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Review Article

A REVIEW ON ROLE OF BERRIES AND ITS BIOACTIVE COMPOUNDS IN TREATING HYPERTENSION

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ABSTRACT

Objective: Hypertension or raised blood pressure leads to the occurrence of morbidity and mortality rate among peoples and it was considered as the primary factor for the occurrence of various cardiac and vascular disorders include ischemic cardiac disease, myocardial necrosis, cardiac failure, renal disorder, atherosclerosis, and cerebrovascular accident. Called "silent killer" because hypertension is an asymptomatic disease in the early stages with no indications on suffered patients and leads to act as a significant factor for the occurrence of severe other cardiovascular diseases (CVDs). As berries show considerable interest in improving cardiovascular diseases because they are rich in polyphenol contents and bioactive compounds. Besides their single usage, a polyherbal combination is much better for the treatment of hypertension.

Methods: The data were collected by reviewing a combination of research and review papers from different databases such as PubMed, Medline, ScienceDirect, and Web of science using search keywords such as "hypertension," "cardiovascular disease," "berries," "cranberry," and "red raspberry" with all their synonyms and related terms.

Result: Various studies shown better associations between higher berry flavonoids and other polyphenolic components and lower the risk of cardiovascular disorders. Based on various scientific evidence, the characteristic of various biochemical processes is treated by berries with its antioxidant, antihypertensive, and anti-sclerotic and other properties.

Conclusion: This paper concludes that in the present day, there is a global increase in berry consumption, which is used in the ailment of various cardiovascular diseases. The studies which are held are needed to define their optimal dose, process, or method of preparation (formulation) and the duration of berry intervention so that these showed better treatment options for hypertension.

Keywords: Hypertension, Cardiovascular disorders, Red raspberry, Cranberry, Anthocyanins, Ellagitannins.

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INTRODUCTION

Globally hypertension (HTN) disease is the most potential growing disorder which is defined by when systolic blood pressure (SBP) is ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg [1-3]. The prevalence ratio of the patients suffering from hypertension are high and raised high blood pressure is most considering factor of other chronic comorbidities [4]. On various communal well-being problems and the healthcare organizations of Indian system have suffered from high blood pressure, which exerts a high impact on these systems in respective humankind [5]. As such, it is estimated that in India, high blood pressure leads to 57% of mortality with stroke and 24% with chronic heart diseases [6]. The blood pressure of an individual is rising with growing age, and hypertension is the most communal chronic non-transmissible disease which is produced either by natural and lifestyle aspects and leads to changes in blood dynamics by arterial stiffness and the major changes showed in the elastic arterial vasculature (aorta), invade the changes in systolic blood pressure and diastolic blood pressure for the occurrence of isolated systolic hypertension in adults [7]. Several cardiovascular diseases have a major effect on personal health in addition to weakness and premature death, which consist of diabetes, smoking, and dyslipidemia. Hypertension is the most widespread activating mediator for CVDs and causes 16.5% of once a year death worldwide and the main reason for sickness and death by cardiovascular disorders in the human populace. Hypertension causes renal disorders, memory loss, or vision loss along with atherosclerosis, stroke, heart failure, and peripheral artery disease because it can play a major part in the onset of these disorders [8]. The individuals who are suffering from hypertension are usually asymptomatic and hence it is described as "silent killer" and it arises from the various genetic abnormalities which cause a minor elevation in blood pressure, but contribute to 30–50% of the individual patient variation about natural and lifestyle aspects which are important and causes fluctuations and elevation in the blood pressure (BP). Commonly remedies/ medicines such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, contraceptive tablets (hormonal), calcineurin inhibitors, and foods which are responsible for the elevation in the lifestyle, dietary patterns in which low consumption of fruits and vegetables, high-fat diets which ultimately lead to hypercholesteremia and correspondingly elevated the levels of blood pressure, and causes hypertension [9,10].

Hypertension is classified into two divisions as primary (essential hypertension) and secondary hypertension. At an earlier age, secondary hypertension occurs with no personal history, as it is caused and triggered either by the kidney, hormonal disorders, or by use of birth control pills. The guiding principle proposed the study that secondary hypertension usually occurred in those who are <40 years of age. The collaboration between natural, genetic, and daily routine factors influences the mid-age or old age individuals and leads to cause essential (primary) hypertension [3,11]. About 5–10% of hypertensive patients, the cause or agents which are responsible for hypertension are elucidated by vigilant assessment and broadly categorized into renal, vascular, endocrine, and neuronal problems. Hypertension divided into four types depending on the level of diastolic blood pressure and some specific pathological changes and these changes responsible for superimposed functional vasoconstriction (narrowing of blood vessels) which have been reviewed by Edward Freis and these are severe hypertension (SBP: above 180 mmHg and DBP: above 115 mmHg), moderate hypertension (SBP: 160–180 mmHg and DBP: 95–114 mmHg), and mild or borderline hypertension (SBP: 140–160 mmHg and DBP: 90–95 mmHg) [12]. The interruption of numerous mechanisms comprises a sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), sodium water retention, which upholds the standard pressure in the blood leads to the manifestation of both primary and secondary high blood pressure disease and any misleading in these systems are responsible for the development and pathogenesis of the disease in an individual patient [13,14]. The pathogenesis of high blood pressure showed by distress in arteries of the vascular region either large arteries (aorta) or small arteries occurred in arterioles and capillaries. The increase in sensitivity and potency of arteries causes dysregulation and disruption in endothelial nitric oxide synthase, which excite and activate calcium channels due to augmented hyperactivity. Constriction in vessels is caused by vascular smooth muscle cell (VSMC) hyperplasia and hypertrophy, and these extreme variations lead to an upsurge in the proportion of vessel wall thickness as compared with the thickness dimensions of the arterial lumen. It is the basic caused by the development of hypertension and increased thickness ratio plays a foremost role in demonstrating the illness [15]. For care of standard blood pressure, the two important factors are cardiac output and peripheral vascular resistance, resulting from the sympathetic dysfunction and dysregulation which ultimately act as triggering agent for the progress of hypertension disease and causes fluctuations in the physiological responses and disrupt the homeostasis of an individual patient of hypertension [16]. The stimulus either naturally or genetically is responsible for SNS and regulation of renin release due to which the electric impulses generate in heart and kidney for the cardiac functioning and the performance of heart for blood circulation [17]. Endothelial dysfunction (ED) is another cause of hypertension which is caused by a reduction in the accessibility of nitric oxide (NO) because of augmented oxidative pressure in an individual patient. The factor which is initiated and has a potential effect on the blood vascular system is endothelial dysfunction, which leads to increased pressure on blood vessels and causes hypertension, which is proved by various shreds of evidence and studies whose main purpose to inhibit endothelium-derived NO synthase [18-22]. As there are various treatment options for hypertension such as pharmacological and non-pharmacological and herbal remedies. The pharmacological treatment is based on antihypertensive drugs such as indapamide, furosemide, clonidine, reserpine, aliskiren, enalapril, losartan, irbesartan, olmesartan, nifedipine, verapamil, diltiazem, prazosin, doxazosin, nebivolol, atenolol, minoxidil which are bind with particular receptors and mechanism of action which used to accomplish the blood pressures stages [23,24]. Most of the individuals who are suffered from hypertension are also undergo for non-pharmacological treatment with pharmacological treatment. As per the appropriate diet and lifestyle activities play a vital role in reducing hypertension. The maintained healthy lifestyle of one individual restrict the occurrence of high blood pressure [25-27]. Moreover, cessation of smoking leads to benefit changes and various studies show reductions in systolic blood pressure [28].

ROLE OF BERRIES

This is due to more than a few aspects, intentions that showed herbal drugs used in the past years [29] and today's era which states that herbal medicines are an economical substitute and employing less and undesired side effects and adverse drug reactions as compared to chemical entities manufactured drugs [30,31]. As it was known, plants and herbs can act as a preliminary point for the synthesis of many pharmaceutical drugs [32]. The plants/herbs such as *Coriandrum sativum* (Cilantro or Coriander), *Crocus sativus* (Saffron), *Cymbopogon citratus* (Lemongrass), *Rubus idaeus* (red raspberry), and *Vaccinium macrocarpon* (cranberry) can play favorable effects and dynamic role on molecular, biological, and cellular paths which are modulated by their active compounds or their extracts to treat high blood pressure disease, as shown in Fig. 1.

