



Nutraceuticals In Cardiovascular Diseases

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ABSTRACT

With increasing incidences of side effects and adverse drug reactions, the consumer choices are more inclining towards natural products and medicines obtained from natural sources. One such emerging class of products are '**Nutraceuticals**'. Nutraceutical is a compound defined as food or parts of a food having health benefits and helps in prevention and treatment of diseases. It includes isolated nutrients, dietary supplements, herbal products and processed foods. Nowadays Nutraceuticals are preferred for providing additional health benefits and for prevention and treatment of diseases due to its safety, potential and therapeutic efficacy. Nutraceuticals have advantage over the drugs or medicines because they are naturally found dietary supplements and don't have side effects. These are classified into three categories which are Nutrients, Herbals and Dietary supplements. Nowadays, sedentary and passive lifestyles have become common causes of many diseases related to lifestyle, metabolism, weight-related disorders, cardiovascular disorders etc. The incidence of cardio-vascular diseases have been increasing since decades throughout the world. Studies show that India is the highest contributor to the number of cases of cardiovascular diseases. Cardio Vascular Diseases (CVD) are the most common health problem faced by the populations it may be fatal at later stages. Recent studies have shown that cardiovascular risk factors like obesity, diabetes, hypertension are highly prevalent even in younger generations. Various Nutraceuticals are used for the prevention and treatment of CVD or to reduce the risk factors which leads to CVD, these risk factors are Atherosclerosis, Dyslipidemia, Hypertension, Diabetes Mellitus. Commonly known Nutraceuticals used to treat CVD or reducing its risk factors are Berberine, β -glucans, Polyphenols, Plant sterols or stanols and these are widely found in plants, foods and food products from plant origin, vegetables, cereals, fruits, legumes.

Keywords: Nutraceuticals, polyphenols, sterols, Cardiovascular diseases (CVD).

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INTRODUCTION

An Introduction to Nutraceuticals

Monotonous and passive lifestyles have increased manifolds among the populations around the world. With passive lifestyles comes disorders and diseases. Diseases like cardiovascular and metabolic diseases have started to penetrate larger populations. Junk food and lower nutritional value food causes malnutrition not only in infants but in people of all ages. Nutrient supplements came into picture to meet the nutritional needs of the body. With further research and enhancement in technology came the concept of 'NUTRACEUTICALS'.³

The word nutraceutical is derived from two words nutrient and pharmaceutical. The term “nutraceuticals” was coined by Stephen DeFelice in 1989. He is the founder and chairman of the Foundation for Innovation in Medicine. A nutraceutical is defined as a “food, or parts of a food, with health benefits, which includes prevention and treatment of disease”. These also include isolated nutrients, dietary supplements, herbal products and processed foods. A nutraceutical must provide additional health benefit other than traditional use.³

Phytonutrients basically is plant nutrients with particular biological activities in supporting human health. The phytochemical work by following way:

1. Substrate for biochemical reactions
2. Cofactors of enzymatic reactions
3. Inhibitors of enzymatic reactions
4. Absorbents that bind to and eliminate undesirable constituent in the intestine
5. Enhance the absorption and/or stability of essential nutrients
6. Selective growth factor for beneficial bacteria
7. Fermentation substrate for beneficial bacteria
8. Selective inhibitors of deleterious intestinal bacteria
9. Scavengers of reactive or toxic chemicals
10. Ligands that agonize or antagonize cell surface or intracellular receptor

Some of the most common ways of classifying nutraceuticals can be based on food sources, mechanism of action, chemical nature, etc. The food sources used as nutraceuticals are all natural and can be categorized as

- Dietary Fiber
- Probiotics
- Prebiotics
- Polyunsaturated fatty acids

- Antioxidant vitamins
- Polyphenols
- Spices

Nutraceutical can be broadly classified into the following 2 groups:

- Potential nutraceuticals.
- Established nutraceuticals.

Nutraceutical has advantage over the medicine because they have naturally dietary supplement and avoid side effects. Nutraceutical on the basis of their natural source, chemical classification and pharmacological conditions categories into three key terms -nutrients, herbals, dietary supplements or dietary fibre.³¹

Nutrients:

Substances which has established nutritional functions e.g. Vitamins, Minerals, Fatty acids, Amino acids etc.

Herbals:

Herbs or botanical products like aloe vera, ginseng, evening primrose oil, garlic, ginger

Dietary supplements:

Probiotics, Prebiotics, Antioxidants, Enzymes etc. Excessive use of modern medicines and antibiotics is would build up tolerance and resistance and make these medicines not effective for long time . So another approach is made to choose natural products and herbs like nutraceuticals in our daily life which are capable in maintaining are normal body functions but also prevents us from various diseases and they also help in building immunity too. Simply this can be said that nutraceuticals are the naturally found alternatives of the pharmaceuticals which also provides physiological benefits and provide protection against chronic diseases. nutraceuticals may be used to delay the aging process , to improve health , to prevent chronic diseases , increases life expectancy and most importantly support and maintain the metabolic functions of body.³¹

These days nutraceuticals are referred as the compounds of interest due to its potential nutritional, safety and therapeutic effects. In a market research it is found that the market of nutraceuticals worldwide is expanding exponentially because people are showing more and more interest in herbal products because herbal products have no side effects. Nearly 2/3rd of the world population rely on the healing power of plant based products for many reasons like affordability, availability, safety or belief in traditional cures. Nutraceuticals usually not have patent protection as pharmaceuticals have. Both nutraceuticals and pharmaceuticals might be used to prevent various

diseases and as a cure for various chronic diseases, but government sanction or patent is only given to pharmaceuticals .²⁹

Various studies showed promising results for nutraceuticals in various pathological complications such as atherosclerosis, dyslipidemia, diabetes mellitus, various CVDs and neurological disorders.

