Chapter

Bioavailability and Metabolic Pathway of Phenolic Compounds

Muhammad Bilal Hussain, Sadia Hassan, Marwa Waheed, Ahsan Javed, Muhammad Adil Farooq and Ali Tahir

Abstract

As potential agents for preventing different oxidative stress-related diseases, phenolic compounds have attracted increasing attention with the passage of time. Intake of fruits, vegetables and cereals in higher quantities is linked with decreased chances of chronic diseases. In plant-based foods, phenolic compounds are very abundant. However, bio-accessibility and biotransformation of phenolic compound are not reviewed in these studies; therefore, a detailed action mechanism of phenolic compounds is not recognized. In this article, inclusive concept of different factors affecting the bioavailability of phenolic compounds and their metabolic processes is presented through which phenolic compounds go after ingestion.

Keywords: polyphenols, bioavailability, biotransformation, metabolism

1. Introduction

In recent past, the awareness of the consumer related to the effect of diet on the health has been improved; therefore, leading to upsurge in the consumption of vegetables, cereal based foods and fruits. Numerous studies have suggested the bioactive characteristics of the bioactive moieties, i.e., phenolic compounds. Nonetheless, bioactive claims are made without taking into consideration the further modifications to which phenolic compounds are subjected once ingested [1].

Phenolic compounds are the secondary metabolites of plants which constitute an important group, i.e., phenylpropanoids. These compounds possess an aromatic ring and various OH groups which are link to it. On the basis of classification, phenolic compounds are prorated into various subgroups. They are grouped as a function of the number of phenolic rings that they contain and the radicals that bind these rings to another one [2, 3]. Phenolic compounds have fetched substantial focus as the ingestion of these bioactive moieties is correlated to lower the prevalence of chronic ailments, for example, diabetes, CVD and cancer. Cereals, fruits, and vegetables are rich sources of phenolic compounds. In fact, the health benefits of their dietary intake have been related, at least in part, to their phenolic compounds content [4]. This manuscript presents the bird's eye view of the health claims as well as bioavailability of the phenolic compounds.

2. Dietary phenolic compounds

Phenolic compounds are the derivatives of secondary metabolism of plants. Chemically phenolic compounds consist of aromatic ring to which one or more OH^- substituents are attached [1, 5]. Despite of diversity of phenolic compounds, they are mainly divided into two subgroups, (1) flavonoids and (2) non-flavonoids. First one constitutes of heterocyclic oxygen which are bonded with two aromatic rings and depends on the amount of hydrogenation. They can be further subdivided into six subgroups, i.e., flavanol, flavones, anthocyanins, flavonols, flavanones and isoflavones. While the later one, like cinnamic and benzoic compounds, they contain aromatic ring which are attached to organic acids. Lignins, stilbenes and tannins are also the subgroups of non-flavonoid compounds. Characteristics like flavor, astringency and color are instigated due to presence of these compounds [1].

3. Food sources with reported bioactivity

Latterly, due to numerous health prompting effects, for example, antimicrobial [6], neuro-protective [7], antioxidant [8], cardioprotective [9], anti-inflammatory [10] and cancer preventive [11] properties, phenolic compounds have much of the attention of the researchers. Phenolic compounds possess different derivatives which have a potential application in the prevention or treatment of these aliments [12]. Likewise, Perez-Vizcaino et al. reported numerous studies which supports the fact that upsurge in the consumption of foods rich in the phenolic compounds might be linked with the prevention of above-mentioned disorders [13]. Vegetables, fruits and cereals have high concentration of the phenolics. **Table 1** includes examples of some foods rich in phenolic compounds with reported biological effects.

Phenolic compound	Source	References
Phenolic acids (gallic acid)	Red wine	[14]
Anthocyanins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin)	Blackberry, blueberry, black grape, cherry, strawberry, red wine, plum	[15]
Condensed tannins (procyanidin)	Red wine, chocolate, cranberry juice and apples	[16]
Flavan-3-ols (catechin)	Fruits, vegetables, chocolate, lentil, green and black tea, wine, grapes and ginkgo	[17, 18]
Flavanones (hespertin, naringenin)	Orange, grapefruit and lemon juices	[19]
Flavones (apigenin, luteolin)	Parsley, celery, capsicum pepper and grape	[18]
Flavonols (quercetin, kaempferol)	Fruits, vegetables, and beverages such as tea and red wine	[20, 21]
Isoflavones (genistein)	Soy	[22]
Stilbenes (resveratrol)	Legumes, grapes, red wine, soy, peanuts and peanut products	[23, 24]

Table 1.
Phenolic compounds from food sources with reported biological effects.

