Chapter 19
Polyphenols: Classifications, Biosynthesis and Bioactivities

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Abbreviations

COX-2	Cyclooxygenase-2
DPPH	1,1-Diphenyl-2-picrylhydrazyl
GST	Glutathione S-transferases
IL-6	Interleukin-6
LDL-c	Low Density Lipoprotein-cholesterol
LOX	Lipoxygenase
NF-kB	Nuclear Factor kappa-light-chain-enhancer
QR	Quinone reductases
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
THF	Tumor necrosis
XO	Xanthine oxidase

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19.1 Introduction

Polyphenols are polyhydroxyphenols, which are structural class of compounds that are mostly composed of natural compounds, and sometimes synthesized or semi synthetic in nature (Cattani et al. 2012). These compounds have the characteristics of multiple phenolic structural units in them, hence, the name polyphenols. Polyphenols are mostly of plant origin and they are among the most studies class of phytochemicals. These natural phytochemicals are readily available in the entire plant kingdom and therefore find their way into human diet as they are found in whole grains, legumes, cereals, coffee, wine and tea. They are also found in fruits like grapes, pear, broccoli, apricot, orange, lemon, cherry and blueberry. More than 8000 of these polyphenolic compounds, including stilbenes, phenolic acids, lignans and flavonoids have been identified in whole plant foods (Pandey and Rizvi 2009). These phytochemicals are secondary metabolites found in plants, where they act as antioxidants, anti-inflammatory, antimicrobial, protect the immune system, defend against pathogens attack and ultraviolet radiations (Beckman 2000; Park et al. 2004; Widyarini 2006; Andarwulan et al. 2010; Chen et al. 2016; Hisanaga et al. 2016). Catechins, curcumin, cyanidin, ellagitannins, kampferol, myricetin, quercetin, resveratrol and rutin (Fig. 19.1) are among polyphenols with important bioactivities.

Catechins
Catechins ((2R,3S)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol) are group of procyanidins, which can be found in the leaves of *Camellia sinensis* (Türközü and Tek 2017). Studies have shown through to both epidemiological and experimental studies, that catechins are potent compounds against cancer, cardiovascular diseases, and aging (Arts et al. 2001). Catechins similarly protects the body against degenerative disease, with strong inverse relationship between the consumption of catechins and mortality through coronary heart disease (Arts et al. 2001).

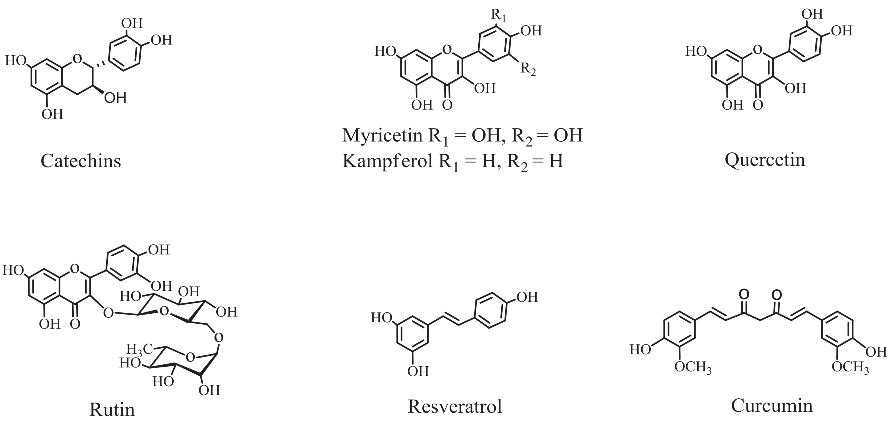

Fig. 19.1 Chemical structures of some polyphenols

They are potent antibacterial compounds when tested on Gram positive than Gram-negative bacteria (Park et al. 2004; Friedman 2007).

Quercetin

Quercetins are flavonoids with reported antioxidant and anti-inflammatory activities (Chen et al. 2016; Hisanaga et al. 2016). They are also important compounds in the prevention of cardiovascular diseases (Guillermo-Gormaz et al. 2015). Other activities of quercetin include their anti-influenza A virus activities, antiulcer, antiallergy, and anti-proliferative effects (Al-Jabban et al. 2015). The free radical scavenging activities of quercetin (Andarwulan et al. 2010) has been linked with the ortho-dihydroxy substitution in their B-ring and their enol moiety in the A-ring (Murota and Terao 2003). These structural features allows quercetin to form additional H-bond with 4-keto group (Murota and Terao 2003). Other bioactivities of quercetins include their anticancer and antidiabetic activities (Hashemzaei et al. 2017; Srinivasan et al. 2018).

Resveratrol

Resveratrol (5-[(E)-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol) is a dietary polyphenol, belonging to the stilbenes group and naturally occurring in fruits and food products (Bhat et al. 2001; Harikumar and Aggarwal 2008) and active during response to injury, fungal attack, or other environmental stress (Baur and Sinclair 2006; Aguirre et al. 2014). Resveratrols are potent antioxidant compounds (Olas et al. 2001) and important in strengthening of the muscle cells (Dolinsky et al. 2012). They are used in the treatment of inflammation, regulation of body metabolism (Palsamy and Subramanian 2009), and the treatment of neurodegenerative diseases, diabetes (Shin et al. 2010), cardiovascular diseases, and cancer (Sun et al. 2008).

Rutin

Rutein is a glycoside of quercetin (3-O-rhamnoglucoside), the most abundant flavonol in vegetable and fruit and widely studies polyphenol (Sharma et al. 2013; Hosseinzadeh and Nassiri-Asl 2014). Rutein is similarly known as quercetin-3-O-rutinoside (Erlund et al. 2000). Rutein is important as an anticancer, anti-hypertension, and anti- hypercholesterolemic compound (Erlund et al. 2000). Studies has indicated that rutein increase the concentrations of High Density Lipoproteins (HDL) and decreases the levels of Low Density Lipoproteins (LDL-c) in diabetic patients (Sattanathan et al. 2010).

