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Review Article

Aloe vera in diabetic dyslipidemia: Improving blood glucose and lipoprotein levels in pre-clinical and clinical studies

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ABSTRACT

Dyslipidemia is a common feature of type 2 diabetes mellitus and is characterised by elevated triglyceride, decreased HDL cholesterol, and increased small dense LDL cholesterol levels. The underlying causes appears to be associated with insulin resistance, increased free fatty acid reflux, and low-grade inflammation, resulting in increased hepatic lipogenesis, and altered lipoprotein metabolism. Improved glycaemic control has been shown to have a positive effect on lipoprotein levels in diabetics. This can be achieved through medications/therapeutics and life style changes. Several classes of pharmacologic agents are currently in use to treat dyslipidemia. However, they may have dangerous long-term side effects, including an increased risk of liver dysfunction, weight gain, and cardiovascular diseases. Therefore, stronger alternatives with fewer side effects are required to reduce the diabetes associated complications. Many secondary plant metabolites have been shown to improve glucose homeostasis and lower lipid levels. *Aloe vera* and its constituents have long been used in a traditional medicine system for a diverse range of biological activities, including hypoglycaemic, antioxidant, anticarcinogenic, anti-inflammatory, and wound healing effects through various mechanisms and they have been covered well in literature. However, studies on the potential role of *Aloe vera* in the treatment of diabetic dyslipidemia are scanty. Therefore, in this systematic review, we focussed on the potential effect of *Aloe vera* and its active components in alleviating diabetic dyslipidemia, as well as their mechanism of action in pre-clinical and clinical studies.
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1. Introduction

There has been an increased prevalence of type 2 diabetes mellitus and metabolic syndrome globally due to the result of easy access to energy-rich food combined with sedentary lifestyles in genetically susceptible individuals [1]. Diabetes currently affects 573 million people, and this figure is expected to rise to 643 million by 2030, posing a significant global threat [2]. One of the hallmarks of hyperglycemia is abnormal lipid and lipoprotein levels, which impairs hepatic lipogenesis and results in diabetic dyslipidemia. It is very common in type 2 diabetes (T2DM), affecting approximately 70% of patients [3]. To treat dyslipidemia, a variety of pharmacologic agents are used. According to a meta-analysis of clinical trials, statins could be used as both primary and secondary interventions in the diabetics [4]. However, the wide range of treatment interventions makes prioritization of drug therapy difficult. Also, these medications may have dangerous long-term effects including, an increased risk of liver dysfunction, weight gain, and cardiovascular disease [5,6]. Therefore, stronger alternatives with fewer side effects are a better approach to reducing diabetes complications. Many secondary plant metabolites have been found to have lipid-lowering properties as well as a better glycaemic control [7,8]. Among the several herbal preparations, *A. vera* and its components play a significant role in traditional

Abbreviations: A.vera, Aloe vera; ASCVD, Atherosclerotic cardiovascular disease; apoB, Apolipoprotein B; BAS, Bile acid sequestrants; CKD, Chronic kidney disease; CF, Carbohydrate fraction; CETP, Cholesterol ester transport protein; FBS, Fasting blood glucose; FFA, Free fatty acid; HOMA-β, Homeostatic model assessment β-cell function; HbA1C, Glycated haemoglobin; HDL, High-density lipoprotein; HOMA-IR, Homeostatic model assessment of insulin resistance; IR, Insulin resistance; LDL-C, Low-density lipoprotein-Cholesterol; MNT, Medical nutrition therapy; PPF, Polypeptide fraction; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9 inhibitors; TG, Triglycerides; T2DM, Type 2 Diabetes mellitus; VLDL, Very low-density lipoprotein.

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medicine systems and plant-derived food. It has a wide range of biological activities, including hypoglycaemic, antioxidant, antibacterial, anti-inflammatory, and hypolipidemic properties [9,10]. Numerous studies have demonstrated that *A. vera* has the potential to reduce blood glucose levels by protecting pancreatic cells and/or improving insulin sensitivity. Furthermore, the lipid-lowering impacts of *A. vera* may be contributed to lipid catabolism or/and anabolism regulation [11–13]. There are review articles on the effect of *A. vera* on wound healing, its laxative properties, and its effects in dentistry. However, scanty reviews are available for the treatment of diabetic dyslipidemia with *A. vera*. Therefore, we focused on the potential effect of *A. vera* and its active components, which play an important role in diabetic dyslipidemia, as well as their mechanism of action in pre-clinical and clinical studies.

1.1. Aloe vera phytocomponents and their potential role in metabolic management

A.vera is a scrumptious plant that belongs to the Liliaceae family, which has over 420 species. *Aloe barbadensis* Miller, the most common species, is known colloquially as *A. vera* [14]. Several potentially active bio-constituents including flavonoids, saccharides, polyphenols, anthraquinones, chromone, phytosterols, proteins, and trace minerals have been identified (Table 1) [15]. However, much remains unknown about their mechanism of action. The rich chemical composition of the plant is influenced by a variety of factors, including location, ripening stage, climatic conditions, harvest time, and harvesting method [16].

The main component of *A. vera* gel is carbohydrates, particularly mannose-containing polysaccharides and their content varies depending on the age of the plant [17]. Acetylated mannan, also known as acemannan, is largely responsible for its mucilaginous properties and has been reported to have anti-diabetic properties as well as the ability to modulate immune function [18]. Recent research has shown that *A. vera* carbohydrate-rich fraction (AVCF) regulates glucose metabolism in diabetic rats by activating glycogenesis and inhibiting gluconeogenesis, as well as modulating the immune functions [19,20].

Polyphenols are another important phytochemical found in *A. vera*, known to exert their effect through their antioxidant properties. Over the last decade, their health effects have been extensively researched, and they are thought to be the most active constituents in alleviating metabolic syndrome *in vitro* and *in vivo* [21]. Administration of a polyphenol-rich extract from *A. vera* containing 181.7 mg/g aloin and 3.6 mg/g Aloe-emodin for a period of 28 days improves insulin sensitivity in experimentally induced diabetic mice [11], implying that, in addition to antioxidative properties, their biological activity is the result of various other complex mechanisms.

Flavonoids have been linked to a variety of health benefits. This is due to their antioxidative and anti-inflammatory properties, in addition to their ability to regulate key cellular enzyme functions [22]. Direct scavenging of free radicals is one way flavonoids protect against free radical damage [23]. With the confirmation of an increasing number of plant flavonoids with anti-diabetic potential, the mechanisms of action of these bioactive constituents are being meticulously elucidated. They play a protect beta cells from oxidative damage by increasing islet cell proliferation, stimulating glucose-stimulated insulin secretion, and inhibiting the α-glucosidase enzyme [24].

