Therapeutic Potential of Plant Polyphenolics and Their Mechanistic Action Against Various Diseases

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Contents

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Abstract

Secondary metabolites such as polyphenols are naturally existing compounds which are especially found in fruits, vegetables, cereals, and various other beverages. These defensive bio-active compounds possess broad range of biological activities in providing treatment against various diseases. Increased dietary intake of polyphenols has been reported to lower the risk of chronic diseases, where, oxidative stress is the main causative factor. Oxidative stress can cause oxidative damage to biological macromolecules such as proteins, nucleic acids, and lipids. They play a vital role in the pathogenesis of aging and other degenerative diseases. Humans possess potent antioxidant defense mechanisms to combat with the altered redox balance which results from excessive generation of free radicals produced during increased oxidative stress. The mechanism by which they exert beneficial effects includes scavenging of reactive oxygen species (ROS), blocking of ROS production, and sequestering of transition metals and antioxidant mechanisms which are produced endogenously and supplied through diet, which is exogenous. Dietary polyphenols have attracted increased attention for study against various disease mechanisms because of their potent antioxidant, antiaging, anticancer, anti-inflammation, neuroprotective, and cardiovascular protection activities. Even though various biological properties of polyphenols have been elucidated, the potent mechanism by which these compounds act in providing beneficial effects in human health against various diseases still needs to be explored. The absorption efficacy of these compounds should be taken into consideration while using in clinical applications. Knowledge of mechanism of action and bioavailability might increase the understanding of biological activity of polyphenols within target tissues. This chapter has emphasized the classification of dietary polyphenolics and bioavailability along with their beneficial mechanism of action in treating various diseases. The chapter will certainly throw limelight in making use of dietary polyphenols as an effective treatment regimen in prevention against various diseases.

Keywords

Polyphenols · ROS · Inflammation · Oxidative stress · Diseases · Activities

14.1 Introduction

Polyphenols are the secondary plant metabolites and rich bio-active compounds. Polyphenols possess one or more benzene rings that bear numerous hydroxyl groups (Del Rio et al. 2013). They are the richest source of antioxidants which are immensely available in our daily diet. The sources of polyphenols are present widely in foods and beverages of plant origin which include legumes, spices, fruits, vegetables, coffee, nuts, olive oil, wine, green tea, and cocoa (Bonita et al. 2007; Vallverdú-Queralt et al. 2015; Talhaoui et al. 2016). The color, odor, flavor, bitterness, acidity, and oxidative stability could be attributed to the characteristic feature of the polyphenols present in the diet. The antioxidants present in polyphenols delay the oxidation of low-density lipoprotein which is the underlying mechanism that

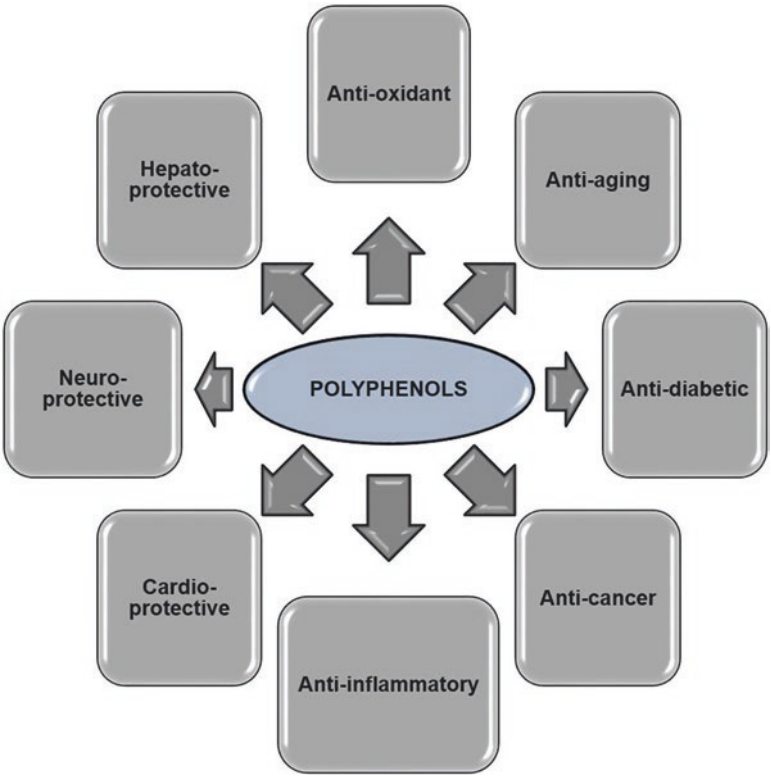

Fig. 14.1 Beneficial role of polyphenols in human health

takes place in atherosclerosis. Numerous epidemiological studies suggest that long-term consumption of dietary polyphenolics could provide hepatoprotection and protective action against development of cardiovascular diseases, osteoporosis, asthma, neuroprotection, diabetes, and cancers and even aging (Baião et al. 2017) (Fig. 14.1). Various forms of oxidants and free radicals are involved in the pathogenesis of numerous chronic diseases. Dietary sources of polyphenols have received greater attention nowadays because of their beneficial effects against broad range of pathologies in various tissues with different efficacies and bio-availabilities. Hence, this chapter focuses on the dietary consumption of polyphenolics, their bioavailability together with their beneficial effects in human disease and health.

14.2 Chemistry and Classification of Secondary Polyphenols

Polyphenolic compounds have at least one aromatic ring attached with one or more hydroxyl groups. These compounds range usually from small molecules to complex polymeric structures (Velderrain-Rodríguez et al. 2014). The natural polyphenols exist typically in conjugation with organic acids and sugars and can be divided into five major classes depending on the chemical structure which are as follows: phenolic acids, flavonoids, stilbenes, lignans, and other polyphenols. The classification

Table 14.1 Major classes of polyphenols and their available food sources

Major classes	Subclasses	Examples	Sources	References
Phenolic acids	Hydroxybenzoic acid	Ellagic acid, gallic acid	Pomegranate, grapes, berries, walnuts, chocolate, wine, and green tea	Manach et al. (2004) and Del Rio et al. (2013)
	Hydroxycinnamic acid	Coumaric acid, caffeic acid, ferulic acid, chlorogenic acid	Coffee, cereal, and grains	Guasch-Ferré et al. (2017)
Lignans	–	Sesamin, diglucoside	Flaxseeds, sesame	Kiso (2004) and Kong et al. (2009)
Stilbenes	–	Resveratrol, pterostilbene, piceatannol	Grapes, berries, red wine	Soleas et al. (1997), Haminiuk et al. (2012), and Guasch-Ferré et al. (2017)
Flavonoids	Anthocyanins	Delphinidin, Pelargonidin, cyanidin, malvidin	Berries, grapes, cherries, plums, and pomegranate	Brouillard et al. (1997), Es-Safi et al. (2002), and Guasch-Ferré et al. (2017)
	Flavanols	EGCG, EGC, ECG, procyanidins	Apples, pear, legumes, tea, cocoa, and wine	Arts et al. (2000a, b) and Rasmussen et al. (2005)
	Flavanones	Hesperidin, naringenin	Citrus fruits	Leuzzi et al. (2000) and Proteggente et al. (2003)
	Flavones	Apigenin, chrysin, luteolin	Parsley, celery, orange, onions, tea, honey, spices	Leuzzi et al. (2000) and Godos et al. (2017)
	Flavonols	Quercetin, kaempferol, myricetin, isorhamnetin, galangin	Berries, apples, broccoli, beans, and tea	Godos et al. (2017), Guasch-Ferré et al. (2017), and Williamson (2017)
	Isoflavones	Genistein, daidzein	Soya beans and other legumes	Reinli and Block (1996), Liggins et al. (2000), and Guasch-Ferré et al. (2017)

and major sources of polyphenols are presented in Table 14.1. The major classes of polyphenols are phenolic acids and flavonoids which account for about 30% and 60%, respectively (Neveu et al. 2010). Some of the major polyphenol chemical structures are represented in Fig. 14.2 and discussed below. Phenolic acids have