4. Bioactivities of polyphenols

Since from the ancient times, bioactive moieties extracted from the natural sources have guarantee medicinal characteristics in combating against certain

disorders [25]. These bioactive components have a wide range of potential applications, i.e., antimicrobial, antitumoral, antimicrobial, hepato-protection and antioxidant. Few phenolic compounds show higher free radical scavenging properties individually, while numerous others showed these characteristics in synergism [26]. The free radical scavenging properties generally influenced by the chemical structure, position and number of OH^- group as well as glycosylation or other forms of replacement [27]. Additionally, despite of nullification of the ROS, nitrosative and oxidative stress such as CVD, neurological disorders, diabetes mellitus, cancer, and hypertension have also been prevented by phenolic compounds [28]. Likewise, literature also showed the anti-inflammatory properties of the phenolic compounds [29]. It is observed during the inflammation several RNS (reactive nitrogen species) as well as ROS (reactive oxygen species) are formed which escalate the action of proinflammatory factors. Phenolic compounds limit the pro-inflammatory enzymes thus prevent the human body from adverse effects [30].

In both developed and developing nations, cancer is the major cause of millions of demises each year [31]. For the treatment of numerous aliments, plants are the important ally in the traditional medicine. In pharmaceutical sector natural components impart important proportion in the synthesis of new anticancer drugs [32]. In the treatment of tumor cell, the uses of synthetic moieties are linked with the toxicity problems. Carocho and Ferreira suggested that without any toxicity or side effects natural compounds extracted from plants can be administered. By using both human trial and *in vivo* models, the effects of phenolic compounds on tumor cells have been comprehensively investigated [26]. Huang et al. reported the capacity of phenolic compounds to induce apoptosis by regulate carcinogen metabolism, ontogenesis and cell cycle arrest, suppress cell adhesion and DNA binding, proliferation, migration and block signaling pathways [11]. Similarly, the effects of phenolic compounds against hepatoprotective capacity have also been comprehensively studied both *in vitro* and *in vivo*. Phenolic acid and flavonoids have fetched the attention due to high free radical scavenging properties which overcome liver injuries frequently caused due to oxidative reaction which endorse lipid peroxidation in hepatic tissues [33].

Beside above-mentioned bioactivities, polyphenols have exhibited numerous other health beneficial effects.

5. Bioavailability of phenolic compounds

It is necessary to have the knowledge about the availability of the bioactive component as they are very effect against in the prevention of the disorders. By definition, the concentration of nutrient that is ingested, absorbed and metabolized via normal passages [34]. The bioavailability profile is not directly improved by the intake of high content of phenolic compounds [35]. Rein and his fellows purposed that to guarantee the bio efficacy of phenolic compounds, bioavailability is recognized as ultimate step, for example, at dietary level; the bioavailability is the proportion of a food which is ingested and consumed and thus a matter of nutritional efficacy [36]. Hence, numerous other factors affected may impart interference in the direct bioavailability of the phenolic compounds present in the food. Examples of several external aspects are interaction with other moieties, food processing and various other intestinal factors [37]. Likewise, different and complex processes, i.e., distribution, liberation, elimination, absorption and metabolism phases also affect the bioavailability whereas, limiting factor, i.e., intestinal level absorption decreased the bioavailability [36].

Through the GIT tract, gallic acid and isoflavones which has small molecular weight are easily absorbed [35]. On the other hand, numerous phenolic compounds

absorbed at a rate of 0.3–43% and the metabolite content circulating in the plasma can be low [36]. Likewise, kaempferol and quercetin belongs to flavonols exhibited several biological *in vivo* effects [38]. Yet, the utilization of these compounds as a potential health promoting components has inadequate efficiency due to the lessen bioavailability as a result of low absorption rate, low water solubility and increase instability in alkaline and neutral media including various organs, i.e., colon, small intestine, kidney and colon [39]. Due to low solubility and instability the use of apigenin is also limited in the pure form [40].