As berries are loaded with antioxidants which keep free radicals generation under control and diminished the risk of diseases. Due to low calories and effective phytoconstituents present in berries, they were produced a lot of attention in the current years [33]. *In-vitro* researches, trials held on an animal which designed to investigate their potential bioactive constituents. However, their results obtained and it should be interpreted with care [34]. Various phytochemicals and bioactive compounds are found in berry fruits which particularly contain polyphenolics with a high content of phytoconstituents flavonoids which include anthocyanins, quercetin, salicylic acids, and ellagitannins [35,36]. The secondary metabolites which are present in many berries or other fruits and green vegetables are polyphenols. Anthocyanins, flavan-3-ols, flavonols, flavanones, flavones, and isoflavones are polyphenols, but in berries, the most plentiful class of flavonoids is the anthocyanins. For human life, nourishment and diet are a vital factor which affects daily life, including cardiac disease, diabetes mellitus, overweightness, and Alzheimer disease. By consuming a balanced diet helps to elevate or reduced the causes of several non-communicable stages of development includes CVDs, Type-II diabetes mellitus, and cancer and neuron disorders. Numerous research and studies related to *in vitro* and animal studies are directed to examine the pharmacological mechanisms berry bioactive compounds either in a small and higher dose of polyphenols. As many of these researches used compartment lines which have complex usage of berry extracts. The nanomolar absorptions are rarely used as the subsequent incorporation in which berry polyphenols appear in plasma fluid, not as the original component, but they were shown their presence in the

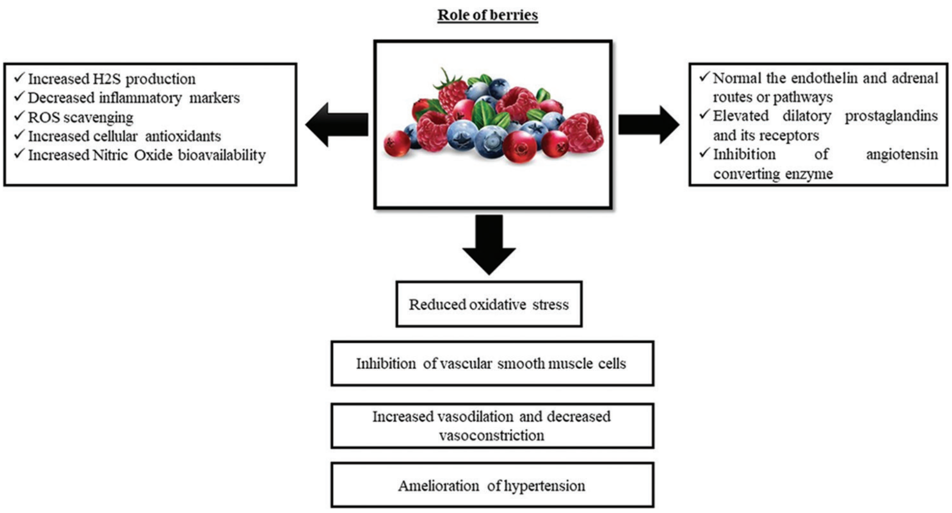

Fig. 1: The importance of berries on different pathways to reduce hypertension

circulatory fluid system after phase-II metabolism biotransformation process [37].

The two main berries specifically mentioned that is cranberry (*Vaccinium macrocarpon*) and red raspberry (*Rubus idaeus*) which evaluates the health-promoting potential and their selected mechanisms used in controlling the risk of contemporary long-lasting illnesses, precisely cardiac disorder. Therefore, the chief objective of this review paper remained to inspect the present scenario and indication on the cardiovascular protective effects of these berries against hypertension with possible mechanisms of action and underlying beneficial effects on human health.

RED RASPBERRY (*RUBUS IDAEUS, FAMILY: ROSACEAE, GENUS: RUBUS*)

The red raspberry (*Rubus idaeus*) is found in Asia and the northern hemisphere. As these are economically and important species which are needed and globally consumed in the form of whole crushes, gels, jams, sauce, juices, pulps, and pastes, but another species consumption by individuals such as black raspberries (*Rubus occidentalis*) is less in range. The foremost emphasis of this assessment will be on red raspberries (*Rubus idaeus*) [38]. As per the botanical aspects of raspberries, as the genus, Rubus is the assemblage of about 250 different types which was further classified in more subgenera. The lifetime planting of red raspberries is about 10–15 years and their fruits were full-grown in three stages, in which each segment continues from 9–12 days. They were having an attractive flavor and color and it will reach extreme when it becomes fully matured and change into drupelets form. The fruit form of cultured raspberries has 5–6 g, but in most of the certain circumstances, the fruit mass overdoes up to 10 g [39]. The berry is the collection or the aggregation of fruit formed by solitary seeds which are called drupelets in an individual form and attached with hairy structures [40]. These berries are having several pharmacological properties and remedies which are traditionally used by human-being. Temperature regulator activity (pyrexia) treatment, gastrointestinal activity, cardiac problems, diabetes are commonly treated. The green leaves of berry fruits were used to inhibit the bacterial infection, act as an anti-inflammatory which is topically applied on the skin for treatment. The extract portion of berries leaves has two main actions which include an active muscle-relaxant property and has antispasmodic activity [41]. The raspberries are made up of vastly gratified antioxidant essentials such as ascorbic acid (Vitamin C) and various polyphenolic phytoconstituents compounds. In addition to their properties such as attractive colors and superior quality flavor, raspberries contain a unique profile which is rich in phytochemical constituents such as ellagitannins and anthocyanins. As ellagitannins are complex structures hydrolyzable by-products of ellagic acid. Ellagitannins and ellagic acid have a wide variety of biological activities such as antioxidant, antimutagenic, antineoplastic, and antiviral on human well-being. Whereas the other phytochemical constituent called anthocyanins were presented in *Rubus idaeus* (Rubus berries), and it comprises of large spectra of natural pigments. The differences between these two contents of ellagitannins and anthocyanins are testified in berries due to discrepancies in the production process and the genomic aspects [42].

The raspberries are virtuous source essential mineral deposits, saturated, and polyunsaturated fatty acids and also an extensive range of polyphenols bioactive phytochemicals compounds. As red raspberries have high nourishment value on human health. Moreover, among these, they also contain ascorbic acid (Vitamin C), Vitamin K, and macroelements such as magnesium, potassium, calcium, and iron [43]. The nutrient composition of red raspberries which is freshly cultivated is having a high amount of nutritional diet [44].

PHYTOCHEMICAL CONSTITUENTS

In raspberry, as phytochemicals or phytoconstituents are the secondary metabolites of the plant which is commonly defined through non-essential herbal ingredients which have the pharmacological activity and helps in the ailment of different diseases because they act as herbal remedies. As in berries, there was a large number of polyphenols which act as one of the largest constituents and consumed by living human and animals in any form. These were classified into hydroxybenzoic and hydroxycinnamic acids to complex polyphenols such as hydrolyzable and condensed tannins, depending upon its chemical structures [41,45]. The flavor and color of the berries are due to anthocyanins [46]. Moreover, these phytochemicals which were present in berries as mentioned in Table 1 help in the ailment of various diseases such as cardiac disorders, overweightness, and tumor growth [47-49].

In raspberry, the flavanols content is about 2–48 mg/100 g fresh weight [51-53], the daily consumption of these flavonoids (1g) is helpful to make the human diet complete [54,55]. It includes a subclass which was classified based on the connection between the two aromatic rings and also based on oxidation states of different rings, and these are catechin, epicatechin, proanthocyanidins, flavonols quercetin, anthocyanins, and cyanidin, found in red, blue, and purple berries [56].

Anthocyanins

It is a flavonoid compound found in many berry drupelets and green vegetables, and it is a water-soluble entity. Anthocyanins are conjugated anthocyanidins, which are present and accumulated in cell vacuoles and responsible for the diversity of colors from orange to red, purple, and blue and red in most of the flowers, fruits, and vegetables [52,57-62]. Anthocyanidins such as cyanidin, peonidin, pelargonidin, malvidin, delphinidin and petunidin, glucose, rhamnose, galactose, arabinose, xylose, rutinose, sambubiose, and others were also found [63]. The basic backbone of anthocyanins is made of C6-C3-C6 and it is mainly for the formation of red color for the drupelets of red raspberry. Moreover, most of the bioactive constituents have a property to inhibit the oxidation process which causes various diseases [64]. High-performance liquid chromatography (HPLC) is used to determine anthocyanins components and their contents are varying in different researches due to climatic variances, evolving phase, numerous dissimilarities, and also usage of a variety of methods used to enumerate the complexes [65-67]. The range of anthocyanins in the diet is in between 3 and 214 mg/d [61,68].

