



Effect of Apple Cider Vinegar on Glycemic Control, Hyperlipidemia and Control on Body Weight in Type 2 Diabetes Patients

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ABSTRACT

Diabetes mellitus is a world-widely public health issue associated with premature mortality, decreased quality of life and increased health-care expenditures. The aim of the review was to elevate the effect of apple cider vinegar on glycemic control, hyperlipidemia and obesity control in type 2 diabetes patients. Many clinical trials showed the hypoglycemic, hypolipidemic and anti-obesity effect of vinegar. Proposed mechanisms action of vinegar for the hypoglycemic, hypolipidemic effect are including slow gastric emptying, it promotes uptake of skeleton muscles glucose in the body and acetic acid may inhibit disaccharides activity in the small intestine blocking the complete digestion of starch molecules, suppression of hepatic glucose production and increased glucose utilization. Results of previous studies showed that apple cider vinegar has the potential of anti-diabetic, antihyperlipidemic and anti-obesity effects in diabetes mellitus patients. **Objective of review:** The objective of the current review study was to investigate the effect of apple cider vinegar on glycemic control, hyperlipidemia and control on body weight in type 2 diabetes patients and other therapeutic and commercial effect of apple cider vinegar. **Data sources:** To collect data for relevant literature PubMed, Google Scholar, science direct and Cochrane sources were used.

Keywords: Hyperlipidemia, Hyperglycemia, Vinegar, Obesity, Diabetes, Nutraceutical

INTRODUCTION

Diabetes mellitus (DM) has been considered as one of the most universal endocrine, metabolic disorders which is characterized by the irregular metabolism of fat, protein, and carbohydrate due to decreased efficacy of insulin secretion or altered insulin activity. Its occurrence worldwide has been increasing with the passage of time. About 14 million patients were suffering in DM in the United State and this ratio has been increasing by about 700,000 each year [1]. Diabetes has been categories into 3 major types: type I diabetes known as insulin dependent diabetes mellitus (IDDM) which result in deficiency of insulin, insulin resistance known as type II diabetes, it's also called non-insulin dependent diabetes (NIDDM) and gestational diabetes is known as type III diabetes which results in glucose intolerance during pregnancy [2].

DM is a global health issue and one of the 5th main mortality and morbidity causes in many areas of the world. More than 171 million people were affected by diabetes globally in the year 2000 and this figure is predicted to reach 366 million by the years 2030 [3,4]. Main causes of diabetes are impaired insulin secretion, insulin resistance and overproduction of hepatic glucose. Insulin resistance is not only a major contributor to diabetes development but also play a merely role in hypertension, dyslipidemia, and atherosclerosis [5]. A complication of diabetes includes cataract, nephropathy, retinopathy, wound infection and atherosclerosis [6]. Diabetes mellitus is a worldwide public health issue associated with premature mortality, decreased quality of life and increased health-care expenditures. The results of previous studies showed that diabetes prevalence is increasing with the passage of time in Pakistan. The

numbers of people affected with diabetes in Pakistan is 6.9 million and this will grow to 11.5 million according to the International Diabetes Federation by 2025 and urgent measures are required to control [7].

Natural food additives have been more popular in recent year for many ailments even showing without any evidence of medical benefits. Traditional beliefs of different racial groups and internet information are easy to access for preference and choices of different natural treatment for various diseases [7]. Natural food products have fewer side effects of this food as compared to medical therapies. Individuals with diabetic are prevailing about more than 1.6 times prone to use a substitute for medical products and complimentary food as compared to non-diabetics individuals [8]. Obese individuals are more prone, who are reluctant usually to decrease their intake of daily calories and use dietary supplements or alternative products for the reduction of their body weight and other beneficial metabolic effects [7].

A lot of medications are accessible for control of diabetes however common herbs are developing the interest of the general population for prevention and management of diabetes, apple juice vinegar have curing characteristic which can possibly control the blood glucose level, acetic acid an active component in apple juice vinegar with anti-glycemic effects. Actually simple inexpensive diet strategies are greatly needed for diabetes control. In the present study, the effect of oral apple cider vinegar consumption on blood biochemical factors in type 2 diabetic and hyperlipidemic patients were investigated.

Global Estimation of Diabetes

Diabetes mellitus is a common health issue all over the world and has been increasing with the passage of time in numbers and in its significance due to changing in lifestyle, decrease physical activities and developed obesity. To estimate the present and future situation of diabetes it is very important to improve the health of the community and resolve the health issues at all national and international level. There is a number of previous estimations of diabetes published by World Health Organization (WHO) for the years 2000 and 2030 with the help of 40 countries data [9-12].

According to the estimation by international diabetes federation in 2011, about 565 different data sources were reviewed of 110 countries and it has been found that 366 million people were suffering from diabetes mellitus and it is expected to rise to 552 million by the year 2030. Most people suffering from diabetes were living in those countries which have low and middle economic status and the burden of diabetes will increase in next 19 years and this global diabetes epidemic continues to grow in future by IDF estimation [13].

Prevalence of diabetes is increasing in all age group but the highest prevalence with specific age group 60-79 years is about 18.6% and the largest numbers of people with diabetes about 184 million is in the age group 40-59 years. In 2013, data of 130 countries were extracted by using 744 different data sources estimated by IDF, 382 million people were suffering from diabetes and also expected that it should be increased to 592 million by the year 2030. The reason for the diabetes epidemic is low and poor economic status and will rise in this epidemic in the future over the next 22 years [11].

Diabetes mellitus is also growing burden in Pakistan. A cross-sectional survey was conducted in rural and urban areas of 4 provinces of Pakistan. The diabetes prevalence in the rural and urban was 3.5% in women and 6.0% in men and newly diagnosed with diabetes was 5.1% in men and in women was 6.8% in urban and 5.0% in men and 4.8% in women in the rural areas. Obesity especially central obesity, age factors, and positive family history is a major risk factor for diabetes development [14].