Sterols found in the leaf and the gel of the Aloe plant appear to influence islet functions. Five phytosterols were isolated and

Table 1
Phytocomponents present in *Aloe vera* [15,17,35,36]

Major classes	Components	Mechanism of action
Anthraquinones	Aloe-emodin, aloetic acid, emodin, aloin A, aloin B, 6′-O-acetyl-aloin A, 6′-O-acetyl-aloin B, 10-hydroxyaloins A, 10-hydroxyaloins B, aloinoside A, aloinoside B, 7-hydroxyaloin A, 7-hydroxyaloin B, 7-hydroxy-8-O-methylaloin A, 7-hydroxy-8-O-methylaloin B, 6′-malonylnataloin A, 6′-malonylnataloin B, homonataloside B, elgonica dimer A, elgonica dimer B, aloindimer A, aloindimer B, aloindimer C, aloindimer D, aloe-emodin-11-O-rhamnoside, chrysophanol, emodin, physcione, aloe-emodin, nataloeemodin, aloesaponarin I, aloesaponarin II, madagascine, 3-Geranyloxyemodin, rhein	Anti-oxidant and anti-inflammatory activity
Saccharides	Pure mannan, acetylated mannan, acetylated glucomannan, glucogalactomannan, galactan, galactogalacturan, arabinogalactan, galactoglucoarabinomannan, pectic substance, xylan, cellulose, Veracylglucan B and veracylglucan C, glucose, galactose, mannose, and arabinose	Regulates glucose metabolism by activating glycogenesis and inhibiting gluconeogenesis. Modulates immune function
Flavonoids	Apigenin, luteolin, isovitexin, isoorientin, saponarin, lutonarin, kaempferol, quercetin, myricetin, quercitrin, rutin, catechin, epicatechin	Protects beta cells from oxidative damage, increasing islet cell proliferation, stimulating glucose-stimulated insulin secretion, and inhibiting the α-glucosidase enzyme
Phytosterols	Cycloartanol, 24-methylene-cycloartanol, lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, lupeol, β-sitosterol, campesterol	Reduces serum-free fatty acid, triglyceride levels, PPARγ levels and improved glucose homeostasis and lipid metabolism
Chromones	Aloesin, aloeresin E, isoaloeresin D, aloeresin D, rabaichromone, aloeresin K, aloesinol	Anti-oxidant activity
Polyphenols	Cinnamic acid, p-coumaric, caffeic acid, ferulic acid, sinapic acid, 3-(4-hydroxyphenyl) propanoic acid, methyl 3-(4-hydroxyphenyl) propionate, 7-demethylsiderin, feralolide, dihydrocoumarin, Aloenin A, aloenin B, p-coumaroyl aloenin, aloveroside A, feroxidin 1-(2,4-dihydroxy-6-methylphenyl) ethenone, *p*-anisaldehyde, salicylaldehyde, *p*-cresol, pyrocatechol, gentisic acid, gallic acid, vanillic acid, syringic acid, ascorbic acid	Improves insulin sensitivity, anti-oxidant property
Proteins	Lectins and lectin like substances, polypetide fractions	Improved glucose and lipid metabolism, Inhibits DPP-IV, reduces intestinal permeability, anti-inflammatory
Trace minerals	Calcium, copper, zinc, magnesium, potassium, manganese, iron, choline, chromium, phosphorous, sodium, vanadium	Insulinotropic effect

identified from *A. vera* gel. At a dose of 1 μg/day, they were able to reduce FBG and HbA1c levels in *db/db* mice when compared to the control group, implying that sterols from *A. vera* could be used to treat type 2 diabetes [25]. Furthermore, phytosterols (lophenol and cycloartanol) isolated from *A. vera* reduced serum-free fatty acid, triglyceride levels, PPARγ levels and improved hyperglycemia and hyperlipidaemia, as well as visceral fat accumulation in Zucker diabetic fatty rats [26]. Phytosterols may have hypolipidemic effects because they are not prevalently absorbed from the intestine and can bind to cholesterol and prevent its absorption. *A. vera* gel containing sterols was known to be possibly involved in brown adipose tissue (BAT) activation in high-fat diet treated mice, and the treated group had increased expression of *Ucp1, Adrb3,* and *Cidea* in comparison to the untreated group, implying that anti-obesity potential of sterols from *A. vera* in diet-induced model is partially contributed by BAT adipogenesis [27].

Anthraquinones are anthracene derivatives of the quinone group that are typically found in the epidermis of the plant. They are well-known for their laxative properties. They are inadequately absorbed in the small intestine and are broken down in the large intestine into active metabolites such as aloe-emodin and aloe-emodin-9-anthrone. [17]. The primary anthraquinones found in *A. vera* are aloe-emodin and aloin. The concentration of these components determines the antioxidant property of *A. vera* [28]. At higher concentrations, aloe-emodin acts as an antioxidant, and at lower concentrations, it acts as a prooxidant [29] and its anti-inflammatory effect was comparable to that of kaempferol and quercetin [30].

In comparison to other constituents, little is known about protein or glycoprotein; however, lectins are a type of glycoprotein found in *A. vera* that differs in the connection between oligosaccharide groups and polypeptide chains [17]. Recent research indicated that the peptide/polypeptide-rich fraction (PPF) inhibited the DPP-IV enzyme in a dose-dependent manner. Furthermore, the fraction was able to restore FBG levels and important enzymes involved in restoring glucose homeostasis and lipid metabolism, implying that PPF from *A. vera* could be used as alternative for diabetes mellitus treatment due to its ability to decrease intestinal permeability [31], improve lipid profile and reduce pro-inflammatory cytokines [9].

Aloesin, aloeresin A, isoaloerersin D and aloesinol are the most significant chromones isolated and identified from *A. vera* and approximately 29 chromone derivatives have been identified, but the absolute configuration has not yet been determined [15]. Usually, they are known to have antioxidant activity, however, the concentrations of chromones determine whether they act as prooxidants or antioxidants [32].

Aloe minerals are reported to have insulinotropic effects, playing a direct or indirect role in insulin secretion in a synergistic way. Earlier studies have reported that the presence of these trace minerals plays a significant role in the anti-diabetic potential of *A. vera*. Zinc is an important mineral that acts as a cofactor and improves insulin effectiveness. The presence of zinc in A. vera can modulate insulin activity targets [33]. Furthermore, the mineral content of *A. vera* has been shown to have hypoglycaemic properties in streptozotocin-induced diabetic rats, where potassium functions as an insulin secretagogue, vanadium elicits glucose levels, copper is associated in insulin binding, and chromium is important in carbohydrate metabolism [34]. To date, a great number of research works and reviews have addressed the bio-efficacy of *A. vera* gel extract and its components on blood sugar levels and lipid profile *in vitro*, *in vivo* and in clinical trials; however, the diversity in its composition and bioavailability varies in its beneficial effect on different signalling pathways.

2. Methods used for literature collection

A literature search for this review was conducted using a variety of reputable and authentic databases, including Google Scholar, Medline, PubMed, Science Direct, Scopus and Wiley online library. The major keywords used in various combinations included: diabetic dyslipidemia, therapeutic strategies, *Aloe vera*, anti-diabetic activity, hypoglycaemic effects, hypolipidemic activity and phytocomponents. The full-length articles from peer-reviewed journals related to the subject of interest, published between (1983−2021) and written in English were included in the review process. Given the large volume of scientific research on the anti-diabetic potential of *A. vera*, the search has been refined using the following inclusion and exclusion criteria: *in vivo* approaches that describe the effect of *A. vera* on glucose-lowering effects via restoration of lipoprotein metabolism and glucose homeostasis. Case-control studies and randomized or controlled clinical trials with therapeutic evidence of *A. vera* in the management of hyperglycemia and hyperlipidaemia were included in this review. There were no restrictions on the sample size, study design, or method of exposure. Duplicated studies, conference abstracts, letters, and guidance articles, which were only available as abstracts but not full texts, as well as those did not fall within the purview of the search were excluded. Aloe species other than *A. barbadensis* Miller were also excluded from this review. Out of the 220 articles, 107 articles were included in this review by following inclusion and exclusion criteria as described in Fig. 1.