An Introduction to CARDIOVASCULAR DISEASE

CVD is most commonly prevalent in adult with greater risk for people above the age of 60. Risk factors for CVD are grouped into modifiable and non-modifiable. Obesity, hypertension, hyperlipidemia, diabetes mellitus, metabolic syndrome and lifestyle risk factors such as unhealthy diet, smoking and physical inactivity are all modifiable risk factors. Dietary supplements and nutrients can contribute to lowering such risk factors either directly or indirectly. These cause an impact by lowering blood pressure or lowering blood lipid content. The impacts range from protecting people from developing CVD or decreasing chances of complications and morbidity in existing patients. Nutraceuticals aim at management and prevention of CVD.³⁴

There are various nutraceuticals found in nature, which have immense efficacy to reduce risk factors of CVD (Cardio Vascular Disease). Nowadays nutraceuticals are preferable along with the medicines that are used to treat CVDs or to reduce the risk factors of CVDs . It enhances the overall effect of those medicines and help in reducing the chances cardiovascular diseases and their risk factors.²⁸

What are these risk factors and what does it even mean? Major risk factors for CVDs are Atherosclerosis, Dyslipidemia (or Hyperlipidemia to be specific), Hypertension, Diabetes mellitus.^{3,4}

Atherosclerosis

It refers to the buildup of fats, cholesterol and other substances in and on your artery walls (plaque), which can restrict blood flow. The plaque can burst, triggering a blood clot. Although atherosclerosis is often considered a heart problem, it can affect arteries anywhere in your body.³⁰

Dyslipidemia

Abnormally elevated cholesterol or fats (lipids) in the blood. Dyslipidemia increases the chance of clogged arteries (atherosclerosis) and heart attacks, stroke or other circulatory concerns.

Hypertension

It also known as high blood pressure (HBP), It is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. A condition in which the force of the blood against the artery walls is too high.

Diabetes Mellitus

It is a metabolic disorder that causes elevation in blood sugar (glucose) levels and is a well established risk factor of CVDs mainly diabetes mellitus type 2. It imposes a very high risk for development of cardiovascular complications. Patients suffering from both diabetes and hypertension has double risk of having CVDs.²⁸

Following is the explanation for 3 major risk factors of CVD:

Hypertension

Systemic arterial hypertension is characterized by determinedly high blood pressure (BP) in the systemic arteries. BP is commonly expressed as the ratio of the systolic BP and the diastolic BP.

According to JNC-8 guidelines, it is differentiated under 4 categories

	Systolic BP(mmHg)	Diastolic BP(mmHg)
Normal	<120	<80
Prehypertension	120-139	80-89
Stage 1 hypertension	140-159	90-99
Stage 2 hypertension	≥160	≥100

Hypertension is the most common preventable risk factor for cardiovascular disease (CVD; including coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation and peripheral artery disease), chronic kidney disease (CKD) and cognitive impairment, and is the leading single contributor to all-cause death and disability worldwide.

BP can be determined by various parameters of cardiovascular system, including cardiac output, blood volume, and balance of arterial tone. The physiological BP levels upkeep involves a intricate interplay of various elements of an integrated neurohumoral system that includes the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), the immune system, role of natriuretic peptides and the endothelium. Any malfunction or imbalance between these systems can cause increase in hypertension directly or indirectly.

PATHOPHYSIOLOGY

RAAS

The RAAS has most crucial of helping to regulate pressure-volume homeostasis in the kidney, where it maintains perfusion in volume depleted states and is suppressed in volume expanded conditions. Renin is stored in juxtaglomerular cells in kidney and are released from various stimuli. It's main role is to convert Angiotensinogen into Angiotensin I. Further Angiotensin- converting enzyme (ACE) converts Angiotensin I into Angiotensin II. This is the main center of RAAS for pathological action in hypertension.

Angiotensin II enhances Na⁺ reabsorption in the proximal tubule by increasing the activity of the sodium-hydrogen exchanger, sodium-bicarbonate exchanger and sodium-potassium ATPase, and by inducing aldosterone synthesis and release from the adrenal glomerulosa. Aldosterone plays important role in increasing blood volume and vasoconstriction by binding with mineralocorticoid receptor. Angiotensin-converting enzyme 2 (ACE2) has appeared as an important modulator in the pathophysiology of hypertension, CVD and renal disease, owing to its role in metabolizing angiotensin II into angiotensin-(1-7). Ang-(1-7) induces systemic and regional vasodilation, diuresis and natriuretic, and exerts antiproliferative and antigrowth effects on vascular smooth muscle cells, cardiac myocytes and fibroblasts as well as glomerular and proximal tubular cells.