The bioavailability and bioaccessibility can be defined as rate and extent absorption of consumed complexes which absorbed by the bloodstream and transfer to tissues and organs to change physiological responses

Table 1: Major phytochemical constituents found in red raspberry [50]

S. No.	Class	Phytoconstituents	Compounds	mg/100 g
1.	Flavonoids	Anthocyanins	Cyanidin-3-sophoroside	25.4
			Cyanidin-3-glucosylrutinoside	7.2
			Cyanidin-3-glucoside	3.9
			Cyanidin rutinoside	2.3
2.	Phenolic acids	Hydroxybenzoic acid	Gallic acid	21.5
		Hydroxycinnamic acid	Cinnamic acid	0.27
3.	Tannins	Ellagitannins	Ellagic acids	0.11
		Proanthocyanidins	Anthocyanidins	78.8
4.	Lignans		Secoisolariciresinol	0.02

on humans [69] and whole overall process leads to the consequence of pharmacokinetics of ingested compounds. The bioavailability of the various polyphenols presents in red raspberries has studied in different studies such as pre-clinical and clinical trials [70-72]. The biochemical transformation of polyphenolic compounds is held earlier and then absorption takes place by circulatory fluid. In general, anthocyanins show lower absorption than others as it absorbed in their glycated form [73,74]. After consumption of anthocyanins, bioabsorption of it is occurring quickly. The plasma concentration (maximum) reached after 15–60 min but consumption with an especially rich fat diet reduced the time-lapse of stomach emptying, then it is level can high after 4 h [75,76]. Egestion of these compounds is characteristically complete within 6–8 h. Anthocyanins are absorbed through two mechanisms one is energetic transport (active) by sodium-glucose cotransport and the other is by hydrolysis of the sugar moiety by brush border. In this transporter theory, the anthocyanins with various sugars and its supplementation are reduced their excretion [77]. The anthocyanins present in berries are directly absorbed in the bloodstream. In animals, the absorption of anthocyanins is done by the gastric and intestine part [78,79]. The studies show that the part of the large intestine that is colon and ileum does not involve in the absorption of anthocyanins and the duodenum region and the jejunum region involved in absorption where it can bind with bilitranslocase enzyme [80-82] and absorption takes place by gastric part [83]. The phase-II biochemical transformation held by glucuronidation, methylation, and glycation and these make the metabolic pathways saturated [84]. The structures which discharge absorption from small intestine continue to the colon where these were transformed to phenolic acids by microbes which were existing in the inferior bowel, and after which they defecated in feces and absorbed in mesenteric circulation [85-87].

The extraction and separation of anthocyanin pigments are held by different techniques in which qualitative and quantitative analysis is done. The anthocyanin pigments are positioned in compartments cells of the external surface [88]. For the extraction, the researchers used acidic solvents, methanol, and hydrochloric acid because of many properties such as denaturation of the cell membranes, liquify the components or pigments, their high boiling points, low Ph, availability of favorable environmental condition, and a medium to form flavylium chloride salt. When the materials are concentrated, then they were extracted with ethyl acetate, methanol, petroleum ether to remove oils, and undesirable phenols [89,90]. After extraction, the refinement and parting of anthocyanins supported by different chromatographic procedures, in which the chief and utmost applicable is paper chromatography [91,92]. HPLC used as preparative work, but only for quantitative analysis [93,94]. There is a large category of developing solvents which can purify the contents based on the nature of compounds [95].

Biological activity and mechanism of anthocyanins polyphenolics compounds found in red raspberries nowadays, significant in the ailment of long-lasting diseases include cardiovascular diseases [96]. The pharmacological action of anthocyanins compound is depending upon the chemical structure of the compounds. The mechanism of action deals with inhibition of inflammatory process, ED, and imbalance NO production, disrupts the oxidative agents which ultimately disturbed the formation of deoxyribonucleic acid (DNA), proteins, lipids, and reactive oxygen species (ROS) [97,98]. The mechanism is followed the two ways either by systemic (bloodstream action) or locally (gut) and by many ways of administration either orally or topically (protect the skin) [99].

Atherosclerosis or coronary artery disease leads to the potential cause of various cardiac disorders and eliminating this anthocyanin has the capability in their bioactive compounds which can reduce the effect by acting on various cells. The monocyte chemotactic protein (MCP)-1 is a type of macrophages cell induced by tumor necrosis factor (TNF)-α which acts as a mediator at the infection site, inflamed area, and involved in formation on atherogenesis. Moreover, the bioactive compound anthocyanins involved its action on TNF-α on the endothelium layer (cells) of blood vessels [100]. VSMC is inhibited by anthocyanins [101]. The oxidative stress which is caused by postprandial hyperglycemia can lead to disruption of the endothelium layer of blood vessels; fruits can show effectiveness in reducing blood pressure by inhibiting the Angiotensin-converting enzyme-1 [102,103].

Ellagitannins

The tannins which are present in plants are water-soluble components and act as protective defensive compounds against the pathogens and oxidative stress [104]. Ellagitannins formed in berries are the more potent active phytoconstituents which are hydrolyzable and have high stability properties with respect to other condensed tannins [105]. Hexahydroxydiphenoyl moiety comprises either glucose or quinic acid core, galloyl clusters which are connected with glucose central part. As when ellagitannins break down in acidic and basic solvents, they release hexahydroxydiphenoyl complexes which certainly form ellagic acid and this reaction is used for recognition food which contained these tannins [106,61]. Various ellagic acid derivatives, including acylated/glycosylated compounds, are also found and identified in berries. The extract portion, fruit pulp, whole crush, of various berries show high content of ellagitannins which was determined by various studies. Hence, as per its multifaceted construction of compounds found in berries showed its content by HPLC and their content is varied according to seasonal and variations aspects [107].

The pharmacokinetics of ellagitannins states that it is the partial breakdown in the stomach to hydrolyze it and causes the release of ellagic acids. The research study was done by Daniel *et al.* [72] who found that breakdown of ellagitannins components or biomolecules produced from raspberry extracts was not undergone the catalytic process of any enzymes in the model of isolated rat intestine, but the breakdown optimally held after 1 h of occurrence in the presence bacterial content of the caecum region of the large intestine of rats in an alkaline pH 8 [108]. Urolithin B is produced when ellagic acid and ellagitannins are undergoing a metabolic process by microorganisms such as bacterial species (*Gordonibacter urolithinfaciens* sp.) present in the colon region and their samples were recognized in bloodstream and urine of the human being [109]. The pharmacological action and biological activity of ellagitannins found in berries showed good relaxation in blood vessels and maintained the endothelium layer and have vasodilation capabilities.

The unhealthy diet and lifestyle is the cause of disease and the red raspberries healthy effects may change the severe effects such as disruption of SNS, disruption of vascular diseases as mentioned in Fig. 2. The phytoconstituents can stabilize the abnormal physiological responses and manifest improvement in vascular function, decreased atherosclerotic development, and improved brain injury in pre-clinical models. Atherosclerosis and plaque formation in vessels are the chief cause of hypertension and intensive study for supervisory claims [110-112]. The poor lifestyle and poor diet and obesity are the various physiological parameters which can modulate these mechanisms and show manifest in the pathogenesis of cardiovascular disorders and human health conditions.

As we know, that endothelial disruption and dysregulation are caused by reduced levels of nitric oxide because it can act as a mediator and for the better efficacy of the blood vascular system and its homeostasis maintained by vascular endothelium layer of blood vessels [113-115]. Due to extremely reactive oxygen species, nitric oxide is damaged due to high oxidation and causes fluctuations in the molecular level by disruption of the signaling pathway of eNOS/NO and inhibits endothelial function [116]. Due to reduced levels of nitric oxide in the body, there is a chance to develop necrosis, ischemia, deposits of fats in between blood vessels, and ultimately produced atherosclerotic plaque and causes vasoconstriction in blood vessels. In various animal studies, it was determined and consider under the hypothesis that the extracts of these berries reduce the activity of oxidative stress and inhibits the formation of free radicals in the body [55,117,118], responsible for hypothesized mechanism in the pathology of chronic diseases. Despite the antioxidant activity of red raspberries, the various other beneficial effects have occurred which are trigger the enzyme activities, biomolecular pathways, and genomic levels [119]. Red raspberries also demonstrated anti-atherosclerotic, reducing the oxidized-LDL formation and anti-inflammatory activities which may provide better protection against cardiovascular diseases such as stroke and hypertension as mentioned in Table 2 [120-123].

