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Flavonols: Sources, Biosynthesis and their protective mechanism in Hypertension

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Abstract
The paper below discusses and delves into the importance and uses of the organic compounds, flavonols, especially their highly integral roles in preventing and alleviating hypertension and cardio-related diseases. Flavonols are polyphenolic, polyhydroxy phenolic compounds found in plants, which contribute to secondary metabolism. The paper also discusses the forms of flavonols including quercetin, kaempferol, myricetin and rutin which can be found in varying compositions in fruits and vegetables such as berries, apples, grapes, peaches, tomatoes, blackberries, cranberry, raspberries, squash, brussels sprouts, leek endive, cucumbers, lettuce, spinach, kale, broccoli and so on. It also discusses the stages involved in the biosynthesis of flavonols which begins with the shikimate pathway, where chorismate-a precursor essential for producing aromatic acids- is formed from simple sugars and ends with flavonoid biosynthesis which entails the formation of various forms of flavonols through a series of reactions. The endothelium helps to keep the vascular tone as well as homeostasis in check by secreting vasoactive molecules while the Renin-Angiotensin-aldosterone-system (RAAS) is highly essential for the control of arterial pressure. Some of these forms of flavonols; quercetin and kaempferol help lower blood pressure by improving endothelial function, enhancing nitric oxide production, and exerting antioxidant effects that reduce oxidative stress, actions which collectively improve vascular relation, reduce inflammation and by extension, reduce blood pressure.
Keywords: Flavonoids, Flavonol, Endothelium, Cardiovascular diseases

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1.0 BACKGROUND

Flavonoids are a group of substances produced as secondary metabolites within plants in response to environmental and natural factors such as temperature, fungi attack, ultraviolet radiation, drought, season and stress (Arpita et. al., 2022). Secondary metabolites are made to protect plants from

external stimuli, natural and environmental-induced stress. They are essential for plant signaling and contribute to plant defense mechanism (Saurabh et al., 2015). They are found in abundant form in almost all growing parts of plants and are produced alongside pigment chlorophyll and carotenoids. In addition to their ability to confer protection to plants, they provide taste and fragrance to flowers, seed making such plants attractive to living organism (Amalesh et al., 2011).

Due to their potential benefits in plants, studies have demonstrated that flavonoids are beneficial to human health when they are included in human nutrition. They have several biological and pharmacological effects ranging from antioxidant activity, anti-inflammatory, antibacterial effects, antiviral effects, protection of the skin from UV light, protection of DNA from oxidative damage, capillary strengthening to cardiovascular benefits (Abhay and Shashank, 2013).

Flavonoids possess a general framework consisting of a linear carbon chain (C- C3 - C6) with two aromatic rings (A and B). These rings, each composed of six carbon atoms, are connected by a three-carbon chain (C3) to form a heterocyclic oxygen-containing ring (ring C), which is closely joined to the A ring (Tsao and McCallum, 2010).

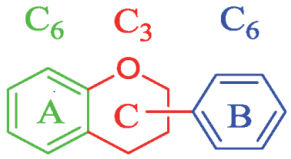


Figure 1: Basic C_6-C_3-C_6 framework in flavonoids (Rehan, 2021)

They exist in over 4,000 forms; however, they have been classified into six major subgroups according to the carbon atom position in the C ring where the B ring is attached, based on the degree of unsaturation, and considering the oxidation state of the C ring. Flavonols, flavones, isoflavones, anthocyanidins, flavanols, leucoanthocyanidins, flavanones and chalcones.

The structural formula of flavonoid subgroups varies around their heterocyclic ring. Different subgroups or classes of flavonoids perform various functions, which depend on the location of the bond between the B ring and the C ring, the extent of hydroxylation, the level of unsaturation, and the presence or absence of oxidation in the C ring.

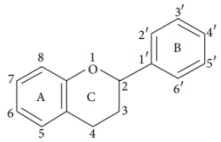


Figure 2: Basic structural backbone of flavonoids consisting of two aromatic rings (A) and (B) linked by the heterocyclic ring (C) (Kumar and Pandey, 2013)

2.0 Flavonols

They are ketone group contain flavonoids which have a 3-hydroxyl flavone backbone with addition of a double bond linking second carbon (carbon 2) and third carbon (carbon 3), a carbonyl group at fourth carbon (carbon 4) and an attached hydroxyl group on carbon 3 of the C ring (Butun *et al.*, 2018; Panche *et al.*, 2016; Mahmud *et al.*, 2023; Ruiz-Cruz *et al.*, 2017).

