Review

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Phenolic compounds in whole-grains of wheat: a review

Monica Sharma[1]* and Pranav Bhaskar[2]

[1]*Rastrapati Bhawan Cabinet Affair Apartments, Sector 10, Dwarka, New Delhi, Delhi-110075, India.*
[2]*Department of Biochemistry, Panjab University, Chandigarh-160014, India.*

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Abstract: Whole-grains are important food resources for human beings, therefore, there is a need to pay special attention to increase their production to feed the world's rapidly increasing population. Whole-grains are highly rich in nutrition and bioactive properties due to the available health-promoting biologically active metabolites such as phenolic compounds. Phenolic compounds are antioxidant-rich secondary metabolites having immense health benefits. Owing to their strong antioxidant activities, they have anti-inflammatory, anti-carcinogenic, and anti-diabetic properties; they exhibit anti-aging effects and can also cure cardiovascular diseases, obesity, etc. Numerous epidemiological studies have proven the inverse correlation between the consumption of whole cereal grains and reduce chronic diseases. This review article focuses on biologically active components of wheat grains, namely phenolic compounds, including their chemical structures, classification, biosynthesis, bioactivity, and bioavailability. Health benefits and functional potential of consumption of whole cereal grains have also been discussed.

Keywords: antioxidant activity; bioactive compounds; bio-availability; phenolic compounds; whole-grains.

Introduction

Whole-grains are cereals that are monocots, and they belong to the grass family *Poaceae*. Cereal crops such as wheat, corn, rice, millets, and barley are cultivated on about 70% of the world's farmland as they are a staple food and fodder crops, both. Among cereals, wheat (*Triticum* sp.) is one of the major food crops throughout the world. It is processed into various food products such as bread, chapatti, pasta, noodles, biscuits, cakes, couscous, and beer [1]. About one-third of wheat produced is used for livestock feed and two-third for human consumption, respectively [2]. Wheat is an extensively grown cereal crop among few crop species because of its nutritional value. It is adapted to the widest geographical and climatic ranges of all major crops. About 80% of wheat (after processing) is used for human consumption in the form of bread, other baked goods (cakes, cookies, crackers, etc.), noodles, and pasta (FAO 2011). The use of stylized wheat spikes in the emblems of the United Nations' Food and Agriculture Organization (FAO) and the Indian Council of Agricultural Research (ICAR) displays the global importance of wheat.

Wheat grain possesses excellent nutritive and bioactive properties due to its fractions, bran, aleurone, and germ, which contains unique health-promoting bioactive components [3–5], which present a more valuable nutritional profile as compared to refined grains [6]. These contemplations have amplified the attention of the researchers towards the phytonutrients of the whole-grain, including phenolic compounds for exploring their effects on human health. According to the report by World Health Organization for 2012–2016, daily intake of whole-grains may cut the peril of several diseases (e.g., cardiovascular disease, type 2 diabetes, the aging process, cancer, hypertension, and obesity) [7]. An inverse correlation has been found between the consumption of whole-grains, including the bran and the decreased risk of chronic diseases [8-13]. Nowadays, there is a surge of interest in phytonutrients, including phenolic compounds. They are potent antioxidants having many curative, nutritious, and preventive properties like anti-inflammatory, anti-carcinogenic, anti-diabetic, etc. in humans [12, 14-17]. It is also reported that whole-grain foods with bran and aleurone have significant biological activity in humans [16, 17]; however, they are considered as byproducts from the flour-mill industry, are discarded and used as animal fodder [18]. They consist valuable phytochemicals, micronutrients, and fiber of the grain, which upon adding to the human food significantly affect its nutritional quality [19]. Bran and aleurone layer of whole-grains provide health-promoting fiber to the body and the antioxidant-rich phytochemicals, such as phenol and their derivatives, which improves the overall health of the person [20–24]. Daily intake of whole-grains (approx. 48 grams) may reduce the risk of type 2 diabetes mellitus, cardiovascular diseases, and cancer [25, 26]. The intake of whole-grains causes the release of indigestible fibers, which alter the microbiotic costitution of humans/animals gut and metabolize the substrates, such as non-starch polysaccharides (β-glucan and arabinoxylans), resistant starch and phenolic compounds into practical microbiotic metabolites [6] and finally, helps to improve the inclusive health of the consumer. The bran and aleurone layer of cereal grains are enriched with phenolic

Dr. Monica Sharma
Independent Researcher
Rashtrapati Bhavan Cabinet Affair Apartments,
Sector 10, Dwarka
New Delhi-110075, Delhi, India
E-mail: monicasharma986@gmail.com

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compounds, minerals, and fibers, but they are generally overlooked in favor of fiber.