INFLAMMATION AND IMMUNE SYSTEM

Inflammation makes an important contribution to the origin of hypertension and related target organ damage. Inflammation is associated with increased vascular permeability and release of potent mediators, such as reactive oxygen species, NO, cytokines and metalloproteinases. Cytokines mediate the formation of neo-intima (a new or thickened layer of arterial intima), thereby decreasing the lumen diameter of resistance vessels and promoting vascular fibrosis, leading to increased vascular resistance and stiffness. Cytokines also affect renal tubular function by increasing local synthesis of angiotensinogen and angiotensin II, as well as promoting sodium and volume retention in hypertension⁶⁸. Matrix metalloproteinases stimulate the degradation of the extracellular matrix, allowing infiltration of immune cells through the vessel in the wall into the interstitium of the affected organs, promoting apoptosis and enhancing collagen synthesis and matrix deposition, leading to target organ damage. Abnormalities in both pro-inflammatory T cells and regulatory T cells. concerned in hypertension-induced target organ damage, as they regulate the inflammatory processes in kidney and vasculature that underlie hypertension-induced kidney disease.

NATRIURETIC PEPTIDES

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) play an vital part in hypertension and salt sensitivity. They have important natriuretic and vasodilator properties that allow maintenance of Na⁺ balance and BP during Na⁺ loading. Natriuretic peptide deficiency promotes hypertension. Corin is a serine protease expressed in the heart and converts the precursors pro-ANP and pro-BNP to their active forms. Corin deficiency has been associated with volume overload, heart failure and salt-sensitive hypertension. Natriuretic peptide deficiency also inclines to insulin resistance and type 2 diabetes mellitus. Obesity is associated with natriuretic peptide deficiency, probably through up regulation of the natriuretic peptide scavenger receptor

NPR-C in adipose tissue. Natriuretic peptides have therapeutic potential for the metabolic syndrome; the metabolic syndrome is a cluster of conditions (including high BP, high fasting glucose levels, abdominal obesity, high triglycerides and microalbuminuria) that occur together, increasing the risk of CVD and diabetes mellitus.

SYMPATHETIC NERVOUS SYSTEM

Baroreceptors, mechanoreceptors that sense pressure changes of the circulatory system, are stored in various locations in the arterial tree, mainly the carotid sinus. When this artery is stretched by elevated BP, nerve bundles projecting from the baroreceptors in the carotid sinus send messages to the brain to reduce sympathetic outflow of nerve impulses thus reducing the BP. The SNS is generally more activated in persons with hypertension than others. SNS activity is also greater in individual with obesity, in men than in women, in younger than in older persons, and in those with advanced kidney disease. Many patients with hypertension are in a state of autonomic imbalance with increased sympathetic and decreased parasympathetic activity. Models of obesity-related hypertension demonstrate that increased renal sympathetic nerve activity and its attendant increase in renal sodium reabsorption are key factors in the maintenance of sustained hypertension. The degree of BP elevation on the high salt diet was directly related to the degree of renal tubulo-interstitial fibrosis and decrease in glomerular filtration rate, suggesting that catecholamine-induced hypertension causes renal interstitial injury and a salt-sensitive phenotype that persists even after sympathetic over activity is no longer present. In addition, enhanced SNS activity results in alpha-1 adrenergic receptor mediated endothelial dysfunction, vasoconstriction, vascular smooth muscle proliferation and increased arterial stiffness, which contribute to the development and maintenance of hypertension.

THE ENDOTHELIUM

The endothelium is a major regulator of vascular tone and major funder to salt sensitivity through NO. NO is continuously released by endothelial cells in response to flow-induced shear stress, leading to vascular smooth muscle relaxation through activation of guanylate cyclase and generation of intracellular cyclic guanosine monophosphate. Interruption of NO production via inhibition of constitutively expressed endothelial NO synthase (NOS) causes BP elevation and development of hypertension in animals and humans.

DIAGNOSIS

Essential or primary hypertension is usually asymptomatic; thus, in clinical practice all adults should have their BP measured at regular office visits. Hypertension is most commonly diagnosed based on repeated BP measurements in a clinical office setting. The evaluation of a patient with

hypertension requires more than the diagnosis of elevated BP. It should also include assessment of the CVD risk, target organ damage, and concomitant clinical conditions that may affect the BP or related target organ damage as well as recognition of features suggestive of secondary hypertension.

ATHEROSCLEROSIS

Atherosclerosis is a disease in which arteries become narrow and hard due to a buildup of plaque around the walls of artery, it can be simply called hardening of arteries. Arteries carry blood from the heart to the rest of the body parts. A thin layer of cells forms a lining that keeps them smooth and allows blood to flow easily, this layer is called endothelium. Atherosclerosis is a major risk factor of the cardiovascular diseases. Atherosclerosis happens when the endothelium becomes damaged due to factors such as high B.P., smoking, fat, high levels of glucose, fat and cholesterol in the blood. This damage allows the collection of substances known as plaque, to build up in the artery wall.³⁰

The plaque which causes atherosclerosis consists of cholesterol, calcium, fat and other substances and it can become even more harder over time. Sometimes, pieces of this plaque break open and if this kind of breakage happens, platelets gather in that particular area and these can stick together forming blood clots. These changes in any person's arteries disrupt the flow of blood around the body and increase the risk of complications, such as heart attack, stroke or other CVDs and these complications can be life threatening and may be fatal. Atherosclerosis can affect any artery, but mainly it is seen in larger, high pressure arteries.³⁰

