostasis

Blood glucose level modulates several biochemical pathways involved in the functioning of various tissues and the secretion of hormones. Preclinical studies have shown that consumption of EOF elevates the expression of enzymes involved in glycogenesis and glycolysis while decreasing the enzymes involved in gluconeogenesis. In vitro studies in 3T3L1 adipocytes have shown that EOF increases glucose uptake by adipocytes in a concentration-dependent manner [64]. Similarly, treatment with gallic acid decreased blood glucose, hepatic lipid peroxides, hepatic glycoprotein components, and hepatic lipid levels and increased hepatic glycogen and plasma insulin in STZ-induced diabetic rats. It also increased the level of hepatic hexokinase activity, suggesting that gallic acid may be beneficial to T2DM patients [65,66]. Furthermore, administration of EOF or its polyphenol-rich fraction was associated with increased levels of adiponectin, a key hormone produced by adipocytes with insulin-sensitizing, anti-inflammatory, and anti-atherogenic properties to lower the risk of T2DM across diverse populations [67].

5.5. Inhibition of Polyol Pathway by EOF

The polyol pathway involves a two-step conversion of glucose to fructose through the production of sorbitol. It is also called the sorbitol-aldose reductase pathway. Acti-
vation of the polyol pathway during chronic hyperglycemia leads to the overproduction of sorbitol causing osmotic stress. The polyol pathway is implicated in diabetic complications such as microvascular damage to the retina, kidney, and nerves, as these tissues lack sorbitol dehydrogenase to metabolize sorbitol. Aldose reductase (AR), an enzyme involved in this pathway oxidizes NADPH to NADP⁺, whereas NADPH is required for glutathione reductase to regenerate GSH in reducing oxidative stress [68]. An increased NADH/NAD⁺ ratio increases diacylglycerol (DAG), an important metabolic regulator, by inhibiting the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) reaction. GAPDH levels play pivotal roles in the overall cellular production of reductants, energy, and carbohydrate metabolites [69]. An increase in DAG level induces various signaling pathways mediated by protein kinase C (PKC) resulting in oxidative stress and vascular complications associated with diabetes. In addition to increased polyol pathway flux and activation of the PKC pathway, increased hexosamine pathway and advanced glycation end product (AGE) formation are also associated with other diabetic complications [70–72] (Figure 4).

**Figure 4.** Diabetes-induced modulation in the metabolism of glucose by the polyol pathway leading to oxidative stress and vascular complications. (Fructose-6-P: fructose-6-phosphate; fructose-1,6-bis-P: fructose-1,6-bisphosphate; glycerol-3-P: glycerol-3-phosphate).

The aqueous extract of EOF is known to inhibit the activity of AR and modulate the polyol pathway. In this context, Suryanarayana et al. found that the hydrolyzable tannins present in EOF limit the conversion of sorbitol to fructose by inhibiting rat lens and recombinant human AR with IC₅₀ values 0.72 and 0.88 mg/mL, respectively [73]. Furthermore, dietary administration of EOF extract in STZ-induced diabetic rats for eight weeks inhibited AR activity, attenuated sorbitol accumulation in the lens, and delayed cataract progression, suggesting its effectiveness in delaying the development of diabetic complications...
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5.6. EOF Alleviates Mitochondrial Dysfunction in Diabetes

