REVIEW ARTICLE

Ancient Wheat as Promising Nutraceuticals for the Prevention of Chronic and Degenerative Diseases

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Abstract: In the context of a balanced diet, wheat, mainly used as whole grains, is a good source of nutrients, including fibers and bioactive compounds. Cereals belong to the Poaceae family and are crucial for maintaining a healthy status, granted by their nutritional and chemical properties. Recent studies have demonstrated that the intake of whole grains and grain-based products may reduce the risk of oxidative stress, thus lowering chronic and age-related disorders, such as obesity, cardiovascular diseases, type II diabetes and cancer. Indeed, several studies report that regular whole grain consumption is associated with lower levels of total and LDL-cholesterol, triglycerides, fasting glucose, blood pressure and body mass index. Moreover, ancient wheat species have become increasingly interested in human health, containing several nutraceutical compounds, such as vitamins and minerals. The numerous phytochemicals present in ancient wheat (polyphenols, carotenoids, phytosterols and phenolic compounds) provide, in fact, antioxidant properties, which are essential in the prevention of various chronic and degenerative diseases. This review aims to report information on ancient wheat species, discussing their composition and nutraceutical properties compared with modern varieties and highlighting the beneficial impact on human health.

Keywords: Wheat, ancient wheat, cereals, whole grain, nutraceuticals, ferulic acid, carotenoids, antioxidants, human health.

1. INTRODUCTION

Wheat is a major cultivated and used staple crop in human nutrition [1]. "Ancient" wheat species (einkorn, emmer, spelled and Khorasan wheat, Fig. **1**) have been cultivated since olden times, but nowadays, they grow only in small areas, and most are hybrids derived from ancient wheat over the last 100-150 years. These "modern" wheat varieties have shown favorable yields compared to the original ancient wheat, but some concerns about their nutritional value have risen. More recently, a renewed idea on the ancient varieties for producing high-value foodstuffs with increased health benefits [2] used for healthy and balanced diets, such as the Mediterranean [3, 4], has been pursued. Indeed, ancient wheat is considered a healthier dietary cereal, thus recommended for preventing/treating metabolic diseases, such as dyslipidemia, but also for other diseases, including colitis and allergies [5]. Moreover, its favorable effects on insulin resistance have been recognized. The mechanisms related to the protecting effects on human health seem to be connected to the physical properties and structure of the grains, such as the granular size of semolina, together with the quantity and quality of phytochemicals, fibers, amylose and amylopectin contents [6].

Ancient cereals are considered forms that did not undergo any modern cultivation or selection, sometimes maintaining features of wild ancestors, including variability, height, fragile rachis, low crop harvest index and hulled kernels, especially in some taxa [8]. Ancient wheat contains higher amounts of phytochemicals, including polyphenols, carotenoids, phytosterols

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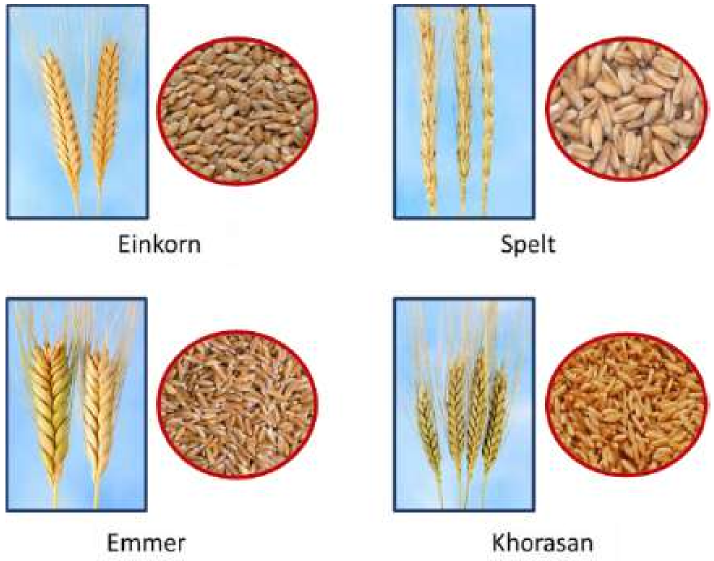


