Comprehensive REVIEWS in Food Science and Food Safety

Vinegar Functions on Health: Constituents, Sources, and Formation Mechanisms

Hengye Chen, Tao Chen, Paolo Giudici, and Fusheng Chen

Abstract: Vinegars are one of only a few acidic condiments throughout the world. Vinegars can mainly be considered grain vinegars and fruit vinegars, according to the raw materials used. Both grain vinegars and fruit vinegars, which are fermented by traditional methods, possess a variety of physiological functions, such as antibacteria, anti-infection, antioxidation, blood glucose control, lipid metabolism regulation, weight loss, and anticancer activities. The antibacteria and anti-infection abilities of vinegars are mainly due to the presence of organic acids, polyphenols, and melanoidins. The polyphenols and melanoidins also provide the antioxidant abilities of vinegars, which are produced from the raw materials and fermentation processes, respectively. The blood glucose control, lipid metabolism regulation, and weight loss capabilities from vinegars are mainly due to acetic acid. Besides caffeoylsophorose (inhibits disaccharidase) and ligustrazine (improves blood circulation), other functional ingredients present in vinegars provide certain health benefits as well. Regarding anticancer activities, several grain vinegars strongly inhibit the growth of some cancer cells *in vivo* or *in vitro*, but related functional ingredients remain largely unknown, except tryptophol in Japanese black soybean vinegar. Considering the discovering of various functional ingredients and clarifying their mechanisms, some vinegars could be functional foods or even medicines, depending on a number of proofs that demonstrate these constituents can cure chronic diseases such as diabetes or cardiovascular problems.

Keywords: vinegar, functional properties, functional ingredients, blood glucose control, lipid metabolism regulation, anticancer

Introduction

Vinegars are one of only a few acidic condiments throughout the world. Based on their raw materials, vinegars can mainly be considered grain vinegars, which contain sorghum, rice, wheat, or other grains as the raw materials, or fruit vinegars, which are based on fruits such as grapes or apples as the raw materials. In addition, vinegars can also be fermented from sugar and alcohol. Shanxi aged vinegar, Zhenjiang aromatic vinegar, Sichuan Baoning bran vinegar, and Fujian Yongchun *Monascus* vinegar, which are the 4 major traditional vinegars in China, are common grain vinegars in addition to Kurosu, a Japanese vinegar. In contrast, Italian balsamic vinegar, Spanish Sherry vinegar, and American apple vinegar are fruit vinegars (Solieri and Giudici 2009). Regardless of the raw materials, vinegars are known to have several physiological functions, especially those made by traditional techniques (Budak and others 2014).

In approximately 400 BC, the ancient Greek Hippocrates began to use fruit vinegars to treat wound inflammations, cough, ulcers, and infectious diseases. The most ancient prescriptions displayed in the Chinese Book *Fifty-Two Diseases* (300 BC) include 17 remedies based on the use of grain vinegars to treat burns, hernias, cellulitis, and psoriasis. Throughout all of the dynasties, subsequent Chinese medical books also described many prescriptions that contained grain vinegars (Xu and others 2003). Since the 18th century, many records have recommended fruit vinegars to treat laryngitis, fever, swelling, stomachache, and the rash from poison ivy exposure in America (Budak and others 2014). Recent research studies have indicated that vinegars possess antibacteria, anti-infection, antioxidation, blood glucose control, lipid metabolism regulation, weight loss, and anticancer properties (Budak and others 2014; Petsiou and others 2014). The functional properties of vinegars have been reviewed in several papers (Budak and others 2014; Petsiou and others 2014; Pazuch and others 2015), but these reports mainly focused on fruit vinegars and did not discuss functional ingredients other than acetic acid. The present review summarizes the functional properties of grain vinegars and fruit vinegars and compares the functional ingredients, sources, and formation mechanisms of grain and fruit vinegars.

Functional Properties of Vinegars

Many active functions of vinegars have been proven and reported. In this section, the main functional properties of vinegars, including antibacteria, anti-infection, antioxidation, blood glucose control, lipid metabolism regulation, weight loss, anticancer, and

MS 20160988 Submitted 21/6/2016, Accepted 25/8/2016. *Authors H. Chen, T. Chen, and F. Chen are with Key Laboratory of Environment Correlative Dietology and College of Food Science and Technology, Huazhong Agricultural Uni., Wuhan 430070, Hubei Province, People's Republic of China. Author P. Giudici are with Dept. of Life Sciences, Uni. of Modena and Reggio Emilia, Via Amendola, 2, 42122 Reggio Emilia, Italy. Direct inquiries to author F. Chen (E-mail: chenfs@mail.hzau.edu.cn).*

doi: 10.1111/1541-4337.12228

so on, will be reviewed, and the relative activities of grain and fruit vinegars will be compared.

Antibacteria and anti-infection

Prior to the work of Pasteur and Koch on bacteria in the 19 century, vinegars were often employed in antibacterial and anti-infection applications. In approximately 400 BC, the ancient Greek medical expert Hippocrates used fruit vinegars to heal wounds, inflammations, coughs, and infections (Budak and others 2014). The Chinese medical book *Compendium of Materia Medica*, which was authored in the Ming dynasty (16 century), also shows records of the use of grain vinegars for Ascaris infection treatment, birth room disinfection, meat preservation, and others (Xu and others 2003). Modern research studies (Table 1) have shown that fruit vinegars containing 0.1% acetic acid effectively inhibit the growth of food-borne pathogens *in vitro,* including those by *Escherichia coli* O157:H7, *Salmonella enteritidis, S. typhimurium, Vibrio parahaemolyticus, Staphylococcus aureus, Aeromonas hydrophila, and Bacillus cereus* (Entani and others 1998). In addition, by soaking in either grain or fruit vinegars for a short time, pathogenic bacteria were successfully eradicated from vegetables (Sengun and Karapinar 2004; Chang and Fang 2007). Grain vinegars can effectively destroy respiratory pathogens such as *Micrococcus catarrhalis, Staphylococcus albus, Diplococcus pneumonia,* and *Alpha streptococcus*, whereas apple vinegar strongly inhibits the growth of pathogenic bacteria such as *Staphylococcus epidermidis, Pseudomonas aeruginosa, Proteus mirabilis,* and *Klebsiella pneumoniae* (Hindi 2013). Moreover, irrigation of the ear canal with diluted vinegar has positive effects on otitis and myringitis (Aminifarshidmehr 1996; Jung and others 2002).

Antioxidative effects

Vinegars are fermented products, mainly, of grains or fruits, and contain large amounts of antioxidants (Table 1). *In vitro* studies have shown that the antioxidant capacities of Shanxi aged vinegar (unpublished) and Italian balsamic vinegar (Tagliazucchi and others 2007; Bertelli and others 2015) were equal to those of 0.1% and 0.2% vitamin C solutions, respectively. Animal and cell experiments have also indicated that both grain vinegars and fruit vinegars can improve antioxidant capacities and reduce oxidative damage *in vivo* (Nishidai and others 2000; Xu and others 2005; Schaefer and others 2006; Tagliazucchi and others 2007; Verzelloni and others 2007; Iizuka and others 2010; Verzelloni and others 2010; Bertelli and others 2015; Liu and Yang 2015).

Blood glucose control

The effect of vinegar on blood glucose levels was first reported by Ebihara and Nakajima in 1988, who found that 2% of acetic acid in diet significantly reduced the blood glucose concentration of rats after starch intake (Ebihara and Nakajima 1988). Subsequently, a large number of human dietary studies also found that the intake of fruit vinegars significantly reduced blood glucose levels after the intake of starchy foods (specific dose effects were observed) (Table 1) (Ebihara and Nakajima 1988; Johnston and Buller 2005; Leeman and others 2005; Ostman and others 2005; Johnston and others 2010; Mitrou and others 2010); however, monosaccharide-induced blood glucose levels remained unchanged (Johnston and others 2010). Moreover, grape vinegars neutralized by alkali or consumed 5 h before a meal did not affect the postprandial blood glucose concentration and insulin response, indicating that vinegar plays a role in food digestion, which may be related to its acidity (Brighenti and others 1995). In diets with high-glycemic indices, apple vinegars significantly reduce the postprandial blood glucose concentration and insulin response and increase satiety. However, in low-glycemic diets, vinegars can only reduce the postprandial insulin response and do not significantly influence the blood glucose concentration, which may be due to the fact that a lower blood glucose level cannot be achieved by the addition of vinegar after the consumption of a diet with a low-glycemic index (Johnston and Buller 2005).

Compared to healthy people, the intake of apple vinegar also increases the insulin sensitivity of patients with type 2 diabetes (Ebihara and Nakajima 1988), and the intake of apple vinegar at bedtime can help patients with type 2 diabetes to control their fasting blood glucose concentration and prevent "diabetes mellitus dawn phenomenon" in the next morning (White and Johnston 2007). In a 12-week experiment, the dietary intake of 1.4 g of acetic acid (2 meals per day) significantly reduced the level of glycated hemoglobin (0.16%) in patients with type 2 diabetes (Johnston and others 2009). The consumption of apple vinegar over an extended period of time (99 – 110 d) can also improve the insulin resistance of patients with polycystic ovary syndrome and improve ovulation function (Wu and others 2013). Although studies on the use of vinegars to control blood glucose levels primarily focused on fruit vinegars, the long-term intake of grain vinegars may also have a positive effect on the blood glucose levels of humans, because acetic acid is able to reduce the postprandial blood glucose concentration (Ebihara and Nakajima 1988; Ostman and others 2005). Moreover, grain vinegars have been shown to lower the blood glucose concentration of mice with diabetes (Ma and others 2010; Gu and others 2012).

Lipid metabolism regulation

Compared to investigations on the effects of vinegars on blood glucose contents, studies on the regulation of blood lipid levels were performed later and were primarily concentrated on animal experiments (Table 1). Many animal experiments have shown that the long-term consumption of a specific amount of acetic acid (Fushimi and others 2006), grain vinegars (Fan and others 2009; Li and others 2009; Liu and others 2015; Liu and Yang 2015), and fruit vinegars (Moon and Cha 2008; Setorki and others 2010; Soltan and Shehata 2012) can significantly reduce the concentration of total cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol and increase the concentration of high-density lipoprotein (HDL) cholesterol. Moreover, the regulation of lipid metabolism by vinegars was also observed in mice with type 2 diabetes and obese mice (Shishehbor and others 2008; Kondo and others 2009a; De Dios Lozano and others 2012; Soltan and Shehata 2012; Liu and Yang 2015). Experiments on humans (8 wk) have revealed that the consumption of 30 mL apple vinegar 2 times per day can significantly reduce total cholesterol, triglycerides, and LDL levels of patients with hyperlipidemia and increase the content of HDL in a nonsignificant manner (Beheshti and others 2012). In another study on the effects of vinegar on lipids, triglyceride levels significantly decreased in obese people consuming 15 mL apple vinegar every day (Kondo and others 2009b). Although reports on the regulation of human lipid metabolism due to grain vinegar consumption have not been published, the long-term intake of grain vinegars may have positive effects, according to previous animal experiments (Fan and others

Table 1–Functional properties of vinegars.