Mitochondrial dysregulation may be considered a hallmark of T2DM leading to diabetes-related complications. The metabolic abnormalities, such as decreased mitochondrial content, disturbances in mitochondrial biogenesis, and intracellular accumulation of lipid products, appear to be associated with impaired mitochondrial function and increased production of ROS, leading to decreased insulin sensitivity and energy metabolism. Hence, boosting mitochondrial function may represent a valuable therapeutic tool for improving insulin sensitivity [75]. Yamamoto et al. [76] investigated the effects of EOF on mitochondrial function in C2C12 myotubes, a murine skeletal muscle cell model with abundant mitochondria. The EOF extract treatment enhanced mitochondrial biogenesis and antioxidant systems accompanied by adenosine monophosphate-activated protein kinase (AMPK) and nuclear-factor-erythroid-2-related factor 2 (Nrf2) activation, resulting in improved spare respiratory capacity and increased production of energy [76]. Reddy et al. observed the protective effect of EOF extract (250 mg/kg bw/day) against alcohol-induced (20% alcohol) brain mitochondrial dysfunction in male Wistar rats for 60 days. Administration of EOF to alcohol-treated rats lowered the levels of NO, protein carbonyls, and lipid peroxidation and elevated the activities of the antioxidant enzymes, SDH, NADH dehydrogenase, and cytochrome c oxidase and the content of cytochromes in alcohol-treated rats [77]. Similarly, Khan et al. [51] showed that β-glucogallin (60 µM and 80 µM), a main constituent found in EOF attenuates the arsenic-trioxide-induced mitochondrial superoxide and mitochondrial membrane potential depolarization in RAW 26.7 macrophage cells in a dose-dependent manner in vitro [51].

5.7. E. officinalis Induces the Regeneration and Rejuvenation of Pancreatic β-Cells

T2DM is generally characterized by insulin resistance and reduced production of insulin by pancreatic β-cells. Optimal pancreatic function is essential for the regulation of glucose homeostasis, and its impairment leads to the development of diabetes. Glucolipotoxicity reduces the functional cell mass of pancreatic β-cells and renders them less efficient in insulin production. Glucose intolerance in association with hyperinsulinemia and insulin resistance are early hallmarks of the prediabetic phase. β-cell dysfunction leads to insufficient insulin production, resulting in hyperglycemia [78,79]. Phyllanthus species were found to be involved in the regeneration and rejuvenation of β-cells, thus leading to increased insulin production and secretion [80]. In vitro studies with RINm5F β-cells have shown that gallic acid, an active constituent of EOF in its natural abundance, dose-dependently increased insulin secretion and prevented glucose- and palmitate-induced apoptosis [81]. Furthermore, gallic acid enhanced insulin levels and stimulated the regeneration of β-cells of islets in STZ-induced diabetic rats when supplemented at a dosage of 20 mg/kg bw for 28 consecutive days [82]. Similar effects were also observed in other studies [65,66]. Similarly, EOF treatment significantly increased serum insulin and c-peptide protein by 57% and 31%, respectively, in arsenic-treated mice compared to those treated with arsenic alone [83].

cataracts in rats. In addition, EOF and its tannins also reduced polyol-pathway-induced oxidative stress by altering lipid peroxidation and protein carbonyl content while increasing activities of antioxidant enzyme activities [74]. Most importantly, β-glucogallin was also found to inhibit aldo-keto reductase family 1 member B1 (AKR1B1) belonging to the aldo-keto reductase superfamily and reduced sorbitol accumulation in diabetic eye disease [50]. Based on the results of the above studies, β-glucogallin may be able to inactivate the hexosamine pathway and AGEs formation by attenuating the polyol pathway, thus eliminating other diabetes-induced complications in addition to potentially inhibiting vascular complications.
5.8. EOF Reduces the Formation of AGEs

The AGEs are diverse and highly reactive complexes formed by the non-enzymatic reaction of circulating glucose with amino groups of proteins, lipids, and nucleic acids. The accumulation of AGEs represents a metabolic burden and contributes to the complications of diabetes by raising intracellular oxidative stress. The antiglycation effects of EOF and its phenolic compounds have been demonstrated both in vitro and in vivo. Ellagic acid, a flavonoid present in EOF, prevented glycation-mediated β-sheet formation in Hb and lysozyme in vitro [84]. Administration of EOF and its bioactive compound gallic acid inhibited the formation of receptor for advanced glycation end products (RAGE), MAPK, and NF-κB levels in HFD-fed rats [85]. The elevated serum levels of glycosylated protein, an indicator of oxidative stress, were significantly reduced dose-dependently in the diabetic rats fed with EOF [53].

