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A Review on the role of Flavonoids and their bioactive compound in Cardiovascular diseases

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ABSTRACT
Flavonoids are polyphenolic compound found in plants with a variety of chemical structures and properties. Flavonoids are absorbed through the gastrointestinal tracts of humans and animals and excreted either unchanged or as flavonoid metabolites in the urine and faeces.As a result, flavonoids are found in the human diet. Flavonoids reduce lipid peroxidation and powerful antioxidants, free radical scavengers and metal chelators. Flavonoids contain antioxidant, anti-inflammatory, anticancer, antiviraland antibacterial properties as well as a direct cytoprotective effect on the heart, circulatory system, pancreasand liver.Recent efforts in the field of high flavonoid–containing foods and cardiovascular disease have begun to provide the first well-controlled demonstrations of particular effects and mechanisms of action. The purpose of this review is to discuss the role of Flavonoids and their bioactive compounds in Cardiovascular diseases.
KEYWORDS: Antioxidant, Cardiovascular diseases, Vessel function, Anti-inflammation and Flavonoids

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INTRODUCTION

Coronary heart diseases, myocardial infarctionand stroke are examples of cardiovascular illnesses, which are a category of conditions that affect blood arteries and the heart. They are the largest cause of death in the world, with 17.9 million fatalities per year. The frequency of cardiovascular illnesses is linked to a number of risk factors. Non-modifiable risk variables (age, gender, ethnicityand family history) coexist with modifiable risk factors (hypertension, hyperglycemia, obesity, oxidative stress, physical inactivity, smoking poor diet and mental stress) [1]. Flavonoids contain anti-atherosclerotic properties such as anti-inflammatory, antioxidant, antiproliferative, antiplatelet and provessel activity, according to early research. Flavonoid's cholesterol-lowering and antihypertensive effects have been researched, but they appear to be minor in people. The studies also show that flavonoids have a variety of mechanisms and pleiotropic effects that may be involved in lowering the risk of cardiovascular disease. Flavones, flavanols, flavanones, catechins, isoflavones, proanthocyanins, and anthocyanidins are some of the subclasses of flavonoids that may contribute to the apparent positive benefits (Fig.1). Excessive consumption of saturated fat, processed red meat, sugarand sodium, as well as a limited intake of fruits, vegetables, whole grains, fibers, and legumes, are linked to an increased risk of cardiovascular disease [2,3].Flavonoids are a group of plant-derived bioactive chemicals that are produced via the shikimic acid pathway from the amino acid phenylalanine. Flavonoids were initially identified in 1930 by Hungarian scientist Albert Szent-Gyorgyi, who named them vitamin P. The French paradox, epidemiological research demonstrating the low incidence of coronary heart disease in the French population despite their high daily intake of saturated fats, sparked interest in the pharmacological and nutraceutical properties of these bioactive molecules only in the 1990s [4,5].

METHODOLOGY

A detailed published literature was searched on various reputed databases using different keywords. The adopted strategy and methodology of review is given below

THERAPEUTIC POTENTIAL OF FLAVONOIDS

Propolis (a resinous material collected by bees from plants and utilized as glue in their hives) has been used to cure a range of human ailments for ages, including inflammation, allergies, headache, cancer, viral infections, the common cold, bee stings, stomach and duodenal ulcers [6]. Flavonoid preparations have been used widely in medical practice for over 40 years to treat disorders of peripheral circulation [7]. Over 100 preparations containing flavonoids, including cyanidol, diosmetin, hesperidin, leucocyanidin, rutinand troxerutin, are marketed in France and Switzerland. However, therapeutic preparations of flavonoids have yet to pass controlled clinical trials. Red wine is high in flavonoidsand frequent red wine drinking has been linked to a lower incidence of coronary heart disease, which could explain the French paradox. The majority of research on flavonoids' biochemical effects has centered on their potential as medicines. The reported benefits of flavonoids have mostly been inferred from results at pharmacological concentrations. Consequently, the reported effects of pharmacological doses of flavonoids are primarily of pharmacological rather than dietary significance. As a result, more research into the biochemical effects of flavonoids in the diet is required [8,9].