A study was conducted to estimate the cost-effectiveness of diabetes mellitus in Pakistan. It is a first study conducted to estimate the cost of diabetes mellitus illness among 6 out patient's department clinics in Karachi. The direct cost of a patient with diabetes estimated was 11,580 Pakistani rupees per year, medicines expenses are a major share of direct cost (46%) and laboratory tests cost (32%) due to longer duration of disease. About 18% of the total family income is been spend on diabetes care among the poorest segment of society [15].

Prevention of Diabetes with Nutraceutical

Curcumin is a popular spice used in all over the Asian cuisine. Curcumin known as curcuminoid found in turmeric (*Curcuma longa Linn*) has anti-inflammatory and anti-diabetes effects [16]. A study was conducted on uses of curcumin extract for prevention of the diabetes type 2, this study shows that curcumin extract delay type 2 diabetes development

and improve beta cell functions, reduce insulin resistance and also reduced the numbers of pre-diabetes individual who are going to develop type 2 diabetes [17]. A double-blind placebo randomized cohort trial for 9-months show that 16.4% diabetic individual was diagnosed in placebo group significantly and none were diagnosed with type 2 diabetes in the curcumin treatment group, also better improvement in beta cell functions in the curcumin-treated group was observed as compared to the placebo group [18].

Polyphenols have unique properties of nutraceutical and supplementary treatment for various aspects of diabetes mellitus type 2. Polyphenols consisting of flavonoids, phenolic acids, and lignans stilbenes have potential efficacies for reduction of disorders and complication of diabetes mellitus. Polyphenols dietary plants and polyphenol-rich products attenuate hyperglycemia, insulin resistance, and dyslipidemia, improve adipose tissue metabolism and modulate carbohydrate, and alleviate oxidative stress. Long term diabetes complications like retinopathy, cardiovascular diseases nephropathy and neuropathy can be prevented by polyphenol compounds [19].

Many recent studies indicated that dietary polyphenol and polyphenol-rich fruits and vegetables are helpful for managing and preventing diabetes [20].

A single-blind randomized cross over study indicated that fiber-rich and polyphenol (PFRF) containing food have potential to effect on the glycemic index by lowering glucose absorption and also decreasing the glycemic response of polyphenol and fiber-rich food. The mechanism of PFRF inhibited alpha-amylase (strawberry, green tea, blackberry, and black currant) and activities of alpha-glycosidase (green tea) *in vitro* [21]. Fruits and vegetables that contain bioactive compound have been consider for the prevention of diabetes, cancer, cardiovascular diseases and is also used as an antibacterial, anti-aging and anti-inflammation agent [22].

A double-blind randomized control trial showed that cinnamon extracts water soluble for the prevention of pre-diabetes and diabetes as lowering glucose level, blood pressure, lipids and also decreases inflammatory markers and work as an insulin sensitizer in type 2 diabetes patients [23].

Water extract of cinnamon (insulin) 250 mg/capsules twice a day of spray dried have insulin potentiating activity lowering blood glucose, decreasing total cholesterol, LDL and enhanced insulin sensitivity in subjects with elevated blood glucose plasma in double-blind placebo randomized control trial [24].

A comprehensive review indicate that cinnamon can be an effective therapy for the reduction of blood sugar fasting and HbA1C in type 2 prediabetes, and diabetes patients result in 6 clinical trials indicate lowering potential for HbA1C and 10 clinical trials indicates reducing fasting blood glucose by using recommended dose of cinnamon (1 g to 6 g (500 mg BID)) with meal [25]. Cinnamon 1 g daily work as insulin sensitizer both in human and animals studies and can be a safe supplement for the prevention of diabetes type 2 as lowering HbA1C (<7.0%) 0.83% in randomized control trial [26].

High-fat diet develops obesity, hyperinsulinemia, hyperglycemia, insulin resistance, and hepatic steatosis, but chenpi (dry peel of the plant citrus reticulata) contain high fat which can reduce the hyperglycemia, hyperinsulinemia, hepatic steatosis, and insulin resistance. Administration of 0.25% to 0.5% of oral chenpi for 15 weeks prevented symptoms of diabetes and also reduced obesity and hepatic steatosis [27].

Fenugreek seeds (*Trigonella foenum graecum*) have hypoglycemia, antioxidant, and nephroprotective effects. About 500 mg daily dose bid showed significant reduction in fasting blood glucose in trial group (83%) and placebo group (62%), postprandial plasma glucose in study group (89%), placebo subjects (72%) and reduction in HbA1c in both group significantly as compared to baseline values in double-blind multicenter randomized control trial [28].

Fenugreek is a natural herb used widely for the prevention of diabetes showed hypoglycemic, lowering effects of total cholesterol. Fenugreek significantly reduced fasting blood glucose, HbA1C, total cholesterol but results for low-density lipoprotein, high-density lipoprotein, and triglyceride of fenugreek were controversial in many randomized controlled trials (RTC) showed by meta-analysis of 10 studies due to low quality of studies because no renal and liver efficacy were checked, side-effect of fenugreek is discomfort for gastrointestinal tracts and further clinical trials are needed [29].

A randomized control trial showed a positive effect of chromium on biomarkers of type 2 diabetes such as fasting blood glucose, HbA1c after taking 200 ug of chromium for 3-month, clinical sign and symptoms, anthropometric

also improve after dietary consoling in newly diagnosed diabetes and no toxicity can be found in renal and liver functioning. These biomarkers improved but did not come to the normal range [30].

Review of 9 randomized control studies indicated a positive effect of ginger (*Zingiber officinale*) on biomarkers of diabetic and hyperlipidemic subjects supplementation of ginger which significantly increased HDL-C and decreased fasting blood glucose and total triglycerides [31]. A double randomized control trial indicates a significant effect of ginger 3 capsules 1 g daily in the ginger group and in placebo group taking 3 capsules containing 1 g microcrystalline for 8-weeks on BSF effects (10.5%), and HbA1C variation was in line in type 2 diabetic patients [32].