2.1. Diabetic dyslipidemia

Dyslipidemia is a common feature of type 2 diabetes mellitus and is characterised by elevated triglyceride levels, decreased HDL cholesterol, and increased small dense LDL cholesterol levels. The reference values for diagnosis of dyslipidemia in adults over the age of 20 [37] are mentioned in Table 2. Dyslipidemia appears to be caused by an insulin-resistant state itself rather than by high insulin levels or obesity [38]. Furthermore, these modifications are linked to increased FFA reflux as a result of the insulin resistance [39]. Insulin deficiency or resistance stimulates intracellular hormone-sensitive lipase, increasing FA release from triglycerides stored in more metabolically active centrally distributed adipose tissue [40]. Excess FFA accumulate in the liver, which has at least three options to deal with them: 1) β-oxidation, 2) storage or 3) export via VLDL (TG-rich) particles Fig. 2. The intestine produces chylomicrons after food consumption, which are high in TG; however, chylomicrons should dissipate within a few hours and should not be detected in a fasting blood sample. These TG-rich lipoproteins (VLDL particles and chylomicrons) work together to deliver fatty acids to tissues such as muscle and adipose tissue Fig. 2 [41]. Insulin resistance, as previously stated, increases hepatic triglyceride production, which is linked to increased apoB secretion. Furthermore, the normal inhibitory effect of insulin on hepatic apoB production and triglyceride secretion in VLDL is lost, resulting in a larger and more triglyceride-rich VLDL secreted [42]. Lipoprotein lipase regulates the rate at which triglycerides are removed from circulation. This lipoprotein lipase, unlike intracellular hormone-sensitive lipase, may be downregulated when there is either insulin deficiency or insulin resistance [43], contributing to post-prandial lipemia [44]. As a result, hypertriglyceridemia has been identified as the impaired blood lipid component most commonly associated with obesity and insulin resistance, which is caused by the liver producing excess VLDL particles, slow clearance from circulation, or both. Furthermore, chylomicrons contribute to hypertriglyceridemia if they are not effectively cleared from the blood after a meal [45].

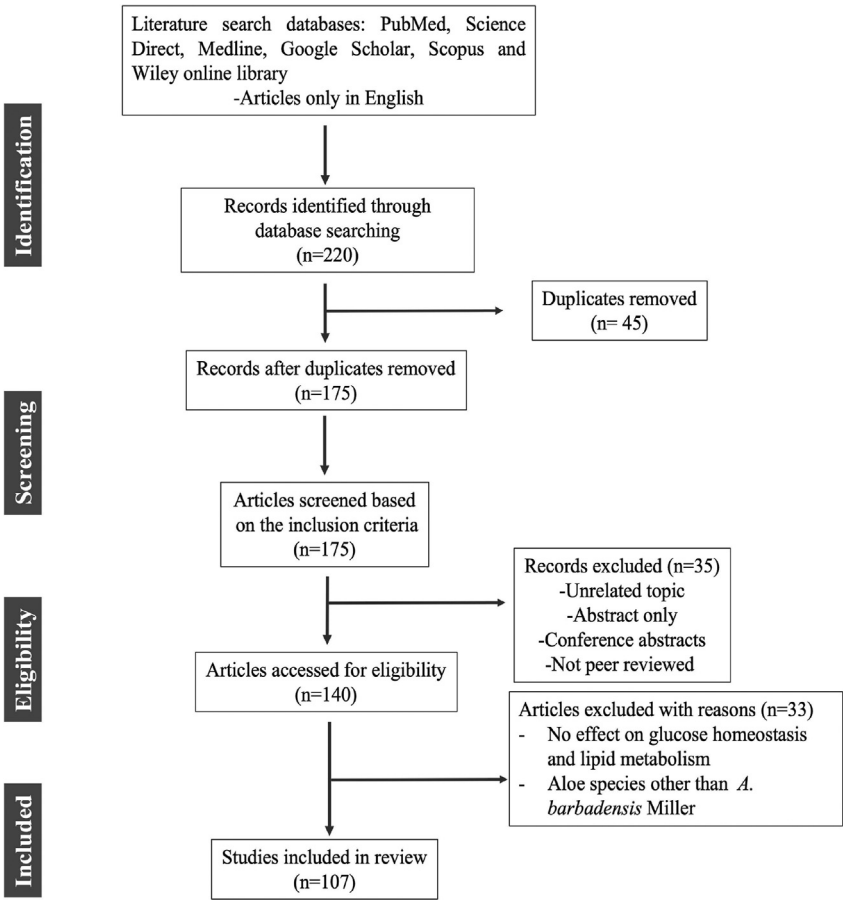

Fig. 1. Methodology for search.

Another feature of dyslipidemia is low HDL-C and an increase in the production of small, LDL-C levels Fig. 2. Although the liver produces HDL particles, a significant portion of them are formed from remnant TG-rich lipoproteins particles as they are metabolized. This metabolism is impaired in diabetes, reducing HDL-C production from this source [46]. Furthermore, CETP transports cholesterol esters away from the HDL particles in exchange for TG from VLDL particles and this will likely result in triglyceride-rich, cholesterol-depleted HDL particles. This lowers HDL-C in the blood. Similarly, lipid exchange by CETP transports cholesterol away from LDL particles resulting in the increased accumulation of small dense LDL-C particles. These changes, when combined, steer the body in an unfavourable direction [47]. Additionally, in diabetic dyslipidemia, inflammatory markers increase insulin resistance and therefore increase the dyslipidemia [48]. Improved blood glucose levels generally have a positive effect on lipoprotein levels in diabetes, with lower cholesterol and triglyceride levels due to decreased circulating VLDL and increased catabolism of LDL due to reduced glycation and up-regulation of LDL receptors [49]. Thus, altered plasma lipid levels in diabetics are one of the key factors that can be addressed for intervention.

Table 2
Reference values for diagnosis of dyslipidemia in adults over the age of 20 [37].

Lipids	Values	Level
Triglycerides	<150	Ideal
	150–200	Borderline
	201–499	High
	≥500	Very High
LDL-Cholesterol	<100	Ideal
	100–129	Desirable
	130–159	Borderline
	≥190	Very High
HDL-Cholesterol	<40	Low
	>60	High
	<150	Ideal

2.2. Therapeutic strategies

There are two types of treatment for diabetic dyslipidemia: non-pharmacological and pharmacological. Non-pharmacological treatment options include weight loss, MNT, and physical activity. While pharmacological therapies include drugs such as statins, niacin, BAS, cholesterol absorption inhibitors, PCSK9 inhibitors, omega-3 fatty acids, fibrates, etc. Table 3[39,50]. Due to the long-term side effects associated with these pharmacological agents, there is a need for an alternative therapy that is both safe and cost-effective for the treatment of diabetic dyslipidemia.

