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REVIEW

Hypoglycemic and Hypolipidemic Effects of *Aloe vera* Extract Preparations: A Review

Ramesh Pothuraju,[1]* Raj Kumar Sharma,[1] Suneel Kumar Onteru,[1] Satvinder Singh[1] and Shaik Abdul Hussain[2]

[1]Division of Animal Biochemistry
[2]Dairy Technology Division, National Dairy Research Institute, Karnal 132001, Haryana, India

Obesity is considered to be an epidemic disease, and it is associated with several metabolic disorders. Pharmacological treatments currently available are not effective for prolonged treatment duration. So, people are looking toward new therapeutic approach such as herbal ingredients. Since ancient periods, different herbs have been used for remedy purposes such as anti-obesity, antidiabetes, and antiinflammatory. Among the several herbal ingredients, *Aloe vera* (*Aloe barbadensis* Miller) is widely used to curb the metabolic complications. Till date, reports are not available for the side effects of *A. vera*. Several researchers are used to different solvents such as aqueous solution, alcohol, ethanol, and chloroform for the *A. vera* extract preparations and studied their hypoglycemic and hypolipidemic effects in animal and human studies. Furthermore, little information was recorded with the active compounds extracted from the *A. vera* and their anti-obesity and antidiabetic effects in clinical studies. In this review, we made an attempt to compile all the available literature by using different search engines (PubMed, Scopus, and Google Scholar) on the *A. vera* extract preparations and the possible mechanism of action involved in carbohydrate and lipid metabolism. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: Aloe vera; obesity; diabetes; hypoglycemic; hypolipidemic.

INTRODUCTION

Energy balance is an equilibrium between the amount of energy extracted from the diet and the amount expended. The body can deal with the excess calories consumed through diet by several ways: (1) it stores as triglycerides (TG) in the adipose tissue; (2) it can burn by means of physical exercise; and (3) it can divert into heat production (a process called thermogenesis) by uncoupling protein (UCP) in the mitochondria (Nelson and Cox, 2008). Obesity is defined by means of body mass index, which is a ratio of body weight in kilograms divided by the height of square meters (kg/m^2). The World Health Organization and National Institutes of Health have defined obesity as having body mass index greater than $30\,kg/m^2$ (Nguyen and El-Serag, 2010). In obesity, alteration in the energy balance further leads to several metabolic disorders including insulin resistance (IR), type 2 diabetes mellitus (T2DM), retinopathy, neuropathy, nephropathy, and cardiopathy. The hallmark of T2DM is IR in which the body is unable to respond to the action of insulin to clear circulatory glucose levels. Different molecular mechanisms are involved in the IR; for example, insulin is unable to activate insulin receptor substrate 1 (IRS-1) because of serine–threonine phosphorylation of IRS-1 instead of its tyrosine phosphorylation. Because of serine–threonine phosphorylation, the glucose transporter -4 (GLUT-4) could not relocate into the plasma membrane for its glucose uptake. Accumulation of free fatty acids (FFAs), inflammation, and oxidative stress are also responsible for the cause of IR, which is not yet well studied at the molecular level (Bunner *et al.,* 2014). Both genetic and environmental factors may have a role for the development of IR. In diabetes, increased circulatory glucose and insulin levels lead to increase the mobilization of FFAs from the adipose tissue to the blood. These circulatory FFAs further accumulate in several organs (liver, kidney, and muscle), and the development of IR occurs mostly in the muscle tissue. Recent reports suggested that more than 300 and 439 million people are considered to be obese and diabetic, respectively (Pothuraju *et al.,* 2014).

Current pharmacological treatments for obesity and diabetes are as follows: orlistat (a potent inhibitor of pancreatic lipoprotein lipase), which is able to decrease the fat absorption and to excrete it into the feces; sulfonylurea (which stimulates insulin release from the pancreas); and pioglitazone (which is able to reduce IR). However, utilization of these drugs are associated with several side effects including gastrointestinal problems, malabsorption, reduced gall bladder function, weight gain, and heart and kidney failure (Mancini and Halpern, 2006). So, people are looking for alternative therapies such as herbal medicines for the treatment of several metabolic diseases as mentioned earlier. Herbal ingredient like *Aloe vera* is being used since ancient periods because of their anti-obesity, antidiabetic, and antiinflammatory properties. Review articles on the effect of *A. vera* on psoriasis (Miroddi *et al.,* 2015), cutaneous wounds