5.9. "E. officinalis" Modulates Diabetes-Induced Gut Dysbiosis

Gut microbiota is recognized as a major factor involved in the pathophysiology of several metabolic disorders including diabetes. Significant associations between the changes in gut microbiota composition and the development of diabetes are well established [86]. Remarkable changes were observed in the gut microbiota, caecum metabolome, and markers of lipid metabolism in ob/ob mice when treated with EOF extract for two weeks. Treatment with a high dose of EOF (125 mg/kg/day) increased the abundance of Firmicutes belonging to the family Eubacteriaceae without affecting the overall microbial diversity. However, the treatment with low doses (13 mg/kg/day) induced modest changes in the microbiota profile [87]. Similarly, EOF extract reduced the abundance of harmful Bacteroidetes while increasing the abundance of beneficial Firmicutes bacteria in reserpine-induced mice, thus helping to restore balance in the microbiome [88].

5.10. "E. officinalis" Modulates Cellular Energy Pathways

Variya, B.C., et al. [89] compared the anti-diabetic potential of gallic acid and fruit juice of "E. officinalis" using fructose-induced diabetic models, in vitro and in vivo. Gallic acid was found to increase levels of pAkt but not pAMPK in fructose-induced diabetes in rats, indicating gallic-acid-mediated insulin sensitivity through stimulation of Akt phosphorylation rather than AMPK. However, the fruit juice of "E. officinalis" increased the level of pAkt as well as pAMPK, indicating stimulation of dual pathways for insulin-sensitizing activity. Gallic acid treatment increases Glut4 and PPAR-γ protein expression through Akt signaling. Mechanistically, treatment increased the expression of PPAR-γ through activation of C/EBPs and simultaneously increased Glut4 translocation in 3T3-L1 adipocytes. Overall findings reveal that "E. officinalis" containing gallic acid as a food supplement could mediate antidiabetic potential by upregulating pAkt and pAMPK, thus providing potential therapy for diabetes and related disorders [89].

6. Evidence from Clinical Studies

Several animal and clinical studies have consistently shown the preventive and therapeutic effects of EOF on diabetes without causing any adverse side effects (Table 1). In most of the studies, the hypoglycemic effects of EOF were quite comparable to the potential therapeutic drugs used in diabetes treatment. β-glucogallin, one of the main constituents of EOF, has been adjudged to be an antioxidant for managing sugar levels and for helping to support digestion and liver health [90]. For instance, Majeed et al. [42] evaluated the anti-diabetic effect of an aqueous extract of EOF containing 10% β-glucogallin along with hydrolyzable tannins in reducing hyperglycemia and dyslipidemia in newly diagnosed T2DM patients.

In a randomized, open-label, three-arm, comparative multicenter study of newly diagnosed T2DM patients, one group of patients received the extract at a dosage of 1 g day⁻¹, whereas the second group received double the dosage of 2 g day⁻¹ for 90 days. Metformin (500 mg day⁻¹), a first-line drug used for treatment in diabetic patients, was given with
breakfast for 90 days to compare the anti-diabetic effect of EOF extract. The results showed that daily administration of 1 g and 2 g of EOF (Saberry®, Sami-Sabinsa Group Limited, Bengaluru, India) or metformin 500 mg for 90 days significantly decreased fasting blood sugar (FBS), post-prandial blood sugar (PPBS), and hemoglobin A1c (HbA1c) in all three treatment groups. Furthermore, a 2 g dose of EOF extract significantly reduced the FBS level and showed superior anti-diabetic and anti-dyslipidemia activities compared to the pharmaceutical drug metformin as well as EOF extract at a 1 g day\(^{-1}\) dose [42]. In an earlier study, EOF powder was given to diabetes patients and normal subjects orally at dosages of 1, 2, or 3 g day\(^{-1}\) for 21 days. A significant decrease in FBS and PPBS was observed in diabetic patients who took EOF powder as compared to baseline values. The reduction in FBS and PPBS by EOF powder in diabetic patients is comparable to the effect of the positive drug glibenclamide [91]. Similar effects were observed in other studies also (Table 2).

Table 1. Anti-diabetic potential of EOF: evidence from preclinical studies.

