Review

Potential Uses of Vinegar as a Medicine and Related in vivo Mechanisms

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Received: February 25, 2017; Accepted: October 23, 2017

Abstract: While the use of vinegar to fight against infections and other crucial conditions dates back to Hippocrates, recent research has found that vinegar consumption has a positive effect on biomarkers for diabetes, cancer, and heart diseases. Different types of vinegar have been used in the world during different time periods. Vinegar is produced by a fermentation process. Foods with a high content of carbohydrates are a good source of vinegar. Review of the results of different studies performed on vinegar components reveals that the daily use of these components has a healthy impact on the physiological and chemical structure of the human body. During the era of Hippocrates, people used vinegar as a medicine to treat wounds, which means that vinegar is one of the ancient foods used as folk medicine. The purpose of the current review paper is to provide a detailed summary of the outcome of previous studies emphasizing the role of vinegar in treatment of different diseases both in acute and chronic conditions, its in vivo mechanism and the active role of different bacteria.

Keywords: Vinegar, fermentation, therapeutics, carbohydrates

Introduction

Generally, vinegars are defined as fluids obtained by the acetic maturation of any reasonable foodstuff. Vinegars are legally characterized in many states of the world and sometimes are subject to particular legislation. They normally have a minimum acidity level. Pure vinegars contain 5 to 12 g of acetic acid per 100 ml, aside from wine vinegar, which has at least 6 g; however, in the United States, the core value is 4 grams [1], while rice vinegar in Japan has an acetic content of 2–4 %, and vinegars used in pickling show a stringent requirement of close to 18 % acetic acid content [2]. The Ministry of Food and Drug Safety of Korea defines vinegar as brewed vinegar that is formed by fermenting fruits, grains or by ripening and mixing them with fruit juices or grain, or as synthetic vinegar that is formed by diluting acetic acid or glacial acetic acid together with drinking water. The total acetic acid content should vary between 4.0 and 29.0 % without detection of tar color. According to the Indian Food Safety and Standard Authority, vinegar is produced by acetic acid and alcoholic fermentation of any reasonable source such as fruit, malt or molasses, without or with the addition of spices and caramel and not fortified with acetic acid. The acidity, total ash content and total solids shall not be less than 3.75 %, 0.18 % and 1.5 % (m/v), respectively [3]. The Codex Alimentarius Commission stated that vinegar is a liquid produced from the starch-rich compounds using alcoholic as well as acetous fermentation processes. According to European law, stabilizers are not allowed to be used in fermented vinegars, and the least permitted amount of alcohol is less than 0.5 %. The Food and Drug Administration of the U.S. has not developed any particular standards for the identity of vinegar. However, the minimum recommended amount of acetic acid is 40 g per liter (w/v) [3]. The European Union regulations state that vinegar is produced through the double fermentation, i.e., acetic and alcoholic, of agricultural origin substances. Raw materials such as rice mesh, cider, wine, malt, concentrated grape must, whey, and different types of spirits are used [4].

Vinegar that is famous as a condiment is mostly used in the treatment of different diseases (Table I). Vinegars are liquid products formed from alcohol and following the acetous fermentation of carbohydrate; this aging process consists of fermentation of glucose in different foods such as grapes, apples, dates and figs. In old times, vinegar was used by a majority of the population because it was known that it has various kinds of therapeutic effects and antimicrobial agents that enhance health [5, 6]. Vinegar has been consumed to reduce obesity starting from the late 18th

century. After World War I, many drugs such as amphetamine were used to cure obesity, but these drugs were found to have many unhealthy side effects [7]. Acetic acid is the main constituent of vinegar. Vinegar acetic acid in liver and the gastrointestinal tract changes the metabolic processes and produces healthy outcomes. Some other components include flavones such as catechin, epicatechin, quercetin, and kaempferol [8], anthocyanins such as cyanidin-3-glucoside and minerals, amino acids, vitamins, and non-volatile organic acids such as citric, malic and lactic acids [6]. Different studies of vinegar have revealed numerous effects such as improvement of glycogen satiety [9], hypertension reduction [10], enhanced consumption of calcium [11] and reduction of cholesterol [12].

Numerous recent studies have shown that vinegar consumption reduces the glucose reaction to carbohydrate food both in diabetic and non-diabetic participants [13, 14]. Vinegar, which is basically a product of food, is produced from alcohol and consequent acetic fermentation in which a carbohydrate-rich material is used as a starting material. The ultimate properties and organoleptic characteristics of vinegar are determined by an effective chemical complex,