Curcumin

Curcumin is a 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, also known as diferuloylmethane. Curcumin is a natural polyphenol strongly found in rhizomes of the plant *Curcuma longa* and are also available in others species of Curcuma (Aggarwal et al. 2003). *Curcuma longa* is a medicinal herb which has wide traditional uses due to its anticancer, anti-inflammatory, antioxidant, antimicrobial and antimutagenic properties (Mahady et al. 2002; Reddy et al. 2005; Vera-Ramirez et al. 2013; Wright et al. 2013; Lestari and Indrayanto 2014). Curcumin is relatively safe in its medicinal usage (Wilken et al. 2011).

Kampferol

Kaempferol is a 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one flavonoid that is present in a wide variety of edible plants including cabbage, beans, tomato, grapes and strawberries (Calderón-Montaño et al. 2011). They are similarly found in *Moringa oleifera, Ginkgo biloba* and *Sophora japonica*. Kaempferol and their glycosides exhibit wide biological activities including analgesic, antiallergic, anticancer, antidiabetic, anti-inflammatory, antimicrobial, anti-osteoporotic, anti-oxidant, cardioprotective, and neuroprotective activities (Calderón-Montaño et al. 2011). The chemical structure of kaempferol, which include the double bound at C2-C3 link with an oxo group at C4 and the presence of an hydroxyl groups at C3, C5 and C4' are reported to be important in its antioxidant activities (van Acker et al. 1996; Rice-Evans 2001).

Myricetin

Myricetin is a flavonoid that is structurally related to quercetin and kaempferol (Semwal et al. 2016). Just like kaempferol, myricetin may occur in its free and glycosidically-bound forms. Its found in beverages including teas, vegetables and fruits. Myricetin is a strong iron-chelating compound (Ong and Khoo 1997) with anticancer, antidiabetic, anti-inflammatory and anti-oxidant properties (Ong and Khoo 1997; Semwal et al. 2016).

19.2 Classifications of Polyphenols

Plant metabolites are classified into primary or secondary metabolites depending on the functions they play in the plant system. While primary metabolites play important roles in plants growth and their survival (Tijjani et al. 2018), secondary metabolites are synthesized as defense system against disease and herbivores (Mazid et al. 2011). These secondary metabolites are bioactive compounds, which are very useful as functional foods (Carović-StanKo et al. 2016). Polyphenols are among the largest group of secondary metabolites found in plants. Over 8000 structurally variants of polyphenols exist which are characterized by aromatic rings with one or more hydroxyl groups (Han et al. 2007). They are majorly classified into groups and subgroups based on the numbers of phenolic rings and structural elements attached to the rings (Butterfield et al. 2002). The major classes are phenolics, flavonoids, stilbenes and lignans (Fig. 19.2) (Pietta et al. 2003). Phenolic acids are subclassified into hydroxybenzoic acids including gallic acid or hydroxycinnamic acid and ferulic, coumaric, caffeic acid. The flavonoid subclass include anthocyanidins, flavanols, flavanones, flavones, flavonols and isoflavones.

Polyphenols are similarly classified into their various sources of origin, major biological functions and based on their chemical structures (Tsao 2010). Majority of these polyphenols that exist in plants are glycosylated with different carbohydrate units and acylated sugars at various positions on their basic polyphenol skeletons (Tsao 2010).

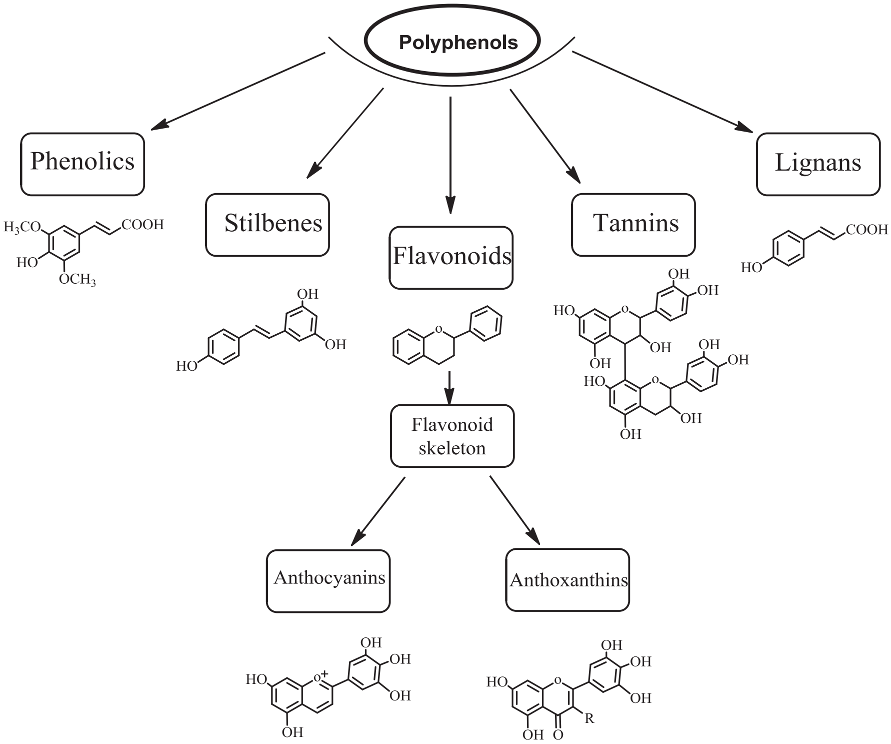

Fig. 19.2 Classifications of major polyphenols

19.3 Distributions of Polyphenols

Polyphenols are widely distributed in nature. The main dietary sources of polyphenols are from vegetables, fruits and beverages. Flavones and flavonols are polyphenols ubiquitous in plants and thus the most common within the flavonoid group of polyphenols (Bravo 1998). Catechins and epicatechin are monomeric flavan-3-ols and gallocatechin, Catechin derivative are majorly found in tea leaves and cocoa beans. They are the most abundant flavonoids in diet, which also include their oxidized products. They are common in dry legumes, cereals, wine, fruit juice, coffee, tea and chocolate.

