

Review

# Implication of dietary phenolic acids on inflammation in cardiovascular disease

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In spite of medical advances, cardiovascular disease remains a significant concern, imposing a great burden upon the economy and public health of nations by causing the highest morbidity and mortality cases globally. Moreover, it is well established that inflammation is closely linked to the pathogenesis of cardiovascular diseases. Hence, targeting inflammation seems to be a promising strategy in reducing cardiovascular risks. Currently, the importance of natural products in modern medicine is well recognised and continues to be of interest to the pharmaceutical industry. Phenolic acids are a class of phytochemical compounds that are well-known for their health benefits. They consist of various phytochemical constituents and have been widely studied in various disease models. Research involving both animals and humans has proven that phenolic acids possess cardioprotective properties such as anti-hypertensive, anti-hyperlipidemia, anti-fibrotic and anti-hypertrophy activity. Furthermore, numerous studies have proven that phenolic acids in phytochemical constituents such as gallic acid, caffeic acid and chlorogenic acid are promising anti-inflammatory agents. Hence, in this review, we outline and review recent evidence on the role of phenolic acids and their anti-inflammatory significance in studies published during the last 5 years. We also discuss their possible mechanisms of action in modulating inflammation related to cardiovascular disease.

## Keywords

Cytokine; chemokine; inflammatory cell; phenolic acids

## 1. Introduction

Cardiovascular disease (CVD) remains a major public health burden with its incidence increasing at an alarming rate each year in both developing and developed countries (Ali et al., 2019a). As reported by the World Health Organization (WHO), CVD represents 31% of all global deaths, accounting for an estimated 17.9 million deaths per year (World Health Organization, 2020). In-

deed, the Malaysian Department of Statistics reported that CVD accounted for 35% of the total premature deaths in Malaysia in the year 2016. Among all CVD, myocardial infarction was recorded as the principle cause of death over a period of 10 years from 2007 to 2017, with a 54% increment of incidence in Malaysia (Department of Statistics Malaysia, 2017). CVD imposes a great burden upon public health and the economy where it is considered as the costliest disease. Dunbar et al. (2018) reported that the productivity losses and medical costs of CVD are expected to rise from US\$555 billion in 2015 to US\$1.1 trillion in 2035.

CVD is a group of heart and blood vessel disorders, including cerebrovascular disease, coronary heart disease and rheumatic heart disease (Ng et al., 2014). Risk factors for CVD can be categorised into modifiable and non-modifiable factors. Modifiable risk factors include tobacco and alcohol use, sedentary lifestyle and an unhealthy diet. They also include physiological factors such as hypertension, hypercholesterolemia, or hyperglycaemia which strongly correlates to social determinants such as aging, urbanisation and income. Meanwhile, non-modifiable factors include age, family history and gender (Fox et al., 2008). In addition, vascular endothelial dysfunction is also considered as an important initiator of CVD (Si et al., 2017).

Recently, there has been a growing research interest in the potential of natural plant-based medicine as cardioprotective agents. The benefits of natural plant-based remedies could be attributed to their ability to enhance the endogenous antioxidant system or through their alteration of redox signalling. This is often related to the unique composition of polyphenols found in plants such as vegetables and fruits (Lee et al., 2017). Phenolic compounds are secondary metabolites from plants that are characterised by their chemical structures as having at least one phenol unit (Roche et al., 2017). They are grouped based on their carbon skeleton, which ranges from basic to highly complex compounds such as phenolic acids, flavonoids, tannins, coumarins, lignans, quinones, stilbenes and curcuminoids (Gan et al., 2019).

Despite the fact that phenolic compounds have been widely reported to have various health-promoting effects, it is only in

the past few decades that we have seen increasing numbers of studies reporting on their cardioprotective potential, as reviewed elsewhere. This may be attributed to their anti-oxidant and anti-inflammatory qualities and other bioactivities. For instance, [Tangney and Rasmussen \(2013\)](#) provided a mechanistic insight into how phenolic compounds may function in CVD risk reduction by focusing on the immunomodulatory and vasodilatory properties of several phenolic compounds. In addition, [Rasines-Perea and Teissedre \(2017\)](#) wrote a comprehensive review on the consumption of polyphenolic grape compounds and their potential benefits as treatment for CVD and diabetes. In 2018, [Reboredo-Rodriguez et al.](#) gave an overview of the therapeutic potential of olive oil phenolic compounds for the management of cancer and CVD. Later in 2019, [Lutz et al.](#) reviewed the possible effects of the dietary intake of phenolic compounds on reducing CVD risk factors, stressing the anti-inflammatory, anti-platelet aggregation, antioxidative and antiglycating actions of phenolic compounds.

Among all of the phenolic compounds, phenolic acids have exhibited remarkable health benefits. Numerous studies reviewing the bioactivity of phenolic acids have been published. For example, [Wu et al. \(2017\)](#) summarised the antiviral characteristics of phenolic acids and structure-activity relationships with their derivatives. In 2018, [Szwajgier et al. \(2018\)](#) reviewed the anticholinesterase and cognition-improving effects of phenolics acids while later in the same year, [Călinoiu and Vodnar \(2018\)](#) reviewed the health benefits of phenolic acids from whole grains, emphasising chemical structure, bioactivity and bioavailability. Following, [Kumar and Goel \(2019\)](#) gave an overview of the therapeutic potential application of phenolic acid by focusing on biosynthesis, metabolism and health effects. Also, in 2019, [Dludla et al. \(2019\)](#) reported on the available evidence for the anti-obesity properties of one of the phenolic acids, gallic acid and its derivatives, by emphasising its modulatory effect on the molecular mechanisms involved in inflammation, insulin signalling and oxidative stress. Although the reviews mentioned have provided valuable information which has improved our understanding of the health benefits of phenolic compounds, particularly phenolic acids, none have discussed the implications of phenolic acids for inflammation in relation to CVD. Hence, in this review, we aimed to outline and review the past 5 years of evidence on the role of phenolic acids and their anti-inflammatory significance in relation to CVD. We also discuss their possible mechanisms of action in modulating inflammation. The literature search was completed on the PubMed database, limiting the time frame from 2015 to 2020 due to the overwhelming quantity of literature. Relevant keywords were used for the search strategy. In addition to phenolic acids we included: gallic acid or protocatechuic acid or chlorogenic acid or caffeic acid or syringic acid or ferulic acid or vanillic acid or rosmarinic acid or ellagic acid; cardiovascular; and inflammation. These phenolic acids were selected since they are the main phenolic acids commonly found in the diet which have proven biological effects, including anti-inflammatory properties.

## 2. The role of inflammation in cardiovascular diseases

It is well documented that inflammation plays a significant role in the pathogenesis of CVD ([Katsiari et al., 2019](#)). Although in-

flammation is mostly deleterious and maladaptive, there are still some exceptions where the inflammatory response is crucial in initiating healing progression ([Ali et al., 2019b](#)). Hence, it is safe to mention that suppressing inflammation does not necessarily exert protective effects but may also result in maladaptive consequences. Several lines of evidence have demonstrated the extensive involvement of inflammation in both acute and chronic cardiovascular manifestations such as atherosclerosis ([Jiang et al., 2020](#); [Kimura et al., 2020](#)), myocardial infarction ([Cremer et al., 2020](#); [Tian et al., 2020](#)), hypertension ([Jan-on et al., 2020](#); [Park et al., 2020](#)) and heart failure ([Molitor et al., 2020](#); [Pop et al., 2020](#)).