Vinegar type	Function	Country	Subjects	Results	Reference
Spirit vinegar	Antibacteria	Japan	Food-borne pathogenic bacteria	The growth of all strains evaluated was inhibited with a 0.1% concentration of acetic acid in the vinegar.	Entani and others (1998)
Rice vinegar	Antibacteria	China	*E. coli O157:H7*	Treatment of inoculated lettuce (10^7 CFU/g bacteria) with vinegar (5% acetic acid) for 5 min would reduce 3 logs population at 25 °C.	Chang and Fang (2007)
Grape vinegar	Antibacteria	Turkey	*Salmonella typhimurium*	Treatment of carrot samples with vinegar (4.03% acetic acid) for different exposure times (0, 15, 30 and 60 min) caused significant reductions ranging between 1.57 and 3.58 log CFU/g.	Sengun and Karapinar (2004)
Acetic acid solution	Anti-infection	Kuwait	96 patients with chronic suppurative otitis media	The patients received ear irrigation with 2% acetic acid solution three times per week (3 weeks, followed for up to 3 years). 55 patients had resolution of their original otorrhen, whereas 19 patients developed healed ear drum perforation. 14 patients (15%) showed recurrence and 8 of them had no response to the treatment.	Aminifarshidmehr (1996)
Fermented vinegar	Anti-infection	Korea	15 patients with chronic granular myringitis	The patients were treated with irrigation of the external canal with dilute vinegar solution (pH = 2.43) twice to four times per day. All patients had resolution of their original otorrhoea within three weeks.	Jung and others (2002)
Shanxi aged vinegar	Antioxidation	China	Hyperlipidemic mouse	Fed with a diet with 1% freeze-dried powder of Shanxi aged vinegar for 35 d resulted in a significant increase of antioxidation ability in mouse.	Liu and Yang (2015)
Shanxi aged vinegar	Antioxidation	China	*In vitro*	Reducing capacity: 98.94 ± 1.58 mg Vc/100 mL Antiradical activity: 124.89 ± 3.37 mg Vc/100 mL	Unpublished
Zhenjiang aromatic vinegar	Antioxidation	China	Ageing accelerating mice	Instilled with 1.2 g/kg·d vinegar for 35 d resulted in a significant increase of antioxidation ability in mouse.	Xu and others (2005)
Kurosu	Antioxidation	Japan	Mice	The ethyl acetate extract of Kurosu significantly suppressed the 12-*O*-tetradecanoylphorbol-13-acetate induced myeloperoxidase activity and H_2O_2 generation in mouse.	Nishidai and others (2000)
Traditional balsamic vinegar	Antioxidation	Italy	*In vitro*	Reducing capacity: 218.85 ± 6.86 mg Vc/100 mL Antiradical activity: 298.10 ± 6.25 mg Vc/100 mL	Tagliazucchi and others (2007)
Traditional balsamic vinegar	Antioxidation	Italy	*In vitro*	Reducing capacity: 27.12 ± 11.1 μM Tes/mL Antiradical activity: 33.52 ± 19.3 μM Tes/mL	Bertelli and others (2015)
Traditional balsamic vinegar	Antioxidation	Italy	Simulated gastric	The vinegar melanoidins (4.5 mg/mL) significantly inhibited the lipid peroxidation during simulated gastric digestion of meat.	Verzelloni and others (2010)
Balsamic vinegar	Antioxidation	Japan	Macrophage:THP-1	Balsamic vinegar (0.01%) significantly inhibited the low density lipoprotein (LDL) oxidation and lipid accumulation in macrophages	Iizuka and others (2010)
Red wine vinegar	Antioxidation	Italy	*In vitro*	Reducing capacity: 48.18 ± 2.00 mg Vc/100 mL Antiradical activity: 85.40 ± 1.73 mg Vc/100 mL	Verzelloni and others (2007)
White vinegar	Blood glucose control	Sweden	12 healthy volunteers	Supplementation of a meal with vinegar (18 g) reduced postprandial responses of blood glucose and insulin and increased the subjective rating of satiety.	Ostman and others (2005)
Bitter buckwheat vinegar	Blood glucose control	China	Diabetic rats	Oral intake of vinegar (2 mL/kg·d) for 4 weeks reduced about 17% blood glucose in rats.	Ma and others (2010)
Rice vinegar	Blood glucose control	China	Diabetic rats	Oral intake of vinegar (2 mL/kg·d) for 30 d improved fasting hyperglycemia and body weight loss through attenuating insulin deficiency, pancreatic beta-cell deficit, and hepatic glycogen depletion in rats.	Gu and others (2012)
Apple vinegar	Blood glucose control	America	11 patients with type 2 diabetes	Vinegar ingestion (30 mL) at bedtime moderates waking glucose concentrations in adults with well-controlled type 2 diabetes.	White and Johnston (2007)
Apple vinegar	Blood glucose control	America	27 patients with type 2 diabetes	Oral intake of vinegar (30 mL/d) for 4 weeks significantly reduced hemoglobin A1c values in individuals with type 2 diabetes mellitus.	Johnston and others (2009)
Apple vinegar	Blood glucose control	America	8 healthy volunteers	Supplementation of a meal with vinegar (10 g) reduced about 20% postprandial responses of blood glucose.	Johnston and others (2010)
Apple vinegar	Blood glucose control	Japan	7 patients with polycystic ovary syndrome	Oral intake of vinegar (15 g/d) for 90 - 110 d improved insulin sensitivity in individuals with polycystic ovary syndrome.	Wu and others (2013)

(*Continued*)

Table 1–Continued.

Vinegar type	Function	Country	Subjects	Results	Reference
Vinegar	Blood glucose control	Greece	10 patients with type 1 diabetes	Supplementation of a meal with vinegar (30 mL) reduced about 20% postprandial responses of blood glucose.	Mitrou and others (2010)
Acetic acid solution	lipid metabolism regulation	Japan	Human umbilical vein endothelial cell	Vinegar intake enhances flow-mediated vasodilatation via upregulation of endothelial nitric oxide synthase activity.	Sakakibara and others (2010)
Shanxi aged vinegar	Lipid metabolism regulation	China	Hyperlipidemic mice	Fed with a diet with 1% freeze-dried powder of vinegar for 35 d resulted in a significant reduction of triglyceride, total cholesterol and LDL in mouse.	Liu and Yang (2015)
Sorghum vinegar	Lipid metabolism regulation	China	Rats	Fed with a diet with extract of vinegar (100 mg/kg) protected the rats against thrombotic death induced by collagen and epinephrine.	Fan and others (2009)
Grape vinegar	Lipid metabolism regulation	Iran	Rabbits with high cholesterol diet	Oral intake of 10 mL vinegar significantly reduced LDL-cholesterol, oxidized-LDL malondialdehyde and total cholesterol in rabbits after 3 hours.	Setorki and others (2010)
Grape vinegar	Lipid metabolism regulation	Egypt	Diabetic rats	Fed with a diet with 15% vinegar for 6 weeks significantly reduced LDL-cholesterol and total cholesterol in rats.	Soltan and Shehata (2012)
Apple vinegar	Lipid metabolism regulation	Iran	19 patients with hyperlipidemia	Oral intake of vinegar (30 mL/d, twice) for 8 weeks significantly reduced triglyceride, total cholesterol and LDL in individuals with hyperlipidemia.	Beheshti and others (2012)
Persimmon vinegar	Lipid metabolism regulation	Korea	Mouse with high lipid diet	Oral intake of vinegar (2 mL/kg·d) for 16 weeks significantly reduced triglyceride and total cholesterol in mouse.	Moon and Cha (2008)
Acetic acid solution	Weight loss	Japan	Obese mice	Fed with 0.3 or 1.5% acetic acid solution for 6 weeks significantly inhibited the accumulation of body fat and hepatic lipids without changing food consumption or skeletal muscle weight.	Kondo and others (2009a)
Corn vinegar	Weight loss	China	Obese mice	Oral intake of vinegar (0.3 mL/d) for 30 d significantly reduced body weight, fat coefficient, triglyceride and total cholesterol in mouse.	Li and others (2009)
Purple sweet potato vinegar	Weight loss	China	Obese mice	Oral intake of vinegar (10 mL/ kg·d) for 30 d significantly reduced body weight, fat coefficient, LDL, triglyceride and total cholesterol in mouse.	Liu and others (2015)
Apple vinegar	Weight loss	Japan	150 obese Japanese	Oral intake of vinegar (15 mL/d) for 12 weeks significantly reduced body weight, body fat mass and serum triglyceride levels in subjects.	Kondo and others (2009b)
Apple vinegar	Weight loss	Mexico	Rats with high-caloric diets	Oral intake of vinegar (0.8 mL/ kg·d) for 4 weeks significantly reduced body weight, fat coefficient, LDL, triglyceride and total cholesterol in rats.	De Dios Lozano and others (2012)
Mulberry vinegar	Weight loss	China	Obese mice	Oral intake of vinegar (0.1 mL/d) for 30 d significantly reduced body weight, fat coefficient, triglyceride and total cholesterol in mouse.	Wei and others (2005)
Hawthorn Vinegar	Weight loss	Turkey	37 Obese patients with cardiovascular disease	Oral intake of vinegar (40 mL/d) for 4 weeks significantly reduced body weight, body fat mass and serum triglyceride levels in subjects.	Kadas and others 2014
Shanxi aged vinegar	Anticancer	China	Cancer cells (A549, Hep-G2, MDA-MDB-231, Hela)	Ethyl acetate extract of vinegar (0.01%) significantly inhibited the proliferation of cancer cells *in vitro*.	Chen and Gullo (2015)
Kurosu	Anticancer	Japan	Rats with colon cancer	Fed with water containing 0.05% ethyl acetate extract of Kurosu for 35 weeks significantly inhibited azoxymethane-induced colon carcinogenesis in rats.	Shimoji and others (2004)
Kurosu	Anticancer	Japan	Cancer cell (Caco-2, A549, MCF-7, 5637, LNCaP)	Ethyl acetate extract of vinegar (0.025%) significantly inhibited the proliferation of cancer cells *in vitro*.	Nanda and others (2004)
Black soybeans vinegar	Anticancer	Japan	Leukemia U937 cells	Ethyl acetate extract of vinegar (10 mg/mL) significantly inhibited the proliferation of cancer cells *in vitro*.	Inagaki and others (2007)
Postdistillation slurry vinegar	Anticancer	Japan	Mice with Sarcoma 180 and Colon 38 tumor cells	Fed with a diet with 0.5% vinegar for 72 d significantly decreased the sizes of tumors and prolonged life spans of mouse.	Seki and others (2004)
Sugarcane vinegar	Anticancer	Japan	Leukemia cells: HL-60, THP-1, Molt-4, U-937, K-562	Fraction eluted by 40% methanol from vinegar significantly inhibited the proliferation of leukemia cells *in vitro*.	Mimura and others (2004)
Zhenjiang Aromatic Vinegar	Antifatigue	China	Mouse	Fed with a diet with vinegar (300 mg/kg·d) for 28 d significantly improved antifatigue abilities of mouse.	Lu and Zhou (2002)
Mulberry vinegar	Antifatigue	China	Mouse	Fed with a diet with vinegar (0.2 mL/d) for 20 d significantly improved antifatigue abilities of mouse.	Zhang and others (2007)
Grain vinegar	Preventing osteoporosis	Japan	Ovariectomized rats	Fed with a diet with 0.4% vinegar for 32 d significantly increased intestinal absorption of calcium in rats.	Kishi and others (1999)

2009; Li and others 2009, Liu and others 2015, Liu and Yang 2015).

Weight loss

Because vinegar alters the regulation of lipids, the long-term intake of vinegars should also have an effect on weight loss (Table 1). Obese animal model experiments have proven that the long-term consumption of a specific amount of acetic acid (Kondo and others 2009a), grain vinegars (Li and others 2009; Liu and others 2015), or fruit vinegars (Wei and others 2005; De Dios Lozano and others 2012) can significantly reduce the body weight, lipid content, and total cholesterol and triglyceride contents of animals. Human experiments have proven that the long-term intake of fruit vinegars can also significantly reduce the body weight, body mass index, and total cholesterol and triglyceride levels of healthy people with obesity (Kondo and others 2009b) and obese people with high blood pressure (Kadas and others 2014). Although the effects of grain vinegars on human weight loss have not yet been researched, previous animal experiments (Fan and others 2009; Li and others 2009; Liu and others 2015; Liu and Yang 2015) suggest that the long-term intake of grain vinegars may help weight loss in obese people.