Table I. Names of different types of vinegar with their health benefits

Type	Model	Dosage and duration	Key Functions	References
Kurosu vinegar	Human squamous cell carcinoma cell line HSC-5	HSC cells were treated with Izumi or ordinary grain vinegar adjusted to 4.2 % acidity for 72 hours	Inhibited the proliferation of cancer cells (HSC-5) $P < 0.05$. $^{**}P < 0.01$ vs. control. Trypan blue dye tests confirmed that the number of dead cells were significantly greater after Izumi treatment	Baba et al. (68)
	Male rats	Seventy-six male F344 rats were divided into 5 experimental and control groups treated with drinking water containing extract of kurosu for 35 days	Enhanced programmed necrosis in cancer cells Possessed anticancer effect against human cells Group 4 treated with Kurosu vinegar had more protective effect as compared to untreated group. $P < 0.05$	Shamoji et al. (69)
Nypa palm vinegar	Adult male sprague-dawley rats	Single oral administration of Nypa palm vinegar 1g/kg for 7 hours	Enhanced anti-glycemic effect compared to metformin up to 56.6 % P < 0.05 Enhanced insulin level up to 79.8 %, percent Aqueous extract showed significant anti-glycemic effect due to presence of acetic acid (35.25 %),	Yusoff et al. (110)
Tomato vinegar	4 week old male sprague-dawley rats	7 ml tomato vinegar/kg/day for 5 weeks	Decreased the body and visceral fat weight 63 % compared to the HFD control group P < 0.05 Reduced hepatic TG and cholesterol levels by 19.80 % and 22.68 % compared to the HFD group p < 0.05 Inhibited adipogenic 3T3–L1 cells differentiation compared to control P < 0.01 Increased fatty acid beta-oxidation carnitine transferase due to high content of lycopene and carotenoid i: e, 3.19 and 6.45 mg/100 mL	Lee et al. (74)
Persimmon vinegar	Sprague-dawley rats	2 ml of persimmon vinegar/kg of body weight for 8 weeks	Decreased hepatic triglycerides and total cholesterol concentration P < 0.05 Decreased ACC mRNA level with increasing doses of PV Level of CPT-I mRNA increased with increasing doses	Moon et al. (66)
Ginseng radix vinegar	ICR mouse model of metabolic syndrome	500 mg of ginseng/kg/day for 8 weeks	Increased insulin resistance up to 90 percent compared to HFD group p < 0.0.5 Decreased fasting and postprandial glucose80 and 94 percent respectively as compared to HFD group Inhibited weight gain	Yun et al. (111)
Pomegranate vinegar	5 groups of rats Ninety healthy females	Treated with high fat diet and PV 0,6.5 and 13 %w/w for 15 weeks One pouch of PV or placebo for 8 weeks	Reduced TG level significantly compared to HFD control p < 0.001 Increased phosphorylation of AMP-activated protein kinase as compared to HFD group p < 0.05 Increased lipolysis and fatty acid oxidation via increased of HSL mRNA and CPT- 1a mRNA in adipose tissue and live respectively. Decreased sterol binding protein-1c and peroxisome proliferator- activated receptor	OK et al. (75)

which is made as the final product and also depends on the used raw material type and process. On the basis of the raw material used as a substrate in the fermentation process, vinegar can be classified as different types such alcohol vinegar, malt vinegar, wine vinegar and cider vinegar. Special types may be specified within the wine vinegar category, with vinegar from red and white wine, called "specialty vinegars", manufactured from some particular kinds of grapes or wine according to conventional procedures [15]. Southern Spain wine vinegar and Italy balsamic vinegar are most famous and are highly ranked within this family of vital commodities. Based on the production method, vinegar has two types of different groups that are commonly known as quick and slow method groups [16]. Alcoholic and acetous fermentation are two fermentation processes that are used for vinegar production. Alcoholic fermentation is a fast process in which complex sugars are generally depleted within three weeks. Conversion of fermentable sugars into ethanol is done through the action of yeasts, usually strains of Saccharomyces cerevisiae. On the other hand, in acetous fermentation, ethanol is further oxidized into acetic acid by acetic acid bacteria that usually belong to the genus Acetobacter. Alcoholic and acetous fermentations are carried out under anaerobic and aerobic conditions, respectively [23].

Vinegar is mostly used for fruit and vegetable pickling, along with manufacturing of salad, mustard and other food condiments. Even though it is useful as a food element for flavor and functional characteristics, the latent health benefits of different types of vinegar require the researchers to consider this food item in further research [17].

Regular intake of bioactive elements is encouraged by many nutritional researchers, and the functional characteristics of vinegar have been stated in different types of scientific and general publications. Vinegar manufacturing has been enhanced since the results of different studies showed the medicinal benefits of vinegar [18]. The observed therapeutic characteristics of vinegar include prevention of microbes, cardiovascular diseases, cancer, obesity and diabetes. [19].