A clinical trial by the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) reported that neutralisation of cytokine interleukin (IL)-1 $\beta$  in atherosclerosis patients improved cardiovascular health, suggesting its strong association with the inflammatory response ([Ridker et al., 2011](#)). Overexpression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) as well as nitric oxide (NO) are considered to be the early indicators for vascular dysfunction ([Habas and Shang, 2018](#)). VCAM-1 and ICAM-1 appear to be key players in atherosclerotic lesion progression ([Varona et al., 2019](#)) where their expression is partly regulated by NF- $\kappa$ B signalling and pro-inflammatory cytokines such as IL-1 $\beta$  or tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) ([Jing et al., 2017](#)). On the other hand, NO, which is produced by nitric oxide synthases (NOS) such as neuronal (nNOS), endothelial (eNOS) and inducible (iNOS), are implicated in the pathogenesis of vascular dysfunction. Pro-inflammatory cytokines trigger the expression of iNOS in macrophages, which in turn increases cellular NO, contributing to inflammation ([Sharma et al., 2007](#)). Moreover, upregulation of NO promotes the production of peroxynitrite and may contribute to vascular dysfunction ([Lind et al., 2017](#)).

Diverse mechanisms are implicated in regulating immune and inflammatory responses relating to CVD. This includes signalling pathways such as the mitogen-activated protein kinases (MAPK) pathway ([Hu et al., 2020](#); [Ramalingam et al., 2020](#)), janus kinase/signal transducers/activators of the transcription (JAK/STAT) pathway ([Shen et al., 2020](#); [Ye et al., 2020](#)) and the NF- $\kappa$ B pathway ([Gao et al., 2020](#); [Manjunatha et al., 2020](#)). Among all of these, the NF- $\kappa$ B transcription factor seems to be the key player in the regulation of the CVD-related inflammatory response ([Choy et al., 2019](#)) where its activation may directly promote the production of cytokines (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ) and chemokines (MCP-1, MIP-1, CXC, CXCL10), besides promoting adhesion molecules (ICAM-1, VCAM-1, P-selectin) and enhancing the recruitment of neutrophils. In addition, upon activation, NF- $\kappa$ B may influence the activation of the M1 subtype of macrophage, and also the activation and differentiation of T lymphocytes (T-cell) ([Liu et al., 2017](#)), as shown in [Fig. 1](#). Complex interactions between components in inflammatory signalling may also intersect with the pro cell survival pathway. Besides regulating the transcription of inflammatory genes, NF- $\kappa$ B may also be involved in the activation of pro-survival kinases such as Akt1 ([Coggins and Rosenzweig, 2012](#)). Although such complex interactions of pro-inflammatory and pro-survival signalling may complicate approaches using these pathways as therapeutic targets, in-

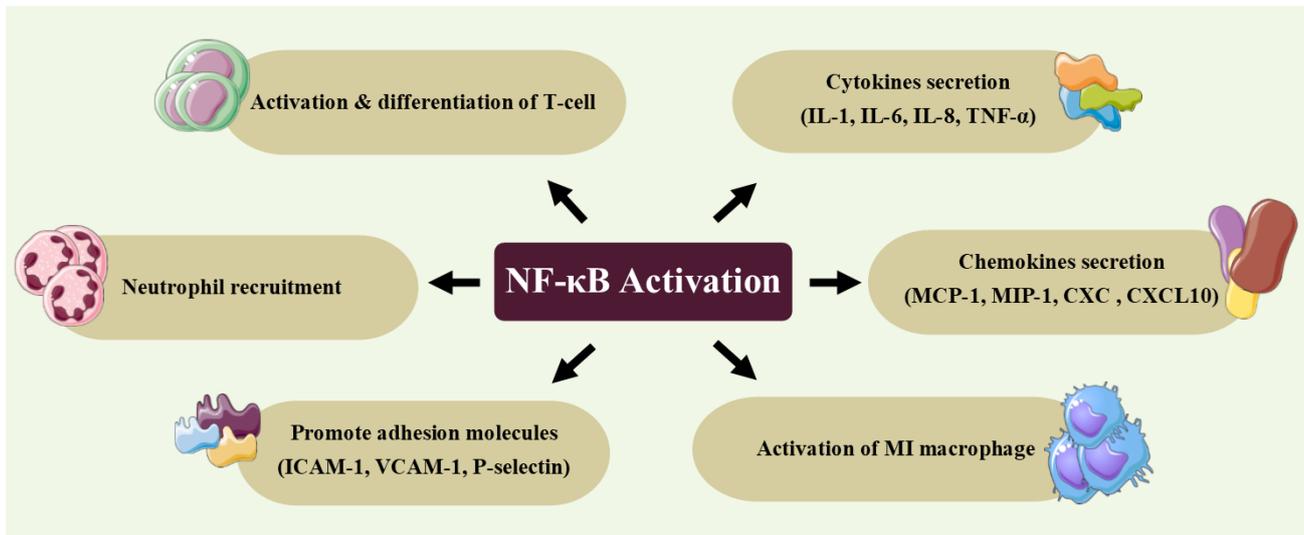


Figure 1.  $\text{NF-}\kappa\text{B}$  is one of the important inducible transcription factors involved in the progression of cardiovascular disease. Upon  $\text{NF-}\kappa\text{B}$  activation, the inflammatory process may be regulated in several ways such as by the activation of the M1 macrophage, and promotion of adhesion molecules. It also may recruit the infiltration of neutrophils, and activation and differentiation of T-cells.  $\text{NF-}\kappa\text{B}$  activation may also initiate cytokines and chemokines secretion.

Inhibition of the  $\text{NF-}\kappa\text{B}$  transcription factor appears to be beneficial in reducing cardiovascular-related complications including cardiac hypertrophy (Yu et al., 2015), cardiac fibrosis (Wang et al., 2018) and atherosclerosis (Song et al., 2018). In parallel, the role of phenolic acids in regulating the  $\text{NF-}\kappa\text{B}$  transcription factor has also been reported previously (Cichocki et al., 2010; Wang et al., 2018).

### 3. Phenolic acids and its subclasses

Phenolic acids are most widely distributed in free, conjugated-soluble or insoluble-bound forms of non-flavonoid phenolic compound (Morton et al., 2000). Phenolic acids are defined as a phenol ring that has a minimum of one carboxylic acid function. They are naturally found in abundance in almost all food groups such as fruits, vegetables, cereals, legumes, oilseeds and herbs, as shown in Fig. 2 (Goleniowski et al., 2013). Phenolic acids are produced as by-products of the monolignol pathway through shikimic acid via the phenylpropanoid pathway and breakdown products of lignin (Mandal et al., 2010).

Depending on its chemical structure, phenolic acids are categorised into two subclasses which are hydroxybenzoic and hydroxycinnamic acid (Działo et al., 2016). Hydroxybenzoic acid contains seven carbon atoms (C6-C1) while hydroxycinnamic acids have nine carbon atoms (C6-C3). Examples of hydroxybenzoic acids include gallic acid, protocatechuic acid, ellagic acid and gentisic acid. Meanwhile ferulic acid, chlorogenic acid, rosmarinic acid and caffeic acid are examples of commonly studied hydroxycinnamic acid (Saibabu et al., 2015). Fig. 3 shows the chemical structure for the subclasses of phenolic acids which are hydroxycinnamic acid and hydroxybenzoic acid.