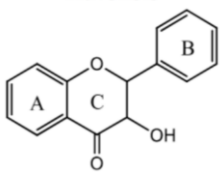


Figure 3: The flavonol backbone (Dias et al., 2021).

Flavonol occur in nature that is, in fresh plants as glycosides where they are bound to

sugars such as glucose, rhamnose, galactose and. glucoronic acid (Ferreres and Barberan, 2012). The glycosylation occurs majorly at the carbon 3,5,7. Aglycones are free forms of flavonoids (flavonols) which exist with no attached sugar moiety in their structure. These acylycone of flavonols include; Quercetin, Myricetin, Rutin, kaempferol, fisetin.

2.1 Biosynthesis of Flavonol

Flavonol biosynthesis involves three key pathways: the shikimate pathway, the phenylpropanoid route, and the flavonoid biosynthesis pathway. The shikimate pathway initiates the biosynthesis process of flavonoids by producing the shikimic acid. The pathway begins with the condensation of phosphoenol pyruvate (PEP) and D-erythrose 4-phosphate (E4P) into a seven-carbon keto acid, 3-deoxy-D-arabino-heptulosonate-7-phosphate (DAHP). This initial step, known as aldol condensation, is catalyzed by the enzyme 3-deoxy-D-arabino-heptulosonate-7-phosphate synthase (DAHPS) (Rehan, 2021). DAHP then undergoes intramolecular cyclization, transforming into 3-dehydroquinic acid (DHQ) through the action of the enzyme 3-dehydroquinic acid synthase (DHS). Following this, 3-dehydroquinic acid loses a water molecule, forming 3-dehydroshikimic acid (DHS). The fourth stage involves transformation of 3-dehydroshikimic acid (DHS) by removal of one water molecule into shikimic acid (Coracini *et al.,* 2014; Blanco *et al.,* 2013). In the fifth stage shikimic acid is phosphorylated with ATP at its 5-OH group. The phosphorylation reaction is initiated by the activation of the shikimate kinase enzyme, resulting in the conversion of shikimic acid into shikimic acid 3-phosphate (S3P). Shikimic acid 3-phosphate is subsequently transformed into 3-enolpyruvyl shikimate-5-phosphate (EPSP) through the action of the 3-enolpyruvyl shikimate-5-phosphate synthase (EPSPS) enzyme (Coracini *et al.,* 2014; Blanco *et al.,* 2013; Rehan, 2021). The final stage of the pathway involves chorismate synthase, which catalyzes the 1,4-transamination of the phosphate group at carbon 3 of 3-enolpyruvyl shikimate-5-phosphate (EPSP), resulting in the formation of chorismic acid, the end product of the shikimate pathway.

The next step is the biosynthesis of phenylalanine. Chorismic acid undergoes conversion into phenylalanine through the activity of prephenate aminotransferase (PAT) and arogenate dehydratase (ADT) (Rehan, 2021; Tariq, 2023). Chorismic acid is initially activated by chorismate mutase (CM), forming prephenic acid. Prephenate aminotransferase (PAT) facilitates the transformation of prephenic acid into arogenic acid (Nabavi et al 2020; Dias et al 2021). Arogenic acid is then transformed into the amino acid phenylalanine through the action of arogenate dehydratase (ADT) (Dias *et a*l., 2021). Arogenate dehydratase is the final enzyme in the biosynthesis of phenylalanine. The production of phenylalanine via the shikimate pathway is a crucial step in flavonol biosynthesis, as it provides the amino acid phenylalanine, leading to the subsequent phenylpropanoid pathway (Nabavi *et al.,* 2020).

In the phenylpropanoid pathway, phenylalanine ammonia lyase (PAL) initiates the process by deaminating phenylalanine to

form cinnamic acid, along with the removal of an ammonium ion. This is followed by the conversion of trans-cinnamic acid into 4-coumaric acid through the action of cinnamate-4-hydroxylase (C4H), after which 4-coumaric acid is converted into 4-coumaroyl-CoA by 4-coumaroyl-CoA ligase (4CL) (Rehan, 2021; Tariq, 2023).