2.3. Plausible role of Aloe vera in adipose tissue, liver, and muscle

Obesity and impaired insulin sensitivity in targeted tissues, primarily the liver, muscle and adipose tissue, remain major risk factors for T2D progression. Insulin resistance impairs glucose disposal, causing an increase in endogenous insulin production to compensate. This leads to weight gain, which perpetuates insulin resistance.

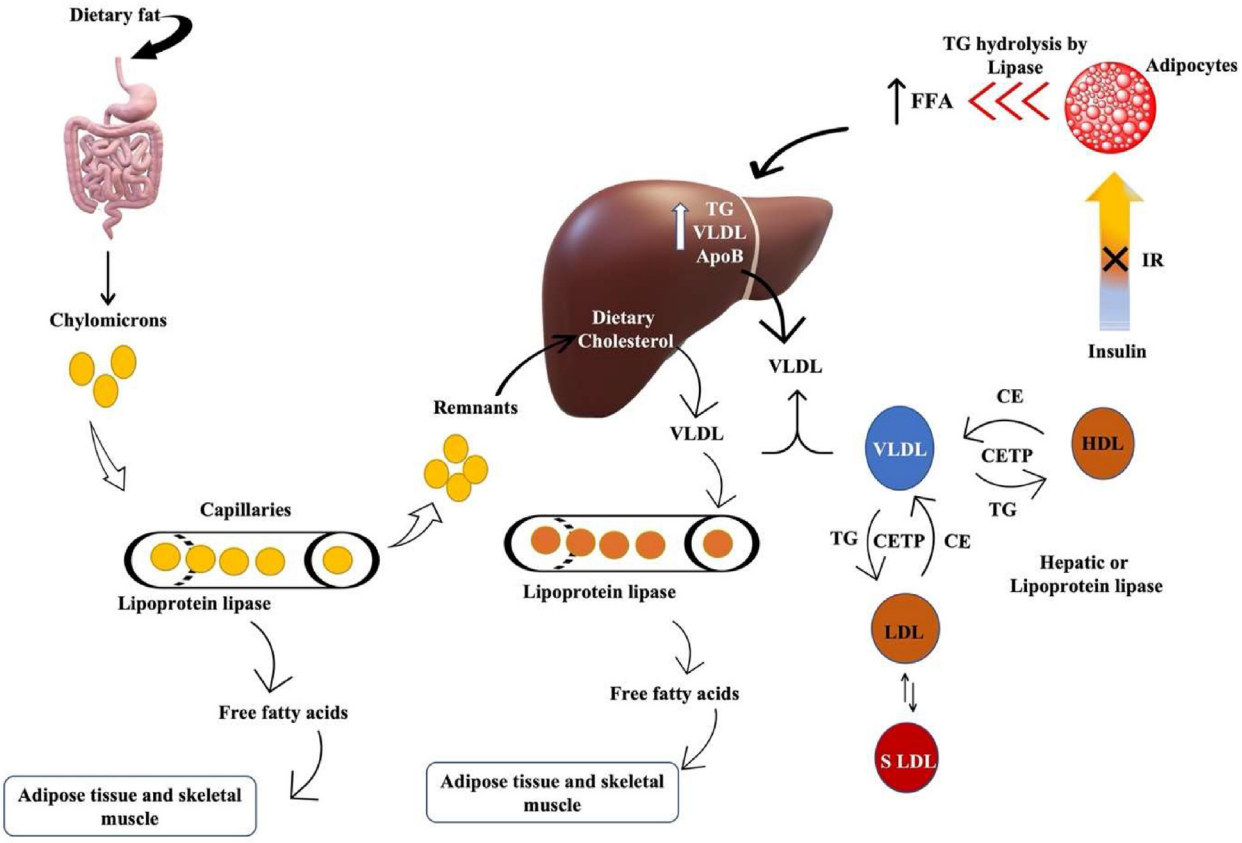

Fig. 2. Diabetic dyslipidemia: Insulin resistance increases TG hydrolysis from adipocytes and increases hepatic triglyceride production and secretion of VLDL & apolipoprotein B. Also promotes lipid exchange via cholesterol ester transport protein resulting in triglyceride-rich HDL particles which are depleted in cholesterol. Similar lipid exchange results in an increase in small dense LDL-cholesterol particles. Chylomicrons are formed by the intestine after consuming food from dietary fats and are cleared within a few hours. Remnants from chylomicrons are transported back to the liver for VLDL production.

Table 3
Pharmacologic agents for treating dyslipidaemias

Drug class	Mechanism of action	Clinical effectiveness	Adverse impacts	Reference
Statins	HMG coenzyme A reductase Inhibition	Very effective	Myalgia, myositis, rhabdomyolysis, elevation in liver enzymes	[51]
Ezetimibe	Reduced intestinal cholesterol absorption by binding to C1-like 1 protein	Moderately effective, Safe in addition to statin therapy	Nasopharyngitis, diarrhea, upper respiratory tract infection	[52]
Inhibitors of PCSK9	Inhibition of PCSK9	Extremely effective in combination with statin therapy	Injection site reaction includes itching, swelling, erythema, and pain	[53]
BAS	Prevent reabsorption of bile acids by binding them in the small intestine	Moderately effective, safe in addition to statin therapy, not recommended if triglycerides are >400 mg/dL	Constipation, bloating, abdominal pain, drug malabsorption	[54]
Nicotinic acid	Lowers LDL 5−25%, TG 20−50%, and small dense LDL. Increases HDL 15−35%	Clinical efficacy and safety uncertain	Hot flashes, hyperglycemia, hyperuricemia, hepatotoxicity	[55]
Fibrates	Activates PPAR-α and lowers triglycerides by 30−50%. Increases HDL	Moderately effective but should be used with prudence in patients with CKD	Dyspepsia, gallstones, hepatotoxicity, myopathy	[56]
Omega-3 fatty acid	Lowers TG	Moderately effective, could be used in conjugation with statins in patients with CVD and increased TG	Gastrointestinal disturbances	[57]

This vicious cycle continues until pancreatic beta-cell activity can no longer meet the insulin demand adequately created by insulin resistance, resulting in impaired glucose homeostasis [58]. The metabolic repercussions of insulin resistance include dyslipidemia, visceral adiposity, elevated oxidative stress and inflammatory markers. Impaired carbohydrate utilisation accelerates lipolysis, resulting in excess triglyceride synthesis in the liver and lipid accumulation [59]. Numerous articles discuss the relationship between obesity, dyslipidemia, and diabetes progression. It is beyond the scope of this review to go into detail about very diverse mechanisms and pathways through which progression occurs. Readers are encouraged to follow some of the publications [60,61]. Here, the

plausible role of *A. vera* in adipose tissue, liver and muscle is discussed further in terms of improving insulin sensitivity and dyslipidemia.