Uses of garlic as food spices are very popular all over the world it's very helpful for the prevention of diabetic dyslipidemia in patients with raised lipid profile. A cross-sectional study showed that local herbal product of garlic had a lowering capacity of serum cholesterol and low-density lipoprotein and increased high-density lipoprotein significantly, but no change occurred in triglyceride when it's taken 300 mg/day for 8-weeks [33]. Anti-oxidant and anti-glycation properties are more potent in old garlic than in fresh garlic. Inhabitation of aged garlic by AGEs (Advanced glycation end products) were 56.4% to 33.5% as compared to fresh garlic, phenolic content is higher (129+1.8 mg/g) in old as compared to (56+1.2 mg/g) in fresh garlic [34].

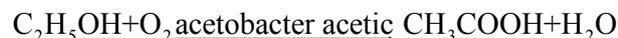
Physical and Chemical Properties of Vinegar

Vinegar is an aqueous solution mainly dilution of acetic acid which is reflected by its physical and chemical properties. The product which is called vinegar is formed by 2 biochemical processes [35].

Alcoholic fermentation process: In this process, the natural sugar converts into alcohol by acid fermentation.



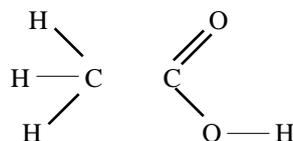
Acid fermentation process: In this process of fermentation the microorganism acetobacter is present in the air which converts alcohol into acid when we breathe.



Due to sour taste vinegar has antiseptic, cleaning and killing of germs properties and it also contains various amount of vitamins, minerals, enzyme, fiber and other organic compound depending on its process of production [35].

Chemical Formula of Vinegar

Vinegar is a diluted acetic acid solution which has the same formula of acetic acid containing 4 hydrogen atoms, 2 carbons, and 2 oxygen atoms formula is often as CH_3COOH [35,36].



Mechanism Action of Apple Cider Vinegar on Glucose Metabolism

Apple cider vinegar has been used as a natural remedy for the management of diabetes for many years in the different areas of the world. Several mechanisms have been reported for mechanism action of glucose metabolisms such as delayed gastric emptying and enteral absorption, increased utilization of glucose, suppression of production of hepatic glucose, up-regulation of flow-mediated vasodilatation, increase in lipolysis and reduced in lipogenesis, insulin secretion facilitation. Other mechanisms are reported including fecal acid bile excretion facilitation, enhanced energy uses and increased satiety [7].

Gastric emptying: A pilot study showed a positive effect of apple cider vinegar in diabetic patients with gastroparesis to delayed gastric emptying. The gastric emptying rate was measured by ultrasonography. GER gastric emptying rate measured after every 15-90 minutes in the antral cross-sectional way after 300 g rice budding ingestion with 200 ml water in group 1 and in group 2 rice budding 300 g and 200 ml water with 30ml apple cider vinegar. For measuring GER 1 the subject drank water 200 ml before breakfast and the second group also drinks water (200 ml) with 30 ml apple cider vinegar. This pilot study indicates further clinical trials [37]. Metformin drug also works

as an antiglycemic agent and decreased effectively fasting plasma glucose and gluconeogenesis in type 2 diabetic patients. Metformin effect on fat content and muscle in the liver and effect remain controversial on insulin resistance in this study. Rosiglitazone and Pioglitazone can also reduce the hepatic, muscle glucose and fat content and insulin resistance can also be improved [38].

The concentration of postprandial blood glucose can be determined by the clearance and appearance rates of glucose and the blood glucose maintained in a narrow range after meal intake. Regulation of postprandial blood glucose by the gastric emptying and other factors, lowering of postprandial glucose level can be occurred due to gastric emptying rates reduction. Hypoglycemia leads to rising in gastric emptying rates in both healthy and diabetic individual. Emptying of stomach occur in liquid food immediately and a few minutes after in solid and semi-solid food [39].

Enteral absorption of carbohydrate: Enteral carbohydrate absorption is another mechanism of vinegar antiglycemic effect, the vinegar suppresses the disaccharide activities and not glucose transport inactivation in the cells of the intestine. A study *in vitro* showed suppression of sucrose, maltose, lactose, and trehalase when treated with acetic acid for 15 days but acetic did not affect sucrose is maltase *de novo* synthesis either at translational or nor transcriptional level, probably suppression occurs during processing of post-translational, inhabitation of post-translational may be by acetic acid like intracellular trafficking and disaccharidases synthesized *de novo* [7,40]. Digestion of molecules of starch interferes by acetic acid which reduced the amount of glucose absorption into the steam of blood after a meal. Many other studies showed apple cider vinegar consumption lead to slow down the high blood sugar after a high carbohydrate breakfast with vinegar [41]. A study conducted in rats showed acetic acid containing diet may not induce super compensation but enhance the glycogen repletion, a major increase of glycogen level is beneficial for improving performance in skeletal muscle and in the liver by transitory glycolysis inhibition. There may also be a possibility of fatty acid oxidation by acetic acid diet in the liver [42].

Metabolism of glucose in skeletal muscles: For disposal of glucose skeletal muscles can be considered as an important issue in the response to insulin especially in the status of postprandial [43]. The metabolic effect of acetic acid on glucose on skeletal muscle is the same as in the liver according to previous studies. Glycogen repletion is enhanced by acetic acid in skeletal muscles [44]. Within the tissue of skeletal muscle the mechanism action of acetic acid is different, it enhances the utilization of fatty acid and decreases the glycolysis ratio in the liver and in skeletal muscle glycogen content which is increased due to glucose-6-phosphate accumulation and suppression of glycolysis without fatty acid oxidation enhancement [7].