The bioavailability of phenolic compounds found in the foods begins in the oral cavity via metabolism reactions. In food transformation, mechanical action, i.e., mastication, impart significant role in the disruption of the food components which releases the compounds. In the oral cavity, the metabolism of glycosylated phenolic compounds commences immediately as the come in contact with the glycosidase enzymes of bacteria [41]. Literature showed that anthocyanin present in the fruit extract rich in phenolic compounds and human saliva, were moderately metabolized by the oral microflora enzymes [42]. During the passage through the stomach, few compounds go through the hydrolysis while on the other hand numerous polyphenols remain intact. Correa-Betanzo and his fellows reported that stability and modification of these food components were interlinked with the reaction of intestinal microbiota. In the G.I tract, various phenolic components need structural modification for their absorption [43]. Few *ex vivo* studies indicated that phenolic acid absorption took place in intestinal portion, i.e., jejunum and colon or at the gastric level [44]. Certain chemical characteristics, for example, molecular weight, lipophilicity, stereochemistry and the presence of group capable of hydrogen bonding, affect the transport and permeability of the polyphenols into the cytosol enterocytes from the gut lumen [45]. It is believed that the phenolic compounds are absorbed by a passive diffusion mechanism or by carriers present in the intestine, such as P-glycoprotein and cotransporters for SGLT1. These transporters are expressed on the cell membrane and transport the drugs into the cell interior [46, 47]. For example, aglycones cross the membrane of the epithelial cells via passive diffusion [41], whereas on the other hand glycosides, esters and polymers cannot cross the membrane by passive diffusion.

As long as biotransformation reaction as concerned, liver is recognized as the main organ in which maximum glycosylated phenolic compounds are metabolized by the action of small intestinal microbiota enzymes as well as by the intestinal cell membrane hydrolases, i.e., lactase phlorizin hydrolase. These first passage reactions took place in the intestine, letting the prior metabolism of compounds, which, in turn, encourage absorption. From the colon these compounds are then transported to the liver through portal vein or distributed in the bloodstream by the plasma proteins. During the metabolism, variation in the concentration of substance in the blood is influenced by the structural changes and absorption. For instance, plasma protein, for example, albumin transports phenolic substances along with their metabolites [48]. Meanwhile in the liver, phenolic compounds are further bio-transformed which aim to make them more polar molecules, assisting in their excretion. In the liver, these biotransformation processes are mainly categorized into two phases, i.e., phase I includes oxidation and reduction, hydrolysis reactions which are catalyzed by the CYP450 enzymes [46], while phase II enhances the hydrophilicity of the molecules prior to their elimination [41].

5.1 Factors affecting the bioavailability

Variation in the phenolic bioavailability ranges from 0.3% in the case of anthocyanins to 43% estimated for isoflavones [49]. In this sense, **Table 2** is imperative

Type of factor			References
Phenolics related factors	Chemical structure	Chemical structure solubility bond with sugars (glycosides), methyl groups, etc. stereo-configuration.	[49]
	Interaction with other compounds	Bonds with proteins (i.e., albumin) or with polyphenols with similar mechanism of absorption.	[50, 51]
Food related factors	Food processing	Thermal treatments lyophilization cooking and methods of culinary preparation storage.	[52, 53]
	Food interaction	Food matrix presence of effectors of absorption (positive or negative) (i.e., fat, fiber).	[54]
Host related factors	Dietary intake	Differences between countries and seasons quantity and frequency of exposure, single or multiple dose.	[55]
	Absorption and metabolism	Intestinal factors (i.e., enzyme activity intestinal transit time colonic microflora). Systemic factors (i.e., gender and age disorders and/or pathologies genetics physiological condition).	[55]
Other factors	Distribution and food content	Exclusivity in some foods (i.e., soy isoflavones, flavanones in citrus, etc.). Ubiquity (i.e., quercetin).	[56]
	External factors	Environmental factors (i.e., different stress conditions, degree of ripeness).	[57]

Table 2.
Factors that can affect dietary phenolic compound bioavailability.

to discuss that bioavailability is influenced by the food matrix and processing, phenolic structure and host; in addition to all these factors can interrelate with one another and effect bioavailability of the phenolic compounds, which make it tough to elaborate the particular mode of action of phenolic compounds. Additionally, pre-systemic elimination, release of a dosage form and absorption as well as route of administration also affects the bioavailability [58]. In order to elucidate the bioactive potential of phenolic compounds, *in vivo* estimation system is based on the inner wall as well as on the surface of the organs of the gastrointestinal tract, nonetheless such system did not reflect antioxidant *in vivo* effects [59], since solubility, base structure, interaction with other components as well as molecular size are the major physiochemical properties which lower the action of phenolic compounds [35].