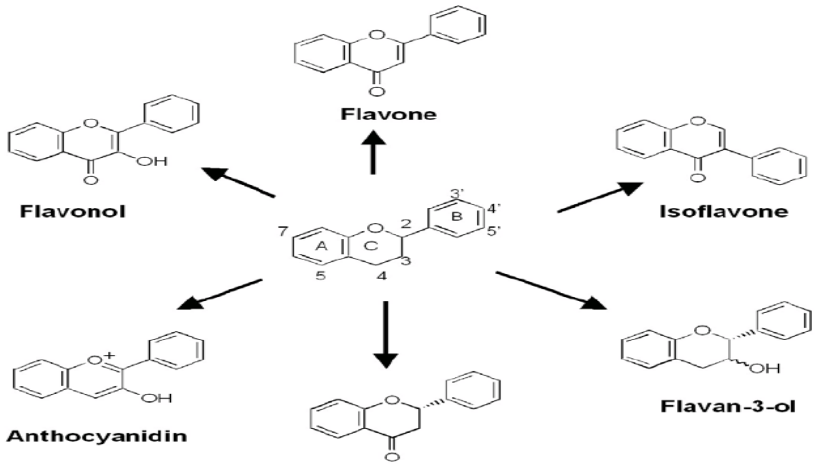

Fig.1: Basic structure of Flavonoids **[10]**

CLASSIFICATION OF FLAVONOIDS

Flavonoids are mainly classified into six types such as Flavanol, Flavanols, Flavones, Isoflavones, Flavanones, Flavanols on the basis of saturation levels and opening of central ring (Fig.2). Accumulating evidence obtained from in vitro, as well as in vivo clinical and epidemiological studies has highlighted the potential of flavonoids as beneficial agents capable of improving cardiovascular health and ameliorating risk factors associated with cardiovascular diseases. The direct antioxidant activity of this family of polyphenols is thought to be responsible for this impact. Flavonoids, on the other hand, have been shown to improve vessel vasodilation through endothelium-dependent and/or -independent mechanisms, reduce smooth muscle cell proliferation, inhibit platelet aggregation, reduce oxidative stress and inflammation, and have anti-obesity, anti-diabetic, and anti-hypertensive properties.

