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Review Article

Pharmacological and Phytochemical Properties of Unripe Grape Juice (Verjuice): A Review

Ahmadi L* and Roney SK

Division of Food and Nutritional Sciences, Brescia University College at the University of Western Ontario, Canada

***Corresponding author:** Ahmadi L, Division of Food and Nutritional Sciences, Brescia University College at the University of Western Ontario, London, Ontario, Canada, 1285 Western Road, London, N6G 1H2, Ontario, Canada

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Abstract

Verjuice is an acidic juice obtained from mechanically pressing unripe green grapes (Vitis L.) native to the Mediterranean. It is commonly used as an alternative to vinegar or lemon juice, as a dressing, and/or to marinade meats. It has an extensive phytochemical profile which may explain its proposed cardio-protective effects which have been investigated in animal and human trials. Through a variety of mechanisms, verjuice may be a useful dietary agent for the treatment of CVD. The present review paper provides a comprehensive analysis of the constituents of verjuice and a review and assessment of the current literature examining the pharmacologic properties of verjuice. Further research in this area which quantifies the phytochemical profile of the supplemented verjuice, and the effective dose required to infer the maximum health benefit are warranted to support these findings.

Keywords: Verjuice; Phytochemicals; CVD; Phenolic compounds

Introduction

Verjuice, also known as verjus, verjust, and unripe grape juice, is an acidic juice with a unique, sour flavour made from the mechanical pressing of un-ripened green grapes with proposed cardio-protective properties [1,2]. Specifically, the effects of verjuice supplementation on serum lipid profile, blood pressure, inflammatory markers, endothelial function, oxidation, glycemic control, and fatty streak formation have been evaluated with *in vivo* and human randomized control trials. Therefore, through these mechanisms, verjuice may be a useful dietary agent for the prevention and treatment of Cardiovascular Disease (CVD).

CVD pertains to diseases and injuries of the heart or blood vessels throughout the body including those within the brain [3]. In Canada, heart disease and stroke are two of the three leading causes of death [4,5]. Heart disease and stroke have been estimated to cost the Canadian economy more than $20.9 billion every year in physician services, hospital costs, lost wages, and decreased productivity [6]. The picture is similar in the United States where CVD is also the leading cause of death and is responsible for 17% of national health expenditures [7]. A policy statement from the American Heart Association forecasted the future of CVD in the United States. This was achieved using projected population counts for 2010-2030 and prevalence estimates for Hypertension (HTN), coronary heart disease, heart failure, and stroke from data from the 1999 to 2006 National Health and Nutrition Examination Survey and the Census Bureau. The policy statement estimated that there will be an approximate 10% increase in prevalence over the next 20 years under status quo CVD prevention and treatment trends. It was also reported that an additional 27 million people will have HTN, 8 million will have coronary heart disease, 4 million will have stroke, and 3 million will have heart failure in 2030 relative to 2010. By 2030, 40.5% of the US population is projected to have some form of CVD [7]. Financial estimates state that between 2010 and 2030, direct medical costs of CVD are expected to triple from $272.5 billion to $818.1 billion [7].

The proposed cardio-protective effects of verjuice are attributed to its extensive phytochemical profile. Verjuice is structurally similar to grape juice in that both have flavonoid compounds such as catechin and anthocyanin [8]. The green grape varieties typically used in Turkey to produce verjuice include Kabarcik and Yediveren [2]. While not suitable for wine production, these grape varieties are ideal for verjuice production as they are characterized by higher juice yield, acidity, and aromatic quality [2]. It is predominantly consumed in the Mediterranean, Southeastern regions of Turkey, and Iran where it is used as an alternative to vinegar and lemon juice, as a dressing or marinade on meats, salads, and appetizers, as an ingredient in the production of various drinks and as an ingredient in the production of several sausages [2]. Table 1 summarizes research articles describing the physico-chemical and antimicrobial properties of verjuice. The present review paper provides a comprehensive analysis of the constituents of verjuice and a review and assessment of the current literature examining its cardio-protective effects.

Phytochemical Composition of Verjuice

Verjuice is a rich source of bioactive compounds such as flavonoids, phenolic acids, hydroxybenzoic acids, and hydroxycinnamic acids which, when consumed, infer extensive health benefits. As described in Table 2, verjuice contains a vast range of phenolic compounds such as caffeic acid, caftaric acid, catechin, epicatechin, fertaric acid, gallic acid, p-coumaric acid, p-coutaric acid, protocatechuic acid, quercetin, quercetin-α-glucoside, and tyrosol.

Phenols are naturally occurring secondary metabolites found in numerous species of the higher plant kingdom [9]. Verjuice is a potent source of numerous phenolic compounds which vary widely in their water solubility, molecular weights, intermolecular complexion, and structural characteristics [1]. The bioavailability of these compounds is highly variable and thus, their maximum concentration in plasma,

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Table 1: Phytochemical studies of unripe grapes.