Anticancer

Until now, only a few studies on the anticancer activities of vinegars have been published, most of which focused on grain vinegars (Table 1). Cell-based experiments indicated that the ethyl acetate extracts of Shanxi aged vinegar and Japanese black vinegar significantly inhibited the proliferation of many types of cancer cells *in vitro*, but the corresponding active ingredients have not been identified (Nanda and others 2004; Seki and others 2004; Baba and others 2013; Chen and Gullo 2015). Meanwhile, the ethyl acetate extracts of Japanese black vinegar increased the expression of *p21* genes, allowing human colon cancer cells in the G0/G1 phase to undergo apoptosis, and enabling the apoptosis of oral cancer cells through receptor binding with serine threonine kinase 3 (Nanda and others 2004; Baba and others 2013). Rat experiments have proven that the ethyl acetate extracts of Japanese black vinegars can inhibit azoxymethane-induced colon cancer by increasing glutathione sulfur enzymes and quinone reductase in the liver and extend the life of these rats (Shimoji and others 2003, 2004). According to the results of epidemiological investigations, the incidence of esophageal cancer in Linzhou (Henan, China) is negatively correlated with grain vinegars consumption (Sun and others 2003). Except for the sugarcane vinegar (Mimura and others 2004), research on the anticancer activities of fruit vinegars has not yet been published. Nevertheless, according to investigations on the anticancer activities of polyphenols (such as resveratrol) in some fruits (Shukla and Singh 2011; Peng and others 2014; Kyrø and others 2015; Zamora-Ros and others 2015), the long-term intake of fruit vinegars may have a positive anticancer effect in humans as well.

Other properties

In addition to the above-mentioned properties, vinegars also improve appetite (Xu and others 2003), reduce fatigue (Lu and Zhou 2002; Zhang and others 2007), and prevent osteoporosis (Kishi and others 1999) (Table 1), but little research on these topics has been published.

Active Ingredients and Their Functional Mechanisms

Many investigations on the active ingredients of vinegars and their corresponding functional mechanisms have been performed. To date, the active compounds identified in vinegars mainly include organic acids, polyphenols, melanoidins, ligustrazine, caffeoylsophorose, and tryptophol. In the following sections, these compounds and their functional mechanisms will be reviewed.

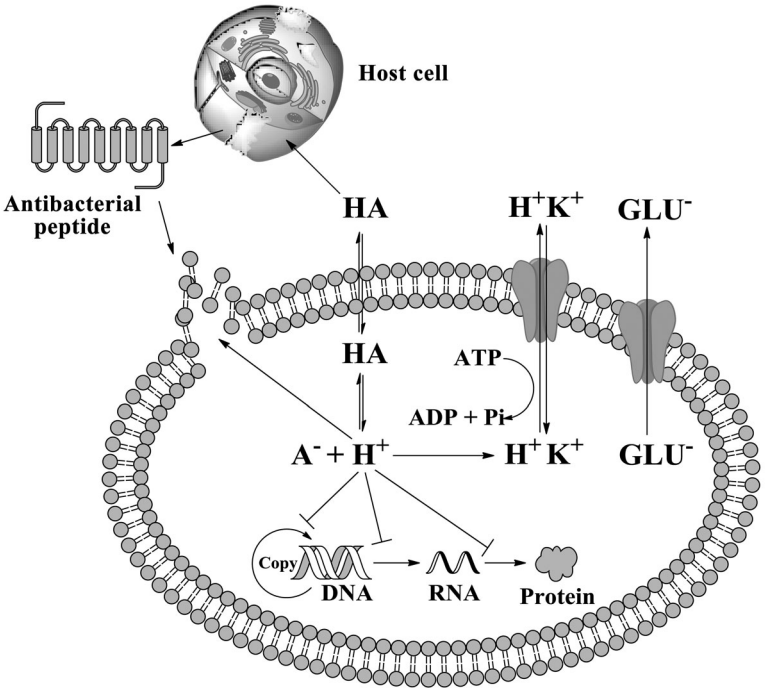
Organic acids

Mechanism of the antibacterial effects of organic acids. Organic acids in vinegars inhibit the growth of bacteria through the following ways (Figure 1) (Zhang and others 2011): (1) destroying the outer membrane of bacteria, (2) inhibiting macromolecular synthesis, (3) consuming the energy of bacteria, (4) increasing intracellular osmotic pressure, and (5) promoting the generation of antibacterial peptides in host cells.

The fat-soluble properties of undissociated organic acids allow them to travel through the cell membrane, become dissociated at intracellular neutral pH values, produce hydrogen ions, and reduce the intracellular pH (Hirshfield and others 2003). First, a decrease in the intracellular pH leads to the protonation of the carboxyl and phosphate groups of lipopolysaccharides on the bacterial cell membrane, undermining its stability (Brul and Coote 1999; Alakomi and others 2000). Second, the lower intracellular pH also affects the enzymatic activities and inhibits DNA replication and transcription as well as protein expression (Cherrington and others 1991). To stabilize the intracellular pH, bacteria must release hydrogen ions via active transport, but this process consumes adenosine triphosphate (ATP) and affects the normal growth of bacteria (Axe and Bailey 1995; Zhang and others 2011). In addition, anions dissociated from organic acids and potassium ions must be pumped from the extracellular fluid (exchanged with hydrogen ions) (Figure 1), which significantly increases the intracellular osmotic pressure and leads to breakage of the cell membrane (McLaggan and others 1994; Alakomi and others 2000). Thus, bacteria must release several necessary nutrients, such as glutamic acid ions, to balance the intracellular osmotic pressure, which inhibits the normal growth of bacteria (Figure 1) (Roe and others 1998). In addition to the direct inhibition of growth, several studies have shown that lactic acid, butyric acid, and other organic acids cause the host cells to produce antimicrobial peptides, which destroy the bacterial outer membrane and indirectly inhibit their growth at the gene transcription and translation level (Figure 1) (Brogden 2005; Ochoa-Zarzosa and others 2009).

Mechanism of the acetic acid–induced control of blood glucose levels. The acetic acid in vinegars regulates the concentration of blood glucose in the following ways (Petsiou and others 2014): (1) delaying gastric emptying, (2) inhibiting disaccharidase activity, (3) improving insulin sensitivity, and (4) promoting the production of glycogen.

Postprandial blood sugar levels are primarily determined by the rate that glucose enters the blood and is consumed *in vivo*. The rate that glucose enters the blood is determined by the rate of gastric emptying, digestion, and absorption in the small intestine. Animal experiments have shown that organic acids delay the emptying of the stomach by stimulating the duodenum or the receptor in the first 150 cm of the small intestine due to the acidity of organic acids (Lin and others 1990). The results of experiments performed on the effects of vinegar on the gastric emptying rate (via real-time ultrasound imaging) of patients with type 1 diabetes have shown that 30 mL of apple vinegar can reduce the postprandial gastric emptying rate by 10% (Hlebowicz and others 2007), which was consistent with the earlier experimental results of using acetaminophen as a marker to study the effects of vinegar on the gastric emptying rate (Liljeberg and Björck 1998). To explore the



ATP: Adenosine triphosphate, ADP: Adenosine diphosphate, Pi: Dihydrogen phosphate, GLU⁻: Glutamic acid ions

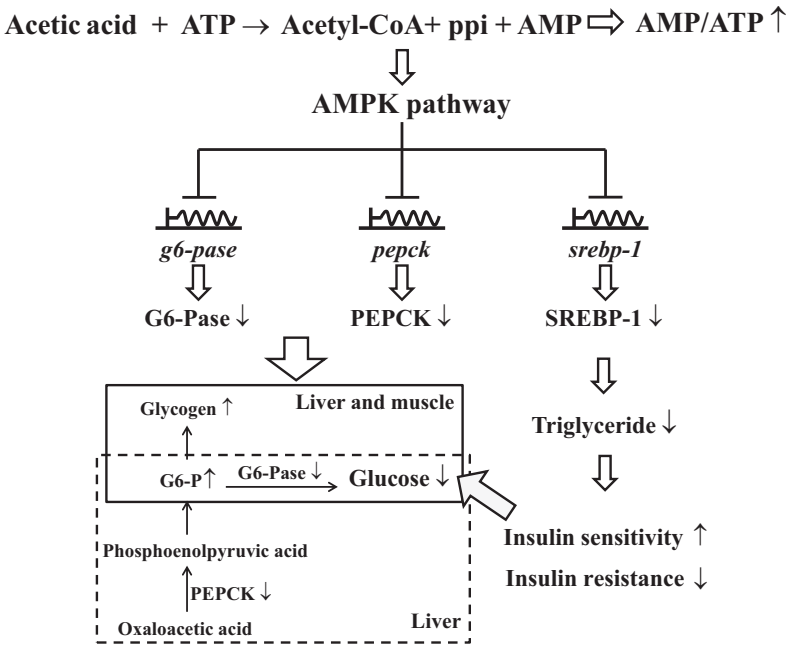
Figure 1–Mechanism of the antimicrobial effects of organic acids (Zhang and others 2011).

effect of organic acids on postprandial glucose absorption, Ogawa and others (2000) used a nutrient solution containing 5 mmol/L of organic acids to cultivate Caco-2 cells and found that acetic acid significantly inhibited the activity of disaccharidase (sucrase, maltase, lactase, and trehalose), but the other organic acids (lactic acid, citric acid, fumaric acid, tartaric acid, succinic acid, and methylene succinic acid) did not show significant effects on inhibition. Further experiments have proven that acetic acid does not affect the *de novo* synthesis of disaccharide (at the gene transcription and translation levels); thus, the acetic acid–induced inhibition of the disaccharide activity may occur during the posttranscription phase (Ogawa and others 2000), which explains why vinegar does not affect the increase in blood glucose levels due to the consumption of monosaccharide beverages (Johnston and others 2010).

In addition to reducing the rate of which glucose enters the blood, increasing the consumption of blood glucose is also an effective way to control postprandial blood glucose levels. Animal experiments have revealed that the consumption of acetic acid promotes the transformation of blood glucose in the liver and muscles to glycogen through the accumulation of glucose-6-phosphate (Fushimi and Sato 2007). The *in vivo* regulation of glucose metabolism by acetic acid is primarily achieved through the activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway (Figure 2) (Sakakibara and others 2006). Acetic acid is a building block for the synthesis of acetyl coenzyme A (acetyl-CoA). During the synthesis of acetyl-CoA, ATP is consumed and adenosine monophosphate (AMP) is generated, which increases the AMP/ATP ratio, activating the AMPK pathway. The activation of the AMPK pathway reduces blood glucose levels and increases glycogen reserves by directly inhibiting the gene expression of related enzymes involved in glycometabolism. Besides, activation of the AMPK pathway also reduces the concentration of triglycerides by inhibiting the gene expression of related lipid metabolism enzymes, which reduces blood glucose levels by increasing insulin sensitivity and decreasing insulin resistance (Figure 2) (Sakakibara and others 2006). The aforementioned features of acetic acid indicate that vinegar ingestion at bedtime can help patients with type 2 diabetes to moderate their waking glucose concentration in the next day (White and Johnston 2007).