6. Biotransformation of phenolic compounds

Transformation of lipophilic compounds into hydrophilic compounds is called biotransformation of heterologous compounds, in which the compounds are easily absorbed and excreted (**Figure 1**). The acetylation and methylation are excluded from this process, which reduces the water solubility of some alien organisms. Phenolic compounds are classified as exotic biological compounds which undertake heterologous biotransformation [61]. Heterogeneous biotransformation reactions can be divided into four categories, i.e., hydrolysis reaction, reduction reaction, oxidation reaction, and conjugation reaction. However, in study of dietary phenols, conjugation and oxidation are considered as most important reactions. Major sites of these reactions are cytoplasm, mitochondria, microsomes, and the tissues of the small intestine and liver [61]. Dietary phenolic compounds present in food have different structures as compared to those present in the tissues and peripheral circulation due to enduring metabolism after ingestion [62]. Phenol-sulfonate transferase, beta-glucosidase, lactase root enzymes hydrolase, and UDP-glucuronyl transferase are the enzymes involved in these processes. Absorption and bioavailability of phenolic

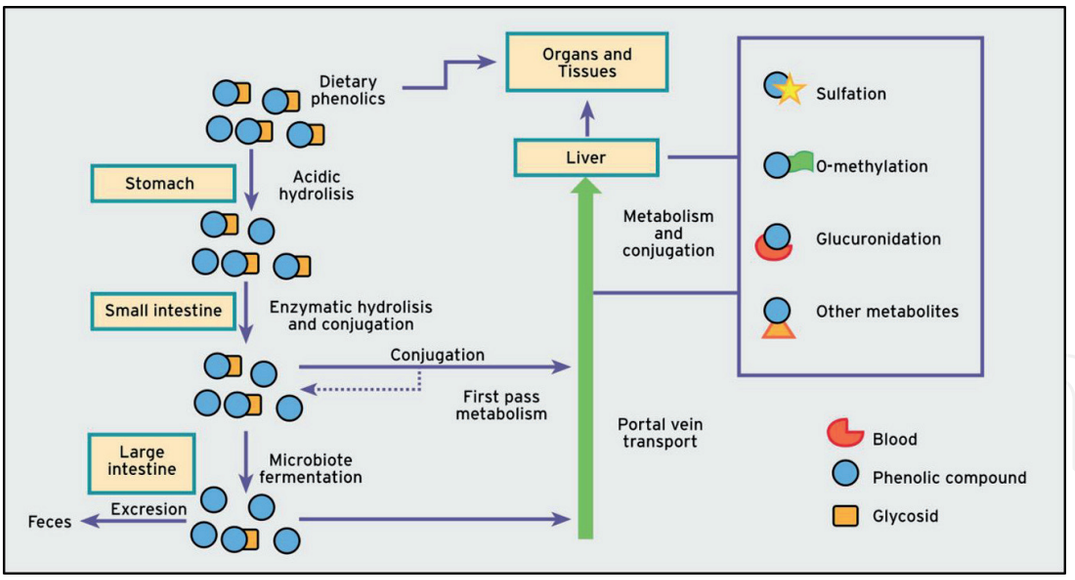

Figure 1.
Schematic representation of the metabolic pathway of phenols in humans after ingestion. Adapted from Grijalva et al. [60].

compounds mostly depend on their metabolic reactions conducted in small intestine. In addition, those compounds which are not absorbed through stomach and small intestine are degraded in large intestine through colonic microorganisms [63].

However, during chewing and digestion inn stomach, the interactions structural characters of phenolic compounds can be modified with other food substrates. This can decrease or increase small intestine's biological accessibility [41]. These binding reactions produce metabolites that bind to albumin mainly through the blood and distributed to different tissues and organs. Phenolic compounds are metabolized by colonic bacteria in parts of the intestine that are not absorbed and reach the large intestine. Colonic bacteria destroy aromatic rings and release aglycones which can be absorbed when processed into derivatives of benzoic acid and combined with glucuronic acid, glycine and sulfate [64]. Conjugated hydroxycinnamic acid *in vivo* has an effect on their biological activity because antioxidant potential of hydroxycinnamic acid is determined through existence of free hydroxyl groups, which are the important spots of sulfation and glucuronidation process [65].