Author(s)	Purpose of study	Sample specification	Measured parameters	Major findings
Shojaee-Aliabadi et al. [34]	Optimizing the extraction time, temperature and solvent ratio (ethanol/water) to improve the efficiency of the extraction process	Unripe grape marc extract (Goreh) harvested 30 days before grape harvesting	The optimal conditions for; temperature and time and the ratio of ethanol to water	The optimal conditions; temperature 44.93°C and time 19.34 h, and the ratio of ethanol to water ; 70.08%
Kontoudakis et al. [33]	Simultaneously reducing the pH and alcohol content of wine made of grapes with complete phenolic maturity	Unripe grapes harvested during cluster thinning (verasion time)	Ethanol, titratable acidity, PH, total anthocyanins, color, astringency index, total phenolic index,	All parameters were lower in wine from the first harvest than the 2nd harvest (more ripened) except; higher acidity, proanthocyanidins, epigallocatechin, epicathechin-3-o-gallate and same amount of epicatechin
Hayoglu et al. [2]	Chemical and sensory properties of verjuice in two Turkish varieties treated with heat, clarified with gelatin and stored at 4°C	The green grapes were harvested 45 days after flowering when acidity was at its maximum level	Properties of clusters, properties of verjuice; acidity, browning index, turbidity, total phenolic compounds, total solid, brix, Vitamin C, sensory evaluation	Clarified sample with gelatin preferred to non-clarified verjuice, Turbidity in treated sample increased , but the amount of polyphenolic compounds decreased
Nikfardjam [35]	Chemical composition of the verjuc sample from Europe countries and Iran	The verjuc samples were bought from different stores and from winery	Alcohol, polyphenols, total extract, density, sugar free extract, sugar content, acidity, SO2, volatile acidity, OD	Sample picked before sugar accumulation contained higher amount of polyphenol compounds such as caffecic acid, catechin, quercetin glucoside but lower in grape reaction product compared to the samples picked at the vegetative stage
Karapinar and Sengn [36]	Antimicrobial effect of koruk (unripe grape juice) against *Salmonella typhimurium* on salad vegetables	Samples obtained from Gulbahce vineyards, Izmir, Turkey and fresh juice prepared by different methods.	Samples were inoculated with two *Salmonella typhimurium* strains, *Salmonella* cells were counted by using direct surface plating.	The antimicrobial effect of koruk juice was found to be dependent on the culture strains and products used .There was no significant difference in cell reduction in samples exposed to koruk juices for different times

Table 2: The biological activities of phytochemicals present in verjuice.

Phytochemical composition	Some of the biological activities	References
Caffeic acid (hydroxycinnamic acids)	Antioxidant activity	Gulcin, [37]
Caftaric acid (non-flavonoid phenolic compound)	Immunomodulatory	Perry et al. [38]
Catechin (flavonoid)	Innate immune responses in HIV-1 infection as a microbicide	*Nance et al. [39]*
Epicatechin	Lower incidence of cardiovascular disease and stroke, antioxidant capacity	Yimaz and Toledo [40] Heiss et al. [41]
Fertaric acid	Antioxidant activity	Marquez et al. [42]
Gallic acid	Anti-obesity effect	Hsu and Yen [43]
p- Coumaric acid	Free-radical scavenger	Roy and Prince [44]
Protocatechuic acid	Role in preventing of esophageal cancer	Peiffer et al. [45]
Quercetin	Reducing cholesterol level and prevent liver inflammatory injury	Lee et al., [46]
Quercetin-glucoside	Antioxidant activity	Li et al. [47]
Tyrosol	Antioxidant abilities, the scavenging abilities and the biological fates	Tuck and Hayball [48]

the time required to reach maximum concentration in plasma, their elimination half-life, and extent of excretion from the body must be considered before beneficial effects of these compounds on health and disease prevention is concluded. Gallic acid and isoflavones are the most readily absorbed polyphenols closely followed by catechins [10], flavanones and querecein glucosides. Information on the metabolism of these compounds is crucial for designing any experiments related to the health effects of polyphenols to ensure the effect seen can truly be attributed to the polyphenolic compounds [1]. The biological activities of phytochemicals present in verjuice are shown in Table 2.

Metabolism of Phenolic Compounds Found in Verjuice

Flavonoids

The two most common flavonoid glycosides consumed in a typical North American diet are querecetin and rutin. The absorption of flavonoids is hindered in the small intestine due to their high molecular weight, the hydrophilic nature of glycosides, and resistance of flavonoid β-glycosides to hydrolyse [11]. Intact compounds pass to the large intestine where microflora of the bowl cleave the sugar molecule and separate the pyrone ring, releasing the aglycone and producing phenyl acetic and phenyl propionic acid, respectively. The glycosidase activity of the microflora acts at a faster rate compared to the ring cleavage and therefore, the intact flavonoid aglycone has a high potential to absorb in the large intestine [12].This is advantageous as recent studies have suggested that bioavailable dietary flavonoids may protect free radical induced damage to DNA via free radical scavenging [13].