* Correspondence to: Ramesh Pothuraju, Division of Animal Biochemistry, National Dairy Research Institute, Karnal, 132001, Haryana, India.
E-mail: rameshbabu933@gmail.com

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(Hashemi *et al.,* 2015), phlebitis (Zheng *et al.,* 2014), and papers describing *A. vera* as a laxative property (Cirillo and Capasso, 2015) and its effects in dentistry (Mangaiyarkarasi *et al.,* 2015) can be found. Till date, scanty reviews are available for the treatment of obesity and diabetes with reference to *A. vera*, and none of the authors reviewed the role of different extract preparations in this area. Therefore, in view of the previous concern, we focused to review the different *A. vera* extract preparations to evaluate their active components that play a significant role in hypoglycemic, hypolipidemic, and antiinflammatory effects and analyzed their possible mechanism of actions involved in animal and clinical studies.

ALOE VERA AND ITS COMPOSITION

A. vera is one of approximately 420 species of genus *Aloe*. It is also referred as *Aloe barbadensis* Miller belonging to the Liliaceae family. *A. vera* origin is believed to be in Sudan, and subsequently, it was introduced throughout the world. It is being used as a folk medicine in several countries like India, China, South Africa, and Japan. However, it was first clinically used for the treatment of skin burns and wound healing in 1930 because of its ability to increase the collagen synthesis. It is being used as a laxative because of the reduction of the intestinal absorption of water and the improvement of bowel movements (Dagne *et al.,* 2000; Grindlay and Reynolds, 1986). In addition, it is used as a functional food, especially in health drinks and beverages in food industry, and as an active ingredient in gels, ointments, tablets, and capsules in pharmaceutical industry. Several phytochemicals, which include anthraquinones (barbaloin), phytosterols, carbohydrates, chromes, enzymes, vitamins, amino acids, and proteins, are present in *A. vera* (Hamman, 2008).

BIOLOGICAL ACTIVITIES

A. vera is being used for anti-obesity, antidiabetic, antiinflammatory, immune modulator, antioxidant, and anticancer effects since ancient periods. The possible mechanism of action of *A. vera* on different organs has been depicted in Fig. 1. A hypoglycemic (lowering of blood glucose levels) property of *A. vera* is associated with pancreatic insulin synthesis and its secretion (Ajabnoor, 1990). However, phytosterols that are present in the *A. vera* are not extensively absorbed from the intestine, but they can bind to the cholesterol and prevent its absorption to show a hypolipidemic effect (lowering of blood lipid levels) (Ralph and Provan, 2000). Ishii *et al.* (1990) reported that anthraquinones (barbaloin and isobarbaloin) are poorly absorbed in the small intestine and are broken down into active metabolites aloe-emodin-9-anthrone and aloe-emodin in the large intestine. These active metabolites are having laxative properties to prevent water absorption by inhibiting Na+/K+ ATPase activity. In addition, aloe-emodin is a potent inhibitor of urokinase (convert plasminogen to active plasmin), the secretion of which is involved in angiogenesis (Cardenas *et al.,* 2006). The polysaccharide (acemannan) of *A. vera* is responsible for the activation of macrophages to secrete cytokines, *viz*. tumor necrosis factor-alpha (TNF-α), interleukin 1 & 6 (IL-1 & 6) and interferon-γ. The active components present in the *A. vera* showed an antiinflammatory activity by inhibiting the cyclooxygenase in arachidonic acid pathway (Ulbricht *et al.,* 2008). The pancreatic β islets destruction is associated with its DNA damage by free radicals, which further leads to damage of other organs. The low antioxidant effect is associated with the lower levels of glutathione peroxidase and superoxide dismutase in pancreatic cells (Beppu *et al.,* 2003). The presence of phenolic and flavanoid compounds in the *A. vera* is responsible for the scavenging of both superoxide and