Production of endogenous glucose by the liver: Exact mechanism of endogenous glucose production is not clear few mechanisms are identified such as consumption of acetic acid in vinegar enhanced the storage of hepatic glycogen by gluconeogenic/glycolysis decreasing in the liver. Digestion of vinegar at bedtime showed reduced in fasting blood glucose in patients with type 2 diabetes having fasting blood glucose >7.2 mmol/L [45].

Acetic acid has a beneficial effect on glucose metabolism and it works as fatty acid of a short chain. Diabetes rats were fed with acetic acid 0.3% containing acetic acid (ACOH) to KK-A(Y) (type 2 diabetic mice elevated glucose with obesity) for 8-weeks and another group is fed with the standard diet for the same period and ACOH fed rat's plasma glucose and HbA1C was lower as compared to the control group. Gluconeogenesis and lipogenesis were also reduced in acetic acid treated group and also (AMPK) activated protein kinase in the liver by the 5-AMP, so hypoglycemic effect has been noted of acetic acid result from activation of AMPK directly in the liver [44].

Insulin secretion: Hypercholesterolemia can leads to beta cells dysfunction or death of the cells in hypercholesterolemic patients. The pathology of beta cells dysfunction or death of the cell in excessive cholesterol accumulation in pancreases. Accumulation of hypercholesterolemia causes impairment of exocytosis of the insulin granule to lead to modulating granule morphology this condition ultimately causes diabetes. Over cholesterol accumulation in beta cell cause of cell by apoptotic mechanism [46].

Insulin resistance also has been one of the suggested etiologies for the development of polycystic ovaries syndrome in female and this PCOS can be prevented by intake of apple cider vinegar 15 g daily for 90-110 days. Follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone hormone, fasting insulin level and fasting glucose has been decreased significantly when compared before and after vinegar indigestion. The finding of this study suggested that the uses of vinegar not only improve the insulin sensitivity but also improve the ovarian functions in PCOS patients. Vinegar reduced the cost and time of medical treatment in insulin resistance and polycystic ovaries syndrome [47] (Figure 1).

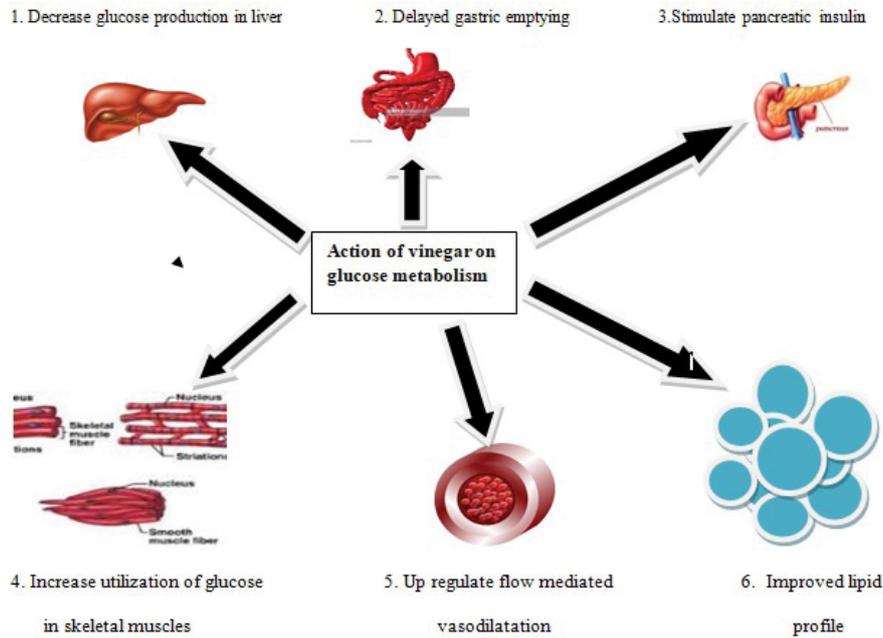


Figure 1 Proposed mechanism of action of vinegar on glucose metabolism

Uses and Health Benefits of Apple Cider Vinegar

Uses of vinegar are known from last 10,000 years and varieties of products of natural vinegar are found all around the world civilization. There are 2 types of vinegar usage, therapeutic usage which can be antibacterial, anti-diabetic, anti-tumor, anti-oxidative, antihypertensive, anti-obesity, and is also used as cholesterol-lowering therapy due to its organic compounds including gallic acid, acetic acid, chlorogenic acid, ferulic acid, caffeic acid, and p-coumaric acid. The second use of vinegar is commercial usage like used as the preservation of different food, pickling of vegetables and fruits preparation of salad dressing, mayonnaise and mustard [48].

Therapeutic Effect of Vinegar

Vinegar can be used for therapeutic purposes for many ailments. Numbers of the therapeutic effect of apple cider vinegar are described below.

Anti-Diabetic Effects or Uses of Vinegar for Diabetes Management

Diabetes mellitus is a metabolic disorder characterized by high blood sugar due to impaired insulin secretion, insulin resistance and overproduction of hepatic glucose [49]. It may be a high blood glucose level in the state of hunger and after meal consumption. Hyperglycemia may occur due to the destruction of the beta cell which results in not enough insulin in type 1 diabetes. Insulin is present in type 2 but tissues are resistant to the insulin which result in high blood glucose level, 19% insulin sensitivity has been improved in type 2 through vinegar uses and 34% in an individual with pre-diabetic [48]. Postprandial blood glucose and insulin response can be influenced by dose and type of vinegar. Uses of vinegar with carbohydrate-rich food are more effective as compared to low glycaemic food in healthy individual [50-52]. Meal oxidative stress is not only improved by vinegar addition in standard meal but it also reduced post-prandial glucose level, and satiety period also prolonged which should be helpful to reduced food cravings and lowering the intake of calories by intake of 1 to 2 spoons of vinegar with high glycaemic index foods like white bread, white rice, etc. which lower the random blood glucose by 25% to 30% in diabetic patients [53]. Apple cider vinegar is a nutraceutical which can be used for the management of diabetes, whole apple cider vinegar is more effective than alone acetic acid. “Mother of vinegar” consumption may be more effective than without this component.