Querecetin-α-glucoside

In foods, querectin is present most abundantly in its glycoside form. The glucoside is formed when one or more sugars binds to the phenolic group through a glycosidic linkage [14]. The amount and size of these sugar moieties vary between food sources and affects the bioavailability of the bound quercetin [11,15]. Their metabolism includes hydrolysis, microbial effects, and conjugation reactions. When quercetin glucosides are ingested, glycosyl groups are released

during chewing, digestion, and absorption. Hydrolysis, the first step of metabolism, is facilitated by enterobacteria to form aglycones which occur predominately in the colon but also in the mouth [15]. The aglycone form is easily absorbed by the epithelial cells of the large intestine due to their high lipophilicity allowing for easy passage through the phospholipid layer. Quercetin glycosides can also pass through the epithelial cell monolayer via the glucose transporter SGLT-1, however not as easily as their hydrolyzed form, quercetin aglycone [14]. Both, quercetin glycosides and aglycones are insoluble in water and therefore lipids are necessary to aid in absorption [14].

When in circulation, the aglycone form goes through 'phase II' conjugation reactions of methylation, glucuronidation, and/or sulfation, converting them into metabolites. Many of these metabolites are excreted through bile into the intestinal lumen. They can be hydrolyzed again and reabsorbed by the intestinal cells or excreted through feces. The type of conjugation that occurs dictates where in the body it will be re-absorbed. For example, quercetin glucoside is re-absorbed in the small intestine whereas quercetin rutinoside is re-absorbed in the colon. After quercetin is absorbed through the small intestine it passes through to the liver to be distributed to different organs in the body. In circulation, quercetin conjugates have a long elimination half life and bind firmly to albumin in the plasma [16]. In the plasma the quercetin conjugates reach peak levels very quickly after ingestion, gathering at concentrations of 10^{-7}-10^{-6} M. The activity of these conjugates in the plasma should be determined when examining the effects of quercetin. The phenolic hydroxyls that make up part of quercetins structure act as electron donors for free radicals inferring a free radical scavenging ability and antioxidant effect [14].

Monomeric flavanols

Catechin: Bioavailability, metabolism, and absorption of catechin differ by food source and species. This is evidenced by catechin levels being at their highest in humans 2-4 hours after ingestion which is not synonymous with rat studies. Studies in rats show that there are large amounts of catechin in the esophagus, large intestine, kidney, bladder, lung, and prostate and that certain forms of catechin are excreted through bile and urine. These findings are disparate to what occurs in humans which may be due humans' ability to further metabolize catechin to simpler compounds. The metabolism of catechins begins in the mouth as saliva contains catechin esterase. Similarly to quercetin, catechins are conjugated to glucuronidated, methylated, and sulfated forms. The specific enzymes involved include catechol-*O*-methyltransferase, UDP-glucuronosyltransferase, and phenolsulfutransferases. In rat studies, it was found that catechins are glucuronidated in the intestinal mucosa, sulfated in the liver, and methylated in the liver and kidney yielding catechins that were glucuronidated, *O*-methylated, and *O*-methylated glucuronide in rat plasma. These metabolites were also observed in human plasma. It is suggested that using higher doses of catechins would change the conjugated metabolites that appear. Catechins are typically absorbed in the small intestine, however, some travel to the large intestine where further metabolism occurs by bacteria in the colon to simpler compounds prior to absorption [17].

Anthocyanins: Large amounts of anthocyanins are present in berries, red wine, juices and grapes. Anthocyanin bioavailability has been reported low as most studies show a low concentration of anthocyanin in plasma despite high intake. There is a possibility of some errors in measurement methods or not accounting for some metabolites [11].

Anthocyanin glycosides may be absorbed through two different methods in the small intestine. The first method that is proposed starts at the brush border membrane of the intestine. Here it is hydrolyzed by lactate phlorizin hydrolase, converting it to an aglycone which can then diffuse into the enterocyte. At this point the aglycone can enter portal circulation or be conjugated before entering the serosal fluid. The second method is direct absorption of anthocyanin glycoside which occurs through a sodium-glucose co-transporter. After being transported into the cell, the glycoside can either enter into portal circulation, or be hydrolyzed by cytosolic *ß*-glucosidase prior to undergoing further metabolism. When anthocyanin is ingested in low quantities the majority of anthocyanin glycoside is metabolized in the intestinal mucosa and the primary conjugation is glucuronidation in the small intestine. This conjugation may also occur in the kidney, but to a lesser extent. After glucuronidation, the next most common conjugation is methylation in the liver. The least common conjugation is sulfation, which can occur in the liver, small intestine, or kidney. Conjugates that are formed in the small intestine are released into systemic circulation, whereas conjugates formed in the liver are excreted in bile. Conjugates released in bile will be further metabolized to simpler compounds in the small and large intestine with the majority occurring as a result of the activity of colonic bacteria. Protocatechuic acid is a metabolite by-product of anthocyanin found in human fecal matter. While the bioavailability of many polyphenols is low in food, their metabolites tend to stay in circulation and exert their effects for long periods of time [18].

Hydroxybenzoic acids

Protocatechuic acid: Protocatechuic acid is a metabolite formed in the small intestine or bloodstream from the breakdown of cyanidin-glucoside [19]. Protocatechuic acid oxidase is a specific catalyst used to convert protocatechuic acid to *ß* -ketoadipic acid with few known competitive inhibitors. Its activity increases with an increasing pH, however peaks at pH 9.0. Protocatechuic acid uses two oxygen atoms to complete this two-step reaction. Protocatechuic acid is first degraded to *ß* -carboxymuconic acid and then further degraded to *ß* -ketoadipic acid. These products accumulate differently depending on the purity of the system [19].