Phenolic acids are widely distributed in almost all food groups, hence humans consume phenolic acids on a daily basis. Phenolic acids may be easily absorbed due to their basic and simple structures, thus it is estimated that humans consume around 25 mg to 1 g of phenolic acids on daily basis, depending on diet habits and

preferences (Shahidi and Naczk, 2004). Fruits with the highest phenolic acids are cherries, blueberries, prunes, grapes and raspberries (Li and Beta, 2013). The health-promoting effects of phenolic acids are not only limited to animal models, but have also been proven in various clinical trials. Table 1 summarises recent clinical studies of phenolic acids. Relevant keywords such as phenolic acids and gallic acid or protocatechuic acid or chlorogenic acid or caffeic acid or syringic acid or ferulic acid or vanillic acid or rosmarinic acid or ellagic acid were used as the search strategy. Filters such as clinical trial and randomised controlled trial were applied and only studies ranging from 2015 to 2020 were included. Among all phenolic acids, chlorogenic acid was most studied, especially in the form of coffee. Although clinical trials of phenolic acids have been gaining interest recently, there is still a lack of clinical trials investigating the impact of phenolic acids on CVD or CVD risk factors.

#### 3.1 Brief overview of metabolism and bioavailability of phenolic acids

Generally, the potential bioefficacy of bioactive compounds greatly depends on the rate of absorption, metabolism and bioavailability. Upon ingestion, only a small amount of the compound is absorbed into the circulatory system (D'Archivio et al., 2010). The metabolic fate of phenolic acids has been studied previously (Azuma et al., 2000; Borges et al., 2013; Lafay et al., 2006; Renouf et al., 2010). The metabolism of phenolic acids occurs mostly in the gastrointestinal tract and is subjected to conjugation reactions such as glucuronidation, methylation and sulfation, resulting in the modification of their structures. In addition, colon microflora plays a major role in the absorption and metabolism of phenolic acids. Moreover, the source of phenolic acids is not only limited to dietary intake, but they may also be produced as metabolites from the metabolism of other phenolic compounds by the microflora in the colon (Piazzon et al., 2012). For instance, ferulic acid is present in food but may also be formed by the methylation

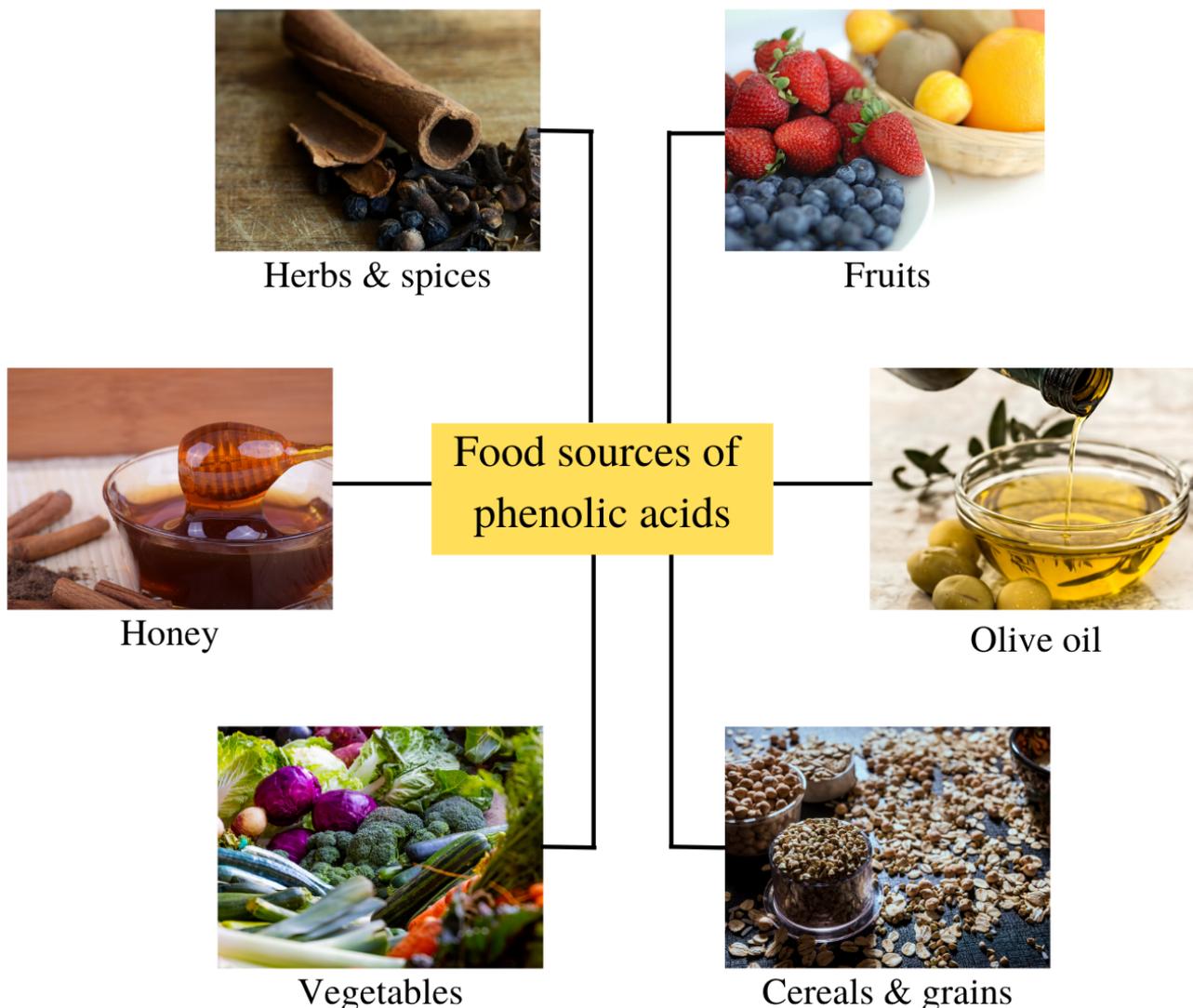


Figure 2. Phenolic acid can be found abundantly in various food sources such as fruits, vegetables, cereals, grains, olive oil, herbs, spices and honey.

of quercetin or caffeic acid (Pérez-Jiménez et al., 2010).

The absorption and bioavailability of phenolic acids is greatly reduced when they are present in the bound form rather than the free form due to the bran matrix hindering access to the necessary enzymes. Bound phenolic acids require release by enzymes of the colonic microflora, such as xylanases and esterases, which may affect bioefficiency as microflora can degrade the aglycones, resulting in the release of simple aromatic acids (Heleno et al., 2015). Azuma et al. (2000) suggested that chlorogenic acid is not so well absorbed from the digestive tract and that it is subjected to almost no changes to its structure upon oral administration, unlike caffeic acid. Another study reported that only one third of consumed chlorogenic acid and almost all consumed caffeic acid is absorbed in the small intestines of humans, implying that only a small percentage of chlorogenic acid enters blood circulation while most will reach the colon (Renouf et al., 2010). Furthermore, Kishida and Matsumoto (2019) suggested that ingested caffeic acid, ferulic acid and p-coumaric acid are mostly absorbed, conjugated and excreted in the urine within 0-6 hours, while chlorogenic acid is

poorly absorbed and may only be detected in urinary excretion at 6-24 hours and 24-48 hours. Meanwhile, almost 70% of gallic acid is absorbed and then excreted in urine as 4-O-methylgallic acid (Daglia et al., 2014). Urinary excretion of phenolic compounds shows that prior to excretion, colonic catabolites are well absorbed into the portal vein and circulate through the circulatory system (Crozier et al., 2010).