<table>
<thead>
<tr>
<th>Experimental Model</th>
<th>EOF Supplement/Dosage and Duration</th>
<th>Study Outcome</th>
<th>References</th>
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<tr>
<td>STZ (200 mg/kg i.p.)-induced diabetic rats</td>
<td>EOF powder: 5, 10, and 15% diet for 21 days</td>
<td>Reduced blood glucose by 21–39% as compared to the basal value.</td>
<td>[92]</td>
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<td>STZ (45 mg/kg)-induced diabetic rats</td>
<td>EOF-Fresh Juice: 5 mL/kg/day and hydroalcoholic extract 100 mg/kg/day</td>
<td>Significantly decreased the serum glucose level and increased the glucose tolerance.</td>
<td>[93]</td>
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<td>Dexamethasone (10 mg/kg, i.p.)-induced insulin resistance in diabetic rat models</td>
<td>EOF extract: 40, 60, and 80 mg/kg doses for 8 days</td>
<td>Showed a significant reduction in blood glucose level similar to Glimepiride (20 mg/kg bw).</td>
<td>[94]</td>
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<tr>
<td>Sucrose (2.5 g/kg body weight) treated Long Evans</td>
<td>EOF extract: 1.25 g/kg</td>
<td>Reduced the percentage of intestinal glucose absorption significantly in a time-dependent manner.</td>
<td>[95]</td>
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<tr>
<td>Beetal goat kids under mild heat stress</td>
<td>EOF extract: 2% of the diet for 90 days</td>
<td>Significantly reduced the blood glucose levels, total cholesterol (TC), and TG levels in the serum as compared to the non-supplemented group.</td>
<td>[96]</td>
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<tr>
<td>STZ (70 mg/kg, i.p.)-induced diabetic Wistar rats</td>
<td>Aqueous EOF extract: 200 and 400 mg/kg for 11 weeks</td>
<td>Significantly reduced blood glucose levels only at the higher dose (400 mg/kg) from week three to the end of the study (week 11). The effect was similar to metformin (600 mg/kg bw).</td>
<td>[43]</td>
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<tr>
<td>Neonatal STZ (90 mg/kg, i.p.)-induced diabetic rats</td>
<td>Methanolic EOF extract: 250 or 500 mg/kg for 28 days</td>
<td>Significantly decreased the fasting blood glucose (FBS) levels and increased serum insulin in a dose- and time-dependent manner comparable to chlorpropamide (5 mg/kg bw).</td>
<td>[97]</td>
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<tr>
<td>STZ (40 mg/kg bw)-induced diabetic Male Albino Wistar rats</td>
<td>Ethanolic EOF extract: 200 mg/kg bw for 45 days</td>
<td>Significantly reduced blood glucose and elevated plasma insulin levels similar to glibenclamide (600 µg/kg bw).</td>
<td>[98]</td>
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<tr>
<td>Alloxan (120 mg/kg)-induced male albino diabetic rats</td>
<td>Aqueous EOF extract: 200 mg/kg</td>
<td>Significantly decreased the blood glucose levels as well as TG in a time-dependent manner comparable to chlorpropamide (120 mg/kg).</td>