7. Metabolism of phenolic compounds

7.1 Phase I

Biotransformation reactions involved during phase I of metabolism are oxidation, reduction, and hydrolysis. The biological activity of phenolic compounds can be increased, decreased or counteracted through these reactions [61]. The first stage of the reaction aims to change the structure of exogenous biomolecules. This amendment is attained through introducing amino, carboxyl and hydroxyl groups, etc. The major purpose of this reaction is to enhance the polarity of heterogeneous phenolic compounds for facilitating their excretion [61].

7.1.1 Hydrolysis

Hydrolysis is mainly aimed at functional groups such as carboxylic esters, amides, and lactones. Carboxylesterases are the most important hydrolysis enzymes in

mammals. However, aldehyde dehydrogenase, carbonic anhydrase, carboxypeptidase, lipase, and protease showed hydrolytic activity [61]. Lactose-phloretin hydrolase (LPH) exists in the human body. It mainly exists on one side of the small intestinal cavity. Lactose is hydrolyzed into galactose and glucose by LPH. It is also stated that flavonoid-*O*-beta-D-glycoside can be hydrolyzed through lactose-phloretin hydrolase resulting decrease of the polarity of the aglycones produced, thereby increasing the cell absorption of flavonoids [46]. However, the function of LPH can be disabled through stearic acid factor, and it cannot further hydrolyze glycosides (e.g., rhamnoside) [63].

7.1.2 Oxidation

During phase I of biotransformation, oxidation of phenolic compounds is the process having major importance. This reaction is primarily facilitated through enzyme-based oxidation process, controlled by CYP450 (microsomal cytochrome). CYP450 in humans has an extensive variety of substrates CYP3A4 (subfamily of CYP450) in gut is responsible for metabolic reactions of exogenous. According to different reports CYP3A4 interrelates with phenolic compounds. Therefore, it is suggested that some toxic consequences can be stimulated by the combined administration of both drugs and phenolic compounds [66]. Main factor affecting the metabolic activity of CYP450 regarding phenolic compounds include binding with different phenolic compounds, functional groups, glycosylation, molecular weight, polymerization and stereo-structure [5]. In addition, hydroxyl-rich flavonoids are unlikely to be processed through CYP450; unexpectedly, catechins from tea (hydroxyl-rich flavonoids) have been reported to inhibit CYP450 [67]. Still metabolic process of phenolic compounds is under research. Yet, the possible health potential of phenols has provoked further research in this area.

7.1.3 Reduction

Majority of the absorption of polyphenol took place in the large intestine where colonic microflora imparts significant role in the catabolism of these compounds. In humans, fission of the Cring both in naringenin and quercetin were done by the enzymes produced by the *C. orbiscindens* and *E. ramulu,* whereas *E. casseliflavus* were characterized for deglycosylation of Quercetin-1-glucode [68]. With the fission of Cring, epicatechin degradation initiated which lead to the synthesis of 1-(3′,4′)-dihydroxyphenyl)-3-(2″,4″,6″-trihydroxy) propan-2-ol, which in turn transformed into 5-(3′,4′)-dihydroxyphenyl-valerolactone. Likewise, in the next step formation of 5-(3′,4′)-dihydroxyphenyl-valeric acid is done by the breakdown of valerolactone ring which further undergo beta oxidation to 3-hydroxyphenylpropionic acid whereas if alpha oxidation is done, the resultant yield is 3-hydroxyphenylacetic acid. Similarly, in epicatechin gallate and epigallocatechin gallate breakdown, the galloyl moiety is removed by the esterase enzyme and the released gallic acid is decarboxylated to pyrogallol [69]. In the liver, metabolites which are synthesize by the colon microglora are transformed to monosulfates of 5-(3′,4′)-dihydroxyphenylvaleric acid, hydroxyphenylpropionic acid and monoglucuronides through conjugation reactions. Afterword, majority of the metabolites are then transported in the blood stream and then eliminated from the body via urine [70], however the unabsorbed metabolites are excreted by the body with feces [71].