#### 4. Role of phenolic acids on inflammation in cardiovascular disease

##### 4.1 Gallic acid

Gallic acid (3,4,5-trihydroxybenzoic acid) is one of the most widely studied hydroxybenzoic acids and can be found abundantly in fruits such as blueberries, strawberries, plums and mangos (Andersen and Jordheim, 2013; Lim et al., 2017). Gallic acid has been proven to be cardioprotective in both in vitro and in vivo settings. A study by Cheng et al. (2015) found that a combination of gallic acid with calycosin or formononetin could synergistically induce expression of LTB4DH in human neutrophils and HepG2 cells,

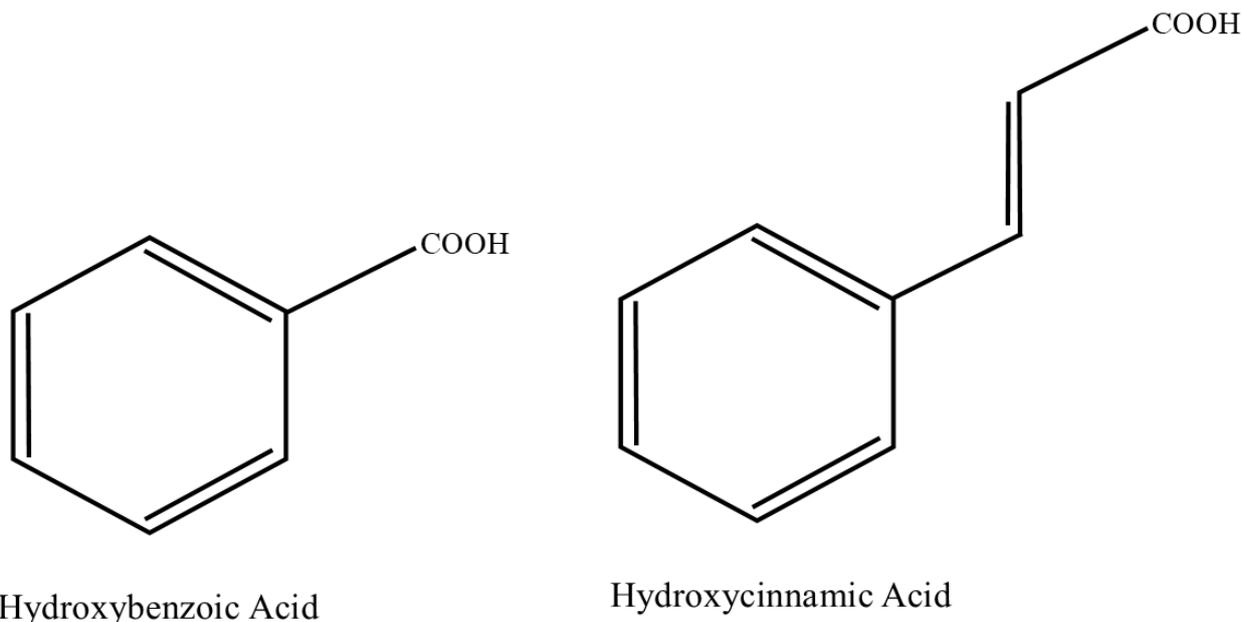


Figure 3. Subclasses of phenolic acids are hydroxycinnamic acid and hydroxybenzoic acid which differ in term of chemical structure. Hydroxybenzoic acid is derived from benzoic acid while hydroxycinnamic acid is from cinnamic acid.

attenuating the LTB4 effect on survival and chemotaxis of neutrophil. The same study also reported that gallic acid and calyculin synergistically attenuated neutrophil infiltration and MPO activity in an isoprenaline induced myocardial infarction model by regulating leukotriene B4 12-hydroxydehydrogenase. In human umbilical vein endothelial cells (HUVECs), gallic acid promotes endothelium-dependent vasorelaxation by increasing NO levels while pretreatment with NG-nitro-L-arginine methyl ester (L-NAME), an eNOS inhibitor, diminishes the effect seen, suggesting that eNOS phosphorylation is responsible for the NO increment. Gallic acid also mediates an anti-hypertensive effect by inhibiting activity of the angiotensin converting enzyme and reducing blood pressure in spontaneously hypertensive rats to an extent comparable to captopril (Kang et al., 2015).

In another HUVEC model, gallic acid dose-dependently inhibited TNF- $\alpha$  induced monocytes adhesion to endothelial cells (Del Bo' et al., 2016). Supplementation of gallic acid in several cardiotoxicity models have shown cardioprotective and anti-inflammatory properties. Gallic acid was able to limit cardiac injury, improve lipid profile and downregulate cardiac inflammatory markers such as NO and TNF- $\alpha$ , although no improvement was seen in circulating NO and TNF- $\alpha$  level (El-Hussainy et al., 2016). Similarly, treatment with gallic acid mitigated diazinon induced cardiorenal toxicity by reducing cardiac and renal NO, besides alleviating oxidative stress and improving the hematological parameters of rats (Ajibade et al., 2016). Akinrinde et al. (2016) reported the protective effects of gallic acid against cobalt-chloride-induced cardiorenal dysfunction via suppression of oxidative stress and activation of the ERK signalling pathway, besides downregulating plasma C-reactive protein (CRP) and the NO level. Also, Ryu et al. (2016) showed that gallic acid limits isoproterenol-induced cardiac

fibrosis and hypertrophy through modulation of Smad3 binding activity and JNK2 signalling in both in vitro and in vivo settings. Although downregulation on NO was reported to be cardioprotective, in the cyclophosphamide-induced cardiorenal dysfunction model, gallic acid was proven to upregulate NO content and attenuate oxidative stress (Ogunsanwo et al., 2017).

Gallic acid restored high fructose diet-mediated metabolic alteration and limited hyperglycaemia, dyslipidemia and oxidative stress, accompanied by downregulation of serum inflammatory markers such as IL-6, IL-8 and TNF- $\alpha$  (Ibitoye and Ajiboye, 2018). Furthermore, in a porcine coronary restenosis model, a gallic acid-eluting stent suppressed neointimal hyperplasia, resulting in lower inflammation scores, as shown across histopathological observations (Lim et al., 2018). Gallic acid improved systolic, diastolic and mean arterial blood pressure, ameliorated oxidative stress and decreased serum MPO, NO, urea and creatinine in bisphenol A treated rats (Ola-Davies and Olukole, 2018). Similar to the study of Ogunsanwo et al. (2017), Omóbowálé et al. (2018) also found that gallic acid promotes upregulation of NO metabolite, which is accompanied by improvement of ECG abnormalities, and that it prevents oxidative stress associated cardiac damage.

Following this, a recent study by Radan et al. (2019) showed that gallic acid protects against particulate matter (PM10) induced cardiac oxidative stress and inflammation, as shown across downregulation of pro-inflammatory cytokines IL-6 and TNF- $\alpha$ , preserving cardiac function and ECG alteration. In a transverse aortic constriction induced cardiac remodelling model, gallic acid reduced infiltration of inflammatory cells and IL-1 $\beta$ , IL-6, and MCP-1 level, limiting cardiac remodelling including hypertrophy

Table 1. Recent clinical studies of phenolic acids in various conditions, published between 2015 and 2020.