Phenolic compounds are plant natural products, which are synthesized via the shikimic acid pathway from an aromatic amino acid phenylalanine. They are commonly classified into phenolic acids, flavonoids, coumarins, tannins, stilbenes, and lignans; in grains, these compounds are present in free form and soluble and insoluble bound form[27, 28]. They exhibit high antioxidant activity due to their phenol ring [18] and are present in abundance with ferulic acid as its major component [27, 28]. Phenolic compounds are generally present in cereal bran, majorly in an insoluble form, covalently cross-linked with the polymers of the cell wall, and a small amount in the free form [27, 29]. Hence, they are not readily available to show their health-associated positive impact. Most of the phenolic compounds are concentrated in the outer layers (bran and aleurone) of the grains that get removed or depleted during the process of grinding and making flours from them. Also, phenolic compounds are not easily discharged in the gut from the food matrix as they are mostly present in an insoluble form by forming covalent bonds with proteins and carbohydrates in the cell walls of the grains and therefore, not easily bio-accessible. So, they have to be resistant to all food-processing methods and in bio-accessible form in order to reach their target in the gut easily. Therefore, now-a-days, more stress is laid on the bioavailability, bioaccessibility and the utilization of agri-waste products containing phenolic compounds to obtain maximum benefits [30, 31].

This study is conducted to review the recent scientific literature targeting the nutritional aspects of whole-grain intake and to focus on phenolic compounds available in their outer layers, i.e., bran and aleurone. This review focuses on biological activities, health benefits, functional potential of phenolic compounds, the effect of food processing on them, and discovering new approaches and skills to reveal bioavailability and bioaccessibility of phenolic metabolites present in the bran and aleuronic fragments of whole-grains.

Cereal grains, their major fractions and bioavailability of micronutrients in wheat

Wheat, rye, rice, oats, and barley are amongst the chief whole-grains, presenting a significant food source for humans, spanning various human civilizations. All these grains have similar structures, containing three discrete fractions: the outer fiber-rich bran, the micronutrient-rich germ, and the starchy endosperm [32]. After food processing, the kernel has to retain the bran, germ, and endosperm proportion as the archetype, to be said "whole-grain" [33].

The wheat kernel is oval, and kernel size varies according to the grain cultivars and production conditions. Tissues that form the wheat kernel are illustrated in Figure 1. They are broadly divided into endosperm (80-85%), bran (13-17%), and embryo (2-3%) [34]. The pericarp (inner and outer) makes about 5% of the kernel and is rich in xylans and fiber (mostly insoluble) [35–37]. In contrast, the testa layer is only 1% of the kernel and is rich in arabinoxylans, lignin and alkyl resorcinols [35, 38]. The aleurone layer is rich in proteins, phenolic compounds, lignans, vitamins, minerals, phytic acid, lipids, and plant sterols and plays an essential role in the germination process [34, 39]. In wheat, the kernel's endosperm contains mainly the food reserves (60-75% starch, 9-13 % proteins, 1.5% lipids, dietary fibers and minerals) to grow the seedling. The Aleurone layer, along with the endosperm, contributes to more than 80% of the mass of a wheat grain [40]. The germ of the wheat kernel comprises 2.5 to 3.5% of the total kernel mass and contains 25% proteins, 8-13% lipids, and 4.5% minerals [41]. It contains the embryonic axis and scutellum. Wheat grains contain about 12% moisture, 60-80% carbohydrates