Condense tannins are found as constituents of woody plants. Anthocyanidins are components of purple, blue and red pigments, which are distributed in some fruits, flower petals and vegetables. These anthocyanidins may also be present in plants as anthocyanins when glycosylated (Bravo 1998). Anthocyanins are water-soluble and are important pigments in plants where they impact colour ranging from vivid red to blue color (Khoo et al. 2017). Table 19.1 shows specific plant sources of polyphenol and the various classes of polyphenol found in them.

Table 19.1 Plant sources of polyphenols

S/No	Plant source	Class of polyphenol	Polyphenol	References
1.	*Oroxylum indicum* seeds	Flavones	Luteolin	Chen et al. (2003)
	Lycopersicon esculentum L.		Apigenin	Barros et al. (2012)
	Cichorium endivia L.			
	Medicago sativa L. leaves			El-Shafey and AbdElgawad (2012)
				Mishima et al. (2015)
2.	Citrus fruit	Flavanones	Hesperetin Naringenin	Mullen et al. (2008)
				Tomás-Navarro et al. (2014)
3.	*Ginkgo biloba* leave	Flavonols	Quercetin Kaempferol	Chan et al. (2007) and Calderón-Montaño et al. (2011)
	Moringa oleífera		Myricetin	
	Sophora japônica			
	Allium cepa			Rodriguez et al. (2008)
4.	*Rhus verniciflua* stoke	Flavanonols	Taxifolin Fustin	Kim et al. (2010)
	Larix gmelinii			Liu et al. (2014)
5.	Green tea, black tea, cocoa	Flavan-3-ols	Catechin	Subhashini et al. (2010)
			Epicatechin	Gadkari and Balaraman (2015)
			Epigallocatechin	
			Proanthocyanidins	Bravo (1998)
6.	Soybean *Vitis vinifera*	Isoflavones	Genistein	Wang and Murphy (1994)
			Genistin	Mazur et al. (1998)
			Daidzein	Kuligowski et al. (2017)
				Lotito and Frei (2006)
7.	Maclura pomifera (Raf.) Schneid.	Chalcones	Isoliquiritigenin	Tsao et al. (2003)
8.	Fruits	Anthocyanidins	Cyanidin Pelargonidin	Mazza (1995)
	Vegetables		Peonidin	Bravo (1998)
			Delphinidin	
			Petunidin	
			Malvidin	
9.	Peanuts	Stilbenoids	Resveratrol	Sanders et al. (2000)
	Cajanus cajan		Piceid	Burns et al. (2002)
			Cajanotone	Counet et al. (2006)
			Cajanamide	Zhang et al. (2012)
10.	*Curcuma longa*	Phenolic acids	p-Hydroxybenzoic acid	Manach et al. (2004)
	Punica granatum L			
	Fruits			
	Vegetables		Gallic acid	Seeram et al. (2006)
			Ellagic acid	
			Curcumin	

Some derivatives of hydroxybenzoic acid includes protocatechuic acid, gallic acid and p-hydroxybenzoic acid. Hydroxycinnamic acids, is however more common than hydroxybenzoic acid has some of its derivatives as caffeic acid, chlorogenic acid, coumaric acid, ferulic acid and sinapic acid. These derivatives are rarely found in free forms but they occur in fermented, frozen or sterilized foods. Berry fruits, apple, chicory, cherry, kiwi, coffee and pear are the foods with high levels of these phenolic acids (Manach et al. 2004).

Stilbenes, one of the sub-classes of flavonoids occur in smaller amount in human diet. Resveratrol (Fig. 19.1) which is one of the well-studied compounds of this group is largely found in red wine and grapes (Manach et al. 2004; Adlercreutz 2007; Pandey and Rizvi 2009). Chun et al. (2007) and Ovaskainen et al. (2008) reported dietary intake of polyphenols is estimated to be approximately 1 g/day. The availability of the important dietary components depend on their food source preparatory methods, their digestions in the gastrointestinal walls, their absorption rates as well as their metabolism in the body systems (Scalbert and Williamson 2000). In the absorption pathway of polyphenols, there must be colonic microflora or intestinal enzyme action in way of hydrolysis, which should be followed by conjugation in the intestinal cells and later glucuronidation, methylation or sulfation by the liver (Scalbert et al. 2002). Polyphenols, thereafter, accumulate in their target tissues to induce biological properties and the excretion of these phenol derivatives majorly occur in through urine and the bile (Scalbert et al. 2002).

19.4 Biosynthesis of Polyphenols

The shikimate pathway is critical to the synthesis of amino acids, which are further acted upon by specific enzymes for the biosynthesis of phenolics, lignins and flavonoids (Tijjani et al. 2018). Other polyphenols obtained from the shikimate pathway include phenolic compounds such as cinnamic acid and gallic acid (Tsao 2010). The aromatic ring B of polyphenols and the chromane ring are derived from phenylalanine obtained from the shikimate pathway while ring A are obtained from the condensation of three units of malonylCoA (Fatland et al. 2004; Tsao and McCallum 2009). Phenylalanine is deaminated by the enzyme phenylalanine ammonia lyase to trans cinnamic acid (Fig. 19.3). Cinnamate-4-hydroxylase catalyze the conversion of trans cinnamic acid to form *p*-coumaric acid. CoASH is added by the enzyme 4-coumaroyl CoA ligase to form *p*- coumaroyl CoA (Bohm 1998; Tsao and McCallum 2009). The *p*-coumaroyl-CoA formed then condenses with three molecules of malonyl-CoA to form chalcone catalyzed by the enzyme chalcone synthase. The enzyme chalcone flavanone isomerase isomerize chalcone into a flavanone which could be further converted to dihydroflavonols or to flavan-3, 4-diols (Bohm 1998; Tsao and McCallum 2009). The glycosylation of flavonoids by the enzyme glucosyltransferase provide addition of a sugar unit to the flavonoid (Bohm 1998; Tsao and McCallum 2009).