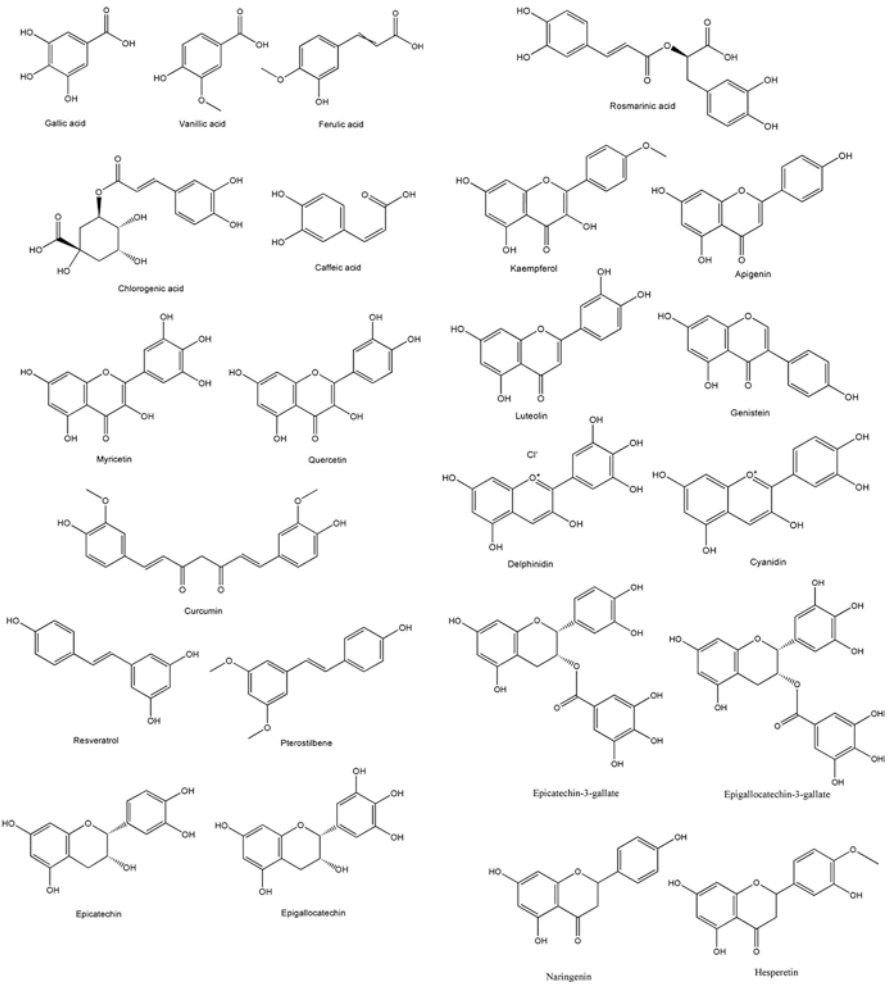

Fig. 14.2 Chemical structure of some major polyphenols

simple structures with the presence of additional carboxyl group which is linked to the aromatic ring of the compound. The subclasses of phenolic acids are benzoic and cinnamic acids with seven and nine carbon atoms, respectively. Benzoic acid is further subdivided into gallic and vanillic acid. Cinnamic acid is further categorized into ferulic acid and chlorogenic acid (Neveu et al. 2010).

Flavonoids comprise of two aromatic rings with 15-carbon units which are bridged via 3-carbon. The subcategories of flavonoids (i.e., C6-C3-C6) include flavones, anthocyanidins, flavanols, flavanones, flavonols, and isoflavones (Tsao 2010). Flavonoids naturally occur in the form of glycosides. The occurrence of flavonols is abundant in nature except in algae and fungi. Most common forms of flavonols are kaempferol, quercetin, myricetin, and isorhamnetin. They conjugate and

occur in the form of glycosides. Flavones are structurally like flavonols which lack oxygenation at C-3 position. The subclasses of flavones are apigenin, chrysin, and luteolin. Flavones are substituted possibly by hydroxylation, alkylation, glycosylation, and methylation. The B-ring of isoflavones occurs naturally at C-3 position rather than C-2 position. The isoflavones, such as daidzein and genistein, occur in the form of aglycones (Del Rio et al. 2013). Flavanones occur as derivatives of hydroxylation, methylation, and glycosylation. The available flavanones are naringenin and hesperetin, which presents a chiral center at second carbon position and lacks double bond. The most common forms of anthocyanidins include delphinidin, pelargonidin, cyanidin, and malvidin which occur in the form of aglycones. They conjugate with organic acids and sugars and generate varying colors of anthocyanins that range from orange to blue and red to purple which appear in flowers and fruits (Jaganath and Crozier 2011).

Flavanols occurs in the form of glycosides. They form the complex group of flavonoids that ranges from simple monomeric forms to complex polymeric proanthocyanidins. They are also referred to as condensed tannins. High levels of flavanols are present in green tea which are abundant in nature. The main constituents of green tea include epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG) (Rahmani et al. 2015). Apart from phenolic acids and flavonoids, stilbenes and lignans have also attracted increased attention because of its multifaceted health benefits in human. Stilbenes have 14-carbon backbone and occur from simpler to complex structures. Resveratrol, pterostilbene, and piceatannol are the subclasses of stilbenes. Lignans occur naturally in bound forms mostly in flaxseeds and sesame. In addition to this, curcumin is a natural antioxidant from turmeric (Zhang et al. 2012).

14.3 Distribution and Content of Polyphenols

The plant polyphenolics present at cellular, tissue, and subcellular levels lack uniformity. Soluble forms of phenolics are located within cell vacuoles of plants, whereas insoluble forms of phenolics are present in cell walls (Nayak et al. 2015). The insoluble forms of polyphenols form covalent bonds with pectin, cellulose, and other cell wall substances which account for 20–60% when compared to soluble forms. Insoluble-bound phenolic forms are mainly available in cereals such as black rice, maize, wheat, corn, and barley (Chandrasekara and Shahidi 2010; Rakli et al. 2012; Li et al. 2014; Alshikh et al. 2015; Chen et al. 2015; Nayak et al. 2015). They are also available in legumes which include lentils, cranberry beans, mung bean, pinto bean, black bean, kidney bean, cowpea, and chickpea (Gutiérrez-Uribe et al. 2010; Pajak et al. 2014; Verardo et al. 2015). They are also present in major source of oil seeds such as sunflower seeds and rapeseed meal. Apart from major oil seeds, *Moringa* seed flour, soya bean, and flaxseed were also studied (Min et al. 2012; Singh et al. 2013; Beejmohun et al. 2007). Bound phenolics are also present in fruit seeds which include blueberry seed meals, blackberry, and black raspberry (Ayoub et al. 2016).

Polyphenols are present in varying amounts in fruits, vegetables, and cereals. In most of the cases, they are present in complex mixtures of polyphenols (Álvarez et al. 2016). Higher content of polyphenols is in the outer layers of plants than in the inner layers (Anwei et al. 2013). The factors which affect the content of plant polyphenols include ripeness during the harvest period, storage, and processing. Environmental factors such as rainfall, exposure to sun, and the type of the soil also influence the polyphenol content of the plants (Kårlund et al. 2014). Ripening of the fruit increases the concentration of anthocyanins; however other polyphenolic content tends to decrease. Decrease in concentration of phenolic acids were observed after infection (Parr and Bolwell 2000). Storage is also considered to be an important factor which also affect the polyphenol content via oxidation. Oxidation results in quality changes and color of foods (Bharate 2014). Storage of flour also causes reduction of polyphenolic content in wheat flour by about 70% (Avramiuc 2015). Storage in cold has very little effect on the polyphenol content of fruits and vegetables but results in subsequent loss of antioxidant capacity (Galani et al. 2017). Cooking results in major effect on polyphenols content by about 80% in tomatoes and 75% in onions (Palermo et al. 2014). The quercetin content in onions and tomatoes were reduced to about 30% in frying and 65% after cooking (Crozier et al. 1997).

14.4 Bioavailability of Polyphenols

The bioavailability refers to the quantity of the polyphenol that is absorbed and metabolized through biological pathways (D'Archivio et al. 2010). The polyphenols will be mostly available in the food in the form of glycosides and esters which are not absorbed in its natural form (Manach et al. 2004). The polyphenolic compounds are hydrolyzed by the enzymes of the intestine or by the gut microflora. Absorption results in modifications of polyphenols in the intestine and in later stages in the liver via glucuronidation, sulfation, and methylation reactions.

Polyphenols are usually absorbed in the gastrointestinal tract, whereas some of the polyphenols are absorbed in the intestine. pH changes in the lumen results in decomposition of polyphenols during digestion. The oligomeric forms are unstable in both acidic and alkaline pH. Monomeric and oligomeric forms were stable even at pH 7 in the intestine, but at pH 7.4, the dimeric forms are degraded. Catechin after incubation for 2 h at pH 7.5 was stable, and about 30% of epicatechin was degraded (Zhu et al. 2002). Except flavanols, other flavonoids exist in its glycosylated forms (D'Archivio et al. 2010). Glycosides usually enters the intestine, from which, only aglycones are absorbed. Flavonoids such as quercetin are usually absorbed at gastric level, whereas anthocyanins are absorbed in the stomach (Crespy et al. 2002). The main species present in plasma are various forms of catechins which are excreted in urine (Actis-Goretta et al. 2012).