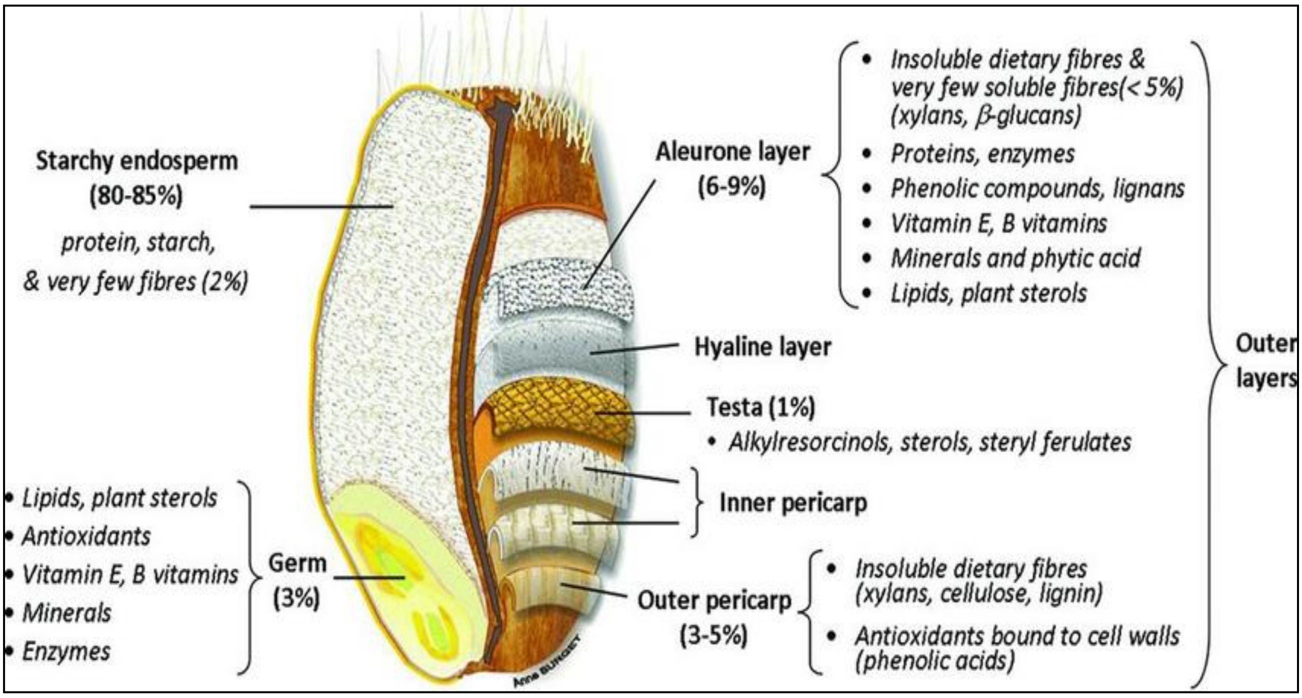

Figure 1. Structure of a wheat whole-grain (Source: Surget and Barron, 2005).

(mainly the starch), 8-15% proteins, adequate quantities of all essential amino acids (except methionine, lysine and tryptophan), 1.5-2% fats, 1.5-2% minerals, vitamins (B complex and E) and 2.2% crude fibers.

Classification of Phenolic Compounds

Phenolic compounds are the plant natural products, synthesized via the pentose phosphate pathway, shikimic acid pathway and phenylpropanoid pathway [42]. They have a carbon skeleton of C_6-C_3. The key substrate found in phenolic compounds is aromatic amino acids – tyrosine or phenylalanine. These substrates are acted upon by the enzymes tyrosine ammonia lyase (TAL) or phenylalanine ammonia lyase (PAL), respectively. The removal of ammonia molecule (-NH_3) from them give rise to *trans*-cinnamic acid. Introduction of hydroxyl group(s) (-OH) to the phenyl ring is the crucial step in the synthesis of the phenolic metabolites, giving rise to a large no. of phenolic compounds: phenolic acids (hydroxycinnamic acid (C_6-C_3) and hydroxybenzoic acid (C_6-C_1) and their derivatives), flavonoids (C_6-C_3-C_6), anthocyanidins ([(C_6-C_3-C_6)*n*]), coumarins (C_6-C_3), stilbenes (C_6-C_2-C_6), lignans (C_6-C_3-C_3-C_6) and lignins [(C_6-C_3)*n*], chalcones (Figure 2) [43].

vanillin [44]. In wheat grains, phenolic acids exist either in free form or insoluble and soluble bound form [27, 28]. They consist of major ferulic acid and *p*-coumaric acid. Using UPLC-Q-TOF-MS, Sharma et al. identified twenty-one phenolic acids in two contrasting bread-making wheat varieties, and sub-categorized them into two phenolic acids (benzoic acid and cinnamic acid), nine HBAs and ten HCAs [27]. In the HBA sub-group, there were two monohydroxybenzoic acids (salicylic acid and *p*-hydroxybenzoic acid), two dihydroxybenzoic acids (*2,4*-dihydroxybenzoic acid and *3,4*-dihydroxybenzoic acid), one trihydroxybenzoic acid (*3,4,5*-trihydroxybenzoic acid or gallic acid), one methoxy derivative (vanillic acid), two aldehyde derivatives (vanillin and *p*-hydroxybenzaldehyde), and acetovanillone (structurally similar to vanillin). Whereas in another study by Sharma et al., in the set of 100 Indian wheat varieties, 115 PCs were distinguished in the free extracts; out of them, 29 were phenolic acids and their derivatives [28]. In most of the studies made earlier for phenolic acids, ferulic acid was the major phenolic acid found in wheat [16, 45-47]. However, Sharma et al. found out that vanillic acid, sinapic acid, 2,4-dihydroxybenzoic acid, and ferulic acid (µg/100g) were