Atherosclerosis generally affects older people, but it can start to develop during adolescence. Inside the artery, streaks of WBC will appear on the artery walls. Often there are no symptoms for decades because the arteries enlarge at all plaque locations, thus there is no effect on blood flow. Signs and symptoms only occur after severe and hard plaque formation and severe narrowing of the arteries, it disrupts the blood flow to different organs and it is enough to produce symptoms. The symptoms still vary depending on which artery or organ is affected.³⁰

Narrowing in the coronary arteries which carries oxygenated blood to the heart, can produce severe symptoms such as shortness of breath, severe chest pain, nausea, sweating, dizziness, palpitations and abnormal heart rhythms (arrhythmia). Narrowing of carotid arteries shows symptoms such as difficulty in speaking, feeling of weakness, becoming dizzy, not being able to think straight, difficulty in standing straight, difficulty in walking, blurred vision, numbness in arms and legs, unconsciousness severe headache. All these symptoms may often lead to stroke which is death of brain cells due to the lack of blood supply to the brain cells.³⁰

Diabetes Mellitus

DM 2 is a major risk factor for CVD. CV complications are one the most common causes of deaths in patients suffering from DM2. Diseases of coronary arteries, peripheral arteries and carotid vessels are common CVD complications in patients with DM 2. Due to consistent high level of glucose in the blood cardiovascular diseases which are prevalent among large populations are stroke, myocardial infarction, angina pectoris, congestive heart failure. Risk factors for CV complication like obesity, dyslipidemia and hypertension are prevalent in patients with diabetes. Controlling cardiovascular effects in DM patients is a difficult task. Patients with DM often experience endothelial dysfunction, increased oxidative stress, autonomic neuropathy and increased coagulability such conditions often lead to CVD. Following are some risk factors of CVD which are prevalent among DM patients. ⁴

Hypertension is the most common risk factor of CVD and is also commonly seen in patients with DM. The percentage of prevalence of hypertension in DM type 1 is 30% and in patients with DM type 2 is 60%. Hypertension often causes diabetic nephropathy in patients with diabetes. Sustained hyperglycemic condition leads to release of growth factors from renal cells. This in turn leads to changes in structure in the glomeruli. Such changes exert unwanted stress on the glomerular filtration. This often leads to release of microalbumin through urine. DN can further progress to conditions like hyperlipidemia, proteinuria and cause CVD complications. ⁴

NUTRACEUTICALS FOR CVD

In natural products there are various nutraceuticals which can be found in food or parts o food and they provide us with medical or health benefits including the prevention and treatment of CVDs . These can also be defined as the medicinal products obtained from natural ingredients, since now several classes of nutraceuticals are proposed which show immense efficacy in reducing the risk factors of CVDs , some of them has a stronger evidence in doing the same .

BEBERINE

It is basically an alkaloid drug and it is found in the plants which belongs to Berberis species and generally it is found in the roots , stems , rhizomes and bark also isolated from a Chinese herb called *Coptis chinensis* .By taking human hepatoma cells (Hepg2) under consideration it is demonstrated that the extracts of berberine can inhibit cholesterol synthesis in the similar manner to the AMP activated protein kinase (AMPK) activator 5- aminoimidazole-4-carboxamide 1- β -ribofuranoside. And its activation is confirmed by measuring phosphorylation of acetyl-CoA carboxylase which serves as the substrate of AMPK , and it is even correlated with fatty acids oxidation . ³²

Its mechanism of action is decreasing the levels of cholesterol in hypercholesterolaemic patients , and it is mediated by increasing the expression of hepatic LDL receptor , and it also attributes to the inhibition of the transcription of mRNA which encodes the proprotein convertase subtilisin/kexin type 9 , which helps in the transition of LDL-C receptor from the surface of the cell towards lysosomes , hence increasing the half life of the receptor , it captures LDL-C receptor from blood plasma and send it to the bile for its elimination . Experiments are also performed on the basis of this mechanism . Hamsters are fed berberine 50 mg per kg twice a day , and it indicated the reduction in total cholesterol upto 27% , a LDL-C lowering of 0.4% , a TG lowering of 0.22% , while no change in HDL-C levels was observed . One other parallel study was focused on the use of 500 mg beberine along with red yeast rice , it involved 80 elderly dyslipidaemic patients intolerant to statins with high LDL-C levels and It showed a significant reduction in total cholesterol(20%) and LDL-C(31%) with the nutraceutical . So it is suggested that berberine based nutraceutical may be used to obtain the acceptable plasma LDL-C levels. Berberine based nutraceuticals showed both high tolerance and safety .The effects have also been shown to be independent of dose: 500 mg day⁻¹ in combination with red yeast rice and other nutraceuticals induced a reduction of approximately 20% of the LDL-C and 25% of triglycerides in patients with either pure hypercholesterolaemia, mixed dyslipidaemia, type 2 diabetes or hepatopathy. And hence overall it reduces the risk factors of CVDs .³²