Fig. (1). Ancient wheat species: Einkorn, Spelt, Emmer and Khorasan [image modified from ref 7]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

and phenolic compounds [9] and vitamin E, steryl ferulates, organic acids, amines, lipids, carbohydrates and glycosides are present [10]. These secondary metabolites have shown biological activities [11], including antioxidants [12]. The polyphenols in whole grains are mainly represented by phenolic acids (PAs), flavonoids, and lignans. In humans, the polyphenols may enhance the immune defenses, decrease the incidence of chronic diseases, and possess several activities, including antiallergic, antiatherosclerosis, antibacterial, anti-inflammation, antioxidation, anticancer and antithrombotic, and also protect heart and blood vessels [13, 14]. The increased antioxidant activity exerted by polyphenols in the body is due to the synergistic effect of numerous bioactive compounds rather than a single active compound [15]. For instance, alkylresorcinols represent some of the main polyphenols in whole grain wheat and the HEALTHGRAIN (Exploiting Bioactivity of European Cereal Grains for Improved Nutrition and Health Benefits) study found increased alkylresorcinol contents in small-seeded ancient wheat (einkorn, emmer, and spelt) than in large-seeded modern wheat (durum and bread wheat) [16]. Recently, there were substantial differences between ancient and modern wheat polyphenol extracts regarding PA content and antioxidant activities. Durum and old soft varieties often provided higher amounts of polyphenols than the modern ones, and PAs gained from old soft varieties showed superior antioxidant actions [17]. Finally, it is noteworthy that the revival of the cultivation and use of ancient wheat in crises, including the actual COVID-19 pandemic [18], could be crucial in safeguarding the right to access to healthy and sustainable food [19]. This review aims to highlight the importance of ancient wheat in human health and the countless biological properties that support its use as a nutraceutical for humans.

2. NUTRACEUTICALS IN ANCIENT WHEAT SPECIES

Several nutrients, fiber and bioactive compounds have been found in dietary wheat, especially whole--grain. Regular consumption has undoubtedly been associated with reducing risk factors for chronic diseases, such as cardiovascular diseases, cancer and many more [20]. The molecular bases of the wheat's protective effects on human health depend on the structure and physical and chemical properties of grains, for instance, the size of granules, type of fiber, and presence of different phytochemicals [21]. Particularly, ancient wheat has been demonstrated to possess a better nutritional profile than modern wheat in terms of vitamins, minerals and nutraceuticals, and the sustainability of its cultivation is a very valuable and topical feature [22, 23].

The most common ancient wheat species commercially available are einkorn (*Triticum monococcum*), emmer (*Triticum dicoccum*), Khorasan (*Triticum turgidum* subsp. *turanicum*) and spelt (*Triticum spelta*) [24]. In addition, some historical cultivars of common wheat (*Triticum aestivum*) and durum wheat (*Triticum durum* Desf) that have been maintained unchanged over the years are Russello, Senatore Cappelli, Timilia or Tumminia, and Urria (*T. durum*), as well as Majorca, Sieve, Solina, Verna and Carosella (*T. aestivum*) [6, 19]. The latter is a typical variety from Southern Italy, especially Cilento and around Calabria and Basilicata regions [25]. KAMUT® Khorasan wheat is a particular variety of ancient grains (*Triticum turgidum* ssp. *turanicum*, commonly called Khorasan wheat). KAMUT® is a registered trademark of Kamut International, Ltd. (Big Sandy, MT) and Kamut Enterprises of Europe (Oudenaarde, Belgium), bvba. The trade name warrants specific characteristics, especially a protein content of 12-18%, a selenium content of 400-1000 ppb, and other quality standards connected to growing conditions and, for this reason, it is often used for comparison among studies [22]. The wheat total protein content (accounting for 10-15% of grain dry weight) and composition are key determinants of texture, nutritional and technological quality traits in wheat [26] and is determined by the genotype, the environment, and the interaction between these factors [27]. Wheat proteins are generally divided into gluten and non-gluten proteins, the first, gliadins and glutenin, represent about 80% of the total proteins, and the second are water-soluble proteins, mainly composed of albumins/-globulins [28]. It has been suggested that ancient wheat species, including spelt, emmer, einkorn and Khorasan, contain proteins more easily digested and induce fewer adverse responses than modern ones [29]. A new class of wheat proteins has recently been discovered, called avenin-like proteins (ALPs), which help to give the dough higher quality and possess antifungal activity, and previous studies showed that they are present in the albumin/globulin fractions of the wheat flour. Interestingly, Zhang *et al.* [30] isolated and characterized 13 homologs of ALPs in this fraction.