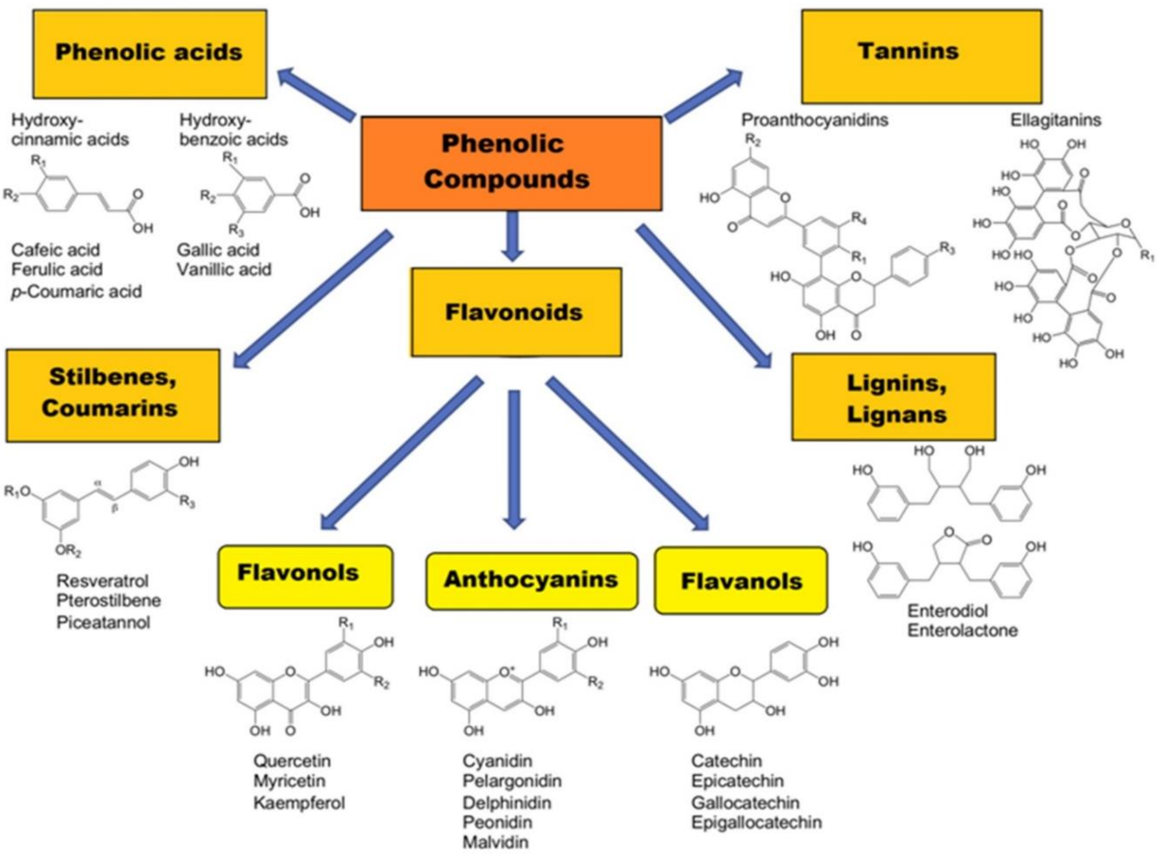

Figure 2. Classification of phenolic compounds

Phenolic acids

Phenolic acids are categorized into hydroxycinnamic acids (HCA) and hydroxybenzoic acids (HBA), along with their respective derivatives. HCA has a C_6-C_3 carbon skeleton and consists of trans-cinnamic acids, ferulic acid, *p*-coumaric acid, sinapic acid, caffeic acid, etc.; in contrast, HBA has a C_6-C_1 carbon skeleton and include benzoic acid, *p*-hydroxybenzoic acid, vanillic acid, gallic acid, and

found abundantly in the free extracts of 100 wheat varieties of India [28]. According to Sharma et al., in Indian wheat varieties, the content of ferulic acid and *p*-coumaric acid, which are common and abundant phenolic acids occurring in wheat grains, was found to agree with previous reports [16, 27, 28, 45, 46, 48]. Also, the range of phenolic acids found in 100 Indian wheat varieties using UPLC-Q-TOFF-MS/MS was from (0.02 ± 0.01 µg/100g) for the ellagic acid to (547.63 ± 12.43µg/100g). The number of phenolic acids

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found and verified was also large compared to other studies, which may be due to environmental and genotypic variations as both of them have prominent effect on the concentration of phenolic compounds in the plants.