Search criteria and database

In this article, we summarize the use and effect of vinegar produced from different natural resources (Figure 1). Selection of research articles was based on the production of vinegar and significant results on different wide-spread diseases from 1999 to 2017.¨

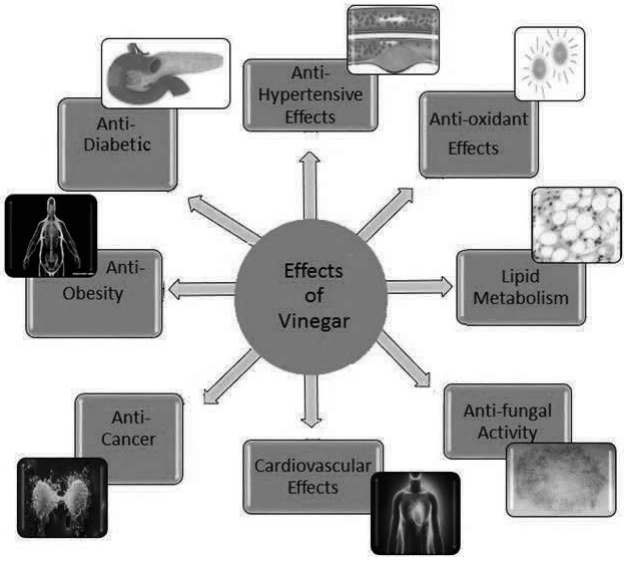

Figure 1. Effect of vinegar on different diseases.

Vinegar as an Anti-microbial agent

Sung Tse, known as a pioneer Chinese forensic scientist, utilized vinegar and sulfur as hand-washing agents to counteract infections in the 10th century [20]. Acetic acid is fabricated typically in over-ripe vegetables and fruits, apparently to assist as a natural insecticide [21], and also exists as an antimicrobial element in human vaginal fluids [22]. Vinegar has antimicrobial properties that make it useful for a number of applications. Since the ancient Greece era, vinegar has been commonly used as an antifungal and anti-microbial element because of its very low pH and the presence of acetic acid as a major component. The entry of acetic acid into the microbe's cell membrane causes their cells to die. The antibacterial activity of vinegar depends on different aspects including the strain of bacteria, aggregation of acetic acid, ionic strength, pH and temperature. Acetic acid was acknowledged as the chief organic acid in deracinating Escherichia coli O157:H7, a food-borne pathogenic bacteria, in comparison with other organic acids such as citric, malic and lactic acids [23]. Apple cider vinegar produced through various techniques has significantly different pH and acidity values, and it is observed that vinegar produced by the submersion method is more acidic [24].

Modern research results have shown that fruit vinegars containing 0.1% acetic acid effectively inhibit the growth of food-borne pathogens *in vitro*, including those of *Escherichia coli* O157:H7, *Salmonella enteritidis, S. typhimurium, Vibrio parahaemolyticus, Staphylococcus aureus, Aeromonas hydrophila, and Bacillus cereus [25]*. In fangled beef, the efficacy of a 2% acetic acid treatment at curtailing Escherichia coli and Salmonella typhimurium was supported for a long time in refrigerated and frosted storage, and this treatment did not produce any hostile sensory changes as recognized by a consumer group [26]. In iceberg lettuce, a mixture of 35% vinegar with 1.9% acetic acid content was efficient at decreasing bacteria levels including

Escherichia coli, and additionally, since lettuce is remarkably sour in taste and its supply is languishing, consumer access was maintained [27].

Wood vinegar is produced from waste wood. Wood vinegar shows antifungal action, but its efficacy depends on the temperature during the pyrolysis procedure. When the results of organic acids for the elimination of foodborne pathogenic bacteria were collated, it was found that acetic acid was the most fatal acid to Escherichia coli O157:H7, followed by lactic, citric, and malic acids. Moreover, irrigation of the ear canal with diluted vinegar was found to have positive effects on otitis and myringitis [28].

Pathogenic bacteria were successfully eradicated from vegetables upon dipping in either grain or fruit vinegars for a short time. Grain vinegars can effectively destroy respiratory pathogens such as *Micrococcus catarrhalis, Staphylococcus albus, Diplodocus pneumonia*, and *Alpha streptococcus*, while on the other hand, apple vinegar strongly inhibits the growth of pathogenic bacteria such as *Staphylococcus epidermidis, Pseudomonas aeruginosa, Proteus mirabilis*, and *Klebsiella pneumonia* [29, 30].

Vinegar as an anti-oxidant agent

Bioactive compounds modify physiological or cellular actions, which promotes health. Compared to nutrients and nutritional supplements, bioactive compounds promote more beneficial health effects. Bioactive compounds are claimed to have the capability of altering the risk of disease rather than counteracting the disease. In addition, there is great interest in polyphenolic compounds as quality determinants because, besides their antioxidant activeness, they also account for the color and astringency of vinegar. Different types of reactive oxidants such as hydrogen peroxide, superoxide and hydroxyl radical have been claimed to modify proteins, lipids and DNA with effects on cancer, aging, and brain-related complications [31, 32]. Recent research has suggested that bioactive compounds in foods may decrease the risk of these degenerative ailments through antioxidant effects [33, 34].