The action of 4-coumaroyl-CoA-ligase on 4-coumaroyl-CoA provides the coumarin skeleton and initiates the flavonoid pathway, indicating its importance in the biosynthesis of flavonoids (Tariq et al., 2023).

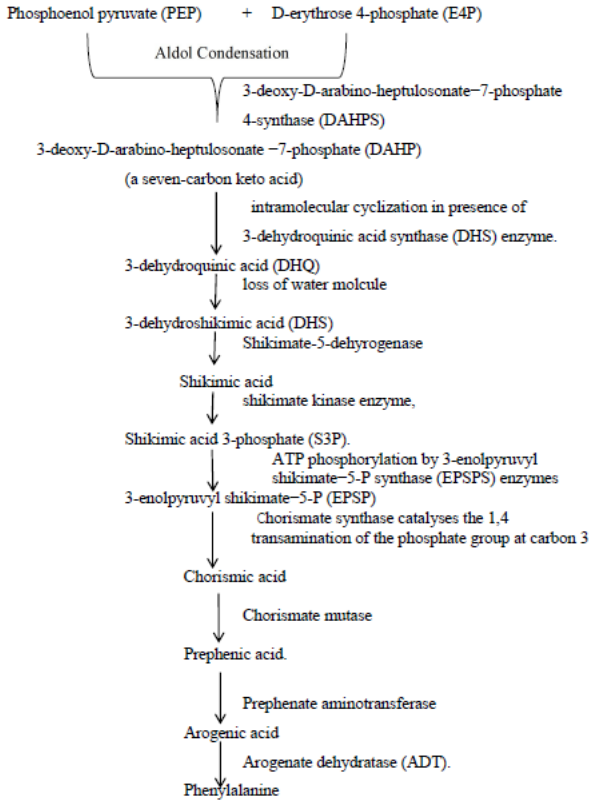


Figure 4: The Shikimate Pathway

The biosynthesis of flavonoids begins with the condensation of one molecule of 4-coumaroyl-CoA with three molecules of malonyl-CoA to produce chalcone (2′,4′,6′,4-tetrahydroxy chalcone), catalyzed by the enzyme chalcone synthase (CHS) (Austin and Noel, 2003). The A ring is synthesized from three malonyl-CoA molecules while 4-coumaroyl-CoA produces the B ring. Condensation of rings A and B by chalcone synthase generates chalcone which subsequently undergoes isomerase-cyclization to form flavanone by chalcone flavanone isomerase (CHI) enzyme, this forms the C ring (Tariq *et al.*, 2023). The flavanone (Naringenin) serves as a major intermediate in the synthesis of flavonoids, and it is modified into different flavonoids subgroups. For the synthesis of flavonols, flavanone undergoes oxidation to flavonols, this is catalysed by flavonol synthase (FLS) (Nabavi *et al.*, 2020).