Flavonoids

Flavonoids form the largest group of PCs. They are formed by two aromatic rings 'A' and 'B', joined by a three-carbon bridge that fuses to create a heterocyclic ring 'C' [49]. Different subgroups of flavonoids such as flavonols, flavones, flavanones, flavanols, anthocyanins, anthocyanidins, etc. are formed by the variation in this 'C' ring [50]. 'A' ring of flavonoids is formed through the acetate/malonate pathway, whereas 'B' ring is derived from the shikimate pathway [51]. Flavonoids are generally colorless or pale yellow except anthocyanins, which provide colors to various plant parts depending upon the structure, pH, temperature, and light [52, 53]. Flavonoids mostly exist in the bound form in the cell wall of wheat grains, but a small amount of them also occur in the free form [16, 27, 45]. Flavonoids occur majorly in C-glycosidic form in wheat grains. It also exists in a small amount in O-glycosidic form and aglycosidic form. Many research groups have reported that cyanidin, cyanidin-3-rutinoside, cyanidin-3-glucoside, peonidin-3-glucoside, apigenindin, apigenin-5-O-glucoside, cyanidin-3-galactoside, pelargonidin-3-glucoside and their derivatives are some common anthocyanins usually found in wheat grains and other cereals, providing blue, red, or purple coloration [16, 27, 28, 45, 54, 55]. A total of 40 flavonoids were identified in two contrasting wheat varieties for chapatti making [27]. Additional 31 flavonoids were identified later in free extracts of 100 Indian wheat varieties – one isoflavone (formononetin), two flavanones (narirutin and neohesperidin), three anthocyanidins (petunidin, procyanidin B-3 isomer, and delphinidin), nine flavones (robinin, astragalin, chrysoeriol, luteoforol, isovitexin, apigenin-*6*-C-beta-galactosyl-*8*-C-beta-glucosyl-O-glucuronopyranoside, vicenin-2, 4,5,7-trimethoxyflavone, and apigenin) and 16 flavonols (amurensin, gossypetin, galangin, icariin, pachypodol, hyperoside, morin, azalein, spiraoeside, natsudadain, troxerutin, kaempferol-3-O-glucoside, azaleatin, rhamnazin, isoquercetin, and fisetin) [28]. In 100 Indian wheat varieties, the concentration of flavonoids were detected using UPLC-Q-TOFF-MS/MS and it ranged between 0.01±0.0 µg/100g for luteolin to 41.59±0.29 µg/100g for prunin [28]. The concentrations of all the flavonoids type detected in 100 Indian wheat varieties showed a large difference among themselves, due to environmental and genotypic variations, which has a significant effect on the phenolic capacity of any type [27, 28, 45, 46].

Lignins, lignans, coumarins, stilbenes, and chalcones

In nature, lignin is the second most abundant biopolymer, after cellulose. It is present in all wood and accounts for approximately 30% of organic carbon in the biosphere [56]. It is a complex aromatic non-carbohydrate polymer. According to Boerian et al., lignins are classified into three types (G, H, and S lignins) depending on their monomer phenylpropanoid content [57]. Lignan is a sub-class of phenylpropanoids produced by secondary metabolic pathways and found in almost all plants. They are phytoestrogens having significant pharmacological activities [58–60]. In a study of old and modern wheat cultivars, Dinelli et al. identified lignans, namely hinokinin, secosiolariciresinol, arctigenis, syringaresinol, and pinoresinol [46, 61]. In bread wheat, Penalvo et al., detected aglycone lignans, namely medioresinol, lariciresinol, syringaresinol, and matairesinol [62], whereas, in the studies conducted by Sharma et al., only two lignans, namely hinokinin and syringaresinol, were identified [27, 28].

Coumarins are the members of the benzopyrone family, consisting of a benzene ring joined to a pyrone ring; they are classified into four sub-categories: the simple coumarins, furanocoumarins, pyranocoumarins, and pyrone-substituted coumarins. They are found to have anticarcinogenic properties [63], and exhibit anticoagulant and anti-inflammatory activites [64]. In research conducted by Lachman et al., coumarins, and their hydroxylated products were detected in wheat grain [65]. In studies conducted by Dinelli et al., only one coumarin was identified, that too, only in the free phenolic extract of one old durum wheat genotype [46]. In a study of two contrasting wheat varieties for chapati making, Sharma et al. found two coumarins - coumarin and esculetin [27]. In free phenolic extracts of 100 Indian wheat varieties, three coumarin - coumarin, dicoumarol, and esculetin, and their derivatives were found [28]. Chalcone is a type of phenolic compound, which is an aromatic ketone and from chalcone as a basic unit, many other biomolecules are also biosynthesized. Two chalcones, namely phloretin and phloridzin, were identified by a study conducted by Sharma et al. [27, 28]. Stilbenes are polyphenols having small molecular weight (~200-300g/mol), contains resveratrol as a basic unit. They have carbon skeleton C_6-C_2-C_6 and share their biosynthesis pathway with chalcones [66]. Stilbenes possess anti-oxidant and anticancer properties, and exhibits anti-inflammatory activity as well. Dinelli et al. identified two stilbenes in bound phenolic fractions of old and modern wheat cultivars [46]. These were glycosylated pinosylvin and double glycosylated pinosylvin. Matus-Cádiz et al. also found double glycosylated pinosylvin in hard winter wheat [67]. Sharma et al. also identified eight stilbenes, namely *trans*-piceid, glycosylated pinosylvin, double glycosylated pinosylvin, glycosylated and acetylated pinosylvin, astringin, piceatannol, rhapontin, and rhapontigenin using UPLC-Q-TOFF-MS/MS [27, 28]. To date, these are the maximum number of stilbenes found in wheat.