Gallic acid: Compared to other polyphenols, gallic acid has a high bioavailability in humans [10]. Many metabolites of gallic acid have been discovered which are very close in structure to terpenes and alkaloids present in plant tissues. Gallic acid is highly prevalent in plants where it is mostly found in an ester form which is biosynthesized in plants via the reaction between gallic acid and UDP-glucose creating the intermediate, B-glucogallin. While there are many other intermediates in the pathway to formation of gallic acid esters, B-glucogallin is a primary galloyl-group donor for all of the intermediate reactions necessary to make the B-1,2,3,4,6-pentagalloyl-D-glucose end product. This pathway resembles the sequence of the chemically mediated esterification of the hydroxyl group of D-glucopyranose. The open-chain form of *D*-glucose helps to form very unique polyphenolic compounds that are derived from gallic acid which are formed in certain species of oak and chestnut [9].

Table 3: Evidence summary for cardio-protective effects of verjuice supplementation in animal trials.

Author(s)	n	Species	Treatment	Sample Specification	Study Duration	Summary of Major Findings
Nematbakhsh et al. [29]	Not specified	Male Wistar Rats	125 mg/kg verjuice, 250 mg/kg verjuice, and 500 mg/kg verjuice	Total phenolic content of verjuice was 8.5% gallic acid equivalents	Cross sectional	In all verjuice treated groups MAP, SP, and DP were less than the control, but only significant in the group receiving 125 mg/kg verjuice.* One hour after administration of verjuice, the HR in the 125 mg/kg gtoup was lower than the control; 286±12 vs. 341±24/min* Verjuice supplementation increased the serum nitrite level in 125 mg/kg and 250 mg/kg groups when compared to control.* Verjuice did not limit effects of angiotensin II administration.
Mousa-Al-Reza et al. [25]	72	Mice	7 ml verjuice/kcal/d and 14 ml verjuice/kcal/d	Phytochemical profile not specified.	12 weeks	Use of verjuice in preventative groups (received verjuice in conjunction to high cholesterol diet) significantly increased serum LDL levels in comparison to negative control group (received high cholesterol diet)* Verjuice supplementation did not result in any significant changes to serum HDL or TC. Receiving the higher dose of verjuice as a treatment after 42 days of receiving a high cholesterol diet decreased the serum TG significantly (76.85 ±5.1) when compared with negative control group (101.85 ± 5.7).* No atherosclerotic plaque formations after consumption of 2% cholesterol regime were present.
Setorki et al. [26]	32	Male White New Zealand rabbits	5 ml verjuice and 10 ml verjuice	Vitamin C: 1.8 ± .5 mg/dl Acetic Acid: 9.81±.04% Anthocyanin: 2.99 ± 1.04 mg/100 g Flavonoids: 1.97± 0.283 g/100ml equivalent naringenin Density: 0.157±0.001 g/cm pH: 3.24±.01	2 months	Supplementation with both amounts of verjuice induced an increase in nitrite and nitrate and a reduction in fibrinogen compared with control* Supplementation with 10 ml verjuice resulted in reduced LDL, MDA, and ox-LDL compared with control* Verjuice supplementation decreased atherosclerotic thickness grade compared to control (1.8 ± 0.45, 0.75 ± 0.25 in right coronary; 1.98±0.65, 0.82±0.42 in left coronary).*
Setorki et al. [1]	32	Male White New Zealand rabbits	5 ml verjuice and 10 ml verjuice	Vitamin C: 1.8 ± .5 mg/dl Acetic Acid: 9.81±.04% Anthocyanin: 2.99 ± 1.04 mg/100 g Flavonoids: 1.97± 0.283 g/100ml equivalent naringenin Density: 0.157±0.001 g/cm pH: 3.24±.01	Cross sectional	Glucose level decreased in groups receiving verjuice compared with control.*. Nitrite level was lower in group receiving 10 ml of verjuice compared with control* Nitrate concentration decreased in group receiving 10 ml compared to group receiving 5 ml verjuice.* MDA decreased 10 ml verjuice group compared to control* Lower ox-LDL in 10 ml verjuice group compared control*
Aminian et al. [23]	50	Rabbits	20 ml verjuice daily with 10 ml egg yolk.	Phytochemical profile not specified.	6 weeks	Supplementation of verjuice did not prevent rising of TC and LDL caused by feeding egg yolk Changes in HDL and TG not statistically significant between placebo and treatment No atheromatous plaque formation of any rabbits at end of trial

* Statistically significant finding ($p<0.05$)

In rats fed a 0.5% gallic acid diet, one major metabolite, along with some gallic acid, was found in their urine. The researchers conclude that the metabolite is likely 4-*O*-methyl gallic acid due to the presence of a carboxylic acid group. A second metabolite in much smaller quantities was also found by the researchers which had properties identical to 2-*O*-methyl pyrogallol. This experiment was repeated with rabbits which yielded the same results [20].