2.4. Adipose tissue

Obesity is regarded as a major contributor to metabolic disorders and the syndrome of energy equilibrium. It is well known that obesity is associated with deranged lipid metabolism and altered insulin-mediated glucose uptake [62]. Previous research has shown that adipose tissue becomes dysfunctional and is associated with hyperplasia and hypertrophy, particularly in the visceral depot [63]. This leads to additional cellular and molecular changes, resulting in inflammation and an altered pattern of adipokine secretion [64]. It has been demonstrated that *A. vera* reduces visceral fat accumulation, and phytosterols derived from *A. vera* gel extract can mitigate hyperlipidaemia and total abdominal fat tissue weight [26]. Further, aloe sterols were found to be involved in brown adipose tissue adipogenesis, and the treated group had higher levels of uncoupling protein-1 (Ucp1) expression than the untreated group [27]. The AMP-activated protein kinase plays an important role in glucose and fatty oxidation. Aloe QDM complex [Aloe formulation containing Chrome (Cr)] suppressed receptor expression levels on adipose tissue macrophages in HFD obese mice, demonstrating its efficacy in fat reduction. Also, the findings point to a reduction in obesity-induced inflammatory cytokines and the translocation of NF—B p65 from the cytosol in the white adipose tissue (WAT) [65]. Furthermore, *A. vera* improved insulin resistance and increased HOMA-β values in non-insulin-dependent genetically obese rats. In addition, the treated group had more lean body mass and a lower fat percentage than the other group's [8]. Perez et al. reported that *A. vera* gel containing a high concentration of polyphenols when administered for 4 weeks was able to reduce body weight and improve insulin resistance when compared to the untreated group and that *A. vera* could be effective for the control of insulin resistance [11]. Furthermore, an ethanolic extract of *A. vera* demonstrated an insulin mimicking effect as evidenced by time-dependent increases in the expression of pIRS1 and pAkt. There was also increased expression of GLUT-4, indicating its potential as a therapeutic [66].

2.5. Liver

In an insulin-resistant state, both gluconeogenesis and lipogenesis increase in hepatocytes [67], and administration of *A. vera* for 15 days in alloxan-induced diabetic rats improved hepatic glycogen content. This could be due to inhibition of glycogenolysis and stimulation of insulin release, which aids in the mobilisation of blood glucose towards liver glycogen reserve or storage. The histopathological analysis also revealed that *A. vera* treatment reduces hepatocyte degeneration and cellular infiltration. There was also a significant decrease in lipogenesis, which could be attributed to improved insulin secretion and action [66]. Hyperglycemia can result in increased oxidative stress and changes the redox potential of glutathione due to increased utilization of antioxidants [68]. *A. vera* treatment improved GSH and SOD levels in the treated group and that lipid peroxidation was significantly decreased [66]. Another study reported that administration of *A. vera* for 21 days in STZ-induced diabetic rats resulted in a significant reduction in hepatic transaminases and liver triglycerides, free fatty acids and phospholipids. The altered liver fatty acid composition analysed by gas chromatography in the diabetic group was brought to normal following treatment with *A. vera* [69]. Further, *A. vera* and its polypeptide-rich fraction (PPF) reduced triglycerides, cholesterol, and hepatic transaminases, possibly due to a reduction in hepatic lipogenesis via the AMP-K pathway. PPF fraction elevated hexokinase activity and liver glycogen levels, with a significant decrease in glucose-6-phosphatase activity (a key enzyme in the gluconeogenesis pathway) which further reduces the production of glucose in the liver. Increased insulin levels after PPF treatment may be responsible for increased enzyme activities and glycogen content because insulin stimulates glucose uptake in the liver via the IRS/PI3K/Akt pathway. PPF treatment improved the architecture of the liver hepatocytes and reduced the damage caused by STZ, according to histopathological observations [9]. *A. vera* carbohydrate-rich fraction (AVCF) reduced FBG, glucagon, and glucose-6 phosphatase levels while increasing insulin, hexokinase, glycogen synthase, and glycogen content, according to another study conducted by the same group. These findings are consistent with the increased hepatic glycogen content observed in the PAS-stained histological section of the liver of diabetic rats given AVCF [20].

2.6. Muscle

In the muscle, defective glucose metabolism, reduction in glucose uptake by GLUT-4 and impaired insulin signalling for peripheral glucose uptake, including insulin receptors and downstream mediators, play a major role in the pathogenesis of the insulin resistance [70]. Further, hyperglycemia can upregulate markers of chronic inflammation and increased oxidative stress may cause interference with glucose uptake and reduce insulin sensitivity [71]. Therefore, the improved glucose uptake and the reduction of pro-inflammatory cytokine secretion by *A. vera* could manifest in a positive effect on IR [11]. *A. vera* treatment for 4 weeks in STZ-induced mice indicated a hypoglycaemic effect and an increase in GLUT-4 mRNA synthesis in mouse embryonic cell lines [72]. Another study reported that *A. vera* treatment increased GLUT-4 expression as well as pAkt and pIRS1 expression, indicating insulin signalling activation after treatment, implying that *A. vera* can be an effective anti-diabetic drug by improving insulin action and thus increasing glucose uptake [66]. High levels of TNF-α and IL-6 can also negatively regulate insulin levels leading to increased glucose levels. Numerous studies have reported that *A. vera* and its phytocomponents have decreased pro-inflammatory cytokines, restored insulin levels and reduced blood glucose levels and these effects might be mediated through improved insulin sensitivity [9,19,73].

2.7. Aloe vera in diabetic dyslipidemia

A.vera and its active components have been shown to have numerous benefits, including hypoglycaemic and hypolipidemic properties in animal models and human studies Fig. 3 [74]. A plethora of reports have revealed various properties of *A. vera*, including the ability to reduce hepatic tissue damage caused by diabetic complications [75] and oxidative damage [76]. It is conjectured that *A. vera* can restore normal fatty acid distribution in the blood by controlling lipid metabolism in the liver. Furthermore, A. vera extract can be used to construct non-saturated fatty acids, which remove free radicals from the bloodstream and regulate fat metabolism in the body [69].

2.8. Pre-clinical studies

A.vera has been studied extensively in various animal models for its hypoglycaemic and hypolipidemic effects [74] (Table 4). The hypoglycaemic action of *A. vera* is attributed to an increase in pancreatic cell function in terms of insulin synthesis and its secretion [77], and the hypolipidemic effect is associated with phytosterols present in *A. vera* inhibiting cholesterol absorption in