The potential therapeutic uses of nutraceutical berberine is limited by its very low oral availability and it attributes to an unclear mechanism of metabolism in intestine, first pass metabolism and poor absorption. Many studies are done to explore how the bioavailability of berberine can be enhanced by reducing first pass metabolism. No serious side effects of berberine are found till now even though some mild side effects are shown like bitter taste of mouth, abdominal cramps, diarrhoea and constipation.³²

β – GLUCANS

A group which consists of β-D-glucose polysaccharides, it occurs naturally in the cell walls of some fungi, yeast and cereals . β-glucans have a linear backbone of β-glycosidic bonds (1-3) . They have different viscosities, solubility , properties and branching structures and that is why they show a variety of physiological effects . This is a viscous soluble fibre which show subsequent cholesterol lowering properties and hence it can reduce risk factors of CVDs . An analysis of random controlled trials showed that the potential of cholesterol lowering and reducing risk factors of CVDs of barley β-glucans on LDL-C , non-HDL-C and apolipoprotein B for cardiovascular disease risk reduction indicated that an average dose ranging from 6.5 to 6.9 gram per day of barley

β -glucan for four weeks reduce LDL-C (average -0.25 mmol.L-1) , non-HDL-C (-0.31 mmol.L-1) significantly , with no such changes to apoB levels compared with control diets . Even in 2006 FDA endorsed a health claim that shows the relationship between β -glucan soluble fibre from whole oatmeal sources and reduced the risk factors of CVDs and coronary heart diseases by simply adding barley as the additional source of the soluble fibre named β -glucan. Similarly in 2011 an opinion was published by EFSA which followed a request from the European Commission, which approved the substantiation of the claim related to β -glucans from barley and oat as they are able to maintain the normal levels of cholesterol in blood plasma and also reduce risk factors of CVDs as a result , as well as the claim related to reduction in the post-prandical glycaemic response.^{31 32}

POLYPHENOLS

Polyphenols are the phytochemicals which are found in wide variety of plants, foods and food products from plant origin. Polyphenols are found in vegetables, cereals, fruits and legumes too. They are also found in beverages produced from plant products as well such as tea, wine, cocoa, and coffee. As per their structures they are diverse, over 8000 polyphenols have been identified till now . Polyphenols includes phenolic acids, flavanoids , lignans and stilbenes. But some of the polyphenols which are found in grapes and grape derivatives, cocoa and tea especially green tea are very useful in the prevention and treatment of CVDs. Phenolic compounds that are found in grapes are flavanols , anthocyanins , phenolic acid , stilbenes , Reseveratol(3,5,4 –trihydroxy-trans-stilbene) is that compound which is studied the most , mainly it is derived from grapes , however it is also found in blueberries , peanuts , cranberries.^{5 6 7}

The frequent and widely spread use of tea makes investigation of its nutraceutical properties useful and essential , polyphenols found in tea are the flavins , catechins , tannins and flavonoids . The more the tea leaves fermented the less will be the amount of catechin left in tea leaves. Green tea which is minimally fermented has the most amount of catechins such as epigallocatechin gallate , epicatechin-3-gallate whereas the black tea is rich in flavins instead.^{5 6 7}

Effect of polyphenol rich grape extract(700mg) has been studied in a study on cardiovascular risk in healthy people and it can treat CVDs and can reduce total cholesterol and LDL-C concentrations in blood plasma. Meta-analysis of non randomized controlled trials showed evidences including 390 participants did not find any effect of grape of grape seed extract on LDL-C , no effect was seen in these participants . One study found that plasma concentration of large LDL-C and large LDL particles was compared with placebo were decreased in obese subjects those are given grape powder for 3 weeks .^{5 6 7}

One study on cocoa products showed that use of cocoa products can help in significantly reducing LDL-C levels, In a meta-analysis of six randomized controlled trials. The result we found are that consumption of cocoa products significantly lowered the levels of LDL-C by 5.87 mg/dl, marginally lowered total cholesterol by 5.82 mg/dl, but there is no effect found on HDL-C levels in blood plasma. The effects are dose dependent and observed in the subjects with high risk of CVDs but not in healthy participants. Some previous studies did not observe any benefits of polyphenols extracts from cocoa on blood lipids in subjects having high blood pressure or hypertension problem stage 1, patients with heart failure and overweight people.⁶

One other recent meta analysis of 19 randomized controlled trials with a total of 1131 participants showed that cocoa flavanols which are associated with increase in HDL-C (-0.06mmol/L) and reduction in total triglyceride (0.10mmol/L) intake. Some results from a recently published results from the Flavoiila Health Study revealed that daily ingestion of 450 mg of cocoa flavanols twice a day for a month, decreased total cholesterol levels by 0.20 mmol/L and LDL-C by 0.17 mmol/L whereas HDL-C levels increased by 0.10 mmol/L in a low risk, primary prevention population. Results from various studies concluded that cocoa flavanols predicted lowering of 10 year risk of CVDs, however only well designed studies can confirm whether this is the case.^{5 6 7}

It has been suggested that if we consume the fruits and vegetables that are rich in flavonoids may help in lowering blood pressure. Diverse studies have been done on the influence of polyphenols on blood pressure and that included a wide variety of foods that contain polyphenols, for example-berries, tea, cocoa product, grapes and other. Several studies showed that consumption of grape derived polyphenols show beneficial effects significantly and may help in lowering the blood pressure. On other side some studies did not encounter such an association, so the confliction between the results may be due to polyphenol source, heterogeneity of study design and population characteristics.⁷

One recently published controlled trial resulted that grape seed extract reduced the systolic B.P. by 5.6% significantly and the diastolic pressure by 4.7% after the subjects (having mildly elevated B.P.) were given this supplement for 6 weeks. The results indicated that B.P lowering effects are found to be dependent on the baseline blood pressure, subjects with higher baseline blood pressure showed the greatest reduction.^{5 6 7}

Following is the detail analysis of role of Berberine, Sterols/Stanol and Polyphenols on Cardiovascular diseases.