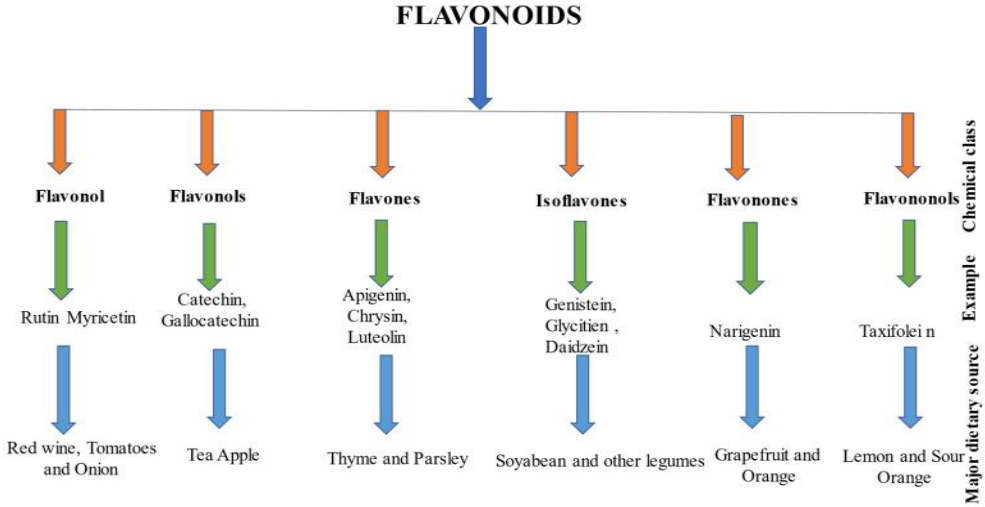

Fig. 2: Classification of Flavonoids

DIETARY INTAKE AND FOOD SOURCES OF FLAVONOIDS

Until recently, the only data on human flavonoid intake came from Ktihnau, who calculated that the average intake of total dietary flavonoids in the United States was around 1 g/day (expressed as glycosides), with flavanols, flavanones and flavones accounting for roughly 170 mg (represented as aglycones). These figures have been extensively publicized, although they are based on food analysis methodologies that are now regarded ineffective. Furthermore, estimates of flavonoid intake were based on analysis of whole foods and estimates of the average American diet extrapolated from the Organization for Economic Cooperation and Development, food consumption statistics thus overestimating food intake and consequently the average flavonoid intake. The content of the flavanols quercetin, kaempferol and myricetin and the flavones luteolin and apigenin in 28 vegetables, 9 fruits and commonly consumed in beverages (Table.1).The Netherlands was analyzed using more recent and advanced methodologies. Based on these analyses and using data from the Dutch National Food Consumption Survey 1987-88, the average dietary flavonoid intake in the Netherlands was estimated to be approximately 23 rag/day (expressed as aglycones). The 23 mg/day estimated flavonoid consumption was based on the concentration of five flavonoids in Dutch foods; consequently, the total flavonoid intake in this population could be higher. Furthermore, because this estimate is based on an investigation of foods typically consumed in the Netherlands, the flavonoid content of foods consumed in other countries may differ. To estimate flavonoid intakes in different populations, a thorough investigation of the flavonoid content of foods consumed in other nations is required [11]. Flavonoids have many beneficial effects on health, the most important being the antioxidant, anti-inflammatory, antiplatelet, antihypertensive and anti-ischemic effects**.**

ANTI-INFLAMMATORY ACTIVITIES

Flavonoids modulate the activity of arachidonic acid metabolizing enzymes, which is one of their direct activities. The rate-limiting step in the synthesis of prostaglandins, leukotrienesand platelet-activating factors is the production of arachidonic acid. Phospholipase A2 activates this pathway. The cyclooxygenase and lipoxygenase pathways are the two principal processes by which arachidonic acid is converted to numerous active molecules (eicosanoids). Acute inflammation is known to play a physiological role in defence and healing, but the mechanisms of inflammation regulation are disrupted in some pathological conditions, resulting in a long-term inflammatory process. Chronic inflammation, which disturbs homeostasis. Chronic inflammation can lead to the development of diseases including cancer, diabetes, cardiovascular disease, and neurological disease in the future. Pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-13, tumour necrosis factor, amyloid A, C-reactive protein) induce tissue damage in chronic inflammation. They attract immune cells and platelets, which secrete pro-inflammatory chemicals in turn. The degradation of lipids, proteins and nucleic acid during the inflammatory process causes oxidative stress, which affects cell integrity [12]. One of the key steps impacted by flavonoids is prostaglandin synthesis. Hesperidin and diosmin have been found to decrease prostaglandin production in vivo [13]. A number of in vitro studies have shown that certain flavonoids (bilobate, morello flavone, amentoflavone), as well as flavonoids in Sophora Flavescent, work by blocking the release of arachidonic acid [14]. Certain citrus flavonoids have been demonstrated to prevent the formation of a variety of pro-inflammatory mediators, the most prominent of which are prostaglandins and thromboxane A2 [15]. Apigenin has a significant anti-inflammatory action anddue to its lack of side effects, may one day be a viable alternative to present anti-inflammatory medications. *Artemisia Copa*, a plant high in flavonoids (spinacetin, penduletin, tricine, and jaceosidin), inhibits nitric oxide synthase and cyclooxygenase, resulting in lower levels of prostaglandins and nitric oxide. The flavonoids in this plant have been shown to be efficient in inhibiting the activity of phospholipase A2, with jaceosidin being the most active of these [16]. Studies have shown the effectiveness of a number of herbs in inhibiting phosphodiesterase, thus improving chronic inflammation and allergic reactions. Aglycones have been found to be the most potent inhibitors of the cAMP phosphodiesterase enzyme. In vitro investigations have also shown that bioflavonoids from *Ginkgo biloba* are PDE inhibitors [17].