The carotenoids are among the major components of ancient wheat; lutein is highly represented, whereas β-carotene is present in small amounts. In addition to carotenoids, wheat constitutes an important dietary source of vitamin E, consisting of four tocopherol and tocotrienol homologues (α- β-, γ-, and σ-), also known as tocochromanols. These compounds are considered potent antioxidants and contribute to protecting proteins and lipids, therefore crucial for human health. Another significant class of antioxidants in wheat are the steryl ferulates, esters of phytosterols with ferulic acid, representing about 10% of the total sterols and possessing antioxidant properties because of the phenolic structures. Moreover, the cleavage of ester bonds during digestion may lead to the release of phytosterols that likely exert a cholesterol-lowering effect [31]. Phenolic compounds may be found, as well, as glycosides coupled with different sugars, organic acids, amines, lipids and carbohydrates, indeed the PAs in whole grains are hydroxybenzoic acids and hydroxycinnamic acids, bearing the C1-C6 and C3-C6 skeletons, respectively [32, 33]. The HEALTHGRAIN project, a major study carried out in the same laboratories and ancient and modern wheat using the same evaluation methodology, is an Integrated Project of the European Union's Sixth Framework Programme's "Food Quality and Safety" activity. Table **1** reports the content of phytochemicals in ancient and modern wheat cultivars obtained from the HEALTHGRAIN study [34]. And it is noticeable that ancient wheat contains higher amounts of folate (especially in emmer), phytosterols and alkylresorcinols than modern ones. Particularly, the emmer contains the highest amount of PAs and ferulic acid, whereas the einkorn and spelt present the highest content of phytosterols and alkylresorcinols, respectively. On the other hand, α-tocopherol and fiber content were higher in modern wheat than in ancient ones, even though the information on this subject is still contradictory [35].

2.1. Minerals, Carbohydrates and Fibers

Wheat is also a wealthy source of minerals of nutritional value; indeed, the crude ash and total protein are present in higher amounts in einkorn and emmer than in modern wheat, which indicates a higher capability of ancient wheat to gather minerals [36]. The concentration of macro- and micro-elements in the grain is mainly due to genetic factors. Moreover, the wheat cultivars are classified based on the grain quality, starting from elite—E, which presents a good cooking value and ending in fodder—C, which is not suitable for baking, and are employed for animal farming [37]. Table **2** shows the data connected to the branded whole wheat flour products from the Food Composition Databases of the U.S. Dept. of Agriculture (USDA) reported by Boukid *et al.* (2018) [38], where the differences or/and similarities between the modern wheat (durum and common) and the ancient ones are indicated. The carbohydrate content in durum and common modern wheat is slightly higher than that in ancient wheat. The spelt provided the lowest carbohydrate and fiber content (about 68 and 5.9%, respectively), followed by the einkorn (about 67 and 6.7%, respectively) than common wheat (75 and 12.7%, respectively) [38]. Conversely, Ranhotra *et al.* (1996) [39] assessed that spelt is a valid source of fibers (11.4%). Finally, differences were also found in the mineral and vitamin content between most ancient grains compared to whole flour.

Table 1. Contents of phytochemicals in ancient and modern wheat cultivars (data obtained from the HEALTHGRAIN study) [34].

Component	Total PAs (μg/g)	Folate (μg/g)	Phytosterols (μg/g)	Alkylresorcinols (μg/g)	Total Tocols (μg/g)	Ferulic Acid (μg/g)	α-tocopherol (μg/g)
Einkorn	615 (449-816)	0.58 (0.43-0.68)	1054 (976-1187)	595 (545-654)	57.0 (42.7-70.2)	298 (207-442)	9.1 (7.0-12.1)
Emmer	779 (508-1161)	0.69 (0.52-0.94)	857 (796-937)	581 (531-714)	36.4 (29.0-57.5)	476 (323-711)	7.7 (6.4-8.6)
Spelt	579 (382-726)	0.58 (0.50-0.65)	928 (893-963)	605 (490-741)	46.2 (40.2-50.6)	365 (223-502)	11.0 (9.9-12.5)
Modern	657 (326-1171)	0.56 (0.32-0.77)	844 (241-677)	432 (421-677)	49.8 (27.6-79.7)	396 (181-742)	13.5 (9.1-19.9)

Table 2. Nutritional composition of ancient wheat, durum wheat and common wheat (whole flour) [38].