Phenolic compounds biosynthesis

Many genes are engaged in the biosynthesis of phenolic compounds in plants (Figure 3). But the key gene is Phenylalanine ammonia lyase lyase (PAL) that directs the flow of carbon to the biosynthesis of numerous such metabolites from the shikimate pathway [68]. This enzyme catalyzes the deamination of Phenylalanine into *t*-cinnamic acid, the first phenolic acid of the phenylpropanoid pathway; which in turn is catalyzed by cinnamate-4-hydroxylase (C4H) and 4-coumarate lyase (4CL) to produce *p*-coumaric acid and *p*-coumaroyl CoA, respectively. *p*-Coumaroyl CoA is the key metabolite that give rise to several other phenolic acids, flavonoids, and

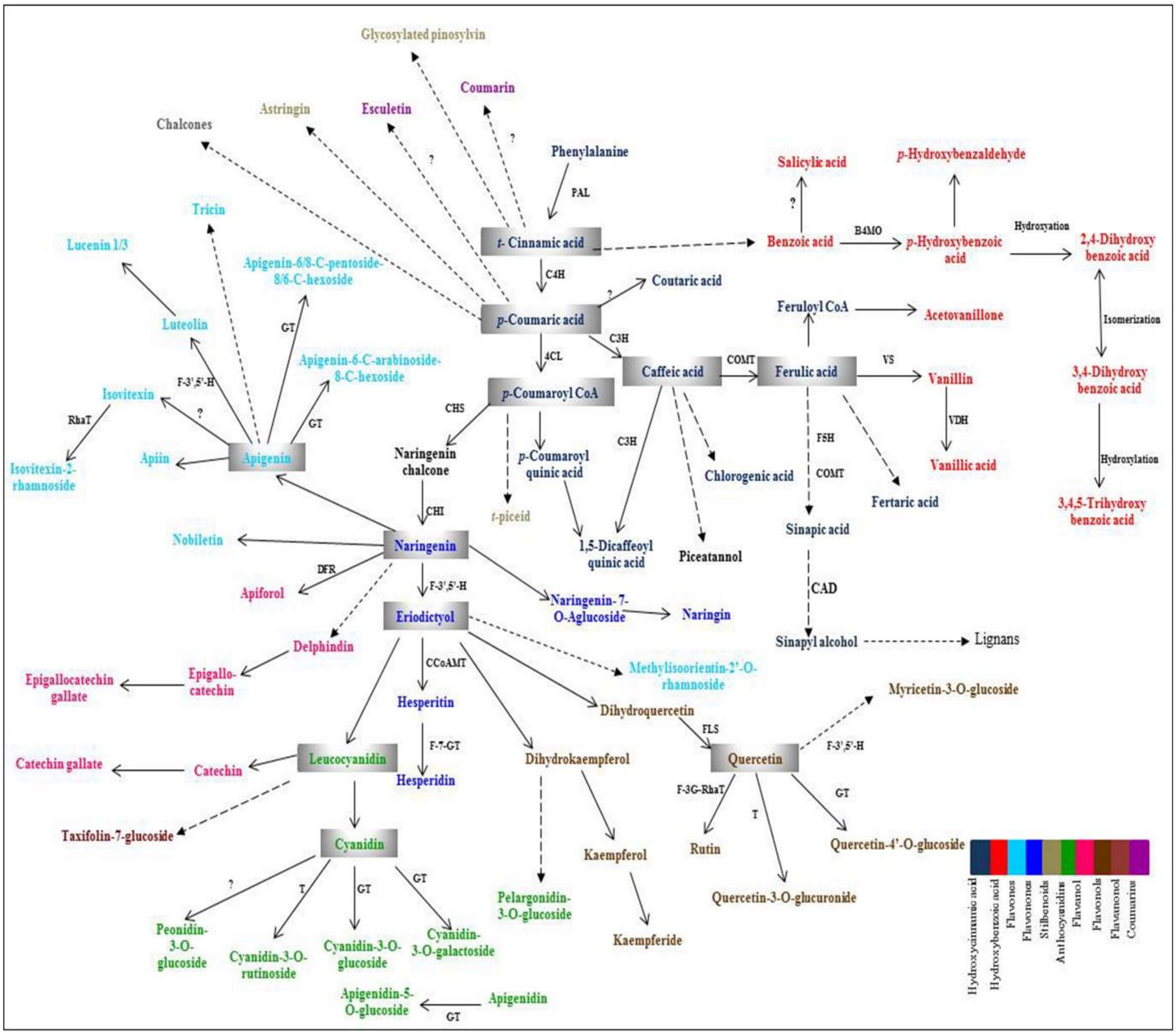

Figure 3. Schematic overview of the biosynthetic pathway of phenolic compounds. B4MO: Benzoate-4-monooxygenase; COMT: Caffeic acid-O-methyltransferase; CCoAMT: Caffeoyl CoA 3-O-methyl transferase; CHI: Chalcone isomerase; CHS: Chalcone synthase; C4H: Cinnamate-4-hydroxylase; CAD: Cinnamyl alcohol dehydrogenase; 4CL: 4-Coumarate CoA ligase; C3H: *p*-Coumaroyl shikimate 3-hydroxylase; DFR: Dihydroflavonol 4- reductase; F5H1: Ferulate-5-hydroxylase 1; F-3',5'-H: Flavonoid 3',5'-hydroxylase; FLS: Flavonol synthase; F-7-GT: Flavanone 7-O-beta-glucosyltransferase; GT: Glucosyl transferase; PAL: Phenylalanine ammonia lyase; Q3G-RhaT: Quercetin-3-O-glucoside L-rhamnosyltransferase; RhaT: Rhamnosyl Transferase; T: Transferase; VDH: Vanillin dehydrogenase; VS: Vanillin synthase. [Source: Sharma et al., 2016]