Compared to balsamic and red wine vinegars, traditional balsamic vinegar has a huge amount of catechin (Table II). Investigations of conventional balsamic vinegars showed that their antioxidant activity was basically due to melanoidins. Further analysis indicated that conventional balsamic vinegar melanoidins anticipate the assimilation and the pro-oxidant and cytotoxic effects of heme during imitated gastric ingestion of meat [35, 36]. The attained values in the peroxidase assay were smaller than the total phenolic aggravates values because decreasing levels of sugars such as fructose and glucose will lead to a response for the total phenolic compounds but will not show a response in the peroxidase assay [37].

Kurusu is a Japanese rice vinegar with a high concentration of phenolic compounds, indicating that it is a powerful source of antioxidant activity [19]. The total anti-oxidant activity and phenolic content of apple cider vinegar produced with the submersion method were found to be smaller than the total anti-oxidant activity and phenolic content of apple cider vinegar produced with the surface method [24].

The antioxidant effect of persimmon vinegar was greater than those of the red and white wine vinegars; this higher antioxidant activity is due to the specific type of yeast strain used in persimmon vinegar production [38]. The salted cherry blossom Sakura-cha is produced from Japanese plum vinegar and is often served at festivals. In the Sakura-cha making process, an extract is made by dipping cherry blos-

Table II. Comparison of bioactive compounds between various types of vinegars.

Analysis of vinegars	BV Verzelloni et al. [37]	RWV [37]	TBV [37]	OV Qui et al. [112]	ZV [112]	BV1 Su et al. [113]	BV2 [113]	BV3 [113]	URV Sakanaka et al. [114]	PV (114)	SV Ubeda et al. [115]	TV Lee et al. [74]
Total phenolic compounds catechin (mg/mL)	1.99	0.71	3.72	5.29	4.18	–	–	–	–	–	–	–
Total flavonoid content (mg/mL)	0.33	0.23	0.58	2.04	1.10	–	–	–	–	–	–	–
Total anthocyanin (mg cyaniding-3-glucoside)/100 mL)	–	–	–	–	–	0.97 ± 0.06	1.37 ± 0.09	3.22 ± 0.13	–	–	–	–
Total phenolic compounds Gallic acid (mg/mL)	–	–	–	–	–	0.89 ± 0.02	1.11 ± 0.03	0.98 ± 0.02	0.73 ± 0.10	0.80 ± 0.11	1.61 ± 0.10	0.37 ± 0.001

BV: Balsamic Vinegar; TBV: Traditional Balsamic Vinegar; OV: Oat Vinegar; ZV: Zhenjiang Vinegar; BV1: Blueberry Wine Vinegar (without skin contact); BV2: Blueberry Wine Vinegar (with skin contact); BV3: Blueberry Vinegar; URV: Unpolished Rice Vinegar; PV: Persimmon Vinegar; SV: Strawberry Vinegar; TV: Tomato Vinegar.

soms in Japanese plum vinegar. This extract was claimed to have noteworthy superoxide anion scavenging effectiveness. Examination of the extract indicated the existence of caffeic acid, cyanidin-3-glucoside and cyanidin-3-rutinoside, as the strongest antioxidant elements [39] (Table II).

Vinegar and Diabetes

Diabetes mellitus is a complicated metabolic disorder of the endocrine system with the symptom of hyperglycemia due to defects in insulin secretion, insulin action, or both. According to the W.H.O definition, diabetes is characterized as high blood glucose levels in both fasting and postprandial conditions. In type 1 diabetes, pancreatic cells are destroyed, causing hyperglycemia due to insulin deficiency. In type 2 diabetes, insulin exists but tissues are dissident to the insulin, and because of this, blood glucose concentrations escalate (WHO 2014). Insulin efficacy has been enhanced by means of vinegar remedy in 19 % of subjects with type 2 diabetes and 34 % of subjects with prediabetes [40]. Vinegar has been used as a diabetic remedy for about a century. In the 1920s, an Indiana doctor, Charles Kaadt, provided a "superb new remedy", which completely cured diabetes. Actually, potassium nitrate mixed in vinegar produced a yellow brown medicine that was declared to aminate digestion. Kaadt claimed that diabetics have a deficiency of hydrochloric acid in their abdomen, and that the acetic acid would aminate "those alkaline glands that are vacant in the duodenum"[41].

Scientific data claiming the anti-glycemic impact of vinegar ingestion at meal-time were first obtained in 1988. Recent studies in humans and animals have demonstrated that vinegar may be consumed as diabetic treatment [42]. In rats, the efficacy of vinegar on blood sugar has been analyzed, and it has been claimed that reduced blood glucose levels were correlated with routine diet after ingestion of a starch load co-administered with a 2% acetic acid mixture [43]. In humans, the domain beneath the curve of insulin retort declined 20 % after consumption of sucrose given along with vinegar [44]. Many placebo-controlled investigations have reported the effectiveness of vinegar at decreasing blood glucose levels [40, 45]. Various systems have been analyzed to demonstrate the efficacy of vinegar for blood glucose absorption. Acetic acid in vinegar may block the entire absorption of tangled carbohydrates [46] by either accelerating gastric purging [47] or by improving the absorption of glucose by tissues resulting in decreased blood glucose levels [48, 49]. These are vital recommendations because reductions in postprandial hyperglycemia may decrease pancreatic problems and delay the progression of diabetes [50].