Glucosides are transported by the sodium-dependent glucose transporter (SGLT1) which is hydrolyzed by cytosolic enzyme β-glucosidase. Nevertheless, the absorption rate of isoflavones is not clear (Farrell et al. 2013). Proanthocyanidins

are high molecular weight compounds with polymeric structure. This nature limits their absorption in the gut, and the oligomeric forms unlikely get absorbed in the small intestine (D'Archivio et al. 2007). Ingestion of free form of hydroxycinnamic acids results in increased absorption in the small intestine; however, esterified forms impair their rate of absorption (Clifford 2000). Majority of polyphenol absorption takes place in the gastrointestinal tract and intestine, but some polyphenols are not absorbed at these sites. Such kinds of polyphenols enter the colon and get hydrolyzed by the gut microflora into aglycones which further gets metabolized into aromatic acids. The metabolites of the polyphenols in the blood bind to albumin which plays a vital role in bioavailability of polyphenols. Binding affinity of polyphenols depends on their chemical structure (Latruffe et al. 2014). Tissue accumulation of polyphenols plays a vital role in exerting beneficial effects in the target sites (Kim et al. 2014). Derivatives of polyphenols such as conjugates are excreted via bile and monosulfates via urine (Crespy et al. 2003). The percentage of excretion of flavanones is higher with the decreasing order of isoflavones and flavonols. Thus, the potent beneficial effects of polyphenols rely on the intake and its availability at the target site (D'Archivio et al. 2007).

Numerous factors influence the rate of absorption which include chemical structure, fat content, and solubility. Absorption rate of the metabolites is determined by the chemical structure of the polyphenolic compound rather than its concentration (Cermak et al. 2003; Cifuentes-Gomez et al. 2015; Guo and Bruno 2015). The postprandial concentration of the polyphenols in the blood is usually less than 1 micromolar, whereas in the gut the concentration will be greater than 10- to 100-fold (Kay et al. 2009). Modified forms of polyphenolic compounds reaching the blood and tissues create difficulty in identifying and analyzing their potent effects (Natsume et al. 2003).

14.5 Therapeutic Potential of Polyphenols in Treating Human Diseases

Polyphenols or phenolic compounds display broad range of medicinal properties such as antioxidant, anti-inflammatory, antibacterial, neuroprotective, cardioprotective, and hepatoprotective action (Yildrim et al. 2017). Phenolic acids have also attracted attention in cosmetic industry as ingredients for application. Hydroxycinnamic acids and its derivatives are used in various applications, because of their antioxidant, anti-inflammatory, antimicrobial, anti-collagenase, and ultraviolet (UV) protective effects. Ferulic (FA) and caffeic acids (CA), which are available commercially, exert anti-collagenase and protective effect against UV-induced skin diseases (Taofiq et al. 2017).

Vegetables are the primary sources of polyphenols which have benefits for human health and disease prevention (Holst and Williamson 2008). Literature evidences suggest that diets rich in fruits and vegetables are closely correlated with decrease in chronic disease risk, which includes CVD, certain cancers, and neurodegenerative diseases (Vauzour et al. 2010). Polyphenols can be considered as a

potent antioxidant compounds which itself explains their basic underlying mechanistic action in various disease processes. Flavonoids also possess antioxidant capacity, which scavenges free forms of hydroxyl and negative oxygen ions (Eghbaliferiz and Iranshahi 2016). Polyphenolic compounds should have enough absorption rate, and the required concentration must reach the bloodstream to display its beneficial effects (Scheepens et al. 2010). Decreased consumption of bioactive compounds results in increased production of reactive oxygen species (ROS) that ultimately results in increased oxidative stress. Excessive generation of ROS creates damage in cellular macromolecules such as DNA, lipids, and proteins which opens the gateway for developing the risk of chronic diseases (Clifford et al. 2015). However, the mechanistic approach of dietary polyphenols is not quite simple, which involves more complex biological interactions involving multiple molecular pathways, and much more progress has been made in this area over the decades. Antioxidant nature does not create an impact in the biological activity of polyphenols; instead the action depends on the bioavailability of the compound at the target-specific site (Williamson 2017).

In this section, we have discussed on the role of polyphenols and their possible mechanistic role in preventing/treating various chronic human diseases such as aging, cancer, diabetes, inflammation, and cardiovascular, neurodegenerative, and hepatic diseases in detail.

14.5.1 Antioxidant Property and Mechanism of Action

Human metabolic system generates excessive ROS as by-products of various metabolic reactions. Mitochondria are the major ROS production site. Increased free radical production results in damage to macromolecules such as protein, nucleic acids, and lipids (Cherubini et al. 2005). ROS is the vital contributor of many chronic diseases in humans which include cancer, cardiovascular diseases, neurodegenerative diseases, and other age-related diseases. Our human body contains antioxidant defense mechanism to counteract the oxidative damage. Phenolic acids can counteract the damage induced by ROS through scavenging of free radicals. It also upregulates the heme oxygenase/biliverdin reductase (HO/BVR) system and other antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD) through which it scavenges free radicals.

FA has been extensively studied for its cardioprotective action (Roy et al. 2013). SOD and CAT activities are increased in the heart and pancreatic tissue of diabetic rats by FA treatment in a time- and dose-dependent manner (Alam et al. 2013). Antioxidant property of protocatechuic acid (PCA) can be measured using antioxidant, scavenging, and chelating activity. PCA exhibits antioxidant nature which could be attributed to the free radical quenching and metal chelating action (Li et al. 2011).

Vanillic acid (VA) when administered at 100 mg/kg can reduce lipid peroxidation (LPO) and increase the antioxidant activity of CAT, glutathione peroxidase (GPx), reduced glutathione (GSH), and SOD in nephrotoxicity-induced rats (Sindhu

et al. 2015). Gallic acid (GA) pretreatment was shown to mitigate both nephrotoxicity and hepatotoxicity by causing reduction in lipid peroxide levels, and it restores the activities of antioxidant enzymes (Nabavi et al. 2013a; Nabavi et al. 2013b).

The polyphenols from grape seed extract when administered for short term displayed that the extract is bioavailable, and it binds to serum lipid fraction and thus reduces lipid peroxidation (Garcia-Alonso et al. 2006). Subjects when administered with tablets containing grape seed extract for 12-week period showed significant reduction in LDL cholesterol levels to a basal level. This experiment suggested that the grape seed extract has exerted its effect in minimizing LDL oxidation (Sano et al. 2007). The polyphenolic compounds of olives are hydroxytyrosols which show antioxidant effects by reducing the markers of oxidative damage and the levels of oxidized LDL in plasma (Raederstorff 2009). Ingestion of green tea polyphenols also showed significant antioxidant activity by quenching the free radicals and minimizing oxidized LDL levels (Pecorari et al. 2010). Consumption of nuts such as almonds or walnuts was shown to increase the concentration of polyphenols' antioxidant capacity and decrease the level of lipid peroxides in plasma (Torabian et al. 2009). Anthocyanins possess various bioactivities such as antioxidant, antitumor, free radical scavenging, antiatherosclerosis, antidiabetic, and antiallergic activities (Deng et al. 2013).

Phenolic acids display antioxidant property not only by scavenging free radicals but also by strengthening the antioxidant defense mechanism. Nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) is the transcription factor which regulates the antioxidant enzymes by ARE (antioxidant response elements) present in the promoter region (Wasserman and Fahl 1997). PCA can induce the activation of antioxidant enzymes such as glutathione reductase (GR) and GPx via activation of Nrf2 which is mediated through Janus kinase (JNK)-mediated phosphorylation (Varì et al. 2011). It can also improve the cellular antioxidant system through induction of antiapoptotic mechanism. Phenolic acids can increase the liver antioxidant levels, and it also activates various antioxidant enzymes of the liver (Varì et al. 2015). Other phenolics such as GA, gentisic acid, coumaric acid, and FA were shown to upregulate the transcriptional activity of Nrf2, and it induces mRNA transcripts in the liver (Yeh and Yen 2006).

14.5.2 Antiaging Property and Mechanism of Action

Aging is well-defined as the accumulation of varied lethal changes that occur in cells and tissues with the advancement of age, which are liable to the higher risks of diseases and demise (Tosato et al. 2007). In other words, aging is a complex process that involves multiple factors, such as the accumulation of molecular errors due to genomic and epigenetic interactions, environmental, hereditary, and stochastic (Rodríguez-Rodero et al. 2011). These factors lead to the gradual weakening of the cell functions. Aging usually manifests postmaturity stage of an individual and triggers to frailty and death. With progress of age, the optimal health condition, immunity, strength, and all physiological activities progressively start to deteriorate, for

example, the decline of thoroughgoing heart, lung, and kidney functions, the lowered secretion of sexual hormones, skin wrinkling, etc. (Rodríguez-Rodero et al. 2011). Though the specific biological and cellular mechanisms accountable for the process of aging are not well-known, several theories have been proposed, and among them cell damages due to oxidative stress or free radicals are highly accepted (De and Ghosh 2017; Stefanatos and Sanz 2018; Viña et al. 2018). Some of the other reasons for the aging include noninfectious chronic inflammation triggered due to amplified secretion of adipokine and cytokines, fatty acid metabolism alterations, tissue insulin resistance, buildup of end products of cellular metabolisms, loss of postmitotic cells, and the deterioration in cells structure and function (De and Ghosh 2017).