CRANBERRY (*VACCINIUM MACROCARPON, LOWBUSH CRANBERRY*)

Furthermore, termed as American cranberry, belongs to the Ericaceae family. North America, Canada, Chile are the most productive regions for cultivation of cranberries all over the world and these regions are collect highest production of berry fruit which is rich in antioxidant value [124]. This cranberry drupelet is the source of polyphenols bioactive compounds, with anti-inflammatory and antioxidant properties in various research models [125].

PHYTOCHEMICAL CONSTITUENTS

The phytochemical constituents and bioactive compounds of the cranberries have different kinds of phytochemical constituents. Vaccinium berry fruits ultimately modulate the manufactured and processed fruits pulps, extracts by maintaining its stability conditions and variations. Kaempferol, quercetin, and myricetin are found in less quantity, but quercetin glycosides are mostly found and their total content is about 200–400 mg/kg fresh weight of drupelets. Cyanidin, peonidin, malvidin, pelargonidin, delphinidin, and petunidin are the major class of biological constituents which involved in pharmacological actions. Hydroxybenzoic acid and hydroxycinnamic acid are the polyphenols which are found in berry fruits and have a potent mechanism of action for elevating the molecular signaling pathways [126-128].

The bioavailability of bioactive compounds showed in plasma at 45–270 min as per the consumption of cranberry juice [129]. After consumption of juice in human urine, there is the presence of the

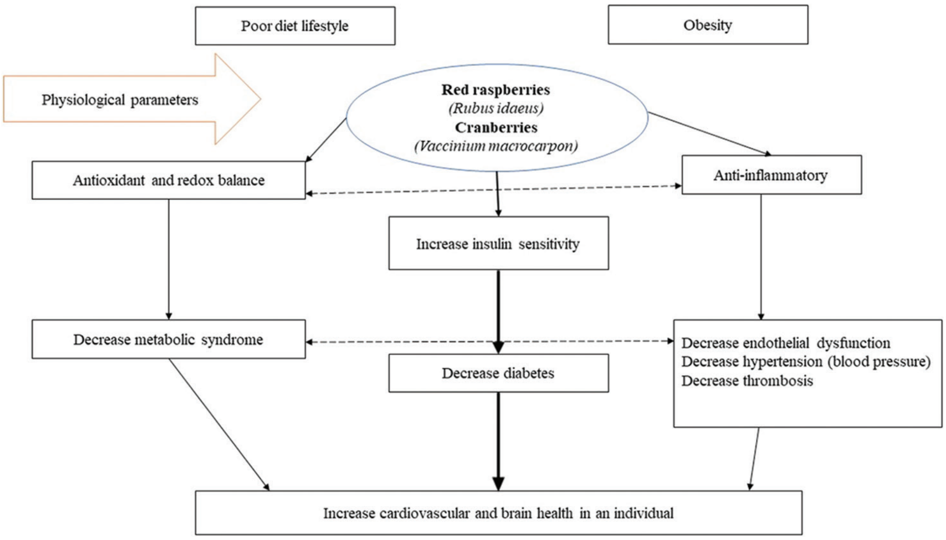

Fig. 2: Berries health benefits of cardiovascular physiological systems

Table 2: Study details of red raspberry effect on biomarkers to treat hypertension

S. No.	Study	Model type	Study details	Biomarkers	References
1.	Yu *et al.*	Endothelial cells *(in-vitro)*	EA effect on IL-β, induced intracellular ROS leads to translocation of NF-κB.	↓ ROS ↓ monocyte adhesion	[142]
2.	Chang *et al.*	RASMC *(in-vitro)*	EA effects on oxidized, LDL induced proliferation, causes activation of cell cycle Activate cell signaling kinases.	↓ oxidative stress	[143]
3.	Ding *et al.*	Endothelial cells; mouse aorta rings *(in-vitro)*	Oxidative stress-induced ED by a high-fat diet of EA	↓ oxidative stress	[144]
4.	Chao *et al.*	Albino mice (in-vivo)	Diabetic mice/EA treatment	↓ oxidative stress, ROS ↓ inflammation in heart tissues	[145]
5.	Yu *et al.*	New Zealand rabbits (in-vivo)	EA treatment.	↓ ROS ↓ caspase-9,8	[146]
6.	Lin *et al.*	Doxorubicin-induced mice (in-vivo)	EA treatment against doxorubicin-induced cardiotoxicity.	↓ ROS ↓ oxidative stress	[147]
7.	Panchal *et al.*	Metabolic syndrome rats	The high-fat diet was given to induce metabolic syndrome	↑ CPT-1 ↓ NF-κB in heart and liver	[148]
8.	Mullen *et al.*	Aorta rings (in-vitro)	Extracts of red raspberries.	↓ SOD, GPx	[121]
9.	Pieszka *et al.*	Male Wistar rats (in-vivo)	The seed oil of red raspberries.	No effect on CRP, Thx-b2	[149]
10.	Freese *et al.*	Healthy human study	Randomized control trials on humans.		[150]

↓: Increase, ↑: Decrease, EA: Ellagic Acid, CRP: C-reactive proteins, SOD: Superoxide dismutase, GPx: Glutathione peroxidase, NF-κB: Nuclear factor kappa B

Table 3: Study details of cranberry (whole/raw/juices) are used to treat metabolic disorders

S. No.	Study	Berries	Model Type	Effects	References
1.	Lee *et al.*	Extracts of cranberries	Overweight adults with T2D	↓ total cholesterol, LDL-C ↓ total cholesterol, HDL-C.	[151]
2.	Wilson *et al.*	Whole cranberry	Obese elderly adults with T2D	↓ in postprandial insulin and glucose.	[152]
3.	Basu *et al.*	Cranberry juices	Obese adults with metabolic syndromes	↑ plasma antioxidant capacity ↓ oxidized LDL, MDA.	[153]
4.	Ruel *et al.*	Cranberry cocktail juices	Adults with abdominal obesity	↑ in plasma HDL-C and apolipoprotein.	[154]

↓: Increase, ↑: Decrease, T2D: Type 2 Diabetes, LDL-C: Low-density lipoproteins cholesterol, MDA: Malondialdehyde, HDL-C: High-density lipoproteins cholesterol

compound and the polyphenols are rapidly absorbed by the gut, whereas the high phenolic compounds reabsorbed by the large intestine and showed less bioavailable to blood [130].

Cranberries used in cardiovascular health, in which previous studies of berry researches by the scientist who use its juice form and show a potential and beneficial effect on blood pressure as mentioned in Table 3 and reduce the risk factors of cardiac diseases which relate to the manifestation of hypertension, stroke, arterial stiffness, ischemic necrosis on heart, and endothelial dysfunction [131,132]. For the clinical trial of cranberry fruit liquor, the volunteers are healthy humans and the patients suffered from severe diseases such as coronary artery disease (CAD), type 2 diabetes mellitus [133-135], the dosage is increasing every 4 weeks ultimately reduced SBP up to 3 mmHg [136]. The dosage of cranberry juice also reduces DBP [137]. The vasodilation property is mediated as per the bioavailability of nitric oxide release in the blood with the stimulation of endothelial cells and whose impairment leads to cause different cardiovascular disorders [138]. Due to oxidative stress caused by free radicals, hypertrophy leads to cause of cardiac remodeling which is a life-risking factor and has disruption of cardiac layers and heart in respect to its size, structure, and functioning. Due to osteoporosis, there is an extensive removal of calcium levels from the body [139,140].

Hence, these berries are consumed by individuals by formulated preparation either in the form of whole crush, jams, jellies, and juices. However, the jam form formulation is widely and applicable because it is a mixture of several fruits that include raspberry, blueberry, mulberry, cranberry, and strawberry. These polyphenolic compounds found in their drupelets and leaves which include anthocyanins, ellagic acid, flavonoids, tannins act as biologically active compounds and show different antioxidant activities which ultimately treat the neurological disorder, cardiovascular diseases (hypertension, stroke, cardiac failure, myocardial infarction, and atherosclerosis), and diabetes [141].

DISCUSSION

In this paper, hypertension and their related disease is the leading cause of globally and worldwide mortality and morbidity. The literature strongly indicates the herbs/plants which are becoming part of evidence-based medicine in the prevention and treatment of CVD. There were many drug delivery systems which were used either pharmacologically or non-pharmacologically treatment options for better efficacy of herbal remedies [155]. As the pharmacological actions of these herbs or its bioactive compounds can modulate the several parameters which are implicated in the pathogenesis of blood pressure, including but not limited to ROS, VSMC phenotype, endothelial function, platelet activation, and pro-inflammatory signaling. The importance of this review article is that it can give information on various recent epidemiological studies have shown better associations between higher berry flavonoid intake and lower risk of CVD, and several human intervention studies have shed some light on the beneficial effects of various berry polyphenol-rich foods on surrogate markers of CVD risk. Various formulated preparations are formed using extracts of leaves and fruits for the consumption of these berries.