Subject	Intervention	Main findings	Reference
Healthy cyclist subjects, males (N = 10), aged 26-31 years.	Single intake of 10 mg/kg green coffee bean extract containing 5 mg/kg of chlorogenic acid post exercise.	No difference observed between glucose concentration in OGTT and insulin concentration.	<a href="#">Beam et al., 2015</a>
Moderately hypercholesterolemic subjects with metabolic syndrome (N = 40), age/gender not reported.	Daily single intake of pills (Trixy®) containing chlorogenic acid, berberine and tocotrienols for 16 weeks.	Significant improvement in anthropometric (body weight, waist circumference and BMI), lipid profile (TC, TG, LDL, HDL), blood pressure (SBP, MAP), fasting insulin, HOMA-IR, GOT and LAP.	<a href="#">Cicero et al., 2015</a>
Healthy subjects, males (N = 19), aged 24-53 years.	Coffee polyphenol extract beverage containing 355 mg chlorogenic acid.	Improved postprandial glucose concentration and endothelial function.	<a href="#">Jokura et al., 2015</a>
Healthy non-diabetic subjects (N = 13), aged 44-46 years, gender not reported.	Single intake of beverage consisting of 600 mg chlorogenic acid.	Significant improvement in endothelial function (flow mediated dilatation), nitric oxide and urinary 8-epi-prostaglandin F2a level.	<a href="#">Ochiai et al., 2015</a>
Primary immune thrombocytopenia patients, males (N = 46) & females (N=57), aged 18-84 years.	Three daily intakes of caffeic acid tablets (0.3 g each tablet) for 12 weeks.	Increased platelet counts with low incidence of side effects.	<a href="#">Qin et al., 2015</a>
Healthy subjects, males (N = 38) & females (N = 37), aged 20-26 years.	Daily single intake of coffee for 8 weeks containing a medium (420 mg) or high (780 mg) amount of chlorogenic acid.	Neutral effect on lipid profile (TC, HDL, TG), plasma NO metabolite and vascular endothelial function (flow mediated dilatation).	<a href="#">Agudelo-Ochoa et al., 2016</a>
Healthy subjects, males (N = 4) & females (N = 7), aged 18-65 years.	Single intake of 300 ml coffee with 17.97 mg (light roast) or 2.18 mg (dark roast) chlorogenic acid.	No difference observed between light and dark roast coffee for AUC for glucose, glucose concentration in OGTT test and insulin concentration.	<a href="#">Rakvaag and Dragsted, 2016</a>
Healthy subjects, males (N = 6) & females (N = 10), aged 18-70 years.	Single intake of beverage containing 450 mg or 900 mg chlorogenic acid.	No significant effect on blood pressure, endothelial function (flow mediated dilatation) and plasma nitrite level.	<a href="#">Ward et al., 2016</a>
Healthy subjects, males (N = 7) & females (N = 5), aged 40-70 years.	Two intakes of 200 ml caffeinated coffee containing 300 mg chlorogenic acid or decaffeinated coffee containing 287 mg chlorogenic acid.	Improvement in endothelial function (flow mediated dilatation), however no changes in glucose concentration and blood pressure.	<a href="#">Boon et al., 2017</a>
Healthy subjects, females with mildly xerotic skin (N = 150), aged 25–40 years.	Daily single intake of beverage for 8 weeks containing 270 mg of polyphenol (sum of chlorogenic acid, dicaffeoylquinic acid and feruloylquinic acid).	Improved skin hydration and permeability barrier function (reduced skin surface pH, transepidermal water loss and increased stratum corneum hydration) with microcirculatory function's improvement.	<a href="#">Fukagawa et al., 2017</a>
Healthy subjects, males (N = 15), aged 18-40 years. Healthy subjects, males (N = 24), aged 18-70 years.	First trial - single intake of coffee containing 89 mg or 310 mg chlorogenic acid. Second trial - single intake of pure 5-caffeoylquinic acid (450 mg or 900 mg).	Significant increase in endothelial function (flow mediated dilatation) and brachial artery dilatation, accompanied by increased chlorogenic acid metabolites. Improved vascular endothelial function (flow mediated dilatation).	<a href="#">Mills et al., 2017</a>
Healthy subjects, males (N = 4) & females (N = 5), age not reported.	Daily single intake of coffee containing 0 or 600 mg of chlorogenic acid for 5 days.	Shortened sleep latency but no effect on sleep architecture (rapid eye movement, slow-wave sleep or waking after sleep onset) observed. Increased fat oxidation observed but energy expenditure during sleep remained unchanged. Enhanced parasympathetic activity was also observed through heart-rate variability assessment during sleep.	<a href="#">Park et al., 2017</a>
Hyperlipidemic subjects (N = 48), aged 20-60 years, gender not reported.	Twice daily intake of a ferulic acid capsule (500 mg each capsule) for 6 weeks.	Significant improvement in lipid profile (decreased cholesterol, LDL and TG, and increased HDL level), reduced oxidative stress biomarker (MDA) and oxidized LDL and inflammatory markers (hs-CRP, TNF- $\alpha$ ).	<a href="#">Bumrungpert et al., 2018</a>
Diabetic patients, male (N = 12) & females (N = 9), aged 66-74 years.	Daily single intake of gallic acid extract (15 mg/kg) for 7 days.	Decreased oxidative DNA damage and inflammatory marker, CRP.	<a href="#">Ferk et al., 2018</a>

Table 1. Continued.

Subject	Intervention	Main findings	Reference
Healthy subjects, males (N = 15), aged 38-46 years.	Daily single intake of beverage A (428 mg chlorogenic acid, 67 mg caffeine, 0.08 mg hydroxyhydroquinone) or beverage B (328 mg chlorogenic acid, 66 mg caffeine, 0.57 mg hydroxyhydroquinone).	Coffee with high chlorogenic acid content and low hydroxyhydroquinone content increases postprandial FOX compared with ingestion of high chlorogenic acids and hydroxyhydroquinone coffee.	<a href="#">Katada et al., 2018</a>
Healthy subjects with normal body weight (N = 76) & overweight (N = 74), aged 45-55 years, gender not reported.	Daily single intake of ellagic acid (50 mg) for 12 weeks.	Prevents cognitive deficits by normalisation of lipid metabolism, increased plasma BDNF level and reduced cortisol concentration in saliva.	<a href="#">Liu et al., 2018</a>
Healthy cyclist subjects (N = 15), aged 19-51 years, gender not reported.	Daily single intake of 300 ml coffee containing 1066 mg or 187 mg chlorogenic acid for 2 weeks.	No differences found for post-exercise plasma IL-6 and hydroxyoctadecadienoic acids, however, reduction seen in total mood disturbance scores.	<a href="#">Nieman et al., 2018</a>
Healthy subjects, males (N = 14) & females (N = 13), age not reported.	Four daily intakes of coffee with 43.6 mg of chlorogenic acid per serving for 12 weeks.	No changes seen in postprandial glucose and lipid response.	<a href="#">Robertson et al., 2018</a>
Patients with metabolic syndrome (N = 50), aged 18-70 years, gender not reported.	Two daily intakes of chlorogenic acid enriched green bean extract containing 186 mg of chlorogenic acid for 8 weeks.	Significant reduction in fasting blood glucose, SBP, insulin resistance, appetite score, waist circumference, weight and BMI but no difference was observed in HbA1c percentage and lipid profile parameters.	<a href="#">Roshan et al., 2018</a>
Healthy subjects with subjective memory complaint (N = 38), aged 50-69 years.	Daily single intake of beverage containing 300 mg chlorogenic acid for 16 weeks.	Improved cognitive function (psychomotor speed, cognitrix domain scores for motor speed, shifting attention test scores, executive function, apolipoprotein A1 and transthyretin).	<a href="#">Saitou et al., 2018</a>
Patients with impaired glucose tolerance (N = 30), aged 30-60 years.	Three intakes of capsules (400 mg chlorogenic acid each capsule).	Decreased fasting glucose and insulin release but increased insulin sensitivity and improved lipid profile.	<a href="#">Zuniga et al., 2018</a>
Normocholesterolemic (N = 25) & hypercholesterolemic subjects (N = 27), age and gender not reported.	Three daily intakes of coffee with 148.4 gm of chlorogenic acid per serving for 8 weeks.	Reduction in lipid profile (TC, LDL, VLDL), haemodynamic parameter (SBP and DBP, heart rate) and body weight.	<a href="#">Martínez-López et al., 2019</a>
Subjects with borderline or stage 1 hypertension (N = 37), gender not specified, aged >30.	Study 1 - single intake of beverage A (412 mg chlorogenic acid, 0.11 mg hydroxyhydroquinone, 69 mg caffeine) or beverage B (373 mg chlorogenic acid, 0.11 mg hydroxyhydroquinone, 69 mg caffeine). Study 2 - single intake of beverage A or beverage C (0 mg chlorogenic acid, 0.1 mg hydroxyhydroquinone, 59 mg caffeine).	Coffee with high chlorogenic acid and low hydroxyhydroquinone content (but not coffee with high chlorogenic acid and hydroxyhydroquinone content or placebo coffee), improved postprandial endothelial function with decreased 8-isoprostane levels in plasma.	<a href="#">Kajikawa et al., 2019</a>
Healthy subjects, males (N = 17), aged 24-26 years.	Single intake of 500 mg ellagic capsule with 237 ml water.	Significantly increased plasma insulin and reduced plasma leptin but no effect on plasma MCP-1 and glucose concentration.	<a href="#">Long et al., 2019</a>
Healthy subjects, males (N = 16), aged 35-56 years.	Daily single intake of 100 ml beverage containing 300 mg chlorogenic acid for 2 weeks.	Improved arterial stiffness as assessed through cardio-ankle vascular index.	<a href="#">Suzuki et al., 2019</a>
Healthy overweight subjects (N = 150), aged 20-65 years.	Daily single intake of coffee containing 369 mg or 35 mg chlorogenic acid for 12 weeks.	Reduced body weight, body mass index, abdominal fat area and waist circumference.	<a href="#">Watanabe et al., 2019</a>