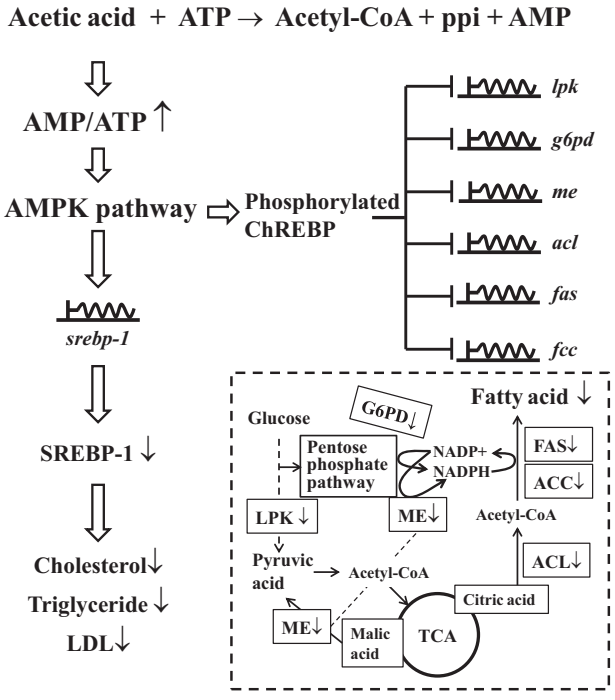
Mechanism of the regulation of lipid metabolism by acetic acid. Similar to blood glucose metabolism, acetic acid in vinegar also decreases the synthesis of lipids and increases the excretion and decomposition of lipids by activating the AMPK pathway *in vivo* (Figure 3) (Sakakibara and others 2006; Yamashita and others 2014). During the conversion of acetic acid into acetyl-CoA, the activation of the AMPK pathway leads to a reduction in the concentration of cholesterol, triglycerides, and LDL by down-regulating the expression of the *srebp-1* gene. Besides, activated AMPK also inhibits the expression of a series of genes related to fatty acid synthesis through the phosphorylation of carbohydrate response element binding protein (ChREBP), which reduces the synthesis of fatty acids (Figure 3) (Sakakibara and others 2006, 2010; Yamashita and others 2014). In addition, acetic acid reduces the blood lipid content of rats by promoting the oxygenolysis of fatty acids and the secretion of bile (Fushimi and others 2006); however, further research is required to determine whether these functional properties are prevalent in humans.

Mechanism of weight loss due to acetic acid. Acetic acid in vinegar affects weight loss through the following mechanisms: (1) decreasing the synthesis of lipids, (2) increasing the oxygenolysis and secretion of lipids, (3) increasing postprandial satiety, and (4) increasing energy consumption. The first 2 methods are similar



ATP: Adenosine triphosphate; CoA: Coenzyme A; ppi: Pyrophosphoric acid; AMP: Adenosine monophosphate; AMPK: AMP-activated protein kinase; G6-P: Glucose-6-phosphate; G6-Pase: G6-P kinase; PEPCK: Phosphoenolpyruvate carboxykinase; SREBP-1: Sterol regulatory element-binding protein-1

Figure 2–Acetic acid reduces the blood sugar content by activating AMPK (Sakakibara and others 2006).



ATP: Adenosine triphosphate; CoA: Coenzyme A; ppi: Pyrophosphoric acid; AMP: Adenosine monophosphate; AMPK: AMP-activated protein kinase; SREBP-1: Sterol regulatory element-binding protein-1; ChREBP: Carbohydrates response element-binding protein; LPK: Pyruvate kinase; G6PD: Glucose-6-phosphate dehydrogenase; ME: Malic enzyme; ACL: ATP-citrate lyase; ACC: Acetyl-CoA carboxylase; FAC: Fatty acid synthetase; LDL: Low-density lipoprotein; TCA: Tricarboxylic acid cycle

Figure 3–Acetic acid reduces the synthesis of lipids by activating AMPK (Sakakibara and others 2006; Yamashita and others 2014).

to those in the regulation of lipid metabolism (see the section Mechanism of the regulation of lipid metabolism by acetic acid), whereas the third mechanism is similar to the mechanism of blood sugar control (see the section Mechanism of the acetic acid-induced control of blood glucose levels), wherein acetic acid increases postprandial satiety by stabilizing postprandial blood glucose levels, thereby reducing dietary intake. In addition, acetic acid also increases biological energy consumption by increasing myoglobin levels and upregulating the expression of genes related to the synthesis of fatty acids (Kondo and others 2009a; Yamashita and others 2009; Hattori and others 2010).

Polyphenols

Mechanism of the antibacterial effects of polyphenols. The antibacterial activities of the polyphenols present in vinegars are primarily achieved by destroying the integrity of the cell membrane and interfering with the activities of enzymes present in bacteria (Yoda and others 2004; Taguri and others 2006; Gradišar and others 2007; Sirk and others 2008). Polyphenols combine with the peptidoglycan and phospholipid bilayer of the outer membrane of bacteria to reduce the integrity of the cell membrane (Yoda and others 2004; Sirk and others 2008). In addition, because polyphenols are a type of polyol, these compounds affect the activities of bacterial intracellular enzymes by reacting with the amino and carboxyl groups of proteins as well as the chelating transition metal ion (coenzyme) (Taguri and others 2006; Gradišar and others 2007) to inhibit the growth of bacteria.

Antioxidation mechanism of polyphenols. The antioxidant activities of polyphenols in vinegar include the abilities to scavenge free radicals, chelate transition metal ions, and reduce oxidants (Rice-Evans and others 1996; Sang and others 2007; Perron and Brumaghim 2009). As an aromatic compound, the conjugated π-bond system on the benzene ring of polyphenols provides a stabilizing effect to free radicals and can effectively block free radical chain reactions (Rice-Evans and others 1996). The hydroxyl structure on the benzene ring of polyphenols (similar to catechols) can effectively chelate transition metal ions, thus preventing oxidation reactions (Perron and Brumaghim 2009). In addition, the phenolic hydroxyl group on the benzene ring of polyphenols can be oxidized to quinone in redox reactions; thus polyphenols also have a reducing effect (Sang and others 2007).

Melanoidins

Mechanism of the antibacterial effect of melanoidins. Melanoidins are brown macromolecular compounds produced by the reduction of sugars and proteins (or amino acids) through the Maillard reaction (Wang and others 2011). The antibacterial activities of melanoidins present in vinegar are due to their ability to chelate metal ions (Rurián-Henares and Morales 2008; Rufian-Henares and de la Cueva 2009). Melanoidins are macromolecular compounds with a negative charge, hence, melanoidins have strong chelating abilities for metal ions (Wang and others 2011). At low concentrations, melanoidins chelate iron ions, affecting their absorption and utilization, which inhibit the growth of bacteria. At high concentrations, melanoidins destroy the cell membrane of bacteria by chelating magnesium ions, resulting in the death of the bacteria (Rurián-Henares and Morales 2008; Rufian-Henares and de la Cueva 2009).

Mechanism of the antioxidation effect of melanoidins. The mechanism of the antioxidation effects of melanoidins in vinegar is similar to that of polyphenols. The antioxidation activities of melanoidins mainly include the abilities to chelate transition metal ions and scavenge free radicals, as well as the power to act as a reducing agent (Wang and others 2011). Owing to their negative charge and macromolecular properties, melanoidins have strong chelating abilities for transition metal ions, effectively preventing oxidation reactions induced by transition metal ions. In addition, melanoidins are a type of macromolecule polymer, containing a large conjugated π-bond system and abundant reduction ketone structures. As a result, melanoidins possess good radical-scavenging abilities and reducing powers (Wang and others 2011).

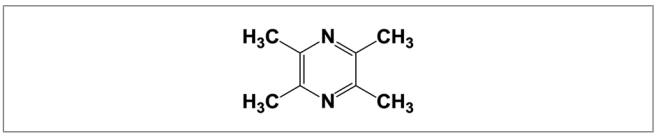


Figure 4–Structure of ligustrazine.

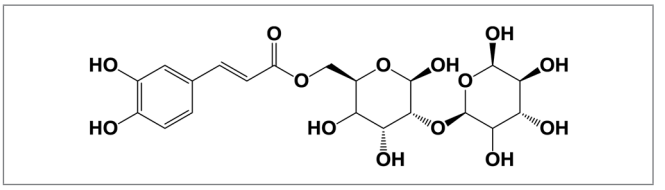


Figure 5–Structure of caffeoylsophorose (Matsui and others 2014).

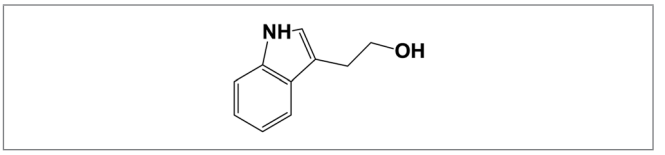


Figure 6–Structure of tryptophol (Inagaki and others 2007).

Mechanism of the improvement in circulation due to ligustrazine

Ligustrazine (Figure 4) effectively improves blood circulation by inhibiting platelet aggregation and expanding blood vessels *in vivo* (Cauvin and others 1983; Zhou and others 1985; Wang and others 2009; Ren and others 2012). Studies have shown that ligustrazine is a good calcium channel blocker (Ren and others 2012), which can inhibit the aggregation of platelets (platelet aggregation is positively correlated with the concentration of intracellular calcium ions) (Zhou and others 1985), and the contraction of muscle cells on blood vessels (the internal flow of intracellular calcium ions can lead to the contraction of muscle) (Cauvin and others 1983) by reducing the internal flow of calcium ion in cells, which improves blood circulation. In addition, ligustrazine can pass the blood–brain barrier, so it is also used in the treatment of cerebrovascular diseases as well as cardiovascular diseases (Wang and others 2009).

Mechanism of the hypoglycemic effects of caffeoylsophorose

Caffeoylsophorose (Figure 5) is a novel, natural α-glucosidase inhibitor that was isolated from the purple sweet potato vinegar by Matsui and others (2014). Rat experiments have showed that the consumption of 0.1 g/kg body weight of caffeoylsophorose can decrease postprandial blood glucose contents by approximately 11.1% and reduce the secretion of insulin. However, caffeoylsophorose did not have a significant effect when the diet consisted

Table 2–Polyphenol compounds in vinegars.

Vinegar type	Country	Detection method	Polyphenolic compounds; μg/mL								Reference
Shanxi aged vinegar	China	LC-MS	Protocatechuic acid (5.00)	Dihydroferulic acid (3.75)	Dihydrosinapic acid (2.56)	P-hydroxybenzoic acid (2.05)	Salicylic acid (1.49)	P-coumaric acid (0.90)	Ferulic acid (0.34)	Sinapic acid (0.41)	Chen and others 2015
Kurosu	Japan	LC-PDA	Dihydroferulic acid (24.8)	Dihydrosinapic acid (4.68)	Vanillic acid (1.44)	Sinapic acid (1.15)	Ferulic acid (0.95)	P-hydroxycinnamic acid (0.17)	/	/	Shimoji and others 2002
Balsamic vinegar	Italy	GC-MS	Protocatechuic acid (18.8)	Gallic acid (18.0)	P-coumaric acid (17.1)	Syringic acid (13.8)	Caffeic acid (10.9)	Ferulic acid (8.8)	Vanillic acid (8.1)	P-hydroxybenzoic acid(6.5)	Plessi and others 2006
Sherry vinegar	Spain	LC-PDA	Gallic acid (447.8)	Caftaric acid (67.4)	Ethyl gallate (52.4)	Protocatechu aldehyde (28.6)	Syringaldehyde (13.0)	P-coumaric acid ethyl ester (12.4)	Vanilline (5.2)	Caffeic acid(3.0)	Parrilla and others 1999
Red wine vinegar	Spain	LC-MS	Malvidin-3-glucoside (53.04)	Malvidin-3-(6-acetyl) -glucoside (26.3)	Malvidin-3-glucoside -4-vinyl (Vitisin B) (14.25)	Acetyl vitisin B (11.77)	Carboxy-pyranomalvidin-3-glucoside (vitisin A) (9.03)	Malvidin3-(6-p-coumaroyl) -glucoside (8.2)	Malvidin-3-glucoside-ethyl-(epi)catechin (7.76)	Catechyl-Pyranocyanidin -3-glucoside (5.63)	Cerezo and others 2010
Red wine vinegar (Tradition)	Turkey	LC-PDA	Gallic acid (16.36)	Catechin (13.76)	Caffeic acid (6.30)	Epicatechin (4.96)	Chlorogenic acid (3.73)	Syringic acid (0.70)	P-coumaric acid (0.23)	Ferulic acid (0.06)	Budak and Guzel-Seydim 2010
Red wine vinegar (Industry)	Turkey	LC-PDA	Gallic acid (18.23)	Catechin (27.50)	Caffeic acid (10.30)	Epicatechin (8.2)	Chlorogenic acid (0.16)	Syringic acid (0.33)	P-coumaric acid (0.56)	Ferulic acid (0.35)	Budak and Guzel-Seydim 2010
Red wine vinegar	Germany	LC-MS	Epicatechin (22)	Caffeic acid (6.7)	Malvidin 3-glucoside (3.8)	Malvidin3-glucoside acetate (1.7)	Petunidin3-glucoside (1.3)	Delphinidin3-glucoside (1.3)	Peonidin3-glucoside (1.2)	Malvidin3-glucoside coumarate (0.9)	Andlauer and others 2000
White wine vinegar	Germany	LC-MS	Catechin (24.0)	Protocatechuic acid (4.1)	Caffeic acid (1.1)	/	/	/	/	/	Andlauer and others 2000
Grape vinegar	Korea	LC-PDA	Epigallocatechin (10.75)	Epicatechin (0.82)	Catechin (0.78)	Gallic acid (0.74)	Chlorogenic acid (0.2)	Epigallocatechin gallate (0.02)	/	/	Jeong and others 2009
Apple vinegar	Turkey	LC-PDA	Chlorogenic acid (347.7)	Catechuic acid (68.2)	Gallic acid (61.2)	Caffeic acid (17.2)	/	/	/	/	Aykın and others 2015
Apple vinegar	China	LC-PDA	Chlorogenic acid (6.56)	Caffeic acid (3.03)	Phlorizin (1.76)	Epigallocatechin gallate (0.77)	Gallic acid (0.35)	P-coumaric acid (0.33)	Ferulic acid (0.24)	Vanillic acid (0.06)	Li and others 2013
Apple vinegar	Japan	LC-MS	Chlorogenic acid (196)	4-p-coumaroylquinic acid (135.0)	Isomer of chlorogenic acid (31.0)	Isomer of p-coumaroylquinic acid (25.0)	Isomer of chlorogenic acid (13.0)	P-hydroxybenzoic acid (7.7)	Caffeic acid (7.6)	Protocatechuic acid (4.1)	Nakamura and others 2010
Apple vinegar	Germany	LC-MS	Chlorogenic acid/Caffeic acid(180)	Catechin (58)	P-coumaroylquinic acid (51)	Phlorizin (41)	Phloretin-xyl-glc (30)	Protocatechuic acid (20)	Quercitrin (20)	Epicatechin (11)	Andlauer and others 2000
Pomegranate vinegar	Turkey	LC-PDA	Gallic acid(67.8)	Caffeic acid (47)	Caffeic acid (13.4)	/	/	/	/	/	Aykın and others 2015