Acetic acid and chlorogenic acid have more potential than other components of ACV for management of diabetes, lipid disorder, hypertension and for weight control [54].

Addition of vinegar in diet can reduce the postprandial glucose level in healthy individual but it is more effective

in high glycaemic index meal (low-fat milk and mashed potato) than in low glycaemic index meal (low-fat cheese, whole grain, lettuce, etc) with the same composition of nutrients in isocaloric meal when random blood sugar and insulin values measured after 2 hours of meal intake [50].

Apple cider vinegar has been used in various doses widely being a helpful health remedy for various conditions like diabetes and obesity control in alternative medicine. A randomized control trial in mice showed that apple cider has been used in 2 concentrations 0.16% and 1.6%, which were more effective on 7th day onwards to 21st day and not on the 3rd day of administration of vinegar in the interventional group as compared to control group. Apple vinegar significantly lowers the blood glucose level in diabetic mice after 60 min of glucose intake and was maintained up to 120 min [55].

An open crossover randomized placebo control trial was conducted in subjects with impaired glucose tolerance by using different arteriovenous techniques for the effects of vinegar on endothelial function and muscle glucose metabolism. This study showed that there was an improvement in blood glucose level uptake by the forearm muscles and reduced the hypertriglyceridemia and postprandial hyperinsulinemia, in this way vinegar may be beneficial for improving metabolic disorder and insulin resistance in human with impaired insulin resistance [56].

It is evident that vinegar has antiglycemic properties, vinegar attenuated postprandial glucose by 20% when compared to the placebo group when ingested with meal in small amount composed of complex carbohydrate, vinegar is more effective in 10 g amount as compared to 20 g and is also more effective when vinegar is taken during meal as compared to 5 hours before meal [57]. Vinegar, pills, and pickles are used for diabetes control but vinegar is more effective than pills and pickle. Values of HbA1c fell 0.16% for vinegar group and 0.06% for pills and 0.22% for pickles group over 12-weeks but no change occurred in blood lipids, mean of body weight and plasma insulin [58].

Biochemical and pathological changes are associated with diabetes mellitus. Apple cider vinegar has beneficial properties for decreasing LDL-C, total cholesterol concentration, and blood glucose have also increased HDL-C in diabetic rats significantly. Apple cider vinegar treated group showed minimal toxicity in diabetic-induced rats due to streptozotocin. Recovery of injured hepatocytes has been noted in diabetic rats by histopathological examination of the liver [41].

A double-blind randomized controlled trial was conducted in patients with type 2 diabetes, in this some biochemical and hematological factors have been evaluated like BSF, HbA1c, fasting lipid profile, CBC and LFTs apple cider vinegar significantly reduced the HbA1c ($p=0.002$) fasting blood glucose ($p=0.006$), MCV ($p=0.0001$), and platelet ($p=0.005$) increase significantly and decrease mean cell hemoglobin ($p=0.002$) in vinegar treated group who were taking 15 ml of vinegar during middle meal as compared in placebo (water) treated group. So hypolipidemic and hypoglycemic properties have been noted for apple cider vinegar [49].

A pilot study was conducted in a pre-diabetic healthy individual ($n=14$). This study showed significant ($p=0.05$) reduction in HbA1C (0.91 ± 0.27 versus -0.26 ± 0.17 mmol/l in apple cider vinegar drink containing 750 mg acetic acid) treated the group as compared to pill (40 mg acetic acid) treated as a control group and average change occurs in fasting blood glucose [45]. Another pilot study was conducted in patients with type 1 diabetes, with gastroparesis to evaluate the effect of vinegar in delayed empty gastric. Result of this study showed statistical significance in delaying gastric empty. GER measured in group 1 took 300 g rice pudding and 200 ml water, in group 2 300 g rice pudding and 200 ml water with 30 ml of apple cider vinegar was taken. Gastric empty rate in group 1 was 27% and gastric empty rate in group 2 were 17% [37].

Studies of the comprehensive review indicate that apple cider vinegar can reduce obesity, hyperglycemia, hyperlipidemia, and hyperinsulinemia in many clinical trials. Several mechanisms for therapeutics effect of apple cider vinegar is proposed like its delay gastric empty, increased glucose utilization and enteral absorption, up-regulation of flow-mediated vasodilatation, suppress the hepatic glucose production, increase in lipases, decrease in lipogenesis, insulin secretion facilitation, fecal bile acid excretion stimulation, enhanced energy expenditure, increase satiety. In spite of these results still, further clinical trials are needed [7]. A randomized control study conducted in alloxan-induced diabetic and non-diabetic rats showed that continued reduction in blood glucose by active component of apple cider vinegar enhanced the insulin secretion of the beta cell of the pancreas. This study showed that apple vinegar is helpful for diabetes management as a complementary agent in the diet [59] (Table 1).

Table 1 Summary of clinical trials evaluating the effects of vinegar on hyperglycemia in diabetes individual and rats