AUC, area under curve; BDNF, brain-derived neurotrophic factor; BMI, body mass index; DBP, diastolic blood pressure; FOX, fat oxidation; GOT, glutamic oxaloacetic transaminase; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein; IL-6; interleukin 6; LAP, lipid accumulation product; LDL, low density lipoprotein; MAP, mean arterial pressure; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; NO, nitric oxide; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TNF- $\alpha$ , tumor necrosis alpha.

and fibrosis. Anti-hypertrophic activity of gallic acid was also seen in the *in vitro* study of Ang II-induced cardiomyocyte hypertrophy. Mechanistically, gallic acid blocked ULK1 and activated autophagy, which in turn induced EGFR, gp130 and calcineurin A degradation, thereby inhibiting the downstream signalling cascades (JAK2/STAT3, AKT, ERK1/2 and NFATc1) (Yan et al., 2019). Gallic acid also ameliorated sodium arsenite-induced NO elevation and oxidative stress in heart and spleen tissues. Furthermore, gallic acid altered hematological parameters and down-regulated serum CK-MB activity (Hosseinzadeh et al., 2019).

#### 4.2 Protocatechuic acid

Protocatechuic acid (3,4-dihydroxybenzoic acid) can be found abundantly, not only in fruits such as plums and grapes, but also widely distributed in spices such as cinnamon, star anise and rosemary (Khan et al., 2015). Protocatechuic acid alters the expression of VCAM-1 and IL-6 in CD40L and oxidized LDL-challenged HUVECs and has the potential to regulate the progression of CVD through alteration of the expression of inflammatory mediators (Amin et al., 2015). TNF- $\alpha$  induced HUVECs is an established model for endothelial dysfunction, with similar expression profiles to arterial endothelial cells in response to inflammatory stimuli. Interestingly, protocatechuic acid inhibited monocyte adhesion to HUVECs in a TNF- $\alpha$  stimulated proinflammatory environment (Del Bo' et al., 2016). Following this, (Warner et al., 2016) also showed that protocatechuic acid reduced secretion of soluble VCAM-1 (sVCAM-1) and gene expression of VCAM-1 besides eliciting a dose-dependent decrease in the secretion of MCP-1, ICAM-1 and VCAM-1 in TNF- $\alpha$  induced HUVECs.

Liu et al. (2016) investigated the effect of protocatechuic acid in mouse endothelial cells (MAECs). Notably, protocatechuic acid increased eNOS activity in macrophage foam cells co-cultured with MAECs but no effect was observed in aortic endothelial cells alone. In the same study, protocatechuic acid supplementation increased endothelium-dependent vasodilation and eNOS activity independent of eNOS and phospho-eNOS Ser1177 and Thr495 protein expression in ApoE<sup>-/-</sup> mice. However, endothelium-dependent vasodilation and eNOS activity was not affected in C57BL/6J.

In addition, protocatechuic acid restored high fructose diet-mediated metabolic alteration, improved lipid profile and blood glucose concentration, besides downregulating pro-inflammatory markers such as IL-6, IL-8 and TNF- $\alpha$  (Ibitoye and Ajiboye, 2018). A study by Rasne et al. (2018) uncovered a conflicting immunomodulatory effect of protocatechuic acid. Surprisingly, it promotes adhesion of neutrophils to nylon fibres, representing a pro-inflammatory capacity of protocatechuic acid in enhancing migration of inflammatory cells from blood vessels to the site of inflammation. However, the mechanism behind this phenomenon is not yet well understood. On the other hand, a study of the effects of 12 weeks of protocatechuic acid supplementation on insulin and insulin growth factor-1 (IGF-1) in aging hypertension rats significantly improved endothelium-dependent vasorelaxation through the modulation of the PI3K--NOS--NO pathway (Masodsai et al., 2019).

#### 4.3 Rosmarinic acid

Rosmarinic acid (a-o-caffeoyl-3,4-dihydroxyphenyl lactic acid) may be abundantly found in herbs and spices such as sage, rosemary, lemon balm mint and sweet basil (Alagawany et al., 2017). In a left anterior descending coronary artery ligation myocardial infarction model, rosmarinic acid ameliorates cardiac dysfunction and fibrosis, likely due to modulation of ACE expression and ACE2 expression via the AT1R/p38 MAPK pathway (Liu et al., 2016).

Wang et al. (2017) investigated the anti-inflammatory effects and *in vitro* biocompatibility of rosmarinic acid supplemented hemodialysis fluid in a HUVECs model. Rosmarinic acid inhibits proinflammatory mediator production in a dose-dependent manner. In LPS-stimulated HUVECs, rosmarinic acid exposure resulted in decreased NO production and NOS expression. It also modulated Akt activation and NF- $\kappa$ B, suppressing inflammation in endothelial cells. Zhou et al. (2017) found that rosmarinic acid alleviated the endothelial dysfunction induced by hydrogen peroxide in rat aortic rings via activation of the AMPK/eNOS pathway. In a further study, rosmarinic acid pretreatment was also found to restore cardiac function and decrease myocardial infarct size and cardiomyocyte apoptosis following ischemia/reperfusion injury. Additionally, rosmarinic acid also downregulates pro-inflammatory cytokines such as IL-6, TNF- $\alpha$  and CRP. These observations were likely due to the ability of rosmarinic acid to up-regulate PPAR $\gamma$  and down-regulate NF- $\kappa$ B expression (Han et al., 2017).

Treatment with rosmarinic acid improves glucose concentration and lipid profile besides exhibiting anti-oxidative effects. In addition, rosmarinic acid limits tissue damage and inflammation to the abdominal aorta, as shown across microscopic observations and the analysis of protein expression (Ou et al., 2018). Rosmarinic acid pretreatment could also prevent cardiac dysfunction, hypertrophy and arrhythmia following myocardial infarction which is associated with the inhibition of lipid peroxidation and overexpression of NCX1 (Javidanpour et al., 2018). Besides this, it also attenuates cardiac fibrosis in long-term pressure overload via AMPK $\alpha$ /Smad3 Signalling (Zhang et al., 2018).