<td>[99]</td>
</tr>
<tr>
<td>Glucose-induced Wistar rats</td>
<td>Ethanolic EOF extract: 100 and 200 mg/kg for 14 days</td>
<td>Significantly reduced the blood glucose level similar to metformin (65 mg/kg).</td>
<td>[100]</td>
</tr>
<tr>
<td>Arsenic (3 mg/kg bw/day) induced mice with hyperglycemia</td>
<td>EOF extract: 500 mg/kg for 30 days</td>
<td>EOF balanced blood sugar level and hepatic glucose regulatory enzyme in arsenic-induced hyperglycemic mice. It also increased the serum insulin levels.</td>
<td>[83]</td>
</tr>
</tbody>
</table>
Table 2. Clinical evidence on the anti-diabetic potential of EOF.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>EOF Supplement/Dosage and Duration</th>
<th>Study Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed T2DM patients (n = 94)</td>
<td>Aqueous EOF concentrate containing 10% β-glucogallin and hydrolyzable tannins: 1 or 2 g/day for 90 days</td>
<td>Significantly decreased FBS and PPBS and hemoglobin A1c (HbA1c) dose-dependently comparable to metformin (500 mg) at 1 g dose; superior to metformin at 2 g dose.</td>
<td>[42]</td>
</tr>
<tr>
<td>T2DM patients (n = 10)</td>
<td>EOF Juice: 50 g/day for 3 months</td>
<td>FBS levels were significantly reduced in subjects on metformin (500 mg) + EOF juice better than the metformin treatment alone.</td>
<td>[101]</td>
</tr>
<tr>
<td>T2DM patients (n = 45)</td>
<td>Fresh EOF fruit: Approximately 35 g/day for 60 days.</td>
<td>Reduced the blood sugar values by around 37.9% compared to the baseline level.</td>
<td>[102]</td>
</tr>
<tr>
<td>T2DM subjects (n = 60)</td>
<td>Fresh EOF fruit: Approximately 35 g/day for 6 months.</td>
<td>A significant decrease in FBS, PPBS and HbA1c and a significant increase in HDL were observed in the EOF-supplemented group.</td>
<td>[103]</td>
</tr>
<tr>
<td>T2DM patients (n = 32)</td>
<td>EOF powder: 1, 2, or 3 g/day for 21 days</td>
<td>The reduction in FBS and PPBS by E. officinalis fruit powder in diabetic patients is comparable to the effect of glibenclamide (5 mg).</td>
<td>[91]</td>
</tr>
<tr>
<td>T2DM patients (n = 60)</td>
<td>EOF powder: 10 g/day for 90 days</td>
<td>Significant reduction in the mean FBS, PPBS and HbA1c levels and a significant increase in the mean hemoglobin levels; improved the glycemic and lipidemic profile. These effects were comparable to those of metformin (500 mg) and glimepiride (1 mg).</td>
<td>[104]</td>
</tr>
<tr>
<td>T2DM patients (n = 30)</td>
<td>EOF Extract: 500 mg/day for 4 months</td>
<td>Improved all the lipid parameters; reduced total cholesterol, LDL cholesterol, and triglycerides; and enhanced HDL cholesterol.</td>
<td>[105]</td>
</tr>
<tr>
<td>T2DM patients (n = 30)</td>
<td>EOF Extract: 500 mg/twice daily for 12 weeks</td>
<td>Alleviated endothelial dysfunction by reducing the biomarkers of oxidative stress similar to atorvastatin (10 mg).</td>
<td>[106]</td>
</tr>
</tbody>
</table>