stilbenes through several modifications and condensation reactions [68–70]. Hydroxybenzoic acids are biosynthesized from *t*-cinnamic acid by different pathways that may co-exist [68,69]. The biosynthesis of the phenolic compounds from phenylalanine involves several cytosolic enzymes, including PAL (phenylalanine ammonia lyase), HCT (hydroxycinnamoyl-CoA: shikimate hydroxycinnamoyl transferase), 4CL (4-hydroxycinnamoyl-CoA ligase), CCR(hydroxycinnamoyl-CoA reductase), CAD (cinnamyl alcohol dehydrogenase), CCoAOMT (caffeoyl-CoA O-methyltransferase), and COMT (caffeic acid/5-hydroxyferulic acid O-methyltransferase) and endoplasmic reticulum membrane-anchored enzymes, including F5H (ferulate-5-hydroxylase), C3H (*p*-coumaroyl shikimate-3 -hydroxylase), and C4H (cinnamate acid 4-hydroxylase). Phenolic compounds, monolignols, and lignans may be coupled by UDP-glucosyltransferase (UGTs) and for their oxidative cross-linking into lignins, catalyzed by laccases and peroxidases present in the apoplast, they are carried to the vacuoles or the cell wall (Figure 4) [71].

Importance of phenolic compounds

Phenolic compounds are extremely diverse, low molecular weight plant secondary metabolites that give metabolic plasticity; they must anticipate and respond to various abiotic and biotic stresses. The presence of hydroxylated aromatic ring(s) made phenolic compounds distinguished from other secondary metabolites. They are among the most exploited and extensively studied metabolic pathways in plant research. They play very crucial roles in plants such as the synthesis of lignin in the cell wall (structural