Antioxidants are known to inhibit free radicals and thus safeguard cells from oxidative damages. In recent times, awareness in correlating a diet to aging is growing widely and is well-acknowledged. Researchers have shown that dietary calorie restriction and consuming natural antioxidants prolong life duration in a number of aging models. Though oxygen is vital to aerobic animals, and acts as electron acceptor in mitochondria, it is injurious for the reason that it can constantly produce reactive oxygen species (ROS), which are alleged for initiating the aging process. However, organisms have the capabilities to eliminate these ROS in cells via an antioxidant defensive system that constitutes a series of enzymes, i.e., catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GR), and glutathione peroxidase (GPx) (Peng et al. 2014). Moreover, natural plant foods possess phytocompounds with anti-inflammatory and antioxidant activities and hence are believed to function as antiaging compounds. Some of the dietary antioxidants include ascorbic acid (vitamin C), vitamin A, α-tocopherol, polyphenols, and flavonoids. Thus, consuming such diet rich in antioxidant phytochemicals found in fruits and vegetables can effectively scavenge ROS and therefore hypothetically extend the life span of organisms.

Polyphenols are shown to ameliorate the adverse effects of the aging process. Anthocyanins (subset of the flavonoids), commonly occurring in darkly colored fruits, namely, berries, apples, grapes, and grape seeds, are proved to possess effective antioxidant and anti-inflammatory properties. Also, they are known to suppress the oxidative degradation of lipids and several inflammatory mediators, including cyclooxygenase (COX)-1 and COX-2 (Seeram et al. 2003). The extracts of spinach, blueberries, and strawberries contain great amounts of flavonoids and are reported to exhibit superior antioxidant activity. A study showed that a regular supplementation of diet containing strawberry or blueberries to aged rats for about 8 weeks showed the reversal of the age-associated structural and functional deficits in brain and behavior. Further, the authors claimed that polyphenolic compounds occurring in berry fruits might exercise their positive effects through lowering oxidative stress and neuroinflammation. Also, they may alter the signals that are involved in neuronal communication, plasticity, neuroprotective stress shock proteins, calcium buffering ability, and stress signaling pathways (Shukitt-Hale et al. 2008). Likewise, catechins found in tea were shown to have a strong antiaging property. Studies have stated that the onset of aging can be delayed by a regular consumption of green-tea

rich in catechins (Rizvi and Maurya 2008). Food polyphenolic compounds are reported to protect the aging brain since they have the capability to cross the blood-brain barrier (BBB) (Pandey and Rizvi 2009). In a recent study, researchers have hypothesized that dietary polyphenols cross the BBB to reach brain cells and modulate microglia-intermediated inflammation via modulation of the nuclear factor (NF)-κB pathway and exert neuroprotection (Figueira et al. 2017). Resveratrol (grape polyphenol) along with caloric restriction (CR) can effectively prevent aging process through inhibiting apoptosis and senescence and reestablishing cognitive injury and oxidative damages. In addition, they upregulate telomerase activity and enhance the expression of longevity-associated gene silencing information regulator (SIRT1), forkhead box 3a, active regulator of SIRT1, and Hu antigen R (Li et al. 2017; Sarubbo et al. 2018). Likewise, resveratrol is reported to target the sirtuin class of nicotinamide adenine dinucleotide (NAD)-dependent deacetylases, mainly SIRT1, which is responsible for health and longevity (Markus and Morris 2008). Further, it increases insulin sensitivity and AMP-activated protein kinase and peroxisome proliferator-activated receptor-c coactivator 1a (PGC-1a) activity but decreases the expression of insulin-like growth factor 1. Further, experimental evidences suggest that resveratrol activates forkhead box O (FOXO), which controls the expression of genes contributing for both longevity and stress resistance (Barger et al. 2008). Similarly, Li et al. (2017) reported that resveratrol and its derivative, pterostilbene, exhibit antiaging properties through modulating inflammation, oxidative damage, telomere attrition, and cell senescence. Though not completely agreed, evidences suggest that polyphenols derived from blueberries may improve the spatial memory efficiency by acting on the dentate gyrus, a hippocampal subregion principally sensitive to the effects of aging (Burke and Barnes 2006; Janle et al. 2010; Vauzour 2012). Several polyphenols, quercetin, rosmarinic acid, and caffeic acid, were shown to activate stress-related genes and augment the antioxidative capability and the lifetime of *Caenorhabditis elegans* (Pietsch et al. 2011). Polyphenols, such as epigallocatechin gallate, quercetin, and curcumin, protect cells against agents that suppress autophagy. They act on targets involved in the AMP-activated protein kinase (AMPK) or mammalian target of rapamycin (mTOR), phosphoinositide 3-kinase (PI3K), extracellular signal-regulated kinase (ERK), and protein kinase B (Akt) signaling pathways showing different effects on the autophagy (Gurău et al. 2018).The polyphenols, quercetin and curcumin, were shown to boost the longevity in flies, yeast, and mice (Pietsch et al. 2009; Liao et al. 2011; Gurău et al. 2018).

14.5.3 Antidiabetic Property and Mechanism of Action

Diabetes also referred as diabetes mellitus is a chronic condition caused due to failure in the regulation of blood glucose levels in the body. Diabetes and obesity have become a major challenge to the global healthcare. Over the past few decades,

diabetes incidence has significantly doubled. In the USA alone, nearly 30 million people are being diagnosed with this condition. The most prevalent form of diabetes is the type 2 diabetes (95%) (Wu et al. 2014a). In type 1 diabetes, the immune system of a patient destroys the pancreatic cells to produce the insulin. Type 2 diabetes is due to numerous causes such as genetics, heredity, lifestyle, or a combination of these factors leading to insulin resistance, i.e., one's body fails to use insulin. However, diabetes causes differ based on the genetic makeup, ethnicity, family history, health factors, and environmental conditions (Asmat et al. 2016). Some of the medical complications of diabetic patients include advancements of retinopathy, i.e., affecting eyes and loss of sight, nephropathy, i.e., the disturbances in renal functions, foot ulcers, sexual dysfunctions, and many more (Pandey and Rizvi 2009).

Several investigations have revealed the role of plant polyphenols to possess the antidiabetic effects. For example, tea catechins were shown to exhibit antidiabetic activity. Polyphenols act as antidiabetic agents via different mechanisms, comprising the inhibition of glucose absorption/uptake in the intestine or its peripheral tissues (Rizvi and Zaid 2001; Rizvi et al. 2005). The most widely examined polyphenols in clinical trials include flavanols, anthocyanins, catechins, isoflavones, and their chief food sources, such as cocoa, chocolate, red wine, green tea, berries, etc. Polyphenols occurring in coffee, tea, guava, whortleberry, propolis, olive oil, chocolate, grape seed, and red wine are reported to exhibit antidiabetic effects in type 2 diabetic patients through increasing glucose metabolism, reducing insulin resistance, and improving vascular function. Further, it is evident from human studies that polyphenols consumed through diet exert useful effects on the improvement of insulin resistance and such interrelated diabetes risk factors, such as oxidative stress and inflammation (Scalbert et al. 2005; Guasch-Ferré et al. 2017). The diacetylated anthocyanins at a dosage of 10 mg/kg diet inhibited α-glucosidase activity in the gut and proved their hypoglycemic activity. Likewise, catechin at a dosage of 50 mg/kg diet or more significantly inhibited the activity of α-amylase and sucrase in rats and controlled blood glucose level (Matsui et al. 2002; Pandey and Rizvi 2009). In few studies, S-Glut-1-mediated intestinal transport of glucose was noticed when animals were treated with individual polyphenols, such as (−)epicatechin, (−)epigallocatechin, (+)catechin, epicatechin gallate, and isoflavones (Matsui et al. 2001). As reported by Chen et al. (2007), resveratrol treatment effectively reduced the secretion of insulin and prolonged the start of insulin resistance. According to the authors, the inhibition of voltage-dependent K(+) channels in pancreatic beta cells could be the possible mechanism of action mediated by resveratrol. Flavonoids can modulate insulin secretion via more than a few pathways, such as inhibition of glucose transport, upregulatory activities of glucose absorption, triggering glucose-stimulated insulin secretions, and renewal of insulin secretion ability. Thus, major subclasses such as flavonols, flavan-3-ols, flavones, flavanones, flavan-3,4-diols, anthocyanidins, dihydroflavonols, chalcones, coumarins, aurones, etc. can be used in treating diabetic patients (Soares et al. 2017).

14.5.4 Anticancer Property and Mechanism of Action

Cancer is the leading cause of human death in recent times around the globe. The major reasons are attributed to our behavioral and nutritional risks, low fruits and vegetables intake, more consumption of tobacco and alcohol, lack of physical activity, and many more (Kumar et al. 2018a; Akhtar and Swamy 2018). Nearly, 8.8 million deaths noticed in 2015 were due to different types of cancers. Also, it is estimated that about one out of six deaths globally is because of cancers. It is a multi-disease, and its development involves different stages, such as initiation, elevation, and progression (Akhtar and Swamy 2018; Ravichandra et al. 2018). Diet-based polyphenols are reported to disturb and modulate manifold biochemical functions, mechanisms, and pathways that lead to cause cancer (Niedzwiecki et al. 2016). Plant-based polyphenols exhibit anticarcinogenic activities through the inhibition of cancer cell growth and metastasis and trigger anti-inflammatory properties in addition to the induction of apoptotic process. Further, they regulate/enhance the body's immunity and shield normal cells against various damages due to free radicals (Niedzwiecki et al. 2016; Narayanaswamy and Swamy 2018). However, polyphenol dosage against cancers should be carefully selected and handled cautiously (Zhou et al. 2016).