ANTIOXIDANT ACTIVITY

Flavonoids are powerful antioxidants that can slow the progression of atherosclerosis by preventing LDL oxidation, blocking LDL absorption by macrophages and preventing the production of foam cells. In support of these possible activities, flavonoids prevent atherosclerosis in an animal model [18]. Flavonoids act as scavengers of superoxide anions and hydroxyl radicals, inhibiting LPO in vitro at the beginning stage. 13'2° Flavonoids are thought to stop chain radical processes by donating hydrogen atoms to the peroxyl radical, resulting in the formation of a flavonoid radical. The flavonoid radical in turn reacts with free radicals thus terminating the propagating chain. I3"46. In addition to their antioxidative

properties, some flavonoids act as metal chelating agents and inhibit the superoxide-driven Fenton reaction, which is an important source of active oxygen radicals. 2° However, there is no clear evidence of the antioxidant and free radical scavenging effects of flavonoids *in vivo* (18).

VASCULAR SMOOTH MUSCLE CELLS

The proliferation of vascular smooth muscle cells is a common component of atherosclerotic plaque formation. Apigenin inhibits the development of rat aorta vascular smooth muscle cells stimulated by growth factors (Kim et al., 2002). Epigallocatechin gallate, a key flavonoid component of tea, is a strong inhibitor of rat aortic smooth muscle cells. This activity is mediated by Ras=JNK and the downregulation of Cajun. The polyphenols in red wine stop vascular smooth muscle cells from migrating. The PI3K activity and the p38 (MAPK) pathways are both involved in the inhibition. As a result, flavonoids may act as a potent inhibitor of vascular smooth muscle migration and proliferation. More research is needed to confirm the effect and evaluate it in different models [18].

PLATELET ACTIVITY AND VESSEL FUNCTION

Platelets have a crucial part in the development of coronary artery disease. The activation of these cellular components results in the production of a wide range of proatherogenic substances, which is a key contributor to the development of thrombosis during acute coronary heart disease episodes. Aspirin, which has long been suggested as a preventive medication in the general population, reduces platelet activity. Flavonoid intake may also reduce platelet activity and the risk of coronary heart disease. Moderate consumption of red wine, a flavonoid-rich beverage, has been linked to a reduced risk of cardiovascular disease. The alcohol in wine, which may change blood lipoprotein levels, including an increase in high-density lipoprotein concentrations, is thought to be responsible for a portion of this beneficial effect [19]. Purple grape juice contains many of the flavonoids found in wine. As a result, there has been a surge in interest in the impact of purple grape juice on the risk of cardiovascular disease in recent years. The flavonoids in purple grape juice have antiplatelet and antioxidant properties. Several studies have shown an inhibition of platelet activity in the Foltz dog model of acute platelet thrombus formation by purple grape juice and quercetin, a constituent of grape juice [20]. Tea, a flavonoid-rich beverage, had no effect on platelet activity in patients with cardiovascular disease [21]. Platelet activity was measured 2 hours after consuming 450 mL of tea and after a 4-week long-term exposure (900 mL/day). The use of aspirin and antiplatelet agents by many of the patients may have reduced the severity of the response. Green tea catechins may stop platelets from clumping together by preventing an increase in cytoplasmic calcium [22]. As a result, the evidence suggesting a link between flavonoid-rich food consumption and platelet inhibition is equivocalnonetheless, the relationship may be complex. The results of platelet tests using meals and pure flavonoids imply that flavonoids work together to decrease platelet function [23]. Identification of the agents in purple grape juice, as well as a better understanding of flavonoid metabolism, are both essential research topics. Various pure flavonoids have been demonstrated to exhibit antiplatelet action in vitro and have been previously documented [24].