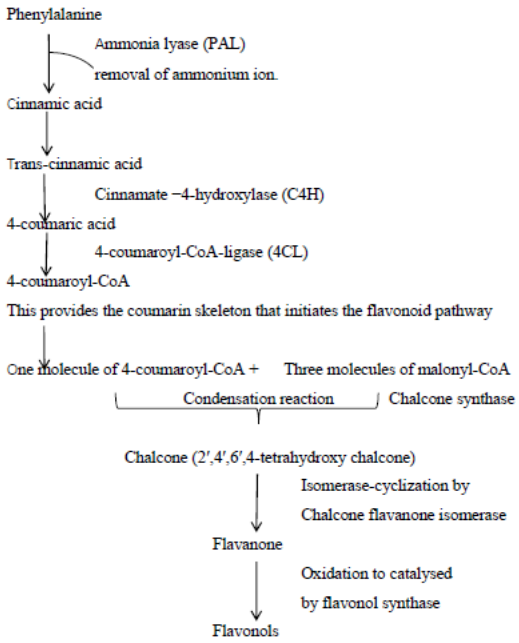
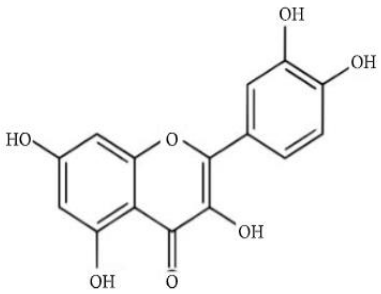
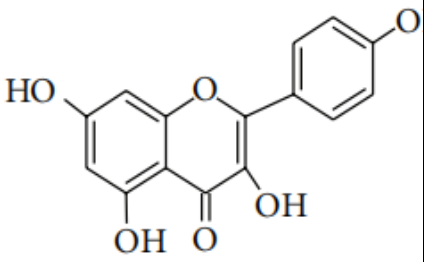
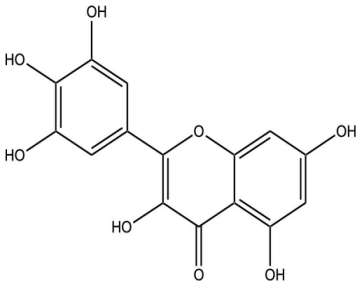
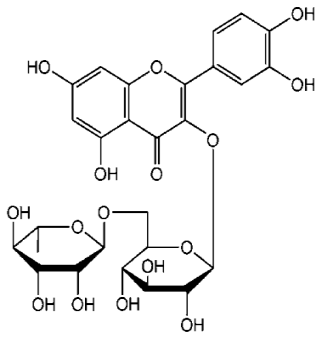
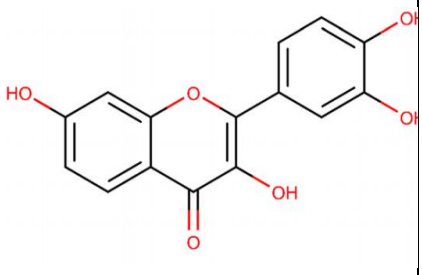


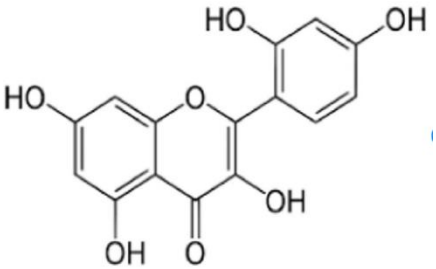
Figure 5: An Illustration of the phenylpropanoid pathway leading to the biosynthesis of flavonols

2.2 Flavonols, Structures and their Sources

Table 1: Flavonols, Structures and their Sources

Quercetin		3,3',4',5,7-pentahydroxyflavone)	Apples, grapes, berries, blackcurrant,tomatoes, apricot, cranberry, peaches, red pepper. onions, kale. broccoli, lettuce, spices, soups, fruit juices, red wine, black tea and infusion, beans, peas (Larson *et al.,* 2009; Duarte *et al.,* 2001; Popiolek-Kalisz and Fornal, 2022; Ożarowski *et al.,* 2018).
Kaempferol		3,4′,5,7-tetrahydroxyflavone	Berries, apples, grapes, peaches, tomatoes, blackberries, cranberry, raspberries, squash, brussels sprouts, leek endive, cucumbers, lettuce, spinach, kale, broccoli, parsley, beans green beans, potatoes, green tea, black tea, infusion tea (Dabeek and Marra, 2019, Jan *et al.,* 2022, Kamisah *et al*., 2022; Alam *et al*., 2019; Kamisah *et al*., 2023).

Myricetin		3,5,7,3',4',5 ' - hexahydroxy-flavone)	Sweetberries, berries, cranberry, blackberry, blueberry, grapes, dock, onions, parsley, spinach, garlic, rutabagas, peppers, hot chili, green broad beans, beans, immature seeds, nuts, tea, and red wine (Nalla and suhasin 2021; Jomová et al.,201; Imran 2021; Huang JH *et al.*, 2010; Jung SK, *et al.*, 2010).
Rutin		3,3' ,4' ,5,7-pentahydroxyflavone-3-rhamnoside)	Buckwheat, asparagus, red pepper,spinach apple, berries, peaches citrus fruits, grape seeds, Green tea (Bazyar *et al.*, 2023; li *et al*., 2017; Raju *et al*., 2019).
Fisetin			Strawberries, apples, persimmons, grapes, onions, cucumbers, kiwi fruit, peaches, tomatoes (Ahmad *et al*., 2017).
Morin		(3,5,7,2′,4′ - pentahydroxyflavone)	guava leaves, onion, and apple, white mulberry, figs, guava, guava leaves, tea,