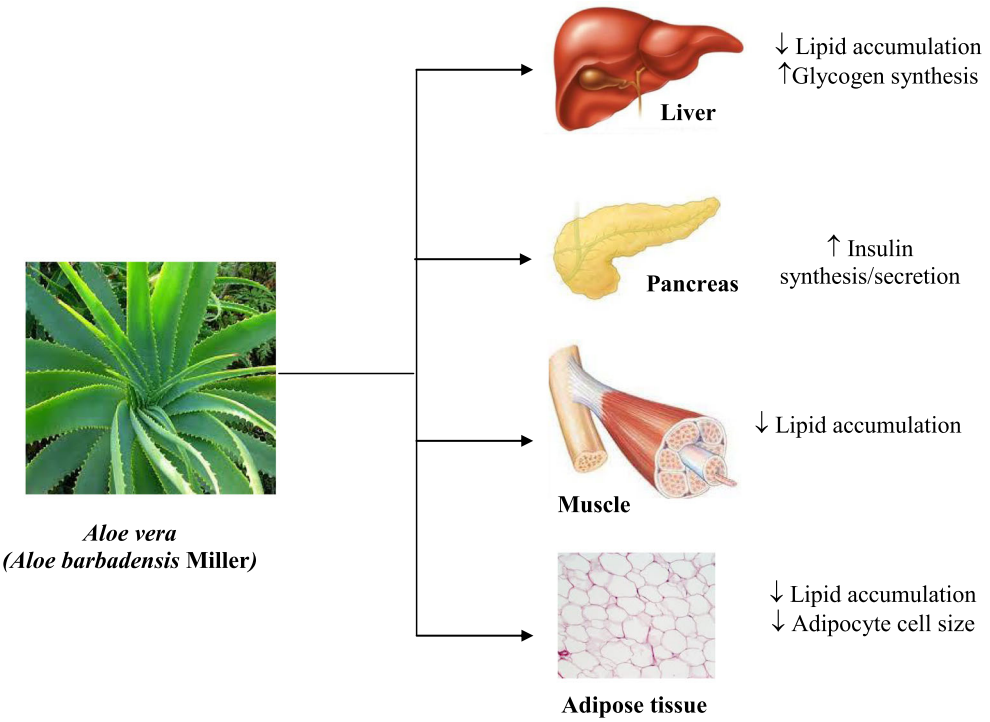

Figure 1. Effect of *Aloe vera* on different organs in obesity and diabetes management. This figure is available in colour online at wileyonlinelibrary.com/journal/ptr.

peroxyl radicals, respectively (Langmead *et al.,* 2004). Phytosterols (lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartanol, and 24-methylene-cycloartanol) isolated from *A. vera* gel extract (AVGE) showed a significant decrease in the fasting blood glucose and glycated hemoglobin (HbA1C) levels in diabetic mice (Tanaka *et al.,* 2006).

EFFECT OF DIFFERENT *ALOE VERA* EXTRACTS ON OBESITY AND DIABETES MANAGEMENT

Different solvents (methanol, ethanol, chloroform, and aqueous solvent) were used for *A. vera* extract preparations to study their hypoglycemic and antihyperlipidemic effects. In the following section, we are going to discuss the effects of different *A. vera* extracts on glucose and lipid metabolism in animal and human studies.

HYPOGLYCEMIC AND HYPOLIPIDEMIC EFFECTS

Because of less insulin secretion or its action, the increase in circulatory glucose levels are responsible for an increase in the FFAs by the action of hormone-sensitive lipase from adipose tissue in the blood. The excess FFAs in circulation enter into the liver for the synthesis of TG and further lipoprotein biosynthesis. Liver plays a vital role in glucose and lipid metabolism. In diabetes, its function is affected and results in liver steatosis (accumulation of lipids) (Seifter and England, 1982; Brixova, 1981). The supplementation of ethanolic extract of *A. vera* leaf gel (300 mg/kg body weight) in diabetic rats showed an increase in the plasma insulin levels from remnant or regenerated pancreatic β-cells, whereas blood glucose levels were brought to normal. In addition, *A. vera* extract administration also showed a decrease in the plasma lipids, liver cholesterol, and kidney TG levels (Rajasekaran *et al.,* 2006). In conclusion, phenolic and saponin compounds present in the *A. vera* extract might be responsible for hypoglycemic and hypolipidemic effects. Beppu *et al.* (2006) demonstrated that 10-KDa fraction powder of Kidachi aloe leaf skin can protect against the streptozotocin (STZ)-induced pancreatic β-cell damage because of the presence of anthrachinonic derivatives (aloenin and barbaloin). The anthrone and phenolic compounds, which are present in the plant, are metabolized in the intestine and enter into the circulation to show the biological effects.