Hydroxycinnamic acids: Intake of esters of hydroxycinnamic acids such as caffeic acid, coumaric acid and ferulic acid is high among coffee drinkers (up to 800 mg/day). While very little is known about bioavailability of these compounds, it is likely that the absorption of chlorogenic acids occurs predominantly in the colon [11].

Caffeic acid: Caffeic acid is absorbed in the small intestine and found throughout the body in either the unconjugated and conjugated forms. Conjugated forms include glucuronidated, sulphated, or *O*-methylated forms known as ferulic acid and isoferulic acid. Caffeic acid is esterified to chlorogenic acid and caftaric acid. These esters are metabolised in the colon by microbial esterases. One study showed that

Table 4: Evidence summary for cardio-protective effects of verjuice supplementation in human randomized control trials.

Author(s)	n	Characteristics of Sample	Treatment	Sample Specification	Study Duration	Summary of Major Findings
ZibaeeNezhad et al. [27]	35	Healthy volunteers	10 mL BID	Phytochemical profile not specified.	60 days (120 doses of verjuice)	HDL was 35.83 ± 4.40 mg/dL before verjuice consumption and 45.86 ± 4.30 mg/dL at end of study* 11% decrease in TG at end of study was observed. TC 190.46 ± 17.3 before and 200 ± 17.7 at end of study (5% increase)*
Alipour et al. [28]	31	Healthy volunteers (n=13), hyperlipidemic patients (n=11), and hyperlipidemic and hypertensive patients (n=7)	200 ml verjuice BID	Phytochemical profile not specified.	1 month	Healthy Volunteers No significant changes in LDL, HDL, TG, TC, HR and BP after verjuice consumption compared to baseline. TAC increased after verjuice supplementation compared to baseline* Index of lipid peroxidation was reduced in response to 4 weeks verjuice consumption* Hyperlipidemic patients Significant reduction in LDL and TC after 4 weeks* Mean amounts of MDA was reduced after verjuice consumption compared to baseline* TAC increased compared to baseline* MDA concentration was lower after 4 weeks than 2 weeks. Hyperlipidemic+hypertensive Decrease of LDL, TC, MDA, and MAP after verjuice consumption compared to baseline* HDL, proportion of HDL:LDL, and TAC were increased following verjuice consumption compared to baseline*
Aminian et al. [24]	97	Patients with 1◦ hyperlipidemia	80 mL/d verjuice	Phytochemical profile not specified.	4 months	Patients receiving verjuice supplementation for first two months on study period saw a mean TC reduction from 230 ± 40 mg/dL at start to 218 ± 32 mg/dL* Those receiving verjuice for the last two months had a mean TG reduction from 278 ± 148 sig mg/dL at start to 226 ± 122 mg/dL at end*
* Statistically significant finding ($p<0.05$)						

the esterification of caffeic acid can reduce its bioavailability. When caffeic acid is degraded it becomes 3-hydroxyphenylpropionic acid and benzoic acid. The former is the major product which is formed within two hours when the double bond in caffeic acid is reduced and dehydroxylation occurs at the fourth carbon atom. Benzoic acid is formed from the metabolism of 3-hydroxyphenylpropionic acid. In the intestine 3-hydroxyphenylpropionic acid is rapidly dehydroxylated to 3-phenylpropionic acid which is then *B*-oxidised to benzoic acid in the liver. This reaction, along with the *ß*-oxidization of cinnamic acid to benzoic acid, occurs in the liver. Hippuric acid is then formed when benzoic acid conjugated to glycine [21].

Coumaric acid: p-Coumaric acid is the form of coumaric acid found in grapes and red wine. It is absorbed in the gastrointestinal tract very easily via the monocarboxylic acid transporter. Absorption of p-coumaric acid is inhibited by benzoic acetic acid [22].

Pharmacological Properties of Verjuice

The large impact on human health and quality of life, and the repercussions of CVD on the economy, highlight the necessity for exploration of dietary agents that may attenuate the risk, slow the progression, or act as a treatment for CVD. Verjuice may elicit beneficial changes to serum lipid profile, blood pressure, inflammatory markers, endothelial function, oxidation, glycemic control, and fatty streak formation. Studies examining the effect of verjuice using animals are summarized in Table 3 and human interventions are in Table 4.

Effects on serum lipid profile

Research by Aminian et al. [23,24] in both animal and human trials have not yielded promising results regarding the lipid-lowering potential of verjuice. A sample of 50 rabbits was rendered hypercholesterolemic using supplementation with egg yolk [23]. The trial consisted of two parts, one in which the rabbits received 20ml/d of verjuice at the same time as the egg yolk supplementation started, and the second in which the rabbits were rendered hyperlipidemic using egg yolk before the verjuice supplementation started. For the initial part, minimal changes in High-Density Lipoprotein (HDL) and Triglycerides (TG) levels were observed. In addition, verjuice supplementation did not attenuate the rise of Total Cholesterol (TC) and Low-Density Lipoprotein (LDL) caused by feeding egg yolk. Similarly, there was no statistically significant difference in lipid levels between the rabbits in the second part of the study. No atheromatous plaque formation in histological examination of aorta secretions were observed in any rabbits, this includes those who were receiving verjuice with egg yolk and those receiving egg yolk alone. Aminian et al [24] found when supplementing hyperlipidemic individuals with 80 mL of verjuice daily for 2 months in a crossover prospective intervention a statistically significant lipid-lowering effect was not observed in most parameters. Specifically, they examined levels of

TG, TC, LDL, and HDL. The only statistically significant differences were a reduction in TC from 230 ± 40 mg/dL at baseline to 218 ± 32 mg/dL at the end of the supplementation period in the first group, and a reduction in TG from 278 ± 148 mg/dL at baseline to 226 ± 122 mg/dL at the end of supplementation period.