7.2 Phase II

The second stage of biotransformation involves the incorporation of different chemical radicals to exogenous compounds. In body transported free radicals are

acquired from endogenous, polar, and highly available molecules. The major goal of this phase is to enhance the polarity of exogenous compounds. Increase in polarity is conducive to urination of exogenous substances [72]. Uridine 5′-diphosphate glucuronide transferase, sulfonate transferase, and catechol *O*-methyltransferase are the related enzymes for metabolism of dietary polyphenol in second phase. The synthesized molecule is bound to sulfate, glucuronic acid and/or methylation group [61]. Phenol conjugated compounds are different from their parent molecules regarding their ionic form, polarity and size. Thus, they are also different physiologically as compared to natural compounds. As a result, there is a growing need to know the possible health potential of these compounds either through *in vitro* studies.

7.2.1 Glucuronidation

It's the major conjugation-based reaction in humans. Through using UDPGA (glucuronic acid diphosphate glucuronic acid) as a substrate, glucuronidation process binds to the exogenous compound like glucuronic acid. UDP glucose, UDP xylose, and UDP galactose can also be used as substrates for this reaction [61]. The enzyme responsible for catalyzing the process of glucuronidation is UDP-glucuronide transferase. This enzyme exists in the microsomal tissue of the skin, brain, kidney, liver, and small intestine [73]. Glucuronidation sites are nucleophilic heteroatoms rich in electrons (like O, N or S). Thus, in glucuronidation reaction mostly involved substrates comprise of functional groups, like phenols and aliphatic alcohols [74]. So, in human body metabolism glucuronidation is main binding reaction of phenolic compounds [75]. Steffen et al. reported the glucuronic acid metabolite (−)-epicatechin binding serum albumin is relatively less than its aglycone. Therefore, the absorption of intestinal cells can be enhanced by the activity of beta-glucuronidase or LPH. In addition, aglycones are more lipophilic than flavonoid glycosides, so they are more easily absorbed. In addition, it is of great significance to evaluate the glucuronidation process of phenolic acid and study its effects regarding bioavailability and biological activities [76].

7.2.2 Methylation

Epicatechin gallate and epicatechins are absorbed without hydrolysis or disruption of conjugated bonds [62]. Different research trials have revealed that about 50% of total epicatechin reaching the intestine is absorbed by metabolites (especially sulfate conjugates) that are cleared into the intestinal cavity, while the clearance of epicatechin is relatively mild. The (−)-epicatechin secreted by bile may also be absorbed and be cleared by efflux in another segment of the intestine [77]. As compared to conjugation process, methylation reaction differs because it normally reduces hydro solubility of phenolics and hides the functional groups to prevent them to be attacked by conjugating enzymes [61]. As mentioned earlier, flavonoids are mainly glucuronidation, however, methylation metabolites have also been detected, for example, *O*-methylation and glucuronidation have been found in perfusion studies of catechins or epicatechins. This reaction is supposed to be facilitated through enzyme COMT (catechol *O*-methyltransferase) [78].

The *O*-methyltransferase is a highly selective enzyme system in plants, microorganisms, and mammals. This enzyme is involved in *O*-methylation of flavonoids, which is a natural xenobiotic transformation [79]. Methylation of phenolic compounds significantly improves their transportation through biological membranes and makes them more stable regarding metabolic reactions. It also improves their efficacy in different biological activities, especially their anti-tumor potential in cell culture research. Thus, as compared to hydroxylated derivatives in cell culture,

O-methylated flavonoids have a much better anticancer potential, due to being more resistant to metabolic reactions in liver and having high absorption in intestine [80]. In addition, methylated flavonoids play an important role in protein transportation having major role central role in the body defense system against toxic substances like MDR proteins [81]. It has been recommended that stability and transportation ability through biological membranes is improved by enhancing methylation degree and decreasing the number of free hydroxyl groups which can be bind with glucuronic acid and sulfuric acid groups [82].