Chronic hyperglycemia harms blood vessels and is a reliable indicator of cardiovascular disease in both type 2 diabetes and pre-diabetes [51]. Therefore, diabetes patients may have the capability to ameliorate glycaemia at meal time by adding vinegar as a condiment in the meal. Acetic acid may interfere with the absorption of starch particles, thereby decreasing the quantity of glucose ingestion into the bloodstream following a meal [46]. This analysis was conducted in cell culture, and because other dietary acids such as lactic acid or citric acid were ineffectual, acidity does not appear to play a role in this inhibition. Others suggested that vinegar moderates the pace of gastric emptying, which would delay the rate of glucose assimilation into the bloodstream[47], or alternatively, acetic acid improves the assimilation of glucose into tissues from the bloodstream so that the blood glucose concentration remains low [9].

Prevention of Cardiovascular Diseases

Hypercholesterolemia is considered to be a major risk factor for cardiovascular diseases [52]. Various factors, including lifestyle, high cholesterol diet, anxiety and age, have been shown to induce heart failure [53]. Elevated cholesterol levels, specifically low-density lipoprotein cholesterol levels, are essentially accountable for hypercholesterolemia [54]. The World Health Organization has anticipated that heart complications and stroke are becoming more lethal, with an estimated total death of 24 million by 2030 [55]. More than half of the total deaths are caused by cardiovascular diseases [56]. Cholesterol, smoking, dormancy and high blood pressure are among the major risk factors for cardiovascular diseases [57–59].

Numerous epidemiological reviews demonstrate that foods with high concentrations of polyphenols provide a defensive effect and decrease fatality from cardiovascular ailments [60, 61]. Polyphenols such as chlorogenic acid available in high concentration in apple cider vinegar could decrease the oxidation of LDL and improve health by reducing the risk of cardiovascular complications [62]. The increase in HDL levels was prominent in a group consuming only apple cider vinegar produced using the surface method including maceration, and the enhancement in LDL levels was significant in the apple cider vinegar produced using the submersion method including the maceration along with surface and submersion methods. On the other hand, the increase in total cholesterol levels was significant in all groups of apple cider vinegar [24]. In spontaneously hypertensive rats given a basic laboratory regime blended with a mixture of acetic acid or deionized water, a

huge decrease in systolic blood pressure (–20 mmHg) was found for the spontaneously hypertensive rats that were given acetic acid [10]. The reduction in systolic blood pressure due to acetic acid was correlated with plasma aldosterone and plasma renin activity, factors combined with blood vessel compression. Vinegar intake (0.57 mmol acetic acid) additionally repressed the renin-angiotensin framework in non-hypertensive, Sprague-Dawley rats[63].

Acetic acid, 0.3% (w/w), decreases the level of total cholesterol and serum triglyceride in rats fed on a high cholesterol diet [12]. Acetic acid treatment also decreases liver ATP citrate lyase action, liver 3-hydroxy-3-methylglutaryl-CoA activity, liver mRNA grades of sterol prevailing component compulsory protein-1, and production of fatty acids; additionally, fecal bile acid matter was notably elevated in rats fed acetic acid compared to controls. This finding suggests that acetic acid treatment decreases the levels of cholesterol and triacylglycerol through the hindrance of hepatic lipogenesis and improvement of the elimination of fecal bile acid. Acetate, which is produced from the acetic acid in the body, activates AMPK, which plays a key role in homeostasis of lipid and which may clarify the lipid-decreasing efficacy of consumed acetic acid in animals [64]. The presence of acetic acid in vinegar will suppress sterol regulatory element-binding protein (SREBP) gene expression mRNA levels and also decreases the activity of ATP citrate lyase (ATP-CL). This may decrease the levels of crucial substrates (HMGCoA and acetyl-CoA) required for production of fatty acids and serum cholesterol [65]. Acetic acid increases alternative oxidase gene expression, thus increasing the oxidation of fatty acids. The study showed that acetic acid does not merely inhibit fatty acid and serum cholesterol synthesis in liver but also increases lipolysis. Ingestion of persimmon vinegar will enhance lipid profiles through raising of the body carnitine level and may enhance lipid oxidation [66].

Vinegar and cancer

Cancer is a disease in which anomalous cells escape from control and can attack nearby tissues. These abnormal cells can also escalate to different parts of the body via lymph and blood systems. There are many types of cancer such as carcinoma, sarcoma, leukemia, lymphoma and malignancy. The antitumor elements in vinegar are still not completely identified. The antitumor characteristics of vinegar have been analyzed in animals and cultured cells. Vinegar obtained from sugarcane incited apoptosis in human leukemia cells [67]. Vinegar obtained from sugar cane (known as 'Kibizu'), Kurosu, a vinegar derived from rice, and Izumi, a Japanese black vinegar made from unpolished rice, show anticancer properties by obstructing the differentiation of human cancer cells via necroptosis and promotion of apoptosis [68].