EFFECTS OF FLAVONOIDS IN HYPERTENSION

In terms of mortality and morbidity, cardiovascular disease ranks first in the globe. High blood pressure, age, obesity, dyslipidemia, sedentary lifestyle, smoking, stress, and an unsuitable lifestyle are only a few of the risk factors for these disorders. Nitric oxideproduced by the endothelium is well known for its role in controlling vascular tone and blood pressure [25]. The activation of the cGMP-protein kinase G cascade in smooth muscle cells in arteries is the mechanism through which Nitric oxide works. Following activation of the cascade, potassium channels are stimulated, resulting in membrane hyperpolarization and blockage of intracellular calcium influx, resulting in vasodilation. Protein kinase G's function is dependent on the phosphorylation of myosin light chains, which causes smooth muscle vasoconstriction in the arteries to diminish [26, 27]. Endothelial denudation was used in in vitro investigations, revealing that quercetin and kaempferol's antihypertensive impact is dependent on Nitric oxide produced in the endothelium. This theory was proposed as a significant reduction of the vasodilator activity of the two flavanols was observed when using endothelial denudation [28, 29].

ANTI-THROMBOTIC ACTIVITY

Interactions between platelets and blood vessels have been linked to the development of thrombosis and atherosclerosis. Flavonoids in particular reduce platelet aggregation and adhesion, lowering the risk of thrombosis. Flavonoids' antiaggregatory actions, on the other hand, cannot be linked to a single molecular mechanism because they appear to affect many platelet function pathways. [30]. Also, flavonoids inhibit platelet aggregation by antagonizing thromboxane formation and thromboxane receptor function. One of the most potent mechanisms by which flavonoids appear to inhibit platelet aggregation is by mediating

increases in platelet cyclic AMP (cAMP) levels by either stimulation of adenylate cyclase or inhibition of cAMP phosphodiesterase activity [31, 32]. The structural features required for flavonoids to inhibit human platelet aggregation and adhesion are similar to those associated with the antioxidant function of flavonoids and the inhibition of cAMP phosphodiesterase and include a double bond between C-2 and C-3, a 3-OH group, and a carbonyl group at C-4. The inhibitory effect of flavonoids on platelet function is diminished by glycosylation at C-3,15 saturation of the double bond between C-2 and C-3, and poly hydroxylation. Platelet function appears to be unaffected by flavonoid glycosides and flavanone derivatives [33, 34].

FLAVONOIDS AND ATHEROSCLEROSIS

Under some circumstances, vessel walls can start to fill up and thicken due to the accumulation of blood-carried or even vessel-wall produced substances, such as cholesterol, fatty acids, calcium, fibrin and cells such as red blood cells, platelets, smooth muscle cells, fibroblasts and macrophages. This process, called arteriosclerosis, hardens, stiffens and narrows the vessel where it occurs, decreasing the supply of blood reaching the tissue. When, due to obesity, an unhealthy diet or a lipid metabolism problem, cholesterol and fatty substances (such as triglycerides and LDL), but also fibrin, calcium and extracellular matrix components, accumulate into the vessel wall, macrophages infiltrate and phagocyte the oxidized LDL (ox-LDL) due to high levels of oxidative stress, becoming “foam cells”, so-called because of their appearance due to the droplets of fat inside them. The infiltrate forms the typical fatty streaks in atherosclerotic vessels. This complex mixture of substances from the blood and vessels, together with the infiltrated vascular cells is named “plaque”, which completely alters the vessel wall, making it harder and narrower, resulting in a particular type of arteriosclerosis called atherosclerosis. With time, plaque can evolve to become so big as to create a thrombus able to obstruct the vessel and produce tissue ischemia. Or, on the other hand, it can become unstable, rupture and release a fragment, and emboli, which could cause an embolism clogging a vessel anywhere in the body. Thus, atherosclerosis is a chronic disease, developed silently during many years until its sudden clinical manifestations appear which are ischemic heart disease, stroke and peripheral arterial disease. Chronic inflammation, oxidative stress, high blood cholesterol and lipid levels, obesity, smoking, increasing age, hypertension, family history, endothelial dysfunction, an unhealthy diet, insulin resistance and diabetes are known risk factors for atherosclerosis. Although mortality derived from ischemic heart disease or stroke has clearly declined since the 90’s in developed countries, ischemic heart disease is still the main cause of premature adult mortality. Therefore, atherosclerosis is the most common, worldwide spread and, hence, the most dangerous form of arteriosclerosis. Flavonoids are endowed with multiple and diverse mechanisms of action such as enzyme inhibition and activation, modulation of gene and protein expression, antioxidant, antimicrobial, antiviral, anti-ulcerogenic, cytotoxic, anti-neoplastic, mutagenic, antihepatotoxic, antihypertensive, hypolipidemic, antiplatelet and anti-inflammatory activities. Because of these actions, flavonoids are able to affect the course of the disease and prevent or reduce it, either in vitro, in vivo or even as observed in clinical trials [35-37].