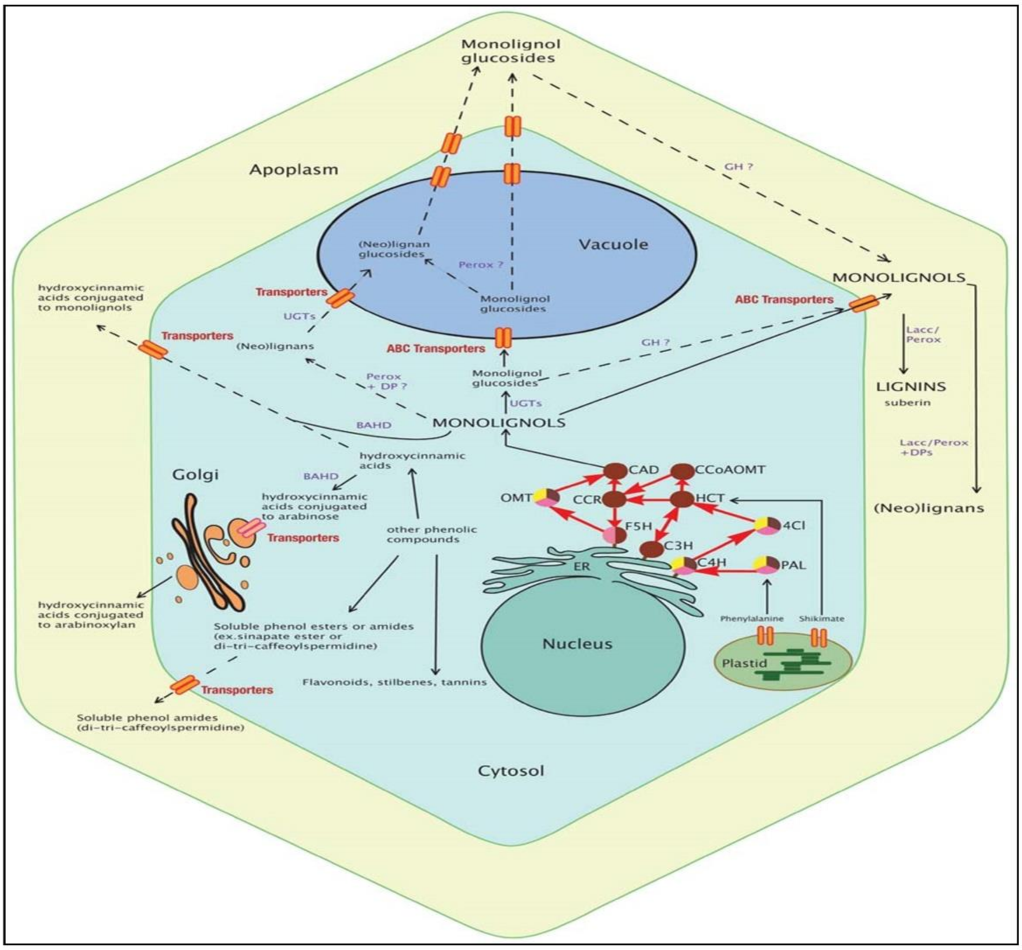

Figure 4. Cellular location of phenylpropanoid biosynthesis pathway [Source: Wang et al., 2014]

function), protecting plants from harmful ultra-violet rays, as signaling molecules [72], prevent microbial attacks [73], help in pollination by imparting colors (anthocyanins) to the plant parts and attracts pollinators [74] and also act as allelochemicals [75]. Apart from playing numerous abiotic and biotic roles, phenolic metabolites are strong antioxidants and quench various free radicals produced during multiple metabolic processes. The removal of the free radicals prevents oxidation of various biomolecules like lipids, proteins, carbohydrates, etc. [76]. Hence, it plays a crucial role in preventing various diseases (Parkinson's disease, Alzheimer's disease, cardiovascular diseases, etc.) [77]; it also has potent anti-carcinogenic [78] and anti-inflammatory properties [77].

Phenolic acids are the most common phenolic compounds in cereal grains [79] and are mostly concentrated in the outer layers of cereal grain [80, 81]. Apart from their nutritional properties, phenolic compounds also affect the bread-making quality [82]; and contribute in imparting them the qualities such as color, aroma, and taste [83]. The content of phenolic compounds also provide structural strength to the cell wall and, hence, it influences the grain hardness, one of the important processing traits in wheat, to some extent [84, 85].

Also, various research works have revealed the nutritional and therapeutic aspects of phenolic compounds. Still, a lot of study is required to know more about the effect of phenolic compounds on the processivity of food products. To improve the processing and nutritive value of end-use food products of wheat, it is essential to have detailed knowledge of the genome-wide distribution and allelic variants of genes and their regulators. However, no such work has been conducted in wheat, which can lead to the improvised processing quality of the end-use wheat food products.

Conclusion

Wheat grains are loaded with phenolic compounds having potential health benefits, but one can fully utilise its nutritional properties only if whole-wheat products are consumed. Phenolic acids and flavonoids are among the most abundant phenolic compounds in wheat grains, that too present in its outer layers. They are potent antioxidants, which exists in both free and bound forms in the grains. Still, as the most phenolic compounds are found in bound form with biomolecules like carbohydrates, proteins, and lipids in the grains' cell wall, they can endure gastrointestinal digestion, reach the colon as a whole and offer an antioxidant environment. Concerning the total phenolic content, the relatively high variations among genotypes within species offer a base for those interested in exploiting or enhancing various Indian wheat varieties to increase nutritional value and improve the processing qualities of end-use food products.

Declarations

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