Conventional Japanese rice vinegar known as Kurosu is claimed to be a major essential source of phenolic amalgam for decreasing the risk of cancer [69]. The ethyl acetate extract of Kurosu vinegar shows greater antioxidant activity than the vinegars obtained from wine and apples [19, 70]. Kibizu is a vinegar manufactured from sugar cane in Japan. Kibizu constrains the proliferation of indicative human leukemia cells by its efficacious radical scavenging action [67].

Quantities of acetic acid and alcohol fermentations that were manufactured during the apple vinegar production were analyzed especially for the alpha-glycan essence, which has an adverse effect on tumors in trial mice. It was observed that medium-sized impartial alpha-glycan was assembled specifically through fermentation of acetic acid, but not via fermentation of alcohol [71]. Vinegars are also a dietary source of polyphenols, produced via plants to protect from oxidative stress. Ingestion of polyphenols intensifies in vivo antioxidant protection and decreases the cancer risk [70]. Nevertheless, epidemiologic facts are rare and evident. Research conducted in Lanzhou, China, showed that vinegar intake was linked with reduced risk for abdominal cancer (OR: 0.37). On the other hand, a significant 4.4-fold increase in the risk of bladder cancer was linked with vinegar ingestion in a study conducted in Serbia [72].

Vinegar and Obesity

Obesity and overweight conditions are described as anomalous or immoderate fat aggregation that gives rise to a risk to health. Generally, the body mass index is used to measure obesity. A person with a BMI of 30 or greater is commonly medicated as obese. A person with a BMI equal to or greater than 25 is considered overweight (WHO). Numerous analyses have shown that vinegar consumption is correlated with satiety and reduces the energy intake at meals; therefore, consistent vinegar intake may decrease the quantity of food consumed at meals, adding to weight reduction [73]. In one experiment, participants ingested white bread (50 g of carbohydrate) only or with 3 parts of white vinegar with acetic acid contents of 1.1, 1.4, or 1.7 grams and were asked about their hunger or satiety feelings using a ranking varying from uttermost hunger (10) to uttermost satiety (–10) before meal ingestion and at 15-minute delays after the meal. Only bread ingestion showed the lowest ranking of satiety (calculated as domain under the arc from 0–120 Minutes). Satiety sensations were enhanced when vinegar was consumed with the bread, and a linear association was observed between

the acetic acid content and satiety level of the trial meals (r – 0.41, p – 0.004) [14].

Vinegar produced from tomatoes has potent anti-visceral obesity properties in high fat diet incited obese rats. Intra-abdominal (visceral) obesity is known as a common type of obesity that is associated with different conditions such as cardiovascular diseases, hypertension, type 2 diabetes mellitus and hyperlipidemia. Intake of tomato vinegar on a daily basis can decrease the visceral fat completely along with epididymis adipocyte mass [74]. Vinegar extract from pomegranate appears to be more famous for obesity treatment because it has been reported to constrain lipogenesis and boost fatty acid beta-oxidation [75, 76]. In addition to this, consumption of pomegranate vinegar may encourage the modulation of peroxisome proliferator-activated receptor alpha (PPARa) [65] and carnitine palmitoyl transferees 1 alpha (CPT-1a) mRNA expression comprising phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) more effectively than acetic acid [75], showing that PV is more powerful than acetic acid at decreasing obesity. In an experimental trial, participants taking two tablespoons of red raspberry vinegar everyday with free access to water and food for 4 weeks lost weight, while the control batch ingesting the same quantity of cranberry juice every day for 4 weeks showed insignificant weight gain [77]. In another experiment, healthy participants ingested three different doses of vinegar (18, 23, and 28 mmol acetic acid) along with a portion of wheat bread, while bread ingestion with no vinegar intake was used as a control meal. When the sensations of hunger and satiety were analyzed, it was claimed that satiety was enhanced with increasing levels of acetic acid [14]. In another study, three different situations (control, ingestion of vinegar containing 1 g of acetic acid, or ingestion of contiguous 1 ounce of peanuts for satiety) were observed. In this experiment, subjects consuming vinegar or peanuts showed smaller subsequent food ingestion of nearly 200–275 calories every day. Following the ingestion of a bagel meal, energy expenditure for the remaining of the day was slightly enhanced by vinegar and peanut treatments (a reduction of almost 200–275 kilocalories, P = 0.111). This daily reduction in calories was manifested in the monthly weight reduction of 1–1.5 pounds [13].