EPIDEMIOLOGY

Several epidemiologic studies have associated flavonoid intake with a low risk of cardiovascular disease. One such study found a relative risk of nonfatal myocardial infarction of 0.77 among male smokers was high as compared with a low intake of flavanols and flavones [38]. The Physicians Health study did not find an association between flavanol and flavone intake and the risk of nonfatal coronary heart disease. A nonsignificant association was found between flavanol and flavone intake and coronary mortality rates [39].

MECHANISMS OF ACTION OF FLAVONOIDS AS CARDIO PROTECTIVE AGENTS

Recently there has been a surge in the number of studies on flavonoids as cardioprotective agents because of their diverse biological activities. The mechanism by which the flavonoids act as significant cardioprotective agents is basically depends on its antioxidant, anti-inflammatory, antiplatelet and anti-apoptotic properties (Fig.3). Several studies indicate that flavonoids have antioxidant properties, which may be related to their ability to chelate metal ions, scavenge reactive oxygen species, inhibit lipid peroxidation reaction and also through the increase of cellular antioxidants enzymes and inhibition of various cellular oxygenase’s such as xanthine oxygenase, NADPH oxidase and Hem oxygenase -1(HO-1) [40]. Flavonoids suppress a number of pro-inflammatory factors including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-a (TNF-a) as well as inflammatory mediators such as Nitric Oxideand leukotriene and acts as anti-inflammatory (Table.2). Antiplatelet aggregation is particularly important in the prevention of ischemic heart diseases [41]. Flavonoids have an anti-platelet

aggregation action through suppressing thromboxane A2 synthesis [42]. Prostacyclin and Thromboxine-A2 promote a dynamic balance in the clotting cascade under normal physiological conditions [43]. Excessive production of Thromboxine-A2 in reperfusion leads to platelet aggregation resulting in lipid peroxidation and release of free radicals which impede the release of prostacyclin. On other hand, prostacyclin prevents platelet aggregation and facilitates vasodilation. Apoptosis of cardiomyocytes results in the loss of cardiac contractile units [44]. This may lead to cardiac fibrosis and heart enlargement [45, 46]. As a result, the heart's ability to contract and relax normally is reduced, which causes systolic and diastolic dysfunction, which ultimately lead to cardiac failure [47]. In this context, the protective potential of different flavonoids has received a lot of attention. Flavonoids suppress caspase-3, Bax and Bcl-2 expression, increase myocardial contractile protein expression and promoting viability of cardiomyocyte through restoring AKT and ERK1/2 activation. In addition, flavonoids inhibit mitochondrial permeability transition pore (mPTP) as well as maintain mitochondrial ATP output and calcium homeostasis [48, 49].