All of these activities were obtained from phenolic compounds such as anthocyanins (i.e., cyanidin, delphinidin, and malvidin), flavonols (quercetin, kaempferol, and myricetin) in flowers, and caffeoylhydroxycitric acid, and neochlorogenic acid in leaves. These compounds show a wide range of antioxidant activities which prevent to degenerate of neuronal disorders, cardiovascular disease, cancer, and diabetes. All of these activities were obtained from phenolic compounds such as anthocyanins (i.e., cyanidin, delphinidin, and malvidin), flavonols (quercetin, kaempferol, and myricetin) in flowers, and caffeoylhydroxycitric acid and neochlorogenic acid in leaves. These compounds show a wide range of antioxidant activities which prevent to degenerate of neuronal disorders, cardiovascular disease, cancer, and diabetes. All of these activities were obtained from phenolic compounds such as anthocyanins (i.e., cyanidin, delphinidin, and malvidin), flavonols (quercetin, kaempferol, and myricetin) in flowers, and caffeoylhydroxycitric acid and neochlorogenic acid in leaves. These compounds show a wide range of antioxidant activities which prevent to degenerate of neuronal disorders, cardiovascular disease, cancer, and diabetes.

CONCLUSION AND FUTURE PERSPECTIVES

In this paper, hypertension and their related illness is the important cause of globally in addition to worldwide mortality and morbidity. The literature strongly indicates that the herbs/plants show better efficacy as compared to allopathy and any other medication system. As the pharmacological actions of the bioelements found in herbs concerned in the pathogenesis of high blood pressure either arterial or venous, by the disruption in ROS, VSMC, endothelial layer function, thrombocytes activation, and pro-inflammatory signaling. Various recent pharmacoepidemiologic researches revealed that improved relations among higher berry flavonoid intake in a balanced diet can ultimately lower down the risk of blood disorders, and several clinical trials show positive effects of berry fruits which are polyphenol-rich nourishments on substitute biomarkers of heart factors. Thus, based on various scientific research indications, berries, particularly raspberry and cranberries, may reduce the effects of a collection of metabolic syndromes. The phytochemical and bioactive compounds of these berries such as flavonoids, ellagitannins, and anthocyanins are potentially showing better effects in the ailments of various CVD such as reduce blood pressure, decreased endothelial dysfunction, which ultimately increases cardiovascular and brain health in an individual. Various research and studies are held over these bioactive compounds which show potential in the ailment of different cardiovascular diseases by altering and modulate the mechanisms involved in pathogenesis.

The polyherbalism is most beneficial for better efficacy and in respect to future goals it is needed to research on berry fruits and their polyphenols in combination. The researcher's studies can define the optimum dose, consumption in the daily diet. Basically, define the mechanism of action of these berries in controlling of oxidative damage and tension and the signaling molecules of inflammation which ultimately in high ranges leads to the production of metabolic syndrome (collection of diseases related to cardiovascular system). Efforts are needed for the preparation of effective dietary chart for trials of berries in the reduction of cardiovascular diseases and their originated targeting biomarkers molecules for therapeutic efficacy in hypertensive patients.

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CONFLICTS OF INTEREST

The authors affirm no conflicts of interest, financial, or otherwise.

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REFERENCES

1. Delacroix S, Chokka RG, Worthley SG. Hypertension: Pathophysiology and treatment. J Neurol Neurophysiol 2014;5:3.
2. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, *et al*. Clinical practice guidelines for the management of hypertension in the community: A statement by the American society of hypertension and the international society of hypertension. J Clin Hyper 2014;16:14-26.
3. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Boehm M, *et al*. 2013 ESH/ESC guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European society of hypertension (ESH) and the European society of cardiology (ESC). Blood Press 2013;22:193-278.
4. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, *et al*. Blood pressure and incidence of twelve cardiovascular diseases: Lifetime risks, healthy life-years lost, and age-specific associations in 125 million people. Lancet 2014;383:1899-911.
5. Reddy KS, Shah B, Varghese C, Ramadoss A. Responding to the threat of chronic diseases in India. Lancet 2005;366:1744-9.
6. Gupta R. Trends in hypertension epidemiology in India. J Hum Hypertens 2004;18:73-8.
7. National Institute for Health and Care Excellence. Hypertension: Clinical Management of Primary Hypertension in Adults. London: National Institute for Health and Care Excellence; 2011.
8. World Health Organization. Cardiovascular Diseases (CVDs). Geneva: World Health Organization; 2013.
9. Yang Y, Chan SW, Hu M, Walden R, Tomlinson B. Effects of some common food constituents on cardiovascular disease. ISRN Cardiol 2011;2011:397136.
10. Kizhakekuttu TJ, Widlansky ME. Natural antioxidants and hypertension: Promise and challenges. Cardiol Ther 2010;28:e20-32.
11. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, *et al*. 2014 evidence-based guideline for the management of high blood pressure in adults: A report from the panel members appointed to the eighth joint national committee (JNC 8). JAMA Intern Med 2014;311:507-20.
12. Freis ED. Age, race, sex and other indices of risk in hypertension. Am J Med 1973;55:275-80.
13. Carretero OA, Oparil S. Essential hypertension: Part II: Treatment. Circulation 2000;101:446-53.
14. Beevers G, Lip GY, O'Brien E. The pathophysiology of hypertension. BMJ 2001;322:912-6.
15. Folkow BJ. Structural factor in primary and secondary hypertension. Hypertension 1990;16:89-101.
16. Mayet J, Hughes A. Cardiac and vascular pathophysiology in hypertension. Heart 2003;89:1104-9.
17. Rostrup M, Mundal HH, Westheim A, Eide I. Awareness of high blood pressure increases arterial plasma catecholamines, platelet noradrenaline and adrenergic responses to mental stress. J Hyper 1991;9:159-66.
18. Cardillo C, Kilcoyne CM, Quyyumi AA, Cannon RO 3rd, Panza JA. Selective defect in nitric oxide synthesis may explain the impaired endothelium-dependent vasodilation in patients with essential hypertension. Circulation 1998;97:851-6.
19. Panza JA, Casino PR, Kilcoyne CM, Quyyumi AA. Role of endothelium-derived nitric oxide in the abnormal endothelium-dependent vascular relaxation of patients with essential hypertension. Circulation 1993;87:1468-74.
20. Panza JA, Garcia CE, Kilcoyne CM, Quyyumi AA, Cannon RO 3rd. Impaired endothelium-dependent vasodilation in patients with essential hypertension: Evidence that nitric oxide abnormality is not localized to a single signal transduction pathway. Circulation 1995;91:1732-8.
21. Panza JA, Quyyumi AA, Brush JE Jr., Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. N Engl J Med 1990;323:22-7.
22. Sander M, Chavoshan B, Victor RG. A large blood pressure-raising effect of nitric oxide synthase inhibition in humans. Hypertension 1999;33:937-42.
23. Archer JS. Evaluation and treatment of hypertension. Prim Care Update OB/GYNS 2000;7:1-6.
24. Susalit E, Agus N, Effendi I, Tjandrawinata RR, Nofiarny D, Perrinjaquet-Moccetti T, *et al*. Olive (*Olea europaea*) leaf extract effective in patients with stage-1 hypertension: Comparison with captopril. Phytol Med 2011;18:251-8.
25. He J, Whelton PK, Appel LJ, Charleston J, Klag MJ. Long-term effects of weight loss and dietary sodium reduction on incidence of hypertension. Hypertension 2000;35:544-9.
26. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: A meta-analysis of randomized, controlled trials. Ann Intern Med 2002;136:493-503.
27. Xin X, He J, Frontini MG, Ogden LG, Motsamai OI, Whelton PK. Effects of alcohol reduction on blood pressure: A meta-analysis of randomized controlled trials. Hypertension 2001;38:1112-7.
28. Elmer PJ, Obarzanek E, Vollmer WM, Simons-Morton D, Stevens VJ, Young DR, *et al.* Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. Ann Intern Med 2006;144:485-95.
29. Frishman WH, Beravol P, Carosella C. Alternative and complementary medicine for preventing and treating cardiovascular disease. Dis Month 2009;3:121-92.
30. Su D, Li L. Trends in the use of complementary and alternative medicine in the United States: 2002-2007. J Health Care Poor Und 2011;22:296-310.
31. Tabassum N, Ahmad F. Role of natural herbs in the treatment of hypertension. Pharmacogn Rev 2011;5:30.
32. Pan SY, Zhou SF, Gao SH, Yu ZL, Zhang SF, Tang MK, *et al*. New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. Evid Based Complement Alternat Med 2013;2013:25.
33. Centres for Disease Control and Prevention. The Behavioral Risk Factor Surveillance System (BRFSS). Atlanta, USA: Centres for Disease Control and Prevention; 2007.
34. Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G, Crozier A. Dietary (poly) phenolics in human health: Structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid Red Sig 2013;18:1818-92.
35. Agricultural Research Services. National Nutrient Database for Standard Reference Service Release 22. Beltsville, MD: Agricultural Research Services, United States Department of Agriculture; 2009.
36. Agricultural Research Services. Database for the Flavonoid Content of Selected Foods Release 2.1, 2007. Beltsville, MD: Agricultural Research Services, United States Department of Agriculture; 2007.
37. Wu X, Kang J, Xie C, Burris R, Ferguson ME, Badger TM, *et al*. Dietary blueberries attenuate atherosclerosis in apolipoprotein E-deficient mice by upregulating antioxidant enzyme expression. J Nutr 2010;140:1628-32.
38. Swanson J, Weber CA, Finn CE, Fernandez-Fernandez F, Sargent D, Carlson JE, *et al*. Breeding, genetics and genomics of *Rubus*. In: Folta K, Kole C, editors. Genetics, Genomics and Breeding of Berries. New Hampshire: Science Publications; 2011. p. 64-113.
39. USDA Agricultural Research Services. National Nutrient Database for Standard Reference Service Release 27 and the Flavonoid Content of Selected Foods Release 3.1. Washington, DC: USDA Agricultural