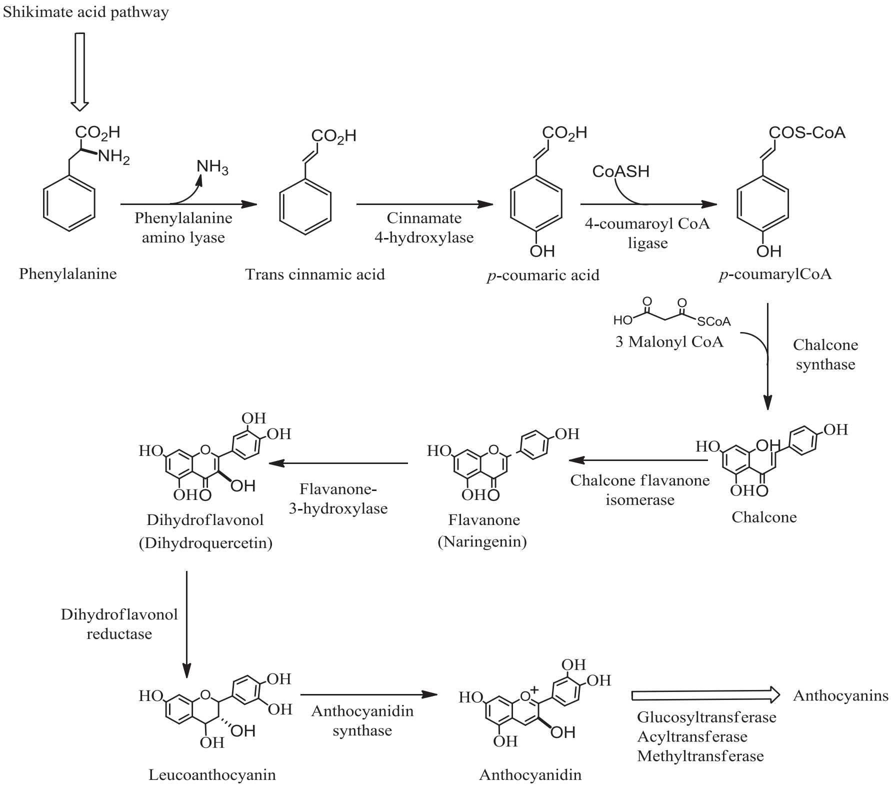

Fig. 19.3 Biosynthesis of polyphenols. (Bohm 1998; Fatland et al. 2004; Tsao and McCallum 2009)

19.5 Medicinal Properties of Polyphenol

Foods obtained from plants provide essential nutrients that are needed by human for growth and development and play important role in human health (Akbari et al. 2012; Bøhn et al. 2014; Rasouli et al. 2017). Over the last 16 years, a lot of studies have been carried out and reported on the importance of secondary metabolites on their medicinal importance and their ability to improve human health (Valdés et al. 2015). These phytochemicals were reported to have been synthesized by various plants, some for their protection against herbivores and predators (Tijjani et al. 2018). They have however played beneficial roles in the area of pharmaceutical and medicinal purposes Yue et al. (2016). Kossel (1891) was the first scientist who showed the significance comparism between the primary metabolites and secondary metabolites. Among these secondary metabolites, plant polyphenols are very crucial members and they've been identified to play significant role in human medicine as secondary metabolites. Recently, polyphenols have served as important prophylactic and therapeutic agents against diseases and have shown to have antioxidant properties, which showed their importance in the field of medicine. Many scientific studies have revealed that people who focused on specific diet, especially polyphenolic rich diets are at low risk of certain chronic diseases such as heart disease, diabetes, obesity, and cancer. Studies on plant polyphenols has been carried out with the intention of discovering protective compounds against certain diseases including their antioxidant, anti-inflammatory and anti-microbial properties. Their blood pressure reducing effects, immune response, skin protection and nutraceuticals have also been reported.

19.5.1 Antioxidant Properties of Polyphenols

The production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) are deleterious to the body system. If the ROS and the RNS produced from cellular reactions are at balanced levels, they serve as beneficial compounds for cellular functions. However, if they are produced at unbalanced levels, which sometimes occur, they lead to oxidative stress, which can cause degenerative disorders, especially to the vital organs in the organism (Valko et al. 2006; Pham-Huy et al. 2008). Many scientist have advocated for the use of antioxidant compounds, which are found in plant based food substances, some of which are polyphenolic compounds. The use of these naturally occurring antioxidant compounds have significantly increased and they've been employed in medical usage as well as in pharmaceutical companies, which serve as substitute for the artificial ones which have been suspected to be one of the major causes of cancer (Carocho et al. 2014). Heim et al. (2002) stated that the arrangement of functional groups, their configuration, substitution and the number of hydroxyl groups also influence the antioxidant activity of flavonoids such as the radical scavenging activity and or metal ion chelation ability. Flavonoids and phenolic compounds have been described by many scientists as phytochemicals with the highest antioxidant properties from plants (Ryu et al. 2006; Okpuzor et al. 2009; Mishra et al. 2013; Wang et al. 2016; Andreu et al. 2018; Zahoor et al. 2018).