			Osage orange, jack fruit, old fustic, apple skin, sweet chestnut, red wine, onion, almond, sweet chestnut, seaweed, coffee, and cereal grains (Oyagbemi *et al*., 2020; Prahalathan *et al*., 2012; Gopal, 2013; Solairaja *et a*l., 2020, Rajput *et al*., 2020, Lotito and Frei ,2006; Rattanachaikunsopon and Phumkhachorn,2010).

3.0 The Endothelium and Cardiovascular Diseases

Cardiovascular disease is a degenerative disease that affects the world population and it has characterized by high mortality and disability rates. It is determined by several pathogenic factors ranging from oxidative stress, inflammation to arterial plaques. Cardiovascular diseases significantly increase the risk of cardiac conditions and vascular endothelial dysfunction in humans (Roth et al., 2017; Ren 2019; Widmer and Lerman, 2014). Hypertension represents a major risk factor for cardiovascular diseases, with numerous studies indicating that oxidative stress, characterized by elevated levels of reactive oxygen species (ROS), plays a central role (Rodrigo, 2011). This chronic condition is defined by endothelial dysfunction, hyperlipidemia, and smooth muscle cell contraction. Over time, it can result in serious complications such as heart failure, stroke, myocardial hypertrophy, and coronary artery disease (Miao et al., 2018). The development of hypertension can be attributed to various mechanisms, including increased salt retention leading to volume expansion, dysfunction in the renin-angiotensin-aldosterone system (RAAS), reduced NO bioavailability, and heightened activation of the sympathetic nervous system.

The endothelium plays an essential role in regulating vascular tone and hemostasis by serving as the primary interface between the blood and the vascular wall. Despite its thin monolayer structure, the endothelium is highly responsive to both physical forces like shear stress from blood flow and chemical signals that affect various vascular functions such as cell adhesion, platelet function, and vessel wall inflammation (Krüger-Genge *et al*., 2019). In hypertension, the endothelium undergoes changes in its three major functions which include functioning as a physical semipermeable barrier, secretion of vasoactive molecules and involvement in the

body's metabolism (Martinez-Quinones *et al*., 2018).

One of the primary functions of the endothelium is to secrete vasoactive molecules, which help regulate vascular tone (Mudau *et al*., 2012). In healthy conditions, these molecules maintain a balance favoring vasodilation and anticoagulation, ensuring appropriate blood flow. However, in hypertension, there is a shift towards increased secretion of factors that promote vessel constriction and decreased release of those that promote relaxation. This imbalance can contribute to elevated blood pressure (Martinez-Quinones *et al*., 2018).

A major way of protecting the vascular health/function is by altering the metabolism of nitric oxide in the body (Tousoulis *et al*., 2012). An alteration in the availability and level of nitric oxide (NO) in the body is a peak in determining endothelial dysfunction (Sandoo et al., 2010). The reduction of NO could be associated with a decrease in the activity and expression of eNOS (Bendall *et al*., 2005). NO reduction can also be attributed to increased consumption by reactive oxygen species and free radicals. This can be achieved by enhancing NO production through the upregulation of endothelial NO synthase (eNOS) expression and the increased availability of its substrate. eNOS is the main source of NO in the vasculature (Alhayaza *et al*., 2020; Tran *et al*., 2022; Duda *et. al*., 2004).

3.1 Antioxidative Mechanism of Flavonols in Hypertension

The impact of oxidative stress on the vascular endothelium is the decrease in the bioavailability of nitric oxide, this leads to endothelial dysfunction, generation of ROS can lead to vascular cell proliferation, inflammation and alteration in the endothelium (Schulz et al., 2011). Flavonols have been shown to have positive effects on endothelial cells thereby conferring vasoprotective properties (Tzemos *et al*., 2008).