The polyphenol-rich (aloin 18.17% and aloe-emodin 0.36%) extract of *A. vera* (350 mg/kg body weight) administration to the Institute of Cancer Research insulin-resistant mice for 4 weeks showed a significant decrease in the fasting blood glucose and a slight increase in the plasma insulin levels, respectively. The possible mechanism is that *A. vera* acts like a fiber effect to delay intestinal digestion and absorption (Wolever *et al.,* 2004). In addition, aloin and high-molecular weight polysaccharides present in the *A. vera* might be having a fiber-like effect. Another important point is that IR in muscle, liver, and adipose tissue is associated with the inflammation. Reduction of pro-inflammatory cytokine secretion by *A. vera* could manifest toward a positive effect against of IR (Perez *et al.,* 2007). Another study by Noor *et al.* (2008) demonstrated that oral feeding with ethanolic *A. vera* extract (300 mg/kg body weight) to diabetic rats for 3 weeks showed a reduction in the fasting blood glucose levels by 50%. They explained that *A. vera* may prevent the damage of pancreatic β-cells or it may recover the partially destroyed β-cells. Similarly, Misawa *et al.* (2008) administered *A. vera* phytosterols (lophenol-Lo and cycloartanol-Cy at 25 μg/kg/day) to Zucker diabetic fatty (ZDF mutation in the leptin receptor, which spontaneously develops severe obesity, hyperglycemia, hyperlipidemia, and IR) rats for 44 days and showed that the random blood glucose and HbA1C levels were statistically decreased and glucose tolerance levels were improved in ZDF rats. Furthermore, phytosterols also reduced the serum FFA and TG levels but not total cholesterol (TC) levels. The lowering of serum FFA levels has additional beneficial effect on insulin sensitivity and insulin secretion, because FFAs are responsible for the development of IR. Researchers thought that no effect on TC levels might be due to the low dosage of *A. vera* phytosterol administration to ZDF rats. Kim *et al.* (2009) reported that oral administration of processed *A. vera* gel (PAG-25, 50 and 100 mg/kg body weight) to diabetic mice for 8 weeks displayed an increase in insulin sensitivity and insulin levels and a reduction in the plasma lipids and liver TG levels.

GUT MICROBIOTA

The gut microbiota plays an important role in obesity that is, in part, still controversial. More than 10^{12} microorganisms are inhabited in the gastrointestinal (GI) tract (Park *et al.,* 2013). Of these, Firmicutes and Bacteroidetes are the major phyla, and alteration of the aforementioned phyla occurs in the GI tract of obese and lean subjects (Arumugam *et al.,* 2011). Several active compounds (anthraquinones, polyphenols, and acemannan) present in the *A. vera* become a major dietary energy source for bacterial growth and are metabolized in the large intestine. For example, acemannan, an important polysaccharide made of β 1→4 glycosidic bond, cannot be degraded in the human GI tract, but it is converted into short-chain fatty acids (SCFAs) such as acetate, butyrate, and propionate by the intestinal gut microbiota under anaerobic conditions (Yagi *et al.,* 1999). Studies showed that SCFAs may have positive and negative effects on both beneficial and harmful microorganisms. Acetate and propionate bind to the G protein-coupled receptors/free fatty acid receptor 2 (GPR43/FFAR2), while butyrate and propionate bind to GPR41/FFAR3. Both receptors are expressed in the intestine and activate adenosine monophosphate activated protein kinase pathway for the β-oxidation of fatty acids to decrease adiposity. Figure 2 showed the possible effects of SCFAs through mediation of GPR/FFAR in relation to the obesity.

A. vera extracts (0.5%, 1%, 1.5%, and 2% w/v) incubated with mixed bacterial cultures for 24 and 48 h showed an increase in the butyric acid production (Pogribna *et al.,* 2008). In our previous study, the effect of *A. vera* gel powder (0.5% and 1% w/v) on angiotensin-converting enzyme inhibitory activity (which is linked with the antihypertensive effect), the extent of proteolysis during fermentation, and the survival of milk fermented by