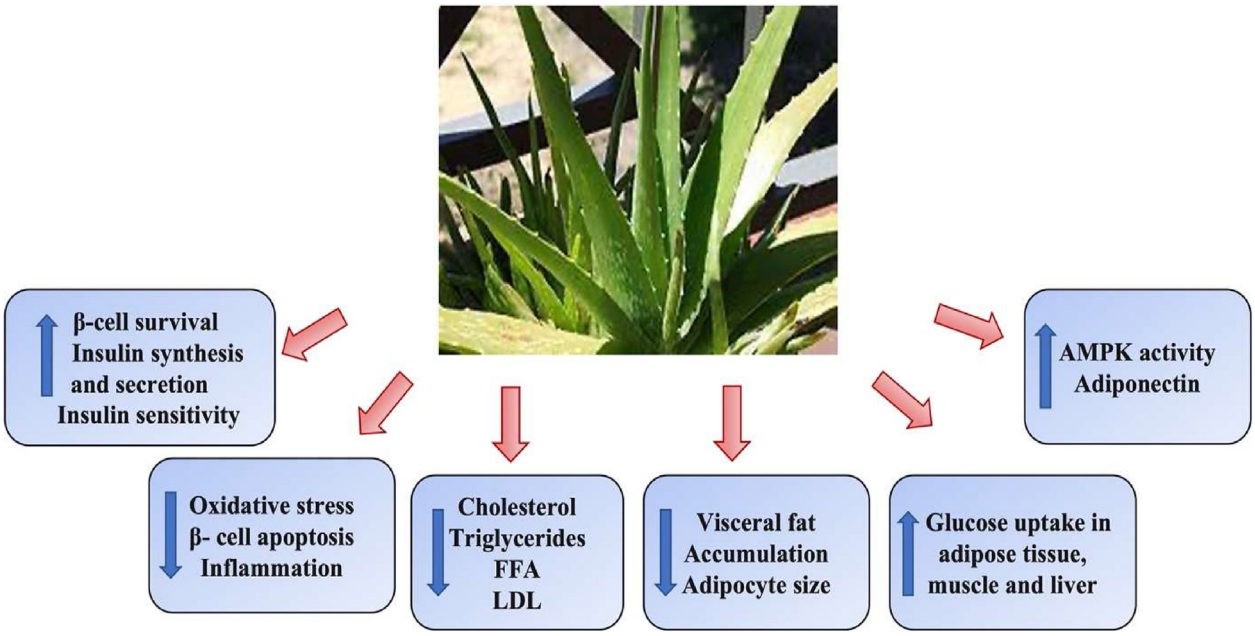

Fig. 3. Beneficial effects of *A. vera* on hyperglycemia and hyperlipidaemia*: A. vera* imparts its beneficial effects on hyperglycemia and hyperlipidaemia by increasing insulin synthesis and secretion, decreased oxidative stress, beta-cell apoptosis, inflammation, lowering cholesterol and lipoprotein levels, decreasing adipocyte size and visceral fat accumulation, increase glucose uptake and increased AMPK activity and adiponectin levels.

Table 4
Hypoglycaemic and hypolipidemic effects of *A. vera* in pre-clinical studies.

Study type	Duration	Beneficial effects	Target organ	Reference
Animal study (STZ induced rats)	21 days	Improved membrane bound phosphatases and lysosomal hydrolases	Liver Kidney	[79]
Animal study (STZ induced rats)	21 days	Reduced FBG, hepatic transaminases Improved Fatty acid composition in liver and kidney and lipid profile	Liver Kidney Pancreas	[69]
Animal study (Alloxan induced mice)	4 days	Insulin synthesis and secretion	Pancreas	[77]
Animal study (STZ induced mice)	73 days	Protective effects on pancreatic beta cells	Pancreas	[80]
Animal study (STZ induced rats)	21 days	Restored FBG, Insulin levels, Qualitative and quantitative restoration of islet cells	Pancreas	[81,82]
Animal study (Zucker diabetic fatty rats)	44 days	Reduce hyperglycemia and visceral fat accumulation. Reduced Triglycerides, FFA, improved insulin sensitivity	Pancreas Adipocytes	[26]
Animal study NIDDM mice	56 days	Reduced FBG, triglycerides in plasma and liver, improved insulin sensitivity Decrease adipocyte size	Pancreas Liver Adipocytes	[83]
Animal study (STZ induced rats)	28 days	Reduced FBG, serum cholesterol, And LDL-C levels Antioxidant activity	Pancreas	[84]
Animal study (*db/db* and HFD-mice)	70 days	Reduce FBG, triglycerides, restored insulin levels, improved insulin sensitivity, increased adiponectin levels	Pancreas Adipocytes	[85]
Animal study (STZ induced rats)	21 days	Reduced FPG, triglycerides, cholesterol levels, Increased adiponectin, restored apolipoprotein levels	Pancreas	[31].
Animal study (High-fat fed diet obese mice)	54 days	Reduced body weight, FPG, leptin levels, improved glucose tolerance, increase adiponectin levels, AMPK activity, improved insulin sensitivity, reduced PPARγ/ LXRα	Pancreas Liver Adipose tissue Muscles	[65,92] [93]
Animal study (Diet induced obese rats)	56 days	Lowering triglycerides, cholesterol, FFA, decrease visceral fat accumulation, inhibit pancreatic lipase and improved oxidative stress	Adipose tissue	[13]
Animal study (STZ induced genetically obese rats)	28 days	Reduced FBG, triglycerides, VLDL, TG:HDL, restored insulin levels, DPP-IV activity, reduced HOMA-IR, restored HOMA-B values. Increased LBM	Pancreas Adipose tissue	[8]

the intestine [78]. In diabetic rats, administration of *A. vera* ethanolic extract (300 mg/kg body weight) restored blood glucose levels while increasing insulin levels. Lipid levels, liver cholesterol, and kidney triglyceride levels were also reduced [69]. Similar findings were reported by another study where *A. vera* extract had beneficial effects comparable to glibenclamide in diabetic models [79]. A 10-KDa fraction powder from aloe leaf skin (Kidachi) showed protective effects against streptozotocin-induced pancreatic β-cell damage, which could be attributed to the presence of anthrachinonic derivatives like Aloenin and barbaloin. These beneficial effects of anthrone derivatives and phenolic plant components are exerted via metabolization in the intestine and then enter the circulation [80]. Furthermore, Noor et al. reported that oral ingestion of *A. vera* extract for 21 days restored FPG levels to

normalcy with an increase in insulin levels in STZ-induced Wistar rats and restored pancreatic beta-cell function [81,82].

The phytosterols identified from *A. vera* were reported to reduce hyperglycemia and visceral fat accumulation in ZDF rats (ZDF mutation in the leptin receptor, which spontaneously develops severe obesity, hyperglycemia, hyperlipidaemia, and IR), and could lower serum free fatty acid and triglyceride levels except for total cholesterol. Even though FFA is engaged in the development of IR, reducing serum FFA levels benefits insulin sensitivity and secretion as well. Furthermore, the lack of effect on TC could be attributed to the *A. vera* phytosterol administration dosage. Treatment with *A. vera*, on the other hand, may increase energy expenditure, and phytosterols derived from *A. vera* may be useful for hyperglycemia and hyperlipidaemia improvement [26]. According to one study, a maximum dose of 50 mg/kg bw of *A. vera* did not have a significant effect on cholesterol levels in diabetic rats, but it did improve blood glucose levels. This implies that the *A. vera* dose required to reduce serum cholesterol levels is greater than the dose required to reduce blood glucose levels [25]. Intriguingly, 8 weeks of administration of processed *A. vera* gel prevented the progression of diet-induced non-insulin-dependent diabetes mellitus in C57BL/6 J mice and it can improve blood glucose levels by decreasing IR. It also reduced triglyceride levels in the liver and plasma, and histopathological analysis of the per-epididymal fat pad revealed a decrease in adipocyte average size, implying that it could be useful in the treatment of diet-induced obesity [83].