Yamashita [78] analyzed the possible mechanisms of vinegar in obesity reduction. A kinase enzyme known as AMPK functions as a vital metabolic controller switch and performs an important role in homeostasis of lipids that increases with the AMP/ATP ratio and is enhanced due to vinegar supplementation. AMPK phosphorylation will incite PPAR-alpha gene expression [79] that moderates mRNA expression of fatty acid oxidation enzymes such as CPT-1a and acetyl-CoA (ACCA) oxidase, which may boost fatty acid oxidation. Triggering of AMPK along with down-regulation of SREBP-1c [76] and carbohydrate-responsive element binding protein (ChREBP) expression will hinder lipid aggregation. AMPK also imparts a critical role in the breakdown of lipid, as it provokes up-regulation of hormone-sensitive lipase, causing a rise in lipid degradation [75]. Therefore, the ability to enhance fatty acid oxidation, hinder lipogenesis and consequently enhance lipolysis suggests that vinegar can be used as a natural medicine against excess weight or obesity [80].

Vinegar and Hypertension

Hypertension is described as elevated blood pressure inside the blood vessels. Blood pressure is the momentum of blood pushing against the walls of arteries as it passes through them. Arteries conduct oxygenated blood from the heart to different body parts.

Different studies have examined the efficacy of vinegar for decreasing blood pressure. These experiments have investigated the effects of oral ingestion of vinegar on the renin-angiotensin framework by using spontaneously hypertensive rats that are stroke-prone both in vitro and in vivo [81–83]. The rats given a controlled laboratory diet blended with an acetic acid mixture or deionized water showed a noticeable decrease (–20 mmHg) in systolic blood pressure [10]. The reduction in systolic blood pressure due to acetic acid was correlated with plasma aldosterone and plasma renin activity, factors associated with blood vessel compression. Vinegar intake (0.57 mmol acetic acid) also repressed the renin-angiotensin framework in non-hypertensive Sprague-Dawley rats [63]. In induced hypertension, acetic acid may constrain renin secretion and decrease the angiotensin I concentration. Acetic acid also constrains the angiotensin-converting enzyme (ACE) [84], which decreases plasma angiotensin II levels [85]. Additionally, Nakamura and co-workers [86][110] have claimed that acetic acid will increase vasodilation due to the blockage of strong vaso-constrictive angiotensin II.

Although several studies showed that only minor components are critical in inducing the anti- hypertensive effect, acetic acid also shows this effect [10, 54]. Melanoidins, which are integrated in the last phase of the Maillard reaction via the manufacturing of conventional balsamic vinegar, disclose promising health advantages together with antihypertensive activity [87].

Vinegar and Injuries

Injuries are damage or physical loss to the body caused by an attack or accident. Hippocrates

testifies that vinegar was utilized medicinally to treat wounds. Mother of vinegar has been evaluated for its healing effect on burns because of its anti-bacterial properties [88]. One study showed that 3.75% apple cider vinegar produced same results comparable to cefotaxime (antibiotic) in reducing bacteria load. However, using an admixture of equitable amounts of apple cider vinegar and cefotaxime resulted in better and rapid healing as compared to using them separately. Another study reported that acetic acid solutions at concentrations (≤ 0.0025%) nontoxic to keratinocytes and fibroblast were ineffective at reducing the growth of *Bacteroides fragilis* bacteria, *Escherichia coli, or* group D *Enterococcus, however, it reduced the growth of Pseudomonas aeruginosa* and Staphylococcus *aureus* [6]. Since the Ancient Greece period, vinegar has been utilized widely as an antifungal and antibacterial agent because of its extraordinary low pH caused by the presence of acetic acid as a major component. Oral administration of acetic acid bacteria was helpful at reducing muscle damage by inflammation after deliberate exercise. Additionally, it was claimed that the extracellular configuration synthesized by Acetobacter xylinum helped tissue healing in rats. *xylinum* is a simple Gram-negative bacterium which has an ability to synthesize a large quantity of high-quality cellulose organized as twisting ribbons of microfibrillar bundles [89].

Vinegar and the Nervous system

It has been proposed that vinegar utilization may enhance cognitive function in humans, and research demonstrates that acetic acid bacteria construct the precursors of critical building blocks of brain tissues, which are known as sphingolipids. The term sphingolipid was first introduced by Herbert Carter and colleagues in 1947. Sphingolipids involve different complex varieties of lipids in which fatty acids are associated through amide bonds to a long-chain base or sphingoid. Sphingolipids are vital building blocks for brain tissues.

Studies have demonstrated that acetic acid bacteria generate precursors of sphingolipids, which are manifested as the alkali-stable lipids (ASL). One of the alkali-stable lipids created by acetic acid bacteria is dihydroceramide. The examination of the impact of ASL on dementia confirmed that after treatment for 10 days, dramatic changes in the subjects' capacity were observed. Further investigations demonstrated that ASL enhanced the growth of neurites in dihydroceramide and pheochromocytoma (PC12) cells, leading to a powerful effect. Fukami and others postulated that vinegar utilization may amend cognitive function in humans [90, 91]. Different studies revealed that gangliosides along with ceramide were useful for ameliorating Alzheimer's patients' symptoms [92]. Still, the exact mechanisms of these effects are undetermined, and the effects of vinegar on the brain are not known exactly, so that more research on this phenomenon is needed.