Nutritional Composition	Einkorn	Emmer	Spelt	Durum	Common
Energy (kcal/100 g)	333	362	324	339	340
Carbohydrate (g/100 g)	67	72	68	71	75
Protein (g/100 g)	13.3	12.8	14.7	13.7	10.7
Fiber (g/100 g)	6.7	10.6	5.9	11.6	12.7
Lipid (g/100 g)	1.7	2.1	2.9	2.5	2
	-	-	-	-	-
Minerals (mg/100 g)	-	-	-	-	-
Calcium	Nd	Nd	17.6	34	34
Iron	3.6	1.5	3.1	3.2	5.4
Magnesium	200	128	Nd	144	90
Phosphorus	Nd	Nd	Nd	508	402
Potassium	Nd	Nd	Nd	431	435
Sodium	Nd	Nd	Nd	2	2
Zinc	15	4.8	Nd	4.2	3.5
	-	-	-	-	-
Vitamins (μg/100 g)	-	-	-	-	-
Vitamin A	Nd	Nd	Nd	0	0
Vitamin B6	0.4	Nd	Nd	0.42	0.38
Vitamin C	Nd	Nd	Nd	0	0
Vitamin E	Nd	Nd	Nd	0	1.01

Nd = not determined

A recent interesting paper by Biel *et al.* [40] on the mineral content of grains of *Triticum* spp. showed a substantial difference in the content of macro- and micro-elements in the grains of the analysed wheat species, as reported in Table **3**. Coefficients of variation (CVs) for calcium, phosphorus, magnesium, and potassium were 9.70%, 5.56%, 3.65%, and 3.00%, respectively, as determined by Tukey's honestly significant difference test (Tukey's HSD). The results indicated a higher difference in calcium amount with respect to the other macroelements, and the highest concentration was shown by phosphorus in common wheat, followed by potassium and magnesium, and then calcium. The descending order K > P > Mg > Ca was found in all the wheat species examined. Except for calcium, the levels of essential elements (P, Mg and K) were greater than the recommended daily allowance (RDA) for macronutrients. The richest species in magnesium among the analysed wheat were represented by the einkorn grain, in which the average magnesium concentration was 61% higher than the RDA. The concentration of phosphorus and potassium was several times higher than the RDA in all the grains tested. In Table **3**, the concentrations of micronutrients are reported [40], and it is

Table 3. Elements' content (mg/kg) in grains of *Triticum* spp [40].

Macroelements				
	Ca	**P**	**Mg**	**K**
Common wheat (*T. aestivum*)	0.11±0.02	5.16±0.13	1.04±0.07	4.74±0.10
Spelt wheat (*T. spelta*)	0.10±0.02	3.71±0.10	1.25±0.07	5.49±0.11
Emmer wheat (*T. dicoccum*)	0.15±0.02	4.73±0.12	1.34±0.07	5.84±0.11
Einkorn wheat (*T. monococcum*)	0.17±0.02	4.74±0.12	1.74±0.08	6.45±0.12
Tukey's test (HSD)	0.024	0.414	0.0831	0.248
Standard error	0.006	0.105	0.0209	0.0689
CV (%)	9.70	5.56	3.65	3.00
	-	-	-	-
Microelements	-	-	-	-
	Fe	**Zn**	**Mn**	**Cu**
Common wheat (*T. aestivum*)	60.8±4.25	28.8±1.28	44.8±1.01	2.345±0.10
Spelt wheat (*T. spelta*)	94.7±5.91	21.9±1.19	62.2±1.39	0.706±0.08
Emmer wheat (*T. dicoccum*)	77.6±5.18	17.8±1.08	47.1±1.15	0.662±0.08
Einkorn wheat (*T. monococcum*)	58.8±3.86	17.8±1.08	32.9±0.92	1.401±0.09
Tukey's test (HSD)	4.02	1.55	2.09	0.155
Standard error	1.10	0.389	0.525	0.0389
CV (%)	3.11	4.42	2.66	7.45

visible that they vary significantly in the grains of the analysed wheat species. The descending order was found to be Fe > Mn > Zn > Cu, with the iron showing the highest concentration in the spelt, followed by the emmer, common and einkorn wheat, and the copper is the lowest in the emmer wheat. It must be emphasized that an insufficient calcium-magnesium ratio (Ca/Mg) is correlated with the risk of inflammatory, metabolic, and cardiovascular diseases, whereas a higher concentration of calcium may lead to a significant reduction of magnesium absorption. The recommended Ca/Mg may be close to 2; for the analysed wheat grains, this ratio was close to 0.1.

2.2. Phenolic Acids (PAs)

PAs represent the main group of nutraceuticals in wheat grain. They bear a phenolic moiety and an organic carboxylic function and are divided into two groups, deriving from cinnamic or benzoic acids. PAs may be found as free compounds or soluble conjugates linked to low molecular weight compounds, such as sugars, or by ester bonds to cell wall polysaccharides [41]. PAs are primarily concentrated in the outside of kernels and contribute to the total antioxidant capacity of cereal grain, and they also exert antimutagenic activity against toxic substances, such as nitrosamine and mycotoxins, in the environment [42]. Significant differences between species, varieties, and grain fractions have been found in the composition of phenolic compounds, as the HEALTHGRAIN study shows that PA content is usually greater in ancient wheat varieties, such as emmer and einkorn, than in modern ones [43].