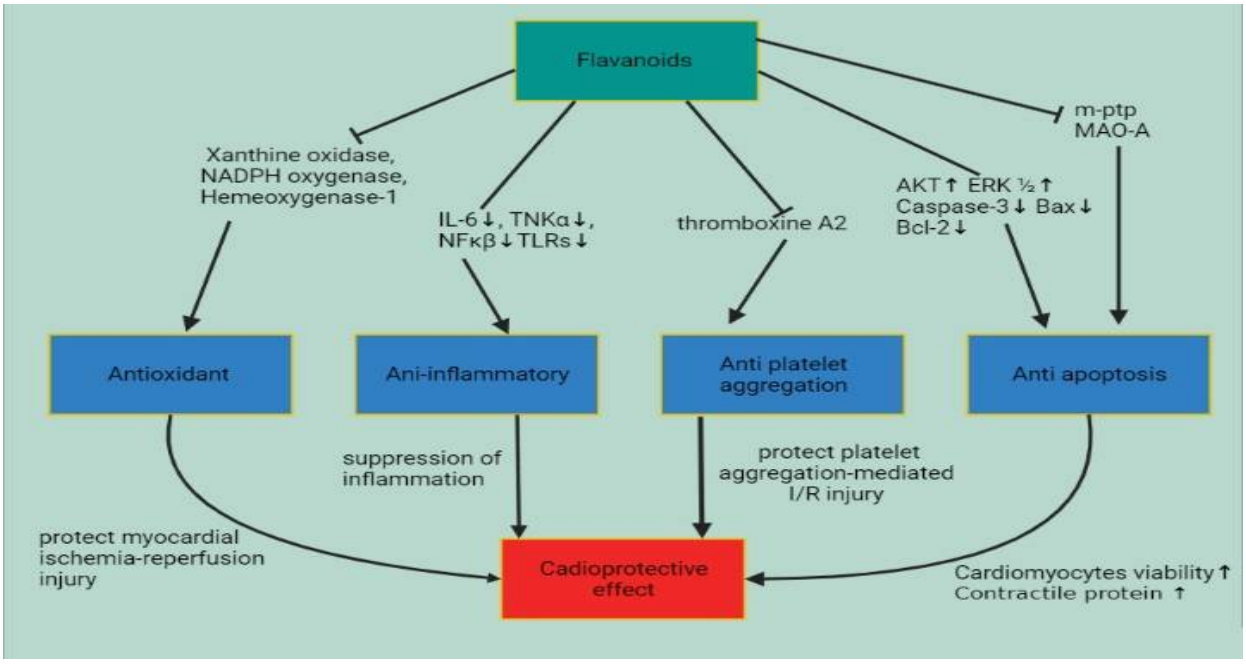

Fig.3: Mechanisms for Cardio protective effects of Flavonoid

Flavonoids groups	Compound	Dietary source
Anthocyanins	Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin	Blueberry, black grapes, cheery, rhubarb, plum, strawberry, red cabbage purple grapes, raspberry seeds
Flavanols	Quercetagetin, Quercetin, Kaempferol, Myricetin, Isorhamnetin	Olive, tomato broccoli, green and black tea, blueberry, black grapes, red apple
Flavanols	Catechin, Epicatechin Epigallocatechin, Silibinin, Silymarin, Taxifolin, Pinobanksin, Proanthocyanins	Apricot, apple, bean, peach, cider, green tea, berries, grapes, cocoa, chocolates
Flavones	Apegenin,Chrysin, Luteolin, Tangeretin, Rutin, Tetrametoxylflavone, Sinensetin, Quercetagetin	Capsicum, parsley, celery, hot peppers, thyme
Flavanones	Naringenin, Eriodictyol, Hesperitin, Dihydroquercetin, Dihydrobinetin	Citrus fruits, Orange, Grapes, lemon
Isoflavones	Daidzein, Genistein, Glycitein	Soya foods, soya cheese, soya flour, tofu, Legumes