Studies have shown that quercetin and kaempferol reduce blood pressure by enhancing endothelial function and regulating the renin-angiotensin-aldosterone system, which subsequently affects smooth muscle contraction in blood vessels and stimulates endothelial NO activity (Olaleye *et al*, 2013; Leeya *et al.,* 2010). Another way of improving the availability of NO is by enhancing the scavenging the radicals that can breakdown NO (McCarty, 2008). Flavonols are significant flavonoids that enhance the activity of endogenous antioxidant enzymes, facilitating the elimination or scavenging of free radicals and reactive oxygen species (Jakub and Karel, 2016). Studies have established flavonols as well-known antioxidants with the ability to protect from free radicals and this mechanism could be linked to cardio-protective properties. The presence of an additional hydroxyl of the third carbon of their flavone backbone is the main feature responsible for.r their antioxidant property (Chen *et al*., 1996).

The antioxidant mechanism involves donating a single electron to a free radical, resulting in the formation of a semiquinone radical, which subsequently donates another electron to generate an orthoquinone. The semiquinone radical in turn donates an electron to produce an orthoquinone. By scavenging these free radicals, formation of

reactive oxygen species (ROS) is reduced and this inbits such oxidative reactions (Yap *et al*., 2010).

Flavonols represented by the symbol (F) donate a hydrogen atom in the reaction

FOH + R• FO• + RH

where R• represents free radicals generated (These include: superoxide anion, peroxyl, alkoxyl, and hydroxyl radicals), O• is the oxygen free radical. (When combined with another radical, the peroxyl radical) (FO•) creates a stable quinone. When flavonols form complexes with free radicals, they stabilize the oxidative free radicals (Stalikas, 2007; Nijveldt *et al*., 2001; Yao *et al*., 2014; Kumar and Pandey, 2013).

The radical-scavenging activity is influenced by the structure of the heterocyclic and B rings, along with their attached substituents. The presence of a catechol group in ring B boosts electron-donating properties and acts as a target for radicals. Additionally, the 2,3-double bond conjugated with the 4-oxo group and the 3-hydroxyl group of the heterocyclic ring contribute to enhanced radical scavenging (Nabil-Adam *et al*., 2023; Kumar and Pandey, 2013). These structural features in flavonols enhance the antioxidant capacity of flavonoids and the stability of the peroxyl radical as flavonoids with a catechol group in ring B exhibit high activity and greater scavenging ability, largely due to the presence of the 3-hydroxyl (Nabil-Adam *et al*., 2023). Flavonoids exhibit antioxidant activity through various mechanisms. Firstly, they directly scavenge reactive oxygen species (ROS) such as superoxide anion, hydroxyl radicals, and hydrogen peroxide, thereby stabilizing these harmful radicals (Dias *et al*., 2021; Hassanpour and Doroudi, 2023). Additionally, flavonoids such as quercetin have the ability to chelate trace elements like iron, thereby reducing the availability of free iron ions that could catalyze the formation of highly reactive hydroxyl radicals through mechanisms such as the Fenton reaction. Moreover, flavonoids can inhibit key enzymes, such as glutathione S-transferase and xanthine oxidase, that are involved in ROS generation, thereby reducing the production of harmful free radicals (Tumilaar *et al.*, 2023, Dias *et al.*, 2021; Hassanpour and Doroudi, 2023). Furthermore, flavonoids contribute to the activation of the body's natural antioxidant defences. They can enhance the production or activity of essential antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, which assist in neutralizing ROS and safeguarding cells against oxidative damage. Flavonols often employ a combination of these mechanisms. For example, they may scavenge radicals directly while also inhibiting specific enzymes involved in ROS generation, leading to a more comprehensive antioxidant effect (Dias *et al*., 2021; Hassanpour and Doroudi, 2023).

3.2 Cadioprotective Mechanism of Flavonols in Hypertension

This may contribute to an increase in the level of NO in the system which in turn improves endothelial function. An example is the oxidation of quercetin which occurs solely on the hydoxyl group of the carbon 4’ (4’ -OH) of the ring B. This favours the donation of two electrons leading to the production of an orthoquinone thus, by

enhancing the delocalization of electrons (Yap *et al*., 2010).

Quercetin has been studied to confer its antioxidant properties on the body by decreasing the level of malondialdehyde and by scavenging free radicals like the superoxide, hydrogen peroxide and hydroxyl radicals. The ability to scavenge free radicals is due to their low redox potential which enables them to donate them to donate hydrogen electrons (Celik *et al.,* 2017). Furthermore, Quercetin provides protection in hypertensive conditions by enhancing endothelial function and regulating the renin-angiotensin-aldosterone system (this is by modulation of the mechanism involving the contraction of smooth muscles in the blood vessels) (Larson *et al*., 2012).