Oki et al. (2002) examined the antioxidant capacity of anthocyanins and other phenolics from different cultivars of purple-fleshed sweet potato (*Ipomea batatas* L.) which is an edible and economic medicinal specie in Japan. Their assessment of the antioxidant activity using diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity shows that a positive antioxidant activity exist the cultivars used for their study. Similarly, they observed that chlorogenic acid showed a dominant DPPH radical scavenging activity in Miyanou-36 cultivar and Bise cultivar in the sweet potato. The other two cultivars; Ayamurasaki and kyushy-132 also showed antioxidant activities but anthocyanins were rather observed to show the DPPH radical scavenging activity in them (Oki et al. 2002).

Mishra et al. (2013) observed that leaf extracts of *Bauhinia variegate* contained flavonoid compounds which showed a great antioxidant ability against oxidative stress through ion binding ability, reducing power ability as well as radical neutralization (Mishra et al. 2013). Andreu et al. (2018) also observed that the cultivars with a significant amount of total phenolic compounds in the peel and pulp of the fruits of six cultivars of *Opuntia ficus-indica* (L.) and young and adult plants of cladodes expressed a significant effect against oxidative stress (Andreu et al. 2018).

Zahoor et al. (2018) also reported that the antioxidant property of 2-hydroxy-2-phenyle acetic acid (mandelic acid) and 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-Chromen-4-one (quercetin), which are the major bioactive molecules in *Aesculus indica* (Wall. Ex Cambess) showed a significant effect in the reduction of oxidative stress which are caused by reactive oxygen species (Zahoor et al. 2018). *Polygonatum verticillatum* L. extract exhibit great antioxidant activity, which has been linked with their phenolic compounds present in the plant (Kumar Singh and Patra 2018).

Meng et al. (2018) evaluated the phytochemical profiling as well as the biological activity of the extract of *Camellia fangchengensis* tealeaves. The result obtained showed that flava-3-ol oligomers and monomers are potent antioxidant compound found in the plant and maybe responsible for the antioxidant activities express by the plant (Meng et al. 2018).

19.5.2 Blood Pressure Reduction Properties of Polyphenols

Polyphenols are present in foods such as soybean (Kim et al. 2008). Black soybeans which contain different colours as a result of the presence of chlorophyll, anthocyanin other pigments. The black colour is due to the presence of anthocyanins in the epidemis palisade layer of the seed coat (Kim et al. 2008). The soybeans are widely consumed in Asia due to its medicinal purposes. Cyanidin-3-glucoside, pelargonidin-3-glucoside and delphinidin-3-glucoside have all been identified in black soybeans seed (Choung et al. 2001). Black soybeans contain some phytochemicals such as isoflavones, phytic acid, saponin and phenolic that are all very effective in the prevention of many chronic diseases and provide a lot of health benefits (Zhang et al. 2011). Black soybeans have been reported to have the greatest antioxidants properties compared to other coloured soybeans and these antioxidant is due to the presence of phenolics, distributed mainly in the seed coats (Kim et al. 2006; Slavin et al. 2009; Zhang et al. 2011). The rich content of soybeans has been found to reduce the effects of cancer and other chronic diseases and metabolic disorders (Kusunoki et al. 2015; Zou 2016; Tan et al. 2016; Matsukawa et al. 2017). Black soybeans contains low concentration of sodium, which enables it to maintain blood pressure at a normal range. The presence of the anthocyanins in it has also been reported as a factor for its ability to reduce the risk of cardiovascular diseases in individuals (Zou 2016; Hooper et al. 2008). The fiber in Black soybeans helps to lower total cholesterol, Low Density Lipoprotein-cholesterol (LDL-c) in the blood and liver which are inversely related to heart disease and also inhibits oxidative stress by increasing antioxidant activity and improving lipid profiles in postmenopausal women (Byun et al. 2010).

19.5.3 Anti-inflammatory and Immune Effects of Polyphenols

Phenolic compounds have antioxidant roles to play which could be relevant in the prevention of carcinogenesis by altering the oxidative stress condition, which reduces inflammatory responses associated with carcinogenesis (D'Alessandro et al. 2003). Reactive oxygen species can damage proteins, DNA and RNA, as well as oxidize fatty acids in cell membranes thus increasing the risk of mutations. It is however believed that majority of the damages caused by ROS can be restored by the body's internal surveillance and its repair system (D'Alessandro et al. 2003). These ROS are also considered to be important in the activation of NF-kB and other transcription factors as they serve as endogenous mitogenic factors in a variety of normal processes (Kovacic and Jacintho 2001). One of the chemoprevention mechanisms of phenolic compounds is associated with their scavenging properties of deleterious reactive species (including hydroxyl radical, superoxide anion, singlet oxygen, peroxynitrite and nitric oxide) (D'Alessandro et al. 2003). Alternatively, polyphenols can inhibit ROS generating transcription factors closely linked to inflammation (e.g., NF-kB24) and enzymes such as xanthine oxidase (XO) and cyclooxygenase-2 (COX-2) as demonstrated by curcumin (Lin and Shih 1994; Zhang et al. 1999) or lipoxygenase (LOX) by polyphenols including curcumin, silymarin, and resveratrol (Hong et al. 2001) which mediate inflammatory processes (Le Corre et al. 2005). Polyphenols have also been reported to behave as detoxifying enzyme inducers, where they modulate gene expression which also include the induction of phase II enzymes, such as quinone reductases (QR) and glutathione S-transferases (GST) (Fiander and Schneider 2000). This action usually leads to protection of cells or tissues where they occur against exogenous and/or endogenous carcinogenic intermediates (Fiander and Schneider 2000). A number of works have been conducted on the effect of flavonoid and other phenolics on their immune boosting effects and anti-inflammatory functions (Middleton 1998; Locatelli et al. 2018). Kumar and Pandey (2013) reported the anti-inflammatory potentials of some flavonoid compounds such as apigenin, hesperidin, luteolin and quercetin. The anti-inflammatory properties for different cultivars of the extract of *Lonicera caerulea* L. was investigated, by focusing on the pro-inflammatory cytokines, using *in vitro* human monocytic cell line THP-1 derived macrophages stimulated by lipopolysaccharide (Vasantha et al. 2015). Their result revealed that Borealis cultivar of haskap berry exhibited anti-inflammatory effect, which is comparable to diclofenac drug. This anti-inflammatory effect was due to the presence of high concentration of phenolic compounds like flavonoid and anthocyanin (Vasantha et al. 2015). The polyphenolic compounds of *Gaillardia grandiflora* Hort. and *Gaillardia pulchella* Foug were similarly observed to possess anti-inflammatory effect with no toxicological effect in mice model. The newly reported compound, 8-hydroxyapigenin 6-*O*-β-D-apiofuranosyl-(1″′→6″)-*C*-β-D-$^{4}C_{1}$-glucopyranoside, from *G. grandiflora* and other known compound which include luteolin 6-C-ß-D-4C1-glucopyranoside 8-methyl ether, schaftoside, isoorientin, apigenin 6-C-ß-D-4C1- glucopyranoside 8-methyl ether, 6-methoxyluteolin isovitexin and hispidulin were also isolated and tested (Moharram et al. 2017).