The compound, curcumin, found in the rhizomes of turmeric (*Curcuma longa*) possesses many health benefits, and exhibits different biological properties, including antioxidant, anti-inflammatory, anticancer properties, etc. (Klinger and Mittal 2018). It has been experimentally proven both in in vivo and in vitro different cancer models that curcumin effectively inhibits tumor growth by preventing cell proliferation and angiogenesis, blocking cell cycle progress in cancerous cells, and inducing apoptosis (Anand et al. 2008; Niedzwiecki et al. 2016). A variety of anticancer mechanisms of curcumin are being recorded. For example, curcumin was shown to suppress pancreatic adenocarcinoma proliferation by inhibiting gene products regulated by NF-κB pathways, such as cyclin D1, C-Myc, apoptosis protein 1 (AP1), Bcl2, cyclooxygenase-2 (COX-2), matrix metalloproteinases (MMPs), and vascular endothelial growth factor (VEGF) (Kunnumakkara et al. 2007). Other studies in lung cancer models have evidenced that curcumin affects via mechanisms that involve the suppression of signal transducer and activator of transcription-3 (STAT-3) pathways (Alexandrow et al. 2012). Further, curcumin interacts with the arachidonic acid pathway and prevents the development and growth of prostate cancer. Moreover, it was shown to exhibit in vivo anti-angiogenic properties in various prostate cancer models (Ng et al. 2006). In colon cancer models, it interacts with vitamin D receptors and enhances cancer growth and progression (Bartik et al. 2010). Several review papers have documented that curcumin is potential against different types of cancers, including colon, breast, pancreatic, prostate, lung, head, neck squamous cell carcinoma, etc. (Ravindran et al. 2009; Gupta et al. 2013; Shanmugam et al. 2015; Niedzwiecki et al. 2016; Narayanaswamy and Swamy 2018). Likewise, resveratrol functions as anti-carcinogenetic activity by controlling signal transduction pathways, controlling cell cycle, cell growth, metastasis, inflammatory responses, apoptotic activities, and angiogenesis (Udenigwe et al. 2008). In vivo studies also have shown that resveratrol effectively prevent or control skin,

gastrointestinal, and colorectal cancers. The mechanisms of actions included the prevention of metastasis, angiogenesis, and the promotion of apoptotic activities (Devipriya et al. 2006; Bishayee 2009; Kukreja et al. 2014; Niedzwiecki et al. 2016). Quercetin reduces cancer progression via antioxidant properties (Gibellini et al. 2011; Ekström et al. 2011). Various other mechanisms of anticancer activity of quercetin is by protecting cells via anti-inflammatory activities and preventing oxidative stress damage and modulating the growth of tumorous cells by hindering cell division and cell cycle progression, and through the induction of apoptotic process (Mu et al. 2007; Jeong et al. 2009; Kumar et al. 2018b; Afrin et al. 2018). Researches have demonstrated that catechins, EGC, EGCG, and ECG, found in tea plants possess cancer-preventive capabilities by inhibiting cell proliferation and inducing apoptosis (Fujiki et al. 1999). Likewise, catechin-rich green tea extract modulates cancer cell growth and development, angiogenesis, and metastasis, inducing apoptosis, suppressing NF-κB pathway activation, downregulating tumor growth factor-α (TGF-α), upregulating TGF-β2, and upregulating the expression of p53, p21, and Bax (BCL2-associated X) proteins (Gupta et al. 2004; Khan et al. 2006; Harakeh et al. 2008; Kürbitz et al. 2011; Rady et al. 2017; Sharma et al. 2018; Saeki et al. 2018). Thus, polyphenols that are abundantly found in dietary sources are a great promise for treating cancers, particularly in view of their safety aspects.

14.5.5 Anti-inflammatory Property and Mechanism of Action

Apart from the antioxidant property of the polyphenols, they also exert various effects on cell signaling pathways related to inflammation which very well explains their beneficial activities on inflammation and endothelial function. Chronic inflammation is the most vital factor for development of various diseases in humans which include obesity, cardiovascular diseases, aging, neurodegenerative diseases, and type 2 diabetes. Anti-inflammatory efficacy of polyphenols has been studied extensively both in vivo and in vitro. Supplementation of berry juice has been reported to decrease the interleukin-12 (IL-12) and overall inflammation score (Kolehmainen et al. 2012), and it has also improved the endothelial function in patients with metabolic syndrome (MetS) (Stull et al. 2015).

Berry juice supplementation has impact on the levels of inflammatory markers such as C-reactive protein (CRP) (Basu et al. 2010a; Johnson et al. 2015), tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1 (Stull et al. 2010), IL-6 (Basu et al. 2011), intercellular adhesion molecule (ICAM)-1, vascular adhesion molecule-1 (VCAM-1), and adiponectin (Basu et al. 2010b). Treatment with hydrocaffeic acid showed significant decrease in the expression of cytokines such as IL-8, IL-1β, and TNF-α. Its treatment was also shown to cause significant reduction in malondialdehyde (MDA) levels and oxidative damage in distal colon (Larrosa et al. 2009). The virgin olive oil with high polyphenol content showed better protective effect against inflammation when compared to oils rich in oleic acid and polyunsaturated fatty acids (Martínez-Domínguez et al. 2001).

Green tea polyphenol consumption display decreases in the levels of proinflammatory cytokines and inflammatory markers in mice which are exposed to UVB

(Meeran et al. 2009). Catechins present in green tea exert anti-inflammatory effects through various mechanisms which include variation in the isoforms of nitric oxide synthase (NOS) (Sutherland et al. 2006). *Hibiscus sabdariffa* extracted polyphenols exhibit potent in vivo and in vitro anti-inflammatory property. It also displays anti-inflammatory action in RAW264.7 cells both on prostaglandin E-2 and nitrite. Lipopolysaccharide (LPO)-induced rats when treated with polyphenols show significant reduction in the aspartate aminotransferase and alanine levels in serum. Significant reduction in lipid peroxidation together with decrease in the lesions of liver and increase in the activity of the glutathione and CAT were observed in the rat liver (Kao et al. 2009). Polyphenolic extracts from the quince peel was shown to decrease the macrophage secretion of the chemokine IL-8 and proinflammatory cytokine such as TNF-α in a dose-dependent manner. On the other side, it was found that it could increase the level of IL-1β, an anti-inflammatory cytokine. Extract from quince polyphenols was shown to inhibit the activation of p38 mitogen-activated protein kinase (p38MAPK), AKT, and NF-κB (nuclear factor kappa B) which confirms the potent inflammatory efficacy (Essafi-Benkhadir et al. 2012). Quince peel is an abundant source of flavonoids which makes it a potent anti-inflammatory agent, and it is also used in various topical applications (Kim et al. 1998). Flavonoid compound, quercetin activates the inflammatory signaling pathway and reduces the atherosclerosis risk (Kostyuk et al. 2011). Grapes contain resveratrol, the rich polyphenolic compound which reduces the inflammation via activation of transcription factors, blocks the activation of proinflammatory cytokines, and overwhelms the expression of inflammatory genes. Thus, the grapes and its products can significantly reduce the chronic inflammation which is mediated by obesity (Fu et al. 2011; Chuang and McIntosh 2011).

Inhibition of the enzymes such as cyclooxygenase (COX) and phospholipase A_2 (PLA2) which generate eicosanoids is one of the anti-inflammatory mechanisms that plays a vital role (Kim et al. 2004). Polyphenols can modulate the gene expression and activity of the enzyme COX-2 in various types of cells (Luceri et al. 2002). Nitric oxide (NO), a key antithrombotic intravascular factor, is responsible for maintaining the vascular health. Polyphenols can inhibit the release of NO through suppression of the NO enzyme expression and their activity (Stangl et al. 2007). Expressions of the cytokines are also modulated by polyphenols. NF-κB plays an important role in the stress, proliferative, apoptotic, and inflammatory processes, and its inhibition could be beneficial in the treatment of inflammatory disorders (Karin et al. 2004). NF-κB plays its role together with the assistance of MAPK. The MAPK pathway is modulated by polyphenols by acting on the downstream effectors and activation cascade (Soobrattee et al. 2005). Literature evidences together suggest that the polyphenols can modulate the immune system and it is a potent anti-inflammatory agent.