Yao et al. (2019) reported that rosmarinic acid inhibits NLRP3 inflammasome activation, resulting in reduced CRP generation in vascular smooth muscle cells. Rosmarinic acid also alleviated cardiomyocyte apoptosis by inhibiting the expression and release of Fas L in cardiomyoblast via the paracrine manner as shown across *in vitro* assessment. Moreover, rosmarinic acid is able to suppress the nuclear factor of activated T cells (NFAT) activation and metalloproteinase 7 expression, hence exerting an anti-apoptotic effect (Zhang et al., 2019). However, Zych et al. (2019) reported that rosmarinic acid was only able to limit oxidative stress and that no significant improvement was seen in the inflammatory marker IL-18 and lipid profile.

#### 4.4 Chlorogenic acid

Chlorogenic acid (5-O-caffeoylquinic acid) falls under the subgroup of hydroxycinnamic acid and is the major phenol compound found in coffee (Meng et al., 2013). In hypochlorous acid-induced vascular oxidative damage, chlorogenic acid supplementation improves *ex vivo* vessel function through increasing NO production and heme oxygenase-1 (HMOX-1) induction (Jiang et al., 2016).

HMOX-1 is a nuclear factor erythroid 2--related factor 2 (Nrf2)-regulated gene that plays a critical role in the prevention of vascular inflammation (Lazaro et al., 2018). In the isoprenaline-induced myocardial damage model, chlorogenic acid reduces cardiac injury marker and oxidative stress, besides limiting myocardial infarct size (Akila and Vennila, 2016). Tom et al. (2016) studied the direct effect of chlorogenic acid on endothelium denuded or intact aortic rings and found out that it increases NOS, COX and EDHF signalling pathways hence resulting in a direct endothelium-dependent vasodilation. Chlorogenic acid also remarkably limits H<sub>2</sub>O<sub>2</sub>-induced apoptosis in H9c2 cardiomyoblasts by inhibition of the ERK/JNK pathway and intrinsic apoptosis (Yu et al., 2016).

In 2017, Huang et al. (2017) showed that chlorogenic acid improves endothelial function by antioxidant, anti-inflammatory and ACE inhibitory effects. It also decreases the protein expressions of ICAM-1, VCAM-1 and MCP-1 induced by TNF- $\alpha$ . In aged senescence accelerated mice subjected to ischemia reperfusion by left anterior descending artery ligation, the chlorogenic acid-phospholipid complex limited myocardial necrosis, oxidative stress and mitochondrial respiratory deficits. Also, it reduced pro-inflammatory cytokines such as IL-1 $\beta$  IFN- $\gamma$ , TNF- $\alpha$  and upregulated the anti-inflammatory cytokines, IL-10 and IL-5. Increased expression of MAPK phosphatase-1 and inhibition of downstream activation of JNK were also observed (Li et al., 2018). Furthermore, chlorogenic acid attenuates glucotoxicity in H9c2 cells via the inhibition of glycation and PKC  $\alpha$  upregulation (Preetha Rani et al., 2018). Chlorogenic acid was also able to limit mitochondrial dysfunction and oxidative damage in oxidized LDL-induced HUVECs (Tsai et al., 2018).

Later in 2019, it was reported that chlorogenic acid improved NO bioavailability and eventually improved blood pressure in cyclosporine induced hypertensive rats (Agunloye et al., 2019). Besides, chlorogenic acid also protects cardiomyocytes from TNF- $\alpha$ -induced injury via inhibition of NF- $\kappa$ B and JNK signals (Tian et al., 2019). Chlorogenic acid supplementation in high-carbohydrate, high-fat diet-fed rats resulted in reduced visceral fat, especially abdominal circumference and retroperitoneal fat. These changes were accompanied by attenuated left ventricular diastolic stiffness, reduced collagen deposition, improved systolic blood pressure and reduced infiltration of inflammatory cells in the left ventricle (Bhandarkar et al., 2019).

#### 4.5 Ferulic acid

Ferulic acid, (4-hydroxy-3-methoxycinnamic acid) is one of the phenolic acids which can be obtained from rice, wheat, barley, orange, coffee, apple and peanuts (Ghosh et al., 2017). Ferulic acid is capable of altering the expression of IL-6 and VCAM-1 in CD40L and oxidized LDL-challenged HUVECs (Amin et al., 2015). Ferulic acid presented inhibitory activity on the expression of TNF- $\alpha$  and IL-1 $\beta$  cytokine by inhibiting the activation of NF- $\kappa$ B in LPS-activated macrophage (Navarrete et al., 2015). Furthermore, ferulic acid improved lipid profiles and insulin sensitivity besides reducing elevated blood pressure in a high carbohydrate high fat diet model. Ferulic acid also improved vascular function and prevented vascular remodelling of mesenteric arteries. These observations could be due to the suppression of oxidative stress by down-regulation of p47phox, increased NO bioavailability with

up-regulation of eNOS and suppression of TNF- $\alpha$  (Senaphan et al., 2015). Moreover, ferulic acid also imposes an endothelium independent vasorelaxation effect on aging and spontaneously hypertensive rats (Fukuda et al., 2015).

A study by Chowdhury et al. (2016) proved that ferulic acid inhibits ER stress, activation of caspase-3, DNA fragmentation and PARP cleavage in streptozotocin-induced diabetic rats. Increased translocation of GLUT-4 to the cardiac membrane through enhanced phosphorylation of Akt, PI3K, and inactivation of GSK-3 $\beta$  improves the hyperglycaemic condition of diabetic rats. Sustained release of ferulic acid from injectable hydrogel recovers oxidative stress-induced damage in Cisd2-deficient cardiomyocytes (Cheng et al., 2016). Ferulic acid also alleviated insulin resistance, restored NO level and alleviated the hypertension that is associated with metabolic syndrome (El-Bassossy et al., 2016).

Furthermore, ferulic acid relaxed rat aortic, coronary arteries and small mesenteric through blockage of the voltage-gated calcium channel and calcium desensitisation via dephosphorylation of Erk1/2 and Mypt1 (Zhou et al., 2017). Meanwhile, a study by Jain et al. (2018) reported that supplementation of ferulic acid alleviates myocardial damage in a rat model of isoprenaline-induced myocardial injury. Ferulic acid lowered circulating cytokines such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6 as well as limiting cardiac injury markers and oxidative stress. A similar observation was also seen in a high fructose diet-mediated metabolic alteration model where ferulic acid downregulates serum IL-6, IL-8 and TNF- $\alpha$  (Ibitoye and Ajiboye, 2018). In a doxorubicin induced cardiotoxicity model, ferulic acid inhibits cardiac apoptosis and oxidative stress via regulation of MAPK activation, NF- $\kappa$ B pathway and PI3K/Akt/mTOR impairment (Sahu et al., 2019). Lastly, ferulic acid ameliorates high glucose-induced oxidative stress and calcium overload via modulation of the mitochondrial function and SERCA/PLN pathway in H9c2 cardiomyoblast (Salin Raj et al., 2019).