Kaempferol a major flavonol in fruts, vegetable, bean, etc demonstrates its antioxidative and cardioprotective property by through the reduction of lipid peroxidation products (like, malondialdehyde, lipid hydroperoxide, thiobarbituric
acid reactive substance and conjugated diene) and by enhancing the function and bioavailability of endothelial nitric oxide (Kamisah *et al*., 2023; Leeya *et al*., 2010). Kaempferol showed its protective effect on cardiac function by its ability to scavenge reactive oxygen species generated during cardiac dysfunction which could disrupt the functioning of the myocardial and molecular components (Kamisah *et al*., 2023).

The renin-aldosterone-system (RAS) is an essential system for the control of blood pressure (Beevers, 2001). In this system, renin is released from the kidney in response to low blood pressure (John, 1991). Renin, an enzyme produced by the kidney cleaves angiotensin I (Ang I) from angiotensinogen. Angiotensin-1-converting enzyme (ACE), another important enzyme in the RAAS system cleaves angiotensin II (Ang II) from Ang I in the lungs. Ang II functions as a potent vasoconstrictor, causing an elevation in blood pressure while simultaneously triggering the release of aldosterone from the adrenal cortex and antidiuretic hormone from the posterior pituitary (Mayet and Hughes, 2003; Craft *et al*., 2015). This release results in an increase in blood volume and subsequently enhances water and salt reabsorption in the nephrons (Beevers, 2001). This over a period of time leads fluid and sodium retention, this increases resistance in vascular system and cardiac dysfunction.

Myricetin treatment exert its cardioprotective ability by causing a decrease in blood pressure in DOCA induced rats (Lee and Park, 2013). Studies also demonstrated that myricetin inhibit the activity of ACE and production of reactive oxygen species describing its antihypertensive characteristics. In addition, Myricetin induces NO synthesis, thereby increasing vasodilation. All these mechanisms leads to protection of the endothelium due to vasodilating effects (Nalla and suhasin, 2021, Jomová *et al*.,2019, imran 2021). Myricetin also inhibits voltage-gated calcium channels in rats' cardiomyocytes of rats and the activities of enzymes which serve as marker enzymes in cardiofuntion such as superoxide dismutase, Lactate Dehydrogenase (LDH), Carbonic Anhydrase (CA), Aspartate aminotransferase, Creatine Kinase (CK) (Huang JH *et al.*, 2010, Jung SK *et al.*, 2010).

According to Dong et al., Fisetin protects against cardiac dysfunction by inhibiting the

ROS generation and enhancing the expression of antioxidative superoxide dismutase and catalase enzymes. Fisetin supplementation improves endothelial function by improving the bioavailability of NO (Dong *et al*., 2018; Mahoney *et al*., 2020; Mahoney *et al.,* 2024).

Rutin as a flavonol can be derived from different plant sources. It has been studied to protect against fragility and embrittlement of capillaries in hypertensive cases. In a study by (Olaleye *et al*., 2015) hypertension was induced by feeding rats with a diet supplement with an 8% increase in sodium chloride (NaCl). This led to an elevation in systolic, diastolic, pulse, and mean arterial blood pressures, as well as increased lipid peroxidation, while the activities of antioxidant enzymes decreased, highlighting the antioxidative and antihypertensive roles of rutin and quercetin (Olaleye *et al*., 2013). Rutin exerts its antioxidant properties by reducing the production of reactive oxygen species and enhancing antioxidant enzymes like GPX, SOD, and CAT (Bazyar et al., 2023; Li et al., 2017; Raju et al., 2019). Treatment with rutin and quercetin not only reduced the elevated blood pressure but also restored the antioxidative defense mechanism, proving more effective than nifedipine, the reference (Olaleye *et al*., 2013).

Daily administration of morin led to a reduction in blood pressure in DOCA-salt model hypertensive rats. Morin also reversed the elevated oxidative stress and reduced nitric oxide levels in the treated rats, indicating the mechanism behind its antihypertensive effects (Oyagbemi et al., 2020; Prahalathan *et al.*, 2012; Gopal, 2013; Solairaja et al., 2020, Rajput *et al*., 2020; Lotito and Frei, 2006; Rattanachaikunsopon and Phumkhachorn, 2010).