Natural products such as standardized extracts of EOF are an attractive lead as a potential supplement for the management of T2DM with associated dyslipidemia since their low toxicity allows them to be used as long-term prophylactics. Further, none of these studies reported any adverse events associated with the consumption of EOF, ensuring its safety.

7. *E. officinalis* against Diabetes-Induced Complications

The incidence of diabetes and its complications are the major causes of morbidity and mortality in the US and around the world [107]. Prolonged diabetes induces damage to many types of tissues, including nerves, skin, retina, kidney, heart, and brain. Diabetes-associated complications are mostly grouped into two groups: those affecting large blood vessels (macrovascular diseases) and those affecting small blood vessels (microvascular diseases). The most prevalent microvascular complications in diabetes patients are retinopathy, nephropathy, and neuropathy, whereas macrovascular complications include the increased risk of cardiovascular disease, leading to myocardial infarction and cerebrovascular disease manifesting as stroke (Figure 5). In addition, impaired lipid metabolism and myocardial dysfunction are also associated with diabetes [5,108]. The growing evidence has shown that natural herbs such as EOF are effective in managing diabetic complications and help to ameliorate the adverse side effects of synthetic pharmaceutical drugs.
7.1. Diabetic Retinopathy

Diabetic retinopathy (DR), associated with systemic microvascular diseases, is one of the most common complications associated with T2DM worldwide. DR is characterized by a spectrum of lesions in the retina that progresses to blindness in adults over 50 years of age. Several mechanisms are involved in the development of DR, including the activation of the polyol pathway, intracellular accumulation of AGEs, activation of PKC and hexosamine pathways, guanosine triphosphate (GTP)-binding proteins, and genetic modifications [10,44]. Specific inhibitors for AR and PKC, as well as anti-angiogenic agents, are proposed as effective agents for delaying or preventing DR complications [10,44,68]. Polyphenol-rich *E. officinalis* fruit targets AR and has a high potential for preventing diabetic retinopathy [109]. *E. officinalis* is found to be effective in modulating polyol pathway via the inhibition of AR and sorbitol accumulation in vitro and in vivo [50,73,74]. In vitro studies showed that pretreatment with β-glucogallin improved antioxidant enzymes and decreased ROS levels in methylglyoxal-exposed lens epithelial cells. In addition, β-glucogallin pretreatment also reduced the levels of sorbitol via attenuating AR and the other proinflammatory cytokines levels in methylglyoxal exposed lens epithelial cells closer to the control cells [110].

Similarly, treatment with crude extract of EOF delayed the onset and progression of cataracts and prevented the accumulation of diabetes-induced oxidation/peroxidation markers in the eye of experimental diabetic rats. Furthermore, β-glucogallin effectively inhibited AR activity and also suppressed infiltration of inflammatory cells into the anterior and posterior chambers of the eye in a dose-dependent manner in LPS-exposed mice [111].

7.2. Diabetic Neuropathy

Diabetic neuropathy (DNe), or diabetic peripheral neuropathy, is one of the major microvascular complications affecting at least 50% of diabetes patients. DNe involves sensory loss and autonomic, peripheral, somatic, sensory, and motor dysfunction, leading to a myriad of symptoms ranging from numbness to unsteadiness and pain as well as complications such as foot ulceration and Charcot’s foot. Hyperglycemia and other metabolic factors, namely hyperlipidemia and impaired insulin signaling, activate multiple pathophysiological...
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7.3. Diabetic Nephropathy (DN)

Diabetic nephropathy (DN) is another important microvascular complication of chronic hyperglycemia, with about 30% prevalence among diabetic patients. DN is characterized by the elimination of proteins through urine—called proteinuria—glomerular enlargement, reduced glomerular filtration, and renal fibrosis, eventually leading to end-stage kidney disease. In vitro study in HeLa cells showed that the tannins present in EOF are potent inhibitors of PARG, with activities similar to that of ADP-(hydroxymethyl) pyrrolidinediol, a potent inhibitor of PARG [60]. Similarly, treatment with gallotannins (20 mg/kg/day, i.p.) for 4 weeks significantly reduced plasma creatinine levels and glomerular hypertrophy in STZ-induced diabetic rats. Furthermore, gallotannins inhibited the level of PARG, an alternative approach to PARP inhibition, in the kidneys of diabetic rats and prevented the progression of apoptotic cell death and ultimately diabetic nephropathy [59]. Rahman et al. investigated the protective effect of EOF in the renal functioning of two-kidneys-one-clip (2K1C) rats. Supplementation of EOF powder (2.5% w/w) ameliorates elevated creatinine and uric acid concentration in the plasma of 2K1C rats. The treatment also increased the antioxidant potential and reduced the levels of various oxidative stress indicators such as malondialdehyde, nitric oxide (NO), and advanced protein oxidation product (APOP) in plasma, heart, and kidney tissues of experimental animals. Moreover, EOF prevented inflammatory infiltration and fibrosis in the 2K1C rats’ tissues [52]. Similar nephroprotective effects of herbal formulation containing EOF were also observed in other studies [117].

7.4. Diabetic Hepatopathy

Diabetes-induced hepatopathy is a common complication of diabetes mellitus due to impaired metabolism of glucose and lipids. Diabetic patients are at high risk of having abnormal deposition of free fatty acids and triglycerides in the liver parenchyma as well as elevated liver enzymes, hepatic fibrosis, and an increase in morbidity and mortality due to diabetes-induced liver injury [118].

Human serum albumin is the most abundant plasma protein which regulates the transport and availability of numerous chemical compounds and molecules in the blood vascular system. In diabetic conditions, decreased serum albumin level is an indicator of insulin deficiency and impaired liver function. An increase in albumin synthesis was observed after insulin infusion in diabetic individuals [119]. In this context, Rao et al. [53] demonstrated that administration of EOF enhanced the albumin level in the serum in the STZ-induced diabetic rats, suggesting the potential hepatoprotective role of EOF. In addition, by attenuating oxidative stress and increasing insulin binding to insulin receptors, EOF improved the liver dysfunction associated with secondary complications of diabetes [53].