(Continued).

Table 2–Continued

Vinegar type	Country	Detection method	Polyphenolic compounds; μg/mL								Reference
Kiwi vinegar	China	LC-PDA	Gallic acid(9.67)	Chlorogenic acid (3.12)	Vanillic acid (1.78)	Catechin (1.47)	Phlorizin (0.49)	P-coumaric acid (0.34)	Caffeic acid (0.04)	Ferulic acid (0.01)	Li and others 2013
Persimmon vinegar	China	LC-PDA	Gallic acid(22.92)	Vanillic acid (0.96)	Phlorizin (0.38)	Catechin (0.16)	Epigallocatechin gallate (0.13)	Chlorogenic acid (0.06)	Caffeic acid (0.04)	P-coumaric acid (0.03)	Li and others 2013
Persimmon vinegar	Korea	LC-PDA	Gallic acid(14.24)	Epigallocatechin (11.98)	Catechin (4.42)	Epicatechin (2.23)	Chlorogenic acid (1.01)	Epigallocatechin gallate (0.02)	/	/	Jeong and others 2009
Plum vinegar	Korea	LC-PDA	Epigallocatechin (6.04)	Epicatechin (0.29)	Catechin (0.27)	Chlorogenic acid (0.21)	Gallic acid (0.03)	Epigallocatechin gallate (0.03)	/	/	Jeong and others 2009
Sugarcane vinegar	Egypt	LC-PDA	Benzoic acid (3.6)	Catechin (2.1)	Gallic acid (0.3)	Ferulic acid (0.1)	/	/	/	/	Soltan and Shehata 2012
Coconut vinegar	Egypt	LC-PDA	Catechin (4.3)	Benzoic acid (3.6)	Salicylic acid (2.1)	Gallic acid (0.3)	Caffeic acid (0.1)	Ferulic acid (0.1)	/	/	Soltan and Shehata 2012
Palm vinegar	Egypt	LC-PDA	Salicylic acid (85.0)	Coumarin (2.9)	Gallic acid (0.2)	Ferulic acid (0.2)	Caffeic acid (0.1)	/	/	/	Soltan and Shehata 2012

Abbreviations: GC, gas chromatography; LC, liquid chromatography; MS, mass spectrometry; PDA, photodiode array detector.

of monosaccharides (Matsui and others 2014). Further studies indicated that the hypoglycemic effect of caffeoylsophorose was related to its structure, including the phenolic hydroxyl group and the unsaturated acyl hydrocarbon, which reduced the rate of polysaccharide decomposition in the small intestine through noncompetitive inhibition of α-glucosidase, which reduced the concentration of postprandial blood glucose (Matsui and others 2014).

Anticancer mechanism of tryptophol

Tryptophol (Figure 6) is a novel anticancer compound that was isolated from Japanese black soybean vinegar by Inagaki and others (2007). Cell experiments have shown that tryptophol denatures DNA repair enzymes by activating caspase-8 and -3, which inhibits the proliferation of human leukemia cells (U937) *in vitro*. Tryptophol was less toxic to normal lymphocytes and did not activate the caspase of lymphocytes (Inagaki and others 2007).

The sources of functional ingredients in vinegars

A number of investigations have proven that the aforementioned functional constituents of vinegars are derived from the raw materials, microorganisms, and technological conditions employed during the fermentation process.

Functional ingredients from raw materials

Organic acids. Organic acids are the major functional and flavor ingredients of vinegars and are mainly produced during the fermentation stage. However, some organic acids in vinegars are derived from the raw materials, especially in fruit vinegars. For example, several studies have revealed that grape, apple, and other types of fruit that are commonly used as raw materials of fruit vinegars contain tartaric acid, malic acid, citric acid, and other nonvolatile organic acids, and that their total contents can reach 0.5%–2% of the total acid quantity of fruits (Rodriguez and others 1992; Guo and others 2012; Cheng and others 2013). In contrast, the organic acid contents of sorghum, rice, and wheat grain, which are common raw materials for grain vinegars, are very low, amounting to only 0.1% of the total raw materials (Yuan and others 2011).

Polyphenols. Polyphenols present in vinegars are mainly derived from the raw materials (Solieri and Giudici 2009), but the types and contents of polyphenols in each type of vinegar are different due to differences in the raw materials and manufacturing processes (Table 2). Grain vinegars mainly contain protocatechuic acid, ferulic acid, and sinapic acid (most of the ferulic acid and sinapic acid are reduced to dihydroferulic acid, and dihydrosinapic acid during the fermentation process) (Shimoji and others 2002; Chen and others 2015). In contrast, grain vinegars contain only a small amount of gallic acid, catechins, and other phenolic compounds, which are high in fruit vinegars (García Parrilla and others 1999; Andlauer and others 2000; Plessi and others 2006; Jeong and others 2009; Budak and Guzel-Seydim 2010; Cerezo and others 2010). Apple vinegars contain large amounts of chlorogenic acid, which is present in the raw material (Andlauer and others 2000; Nakamura and others 2010; Li and others 2013; Aykın and others 2015). In addition, the fermentation process also affects the types and contents of polyphenols. For instance, acetic acid fermentation reduces the polyphenol content of vinegars (Andlauer and others 2000), and the wooden containers used in the aging process also influence the types and contents of polyphenols present in fruit vinegars (García Parrilla and others 1999).

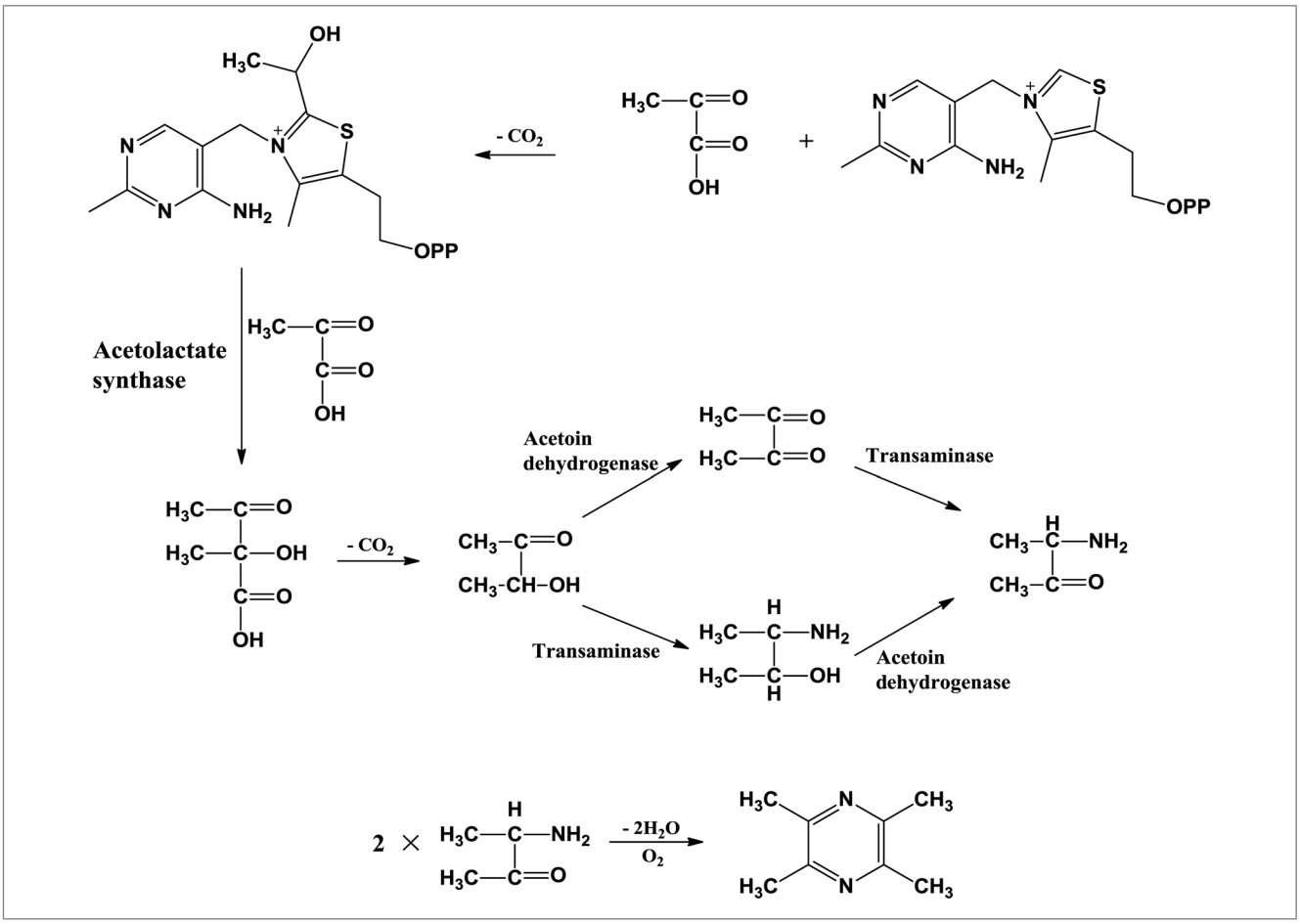


Figure 7–Proposed pathway for the biosynthesis of ligustrazine (Dickschat and others 2010).