Ma and his team examined the anti-inflammatory ability of the polyphenolic fractions of sixteen cultivars of Chinese blueberry against tumor necrosis-(THF-) and interleukin-6 (IL-6). The anti-inflammatory effect of these blueberry samples were tested using lipopolysaccharide induced RAW 264.7 macrophages; anti-inflammatory potential of the polyphenol fractions were in the same trend phenolic their phenolic acid contents (Su et al. 2017). Likewise the anti-inflammatory activity, and evaluation of total phenolic content as well as the total flavonoid content of different fractions of *Bidens engleri* and *Boerhavia erecta* were evaluated (Compaore et al. 2018). Dichloromethane solvent was observed to extract flavonoid compounds more and the fraction exhibited the highest anti-inflammatory effect, via COX-2 and LOX-15 inhibition.

Macrophages have been documented to maintain the balance in pro-inflammatory and anti-inflammatory activities by controlling the switches in immune systems. Polyphenols extracted from roasted cocoa beans (*Theobroma cacao*) lower pro-inflammatory cytokine secretion significantly in *in vitro* THP-1 cells and also promotes oxidative stress by suppressing inflammation which led to ATP production as a result of increase in oxygen consumption (Dugo et al. 2017). *In vitro* evaluation of anti-inflammatory effects of the ethanolic extract of rhizome in astilbin (dihydroflavonol) from Smilax glabra was conducted by Lu et al., (2015). The result obtained revealed the suppression of nitric oxide production, TNF-a, tumor necrosis in factor-a as well as expression of mRNA inducible nitric oxide synthase in tested cells (Lu et al. 2015).

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The anti-inflammatory ability of the polyphenolic fractions of sixteen cultivars of Chinese blueberry against tumor necrosis-(THF-) and interleukin-6 (IL-6). The anti-inflammatory effect of these blueberry samples were tested using lipopolysaccharide induced RAW 264.7 macrophages; anti-inflammatory potential of the polyphenol fractions were in the same trend phenolic their phenolic acid contents (Su et al. 2017). Likewise the anti-inflammatory activity, and evaluation of total phenolic content as well as the total flavonoid content of different fractions of *Bidens engleri* and *Boerhavia erecta* were evaluated (Compaore et al. 2018). Dichloromethane solvent was observed to extract flavonoid compounds more and the fraction exhibited the highest anti-inflammatory effect, via COX-2 and LOX-15 inhibition.

19.5.4 Anti-microbial Properties of Polyphenols

Polyphenols possess anti-microbial properties according to evidences obtained from studies using plant polyphenols. These properties of polyphenol are believed to be beneficial to health from the consumption of food rich in polyphenols such as vegetables, fruits and other plant-derived products. Food is the main source of polyphenols, which when consumed pass through the gut. Selma et al. (2009) suggested that such phytochemicals could modify the microbes in the gut and influence their biological activity. Similarly, it has been observed that the plant-derived phytochemicals could also convert the colonic microbiota to active bio-compounds, which can influence the host health (Selma et al. 2009). Such health issues underline one aspect of a wider, more important and complex relationship between microbes, plant products and animal species.

This might affect the interpretation of the phenolics in their consideration as real antibacterial chemicals in human life. Some phenolic compounds and flavonoids such as quinic acid, caffeic acid, gallic acid and chlorogenic acid have been proved to be potent antimicrobial compounds against typical microbial strains which affect the human respiratory system or urinary tract system, including *Candida* species (Chirumbolo 2010). Galangin, which is a flavonoid compound, has been reported to inhibit the replication of the bacterium *Klebsiella pneumoniae* (Gram negative bacteria) by suppressing the bacterial enzyme DNA-B helicase (Gordon and Wareham 2010).

19.5.5 Skin Protective Effect of Polyphenols

Over exposure to ultraviolet radiation can cause harm to the skin. It induces extensive production of reactive oxygen species and eventually causes skin damages (Ichihashi et al. 2003). However, there are several strategies applicable for skin protection. Phytochemical compound, especially phenolics and flavonoids is one of the most interesting choices that exhibit beneficial effects on UV-irradiated skin (Svobodová et al. 2003; Korác and Khambholja 2011). The antioxidant ability of flavonoids makes them to possess photo-protective effects, based on their iron chelating ability, averting the destructive effects against oxidative damage which can destroy protein and lipids on cell membrane and also modulate several signaling pathways such as the inhibition of xanthine oxidase which is considered as a source of reactive oxygen species that contributes to oxidative stress (Ferrali et al. 1997; Cos et al. 1998).