As previously stated, *A. vera* contains a variety of phytoconstituents that are known to work synergistically and/or alone to impart therapeutic effects. Oral administration of polyphenolic and flavonoid-enriched *A. vera* skin extract for 4 weeks significantly reduced serum glucose levels, with a 25% reduction in total cholesterol levels and a 69% reduction in LDL-C levels after treatment [84]. UP780, a chromone-enriched aloe composition formulated with *A. vera* gel polysaccharides at 200 mg/kg bw, showed a reduction in fasting triglyceride and glucose levels after 10 weeks of treatment and improved insulin sensitivity [85]. Peptides or polypeptides and carbohydrates are a few of the components which exert their antidiabetic activity via various mechanisms. It was found that treatment of STZ-induced Wistar rats with PPF and CF reduced the levels of FPG by 74.8% and 64.9% respectively, as well as cholesterol levels by 40.4%, and 33.3%, and the triglycerides levels by 58.5% and 52.3%, respectively [31].

The role of adipose tissue as an endocrine organ in the progression of dyslipidemia has become increasingly popular [86]. Adiponectin, a major adipokine, is exclusively found in adipose tissue and has insulin-sensitizing, antiapoptotic, and anti-inflammatory properties [87]. It actively regulates glucose levels by increasing uptake through its receptors found in adipose tissue, skeletal muscle, and the liver [88]. The expression of adiponectin and its plasma concentrations are all inversely related to IR, fatty acid oxidation, lipid metabolism, and obesity [89]. Decreased expression of adiponectin and its receptors in the visceral and subcutaneous tissue is linked with diabetic dyslipidemia [90]. Interestingly, adiponectin levels were increased by 82.8%, and 81% post-treatment with CF and PPF. Furthermore, CF and PPF have restored apolipoproteins, which play an important role in glucose homeostasis and lipid metabolism, to normal/near normal levels, lowering the risk of diabetes-related cardiomyopathy [31]. Adiponectin levels are significantly related to insulin levels, inferring that increased insulin levels may have caused a spike in adiponectin levels, resulting in lower cholesterol and triglyceride levels [91]. Previously, dietary Aloe QDM complex [Aloe formulation containing Chrome (Cr)] administered for 54 days to high-fat fed diet C57BL/6 obese mice reduced body weight, FBG, plasma insulin, and leptin levels, as well as markedly reduced impairment of glucose tolerance. Additionally, AMPK activity in muscles increased plasma adiponectin levels and insulin sensitivity. Simultaneously, PPARγ/LXR and scavenger receptor mRNA and protein levels in white adipose tissue decreased. Thus, the Aloe QDM complex reduces obesity-induced glucose tolerance by suppressing PPARγ/LXR but increasing AMPK activity, both of which are important for peripheral tissues influencing the IR [65,92]. Furthermore, there was a reduction in obesity-induced inflammatory cytokine (IL-1β, −6, −12, TNF-α) and chemokine (CX3CL1, CCL5) levels, as well as macrophage infiltration and hepatic triglycerides levels. PPARγ/LXRα and 11β-HSD1 mRNA and protein levels were reduced in both liver and white adipose tissue by Aloe QDM [93].

Pancreatic lipase is a key lipid-digesting enzyme that aids in the absorption of dietary triglycerides by hydrolyzing triacylglycerols to monoacylglycerols and fatty acids [94]. As a result, inhibiting pancreatic lipase is an intriguing step toward developing potent agents that can reduce dietary fat absorption. In diet-induced obese rats, *A. vera* has been shown to improve lipid profile by lowering triglycerides, total cholesterol, and free fatty acids while decreasing adipose tissue accumulation, inhibiting pancreatic lipase, and improving oxidative stress [13]. These findings are consistent with our previous study in which *A. vera* showed beneficial effects on diabetes and dyslipidemia in WNIN/GR-Ob rats vis-à-vis β-cell dysfunction. The *A. vera* treated group significantly decreased TG, VLDL, and the TG: HDL ratio, along with fasting blood glucose levels and DPP-IV activity, with a concurrent elevation of serum insulin levels. *A. vera* was also efficient in decreasing HOMA-IR and increasing HOMA- βvalues. In comparison to the other groups, the treated group had more LBM and decreased fat per cent [8]. Unpublished findings from our lab showed that *A. vera* can inhibit pancreatic *lipase* and that Aloenin-a, a glycoside found in *A. vera,* can competitively inhibit this enzyme. These findings are supported both by molecular docking studies and biochemical experiments, which suggested that the anti-hyperlipidemic effects of *A. vera* on pancreatic *lipase* can be attributed in part to the presence of Aloenin-a. There have been numerous reports on the effects of *A. vera* on hypoglycaemic and hypolipidemic properties; however, animal experiments are not a substitute for clinical trials in determining efficacy.

2.9. Clinical studies

Over a 5 years trial, the impact of *A. vera* on 5000 diabetics showed a significant decrease in TC, TG, LDL-C, fasting, and postprandial blood glucose levels. The level of HDL-C increased dramatically within 60 days of treatment. Interestingly, no untoward side effects were reported during the study [95]. A 12-week controlled clinical trial on 60 patients with hyperlipidaemia who had previously not responded to dietary interventions found that 20 ml of *A. vera* reduced serum cholesterol by 15.4%, TG by 31.9%, and LDL by 18.2%. There was no significant difference in the group treated with 10 ml of *A. vera*. Because this trial was only available as a conceptual, there was no mention of intergroup comparisons, random sampling, or blinding [96]. Another study divided 72 diabetic women who were not on medication into two groups. For 42 days, they were given one tablespoon of *A. vera* gel or a placebo. Fasting blood glucose levels in the experimental group reduced from 250 mg to 141 mg %, while controls showed no significant changes. Other variables such as TC, serum triglycerides, weight, and appetite were also assessed. Except for triglyceride levels, which decreased significantly in the actively treated group from 220 mg to 123 mg%; these variables remained constant across both groups. There was no randomization in this study, and neither the patient nor the investigator was blinded [97].

A.vera was found to be effective in another clinical trial involving 36 patients with type 2 diabetes, where it could lower TG levels but

did not affect TC levels after 6 weeks of regular use of one tablespoon of *A. vera* along with glibenclamide [98]. As previously stated, high blood glucose levels result in elevated blood lipid levels in diabetics. Perhaps, improved glycaemic control in patients receiving glibenclamide and *A. vera* may have reduced triglyceride levels, though the effect remained modest in magnitude. Another study found that consuming a high molecular weight fraction of *A. vera* containing less than 10 ppm of barbaloin and polysaccharide (MW: 1000 kDa) with glycoprotein, verectin (MW: 29 kDa) for 12 weeks (2 tablespoons three times a day) could lower serum triglyceride levels without affecting cholesterol levels, with no evidence of renal or hepatic toxicity [99].