Further *in vivo* trials have been conducted that show more promising results. Mousa-Al-Reza et al. [25] induced hypercholesterolemia in mice and examined the effect of verjuice supplementation on serum lipid levels for 12 weeks. The study consisted of two controls, one receiving a regular diet and the other a high cholesterol diet, and four different treatment groups. The treatment groups consisted of two preventative arms receiving varying doses of verjuice at baseline (7 ml/kcal/d and 14ml/kcal/d), and two treatment arms receiving varying doses of verjuice initiated after 42 days of receiving the high cholesterol diet (7 ml/kcal/d and 14 ml/kcal/d). Findings include a significantly higher serum LDL level in both the preventative groups at the end of the study compared to the hyperlipidemic control group however no significant changes in this parameter were observed in the treatment groups. Verjuice did not change HDL or TC in any of the verjuice groups when compared to the hyperlipidemic control. TG was the only other blood lipid parameter which showed some beneficial changes in this study. Treatment of mice with high dose verjuice (14ml/kcal/d) decreased the serum TG levels significantly from 76.85 ± 5.1) when compared with the high cholesterol diet only group (101.85 ± 5.7).

Setkori et al. [1] set out to determine the acute effects of verjuice supplementation on blood lipid levels when rabbits were fed a high cholesterol meal. The study consisted of a control group, a high cholesterol group which received a 1% cholesterol meal without verjuice, a group which received 5 ml of verjuice in conjunction to the 1% cholesterol meal, and the final group whom received 10 ml of verjuice with the 1% cholesterol meal. No significant difference was found in the post-prandial lipid profile (TC, LDL-C, HDL-C, TG, apo-lipoprotein A1, and Apo-lipoprotein B100) between any of the groups. It is important to recognize that there was no significant change in any of these lipid parameters between the high cholesterol meal and the normal meal, suggesting that the cholesterol meal was ineffective at inducing a hyperlipidemic state. The lack of effect of verjuice in this trial may be related to the fact that the rabbits were normo-lipidemic and the lack of response from the acute dose.

A more recent trial by Setorki et al [26] examined the chronic effects of verjuice on lipid levels and other risk factors for atherosclerosis. The study consisted of four groups of rabbits identical to their previous study (one control, one high cholesterol, two verjuice and cholesterol), however, in this study the diet was carried out over two months. The high cholesterol diet was effective at significantly increasing the LDL level compared to the normal diet group. Contrary to their previous study, supplementation with 10 ml/d of verjuice with the high cholesterol diet significantly decreased the LDL level compared to the high cholesterol diet group without verjuice. A significant reduction was not observed between the low dose (5ml/d) verjuice group and the cholesterol only group suggesting a dose-response effect.

In humans, ZibaeeNezhad et al. [27] observed a significant increase in HDL and decrease in TC after 60 days of supplementing 20ml/d of verjuice. The study included 35 healthy men and women with a mean age of 43.3 years and BMI of 27.23 kg/m^2. Specifically, an increase in HDL from 35.83+40 mg/dL at baseline to 45.86+4.30mg/dL at the end of the intervention period was observed. No significant difference in LDL or TG was observed in this sample before and after verjuice supplementation. Interestingly, with verjuice supplementation TC was increased significantly by 5% from 190.46+17.3 mg/dL to 200+17.7 mg/dL. The authors attributed this increase to the significant rise in HDL that occurred concomitantly.

An insightful human intervention trial conducted by Alipour et al. [28] examined the effect of 200 ml verjuice twice per day for one month. The study was conducted on men only and consisted of three groups; thirteen healthy volunteers (20-30 yrs), eleven hyperlipidemic patients (30-60 yrs), and seven patients with hyperlipidemia and HTN (30-60 yrs). The study revealed that after one month of verjuice consumption LDL, HDL, TG, and TC in healthy volunteers were not significantly lesser than they were before consumption. Hyperlipidemic individuals however, saw significant reductions in LDL and TC after the 4 week intervention. Additionally, positive but non-significant changes were seen in TG and HDL:LDL. Similarly to the hyperlipidemic group, in patients that were both hyperlipidemic and hypertensive, a significant decrease in LDL and TC was observed. Additionally, these patients had significantly increased levels of HDL and proportion of HDL: LDL following verjuice consumption compared to baseline. These findings suggest that verjuice has a cardio-protective effect on individuals with abnormal blood lipids but little or no effect on normolipidemic individuals.