14.5.6 Cardioprotective Property and Mechanism of Action

Cardiovascular disease (CVD) is a multifactorial and chronic disease which involves wide range of environmental and genetic factors that play a vital role in stages of the disease. Environmental factors include physical inactivity, high-saturated-fat diets,

and smoking which increase the CVD risk (Ambrose and Barua 2004; Tanasescu et al. 2002). Numerous studies have reported the reduced incidence of CVD after consumption of polyphenols (Nardini et al. 2007). Oxidative stress and hyperlipidemia are the major risk factors for the development of atherosclerosis which can be minimized by the consumption of polyphenols (Vita 2005). The dietary polyphenols can reduce the thrombosis risk which is the main causative factor for the development of ischemic heart disease, myocardial infarction, and others (Singh et al. 2008a; Santhakumar et al. 2014). Literature evidences suggest that the CVD incidence is relatively low in Mediterranean population who consume diets which are rich in polyphenols such as fruits, green vegetables, fish, and particularly red wine (Nadtochiy and Redman 2011; Khurana et al. 2013). Several experimental studies have reported that consumption of mild or moderate quantity of red wine can reduce the morbidity and mortality that results from coronary heart disease (Sato et al. 2002). Red wine contains the polyphenolic antioxidants such as proanthocyanidins and resveratrol which is responsible for exerting its cardioprotective action. Resveratrol occurs in abundance in wine and grapes (Deng et al. 2012).

Cardiovascular health depends on the normal function of NO which is essential for vasorelaxation. Significant reduction in the NO levels directly predisposes the individuals to the risk of developing cardiovascular diseases. Reduction in NO levels occurs when there is decrease in the endothelial nitric oxide synthase (eNOS) expression, which in turn might decrease due to ROS degradation (Cai and Harrison 2000). Significant contributors of ROS are xanthine oxidase, mitochondrial enzymes such as NADH/NADPH oxidase, and others (Paravicini and Touyz 2008). Study from human umbilical cord cells shows that resveratrol can increase eNOS expression and thereby can increase the production of NO (Wallerath et al. 2002). It has been also reported to be protective against cardiac reperfusion/ischemia, and treatment with resveratrol significantly improved the size of the infarct and left ventricular function of the rat hearts. In cultured cardiac tissue of rat, resveratrol decreased ROS production and improved the mitochondrial membrane potential. Resveratrol can increase Na^+ and Ca^{2+} concentrations in cardiac tissue of H_2O_2-exposed rats (Thuc et al. 2012). Sirtuin 1 (SIRT1) has potential regulatory role with several coactivators and transcription factors such as NO production, hypoxia-inducible factor alpha (Hif-2α), and forkhead box O that play a critical role in cardioprotection (Mattagajasingh et al. 2007; Wong and Woodcock 2009; Dioum et al. 2009). Resveratrol was also reported to have impact on the SIRT1-mediated deacetylation that inhibits potent mechanisms linked with myocardial infarction (Rajamohan et al. 2009).

Atherosclerosis is an inflammatory disease which develops mainly in the medium size arteries. It appears in an asymptomatic manner for longer periods and once become active results in chronic conditions such as unstable angina, myocardial infarction, and unexpected cardiac arrest (Vita 2005). Inhibition of LDL oxidation is the key regulatory event in atherosclerosis development which is possible by consumption of polyphenols (Aviram et al. 2000). Other mechanisms are antiplatelet, antioxidant, and anti-inflammatory properties together with increasing HDL levels which altogether contribute to the reduction of atheromatous plaques (García-Lafuente et al. 2009). Therapies targeted with antioxidants have gained increased

attention because of their ability in minimizing the harmful effects caused by ROS. Angiotensin II (Ang II), statins, and vitamins C and E were used extensively in combination with other drugs for minimizing oxidative stress, and in addition the polyphenols display protective effects in patients with cardiovascular diseases.

Atherosclerosis development can be prevented by reducing LDL oxidation and cholesterol levels, safeguarding endothelium, and limiting the synthesis of adhesion molecules and proinflammatory cytokines (Hamilton et al. 2004; Habauzit and Morand 2012). Polyphenols are reported to target specific sites to exert its beneficial effects that include NO, eNOS, and inflammatory molecules such as IL-6, IL-8, TNF-α, VCAM-1, and ICAM-1, and it also modulates and alters signaling pathways such as NF-κB, MAP38 kinase, SIRT1, and others (Vita 2005; Stangl et al. 2007; Pandey and Rizvi 2009; Basu et al. 2010a, b). Quercetin can inhibit metalloproteinase 1 (MMP-1) expression and thereby can disrupt the atherosclerotic plaques. Tea catechins can slow down or inhibit the smooth muscle cell proliferation which is responsible for formation of atheromatous plaques. Antithrombotic effect is exerted by polyphenols via inhibition of platelet aggregation. Polyphenols from tea can also lower blood pressure which may be mediated via antioxidant activity. Resveratrol inhibits platelet aggregation via COX-1 inhibition. Resveratrol also acts as vasorelaxant by enhancing NO signaling (García-Lafuente et al. 2009). Cardiovascular health benefits of polyphenols depend on the level and bioavailability of nitric oxide at endothelium (Appeldoorn et al. 2009; Schmitt and Dirsch 2009). Consumption of polyphenols such as coffee, black tea, grape juice, and cocoa is closely related to the inhibition of platelet aggregation (Freedman et al. 2001).

14.5.7 Neuroprotective Property and Mechanism of Action

Alzheimer's disease (AD), Parkinson's disease (PD), and stroke are the neurodegenerative disorders which represent major diseases of clinical importance and create economic burden all over the world. Numerous genetic, molecular, and dietary factors are the vital contributors for the progression of neurodegenerative diseases (Hung et al. 2010; Ross and Tabizi 2011; Olesen et al. 2012; Albarracin et al. 2012). Elevated concentration of cytokines such as IL-6, TNF-α, transforming growth factor beta (TGF-β), IL-18, and IL-12 in the blood contributes to the proinflammatory response in the pathology of AD (Swardfager et al. 2010). Multiple sclerosis (MS) is a neurodegenerative disease which is characterized by chronic inflammation and demyelination of neurons (Dutta and Trapp 2012). Symptoms of MS are fatigue, muscle weakness, motor changes, and vision changes (Ziemssen 2011). Major mediators of neuroinflammation in MS include chemokines such as IL-17, chemokine (C-C motif) ligand 20 (CCL20), and CCL17 (Łyszczarz et al. 2011). Stroke is also a pathological condition accompanied by disease of the immune system and inflammation (Luheshi et al. 2011). Stroke is also accompanied by inflammatory cytokines like IL-6, TNF-α, and IL-1. NF-κB, the transcription factor, plays an important regulatory role in cell survival and inflammation (Tuttolomondo et al. 2008). In cerebral ischemia, activation of NF-κB results in cell death (Zhang et al.

2005). PD, like other neurodegenerative diseases, results in increased levels of pro-inflammatory cytokines such as TNFα, IL-8, IL-1β, interferon gamma (IFNγ), CCL-5, and monocyte chemoattractant protein-1 (MCP-1) (Menza et al. 2010).

Neuroprotection refers to protection of nerve cells from dying which involves the treatment with polyphenols. Extensive array of natural compounds from plants are of critical importance and attracted research interest. Phenolic acids might act as beneficial compound because of their potent free radical scavenging, antioxidant, and antiapoptotic effect. Hydroxycinnamic acids, such as chlorogenic acid (CGA) and PCA are closely associated with anti-Alzheimer's property (Oboh et al. 2013). FA when it is glycosylated with chitosan nanoparticle (FA-GC) has been shown to restore the spinal cord injury. Glutamate-induced excitotoxicity in the primary neurons can be protected via administration of these nanoparticles. The nanoparticles can significantly cause locomotor function recovery in spinal cord of contusion injury rat models. Treatment with the nanoparticle resulted in significant reduction in inflammation, cavity volume, and astrogliosis (Wu et al. 2014b). PCA significantly decreases the levels of inflammatory cytokines such as IL-6, IL-8, IL-1β, and TNF-α and thereby improves the cognitive deficits in AD-affected animals. In animal model of PD, curcumin exerts potent anti-inflammatory property via reduction of TNF-α and IL-6 (Yu et al. 2016). EGCG has potent anti-myeloid property and it acts as β-sheet breaker, thereby resulting in neuroprotective characteristics (Boyanapalli and Tony Kong 2015). EGCG can cross the blood-brain barrier (BBB), and thereby it shows protective effect against oxidative stress-induced cell death in cortical neurons (Pogacnik et al. 2016). The mechanism by which EGCG can exert protective action includes Bax inhibition and translocation of cytochrome c and modulates mitochondrial functions (Lee et al. 2015).