Table.1: Flavonoid types with their major dietary source

S. No	Plant	Flavonoids	Action on Cardiovascular System	Targeted condition
1	*Abelmoschusesculentus*	Quercetin	Antioxidant, hypolipidemic and anti-inflammatory	Atherosclerosis, stroke, hypertension
2	*Ajuga iva*	Naringenin, apigenin-7-O-neohesperidoside	Antioxidant, anti-inflammatory anti-hypercholesterolemia	Atherosclerosis
3	*Corchoruscapsularis*	Luteolin	Antioxidant, hypotensive, diuretic	Hypertension, ischemic cardiac disease
4	*Cymbopogoncitratus*	Tannins, luteolin, apigenin	Vasorelaxation, antioxidant, anti-inflammatory	Hypertension
5	*Dracocephalummoldavica*	Tallianine, luteolin, apigenin, diosmetin	Antioxidant	Ischemic heart disease
6	*Equisetum arvense*	Resveratrol, apigenin, quercetin	Antioxidant and anti-inflammatory	Hypertension, ischemic cardiac disease
7	*Ephedra gerardiana*	Epiafzelechin (flavanol), quercetin, Gallo catechin, apigenin, luteolin	Diuretic, anti-inflammatory, hypotensive, antioxidant	Hypertension
8	*Heliotropiumtaltalense*	Naringenin, pinocembrin, Quercetin	Anti-inflammatory, antioxidant, vasorelaxation	Hypertension
9	*Lens culinaris*	Quercetin, kaempferol	Anticoagulant, anti-platelet	Cardiovascular diseases associated with hyperactivation of platelets
10	*Moringaoleifera* Lam.	Catechin, epicatechin, kaempferol, quercetin	Antioxidant, anti-inflammatory	Hypertension, ischemic cardiac disease
11	*Polygonum minus* (*Persicaria minor*)	Myricetin, quercetin, methyl-flavanols	Antioxidant, anti-inflammatory	Atherosclerosis, hypertension, ischemic heart disease
12	*Trichosantheskirilowii*	Luteolin	Hypolipidemic, antioxidant, anti-atherosclerotic	Ischemic cardiac disease, hyperlipidemia, hypertension

Table.2: Recent studies discussed the relationship of flavonoids–cardiovascular disease

CONCLUSIONS

Recent research has made significant progress in identifying the biological actions of these chemicals, particularly in the area of activities that may act to prevent cardiovascular disease. Several fields of research appear promising and could have significant health implications. Anti-atherosclerotic properties of flavonoids include anti-inflammatory, antioxidant, antiproliferative, antiplateletand pro-vascular function. The flavonoids appear to have minimal cholesterol-lowering and antihypertensive effects. Many of these functions have been demonstrated in cellular systems and animals in the lab. A number of these activities have been evaluated using human participants. However, further human research is needed to confirm the majority of flavonoid effects and assess their health consequences. Studies are especially important for evaluating dose effects, which are frequently missing in current research. Flavonoids' pleiotropic effects and the probability that their cumulative effect will increase the risk of cardiovascular disease more than individual effects, such as improved artery function, should be considered in the design and analysis of such trials. Another factor that influences how these studies are interpreted is the need for a better knowledge of flavonoid absorption and metabolism. Despite considerable advances in this field, flavonoid metabolism is complex, and the real flavonoid or metabolite with biological activity in vivo is rarely identified. Understanding the role of flavonoids in the prevention of cardiovascular disease will require the identification of flavonoids that occur in vivo as well as their biological activity. Another drawback of many current human research is that they have only looked at flavonoid-rich diets, which can contain a wide range of flavonoids and phytochemicals. As a result, pinpointing a single flavonoid that triggers the effects has been difficult. The identification of flavonoid-specific effects in humans, as well as the active molecules and their impact on the risk of cardiovascular disease, will necessitate more advancement in various areas. Following these discoveries, clinical trials to determine the impact of particular flavonoids on human health should be possible.

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CONFLICTS OF INTEREST
The authors declare no conflict of interest.

AUTHOR'S CONTRIBUTION
All the authors have contributed equally.

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