Functional ingredients from microbial fermentation

Organic acids. Organic acids in vinegars are mainly produced by microorganisms during the fermentation stage (Solieri and Giudici 2009). Organic acids in vinegars can be considered volatile (organic acids without hydroxyl groups, such as acetic acid and propionic acid) or nonvolatile (organic acids with hydroxyl groups such as lactic acid and tartaric acid) acids, according to their chemical properties (Xu 2008). Among them, acetic acid is the main organic acid present in vinegars and is one of the most important functional ingredients. Acetic acid is mainly produced by acetic acid bacteria during the fermentation stage (Xu 2008). Lactic acid, which shows the highest content among nonvolatile organic acids in vinegars, is mainly produced during the alcoholic fermentation stage (Xu 2008). Propionic acid, tartaric acid, malic acid, citric acid, and other organic acids in vinegars are produced throughout the whole fermentation stage (Xu 2008). Moreover, the fermentation conditions also influence the contents of organic acids. Heating, steaming, and fermenting techniques used during the fermentation process reduce the contents of volatile organic acids and water, which increases the contents of nonvolatile organic acids, and thereby the ratios of nonvolatile organic acids to volatile organic acids (Xu 2008).

Ligustrazine. Ligustrazine (Figure 4), which is also called tetramethyl pyrazine, can inhibit platelet aggregation, expand blood vessels, and promote blood circulation (Cauvin and others 1983; Zhou and others 1985; Wang and others 2009). Therefore, ligustrazine is often used in the treatment of ischemic cerebrovascular disease (Zhou and others 1985). Initially, ligustrazine was obtained from natto, a fermented food, and was used as a flavoring composition by Kosuge and Kamiya (1962), who thought that it might be a secondary metabolite of *Bacillus subtilis*. Ligustrazine was identified in vinegar by Kosuge and others (1971), and its corresponding content reached 1.5 μg/kg. The ability of ligustrazine to improve blood circulation was discovered by Beijing Pharmaceutical Research Institute in 1977, based on the traditional Chinese medicine "Guanxin Prescription 2" and "Little Guanxin Prescription 2" (*Ligusticum wallichii* and *Carthamus tinctorius*) (Anonymous 1977). Many studies have indicated that the production of ligustrazine by microorganisms is due to the transformation of acetoin (3-hydroxy-2-butanone) (Figure 7) (Dickschat and others 2010).

Dihydroferulic acid and dihydrosinapic acid. Dihydroferulic acid and dihydrosinapic acid (Figure 8) were isolated from Kurosu, a Japanese vinegar, by Shimoji and others (2002). These two compounds were the main radical-scavenging components in Kurosu, but were not present in the primary raw material, unpolished rice (Shimoji and others 2002). Based on the compositional analysis of Kurosu and its raw materials as well as the results of previous studies, dihydroferulic acid and dihydrosinapic acid were likely produced through the reduction of ferulic acid and sinapic acid in unpolished rice by microorganisms during the fermentation process, respectively (Shimoji and others 2002).

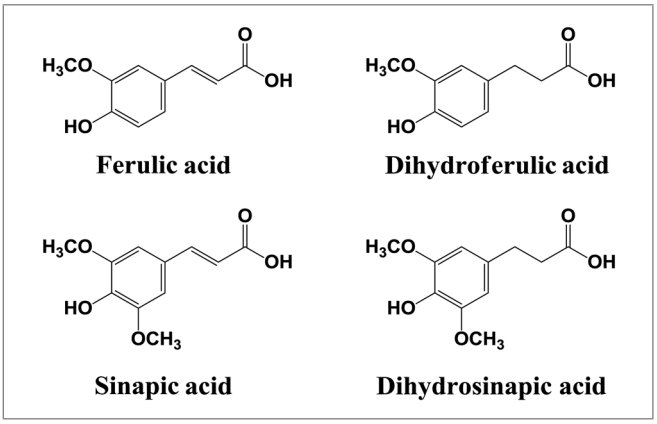


Figure 8–Structures of ferulic acid, dihydroferulic acid, sinapic acid, and dihydrosinapic acid (Shimoji and others 2002).

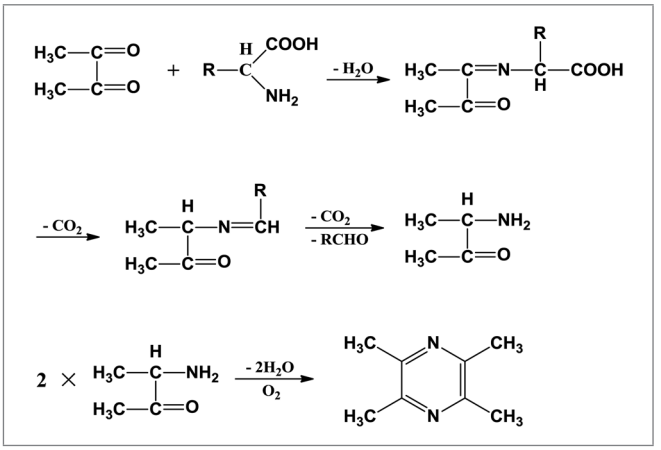


Figure 9–Proposed pathway for the formation of ligustrazine in the Maillard reaction (Rizz 1972).

Tryptophol. Tryptophol (Figure 6), which shows anticancer activities, was isolated from Japanese black soybean vinegar by Baba and others (2013). Composition analyses revealed that tryptophol did not exist in black beans, rice, and distiller's yeast (Baba and others 2013). Thus, tryptophol may be produced by microorganisms during the fermentation process.

Functional ingredients produced by chemical reactions during fermentation

Melanoidins. Melanoidins are brown macromolecular compounds produced by the reduction of sugar and protein (or polypeptide, amino acid) through the Maillard reaction (Wang and others 2011). In vinegars, melanoidins are mainly produced during the baking (grain vinegars), steaming (grain vinegars), and aging process (grain vinegars and fruit vinegars) (Tagliazucchi and others 2010; Yang and others 2014). In addition to the reaction of sugars and amino acids, phenolic compounds in vinegars can also polymerize with melanoidins, becoming a part of their skeleton, which increases the antioxidant capacity (Tagliazucchi and others 2010). The majority of melanoidins in vinegars possess molecular weights ranging from 10 to 80 KDa (Tagliazucchi and others 2010; Wang and others 2011; Yang and others 2014).

Ligustrazine. Ligustrazine was identified (see the section Ligustrazine of Functional ingredients from microbial fermentation; produced by microorganisms) in vinegars as early as 1971, but its content was very low (1.5 μg/kg), and it only was used as a fragrance ingredient. Ligustrazine was first proposed by He and others (2004) to be a functional component of vinegars. After 2 months of aging, the content of ligustrazine in Zhenjiang aromatic vinegar reached 77 μg/mL (He and others 2004). In vinegars, ligustrazine is produced through the Maillard reaction during the baking, steaming, and aging processes, which could be the reason why the ligustrazine content of Zhenjiang vinegar (through baking and aging) was higher than that of the samples tested in 1971 (Kosuge and others 1971; He and others 2004). The mechanism of ligustrazine formation in vinegars through the Maillard reaction is shown in Figure 9 (Rizz 1972). Although data on the presence of ligustrazine in fruit vinegars have not been reported, based on the process used for the production of fruit vinegars (mixed microbial fermentation, aging for a long time), fruit vinegars may also contain a certain amount of ligustrazine.

Conclusion

Vinegar is an acidic condiment with a variety of functional properties, including antibacteria, anti-infection, antioxidation, anticancer activities, blood glucose control, lipid metabolism regulation, and weight loss. The antibacterial and anti-infection effects of vinegars are mainly due to the presence of organic acids, although polyphenols and melanoidins in some vinegars also contribute to these properties. The antioxidant abilities of vinegars are mainly derived from polyphenols and melanoidins, which are affected by the raw materials and fermentation conditions, respectively. The effects of some vinegars on blood glucose control, lipid metabolism regulation, and weight loss are due to the presence of acetic acid, which is mainly produced by acetic acid bacteria during fermentation. Furthermore, caffeoylsophorose (inhibits disaccharidase), ligustrazine (improves blood circulation), and other functional ingredients in vinegars also provide assistance. In terms of its anticancer properties, some vinegars strongly inhibit the growth of cancer cells *in vivo* or *in vitro*. However, these results were primarily obtained from cell or animal experiments, and the identity of the responsible functional ingredient remains unclear, except for tryptophol, which occurs in Japanese black soybean vinegar. Both grain and fruit vinegars contain these functional ingredients, including organic acids (especially acetic acid), polyphenols, and melanoidins. Researches on the properties of acetic acid have primarily focused on fruit vinegars. The other functional ingredients, such as ligustrazine, dihydroferulic acid, dihydrosinapic acid, tryptophol, and caffeoylsophorose, were all found in grain vinegars. In addition, phenyllactic acid, a highly effective antibacterial compound, was isolated and identified from Shanxi aged vinegar (unpublished data 2016).

Owing to its properties and components, vinegar is not just an acidic condiment, several types of vinegars, especially those produced through traditional fermentation technologies, including Shanxi aged vinegar, Zhenjiang aromatic vinegar, Sichuan Baoning bran vinegar, Fujian Yongchun *Monascus* vinegar, Japanese black vinegar, Italian balsamic vinegar, and other fruit vinegars could be developed into functional foods. Through the discovery of various functional ingredients and the clarification of their mechanisms, some vinegars and vinegar derivatives could be used as pharmaceutical agents to prevent chronic diseases such as diabetes and cardiovascular disease.

Acknowledgments

The authors have declared that no conflicting interest exists. This review was supported by Programs of International S & T Cooperation, Ministry of Science and Technology, People's Republic of China (no. 2014DFG32380) and the Fundamental Research Funds for the Central Universities (nos. 2013PY006, 2014PY034, and 2662015PY167), and the project of Wuhan Science & Technology Bureau (no. 2015030809020368).

References

Alakomi HL, Skyttä E, Saarela M, Mattila-Sandholm T, Latva-Kala K, Helander I. 2000. Lactic acid permeabilizes Gram-negative bacteria by disrupting the outer membrane. Appl Environ Microbiol 66:2001–5.

Aminifarshidmehr N. 1996. The management of chronic suppurative otitis media with acid media solution. Am J Otol 17:24–5.

Andlauer W, Stumpf C, Fürst P. 2000. Influence of the acetification process on phenolic compounds. J Agric Food Chem 48:3533–6.

Anonymous. 1977. Experimental study and clinical observation of ligustrazine. New Med J 4:45.

Axe DD, Bailey JE. 1995. Transport of lactate and acetate through the energized cytoplasmic membrane of *Escherichia coli*. Biotechnol Bioeng 47:8–19.

Aykın E, Budak NH, Güzel-Seydim ZB. 2015. Bioactive components of mother vinegar. J Am Coll Nutr 34:80–9.

Baba N, Higashi Y, Kanekura T. 2013. Japanese black vinegar "Izumi" inhibits the proliferation of human squamous cell carcinoma cells via necroptosis. Nutr Cancer 65:1093–97.

Beheshti Z, Chan YH, Nia HS, Hajihosseini F, Nazari R, Shaabani M. 2012. Influence of apple cider vinegar on blood lipids. Life Sci J 9:2431–40.

Bertelli D, Maietti A, Papotti G, Tedeschi P, Bonetti G, Graziosi R, Brandolini V, Plessi M. 2015. Antioxidant activity, phenolic compounds, and NMR characterization of balsamic and traditional balsamic vinegar of modena. Food Anal Method 8:371–9.

Brighenti F, Castellani G, Benini L, Casiraghi M, Leopardi E, Crovetti R, Testolin G. 1995. Effect of neutralized and native vinegar on blood glucose and acetate responses to a mixed meal in healthy subjects. Eur J Clin Nutr 49:242–7.

Brogden KA. 2005. Antimicrobial peptides: pore formers or metabolic inhibitors in bacteria? Nature Rev Microbiol 3:238–50.

Brul S, Coote P. 1999. Preservative agents in foods: mode of action and microbial resistance mechanisms. Int J Food Microbiol 50:1–17.

Budak HN, Guzel-Seydim ZB. 2010. Antioxidant activity and phenolic content of wine vinegars produced by two different techniques. J Sci Food Agric 90:2021–6.