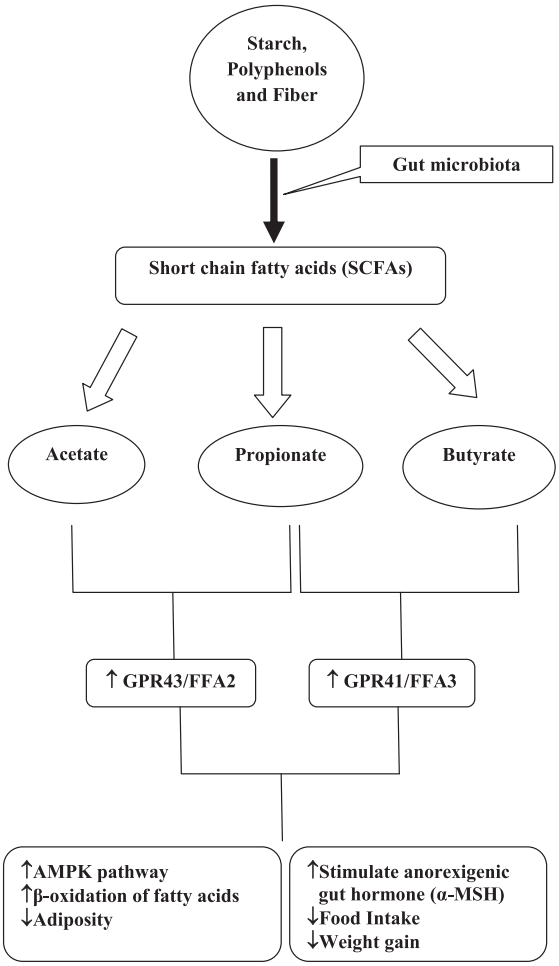

Figure 2. Possible effects of SCFAs (acetate, propionate, and butyrate) on regulation of adiposity through G-coupled receptors (abbreviations: GPR, G protein-coupled receptor; FFA, free fatty acid; AMPK, adenosine monophosphate-activated protein kinase; MSH, melanocyte-stimulating hormone).

Lactobacillus casei during storage were studied. We observed that, in the presence of *A. vera* (0.5% and 1% w/v), the extent of proteolysis (0.460 ± 0.047 and 0.480 ± 0.027), the percentage of angiotensin-converting enzyme inhibitory activity (44.32 ± 2.83 and 47.52 ± 1.83), and the viable counts of *L. casei* (>11 log cfu/mL) during the 7-day storage period was increased (Basannavar *et al.,* 2014). Increased butyric acid production was responsible for the growth of lactobacilli and bifidobacteria, while decreased lipopolysaccharides (which are released from the harmful bacteria) are responsible for an increase in the intestinal permeability, leading to the degradation of intestinal tight junction proteins (ZO1 and occludin). An increase in the circulatory lipopolysaccharide levels results in metabolic endotoxemia, which further developed into inflammation and metabolic disorders (Cani *et al.,* 2008). In addition, intestinal fasting-induced adipose factor (a lipoprotein lipase inhibitor) expression was affected by the alteration of gut microbiota. Other hormones (ghrelin, cholecystokinin, and neuropeptide YY) secreted from the GI tract operated through satiety signals in obesity and diabetic individuals. However, no information was available in this regard on how the *A. vera* extract may act on gut-related hormones to play a significant important role in the hypoglycemic and hypolipidemic effects. Therefore, further studies are necessary to strengthen the role of *A. vera* on gut microbiota.

ANTIOXIDANT ACTIVITY AND BIOCHEMICAL MARKERS

In diabetic state due to insulin depletion, structural degenerative changes of the liver result in less antioxidant property, which leads to loss of detoxification function of glutathione activity and, in turn, elevates reactive oxygen species levels. Moreover, an increase in the circulatory glucose levels in diabetes is responsible for the nonenzymatic glycosylation of proteins in the liver. In addition, lipid peroxidation (LPO) was also observed in the liver damage. The biochemical markers of liver such as alkaline phosphatase and alanine transaminase (ALT) levels were elevated in the serum because of hepatic damage (Wohaieb and Godin, 1987; Saito-Yamanaka *et al.,* 1993). Can *et al.* (2004) administrated *A. vera* leaf pulp (500 mg/kg) and gel (63 mg/kg body weight) extracts to STZ-induced diabetic rats for 15 days. At the end of the experiment, a significant increase in the glutathione levels and nonenzymatic glycosylation of proteins and a decrease in the LPO and liver marker enzymes (alkaline phosphatase and ALT levels) were noted in diabetic animals. In conclusion, both *A. vera* extracts had protective effect against hepatic damage, and the effect of glibenclamide used in this study is to increase insulin secretion.

An increase in the circulatory glucose levels (hyperglycemia) was observed because of pancreatic β-cell damage. Hyperglycemia is also associated with increased production of free radicals, which results in damage of the cell membrane and its function (Baynes, 1991). Enzymes that are present in the cell membrane play an important role in the maintenance of electrolyte balance and ionic gradient for the cotransport of amino acids and sugars (Sweeney and Klip, 1998). Na+−K+ ATPase is a membrane enzyme responsible for the transport of sodium and potassium ions across the membrane by generating gradient system to regulate cell volume and nutrient uptake (Hernández, 1992). The inactivity of Na+−K+ ATPase and other Ca+ and Mg+ ATPase activities were observed because of the oxidation of thiol groups in ATPase by reactive oxygen species, especially in diabetes (Thomas and Reed, 1990). In addition, lysosomal enzymes such as β-D-glucuronidase, β-D-N-acetyl glucosaminidase, acid phosphatase, and cathepsin-D activities were also increased. The ethanolic extract of *A. vera* supplementation restores the membrane-bound phosphatase and lysosomal hydrolase activities in STZ diabetic rats (Rajasekaran *et al.,* 2005a, 2005b, 2007).