Vinegar Effects on Warts, Otitis Media, Nail Fungus, and Head Lice

While a wide variety of studies have demonstrated many health benefits of vinegar, some claimed vinegar benefits still require further investigations or are dubious. Even though the efficiency of attenuated vinegar (2% acetic acid mixture at the same pH) for the treatment of ear conditions (otitis media, otitis externa and granular myringitis) has been demonstrated [93, 94], the low pH of these mixtures may aggravate inflamed skin and harm cochlear outer hair cells [95]. Considering that vinegar can deactivate nematocysts, quick application of vinegar in the area of jellyfish sting has been evaluated around the world [96, 97]. Nevertheless, hot water drenching was concluded to be the best treatment for jellyfish envenomation, based on the deactivation of the venom by heat [98, 99]. In conventional media, vinegar is consistently advised for curing head lice, nail fungus, and warts, even though further research regarding these effects is needed. Takano-Lee and colleagues [100] claimed that out of seven remedies examined, vinegar was the least useful for removing lice or suppressing the incubating eggs. Unproven statements have been made that the progressive topical utilization of extremely congregated acetic acid mixtures (up to 99%) mitigated warts [101, 102], apparently because of the mechanical levigation of wart tissue. On the other hand, one cure procedure required limited anesthesia, excision, and brisk counteracting at the area of application, in this way constraining its use by the lay public.

Despite the fact that it is not a cure methodology, vinegar washes are utilized by birthing specialists in distant, ineffectively resourced areas (e.g., the Amazon wilderness and Zimbabwe) to protect women from the human papilloma infection [103, 104]. Treatment with acetic acid produces prominent changes in viral injuries allowing for fast localization of contamination with 77% sensitivity and the option for a prompt cure with cryotherapy [105].

Vinegar Safety And Tolerance

Vinegar has been used as a therapeutic agent and food element for thousands of years and is free of harmful side effects. Oxymel, a famous old medicine that consists of vinegar and honey, was recommended for chronic coughs by Hippocrates as well as by contemporary medicine. The complete manufacturing process of oxymel was mentioned in the British and German Pharmacopoeia (1872), and as

per the French Codex (1898), the medicine was manufactured by blending one portion white wine vinegar with four portions of virgin nectar, consolidated with paper pulp.

However, when utilized for therapeutic purposes, a large quantity of acetic acid may have harmful outcomes. Acetic acid with a concentration of more than 20 % is considered to be a toxin and can bring about extreme damage to the throat. Most of the vinegars used in the US have 4–7 % acidity; and there are few reports in the literature regarding the conflicting reactions to vinegar utilization. Second-degree burns of the throat along with cardia and inflammation of the oropharynx were observed in a 39-year-old woman who drank one tablespoon of rice vinegar[106], and the inadvertent consumption of vinegar has been connected with laryngospasm and resulting vasovagal syncope that appeared suddenly [107]. Hypokalemia was diagnosed in a 28-year-old woman who had ingested 250 ml of apple cider vinegar for almost 6 years on a daily basis [108]. As described by the Food Standard Agency, intake of vinegar in huge amounts is not more effective than the intake of vinegar in dilute form of 5 % acetic acid. Vinegar intake in high amounts can produce a negative health impact. There are diverse reported instances of death that support this announcement. Paul Byrne in 2014 reported that in Manchester, UK, a thirty-eight-year-old pregnant mother of five babies died by drinking ½ measure of vinegar to end her pregnancy. The victim had read online that she could induce premature birth by drinking concentrated vinegar[109].

Most studies of vinegar demonstrate that persistent vinegar consumption may affect glucose regulation in type 2 diabetes subjects and may also involve consequences on liver function and digestive pathways in addition to glucose digestion. Since liver enzymes and a rise in urine corrosiveness can induce unexpected variations in metabolism, more analysis is required to better identify these vinegar-incited variations in metabolism along with other related pathways and to evaluate the quantity of required vinegar consumption.

Conclusions

Vinegar is produced worldwide from various types of starting materials using a wide variety of manufacturing techniques. A considerable amount of data suggest that vinegar has remedial value, especially for control of blood glucose in diabetic or pre-diabetic populations. As a medicinal food, vinegar is bearable and engaging, but future studies must better characterize the importance of vinegar for health advancement. Operative therapeutic characteristics of vinegar include reduction of blood pressure, reduction of the diabetes effects, prevention of cardiovascular diseases, and antibacterial and antioxidant activities. Initial information recommends that consuming vinegar, as a correlate to its consumption as a condiment, may be associated with adverse reactions. Depending on the different types of vinegar, total phenolic contents and inherent acetic acid, regular ingestion of vinegar may modify human metabolism and health. More research is required to determine the therapeutic role of vinegar in different diseases, especially to determine the mechanism of its effects.

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