Research Services; 2014.

40. Rao AV, Snyder DM. Raspberries and human health: A review. J Agric Food Chem 2010;58:3871-83.
41. Jennings DL. Raspberries and Blackberries: Their Breeding, Diseases and Growth. United States: Academic Press; 1988.
42. US Department of Agriculture Research Service. USDA National Nutrient Database for Standard Reference, Release 21: Fruits and Fruit Juice. United States: US Department of Agriculture Research Service; 2008. p. 719-20.
43. Hummer KE. *Rubus* pharmacology: Antiquity to the present. Hort Sci 2010;45:1587-91.
44. Tasaki M, Umemura T, Maeda M, Ishii Y, Okamura T, Inoue T, *et al*. Safety assessment of ellagic acid, a food additive, in a subchronic toxicity study using F344 rats. Food Chem Toxicol 2008;46:1119-24.
45. Graham J, Woodhead M. *Rubus*. In: Wild Crop Relatives: Genomic and Breeding Resources. Berlin, Heidelberg: Springer; 2011. p. 179-96.
46. Bravo L. Polyphenols: Chemistry, dietary sources, metabolism, and nutritional significance. Nutr Rev 1998;56:317-33.
47. Waterman PG, Mole S. Analysis of Phenolic Plant Metabolites. 1st ed. Hoboken, NJ: Wiley-Blackwell; 1994.
48. Vainio H, Bianchini F. Fruit and Vegetables. Lyon, France: IARC; 2003. p. 1-19.
49. Arts IC, Hollman PC. Polyphenols and disease risk in epidemiologic studies. Am J Clin Nutr 2005;81:317-25.
50. Kaur C, Kapoor HC. Antioxidants in fruits and vegetables-the millennium health. Int J Food Sci Technol 2001;36:703-25.
51. Prior RL, Wu X, Gu L, Hager TJ, Hager A, Howard LR. Whole berries versus berry anthocyanins: Interactions with dietary fat levels in the C57BL/6J mouse model of obesity. J Agric Food Chem 2008;56:647-53.
52. Määttä-Riihinen KR, Kamal-Eldin A, Törrönen AR. Identification and quantification of phenolic compounds in berries of *Fragaria* and *Rubus* species (family *Rosaceae*). J Agric Food Chem 2004;52:6178-87.
53. de Pascual-Teresa S, Santos-Buelga C, Rivas-Gonzalo JC. Quantitative analysis of flavan-3-ols in Spanish foodstuffs and beverages J Agric Food Chem 2000;48:5331-7.
54. Arts IC, van de Putte B, Hollman PC. Catechin contents of foods commonly consumed in the Netherlands. 1. Fruits, vegetables, staple foods, and processed foods. J Agric Food Chem 2000;48:1746-51.
55. Heinonen IM, Meyer AS, Frankel EN. Antioxidant activity of berry phenolics on human low-density lipoprotein and liposome oxidation. J Agric Food Chem 1998;46:4107-12.
56. Harborne JB, Baxter H. The Handbook of Natural Flavonoids. Vol. 1., Vol. 2. United States: John Wiley and Sons; 1999.
57. Middleton E, Kandaswami C, Harborne J. The Flavonoids: Advances in Research Since 1986. New York: Chapman & Hall/CRC; 1993.
58. Williams RJ, Spencer JP, Rice-Evans C. Flavonoids: Antioxidants or signalling molecules? Free Radic Biol Med 2004;36:838-49.
59. Kassim A, Poette J, Paterson A, Zait D, McCallum S, Woodhead M, *et al*. Environmental and seasonal influences on red raspberry anthocyanin antioxidant contents and identification of quantitative traits loci (QTL). Mol Nutr Food Res 2009;53:625-34.
60. Mattila P, Hellström J, Törrönen R. Phenolic acids in berries, fruits, and beverages. J Agric Food Chem 2006;54:7193-9.
61. Koponen JM, Happonen AM, Mattila PH, Törrönen AR. Contents of anthocyanins and ellagitannins in selected foods consumed in Finland. J Agric Food Chem 2007;55:1612-9.
62. Hellström JK, Torronen AR, Mattila PH. Proanthocyanidins in common food products of plant origin. J Agric Food Chem 2009;57:7899-906.
63. Gu L, Kelm MA, Hammerstone JF, Beecher G, Holden J, Haytowitz D, *et al*. Concentrations of proanthocyanidins in common foods and estimations of normal consumption. J Nutr 2004;134:613-7.
64. Mazur WM, Uehara M, Wähälä K, Adlercreutz H. Phyto-oestrogen content of berries, and plasma concentrations and urinary excretion of enterolactone after a single strawberry-meal in human subjects. B J Nutr 2000;83:381-7.
65. Bobinaitė R, Viškelis J. Anthocyanins: Occurrence, bioactivity and bioavailability, with special reference to the anthocyanins of raspberries (a review). Sodininkystė Daržininkystė 2013;32:39-47.
66. Beekwilder J, Jonker H, Meesters P, Hall RD, van der Meer IM, de Vos CH. Antioxidants in raspberry: On-line analysis links antioxidant activity to a diversity of individual metabolites. J Agric Food Chem 2005;53:3313-20.
67. Wu X, Beecher GR, Holden JM, Haytowitz DB, Gebhardt SE, Prior RL. Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. J Agric Food Chem 2006;54:4069-75.
68. Mazur SP, Nes A, Wold AB, Remberg SF, Aaby K. Quality and chemical composition of ten red raspberries (*Rubus idaeus* L.) genotypes during three harvest seasons. Food Chem 2014;160:233-40.
69. Frankel EN, Waterhouse AL, Teissedre PL. Principal phenolic phytochemicals in selected California wines and their antioxidant activity in inhibiting the oxidation of human low-density lipoproteins. J Agric Food Chem 1995;43:890-4.
70. Kuhnau J. The flavonoids. A class of semi-essential food components: Their role in human nutrition. World Rev Nutr Diet 1976;24:117-91.
71. Wood RJ. Bioavailability: Definition, general aspects and fortificants. In: Encyclopaedia of Human Nutrition. 2nd ed. Oxford: Elsevier Ltd.; 2005. p. 195-201.
72. Daniel EM, Ratnayake S, Kinstle T, Stoner GD. The effects of pH and rat intestinal contents on the liberation of ellagic acid from purified and crude ellagitannins. J Nat Prod 1991;54:946-52.
73. Laitinen LA, Tammela PS, Galkin A, Vuorela HJ, Marvola ML, Vuorela PM. Effects of extracts of commonly consumed food supplements and food fractions on the permeability of drugs across Caco-2 cell monolayers. Pharm Res 2004;21:1904-16.
74. Cao G, Muccitelli HU, Sanchez-Moreno C, Prior RL. Anthocyanins are absorbed in glycated forms in elderly women: A pharmacokinetic study. Am J Clin Nutr 2001;73:920-6.
75. Kay CD. Aspects of anthocyanin absorption, metabolism and pharmacokinetics in humans. Nutr Res Rev 2006;19:137-46.
76. McGhie TK, Walton MC. The bioavailability and absorption of anthocyanins: Towards a better understanding. Mol Nutr Food Res 2007;51:702-13.
77. Mullen W, Edwards CA, Serafini M, Crozier A. Bioavailability of pelargonidin-3-O-glucoside and its metabolites in humans following the ingestion of strawberries with and without cream. J Agric Food Chem 2008;56:713-9.
78. Mazza G, Kay CD, Cottrell T, Holub BJ. Absorption of anthocyanins from blueberries and serum antioxidant status in human subjects. J Agric Food Chem 2002;50:7731-7.
79. Mülleder U, Murkovic M, Pfannhauser W. Urinary excretion of cyanidin glycosides. J Biochem Biol Meth 2002;53:61-6.
80. Talavera S, Felgines C, Texier O, Besson C, Lamaison JL, Rémésy C. Anthocyanins are efficiently absorbed from the stomach in anaesthetized rats. J Nutr 2003;133:4178-82.
81. Talavera S, Felgines C, Texier O, Besson C, Manach C, Lamaison JL, *et al*. Anthocyanins are efficiently absorbed from the small intestine in rats. J Nutr 2004;134:2275-9.
82. Matuschek MC, Hendriks WH, McGhie TK, Reynolds GW. The jejunum is the main site of absorption for anthocyanins in mice. J Nutr Biochem 2006;17:31-6.
83. McDougall GJ, Dobson P, Smith P, Blake A, Stewart D. Assessing potential bioavailability of raspberry anthocyanins using an in the *vitro* digestion system. J Agric Food Chem 2005;53:5896-904.
84. Passamonti S, Vrhovsek U, Mattivi F. The interaction of anthocyanins with bilitranslocase. Biochem Biophys Res Commun 2002;296:631-6.
85. Passamonti S, Vrhovsek U, Vanzo A, Mattivi F. The stomach as a site for anthocyanins absorption from food. FEBS Lett 2003;544:210-3.
86. Hollman PC. Absorption, bioavailability, and metabolism of flavonoids. Pharm Biol 2004;42:74-83.
87. Felgines C, Talavera S, Texier O, Gil-Izquierdo A, Lamaison JL, Remesy C. Blackberry anthocyanins are mainly recovered from urine as methylated and glucuronidated conjugates in humans. J Agric Food Chem 2005;53:7721-7.
88. Francis FJ. Analysis of anthocyanins. In: Markakis P, editor. Anthocyanins as Food Colours. United States: Academic Press; 1982. p. 182-208.
89. Fuleki T, Francis FJ. Quantitative methods for anthocyanins. 1. Extraction and determination of total anthocyanin in cranberries. J Food Sci 1968;33:72-7.
90. Harborne JB. The chromatographic identification of anthocyanin pigments. J Chroma A 1958;1:473-88.
91. Francis FJ, Harborne JB. Anthocyanins of the garden huckleberry, *Solanum guineense*. J Food Sci 1966;31:524-8.
92. Andersen OM. Chromatographic separation of anthocyanins in cowberry (lingonberry) *Vaccinium vitis-idaea* L. J Food Sci 1985;50:1230-2.
93. Bakker J, Timberlake CF. The distribution of anthocyanins in grape skin extracts of port wine cultivars as determined by high-performance liquid chromatography. J Sci Food Agric 1985;36:1315-24.
94. Harborne JB. Comparative Biochemistry of the Flavonoids. London, England: Academic Press; 1987. p. 1-36.
95. Vauzour D, Rodriguez-Mateos A, Corona G, Oruna-Concha MJ, Spencer JP. Polyphenols and human health: Prevention of disease and