Authors have reported various methods for the treatment of skin diseases as well as skin disorders caused by ultraviolet radiations with use of antioxidant ability of phenolic compounds (Działo et al. 2016; Korác and Khambholja 2011). Ferrali et al. (1997) reported the skin protective ability of apigenin, a major flavone found in edible medicinal plants and beverages such as beer, chamomile tea and red wine. Apple peel, onion skin and *Hypericum perforatum* leaves also contain flavonol, such as quercetin and has been proved to inhibit skin damage induced by UVB, in hairless mice. Similarly, extracts form *Ginkgo biloba* L. (EGb 761), which contains high content of quercetin derivatives has been proved to reduce sun burn symptoms in *in vivo* studies using UVB irradiated-skin mice model (Casagrande et al. 2006).

Sillymarin which is an extract of flavono-lignans obtained from the milk thistle of the plant *Silybum marianum* (L.) Gearnt fruit contains silybin, a major active component in the plant (Bijak 2017). Silymarin has been reported to stimulate the repair of DNA damage caused by induced-UVB and prevent cell apoptosis in UVB-exposed human epidermal keratinocytes and fibroblasts in *in vitro* study (Katiyar et al. 2011). Another photo-protective isoflavone compound reported is genistein, extracted from soybean and with the ability to inhibit UV induced DNA damage in the skin of human and therefore prevents photocarcinogenesis as observed in *in vitro* experiment (Moore et al. 2006). Wang et al. (2010) reported that genistein has the ability of maintaining antioxidant enzyme activities and modulate mitochondrial oxidative stress in human fibroblast on UVB induced senescence.

Equol is an isoflavonoid metabolite of the genistein or isoflavone daidzein produced from the gut of microflora (Setchell and Clerici 2010). Topical application of equol can inhibit DNA photodamage, prevent UV induced erythema associated with edema and prevent skin cancer when acting as sun-screen in hairless mice (Widyarini 2006). Additionally, Choi et al. reported that ultraviolet UVB induced photo aging in *in vivo* using hairless mice, in the evaluation of skin protective effects of spent coffee revealed the coffee ground extract made up of flavonoids were able to show protection on mouse skin by the down-regulating of matrix metalloproteinases (Choi et al. 2016). Kano et al. evaluated the photo-protective effects of isoflavones extracted from soy milk on the photo-damage of ovariectomized hairless mice skin in a 28 days administration. Their report revealed that there was an increase of isoflavone in the blood and skin of mice, which on the long run can scavenge reactive oxygen species generated by UV irradiation and the effect can also exert estrogenic activity. This in turn led to photo-protective effect on the skin of the mice (Kano et al. 2016).

19.5.6 Cardioprotective Activities of Polyphenols

The cardioprotective effects of phytochemicals (phenolics and/or flavonoids) which occur naturally in medicinal plants have been reported (Kumar and Pandey 2013; Craig 1999; Garjani et al. 2017; Dludla et al. 2017; Cook and Samman 1996). For example, the cardiotoxicity of doxorubicin, an extensively used anticancer drug for breast cancer, leukemia and lymphoma with side effects including pericarditis, arrhythmias, myocarditis and acute heart failure (Razavi-Azarkhiavi et al. 2016). The cardio-protective effects of many phenolic compounds on the adverse effects of doxorubicin on heart have also been studied (Razavi-Azarkhiavi et al. 2016). They are recommended as antioxidant as solution to the side effects of this anticancer drug. The role of many phenolics and flavonoids in cardioprotection has been attributed to their ability to inhibit generation of ROS, apoptosis, mitochondrial dysfunction, NF-kB, p53 and DNA damage in an *in vitro*, *in vivo* and clinical study. These phenolics and flavonoids (kaempferol, luteolin, rutin and resveratrol) showed efficacy against cardiotoxicity induced by doxorubicin but do not have effect on the activity of antitumour of this drug (Repo-Carrasco-Valencia et al. 2010; Morrison 2012; Han et al. 2012). Isorhamnetin, another interesting compound with report of its cardioprotective effect against doxorubicin toxicity and served as anticancer efficacy for the drug (Sun et al. 2013). Plant extracts contain phytochemicals, which possess cardioprotective effects. Example include phenolic composition of the methanolic extract from aerial part of *Centaurea borysthenica* Gruner and *Centaurea transcaucasica* Sosn Ex Grossh) plants with cardiomyocytes protective roles (Korga et al. 2017).

Alhaide et al. (2017) evaluated the cardioprotective effects of four varieties of date palm fruits and the total phenolic, total flavonoid, *in vivo* myocardial infarction and *in vitro* antioxidant capacity. The cardioprotective effects in the *in vivo* myocardial infarction study were attributed to the high flavonoid and phenolic contents in the fruit extracts, which led to the mobilization of the circulating progenitor cells from the bone marrow of the myocardial infarction animals, so as to promote tissue repair from ischemic injury (Alhaider et al. 2017).