Furthermore, flavonols can improve vascular function by direct stimulation or inhibition of vascular calcium ion channel. Flavonols activate endothelial nitric oxide synthase (eNOS) via the PI3K/Akt/eNOS pathway or by raising intracellular calcium ion concentration ([Ca2+]i). The rise in [Ca2+] i futher activates Ca2+-activated potassium channels, specifically small-conductance (SKCa) and intermediate-conductance (IKCa) channels. The activation of these channels generates an outward potassium current, leading to endothelial cell hyperpolarization (Maaliki et al., 2019). This hyperpolarization is transmitted to vascular smooth muscle cells (VSMCs) via myoendothelial junctions (MEJs), which inhibits calcium ion influx into VSMCs, ultimately inducing vasorelaxation. Besides their endothelial effects, flavonoids can directly impact VSMCs independently of endothelial cells. They induce vasorelaxation either by activating large-conductance Ca2+-activated potassium (BKCa) channels or inhibiting calcium channels. The activation of BKCa channels serves as a feedback mechanism to reduce [Ca2+]i influx, thus limiting vessel constriction. Conversely, calcium channel inhibition prevents contraction, avoiding vasoconstriction (Maaliki et al., 2019). Quercetin, in particular, has a positive effect on reversing endothelial dysfunction. It exerts its antihypertensive properties by elevating nitric oxide (NO) levels, which occurs through an increase in intracellular calcium concentration ([Ca2+]i) in endothelial cells

(ECs). This [Ca2+]i rise leads to endothelial hyperpolarization via the activation of Ca2+-activated potassium channels, especially small-conductance Ca2+-activated K+ (SKCa) channels. This activation results in an endothelium-derived hyperpolarizing factor (EDHF)-mediated response. Myoendothelial gap junctions (MEJs) then transfer this hyperpolarization to vascular smooth muscle cells (VSMCs) via direct electrical coupling (Jones *et al*., 2016; Kunasegaran *et al.*, 2017).

4.0 CONCLUSION

Hypertension is a widespread chronic condition and a major risk factor associated with cardiovascular disease. It is a major concern today due to its impact on the health of the world population and the world economy, and this has been since the global prevalence of hypertension surged from 594 million to 1.13 billion individuals between 1975 and 2015. Due to this, attention has been shifted to the use of both pharmacological and alternate dietary interventions (non-pharmacological methods) to treat or manage hypertension. This will help to reduce the risks associated with the use of anti-hypertensive drugs and slow down the progression of hypertension in humans.

Flavonols are bioactive compounds abundant in fruits, vegetables, spices, and many other food sources, and they have demonstrated a wide range of pharmacological and therapeutic properties for various diseases, including hypertension management and treatment. This study reviewed literature on the mechanisms by which flavonols influence hypertension, including their antioxidant activity that protects against oxidative damage, regulation of the RAAS system, restoration of endothelial function, inhibition of calcium ion channels, and overall blood pressure regulation, highlighting their cardioprotective properties. This information could offer valuable insights into the potential use of flavonols in treating hypertension and other degenerative and infectious diseases.

Authors contributions

JAO. participated in writing the manuscripts. JAO, SAA. and GO. study framework and organization. The manuscript was read and approved by all authors.

Consent for publication

All authors have assumed responsibility for the overall content of the submitted manuscript and have given their approval for its submission

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Disclosure statement

The authors declare they have no known conflict of interest whatsoever

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Sys Rev Pharm 2021; 12(12): 3940-3950 A multifaceted review journal in the field of pharmacy E-ISSN 0976-2779 P-ISSN 0975-8453 Review Article 3940 Systematic Review Pharmacy Vol 12, Issue 12, Nov Dec, 2021 A Recent Review on Dietary Flavonoid-Myricetin Swathi Nalla1*, Ganta Suhasin2 1 Department of Pharmacology, Maharajah's College of Pharmacy, Vizianagaram, India 2 Department of Pharmacology, Gitam Institute of Pharmacy, GITAM Deemed to be University, Visakhapatnam, India

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