BERBERINE

Berberine (BBR) is an alkaloid of bright yellow color naturally isolated from the plant *Coptis chinensis*. This plant has been used in Chinese medicine for more than 2500 years. Recent researches showed that BBR had the effect of anti-heart failure, anti-hypertension, anti-hyperlipidemia, anti-insulin resistance, anti-arrhythmias, and anti-platelet aggregation.⁸ Berberine chemical characteristics and pharmacokinetics

BBR is a plant quaternary ammonium salt from the group of isoquinoline alkaloids with a molar mass of 336.36122 g/mol. BBR is yellow in color, which is why it was used to dye wool, leather, and wood. As a natural dye, berberine has a color index of 75160. Berberine has low bioavailability and shows poor absorption through the gut wall (<5%) and bowel P-glycoprotein appears to contribute to its poor absorption, actively expelling the alkaloid from the lumen mucosal cells. Standard doses of berberine are generally well tolerated and eventual adverse events are rare and mild. On the contrary, high doses have been associated with arterial hypotension, dyspnea, flu-like symptoms, gastrointestinal discomfort, constipation, and cardiac damage. The most studied side effects are those in the gastrointestinal system. Berberine and derivatives can also produce gastric lesions.^{9 10}

EFFECTS OF BERBERINE ON:

Heart Failure

Recent studies suggested that the mechanism of BBR for improving cardiac function may be related to increasing the concentration of calcium in cardiac muscle cells. It increases high energy phosphate in heart failure and prevented ventricular fibrillation due to its effects on potassium channels, increased intracellular calcium, and suppressed the delay of depolarization partly due to sodium influx. On the other hand, BBR has a sympathetic activity-modulated effect on myocardium.¹¹

Examination of hemodynamic parameters in humans reveals results with an increased cardiac index, increased left ventricular ejection fraction, decreased systemic and pulmonary vascular resistance and left ventricular end-diastolic pressures. In a clinical trial carried out on chronic heart failure patients, BBR decreased the frequency and complexity of ventricular premature complexes and increased the left ventricular ejection fraction.¹²

BBR has been recognized as being capable of decreasing cardiovascular through reducing oxidative stress, low-density lipoprotein (LDL), triglycerides, and insulin resistance and improving the mood.^{13 14}

Regulating Blood Pressure

Systolic and diastolic blood pressures are correlated with cardiovascular events. A consistent theme in the literature has confirmed that there is a close correlation between blood pressure and atherosclerosis.¹⁵

BBR can competitively block the α_1 receptor of VSMC, inhibit activity of the cholinophospholipid enzyme, and enhance the effect of acetylcholine. So it can dilate blood vessels and decrease blood pressure. It is reported that BBR can act on both endothelium and the underlying vascular smooth muscle to induce relaxation. Nitric oxide released from endothelium might primarily account for the BBR-induced endothelium-dependent relaxation, while activation of 4-aminopyridine and Ba²⁺-sensitive K⁺ channels, inhibition of intracellular Ca²⁺ release from caffeine-sensitive pools, or a direct relaxant effect are likely responsible for the BBR-induced endothelium-dependent relaxation. Mechanisms related to either Ca²⁺ influx or protein kinase C activation may not be involved. Both vaso relaxant and antiproliferative effects may contribute to a long-term benefit of BBR in the vascular system.¹⁵

Arrhythmia

Recent studies indicate that BBR may significantly prolong the duration of the action potential and the effective refractoriness of the cardiac cells and may improve cardiac reentry rhythm by modifying the unidirectional conduction block to a bidirectional conduction block or delaying the duration of the reentrant pathway. It has been demonstrated that berberine may protect the cardiac cellular membrane from interference by hydroxyl radicals and intracellular calcium overload. By its action, BBR may abolish the delay after depolarization induced by intracellular calcium overload and may thereby terminate arrhythmias associated with triggered activation. In the 24–48 h ambulatory monitoring of 100 patients with ventricular tachyarrhythmia, berberine caused a 50% or greater reduction in ventricular premature contractions in 62% of patients and a 90% or more reduction in 38% of patients.^{16 17 18}

Platelet Aggregation

Some studies show that BBR has a significant anti-platelet effect, explained by inhibition of arachidonic acid metabolism and calcium influx, but also by a partial agonistic effect on platelet α_2 adrenoreceptors. BBR inhibited thromboxane synthesis induced by collagen, adenosine diphosphate and arachidonic acid, and it might inhibit arachidonic acid metabolism in platelets and endothelial cells. BBR can cause potassium channel blockade resulting in prolongation of the action potential in cat ventricular monocytes. On the other hand, recent evidence suggests that BBR can also have prothrombotic effect-enhancing tissue factor activity.^{19 20}