#### 4.6 Ellagic acid

Ellagic acid (4,4',5,5',6,6'-hexahydroxydiphenic acid 2,6,2',6'-dilactone) is abundantly found in a variety of berries such as blackberries, strawberries, cranberries, raspberries, goji berries and pomegranates (Ceci et al., 2018). Mele et al. (2016) investigated the anti-atherogenic effect of ellagic acid and indicated that ellagic acid was able to reduce THP-1 monocytes adhesion to HUVECs and decrease sVCAM-1 and IL-6 secretion. Ellagic acid was also proven to reduce the accumulation of cholesterol in THP-1-derived macrophages, however it failed to promote cholesterol efflux.

Dhingra et al. (2017) reported that ellagic acid was able to suppresses mitochondrial injury and necrotic cell death of cardiac myocytes by functionally abrogating Bnip3 activity. Ellagic acid decreases endothelial ROS level and vascular oxidative stress, and ameliorates vascular relaxation impairment through modulation of the ERK1/2/NOX4 signalling pathway (Rozentsvit et al., 2017). Also, in 2017, ellagic acid improved ventricular remodelling following myocardial infarction by up-regulating miR-140-3p expression and inhibiting MKK6 expression (Wei et al., 2017). In a N $\omega$ -Nitro-L-arginine methyl ester hydrochloride-induced hypertension model, ellagic acid improved blood pressure, possibly through improving NO bioavailability. In addition, ellagic acid also attenuated plasmatic alkaline phosphatase activity, calcium content, and

vascular hypertrophy (Jordão et al., 2017).

Furthermore, supplementation of ellagic acid in sodium arsenite-induced cardiotoxicity rats resulted in attenuation of injury markers AST, CK-MB, LDH and cTnI. Ellagic acid also downregulated the NO level and normalised the cardiac anti-oxidant status, besides positively modulating the hematological parameter, hence exerting a cardioprotective effect (Goudarzi et al., 2018). Similarly, ellagic acid has beneficial cardioprotective effects against another cardiotoxicity model (Hemmati et al., 2018).

#### 4.7 Vanillic acid

Vanillic acid (4-hydroxy-3-methoxybenzoic acid) is a naturally occurring aromatic acid; olive oil is known as one of the rich sources of this compound (Franco et al., 2014). Vanillic acid effectively reduced infarct size and improved ventricular function in ischemia/reperfusion subjected isolated rat heart (Dianat et al., 2015). Evidence from other studies has shown that vanillic acid downregulates gene expression of VCAM-1 and secretion of sVCAM-1 (Warner et al., 2016). Moreover, vanillic acid improved heart function and ECG alteration, reduced cardiac injury markers and normalised gene expression of iNOS and eNOS in particulate matter (PM10)-induced damaged heart which was then ischemia/reperfusion challenged (Dianat et al., 2016).

In hypoxia/reoxygenation-subjected H9c2 cardiomyoblast, vanillic acid pretreatment was able to preserve cell viability and reduce the percentage of apoptotic cell and caspase-3 activity. It reduced cardiac injury and oxidative stress markers as well as restoring mitochondrial membrane potentials. Moreover, preincubation with vanillic acid significantly attenuated mitochondrial permeability transition pore activity and upregulated adenosine monophosphate-activated protein kinase  $\alpha 2$  (AMPK $\alpha 2$ ) protein expression (Yao et al., 2020). Furthermore, vanillic acid exerts cardioprotective effects against DOX-induced cardiotoxicity by decreasing oxidative stress and suppressing TLR4 signalling and consequently confers an anti-inflammation effect (Baniahmad et al., 2020).

#### 4.8 Caffeic acid

Caffeic acid (3,4-dihydroxycinnamic) is present not only in coffee beans and roselle but also in commonly used medications such as propolis (Espindola et al., 2019; Si et al., 2019). In 2015, Fukuda et al. reported caffeic acid to have a vasorelaxation effect in both aging and spontaneously hypertensive rats. In another study, caffeic acid increased basal and acetylcholine induced NO release, independent of eNOS phosphorylation and expression. In addition, caffeic acid also increased angiogenesis and proliferation while inhibiting leukocyte adhesion and endothelial cell apoptosis that were induced by either hypoxia, p-cresyl sulfate, indoxyl sulfate, or uremic toxins ADMA (Migliori et al., 2015).

In response to a myocardial ischemia reperfusion stress in vivo model, caffeic acid attenuated lipid peroxidation and troponin release. Following this, caffeic acid also maintained cell viability and alleviated intracellular ROS in H<sub>2</sub>O<sub>2</sub> exposed cardiomyocytes (Ku et al., 2016). Furthermore, caffeic acid reduced pro-inflammatory cytokines such as serum IL-6, IL-8 and TNF- $\alpha$  in a high fructose diet-mediated metabolic alteration model, hence exerting anti-inflammatory, anti-hyperglycaemia and anti-

hyperlipidemia effects (Ibitoye and Ajiboye, 2018). Interestingly, Agunloye et al. (2019) reported that caffeic acid positively regulates blood pressure in cyclosporine-induced hypertensive rats by improving the bioavailability of NO.

#### 4.9 Syringic acid

Syringic acid (4-hydroxy-3,5-dimethoxybenzoic acid) belongs to a subclass of hydroxybenzoic acid and is present in olives, spices, acai palm, dates, pumpkin and honey (Srinivasulu et al., 2018). Following myocardial injury, syringic acid was reported to avert myocardial damage by regulating oxidative stress, besides downregulating circulating pro-inflammatory cytokines, IL-6 and TNF- $\alpha$ . In addition, syringic acid limited adhesion of monocytes towards TNF- $\alpha$  stimulated HUVECs (Del Bo' et al., 2016).

Later in 2017, Ding et al. investigated the bioactivity of syringic acid in hypoxia/reoxygenation-exposed H9c2 cardiomyoblast. Syringic acid markedly downregulated expression of B-lymphocyte lymphoma 2 (Bcl-2) and inhibited the expression of Bcl-2-like protein 4 (Bax) and cleaved caspase-3 through downregulation of JNK and p38MAPK signalling pathways. In an isoprenaline induced cardiac injury model, syringic acid dose-dependently reduced myocardial injury and oxidative damage markers, besides lowering the proinflammatory cytokines, TNF- $\alpha$  and IL-6. Furthermore, improvements in myocardial infarct size and erythrocyte morphology were also observed (Shahzad et al., 2019).

## 5. Conclusion

In this review, we have summarised evidence on the potential activities of phenolic acids in the management of inflammation-related CVD. Although vast numbers of preclinical studies have reported on the cardioprotective potential of phenolic acids, there are still a limited number of clinical studies reporting on the efficacy of phenolic acids in CVD. Despite these promising findings, the therapeutic application of phenolic acids might be impeded by its shortcomings such as low stability, poor aqueous solubility and absorption, and low bioavailability that causes administration at therapeutic doses to be unrealistic (Hussain et al., 2019). Furthermore, it is undeniable that phenolic compounds work better in synergistic nature, rather than only as a single compound (Tangney and Rasmussen, 2013). It is also noteworthy to mention that sometimes the metabolites produced upon the metabolism of phenolic acids may actually exert better health-promoting effects in comparison to the parent compound. The fact that phenolic compounds may exert pleiotropic immunomodulatory effects may complicate therapeutic strategies that target inflammation in CVD. Furthermore, the potential side effects of phenolic acids also remain unknown. In addition, the exact mechanism involved in the implication of phenolic acids on the inflammatory response remains unclear. Hence, further studies and clinical trials are greatly needed to fully establish the therapeutic efficacy of phenolic acids as well as to determine their safety for human consumption.

## Authors' contributions

S.Z. received the review invitation. S.Z. and S.S.A. collected relevant literature. S.S.A. wrote the first draft of the manuscript. W.A.N.W.A., S.B.B. and S.Z. critically revised the manuscript and approved the final version of manuscript.

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## Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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