Another important biochemical marker is glucose 6 phosphatase (G6Pase), which catalyzes the final reaction of liver glycogenesis and gluconeogenesis. The enzyme activity was increased in diabetic state. Administration of aqueous extract of *A. vera* leaf gel (AALGEt-300 mg/kg body weight) restores the G6Pase activity in alloxan-induced diabetic rats. They suggested that lowering of blood glucose levels with AALGEt might be similar with the hypoglycemic agent, that is, metformin (Mogale *et al.,* 2011). Similarly, Mohamed (2011) reported that oral administration of AVGE showed antioxidant activity by decreasing the serum malondialdehyde (an LPO product) levels and by increasing the activity of serum nitric oxide activity in diabetic rats. In another study, *A. vera* leaf extract showed inhibition of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals because of more phenolic and flavanoid contents (Moniruzzaman *et al.,* 2012).

GENE EXPRESSION STUDIES

White adipose tissue is a major site for energy storage and is important for energy homeostasis. It has been increasingly recognized as an important endocrine organ that secretes a number of biologically active 'adipokines' (Lazar, 2006). Some of these adipokines have been shown to be directly or indirectly involved in glucose and lipid metabolism (Kershaw and Flier, 2004). In addition to its classical function as an energy storage depot, adipose tissue produces a number of adipokines such as adiponectin, leptin, resistin, UCP-2, TNF-α, IL-6, and peroxisome proliferator-activated receptor-gamma (PPARγ), which have significant roles in the regulation of insulin sensitivity and other physiological processes.

The PPARγ is a member of the PPAR subfamily of nuclear hormone receptors. The name PPAR derives from the ability to induce peroxisome proliferation. It is a ligand-activated transcription factor with a major role in the development of adipose cells and also serves as the receptor for an important class of antidiabetic drugs. It plays a dominant role in adipose cell differentiation and modulates metabolism and inflammation. These compounds increase insulin sensitivity in both rodents and humans; hence, these are useful in the treatment of type 2 diabetes (Sears *et al.,* 1996).

A. vera phytosterols (lophenol-Lo, 24-methyl-lophenol 24-M-Lo, and 24-ethyl-lophenol 24-E-Lo) showed the upregulation of PPARα and PPARγ expressions at both 10- and 50-μM concentrations, respectively, in a dose-dependent manner (Nomaguchi *et al.,* 2011). Administration of *A. vera* phytosterols (Lo and Cy) to diet-induced obese mice results in the increase of expression of genes related to fatty acid transport (Acsl1), fatty acid oxidation (Acaa1a, Acox1, Cpt1a, Cpt2, Cyp4a10, and Cyp4a14), cholesterol metabolism (Cyp7a1), ketogenesis (Hmgcs2), gluconeogenesis (Pck1), lipogenesis (Fads2, Scd1, and Scd2), and PPAR signaling (Retenoid X Receptor-RXR) compared with high-fat diet (HFD) group. To conclude, phytosterols act as ligands for both PPARα and PPARγ expressions for the regulation of genes involved in the liver lipid metabolism.

Different glucose transporter systems are available for the glucose export into the cells by concentration gradient. The major system is GLUT-4, which is highly expressed in the adipose tissue and muscle. Several researchers reported that *A. vera* supplementation had shown glucose-lowering effect. Kumar *et al.* (2011) demonstrated that lyophilized aqueous *A. vera* extract (1 mg/mL) upregulated GLUT-4 gene expression in mouse embryonic fibroblast (NIH/3T3) cells. The increased expression of GLUT-4 by *A. vera* was due to stimulatory effects on cytoskeletal proteins to transport GLUT-4 vesicle from the cytoplasm to the plasma membrane. They suggested that before using as a drug, toxicological analysis needs to be performed because of potential toxic residues present in it.