Effects on blood pressure

Nematbakhsh et al. [29] examined the acute effects of verjuice by supplementing four groups of rats with increasing amounts of concentrated, air dried verjuice and measuring Blood Pressure (BP) and serum nitrite level one hour following verjuice administration. The groups received saline (control), 125 mg of verjuice/kg, 250 mg of verjuice/kg, or 500 mg of verjuice/kg. In all treatment groups mean arterial pressure (MAP), systolic pressure, and diastolic pressure were less than the control group, however, significant changes only occurred at the dose of 125 mg/kg. In addition, the group receiving this dosage had a significantly lower heart rate (HR) one hour post verjuice administration than control. Interestingly, this study also tested the rats' response to angiotensin II infusion and found no statistically significant differences in BP level between groups. The researchers concluded that verjuice did not limit angiotensin II effects.

Verjuice may also show promise as an anti-hypertensive agent as evidenced by the human intervention by Alipour et al. [28]. which found a significant reduction in MAP at two and four weeks of verjuice supplementation compared to baseline in patients who were hypertensive. No significant changes in HR were observed for these patients and no significant changes to BP or HR were observed in any of the other groups of the study (healthy volunteers and hyperlipidemic patients).

Effects on inflammatory markers

Setorki et al. [1] observed significant differences in fibrinogen after consumption of a high cholesterol meal between both groups of rabbits receiving verjuice (high dose of 10ml/d and low dose of

5 ml/d) and the group receiving the high-cholesterol meal without verjuice. No significant differences between the doses of verjuice administered were observed. While the cholesterol only group had a significantly increased level of C-reactive protein compared to the normal meal, no significant differences were observed between either of the verjuice groups and the groups receiving the high cholesterol diet alone.

The study by Setorki et al. [26] that examined the effect of verjuice supplementation on inflammatory markers over a 2 month period found significant differences in fibrinogen between both doses of verjuice and the high-cholesterol diet. There was no significant difference in fibrinogen level between the two verjuice groups. No significant differences were observed in C-reactive protein and factor VII between the verjuice groups and the high cholesterol diet group.

Effects on oxidative factors

In healthy conditions, disease is prevented through a balance between free-radical generation and antioxidant defense system. This balance becomes disrupted in hyperlipidemic and hypertensive patients as evidenced by elevated lipid peroxidation products [10]. This is due to increased production of reactive oxygen species and increased oxidative stress. Malondialdehyde (MDA) reflects the oxidative status of the biological system, specifically both autoxidation and oxygen mediated peroxidation of polyunsaturated fatty acids. MDA causes damage to LDL which in turn forms foam cells [10]. Therefore it is a useful marker for oxidation that can be used in research.

Supplementation with 10 ml/d of verjuice in rabbits consuming a high cholesterol diet was found to significantly reduce MDA three hours after receiving the verjuice compared to rabbits consuming the same high cholesterol diet alone [1]. In this study feeding rabbits a high cholesterol diet was effective at increasing the MDA levels as evidenced by the significant difference between this group and the group consuming a normal diet. A significant difference between these two groups was also observed for oxidized LDL (ox-LDL). In addition, ox-LDL was significantly reduced in rabbits who consumed the 10ml/d of verjuice compared to those on the high-cholesterol diet alone. The differences in both MDA and ox-LDL between the two doses of verjuice (10 ml and 5 ml) were not significant. When these diets and treatments are administered over a two month period MDA and ox-LDL were significantly reduced in the rabbits consuming the high dose of verjuice compared to those on the high-cholesterol diet alone [26]. The differences in MDA and ox-LDL between the two doses of verjuice were not significant.

The human intervention by Alipour et al [28] assessed both MDA and Total Antioxidant Capacity (TAC) in three groups of individuals. MDA levels were significantly higher in the hyperlipidemic patients than the healthy volunteers. In the hyperlipidemic patients specifically, the mean amounts of MDA were significantly reduced after two and four weeks of verjuice supplementation compared to baseline. Interestingly, this reduction was greater at four weeks compared to two weeks. Hyperlipidemic patients also saw an increase in TAC over the 4 weeks which again, was influenced by time as the levels were high at 4 weeks compared to 2 weeks. A significant reduction in MDA was also observed following verjuice supplementation in patients with both hyperlipidemia and HTN. TAC for two and four weeks after starting the trial were significantly higher than the corresponding levels at baseline in healthy individuals and the index of lipid peroxidation was significantly reduced in response to four weeks verjuice consumption. Finally, patients with both hyperlipidemia and HTN saw a significant reduction and significant elevation in plasma levels of MDA and TAC, respectively.

From these results it can be concluded that due to its antioxidant properties, verjuice consumption increases the TAC and helps to eliminate the harmful effects of free radicals. Therefore, its beneficial effects may be related to this antioxidant effect [28].