Beneficial effects of curcumin result from numerous epigenetic modulation that includes DNA methyltransferase inhibition, regulation of microRNAs, and regulation of modifications in histone such as histone deacetylases (HDACs) and histone acetyltransferases (Boyanapalli and Tony Kong 2015). EGCG protects neurodegenerative diseases via protecting the entry of toxic substances inside the BBB through epigenetic regulation of NF-κB (Liu et al. 2016). Resveratrol have been reported to be protective against β-amyloid-induced toxicity in Alzheimer's disease model via SIRT1 activation (Markus and Morris 2008). Polyphenol consumption such as vegetables and fruits for at least 3 weeks can slow down the Alzheimer's disease progression (Singh et al. 2008b). Green tea polyphenols exert protective effect and reduce the risk of Parkinson's disease in animal models induced by MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Protective action of EGCG can be activated by several signaling pathways such as MAPK which are essential for cell survival (Rossi et al. 2008). The protective ability of EGCG in PD might be due to its metal chelating, antioxidant, and detoxifying property. FA displays anti-inflammatory and antioxidant property which proves it to be protective against AD (Aquilano et al. 2008). Neuroprotective efficacy of resveratrol against brain ischemia is mediated through Akt/PI3K pathway wherein it downregulates cAMP response element-binding protein (CREB) and glycogen synthase kinase-3

(GSK-3β) (Simao et al. 2012). Ischemia is also protected by baicalein via PI3K/Akt pathway (Liu et al. 2010).

Dietary polyphenols and flavonoids display their potent neuroprotective effects through NF-κB pathway. Quercetin, kaempferol, apigenin, and luteolin were reported to downregulate NF-κB pathway which eventually results in inhibition of Aβ (amyloid beta) 1-42 and Aβ1-40 (Paris et al. 2011). Memory impairment in rats can be restored by soybean isoflavone by modulating NF-κB expression (Ding et al. 2011). Beta amyloid-induced neuroinflammation can be inhibited by baicalein and resveratrol that involves NF-κB downregulation (Xue et al. 2010; Capiralla et al. 2012). Silymarin from milk thistle protects against cerebral ischemia via inhibition of NF-κB and signal transducer and activators of transcription (STAT-1) pathway (Hou et al. 2010). Administration of quercetin, catechin hydrate, and fisetin significantly protects rats against hypoxia-induced damage and oxidative stress via inhibition of NF-κB, TNF-α, and IL-1β (Patir et al. 2012; Ashafaq et al. 2012; Gelderblom et al. 2012).

Peroxisome proliferator-activated receptor gamma (PPAR gamma) plays an important role in cerebral ischemia. Baicalein was shown to inhibit the PPAR expression via inhibition of its translocation to nucleus (Xu et al. 2010). In hypoxia model, the resveratrol can inhibit the MMP-9 expression through modulation of PPAR alpha expression (Cheng et al. 2009). Epicatechin and resveratrol were found to protect neurons of the brain against oxidative stress and stroke through upregulation of Nrf2 pathway and heme oxygenase-1 (HO-1) enzyme expression and downregulation of caspase-3 (Shah et al. 2010; Ren et al. 2011a). Besides Nrf2 and HO-1 expression, resveratrol can protect against ischemic injury through downregulation of mRNA expression of hypoxia-inducible factors-1α (HIF-1α).

Upon oxidative stress, in PC12 cells, resveratrol upregulates Bcl-2, antiapoptotic protein, and downregulates Bax expression, thereby preventing apoptosis of the neurons (Agrawal et al. 2011). Ischemic injury in mice was protected by lutein which enhanced Bcl-2 levels and downregulated pancreatic ER kinase (PERK) (Li et al. 2012). Baicalein also prevented apoptosis via inhibiting cytochrome c release into cytosol and ensuing apoptosis (Liu et al. 2010). Red wine polyphenols combat oxidative stress through modulation of GPx levels (Fernández-Pachón et al. 2009). EGCG can lower inflammation by reducing JNK and AP-1 transcription (Cavet et al. 2011). Modulation of JNK expression has been proved to be protective against AD as its activation can result in tau hyperphosphorylation and pathogenesis of beta amyloid formation (Ploia et al. 2011). Glycoside exerts neuroprotection through PI3K and MAPK pathway (Nones et al. 2011). In astrocytes, resveratrol and curcumin display neuroprotective effects by increasing NADPH quinone oxidoreductase (NQO1) through Nrf2 pathway (Erlank et al. 2011). Etiology and pathogenesis of neurodegenerative diseases such as PD, AD, and MS involve various mechanisms. These disorders can be treated using novel therapeutic strategies at specific target of proteins and genes which could be beneficial (Bhullar and Rupasinghe 2013).

14.5.8 Hepatoprotective Property and Mechanism of Action

Hepatic pathologies range from steatosis, hepatitis cirrhosis, finally to hepatocellular carcinoma (HCC) which represent as leading cause of death all over the world. The causative factors are hepatitis virus infections, alcohol abuse, and metabolic syndrome (Li et al. 2015). The pathological processes which finally contribute to liver diseases are lipid peroxidation, disruption of immune system, inflammation, and oxidative stress (Li et al. 2016). The liver being the central organ for metabolism plays a major role in detoxification. The toxic damages can occur because of various pathological mechanisms such as oxidative stress, cytochrome P450 dysfunction, dysfunction of mitochondria, and inflammation (Malaguarnera et al. 2012). The mechanisms underlying the pathological conditions involve reducing inflammation by MAPK inactivation, NF-κB signaling, improving antioxidant defense systems through Nrf2/cytochrome P450 2E1 (CYP2E1) expression, and inhibiting apoptosis via regulation of Bcl-2 protein/inhibiting caspase activation/protein kinase B (PKB) expression. Carbon tetrachloride-induced hepatotoxicity was shown to be protected by a natural flavonoid quercetin through its anti-inflammatory and antioxidant mechanisms. The mechanism of quercetin action might be attributed to the activation of toll-like receptor 4 (TLR4), phosphorylation of MAPK, inhibition of TLR2, and NF-κB inactivation which might have resulted in the reduction of inflammatory cytokines expression in the liver (Ma et al. 2015).

A well-known flavonoid, baicalein, has been reported to be protective against acetaminophen (AAP)-induced liver injury, and it acts via downregulation of ERK signaling pathway (Liao et al. 2017). Polyphenol extract of *Hibiscus sabdariffa* L. protects against AAP-induced steatosis of the liver which is mediated by reduced Bax, Bid, p-JNK, and apoptosis-inducing factor (AIF) expression (Lee et al. 2012). Curcumin protects liver against LPO-induced injury in rats where it acts by improving antioxidant status, reducing the levels of liver enzymes in serum, and inhibiting P38/JNK activation. It has also been reported to cause reduction in serum cytokine levels of IL-1β, IL-6, and TNF-α, and it inhibits the CREB and PI3K/AKT signaling pathways. Thus, this proves the efficacy of curcumin as a potent candidate for treatment of liver failure (Zhong et al. 2016). Resveratrol significantly protects liver against thioacetamide (TAA)-induced injury. In such cases, it was shown to inhibit oxidative stress and inflammation through downregulation of CYP2E1 and NF-κB expression. It also promotes apoptosis via upregulation of caspase-3 (Seif El-Din et al. 2016).

Exposure to alcohol either acute or chronic results in fatty liver. The consequences of alcohol exposure are mitochondrial dysfunction, increased ROS production, oxidative stress, and hepatic steatosis (Louvet and Mathurin 2015). Proanthocyanidins can protect the liver in alcohol-induced liver damage. It acts by downregulating the genes which are involved in inflammation such as IL-1β, TNF-α, and IL-6 (Wang et al. 2015a). Alcoholic liver disease is usually associated with increased deposition of iron which turns out to be fatal (Milic et al. 2016). EGCG was shown to be potent against iron overload because of its well- known iron chelating activity. It was shown to inhibit both intake and absorption of iron, thereby

reducing the iron levels in both serum and liver (Ren et al. 2011b). The major processes which are involved in the development of nonalcoholic fatty liver disease are accumulation of fat in the liver, injury of cells, and insulin resistance. Polyphenols with potent beneficial role in multiple signaling pathways and antioxidant and anti-inflammatory properties are considered as a promising treatment option for NAFLD (Van De Wier et al. 2017). The pathways involved under these conditions are Janus kinase/signal transducers and activators of transcription (JAK/STAT), NF-κB, AMPK, PPARs, PI3K/AKT, and TLR. Numerous polyphenols act through multitude of pathways in protection against NAFLD (Michelotti et al. 2013).

In insulin resistance and type 2 diabetes mellitus mice, kaempferol was found to significantly reduce the inflammatory cytokine levels, and it also inhibited the phosphorylation of insulin receptor substrate-1 (IRS-1) with concomitant reduction of NF-κB levels in cytoplasm and nucleus (Luo et al. 2015). In NAFLD, quercetin exerts its activity via NF-κB pathway inhibition (Porras et al. 2017). Polyphenols such as apple and cocoa show their beneficial effects in NAFLD through targeting of MAPK pathway (Xu et al. 2015; Cordero-Herrera et al. 2015). Increased expression of PPARα in liver is closely associated with transport of free fatty acids, β-oxidation, inhibition of CRP, and NF-κB expression, thereby reducing inflammation (Zeng et al. 2014). Several polyphenols were reported to upregulate the gene or protein expression of PPARα (Medjakovic et al. 2010; Jia et al. 2013). Another transcription factor which serves as a potent candidate for treatment of NAFLD is SREBP (sterol response element-binding protein)-1c. Upregulated expression of SREBP-1c has been reported to promote the steatosis progression (Zeng et al. 2014). Genistein, rutin, and luteolin can downregulate SREBP-1c protein or gene expression, thereby playing a critical role in inhibiting steatosis progression (Shin et al. 2007; Liu et al. 2011; Wu et al. 2011).