Another study found contradictory results, with 300 mg of *A. vera* extract given to diabetics resistant to oral hypoglycaemic agents and using insulin for two months showing a significant decrease in FBG and HbA1c levels without any significant effects on the lipid profile. The lack of response in this study could be attributed to chronic hyperglycemia in patients, which can cause oxidative stress, or to the low dose of *A. vera* [100]. Over 8 weeks, a pilot study of two aloe products (UP780 and AC952) in patients with prediabetes/metabolic syndrome reported that the AC952 resulted in significant reductions in TC and LDL-C levels, as well as concomitant reductions in blood glucose levels, HbA1C levels, and improved insulin sensitivity. However, it was not found to be effective in lowering triglyceride levels and increasing HDL-C levels in the serum [101]. These disparities in the therapeutical effects of different *A. vera* preparations could be attributed to several factors, including inconsistencies among studies in terms of standardization of the *A. vera* manufacturing process, dosing frequency, length of treatment, laboratory test units, and race of the patients chosen. Such variation complicates the interpretation of clinical findings [102]. Interestingly, another study reported that non-insulin-dependent diabetics supplemented with 100 mg and 200 mg of *A. vera* gel powder for 3 months combined with healthy lifestyles experienced a significant reduction in FBG levels of 11.4% and 15.4%, respectively, and postprandial glucose level of 18.5% and 27.8%. TC was reduced by 8.6% and 10.1%, TG by 9.6% and 12.2%, LDL-C by 12.8% and 14.6%, VLDL by 9.6% and 12.2%, and an increase in HDL-C by 7.3% and 9.4% was observed. Total cholesterol to HDL-C ratio reduced from 5.6 to 4.8 and 6.1 to 5.0, respectively, and LDL-C to HDL-C ratio decreased from 3.7 to 3.0 and 4.1 to 3.1. According to these findings, a 200 mg dose was more effective in improving blood glucose and lipoprotein metabolism in the diabetics [12]. In a randomized controlled trial of pre-diabetics, A. vera 300 mg (AL300), 500 mg (AL500), and placebo (PL) capsules were taken twice daily. FBS, HbA1C, and lipid profiles were measured at baseline, 4 weeks, and 8 weeks. It was observed that using A. vera in pre-diabetics can significantly regulate blood glucose levels within four weeks and revert lipid profile levels within eight weeks [103]. This implies that the *A. vera* dose needed to normalize lipid levels is higher than the dose required to regulate blood glucose levels. These results are consistent with the findings of Choudhary et al. and that the duration of treatment may also play a role in regulating blood lipid levels [12]. The phytosterols present in *A. vera*, which are similar in structure to cholesterol and aid in lowering serum cholesterol concentrations by reducing the absorption of cholesterol from the gut by competing for the limited space for cholesterol in mixed micelles, could be attributed to the per cent reduction in TC. Increased hormone-sensitive lipase activity as a result of IR increases free fatty acid release from fat tissue. As a result of the FFA accumulation in plasma, the hepatic production of phospholipids and cholesterol increases. This can raise the level of triglycerides in the blood, which raises the level of lipoproteins in the blood. It has been postulated that *A. vera* can lower blood lipid levels by regulating fat metabolism in the liver [104]. Furthermore, two studies investigated the effects of polyherbal formulations containing *A. vera* in addition to conventional drugs on diabetic patients with uncontrolled dyslipidemia. Serum TG, total cholesterol, LDL, and HbA1c levels improved significantly in the intervention group, and the tested compound, as an add-on, was efficient in decreasing serum lipids in diabetics with uncontrolled dyslipidemia [105,106]. In both studies, no untoward effects on the liver and kidney were observed. In obese individuals with prediabetes or early untreated diabetes, administration of Aloe QDM complex for 8 weeks reduced fasting blood glucose, body weight, body fat mass, and IR [107]. Another randomized double-blind placebo-controlled clinical trial suggested that 300 mg of Aloe gel capsule for 2 months in 30 hyperlipidemic type 2 diabetics significantly reduced FBG, HbA1c, TC and LDL levels without any significant effects on liver/kidney function tests suggesting it to be safe for antihyperglycemic and anti-hypercholesteraemic agent [108] Table 5 briefly summarizes the clinical trials.

Table 5
Hypoglycaemic and hypolipidemic effects of *A. vera* in clinical studies.

Study type	Duration	Beneficial effects	Study population	Reference
Randomized controlled clinical trial	5 years	Decrease in TC, TG,LDL-C, FBG and postprandial blood glucose	5000 diabetics	[95]
Controlled clinical trial	84 days	Reduced TC by 15.4%, TG by 31.9% and, LDL by 18.2%	60 hyperlipidemic patients	[96]
Controlled clinical trial	42 days	Reduced FBG, triglycerides	72 diabetics	[97]
Controlled clinical trial	42 days	Reduced FBG, triglyceride levels	36 diabetics	[98]
Uncontrolled clinical trial	84 days	Decreased blood glucose and triglyceride levels. Improved HbA1c levels	15 diabetics	[99]
Double blind-placebo controlled clinical trial	61 days	Decrease in FBG and HbA1c	35 diabetics	[100]
Double blind-placebo controlled clinical trial	56 days	Decrease in FBG, HbA1c, TC, LDL-C	45 pre-diabetics	[101]
Placebo controlled clinical trial	90 days	Reduced FBG, TC, TG, VLDL, LDL-C, HbA1c, TC:HDL and increase in HDL-C	90 diabetics	[12]
Open label phase 1 trial	40 days	Decreased FBG, HbA1c, TC, LDL and triglycerides	30 diabetics	[105]
Randomized controlled trial	84 days	Decreased HbA1c, TC, LDL and triglycerides	50 diabetics	[106]
Randomized controlled trial	56 days	Reduced FBG, insulin resistance, body weight and body fat mass	136 pre-diabetics	[107]
Randomized-double blind placebo controlled clinical trial	61 days	Reduced FBG, HbA1c, TC and LDL levels	30 diabetics	[108]

3. Conclusion

From this review, shreds of evidence strongly suggest that the oral administration of *A. vera* may be effective in improving blood glucose homeostasis and lipid metabolism. However, many studies are associated with limitations. The most significant limitation is that not all of the preparations of *A. vera* included reviewed here were assumed to be equivalent in composition and bioactivity, which could result in variations in glucose-lowering and hypolipidemic effects. Given the widespread use of *A. vera*, the lack of controlled clinical trials is perhaps the most surprising finding. Other limitations include a lack of random sampling, a lack of blinding, and the sample size in various studies. Because of the variation in the dosage used in clinical trials, determining the minimum effective dose of *A. vera* that can produce beneficial effects in clinical studies is difficult. Except for one 5-year study, the selected trials used *A. vera* for 6–12 weeks. Given the short duration of these studies, the long-term safety of *A. vera* consumption appears to be uncertain. Despite some limitations, the current findings are promising and can be useful for future research. Thus, prospective trial investigators must include surveillance time - frame in clinical trials to oversee any medium-to long-term adverse events associated with *A. vera* use.

Furthermore, future research should focus on the effect of *A. vera* on other lipid metabolism targets by modulating adipogenesis and adipolysis-related transcriptional factors such as peroxisome proliferator-activated receptors (PPARs) and UCP-1 (mitochondrial uncoupling protein). Its beneficial effects on Ghrelin, Leptin, Neuropeptide Y, and adiponectin, all of which are important targets for obesity, can also be investigated further. Integrating modern diagnostic procedures with complementary and/or alternative medicine would go a long way toward achieving any society's health and well-being.

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Authors contribution

Neha Deora: Lead author carried out conceptualization, review of literature, data collection, curation, validation, manuscript writing, reviewing, editing text and art work.

Krishnan Venkataraman: Conceptualization, review of literature, manuscript, editing text, art work and correspondence of the manuscript.

Both the authors have read the manuscript and accepted the content for publication.

Declaration of Competing Interest

None.

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