S. No	References	Participants	Trial Design	Intervention	Placebo	Duration	Outcome
1	[55]	Diabetes mice n=60	Placebo RCT	Apple cider vinegar in two concentration 0.16% and 1.6%	Acetic acid and water	21 days	Significantly reduced blood glucose level
2	[56]	Healthy individual n=8	Open cross over placebo RCT	50 ml apple cider vinegar (5% acidity containing)	50 ml water	2 weeks	Significantly reduced postprandial hyperinsulinemia, hypertriglyceridemia
3	[57]	Diabetic individual trial 1 and healthy individual 3 trials n=9	Double-blind RCT	2 spoons 10 g vs 20 g ACV, timing After meal vs 5 hrs before a meal	Neutralized salt in water in the same dose	1 week	Significantly reduced PPG after a meal as compared to before meal
4	[58]	Diabetic individual n=27	RCT	1 vinegar pill (15 mg acetic acid) 1 pickle (700 mg acetic acid) 2 spoons ACV (1400 mg acetic acid)	No placebo group	12 weeks	HbA1c reduced in vinegar group as compared to pills and pickle groups
5	[41]	Diabetes rats n=30	Single Placebo RCT	ACV 2 ml/kg body wt with concentration 1:5	Plain water in the same dose	30 days	Significantly reduced blood glucose level.
6	[49]	Type 2 diabetes individual	Double blind placebo RCT	15 ml ACV containing 5% acidity	15 ml plain water	1 month	Significantly reduced HbA1C, blood sugar fasting
7	[45]	At risk of type 2 diabetes individuals	Plot study	750 mg acetic acid as ACV	40mg acetic acid as control pills	12 weeks	Postprandial blood glucose decrease in vinegar indigested group.
8	[59]	Diabetes-induced rats	RCT	2 ml/kg body wt ACV through a nasogastric tube	10 ml tap water	14 days	Significantly reduced blood sugar level and produced hypoglycemia in vinegar treated group
9	[60]	n=110 diabetic individuals	Single blind RCT	15 ml ACV	The artificial flavor of ACV in water	12 weeks	HbA1C and blood sugar fasting significantly reduced

RCT: Randomized Control Trial; ACV: Apple Cider Vinegar; n=Number of samples/participants; PPG: Post Prandial Glucose; HbA1C: A Form of Hemoglobin (a blood pigment that carries oxygen) mg milligram and ml milliliter

Hypolipidemic Effects or Management of Hyperlipidemia with Apple Cider Vinegar

An apple cider vinegar used traditionally has been reported for various diseases since many years ago. A quasi-experimental study showed the hypolipidemic property of apple cider vinegar in hyperlipidemic patients. ACV significantly reduced total cholesterol and LDL ($p < 0.001$) but not significantly affect HDL and triglyceride after 8-weeks of ACV intervention. So ACV can be recommended cost-effective and simple diet strategy for hyperlipidemic patients for the prevention of cardiovascular diseases [61]. Apple cider vinegar produced by different technique significantly decreased VLDL, triglyceride and increased HDL, LDL cholesterol level in high cholesterol diet-treated rats with vinegar supplementation as compared with only high cholesterol diet treated group without vinegar and high-fat diet also result in hepatic steatosis [62].

A herbal mixture consisting of ginger, garlic, honey, apple cider vinegar, and lemon extract has the property of lowering the cardiometabolic risk factors. It has reduced significantly plasma triglyceride (TG) ($p < 0.05$), very low-density lipoprotein (VLDL) and also decreased total plasma cholesterol ($p < 0.05$), high-density lipoprotein (HDL) and low-density lipoprotein were raised ($p < 0.05$). Change in blood glucose, and ALT result is not significant [63]. A

study conducted in female rats fed with high cholesterol diet through a nasogastric tube and produced hyperlipidemia than these rats were treated with apple cider vinegar (0.6%) containing acetic acid for 28 days. Biomarkers of this study showed a protective effect of apple cider vinegar against liver and kidney oxidative injury and also lowering the serum lipid, inhibits lipid peroxide and antioxidant enzymes, vitamin level is also improved in vinegar treated group [64]. An animal study showed that vinegar intake with diet can lower the triglyceride levels (TG), low-density lipoprotein cholesterol (LDL-C) and raise the high-density lipoprotein cholesterol (HDL-C) [65]. The result of previous experiments studies conducted on animals getting 1:10+0 dilutions of the ACV in drinking water indicates that total cholesterol (TC) and triacylglycerols (TG) had been decreased in serum blood [66].

Several animals and few human studies showed hyperlipidemic, hyperglycemic, hyperinsulinemia and obesity control effect of apple cider vinegar. Reduction in lipogenesis raised in lipolysis, acid bile excretion stimulation and increase the expenditure of energy reduced the energy intake due to increase in satiety is the mechanism of lipid metabolism, fat accumulation, and body fat reduction also. Reducing total cholesterol and triglyceride also has been reported in several animals and little human studies by the uses of vinegar regularly in diet [7].

Type of different vinegar including apple, sugarcane, grape, coconut, and other artificial vinegar has been used for different ailments and has health benefits. Study conduct in rats showed a significant decrease in LDL-C, TC, glucose and also raised in HDL-C ($p < 0.05$) when administrated 15% with the diet for 6-weeks. No histopathological change was found in the stomach and pancreas when administrated different vinegar in rats [67]. Acetic acid is an active component of vinegar which significantly effect on hyperlipidemia in hyperlipidemic rats. These rats were given a cholesterol-containing diet with vinegar and without vinegar for 19 days in 2 groups. Serum triglyceride, serum total cholesterol, ATP citrate lyase activity, 3-methyl glutaryl, 3-hydroxy element, and fatty acid synthesis, protein binding-1 is significantly reduced in those rats which were taking vinegar and cholesterol containing diet and raised these values in only cholesterol. The mechanism of action of vinegar in the liver is lipogenesis inhabitation and increment of excretion of fecal acid bile in the cholesterol-containing diet of the rats [68] (Table 2).