The metabolic role of AMPK is to regulate the fatty acid metabolism via stimulating the biosynthesis of fatty acids (Zeng et al. 2014). Accumulation of lipid in the liver and insulin resistance are the major pathogenic mechanisms of AMPK in NAFLD (Van De Wier et al. 2017). Polyphenols of major importance such as curcumin and resveratrol protect hepatocytes from injury via activation of AMPK signaling pathway (Jimenez-Flores et al. 2014; Choi et al. 2014).

Various classes of polyphenols are reported to have potent apoptotic and antiproliferative activities which act via multiple pathways (Mutalib et al. 2016; Li et al. 2018). Hesperidin induces apoptosis in HepG2 cells through downregulation of Bcl-2 and upregulation of Bax via both extrinsic and intrinsic mechanisms. GA and CGAs are also capable of inducing apoptosis in hepatic cells via induction of endoplasmic stress. Baicalein induces apoptosis in HepG2 cells via blocking/inhibition of mTOR pathway or MEK-ERK signaling pathway (Liang et al. 2012; Wang et al. 2015b). EGCG, a well-known green tea polyphenol, induces apoptosis in various hepatic cell lines through NF-κB inactivation, downregulation of PI3K/AKT pathway and Bcl-2, and upregulating Bax (Nishikawa et al. 2006; Shimizu et al. 2008; Shen et al. 2014). Hesperidin and naringenin have been studied extensively both in vivo and in vitro, and these have been reported to inhibit metastasis of liver cancer cells. The mechanism of action of these flavanones are inhibition of NF-κB and

AP-1 and downregulation of MMP-9 expression. Theaflavins block metastasis of liver cancer cells via blockage of STAT-3 pathway (Li et al. 2018). Curcumin and EGCG also blocks the progression of liver cancer to HCC via modulating the carcinogenic process involved (Sur et al. 2016; Afrin et al. 2017).

14.6 Conclusions and Future Prospects

The beneficial role of polyphenols may be attributed to their antioxidant, free radical scavenging, and metal chelating action and their ability to upregulate or downregulate the activity of various enzymes or proteins involved in multiple signaling pathways. The biological action of polyphenols depends on the availability of those compounds with necessary concentration at the target site after ingestion. Even exposure to high polyphenol concentration can result in negative effects including DNA damage, and increased ROS generation creates increased oxidative stress resulting in damage to macromolecules, such as DNA, protein, and nucleic acids. This might result in stimulating chronic inflammation which is the root cause for majority of human diseases. Antidiabetic nature of polyphenols is based on their modulatory effect on signaling pathways wherein they reduce oxidative stress, apoptosis, insulin resistance, and inflammation, promote/enhance insulin secretion, and upregulate proliferation of β-cells of the pancreas and they also promote GLUT4 translocation via AMPK and PI3K/AKT pathways (Vinayagam and Xu 2015).

Anticancer properties of polyphenols have been studied extensively in EGCG, curcumin, resveratrol, and anthocyanins. Their mechanism of action involves modulation of cellular signaling pathway which is associated with proliferation, differentiation, survival, detoxification, metastasis, and immune responses. Besides these properties the dosage of polyphenols for cancer treatment should be handled in a cautious manner. Diets rich in polyphenols such as fruits and vegetables can reduce the risk of cardiovascular diseases and mortality rate. Literature evidences in vitro and in vivo suggest that treatment with polyphenols can counteract increased ROS generation and influence signaling pathways which are associated with human disease pathologies. Polyphenols can alter the lipid levels; inhibit LDL oxidation, platelet aggregation, and lipid peroxidation; reduce atherosclerotic lesion; improve endothelium; and minimize blood pressure in cardiovascular complications. Besides consumption of single polyphenols, studies suggest that combination of polyphenols might work in the betterment of human health (Wersching 2011).

Oxidative stress, inflammation, and vascular dysfunction are the major contributors of neurological disorders. They are also associated with various other environmental and genetic factors. Polyphenol consumption might serve as a beneficial therapeutic strategy in protection against neurodegenerative diseases (Vauzour 2017). Treatment of liver diseases by polyphenols involves regulations at multiple sites such as inflammation and ER stress and alteration of lipid metabolism, immune response, insulin resistance, and oxidative stress. The key regulatory factors which are involved in the beneficial action of polyphenols have been summarized (Table 14.2). However, the pharmacological and therapeutic properties of polyphenols need to be still

Table 14.2 Key regulatory factors involved in the beneficial action of polyphenols

Role of polyphenols	Key regulatory factors	References
Antioxidant	Upregulation of CAT, SOD, and GPx activity Inhibition of LPO and ROS generation	Wasserman and Fahl (1997), Azzi et al. (2004), Choi et al. (2012), Sindhu et al. (2015), Schottker et al. (2015), and Shen et al. (2017)
Antiaging	Upregulation of antioxidant enzymes, sirtuins, AMPK, and PGC-1α expression	Markus and Morris (2008), Barger et al. (2008), Li et al. (2017), and Gurău et al. (2018)
Antidiabetic	Inhibition of glucose absorption/uptake in the intestine or its peripheral tissues Increasing glucose metabolism, reducing insulin resistance, improving vascular function	Rizvi and Zaid (2001), Rizvi et al. (2005), Scalbert et al. (2005), and Guasch-Ferré et al. (2017)
Anticancer	Upregulation of Bax, caspase-3 and caspase-9, p21, p53, and TGF-β expression Downregulation of TGF-α, Bcl-2, STAT-3, PI3K/AKT, COX-2, MMP, VEGF, Myc, and NF-κB expression Controls signal transduction pathways, cell cycle, cell growth, metastasis, inflammatory responses, apoptotic activities, and angiogenesis	Guptaet al. 2004, Khan et al. (2006), Kunnumakkara et al. (2007), Udenigwe et al. (2008), Harakeh et al. (2008), Kürbitz et al. (2011), Alexandrow et al. (2012), Rady et al. (2017), Sharma et al. (2018), and Saeki et al. (2018)
Anti-inflammation	Downregulation of IL-1β, IL-12, IL-6, TNF-α, NF-κB, iNOS, COX-2, ICAM-1, VCAM-1 and AKT, NF-κB, NO, and p38MAPK expression	Luceri et al. (2002), Stangl et al. (2007), Basu et al. (2010b), Basu et al. (2011), Larrosa et al. (2009), and Essafi-Benkhadir et al. (2012)
Cardioprotective	Upregulates eNOS expression, NO production, and improves HDL level Inhibition of COX-1 Downregulates MMP-1 expression and decrease LDL level Modulates and alters signaling pathways such as NF-κB, MAP38 kinase, SIRT1, and others	Wallerath et al. (2002), Vita (2005), Stangl et al. (2007), García-Lafuente et al. (2009), Pandey and Rizvi (2009), and Basu et al. (2010a, b)

(continued)

Table 14.2 (continued)

Role of polyphenols	Key regulatory factors	References
Neuroprotective	Downregulates STAT-1, IL-6, IL-1β, IL-8, TNF-α, CREB, GSK-3β, and NF-κB expression Bax inhibition, translocation of cytochrome c, and modulation of mitochondrial functions Upregulation of Nrf2 pathway and heme oxygenase-1 (HO-1) enzyme expression and downregulation of caspase-3	Hou et al. (2010), Shah et al. (2010), Paris et al. (2011), Ren et al. (2011a), Simao et al. (2012), Lee et al. (2015), and Yu et al. (2016)
Hepatoprotective	Downregulation of NF-κB, IL-1β, IL-6, TNF-α, IκB-α, JNK, p38, CYP2E1, and CRP expression Upregulation of PPAR-α and caspase-3 expression	Medjakovic et al. (2010), Jia et al. (2013), Zeng et al. (2014), Zhong et al. (2016), and Seif El-Din et al. (2016)

elucidated in humans. Randomized clinical trials should be undertaken to establish their potent benefits and their usage among human diseases. The administration route for polyphenols should be standardized to attain proper absorption and bioavailability. Even though translational research regarding polyphenols is challenging, improving bioavailability via standardization of administration route could help in betterment. Besides their beneficial role, certain polyphenols have carcinogenic and other side effects which might increase the disease risk. Analysis of safe dosage concentration of polyphenols should be performed to overcome the toxicity risk. In future, studies on bioavailability and absorption kinetics of polyphenols should be performed to find specific target site and as a whole to reduce the economic burden of chronic disease outburst and to ensure the future population toward healthier environment. The outcomes of these studies should provide specific dietary recommendations of polyphenols in preventing against chronic diseases, and it should serve as an effective treatment approach against chronic diseases.

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