As previously mentioned, accumulation of lipids takes place other than adipose tissue (i.e., liver): this could result in diseases known as fatty liver disease, namely alcoholic fatty liver (excess intake of alcohol) and nonalcoholic fatty liver diseases. Excessive alcoholic consumption leads to accumulation of TG and cholesterol levels in the liver. In alcoholic fatty liver disease, *de novo* fatty acid synthesis is increased, and lipid oxidation is inhibited (Diehl, 2004; Walsh and Alexander, 2000; Purohit *et al.,* 2009). Furthermore, mRNA expression of PPARα and its target genes such as carnitine palmitoyl CoA transferase-1, acyl-CoA oxidase, and medium chain acyl-CoA dehydrogenase expressions were decreased. Saito *et al.* (2012) reported that AVGE administration to ethanol-induced transient fatty liver in mice showed no effect on PPARα target genes. The reason might be that a significant increase in the PPARα mRNA expression was not sufficient to prevent ethanol-induced fatty liver. But ethanol-induced TG accumulation was observed because of the increased expression of the lipogenic genes like sterol regulatory element-binding protein-1, fatty acid synthase, stearoyl-CoA desaturase 1, and diacylglycerol acyltransferase 2 expression levels. The AVGE supplementation as mentioned brought lipogenic genes to normal. They speculated that accumulation of lipids in the liver by means of ethanol and HFD supplementation was decreased by AVGE treatment in fatty liver mice.

Misawa *et al.* (2012) studied the effect of aloe phytosterols (Lo and Cy) on liver glucose and lipid metabolism in ZDF rats. They observed that phytosterols significantly upregulated glucose kinase and downregulated gluconeogenic enzymes (G6Pase and phospho-enol-pyruvate carboxykinase) in rats by stimulating glucose breakdown and suppression of *de novo* glucose synthesis. In contrast, hepatic pyruvate dehydrogenase kinase 4 expression was suppressed upon aloe sterols administration. A decrease in the pyruvate dehydrogenase kinase 4 expression by phytosterols might be helpful to prevent the glucose utilization. In addition, lipogenic enzymes, acetyl-CoA carboxylase, and fatty acid synthase expression were downregulated by aloe sterols to prevent the endogenous fatty acid synthesis and increased the fatty acid oxidation in the liver. PPARα is a ligand-activated transcription factor expressed in the liver to activate β-oxidation by controlling target genes such as acyl-CoA oxidase and carnitine palmitoyl-transferase levels (Hus and Huang, 2006). These target genes were upregulated by oral administration of aloe sterols in ZDF rats. It was concluded that Lo and Cy phytosterols were absorbed in the small intestine and enter into the liver via systematic circulation to show the hepatic gene regulations in glucose and lipid metabolism. In our recent study, administration of *A. vera* gel powder (1% w/w) added to HFD along with probiotic fermented milk by *Lactobacillus rhamnosus* to C57BL/6J mice for 12 weeks showed a downregulation of pro-inflammatory cytokine (TNF-α and IL-6) levels and an upregulation of adiponectin and UCP-2 mRNA expression levels (Pothuraju *et al.,* 2015).

CLINICAL STUDIES

In Table 1, studies showed clinical trials involving the effect of different *A. vera* preparations. Oral administration of *A. vera* high-molecular weight (AHM-0.05 g) fractions containing polysaccharide (acemannan) and glycoprotein (verectin) daily three times for 12 weeks to diabetic patients showed a decrease in the fasting blood glucose and TG levels and no effect on TC levels as well as on serum aspartate transaminase and ALT

Table 1. Studies on clinical trials involving the effect of *Aloe vera* preparations

Study type	Dose	Patients (no.)	Results	Duration (weeks)	Adverse effects	Reference
—	0.05 g, three times per day	15	↓ FBG and TG levels ↓ HbA1C No effect on TC, AST, ALT, and creatinine levels	12	None	Yagi *et al.* (2009)
Randomized double blind	300 mg	30	↓ FBG and HbA1C levels ↓ LDL-C and TC levels	8	None	Huseini *et al.* (2012)
Randomized controlled trial	147 mg	136	↓ body weight and body fat mass ↓ FBG and insulin levels	8	None	Choi *et al.* (2013)
Double blind	500 mg	45	↓ FBG, HbA1C, and insulin levels ↓ TC and LDL-C levels	8	None	Devaraj *et al.* (2013)
—	100 and 200 mg	90	↓ FBG, TC, TG, LDL-C, and VLDL-C levels ↑ HDL-C ↓ blood pressure	12	None	Choudhary *et al.* (2014)
Randomized controlled trial	300 and 500 mg	72	↓ FBG, HbA1C, TC, and LDL-C ↑ HDL-C	8	None	Alinejad-Mofrad *et al.* (2015)