Studies have indicated that oxidative stress in diabetes coexists with a reduction in anti-oxidative enzymes and contributes to increased formation of free radicals [120].
Patel et al. reported that decreased SOD, GSH, and catalase enzyme levels in the liver were observed in STZ-induced diabetic rats compared to the control. Treatment with EOF increased the levels of antioxidant enzymes and protected the liver tissues from highly reactive hydroxyl radicals [121].

In an earlier study, the same authors also reported that a herbal formulation containing EOF has potential to increase the antioxidant level, thereby improving liver metabolism and maintaining the integrity of liver tissue in T2DM. Thus, it can be used in managing diabetic liver disease [122].

Nonalcoholic steatohepatitis (NASH) is a chronic liver injury associated with abnormal liver histopathologic conditions including steatosis with inflammation and fibrosis. It is often associated with obesity, T2DM and metabolic syndrome [123]. Tung et al. showed that EOF significantly decreases the severity of NASH by downregulating lipid peroxidation and liver-specific enzymes in methionine- and choline-deficient diet (MCD) diet-induced NASH mice, suggesting the potential role of EOF in hepatoprotection [124].

High-fructose diet (HFD)-induced rat models that mimic the symptoms of T2DM in humans are widely used as a model for investigating T2DM. Huang et al. [125] studied the mechanism of action gallic acid (GA), a bioactive component of EOF, on glucose metabolism in rats with HFD-induced T2DM. Administration of GA was associated with upregulated the hepatic glycogen synthase expression and decreased hepatic-gluconeogenesis-related proteins, such as fructose-1,6-bisphosphatase expression, suggesting that GA improved hepatic glycolysis and glycogen synthesis by decreasing reversible metabolic hepatic gluco-neogenesis, decreasing hyperglycemia, and ameliorating hepatic glucose metabolism in diabetic rats [125].

Gallic acid treatment significantly increased the levels of glycogen and significantly decreased the levels of lipid peroxidation and TBARS in the liver of the STZ-induced diabetic rats, suggesting the hepatoprotective role of gallic acid, which could be attributed to its free-radical-scavenging effect [65].

Similarly, ellagic acid, another of the bioactive components of EOF, also exerts overall hepatoprotective effects by increasing the antioxidant marker GSH level and the production of lipid peroxidation marker TBARS in the liver tissues of the STZ-induced type 2 diabetic rats [97].

7.5. Diabetes-Induced Cardiac Complications

7.5.1. Cardiovascular Diseases

Diabetes has been identified as one of the prominent risk factors for macrovascular complications like cardiovascular diseases. Hyperglycemia and dyslipidemia induce progressive damage to the vascular wall, manifesting as a low-grade inflammatory process and cardiovascular complications. Cardiovascular disorders include myocardial infarction and stroke, as well as impaired cardiac function and predominantly diastolic dysfunction, [126]. EOF, rich in bioactive compounds, is reported to have antihyperlipidemic and cardioprotective potential in rats fed a high-fat diet [127,128].

Atherosclerosis, a chronic progressive arterial disease, is caused by the deposition of cholesterol and immune response to oxidated lipoproteins in the arterial walls, leading to the narrowing of arteries, impeding blood flow [129]. Dyslipidemia is a major risk factor for atherosclerosis, and EOF is found to be effective in the management of dyslipidemia in humans. Supplementation of EOF extract (500 mg/day) significantly improved the lipid profiles of dyslipidemia patients by reducing TC, LDL-C, and TG and—more importantly—by increasing beneficial HDL-C levels. EOF also reduced the high-sensitivity C-reactive protein (hs-CRP), a clinically used sensitive marker for systemic inflammation and an indicator of first myocardial infarction [105,130,131]. Gopa et al. [132] suggested EOF as a safe hypolipidemic agent against atherosclerosis and coronary artery disease comparable to simvastatin, a drug generally used to treat high cholesterol levels [132]. In a recent clinical study, Majeed et al. compared the efficacy of the standardized E. officinalis extract containing 10% β-glucogallin (Saberry®) with metformin in newly diagnosed T2DM