Insulin Resistance

It has been observed that berberine acts as an insulin-sensitizing agent, therefore its activity has been compared with metformin in different animal models. In a rat model of type 2 diabetes, berberine showed better fasting plasma glucose and LDL-C lowering and better homeostasis model assessment of insulin resistance (HOMA-IR) than metformin by a mechanism involving retinol binding protein-4 (RBP-4) and glucose transporter-4 (GLUT-4). However, in another study, berberine was not inferior to metformin as an insulin-sensitizer.^{21 22 23}

Beyond the large preclinical literature, data on human glucose metabolism are really preliminary. However, a study carried out on subjects affected by type 2 diabetes, showed that 500 mg of berberine three times a day was associated with a significant reduction in hemoglobin- α 1 (HbA1) (-2%), fasting plasma glucose (-44%), postprandial glucose (-45%), fasting plasma insulin (-28%), and HOMA-IR index (-44.7%). In this study, berberine also significantly reduced the plasma total and LDL-C levels. Another study showed a nutraceutical containing berberine and chlorogenic acid was able to increase insulin-sensitivity and liver parameters for the short-term in overweight patients with mixed hyperlipidemia.^{21 22 23}

Sterols/Stanoles

Plants sterols also called phytosterols and stanols (saturated form of sterols) are the natural constituents of plants abundantly found in nature, as these are natural constituents of plants they are referred as non-nutritive compounds. They are structurally related to cholesterol. The difference between sterol and cholesterol is structure is very slight by a difference of a methyl or an ethyl group at the C-24 position. Saturated form of plant sterols are called plant stanols, they have a double bond in sterol ring. Saturation of plant sterols results in the formation of plant stanols and it can be done in laboratories. Plant sterols or stanols are a major group of nutraceuticals that has immense beneficial effects in treating diseases like dyslipidemia and reducing the risk factors of cardiovascular diseases.³⁰

Plant sterols or stanols are abundant in natural oils like olive oils and vegetable oils, but also in fruit and nuts. Further advancement in food technology indicated that food products like yoghurt, milk, margarine and cereal products are rich in plant sterols or stanols. Plant sterols or stanols reduce the cholesterol absorption in the intestinal gut thereby reducing plasma LDL levels. Intestinal absorption of plant sterols ranges from 0.4 to 5% and that of plant stanols is from 0.02 to 0.3%. As a result we can say blood plasma levels of plant sterols are 10 times more than the plant stanols. So plant sterols or stanols can be referred as the food that can help in reducing blood cholesterol and LDL-C levels and hence help in reducing the risk factors of CVDs. The plus point

is that there are no severe side effects seen after the administration of plant sterols or stanols in various studies and experiments.³⁰

A meta- analysis of 41 randomized controlled trials indicated that consumption of 2g/day of plant sterols or stanols reduced LDL-C levels in blood plasma by 10-11% . Additional effects were shown at little higher doses(2.5g/day) , But HDL levels are not affected by this . Plant sterols or stanols along with the drugs can help in treating hyperlipidemia or dyslipidemia more effectively . As such eating foods that are low in saturated fat and cholesterol and high in stanols or sterols has shown further reduction in LDL levels by 20% and adding sterols or stanols to statin medication seems more effective than doubling the statin dose .Circulating LDL-C levels are inversely proportional to the extent of sterol or stanol consumption. This could lead to reduction in cardiovascular diseases if this effect is associated with a reduction in cardiovascular events similar to that induced by other lipid lowering drugs. Esterified plant sterols or stanols showed similar results. When plant sterols or stanols were added to milk (15.9%) and youghurt (8.6%) and given to the subjects significant reduction in LDL and total cholesterol levels in blood plasma were seen , but significant less when added to bread(6.5%) and cereal(5.4%) . Hypercholestrolemia or dyslipidemia can be managed or treated by routine prescription of plant sterols or stanols in the clinical setting and as a whole it can help in the reduction of risk factors of CVDs . Some evidences exist that shows effect of sterol consumption on cardiovascular outcomes . Observation revealed that high intake of plant sterols might be associated with MI prevention in men. A meta-analysis of 15 trials revealed that a combination of statins and sterols or stanols lowered the levels of total cholesterol and LDL-C to a greater extent than statins alone . HDL-C and triglyceride levels were not affected by this .^{28 30}

The American Heart Association and the Current Dietary Guidelines support plant sterols as a therapeutic option for individuals with elevated cholesterol levels and those who have high risk of having CVDs .Various studies are also done to find anti-hypertensive effects of plant sterols or stanols but there are no evidences relating to their effects on blood pressure despite continuing treatment for a year more . However there are no adverse effects of plant sterols or stanols were seen on blood pressure .^{28 30}

Polyphenols

Polyphenols fall under the category of secondary metabolites found in plants. These play major role in plants by decreasing oxidative stress, by protecting plants from ultraviolet radiations and pathogens. Polyphenols are present in abundant amounts in fruits, vegetables, cereals, beverages like coffee, tea, red wine etc. Polyphenols show therapeutic and protective effects in cardiovascular

diseases like myocardial infarction, coronary artery disease, atherosclerosis. Polyphenols also are effective against osteoporosis, diabetes and cancer. Chemically, polyphenols contain one or more aromatic rings. These rings contain either one or more than one hydroxyl group. Polyphenols are further classified into flavonoids, stilbenes, phenolic acids and lignans. Polyphenols are generally found in conjugation with sugar moieties.^{5 6 7}

Classification:

1) Phenolic acids: These are found in two forms either as derivatives of benzoic acids or as derivatives of cinnamic acid. The hydroxy derivatives of cinnamic acids are found in abundant amount in fruits and vegetables whereas hydroxybenzoic acid is found in limits quantities in black radish, onions and other red fruits.