Budak NH, Aykin E, Seydim AC, Greene AK, Guzel-Seydim ZB. 2014. Functional properties of vinegar. J Food Sci 79:R757–64.

Cauvin C, Loutzenhiser R, Breemen C. 1983. Mechanisms of calcium antagonist-induced vasodilation. Annu Rev Pharmacol Toxicol 23:373–96.

Cerezo AB, Cuevas E, Winterhalter P, Carmen Garcia-Parrilla M, Troncoso AM. 2010. Anthocyanin composition in Cabernet Sauvignon red wine vinegar obtained by submerged acetification. Food Res Int 43:1577–84.

Chang JM, Fang TJ. 2007. Survival of *Escherichia coli* O157:H7 and *Salmonella enterica* serovars Typhimurium in iceberg lettuce and the antimicrobial effect of rice vinegar against E. coli O157:H7. Food Microbiol 24:745–51.

Chen F, Gullo M. 2015. 4th international conference on acetic acid bacteria-vinegar and other products (AAB 2015). Acetic Acid Bacteria 4:17.

Chen H, Zhou Y, Shao Y, Chen F. 2015. Free phenolic acids in Shanxi aged vinegar: changes during aging and synergistic antioxidant activities. Int J Food Prop 19:1183–93.

Cheng B, Zhang JF, Xu HY, Hou LX, Wang YH, Zhang Y, Wang C. 2013. Analysis of organic acid contents in wine grape from different cultivars. Food Sci 34:223–8.

Cherrington C, Hinton M, Mead G, Chopra I. 1991. Organic acids: chemistry, antibacterial activity and practical applications. Adv Microb Physiol 32:87–108.

De Dios Lozano J, Juárez-Flores BI, Pinos-Rodríguez JM, Aguirte-Rivera J, Alvarez-Fuentez G. 2012. Supplementary effects of vinegar on body weight and blood metabolites in healthy rats fed conventional diets and obese rats fed high-caloric diets. J Med Plants Res 6:4135–41.

Dickschat JS, Wickel S, Bolten CJ, Nawrath T, Schulz S, Wittmann C. 2010. Pyrazine biosynthesis in corynebacterium glutamicum. Eur J Org Chem 2010:2687–95.

Ebihara K, Nakajima A. 1988. Effect of acetic acid and vinegar on blood glucose and insulin responses to orally administered sucrose and starch. Agric Biol Chem 52:1311–2.

Entani E, Asai M, Tsujihata S, Tsukamoto Y, Ohta M. 1998. Antibacterial action of vinegar against food-borne pathogenic bacteria including *Escherichia coli* O157:H7. J Food Prot 61:953–9.

Fan J, Zhang Y, Chang X, Zhang B, Jiang D, Saito M, Li Z. 2009. Antithrombotic and fibrinolytic activities of methanolic extract of aged sorghum vinegar. J Agric Food Chem 57:8683–7.

Fushimi T, Sato Y. 2007. Effect of acetic acid feeding on the circadian changes in glycogen and metabolites of glucose and lipid in liver and skeletal muscle of rats. Br J Nutr 94:714–9.

Fushimi T, Suruga K, Oshima Y, Fukiharu M, Tsukamoto Y, Goda T. 2006. Dietary acetic acid reduces serum cholesterol and triacylglycerols in rats fed a cholesterol-rich diet. Br J Nutr 95:916–24.

García Parrilla MC, Heredia FJ, Troncoso AM. 1999. Sherry wine vinegars: phenolic composition changes during aging. Food Res Int 32:433–40.

Gradišar H, Pristovšek P, Plaper A, Jerala R. 2007. Green tea catechins inhibit bacterial DNA gyrase by interaction with its ATP binding site. J Med Chem 50:264–71.

Gu X, Zhao HL, Sui Y, Guan J, Chan JC, Tong PC. 2012. White rice vinegar improves pancreatic beta-cell function and fatty liver in streptozotocin-induced diabetic rats. Acta Diabetol 49:185–91.

Guo Y, Liang J, Li MM, Zhao ZY. 2012. Determination of organic acids in apple fruits by HPLC. Food Sci 33:227–30.

Hattori M, Kondo T, Kishi M, Yamagami K. 2010. A single oral administration of acetic acid increased energy expenditure in C57BL/6J mice. Biosci Biotechnol Biochem 74:2158–9.

He ZY, Ao ZH, Wu J. 2004. Study on the mensuration of tetramethylpyrazine in Zhenjiang vinegar and its generant mechanism. China Condiment 2:36–9.

Hindi NK. 2013. In vitro antibacterial activity of aquatic garlic extract, apple vinegar and apple vinegar-garlic extract combination. Am J Phytomed Clin Ther 1:42–51.

Hirshfield IN, Terzulli S, O'Byrne C. 2003. Weak organic acids: a panoply of effects on bacteria. Sci Prog 86:245–69.

Hlebowicz J, Darwiche G, Bjorgell O, Almer LO. 2007. Effect of apple cider vinegar on delayed gastric emptying in patients with type 1 diabetes mellitus: a pilot study. BMC Gastroenterol 7:46.

Iizuka M, Tani M, Kishimoto Y, Saita E, Toyozaki M, Kondo K. 2010. Inhibitory effects of balsamic vinegar on LDL oxidation and lipid accumulation in THP-1 macrophages. J Nutr Sci Vitaminol 56:421–7.

Inagaki S, Morimura S, Gondo K, Tang Y, Akutagawa H, Kida K. 2007. Isolation of tryptophol as an apoptosis-inducing component of vinegar produced from boiled extract of black soybean in human monoblastic leukemia U937 cells. Biosci Biotechnol Biochem 71:371–9.

Jeong CH, Choi GN, Kim JH, Kwak JH, Kang ST, Choi SG, Heo HJ. 2009. In vitro antioxidant properties and phenolic composition of Korean commercial vinegars. Food Sci Biotechnol 18:1258–62.

Johnston CS, Buller AJ. 2005. Vinegar and peanut products as complementary foods to reduce postprandial glycemia. J Am Diet Assoc 105:1939–42.

Johnston CS, Steplewska I, Long CA, Harris LN, Ryals RH. 2010. Examination of the antiglycemic properties of vinegar in healthy adults. Ann Nutr Metab 56:74–79.

Johnston CS, White AM, Kent SM. 2009. Preliminary evidence that regular vinegar ingestion favorably influences hemoglobin A1c values in individuals with type 2 diabetes mellitus. Diabetes Res Clin Pract 84:e15–7.

Jung HH, Cho SD, Yoo CK, Lim HH, Chae SW. 2002. Vinegar treatment in the management of granular myringitis. J Laryngol Otol 116:176–80.

Kadas Z, Akdemir Evrendilek G, Heper G. 2014. The metabolic effects of hawthorn vinegar in patients with high cardiovascular risk group. J Food Nutr Res 2:539–45.

Kishi M, Fukaya M, Tsukamoto Y, Nagasawa T, Takehana K, Nishizawa N. 1999. Enhancing effect of dietary vinegar on the intestinal absorption of calcium in ovariectomized rats. Biosci Biotechnol Biochem 63:905–10.

Kondo T, Kishi M, Fushimi T, Kaga T. 2009a. Acetic acid upregulates the expression of genes for fatty acid oxidation enzymes in liver to suppress body fat accumulation. J Agric Food Chem 57:5982–6.

Kondo T, Kishi M, Fushimi T, Ugajin S, Kaga T. 2009b. Vinegar intake reduces body weight, body fat mass, and serum triglyceride levels in obese Japanese subjects. Biosci Biotechnol Biochem 73:1837–43.

Kosuge T, Kamiya H. 1962. Discovery of a pyrazine in a natural product: tetramethylpyrazine from cultures of a strain of *Bacillus subtilis*. Nature 193:776.

Kosuge T, Zenda H, Tsuji K, Yamamoto T, Narita H. 1971. Studies on flavor components of foodstuffs, part I: distribution of tetramethylpyrazine in fermented foodstuffs. Agric Biol Chem 35:693–6.

Kyrø C, Zamora-Ros R, Scalbert A, Tjønneland A, Dossus L, Johansen C, Bidstrup PE, Weiderpass E, Christensen J, Ward H. 2015. Pre-diagnostic polyphenol intake and breast cancer survival: the European prospective investigation into cancer and nutrition (EPIC) cohort. Breast Cancer Res Treat 154:389–401.

Leeman M, Ostman E, Bjorck I. 2005. Vinegar dressing and cold storage of potatoes lowers postprandial glycaemic and insulinaemic responses in healthy subjects. Eur J Clin Nutr 59:1266–71.

Li B, Li ZX, Ying W, Zhang XL, Wu RQ, Fan YL, Bu LQ. 2009. Study on the effects of brans and aspergillus niger about corn vinegar on reducing obesity and blood lipids in rat. J Northwest A & F Uni (Nat Sci Ed) 37:194–8.

Li XJ, Wang XY, Yuan J, Lu M, Wang RH, Quan ZJ. 2013. The determination and comparison of phenolics in apple vinegar, persimmon vinegar and kiwifruit vinegar. Food Ferment Ind 39:186–90.

Liljeberg H, Björck I. 1998. Delayed gastric emptying rate may explain improved glycaemia in healthy subjects to a starchy meal with added vinegar. Eur J Clin Nutr 52:368–71.

Lin HC, Doty JE, Reedy TJ, Meyer JH. 1990. Inhibition of gastric emptying by acids depends on pH, titratable acidity, and length of intestine exposed to acid. Am J Physiol Gastrointest Liver Physiol 259:G1025–30.

Liu L, Han YW, Wang N, Zhao L, Kou X, Li ZX. 2015. Effect of purple sweet potato vinegar on hepatoprotective of acute liver injury and mass-reducing, hypolipidemic in mice. Acta Agric Boreali-Occident Sin 24:28–33.

Liu L, Yang X. 2015. Hypolipidemic and antioxidant effects of freeze-dried powder of Shanxi mature vinegar in hyperlipidaemic mice. Food Sci 36:141–51.

Lu PJ, Zhou YZ. 2002. Anti-fatigue function of Hengshun vinegar capsules. China Condiment 10:8–13.

Ma TJ, Xia F, Jia CX. 2010. The influence of bitter buckwheat vinegar in blood glucose of diabetic model mice. J Chin Cereals Oils Assoc 25:42–8.

Matsui T, Ebuchi S, Fukui K, Matsugano K, Terahara N, Matsumoto K. 2014. Caffeoylsophorose, a new natural α-glucosidase inhibitor, from red vinegar by fermented purple-fleshed sweet potato. Biosci Biotechnol Biochem 68:2239–46.

McLaggan D, Naprstek J, Buurman ET, Epstein W. 1994. Interdependence of K^+ and glutamate accumulation during osmotic adaptation of *Escherichia coli*. J Biol Chem 269:1911–7.

Mimura A, Suzuki Y, Toshima Y, Yazaki S-I, Ohtsuki T, Ui S, Hyodoh F. 2004. Induction of apoptosis in human leukemia cells by naturally fermented sugar cane vinegar (kibizu) of Amami Ohshima Island. BioFactors 22:93–7.

Mitrou P, Raptis AE, Lambadiari V, Boutati E, Petsiou E, Spanoudi F, Papakonstantinou E, Maratou E, Economopoulos T, Dimitriadis G. 2010. Vinegar decreases postprandial hyperglycemia in patients with type 1 diabetes. Diabetes Care 33:e27.

Moon YJ, Cha YS. 2008. Effects of persimmon-vinegar on lipid metabolism and alcohol clearance in chronic alcohol-fed rats. J Med Food 11:38–45.

Nakamura K, Ogasawara Y, Endou K, Fujimori S, Koyama M, Akano H. 2010. Phenolic compounds responsible for the superoxide dismutase-like activity in high-Brix apple vinegar. J Agric Food Chem 58:10124–32.