mechanisms of action. Nutrients 2010;2:1106-31.
96. Juránek I, Bezek S. Controversy of free radical hypothesis: Reactive oxygen species-cause or consequence of tissue injury? Gen Physiol Biophys 2005;24:263-78.
97. Hori M, Nishida K. Oxidative stress and left ventricular remodelling after myocardial infarction. Cardiovasc Res 2009;81:457-64.
98. Garcia-Alonso M, Rimbach G, Sasai M, Nakahara M, Matsugo S, Uchida Y, *et al*. Electron spin resonance spectroscopy studies on the free radical scavenging activity of wine anthocyanins and proanthocyanins. Mol Nutr Food Res 2005;49:1112-9.
99. García-Alonso M, Rimbach G, Rivas-Gonzalo JC, de Pascual-Teresa S. Antioxidant and cellular activities of anthocyanins and their corresponding vitisins a study in platelets, monocytes, and human endothelial cells. J Agric Food Chem 2004;52:3378-84.
100. Oak MH, Bedoui JE, Madeira SF, Chalupsky K, Schini-Kerth VB. Delphinidin and cyanidin inhibit PDGFAB-induced VEGF release in vascular smooth muscle cells by preventing activation of p38 MAPK and JNK. Br J Pharmacol 2006;149:283-90.
101. Sies H, Stahl W, Sevanian A. Nutritional, dietary and postprandial oxidative stress. J Nutr 2005;135:969-72.
102. Actis-Goretta L, Ottaviani JI, Keen CL, Fraga CG. Inhibition of angiotensin-converting enzyme (ACE) activity by flavan-3-ols and procyanidins. FEBS Lett 2003;555:597-600.
103. Barbehenn RV, Jones CP, Hagerman AE, Karonen M, Salminen JP. Ellagitannins have greater oxidative activities than condensed tannins and galloyl glucose at high pH: Potential impact on caterpillars. J Chem Econ 2006;32:2253-67.
104. Quideau S. Chemistry and Biology of Ellagitannins: An Underestimated Class of Bioactive Plant Polyphenols. Singapore: World Scientific; 2009.
105. Clifford MN, Scalbert A. Ellagitannins-nature, occurrence and dietary burden. J Sci Food Agric 2000;80:1118-25.
106. Haddock EA, Gupta RK, Al-Shafi SM, Layden K, Haslam E, Magnolato D. The metabolism of gallic acid and hexahydroxy diphenic acid in plants: Biogenetic and molecular taxonomic considerations. Phytochemistry 1982;21:1049-62.
107. Bobinaitė R, Viškelis P, Šarkinas A, Venskutonis PR. Phytochemical composition, antioxidant and antimicrobial properties of raspberry fruit, pulp, and marc extracts. CyTA J Food 2013;11:334-42.
108. Cerdá B, Tomás-Barberán FA, Espín JC. Metabolism of antioxidant and chemopreventive ellagitannins from strawberries, raspberries, walnuts, and oak-aged wine in humans: Identification of biomarkers and individual variability. J Agric Food Chem 2005;53:227-35.
109. González-Barrio R, Edwards CA, Crozier A. Colonic catabolism of ellagitannins, ellagic acid, and raspberry anthocyanins: *In vivo* and *in vitro* studies. Drug Metab Dispos 2011;39:1680-8.
110. González-Barrio R, Borges G, Mullen W, Crozier A. Bioavailability of anthocyanins and ellagitannins following consumption of raspberries by healthy humans and subjects with an ileostomy. J Agric Food Chem 2010;58:3933-9.
111. Zafra-Stone S, Yasmin T, Bagchi M, Chatterjee A, Vinson JA, Bagchi D. Berry anthocyanins as novel antioxidants in human health and disease prevention. Mol Nutr Food Res 2007;51:675-83.
112. European Food Safety Authority Panel on Dietetic Products, Nutrition and Allergies. Guidance on the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health. EFSA J 2011;9:24-74.
113. Reriani MK, Lerman LO, Lerman A. Endothelial function as a functional expression of cardiovascular risk factors. Biomark Med 2010;4:351-60.
114. Deanfield J, Donald A, Ferri C, Giannattasio C, Halcox J, Halligan S, *et al*. Endothelial function and dysfunction. Part I: Methodological issues for assessment in the different vascular beds: A statement by the working group on endothelin and endothelial factors of the European society of hypertension. J Hypertens 2005;23:7-17.
115. Lekakis J, Abraham P, Balbarini A, Blann A, Boulanger CM, Cockcroft J, *et al*. Methods for evaluating endothelial function: A position statement from the European society of cardiology working group on peripheral circulation. Eur J Cardiovasc Prev Rehabil 2011;18:775-89.
116. Tousoulis D, Kampoli AM, Tentolouris C, Papageorgiou N, Stefanadis C. The role of nitric oxide on endothelial function. Curr Vasc Pharmacol 2012;10:4-18.
117. Viljanen K, Kylli P, Kivikari R, Heinonen M. Inhibition of protein and lipid oxidation in liposomes by berry phenolics. J Agric Food Chem 2004;52:7419-24.
118. Seeram NP, Nair MG. Inhibition of lipid peroxidation and structure-activity-related studies of the dietary constituent anthocyanins, anthocyanidins, and catechins. J Agric Food Chem 2002;50:5308-12.
119. Meyer AS, Heinonen M, Frankel EN. Antioxidant interactions of catechin, cyanidin, caffeic acid, quercetin, and ellagic acid on human LDL oxidation. Food Chem 1998;61:71-5.
120. Serraino I, Dugo L, Dugo P, Mondello L, Mazzon E, Dugo G, *et al*. Protective effects of cyanidin-3-O-glucoside from blackberry extract against peroxynitrite-induced endothelial dysfunction and vascular failure. Life Sci 2003;73:1097-114.
121. Mullen W, McGinn J, Lean ME, MacLean MR, Gardner P, Duthie GG, *et al*. Ellagitannins, flavonoids, and other phenolics in red raspberries and their contribution to antioxidant capacity and vasorelaxation properties. J Agric Food Chem 2002;50:5191-6.
122. Wang J, Mazza G. Effects of anthocyanins and other phenolic compounds on the production of tumour necrosis factor α in LPS/IFN-γ-activated RAW 264.7 macrophages. J Agric Food Chem 2002;50:4183-9.
123. Wang J, Mazza G. Inhibitory effects of anthocyanins and other phenolic compounds on nitric oxide production in LPS/IFN-γ-activated RAW 264.7 macrophages. J Agric Food Chem 2002;50:850-7.
124. Vattem DA, Ghaedian R, Shetty K. Enhancing health benefits of berries through phenolic antioxidant enrichment: Focus on cranberry. Asia Pac J Clin Nutr 2005;14:120.
125. Côté J, Caillet S, Doyon G, Sylvain JF, Lacroix M. Bioactive compounds in cranberries and their biological properties. Crit Rev Food Sci Nutr 2010;50:666-79.
126. Neto CC. Cranberry and blueberry: Evidence for protective effects against cancer and vascular diseases. Mol Nutr Food Res 2007;51:652-64.
127. Grace MH, Esposito D, Dunlap KL, Lila MA. Comparative analysis of phenolic content and profile, antioxidant capacity, and anti-inflammatory bioactivity in wild Alaskan and commercial *Vaccinium* berries. J Agric Food Chem 2013;62:4007-17.
128. Blumberg JB, Camesano TA, Cassidy A, Kris-Etherton P, Howell A, Manach C, *et al*. Cranberries and their bioactive constituents in human health. Adv Nutr 2013;4:618-32.
129. Pappas E, Schaich KM. Phytochemicals of cranberries and cranberry products: Characterization, potential health effects, and processing stability. Crit Rev Food Sci Nutr 2009;49:741-81.
130. Zuo Y, Wang C, Zhan J. Separation, characterization, and quantitation of benzoic and phenolic antioxidants in American cranberry fruit by GC-MS. J Agric Food Chem 2002;50:3789-94.
131. Mazur B, Borowska EJ, Polak M. Content of Vitamin C in and antioxidant capacity of wild and cultivated cranberry fruit and their pulps. Zyw Nauka Technol Jak 2009;2:130-7.
132. McKay DL, Chen CY, Zampariello CA, Blumberg JB. Flavonoids and phenolic acids from cranberry juice are bioavailable and bioactive in healthy older adults. Food Chem 2015;168:233-40.
133. Zhang K, Zuo Y. GC-MS determination of flavonoids and phenolic and benzoic acids in human plasma after consumption of cranberry juice. J Agric Food Chem 2004;52:222-7.
134. Ohnishi R, Ito H, Kasajima N, Kaneda M, Kariyama R, Kumon H, *et al*. Urinary excretion of anthocyanins in humans after cranberry juice ingestion. Biosci Biotechnol Biochem 2006;70:1681-7.
135. Wang C, Zuo Y, Vinson JA, Deng Y. Absorption and excretion of cranberry-derived phenolics in humans. Food Chem 2012;132:1420-8.
136. Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Low-calorie cranberry juice supplementation reduces plasma oxidized LDL and cell adhesion molecule concentrations in men. Br J Nutr 2008;99:352-9.
137. Ruel G, Pomerleau S, Couture P, Lamarche B, Couillard C. Changes in plasma antioxidant capacity and oxidized low-density lipoprotein levels in men after short-term cranberry juice consumption Metabolism. Br J Nutr 2005;54:856-61.
138. DiCorleto PE, Gimbrone MA. Atherosclerosis and coronary artery disease. Vasc Endothelium 1996;1:387-99.
139. Shukla R, Omray LK. Formulation and characterization of diltiazem transdermal system for the treatment of hypertension. Int J Curr Pharm Res 2016;8:12-5.
140. Nakagami H, Morishita R. Hypertension and osteoporosis. Clin Calcium 2013;23:497-503.
141. Thungmungmee S, Wisidsri N, Khobjai W, Dumrongphuttidecha T, Jamkom K, Techaeoi S. The characteristics and antioxidant activities of chaba maple (*Hibiscus acetosella*) homemade jam. Int J Appl Pharm 2019;11:52-5.
142. Yu YM, Wang ZH, Liu CH, Chen CS. Ellagic acid inhibits IL-1betainduced cell adhesion molecule expression in human umbilical vein endothelial cells. Br J Nutr 2007;97:692-8.
143. Chang WC, Yu YM, Chiang SY, Tseng CY. Ellagic acid suppresses