2) Flavonoids: These are the most commonly researched and studied polyphenols. All flavonoids have a structure of 3 aromatic rings in common. Based on the position of hetero-atom, flavonoids are classified into following:

- flavanols
- flavones
- flavanones
- flavanols
- anthocyanins
- isoflavones

3) Stilbenes: These are present in low amounts in human food intake. The most common stilbene found and known is resveratrol. Stilbenes act as antifungal in plants.

4) Lignans: These contain 2 phenol rings and 2,3-dibenzylbutane in their structure. The richest source of secoisolariciresinol (a common lignan) is linseed.

Different polyphenols are absorbed at different sites in human body, generally in different parts of gastro-intestinal tract.^{5 6 7}

Polyphenols are cardio-protective agents as they show following properties:

- antioxidant
- antiplatelet
- anti inflammatory
- HDL level enhancer
- improved endothelial functions.

Polyphenols show anti-oxidant properties as the phenol group by accepting electron reduces itself to phenoxyl radical and hence disrupts the chain of oxidation reaction. This anti-oxidant activity

prevents cells from oxidative stress and in turn show a protective activity against degenerative diseases.^{5 6 7}

Atherosclerosis is the condition in which lesions block the arteries compromising blood flow. This condition in turn lead to conditions like myocardial infarction, angina, cardiac arrest and other related cardiovascular conditions. LDL oxidation is one of the main mechanisms for atherosclerosis. Polyphenols are known to inhibit this type of oxidation. Hence, polyphenols show protective action against atherosclerosis.^{5 6 7}

The antiplatelet action of polyphenols is largely attributed to the prevention of adhesion and aggregation of platelets to collagen. Various studies have shown that polyphenols present in grape seed and polyphenols like resveratrol have efficient antiplatelet action owing to prevention of adhesion of platelets to collagen. Many polyphenols like flavonoids show antiplatelet action by preventing aggregation of platelets. Cyclooxygenase and lipooxygenase are generally the target sites for polyphenols. Synthesis of TXA₂ is known to be reduced by flavonols present in cocoa. Resveratrol inhibits calcium channels, calcium influx and hence platelet activation.^{5 6 7}

Many research studies have reported that catechins prevents the neutrophils migrating through the endothelial layer hence inhibits the production of chemokines at the inflammation site. Many polyphenols present in red wine are reported to prevent the granulocytes and monocytes from reaching the inflammation site. Other similar studies have shown evidence regarding the polyphenols present in curcumin causing reduction in the production of pro-inflammatory cytokines.^{5 6 7}

There are evidence of in-vitro studies illustrating the polyphenols present in beverages like green tea and wine prevents the process of angiogenesis. Angiogenesis is a common cause of proliferation of atherosclerotic plaque as it is known to deliver nutrients to it. Polyphenols inhibits the migration of endothelial cells and hence prevents proliferation of the plaque. The primary mechanism of anti-angiogenesis is the prevention of growth of endothelial cells of capillary vessels by inhibiting phosphorylation of mitogen activity protein kinase (MAPK).^{5 6 7}

Diabetes is a known risk factor for cardiovascular diseases. There are many studies providing evidence of effectiveness of polyphenols in lowering blood glucose levels in diabetic patients. In one such study, the effect of high concentration of polyphenols in aloe vera extract was tested in mice. In these mice insulin resistance was generated experimentally. The extracts of aloe vera contained known concentration of aloe-emodin and aloin. The positive control was pioglitazone and negative control was bi-distilled water. The factors measured were- body weight, blood glucose and insulin levels, food intake. Insulin tolerance test were conducted. Specimen which

were given aloe vera extract had lower blood glucose levels and body weight when compared to the one's in negative control group. Also, negative control group had highest blood glucose levels when compared to both specimen with aloe vera extract and specimen given pioglitazone. Oxidative stress due to elevated hyperglycemia is one of the major risk factors of cardiovascular diseases in patients with type 2 diabetes mellitus. Polyphenols are effective in controlling and preventing such conditions due to its therapeutic effects.^{4 5 6 7}

CONCLUSION

The aim of this review was to give a better understanding on the mechanism of action, potent uses and popular benefits of nutraceuticals in prevention, treatment of Cardio Vascular diseases. Nutraceuticals mentioned above gave us an overview about the available products that can be used according to the major risks factors contributing to CVDs. Overall scenario depicts the beneficial behavior of these products on hypertension, diabetes induced heart problems, arrhythmia, heart failure, atherosclerosis etc. Though there is still a room for exploration and confirmation about the understanding of their mechanism of action and exact effect and potency. There is often insufficient data available on long term safety and effectiveness against clinical outcomes like in myocardial infarction. Further clinical researches should be conducted to identify nutraceuticals to benefit the alternatives for treatment of these major diseases.

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