FBG, fasting blood glucose; TG, triglycerides; HbA1C, glycated hemoglobin; TC, total cholesterol; AST, aspartate transaminase; ALT, alanine transaminase; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

levels (Yagi *et al.*, 2009). They observed that the biological effect of AHM was due to the presence of acemannan, which is degraded by the intestinal microbiota to form oligosaccharides to inhibit intestinal glucose absorption (Yagi *et al.,* 2001; Jain *et al.,* 2007; Boban *et al.,* 2006). Similarly, oral administration of *A. vera* leaf gel containing an active compound, that is, acemannan (600-mg capsule/day), to T2DM patients for 60 days showed a decrease in the blood glucose, TC, and low-density lipoprotein cholesterol (LDL-C) levels and no effect on TG and high-density lipoprotein cholesterol levels (Huseini *et al.,* 2012). In conclusion, it was speculated that large number of sampling is required to assess the antihyperglycemic and antihyperlipidemic effect of *A. vera* gel in diabetic patients. On the other hand, Choi *et al.* (2013) studied the metabolic effects of *A. vera* gel QDM complex in obese prediabetes or early-diabetes patients for 8 weeks. They observed that supplementation of *A. vera* QDM complex decreased body weight, body fat mass, and fasting blood glucose, and insulin levels significantly at the end of experiment. Similarly, administration of two aloe products (UP780 and AC952) to diabetic subjects for 8 weeks showed that a significant reduction in TC, LDL-C, and glucose levels was observed with AC952 only. However, in the case of UP780, a statistical decrease in the HbA1C and insulin levels demonstrate that the supplementation of *A. vera* inner leaf gel powder preparations could be an effective strategy for hypoglycemic and hypolipidemic effects (Devaraj *et al.,* 2013). Choudhary *et al.* (2014) reported an oral administration of *A. vera* gel powder at a dose of 100 and 200 mg for 3 months to noninsulin-dependent diabetic persons and observed a significant reduction in the fasting and postprandial glucose, blood pressure, TG, TC, LDL-C, and very LDL-C levels and a significant increase in the high-density lipoprotein cholesterol levels. They concluded that supplementation of *A. vera* gel powder to diabetic persons showed significant hypoglycemic and hypolipidemic effects. A recent study by Alinejad-Mofrad *et al.* (2015) reported an oral administration of *A. vera* extract (AL300 and AL500 mg twice a day) to prediabetic subjects for 8 weeks. After 4 weeks of treatment, fasting blood glucose levels are significantly lowered with AL300 alone, whereas HbA1C, TC, and LDL-C levels were significantly reduced by AL500 supplementation after 8 weeks.

TOXICITY AND SIDE EFFECTS

Up to now, no report is available in literature regarding a toxic effect of *A. vera* extract preparations. Oral administration of *A. vera* leaf gel extract (600-mg capsule/day) to T2DM patients for 60 days did not have any adverse effect on circulatory lipids and no effect on renal and liver tissues (Huseini *et al.,* 2012). Similarly, Yagi *et al.* (2009) reported that AHM fractions containing barbaloin and verectin administration to diabetic patients for 12 weeks determined no side effects and it was beneficial for peripheral blood vessel complications relief by activating immune system. However, in another study, oral supplementation of *A. vera* might cause diarrhea, and vomiting was observed because of contamination with anthraquinones present in the gel (Morrow *et al.,* 1980; Wang *et al.,* 2003; Chinnusamy *et al.,* 2009). In addition, oral administration of *A. vera* gel was reported to reduce higher plasma glucose levels in diabetic rats (Koo, 1994), while chronic administration of *A. vera* had positive effects in humans (Bunyapraphatsara *et al.,* 1996; Yongchaiyudha *et al.,* 1996). Different reports suggested that the part of *A. vera* and the extract preparations have different results.

CONCLUSION

To conclude, different *A. vera* extracts were prepared with several solvents for the management of obesity and diabetes. However, different extract preparations showed different effects for antihyperglycemic, antihyperlipidemic, and antioxidant activities in animal and human studies. However, scanty information was recorded with clinical studies. In addition, several researchers are focused on the whole extract of *A. vera* instead of the bioactive components, and future studies are required in this area for their possible mechanism of actions at molecular level.

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Conflict of Interest

The authors have declared that there is no conflict of interest.

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