Table 2 Summary of clinical trials evaluating the effects of vinegar on hyperlipidemia in human and animals

Sr no	References	Participants	Trial Design	Intervention	Placebo	Duration	Outcome
1	[61]	n=19 hyperlipidemic individual	Quasi-experimental study	30 ml ACV	No placebo group	8 weeks	Significantly reduced total cholesterol. LDL triglyceride levels but not significantly increased in HDL
2	[62]	n=54 hyperlipidemic rats	RCT	1 ml ACV via oral gavage	1ml physiological saline via oral gavage	7 weeks	Triglyceride and VLDL reduced significantly
3	[64]	n=10 female hyperlipidemic rats	RCT	1 ml ACV containing 0.6% acetic acid orally	Plain water 1 ml orally	28 days	Serum lipid level improved significantly
4	[66]	n=60	RCT	ACV 1 ml in 100 ml water in 1:100 ratio	Water in same quantity	21 days	Helpful in lowering lipid plasma
5	[67]	n=48	RCT	1 ml ACV (5% acetic acid) diluted in 10 ml water	Artificial vinegar in the same dose	6 weeks	ACV was most effective in lowering glucose LDL, TC increasing HDL as compare to other vinegar
6	[60]	n=110 obese individual	Single blind RCT	15 ml ACV	The artificial flavor of ACV in water	12 weeks	Total cholesterol and triglyceride significantly reduced but no significant change in LDL, HDL

RCT: Randomized control trial; ACV: Apple cider vinegar; n=number of samples/participants; PPG postprandial glucose; HbA1C: A form of hemoglobin (a blood pigment that carries oxygen) mg milligram and ml milliliter

Uses of Vinegar for Weight Control

The prevalence for overweight among teenage noted in Sri Lanka is 11.0% and in India is 19.0% and obesity ranged in Sri Lanka is 2.4% and in Pakistan is 11.0%. Prevalence range of overweight in young adult is 7.9% in Nepal and

15.0% in Pakistan and obesity ranged is much higher in Nepal of about 0.005%, in India is 22.8% and identified risk factors for overweight and obesity are low consumption of fruits and vegetable, high intake of fast food and soft drink, total vegetarian diet and breakfast skipping [69].

Apple cider vinegar can also be used as a supplement for weight reduction. A study conducted in obese and normal weight rats. There were 2 groups of rats, one group was fed with conventional diet and another group was fed with the high caloric diet for 4-week than obese and normal rats further divided into 2 groups: control group (water treated) and interventional group (vinegar treated) which used 0.8 ml/kg body weight. The significant reduction has been found in plasma glucose, total cholesterol in both groups normal and obese rats group. But no change occurs in HDL and LDL so which gains excessive body weight and high concentration of plasma glucose which might be avoided by apple cider vinegar uses in obese and normal weight rats [70]. Vinegar containing 6% acetic acid significantly reduced body weight and also influence appetite and reduced the postprandial glycaemic [71].

A study was conducted to assess the effect of acetic acid with water on body weight in fatty mice. The dose of acetic acid 0.3 or 1.5% for 6-weeks showed a significant reduction in fat cells in both higher and low dose of vinegar in the area of perinephric, mesenteric tissue and retroperitoneal tissue when compared with a control group of mice. No change occurs in skeletal muscle weight in both groups, no dose dependency was needed even the lowest dose can be effective for fat cells reduction [72].

A double-blind study was conducted in obese Japanese to investigate the effect of vinegar on obesity. Three doses of vinegar have been used in 3 group's: group 1, 30 ml vinegar with 500 ml daily intake of beverage, for group 2, 15 ml of vinegar with 500 ml of daily beverage, and 0 ml of vinegar with 500 ml beverage for control group for 12-weeks. All these 3 groups have the same body mass index (BMI), body weight, and wrist circumference. The result of this study showed a significant reduction in serum triglyceride and body weight. This study also showed no side effect of vinegar on the health status of human [73] (Table 3).

Table 3 Summary of clinical trials evaluating the effects of vinegar on obesity in human and animals

Sr no	References	Participants	Trial Design	Intervention	Placebo	Duration	Outcomes
1	[70]	n=20 10=normal wt 10=obese rats	RCT animal study	0.8 ml ACV	0.8 ml plain water	4 weeks	Fat cell reduced significantly in ACV group
2	[72]	n=9-10 obese rats	RCT animal study	Acetic acid 1.5% or 0.3 ml	Water as placebo	6 weeks	Significantly observed Suppression of fat cell accumulation
3	[73]	n=175 Obese individual	Double blind RCT	30 ml ACV 15 ml ACV	Artificial flavor of ACV in water	6 weeks	Significantly decrease in body weight
4	[60]	n=110 obese individual	Single blind RCT	15 ml ACV	The artificial flavor of ACV in water	12 weeks	Weight not significantly reduced but the H/W ratio and mid-upper arm significantly reduced

RCT: Randomized Control Trial; ACV: Apple Cider Vinegar; n: Number of samples

Management of Hypertension with Apple Cider Vinegar

Dietary vinegar has the potential to prevent hypertension when consumed it for a long time. A study conducted in spontaneously hypertensive rats showed a significant reduction in blood pressure ($p=0.05$) and rennin activity which is ($p=0.01$) in vinegar treated group for 8-weeks as compared to control group which has no use of acetic acid and vinegar. Reduced in rennin activity is a suggestive mechanism for the reduction in blood pressure and further clinical trials are needed to investigate the exact mechanism for lowering the blood pressure [74].

Autonomic nervous system and endothelium may be affected by diabetes result in complications of microvascular which impairs the blood flow auto-regulation. The lower level of vasodilator nitric oxide and raised vasoconstriction endothelin-1 level can be seen in diabetes subjects [75]. About 4% of acetic acid can be found in rice vinegar and acetic acid is more potent as compared to the vinegar solution. Calcium absorption can be increased by acetic acid, an increase in calcium absorption may be helpful for blood pressure control [54] (Table 4).

Table 4 Summary of clinical trials evaluating the effects of vinegar on hypertensive in human and animals

S. No	References	Participants	Trial Design	Intervention	Placebo	Duration	Outcomes
1	[74]	Hypertensive rates n=18	RCT	Acetic acid 4% solution (46.2 g/l)	Deionized water	8-weeks	HTN, rennin activity Significantly reduced
2	[76]	Hypertensive rates n=6	RCT	Red wine vinegar	No placebo	2-weeks	HTN significantly reduced

HTN: Hypertension; RCT: Randomized Control Trial

Antimicrobial Effect of Vinegar

Vinegar work as an antimicrobial agent in many conditions. Acetic acid is an active component in organic vinegar which can penetrate the cell membrane of bacteria and bring the death of cells of bacteria. It is also used in many conditions like oral hygiene, cleaning agent, killing head lice, ear infection, treating nails fungus and warts [48]. Vinegar also has the ability to treat the site infection caused by *Pseudomonas* in peritoneal dialysis patients and it also reduces antibiotics use, prevents the antibiotics resistance in PD patients by using organic vinegar containing 4% acidity (acetic acid) [77].