Nanda K, Miyoshi N, Nakamura Y, Shimoji Y, Tamura Y, Nishikawa Y, Uenakai K, Kohno H, Tanaka T. 2004. Extract of vinegar "Kurosu" from unpolished rice inhibits the proliferation of human cancer cells. J Exp Clin Cancer Res 23:69–76.

Nishidai S, Nakamura Y, Torikai K, Yamamoto M, Ishihara N, Mori H, Ohigashi H. 2000. Kurosu, a traditional vinegar produced from unpolished rice, suppresses lipid peroxidation in vitro and in mouse skin. Biosci Biotechnol Biochem 64:1909–14.

Ochoa-Zarzosa A, Villarreal-Fernández E, Cano-Camacho H, López-Meza JE. 2009. Sodium butyrate inhibits Staphylococcus aureus internalization in bovine mammary epithelial cells and induces the expression of antimicrobial peptide genes. Microb Pathog 47:1–7.

Ogawa N, Satsu H, Watanabe H, Fukaya M, Tsukamoto Y, Miyamoto Y, Shimizu M. 2000. Acetic acid suppresses the increase in disaccharidase activity that occurs during culture of caco-2 cells. J Nutr 130:507–13.

Ostman E, Granfeldt Y, Persson L, Bjorck I. 2005. Vinegar supplementation lowers glucose and insulin responses and increases satiety after a bread meal in healthy subjects. Eur J Clin Nutr 59:983–8.

Pazuch CM, Siepmann FB, Canan C, Colla E. 2015. Vinegar: functional aspects. Cientifica 43:302–8.

Peng YT, Chen TY, Chen MC, Lin E, Lin H. 2014. Resveratrol regulates phospho-serine 81 androgen receptor and its stability to inhibit growth of prostate cancer cells. Cancer Res 74:2121.

Perron NR, Brumaghim JL. 2009. A review of the antioxidant mechanisms of polyphenol compounds related to iron binding. Cell Biochem Biophys 53:75–100.

Petsiou EI, Mitrou PI, Raptis SA, Dimitriadis GD. 2014. Effect and mechanisms of action of vinegar on glucose metabolism, lipid profile, and body weight. Nutr Rev 72:651–61.

Plessi M, Bertelli D, Miglietta F. 2006. Extraction and identification by GC-MS of phenolic acids in traditional balsamic vinegar from Modena. J Food Compost Anal 19:49–54.

Ren Z, Ma J, Zhang P, Luo A, Zhang S, Kong L, Qian C. 2012. The effect of ligustrazine on L-type calcium current, calcium transient and contractility in rabbit ventricular myocytes. J Ethnopharmacol 144:555–661.

Rice-Evans CA, Miller NJ, Paganga G. 1996. Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free Radical Biol Med 20:933–56.

Rizz GP. 1972. Mechanistic study of alkylpyrazine formation in model systems. J Agric Food Chem 20:1081–5.

Rodriguez MR, Oderiz MV, Hernandez JL, Lozano JS. 1992. Determination of vitamin C and organic acids in various fruits by HPLC. J Chromatogr Sci 30:433–7.

Roe AJ, McLaggan D, Davidson I, O'Byrne C, Booth IR. 1998. Perturbation of anion balance during inhibition of growth of *Escherichia coli* by weak acids. J Bacteriol 180:767–72.

Rufian-Henares JA, de la Cueva SP. 2009. Antimicrobial activity of coffee melanoidins a study of their metal-chelating properties. J Agric Food Chem 57:432–8.

Rurián-Henares JA, Morales FJ. 2008. Antimicrobial activity of melanoidins against *Escherichia coli* is mediated by a membrane-damage mechanism. J Agric Food Chem 56:2357–62.

Sakakibara S, Murakami R, Takahashi M, Fushimi T, Murohara T, Kishi M, Kajimoto Y, Kitakaze M, Kaga T. 2010. Vinegar intake enhances flow-mediated vasodilatation via upregulation of endothelial nitric oxide synthase activity. Biosci Biotechnol Biochem 74:1055–61.

Sakakibara S, Yamauchi T, Oshima Y, Tsukamoto Y, Kadowaki T. 2006. Acetic acid activates hepatic AMPK and reduces hyperglycemia in diabetic KK-A(y) mice. Biochem Biophys Res Commun 344:597–604.

Sang S, Buckley B, Ho C-T, Yang CS. 2007. Autoxidative quinone formation in vitro and metabolite formation in vivo from tea polyphenol (–)-epigallocatechin-3-gallate: studied by real-time mass spectrometry combined with tandem mass ion mapping. Free Radical Biol Med 43:362–71.

Schaefer S, Baum M, Eisenbrand G, Dietrich H, Will F, Janzowski C. 2006. Polyphenolic apple juice extracts and their major constituents reduce oxidative damage in human colon cell lines. Mol Nutr Food Res 50:24–33.

Seki T, Morimura S, Shigematsu T, Maeda H, Kida K. 2004. Antitumor activity of rice-shochu post-distillation slurry and vinegar produced from the post-distillation slurry via oral administration in a mouse model. BioFactors 22:103–5.

Sengun IY, Karapinar M. 2004. Effectiveness of lemon juice, vinegar and their mixture in the elimination of *Salmonella typhimurium* on carrots (*Daucus carota* L.). Int J Food Microbiol 96:301–5.

Setorki M, Asgary S, Eidi A, Rohani A, Khazaei M. 2010. Acute effects of vinegar intake on some biochemical risk factors of atherosclerosis in hypercholesterolemic rabbits. Lipids Health Dis 9:10.

Shimoji Y, Kohno H, Nanda K, Nishikawa Y, Ohigashi H, Uenakai K, Tanaka T. 2004. Extract of Kurosu, a vinegar from unpolished rice, inhibits azoxymethane-induced colon carcinogenesis in male F344 rats. Nutr Cancer 49:170–3.

Shimoji Y, Nanda K, Nishikawa Y, Hayashi R, Ohigashi H. 2003. Extract of vinegar "Kurosu" from unpolished rice inhibits the development of colonic aberrant crypt foci induced by. J Exp Clin Cancer Res 22:591–7.

Shimoji Y, Tamura Y, Nakamura Y, Nanda K, Nishidai S, Nishikawa Y, Ishihara N, Uenakai K, Ohigashi H. 2002. Isolation and identification of DPPH radical scavenging compounds in Kurosu (Japanese unpolished rice vinegar). J Agric Food Chem 50:6501–3.

Shishehbor F, Mansoori A, Sarkaki A, Jalali M, Latifi S. 2008. Apple cider vinegar attenuates lipid profile in normal and diabetic rats. Pak J Biol Sci 11:2634–8.

Shukla Y, Singh R. 2011. Resveratrol and cellular mechanisms of cancer prevention. Ann N Y Acad Sci 1215:1–8.

Sirk TW, Brown EF, Sum AK, Friedman M. 2008. Molecular dynamics study on the biophysical interactions of seven green tea catechins with lipid bilayers of cell membranes. J Agric Food Chem 56:7750–8.

Solieri L, Giudici P. 2009. Vinegars of the world. Milan, Italy: Springer.

Soltan SS, Shehata M. 2012. Antidiabetic and hypocholesrolemic: effect of different types of vinegar in rats. Life Sci J 9:2141–51.

Sun X, Hu M, Henrik M, Evans HS, Dai D, Duan W, Lu J. 2003. Risk factors for oesophageal cancer in Linzhou, China: a case-control study. Asian Pac J Cancer Prev 4:119–24.

Tagliazucchi D, Verzelloni E, Conte A. 2007. Antioxidant properties of traditional balsamic vinegar and boiled must model systems. Eur Food Res Technol 227:835–43.

Tagliazucchi D, Verzelloni E, Conte A. 2010. Contribution of melanoidins to the antioxidant activity of traditional balsamic vinegar during aging. J Food Biochem 34:1061–78.

Taguri T, Tanaka T, Kouno I. 2006. Antibacterial spectrum of plant polyphenols and extracts depending upon hydroxyphenyl structure. Biol Pharm Bull 29:2226–35.

Verzelloni E, Tagliazucchi D, Conte A. 2007. Relationship between the antioxidant properties and the phenolic and flavonoid content in traditional balsamic vinegar. Food Chem 105:564–71.

Verzelloni E, Tagliazucchi D, Conte A. 2010. From balsamic to healthy: traditional balsamic vinegar melanoidins inhibit lipid peroxidation during simulated gastric digestion of meat. Food Chem Toxicol 48:2097–102.

Wang HY, Qian H, Yao WR. 2011. Melanoidins produced by the Maillard reaction: structure and biological activity. Food Chem 128:573–84.

Wang LS, Guo Q, Han J, Zhang YF, Chen XJ. 2009. Pharmacokinetics of ligustrazine in blood, brain, and liver of mice. Chin Tradit Herb Drugs 40:935–8.

Wei ZP, Li ZX, Yu XZ, Liu ZM, Cui XY, Jin J. 2005. Effect of mulberry vinegar on reducing obesity of animals. China Brewing 12:5–7.

White AM, Johnston CS. 2007. Vinegar ingestion at bedtime moderates waking glucose concentrations in adults with well-controlled type 2 diabetes. Diabetes Care 30:2814–5.

Wu D, Kimura F, Takashima A, Shimizu Y, Takebayashi A, Kita N, Zhang G, Murakami T. 2013. Intake of vinegar beverage is associated with restoration of ovulatory function in women with polycystic ovary syndrome. Tohoku J Exp Med 230:17–23.

Xu Q, Ao Z, Tao W. 2003. Progress in vinegar function study. China Condiment 12:11–23.

Xu QP, Tao WY, Ao ZH. 2005. Antioxidation effects of vinegar on ageing accelerating model mice. Food Sci 26:205–7.

Xu QP. 2008. The vinegar production technology. Beijin, China: Chemical Industry Press.

Yamashita H, Fujisawa K, Ito E, Idei S, Kawaguchi N, Kimoto M, Hiemori M, Tsuji H. 2014. Improvement of obesity and glucose tolerance by acetate in type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. Biosci Biotechnol Biochem 71:1236–43.

Yamashita H, Maruta H, Jozuka M, Kimura R, Iwabuchi H, Yamato M, Saito T, Fujisawa K, Takahashi Y, Kimoto M, Hiemori M, Tsuji H. 2009. Effects of acetate on lipid metabolism in muscles and adipose tissues of type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. Biosci Biotechnol Biochem 73:570–6.

Yang L, Wang X, Yang X. 2014. Possible antioxidant mechanism of melanoidins extract from Shanxi aged vinegar in mitophagy-dependent and mitophagy-independent pathways. J Agric Food Chem 62:8616–22.

Yoda Y, Hu ZQ, Zhao WH, Shimamura T. 2004. Different susceptibilities of Staphylococcus and Gram-negative rods to epigallocatechin gallate. J Infect Chemother 10:55–8.

Yuan R, Ao ZH, Ding HL, Shen CH, HUang ZG, Ren JB, Fu X. 2011. Measuring on the fatty acids and low molecular weight organic acids from sorghum by gas chromatography. Liquor Making 38:42–3.

Zamora-Ros R, Knaze V, Rothwell JA, Hémon B, Moskal A, Overvad K, Tjønneland A, Kyrø C, Fagherazzi G, Boutron-Ruault M-C. 2015. Dietary polyphenol intake in Europe: the European prospective investigation into cancer and nutrition (EPIC) study. Eur J Nutr 1–17.

Zhang J, Tian Z, Wang J, Wang A. 2011. Advances in antimicrobial molecular mechanism of organic acids. Acta Vet Zootech Sin (Chin J Anim Vet Sci) 42:323-8.

Zhang L, Li Z, Du S. 2007. Study on the effects of mulberry vinegar on weight losing and antifatigue in rat. J Northwest Sci-Tech Uni Agric For 35:227–30.

Zhou X, Salganicoff L, Sevy R. 1985. The pharmacological effect of ligustrazine on human platelets. Acta Pharm Sin 20:334–9.