Tian et al. (2018) studies on the cardioprotective role of polyphenolic extract of apple peel and apple flesh polyphenol in *in vivo* mice model on cardiovascular risk factors revealed that the extract of apple peel exhibited higher cardioprotective capacity than the apple flesh and this could be due to higher phenolic content and higher flavonoids in apple peel (Tian et al. 2018). Another research on the aerial part of aqueous extract from *Marrubium vulgare* L. against ischemia reperfusion injury *in vivo* on their cardioprotective ability shows that the aqueous extract from this plant provided cardioprotective potentials against cardiac injury on the animal (Garjani et al. 2017). Two main compounds isolated from *Aspalathus linearis* (Burm.f.) R. Dahlgren (i.e Aspalathin and phenylpyruvic acid-2-O-ß-D-glucoside) were observed to be potential cardioprotective compounds in myocardial infarction case caused by chronic hyperglycemia (Dludla et al. 2017). Polyphenolic compounds such as cinnamic acid, ferulic acid, gallic acid, gellanic acid, quercetin and syringic acid were discovered to be the major flavonoids and phenolic in the different fractions obtained from seeds extract of *Syzygium cumini* (L.) Skeels (Syama et al. 2017). Their cardioprotective role in *in vitro* H9c2 cardiac cell lines such as angiotensin converting enzyme modulation, HMG-CoA reductase, LDL oxidation and tertiary butyl hydrogen peroxide induced oxidative stress shows that the fractions obtained were observed to attenuate oxidative stress in H9c2 cardiomyoblasts and this was also demonstrated by molecular docking studies which revealed the correlation between the major phytochemicals compounds and key enzymes for the prevention of these cardiovascular diseases. Gao et al. (2007) reported the interest in the use of puerarin as a cardioprotective candidate which acts by protecting myocardium from ischemia and reperfusion damage by activating protein Kinase C through its ability to open Ca^{2+}-activated K^+ *in vivo* in Sprague Dawley rats (Gao et al. 2007).

19.5.7 Anticancer Activities of Polyphenols

Polyphenols are reported with anticancer activities. The ethanolic extract of two members of the Zingiberaceae family; *Zingiber officinale* (rhizome) and *Curcuma longa* L. were reported to be natural promising anticancer compound for the fight against malignant melanoma due to the potential anticancer property on murine melanoma B164A5 cell line (Danciu et al. 2015). Their report also suggested *Curcuma longa* based on the increasing anticancer property of its extract, to be due to high concentration of polyphenolic compounds present in the extract (Danciu et al. 2015). Many biomedical researches have indicated flavonoid to be a potential apoptosis in various cancer cells (Zhishen et al. 1999; Brusselmans et al. 2003, 2005). Reports have been made on the anticancer role of quercetin, which is a major flavonol member against breast and prostate cancers (Kumar and Pandey 2013; Brusselmans et al. 2005).

Flavonoids (Gliricidin7-O-hexoside and Quercetin7-O-rutinoside) isolated from medicinal fern (*Asplenium nidus*) have been suggested to be potential anticancer compound against human carcinoma Hela and human hepatoma HepG2 cells (Jarial et al. 2018). Similarly, studies on the apoptosis inducing ability of quercetin in *in vivo* and *in vitro* studies using 9 different cancer cell lines, such as acute lymphoblastic leukemia MOLT-4 T-cells, pheocromocytoma PC12 cells, colon carcinoma CT-26 cells, human lymphoid Raji cells, ovarian cancer CHO cells, and colon carcinoma CT-26 cells among others, shows that quercetin can significantly induce apoptosis of every tested cell lines significantly at $p < 0.001$ compared with control group (Hashemzaei et al. 2017). For the *in vivo* studies using mice carrying MCF-7 tumors and mice bearing CT-26 tumors, the tumor in quercetin treated mice were significantly reduced in size and volume at significantly at $p < 0.001$ when compared with the control, with prolonged survival period (Hashemzaei et al. 2017).

Curcumin is a natural phenolic compound, it exert its anticancer effect on skin cancer and has been described as a compound that can influence cell cycle by acting as a pro-apoptotic agent (Działo et al. 2016). Antiproliferative effect of curcumin was investigated by Abusinina et al. on melanoma cancer in *in vitro* studies, using B16F10 murine melanoma cells. Their report indicated that curcumin served as an inhibitor to melanoma cell proliferation by acting as a non-selective cyclic nucleotide phosphodiesterase and this is related to epigenetic integrator UHRF1. They also suggested that curcumin which occur in food and diets can help in cancer prevention and contribute to gene expression via epigenetic control (Abusnina et al. 2011).

Curcumin mechanism involves the inhibition of the proliferation of selected cell lines and also induced apoptosis of cancer cells with dose-dependent response (Ide et al. 2018). The *in vivo* experiment on transgenic adenocarcinoma in mouse prostate model, with oral administration of curcumin for 1 month revealed that the curcumin regulated the transgenic enzyme expression, including AKR1C2, suppressed growth of prostate cancer cells, and decrease testosterone levels in prostate tissues of TRAMP mice (Ide et al. 2018).

19.6 Nutraceutical Application of Polyphenols

Cancer is one of the world's second leading deadly diseases, which has claimed many lives (WHO 2018). Reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) can as well serve as carcinogenic and mutagenic agents, which can later contributes to cancer development. The most proffered solution to treatment of cancer globally is through chemotherapy and this has been discovered to have many side effects (Huang et al. 2017). A flavonoid derived drug for the treatment of cancer known as flavopiridol is a phytochemical compound obtained from the plant *Dysoxylum gotadhora* (Buch.-Ham.), which is active for leukemia and lymphomas treatment (Shah et al. 2003; Cragg and Newman 2005). Some dietary supplements, made up of phenolic compounds, most especially flavonoids have long been reported to have chemopreventive ability and also have roles to play in management of cancer (Block et al. 1992; Zhishen et al. 1999; Brusselmans et al. 2003; Ahmed et al. 2016).

19.7 Conclusion

Polyphenols are class of aromatic compounds with polyhydroxyphenol structures. These compounds can be divided into several subclasses including phenolics, stilbenes, flavonoids, tannins, and lignan. These polyphenols are mostly natural compounds, which are readily found in plant-based foods while some are synthetic. Polyphenols have antioxidant, anti-inflammatory, antimicrobial, skin protection, immune system, blood pressure reduction, cardioprotective and anticancer properties. Polyphenols antioxidant properties can bring about the prevention and treatment of disease resulting from the imbalance in ROS and RNS that bring about oxidative stress and tissue degenerative diseases. Polyphenols are also promising nutraceutical agents; their inherent benefits should be exploited more for their bioactivity and nutraceutical applications.

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