oxidised low-density lipoprotein-induced aortic smooth muscle cell proliferation: Studies on the activation of extracellular signal-regulated kinase 1/2 and proliferating cell nuclear antigen expression. Br J Nutr 2008;99:709-14.
144. Ding Y, Zhang B, Zhou K, Chen M, Wang M, Jia Y, *et al*. Dietary ellagic acid improves oxidant-induced endothelial dysfunction and atherosclerosis: Role of Nrf2 activation. Int J Cardiol 2014;175:508-14.
145. Chao PC, Hsu CC, Yin MC. Anti-inflammatory and anti-coagulatory activities of caffeic acid and ellagic acid in cardiac tissue of diabetic mice. Nutr Metab (Lond) 2009;6:33.
146. Yu YM, Chang WC, Wu CH, Chiang SY. Reduction of oxidative stress and apoptosis in hyperlipidaemic rabbits by ellagic acid. J Nutr Biochem 2005;16:675-81.
147. Lin MC, Yin MC. Preventive effects of ellagic acid against doxorubicin-induced cardiotoxicity in mice. Cardiovasc Toxicol 2013;13:185-93.
148. Panchal SK, Ward L, Brown L. Ellagic acid attenuates high-carbohydrate, high-fat diet-induced metabolic syndrome in rats. Eur J Nutr 2013;52:559-68.
149. Pieszka M, Tombarkiewicz B, Roman A, Migda1 W, Niedzió1ka J. Effect of bioactive substances found in rapeseed, raspberry and strawberry seed oils on blood lipid profile and selected parameters of oxidative status in rats. Environ Toxicol Pharmacol 2013;36:1055-62.
150. Freese R, Vaarala O, Turpeinen AM, Mutanen M. No difference in platelet activation or inflammation markers after diets rich or poor in vegetables, berries and apple in healthy subjects. Eur J Nutr 2004;43:175-82.
151. Lee IT, Chan YC, Lin CW, Lee WJ, Sheu WH. Effect of cranberry extracts on lipid profiles in subjects with Type 2 diabetes. Diab Med 2008;25:1473-7.
152. Wilson T, Luebke JL, Morcomb EF, Carrell EJ, Leveranz MC, Kobs L, *et al*. Glycemic responses to sweetened dried and raw cranberries in humans with Type 2 diabetes. J Food Sci 2010;75:H218-23.
153. caBasu A, Betts NM, Ortiz J, Simmons B, Wu M, Lyons TJ. Low-energy cranberry juice decreases lipid oxidation and increases plasma antioxidant capacity in women with metabolic syndrome. Nutr Res 2011;31:190-6.
154. Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Favourable impact of low-calorie cranberry juice consumption on plasma HDL-cholesterol concentrations in men. Br J Nutr 2006;96:357-6.
155. Verma H, Prasad SB, Yashwant SH. Herbal drug delivery system: A modern era prospective. Int J Curr Pharm Res 2013;4:88-101.