A study was conducted against 5 oral organisms (*Lactobacillus*, *Streptococcus mutans*, *Staphylococcus aureus*, *Streptococcus salivarius*, and *Enterococcus faecalis*) *in vitro* to compare the effectiveness of vinegar and mouth rinses (chlorhexidine gluconate containing 0.12%) at 37°C all dishes were incubated for 24 hours. Four out of five organisms were found to be sensitive to vinegar and chlorhexidine gluconate significantly (p=0.01) but vinegar was more effective as compared to chlorhexidine gluconate [78]. A study was conducted to evaluate the effectiveness of vinegar with different concentrations 5%, 10% and 15% with 6% acetic acid against *E. coli* and MNV-1 count in vinegar green laver salad during storage of refrigerator of Korean food. Values decreased gradually in the proportion of MNV-1 and *E. coli* when increased the concentration of vinegar and storage time but MNV-1 was resistant when compared to *E. coli* to vinegar [79].

Buffered dry vinegar can also have antimicrobial properties for inhibition of microorganism like *Listeria monocytogenes* in sodium reduced readily to eat uncured Turkey fish when the sample was stored for 12-weeks at 48°C. The sample was taken from a different side and then incubated with buffered vinegar with sodium base and dry vinegar with potassium base for 2-weeks then *L. monocytogenes* population were count in the control group and vinegar treated group. 1 log *L. monocytogenes* increase in count in the control group and the buffered dry vinegar treated group showed significant (p=0.05) inhabitation of *L. monocytogenes* growth at the end of the 2-week [80].

Salmonella is commonly found in animal region food and also even in fresh fruits and vegetables in 100-400 cases. *Salmonella* can be eliminated significantly with lemon juices, vinegar and mixture of vinegar and lemon in carrot with different exposure times (0 min, 15 min, 30 min and 60 min) which result in reduction of *Salmonella* count significantly ranging from 0.79-3.95 CFU/g and 1.57-3.58 log CFU/g and also reduced in count of pathogens in the lemon and vinegar mixture group after 30 min treatment to an undetectable level [81] (Table 5).

Table 5 Summary of clinical trials evaluating the effects of vinegar against microbial growth

S. No	References	Organisms	Trial Design	Intervention	Placebo	Duration	Outcomes
1	[78]	<i>Streptococcus mutants</i> , <i>Enterococcus faecalis</i> , <i>Staphylococcus aureus</i> , <i>Candida albicans</i> , and <i>Lactobacillus salivarius</i>	Experimental Study (<i>in vitro</i>)	White vinegar	0.12% chlorhexidine gluconate	Incubation period 24hrs at 37°C	Both kinds of vinegar were significantly effective as compare to chlorhexidine gluconate

2	[80]	Two different five-strain inoculums of <i>L. monocytogenes</i>	Experimental Study (<i>in vitro</i>)	dry buffered vinegar with a potassium base (BDV-PB) at 0.7 and 0.9% controlled	Unbuffered dry vinegar	12 weeks	<i>L. monocytogenes</i> growth significantly decreases as compared with the untreated control group
3	[81]	<i>Salmonella typhimurium</i> (inoculated)	Experimental Study (<i>in vitro</i>)	Lemon juices vinegar	No comparative group	(0, 15, 30 and 60 min)	<i>Salmonella typhimurium</i> growth significantly reduced

Commercial Uses of Vinegar

Vinegar has the potential of health benefits if used for a long time, is its flavor and functional properties vinegar can be used for the preparation of salad dressing, for fruits and vegetable pickling and for preparation of mayonnaise in markets [48].

Vinegar has antibacterial properties against *Salmonella*, *Staphylococcus aureus*, and *Escherichia coli* which cause food poisoning in human when compared to antibiotics and can be used for food preservation in different concentration 20%, 14%, 10%, 5%, 7%, 3%, and 1%, 0.5%, 0.25% but 20% concentration was more effective against selected 3 microorganisms and 0.25%, 0.5% did not show any inhibitory effect against anyone from the 3 organisms [82].

Acetic acid has properties of food safety and preservative ability against microorganism (anaerobic bacteria, yeasts, and molds) growth in refrigeration in breast chicken with different concentration 1%, 2% and 3% of acetic acid. After examination of 0, 7, 14, and 21 days refrigeration of breast meat showed significant improvement of microbial growth in acetic acid treated group as compared to control group (no acetic acid treatment) with all concentration of acetic acid [35].

CONCLUSION

The current review study concluded that the results of many clinical trials showed an active component of apple cider vinegar which has the potential for lowering hyperglycemia, hyperlipidemia, and reduced body weight. Hypertension should be controlled with the intervention of apple cider vinegar. Results of many studies also showed the anti-microbial effect of apple cider vinegar. Commercial and another therapeutic effect also has been reported in many studies. Few studies showed the controversial effect of apple cider vinegar. These discrepancies could be attributed to many factors such as doses of vinegar, the timing of vinegar digestion, duration of studies, physiological characteristics of human and animals, the acidity of the vinegar, level of remaining pancreatic secretion, level of insulin secretions and glycemic index of the meal. Several mechanisms have been reported for mechanism action of glucose metabolisms such as delayed gastric emptying and enteral absorption, increased utilization of glucose, suppression of production of hepatic glucose, up-regulation of flow-mediated vasodilatation, increase in lipolysis and reduction in lipogenesis, insulin secretion facilitation. Other mechanisms are reported including fecal acid bile excretion facilitation, enhanced energy uses and increased satiety.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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