Effects on endothelial function

Endothelial dysfunction is associated with the onset and progression of various forms of CVD including, but not limited to, HTN, coronary artery disease, chronic heart failure, and peripheral artery disease [30]. The actions of the endothelium are shifted to reduced vasodilation, a pro-inflammatory state, and prothrombic properties and hence, endothelial dysfunction precedes development of atherosclerosis [31]. Therefore, the severity of endothelial dysfunction has been shown to be an independent predictor for cardiovascular events [30,31]. Reduced nitric oxide generation, among other factors, is the underlying mechanisms contributing to reduced vasodilatory responses [30,31]. Correction of endothelial dysfunction is associated with reduced cardiovascular risk and hence, the effect of verjuice on nitric oxide levels is worthy of investigation.

In the study by Nematbakhsh et al [29] described previously, verjuice supplementation increased the serum nitrite level in all treatment groups significantly when compared to the control. Furthermore, both studies by Setorki et al [1,26] looking at acute and chronic effects of verjuice supplementation found that serum nitrite level in the animals receiving a high cholesterol meal/diet was significantly increased compared to the normal meal/diet control animals. The acute effects of supplementation of 10ml of verjuice with the high cholesterol meal induced a significant decrease in nitrite compared with the high-cholesterol meal alone. There was a non-significant reduction in nitrite in the low-dose verjuice (5mL/d) with high-cholesterol diet compared with the rabbits fed the high cholesterol meal alone. A significant difference in nitrate concentration was observed between the high (10ml/d) and low (5ml/d) dose verjuice meals, with the high-dose diet being lower in concentration. This, along with previous findings from Nematbakhsh et al [29] indicate that verjuice may only exert a beneficial effect at a certain dose. No significant difference in nitrate concentration was found between 5 and 10 ml of verjuice with the high-cholesterol meal compared with the high-cholesterol meal alone. Contrarily, the study examining the chronic effects of verjuice supplementation saw a significant increase in nitrite and nitrate levels in both the high and low verjuice groups compared to the high cholesterol alone diet. No significant difference in either nitrite or nitrate was found between the two doses of verjuice. These conflicting findings exemplify the necessity for further research in this area.

Effects on glycemic control

Post-prandial serum glucose level was observed to be significantly higher in Setoki et al.'s [1] intervention in rabbits who were subject to a high cholesterol meal compared to those fed a normal meal.

Following concurrent use of 5ml/d (low-dose) or 10 ml/d (high-dose) of verjuice with the high cholesterol meal, the glucose level post-prandial was significantly decreased compared to the cholesterol-only group by approximately 10-20 mg/dL, respectively. However, no significant difference was found between the two doses of verjuice administered. This was the only study identified which examined the effect of verjuice consumption on glycemic control.

Effects on fatty streak formation

The 2011 *in vivo* trial by Setorki et al. [26] described previously also examined the effect of verjuice supplementation on fatty streak formation. Histologic examination of the coronary arteries revealed that atherosclerotic changes were absent in normal diet group whereas many fat-laden macrophages were present in the high-cholesterol diet group. In this group, the cytoplasm of the macrophages filled with lipid droplets as a result of lipid digestion by the macrophage. Plaque thickness was also increased to more than half of media thickness, equal to degree 3 of the Chekanov scale. The Chekanov scale is an arbitrary atherosclerotic thickness grading from 1 to 4 described by Chekanov and colleagues in 2003 [32] The groups receiving verjuice supplementation with the high-cholesterol diet had some evidence of endothelial dysfunction as indicated by foam cells and macrophages on the coronary arteries. These changes were reflective of a plaque degree of 1 on the Chekanov scale. Atherosclerotic thickness grade in the groups supplemented with verjuice decreased significantly compared to the high-cholesterol diet group [26].

Limitations of current literature

The effect of verjuice consumption on risk factors for CVD, while promising, are still ambiguous and contradictory requiring further investigation. Randomized controlled human intervention trials are limited in this area and therefore, more carefully and strategically designed research is warranted. Unfortunately, the phytochemical composition of the verjuice is rarely specified in the presented research. Only three animal trials made an attempt to report on this [1,26,29] and none of the human intervention trials made mention of the phytochemical composition of verjuice despite reporting an antioxidant potential [24,26,27]. Due to the varying stages of ripeness, grape species, verjuice storage condition (temperature, light, freshness), and method of juice extraction that could be present, it is important for future studies to analyze the phytochemistry of the juice as this could have an important and significant impact on the research findings. This could also explain some of the conflicting findings reported in the reviewed research. In addition, it is unclear from the currently published human intervention trials if additional dietary factors are acting as confounders as their diets during the treatment periods were not quantified. While one study did report that a registered dietitian instructed the control participants to maintain the same diet [24], it is well documented that diet has a profound impact on CVD risk factors. For this reason, research moving forward should make every attempt to control for potential dietary confounders and quantify additional sources of phytochemicals that may affect the results.

Conclusion

Verjuice may have significant beneficial cardio-protective effects through normalization of blood lipids and other CVD risk factors in hyperlipidemic patients [24,28]. Further research in this area which quantifies the phytochemical profile of the supplemented verjuice is warranted to support these findings. Furthermore, the effective dose required to infer the maximum health benefit it is currently unknown. Future research on humans should include multiple groups receiving varying amounts of verjuice with a similar phytochemical profile to ascertain evidence on the appropriate dose of verjuice required to allow for the development of recommendations.

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