8. Applications in functional foods and nutraceutical formulations

Nowadays, some functional foods and health products can be found commercially to capture consumers' interests. The scientific community can prove the beneficial health effects of these products, and the food and pharmaceutical industries have followed suit to develop feasible production of novel high-yield products [83]. Medicinal and aromatic plants play an important role in the field because

Phenolic compound	Source	Application	Bioactivity		References
			Antioxidant	Antimicrobial	
Phenolic acids	Commercial	Infant cereals	✓	_	[85]
Anthocyanins	Cranberry (*Vaccinium macrocarpon* Ait.)	Nutraceutical capsules	✓		[86]
Phenolic extracts	Blackberry flower (*Rubus ulmifolius* Schott)	Yogurt	✓	_	[87]
	Borage (*Borago officinalis* L.)	Fresh pasta	_	✓	[83]
	Chamomile flower (*Matricaria recutita* L.)	Cottage cheese and yogurt	✓	✓	[88, 89]
	Fennel aerial parts (*Foeniculum vulgare* Mill.)	Cottage cheese and yogurt	✓	✓	[88, 90]
	Garcinia fruit (*Garcinia cowa* Roxb)	Bread	✓	_	[91]
	Grape seed (*Vitis vinífera* L.)	Yogurt	✓	_	[92]
	Green tea (*Cammelia sinensis* L.)	Bread	✓	_	[93]
	Guava flower (*Psidium guajava*)	Bread melanoidins	✓	_	[94]
	Pomegranate fruit (*Punica granatum* L.)	Yogurt and pasta	✓	_	[95, 96]
	Pomegranate peels (*Punica granatum* L.)	Ice cream	✓	_	[97]
	Rosemary (*Rosmarinus officinalis* L.)	Cottage cheese	✓	_	[98]
	Veronicas (*Veronica montana* L.)	Cream cheese	_	✓	[99]

Table 3.
Phenolic compounds used as nutraceuticals or bioactive compounds in functional foods.

of their antioxidant, antimicrobial, and other beneficial effects in the prevention and treatment of certain diseases. The incorporation of these compounds in food can be carried out directly in free form; however, microencapsulation technology has emerged as a very effective and promising strategy to ensure the bioavailability of these compounds and help overcome the problems of food processing and intake [84]. After ingestion, these compounds are absorbed into the blood, causing changes in various cellular mechanisms, thus preventing various diseases. Many kinds of literature have proved the biological activity of phenolic compounds in various plants and fruits, and few studies have reported its application in the development of functional food or nutritional preparations (**Table 3**).

9. Potential toxicity

In recent past years, the potential toxicity of some polyphenols, such as catechins, to DNA of mouse spleen cells has been reported. DNA can be damaged due to high concentration of catechin on spleen cells of mice [100]. In addition, grape extract could also promote sister chromatid exchange induced by mitomycin C in human peripheral blood lymphocyte at a concentration of 75–300 μg/mL [101]. At the same concentration, the mixture of caffeic acid, gallic acid, and rutin hydrate could enhance mitomycin C induced fragmentation. In addition, after 24 h or more of high concentration epicatechin treatment, there was a significant negative effect on fibroblasts and keratinocytes. In addition, compounds with gallate groups showed more potential toxicity than compounds without gallate groups [102]. The results showed that polyphenols could play a positive role in the safe concentration range. However, polyphenol concentration is not the only determinant, and its negative effects are related to synergistic effects and exposure time. Therefore, the dosage and composition of polyphenols should be further studied for safe and healthy application [103].

10. Conclusion

Phenolic compounds, group of antioxidant phytochemicals have health promoting effects and potential to decrease the chances of chronic diseases linked with high consumption of fruits, vegetables and cereals. Several epidemiological studies relate health promoting effects of plant-based foods to phenolic compounds. Still, there is a deficiency of studies and research work regarding metabolic pathway of these compounds; leading to a less understanding of their mechanism of action. Therefore, it's essential to conduct further research to create improved approaches to take advantage of health promoting effects of these compounds.

Conflicts of interest

No competing interest.

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Author details

Muhammad Bilal Hussain[1], Sadia Hassan[1,2*], Marwa Waheed[1], Ahsan Javed[1], Muhammad Adil Farooq[3] and Ali Tahir[1]

1 Institute of Home and Food Sciences, Faculty of Life Sciences, Government College University, Faisalabad, Pakistan

2 Food Processing Centre, Department of Food Science and Technology, University of Nebraska-Lincoln, Nebraska, USA

3 School of Food Science and Engineering, Guangdong Province Key Laboratory for Green Processing of Natural Products and Product Safety, South China University of Technology, Guangzhou, China

*Address all correspondence to: sadiahassan88@gmail.com

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