EOF: Echinacea officinalis

Saberry®: Extract containing 10% β-glucogallin
patients with diabetic dyslipidemia. Administration of EOF extract at 1000 mg/day and 2000 mg/day for 90 days reduced TG, LDL, VLDL, and TC dose-dependently, and the reductions were comparable with metformin (500 mg day) treatment. All three regimens with EOF extract 1 g and 2 g, and metformin significantly increased HDL values in newly diagnosed T2DM patients with diabetic dyslipidemia. Interestingly, Saberry® at a dose of 2000 mg/day showed better anti-diabetic and anti-dyslipidemia activities compared to the pharmaceutical drug metformin, indicating its superior beneficial effects [42].

7.5.2. Endothelial Dysfunction

Endothelial dysfunction is another macrovascular complication associated with the progression of diabetes. The elevated glucose level, oxidative stress induced by hyperglycemia, and reduced NO play pivotal roles in the pathophysiology of endothelial dysfunction [133]. Consumption of EOF juice plays a crucial role in preventing vascular smooth muscle cell dysfunction by inhibiting the phosphorylation of Akt, accumulation of β-catenin, and transcription of proto-oncogenes c-Myc and cyclin D1 in the aortas of STZ (60 mg/kg, i.v)-induced hyperglycemic rats, suggesting its efficacy in maintaining vascular health [134]. The cardioprotective activities of EOF were highlighted in human clinical studies also. For instance, administration of EOF aqueous extract at dosages of 250 mg and 500 mg twice daily for 8 and 12 weeks showed a significant reduction in mean reflection index, a measure of endothelial function in individuals with metabolic syndrome (MetS). Additionally, it showed significant improvements in markers of oxidative stress, systemic inflammation, and lipid profile in the EOF group compared to baseline and placebo [106].

People with diabetes usually have elevated blood pressure and are more likely to be at increased risk of developing cardiovascular disease. Lowering blood pressure is one of the established strategies for preventing cardiovascular complications in diabetic patients [135]. Chronic treatment with gallic acid showed a dose-dependent decrease in hyperlipidemia, hypertension, bradycardia, and structural alterations in cardiac tissue in diabetic rats as compared to diabetic control animals [136]. Similarly, treatment with E. officinalis decreased arterial blood pressure and heart rate along with cardiac and renal hypertrophy in DOCA/HS-induced hypertensive rats via the activation of eNOS, improved serum NO levels, and endogenous antioxidants and also via the correction of electrolyte imbalance [137]. The effectiveness of EOF in the prevention of hypertension has also been reinforced by clinical trials. EOF showed a significant reduction in blood pressure and hypolipidemic effect in hyperlipidemic humans. The cardioprotective activities of the EOF-treated group were more prevalent than those of the simvastatin-treated group [132].

8. Conclusions and Future Directions

Amla (Emblica officinalis) has been used in the management of various diseases since ancient times. E. officinalis fruits are well known as antioxidant, immunomodulatory, antipyretic, analgesic, cytoprotective, antitussive, and gastroprotective agents. It was believed that regular consumption of EOF rejuvenates our bodies and provides longevity. The bioactive phytoconstituents of EOF, such as β-glucogallin, tannins, polyphenols, fibers, minerals, proteins, and amino acids, are responsible for its beneficiary effects in humans. In vitro and in vivo studies have confirmed the efficacy of EOF in managing diabetes and its complications by controlling various biological activities. Diabetes is a chronic condition requiring life-long medications, many of which are toxic over a longer duration of time. Wherever possible, reduction of drug dosage with concurrent administration of EOF should be explored. It is increasingly recognized that gut microbiota dysbiosis is an important factor for diabetes, and more research is required to understand how EOF modulates gut microbial population. Since mono-galloyl esters are recognized as the important structural features for controlling PARP/PARG activation, EOF offers several galloyl esters for further research. EOF also offers a powerful candidate for screening microvascular complications.
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