In work by Truzzi *et al.* (2020) [17], old, soft and durum varieties of wheat were demonstrated to contain higher amounts of polyphenols than the modern ones; moreover, PAs obtained from old soft species had higher antioxidant potential, as determined by 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) and ferric ion reducing power (FRAP) analyses. All the PAs derived from ancient or modern varieties were shown to induce migration of fibroblasts, as observed from a wound-healing assay, with a higher efficacy found in the Verna variety that induced the cells migration only after 4 h from the treatments.

The ferulic acid (FA, $C_{10}H_{10}O_4$, 4-hydroxy-3-methoxycinnamic acid, Fig. **2**) is the major free PA in cereal grain, whereas the *p*-coumaric acid and vanillic acid are present in lower amounts and very small amounts of the caffeic, *p*-hydroxybenzoic, and sinapic acids (0.5-1.5 μg g^{-1}) may also be found [44]. FA is a structural element of cell wall polysaccharides, and the highest concentration is found in the outer layer of cereal grains, whereas the lowest one was ascertained in the endosperm layer. The amount of free FA in grains is 0.1-0.5%, most of which is bound to polysaccharides and sterols [45].

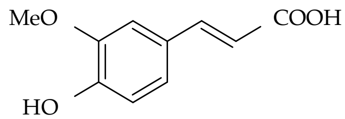


Fig. (2). Chemical structure of ferulic acid.

Several animal tests suggested that the FA has neuroprotective, antioxidant, antidiabetic, hepatoprotective, anti-atherosclerotic, anticarcinogenic and antibacterial activities. These properties may derive from its reducing capacity, balancing unpaired electrons (removing free radicals), chelating metals, and a role in interrupting other oxidative reactions. Its use in cosmetics, food and pharmaceutical industries is related to the lack of known side effects [46]. Studies conducted by Balasubashini *et al.* (2004) [47] showed that the FA increases the antioxidant activity of streptozotocin-induced diabetic rats by neutralizing free radicals and could be potentially helpful in diabetic patients. The supplementation of the FA determined a decrease in glucose levels, thiobarbituric acid reactive substances (TBARS), hydroperoxides and free fatty acids and enhanced the level of reduced glutathione (GSH) in the liver of tested animals. Moreover, an increase in superoxide dismutase (SOD) activity, catalase, glutathione peroxidase, and pancreatic islet increase was observed. Results also showed that the antioxidant effect was more pronounced using low doses of the FA (10 mg/kg) than high doses (40 mg/kg). This strange finding seems to be related to the capacity of the FA to increase islet cell mass which was better with the low dose. Other studies carried out on diabetic rats demonstrated that the FA might inhibit lipid peroxidation in brown adipose tissue, regenerate pancreatic beta cells and lower diabetic nephropathy *via* the reduction of oxidative stress and inflammation [48-50]. Moreover, Elhessy *et al.* (2020) [51] studied the potential protective effect exerted by the FA on oxidative stress and against several nitric oxide synthase isoforms (NOS) in the cerebellum of streptozotocin-induced diabetic rats. The authors showed that the FA strengthens the cerebellar function and histopathological changes caused by diabetes and has been suggested as an efficacious natural hepatoprotective agent. Ahmadipour *et al.* (2021) investigated the properties of the FA against the hepatotoxicity induced by isoniazid in Wistar rats. The authors showed that the administration of the FA enhanced the activity of antioxidant enzymes and subsequently reduced lipid peroxidation in the liver [52]. Alam (2019) reported that foods rich in FA might play a role in the prevention of hypertension, indeed behaving as an effective scavenger of free radicals (ROS, reactive oxygen species), the FA reduces oxidative stress, enhances the endothelial function and increases the bioavailability of the nitric oxide in the vascular system responsible, inducing a lowering of the blood-pressure [53]. The proven ability of FA as a ROS scavenger, stimulator of cytoprotective enzymes, regulator of cell proliferation and growth and inhibitor of the cytotoxic systems both *in vitro* and *in vivo* supports the idea of a potential positive role of FA for the treatment of cancer [54], as reported by Baskaran *et al.* (2010) r. Indeed, breast carcinogenesis in Sprague-Dawley rats induced by 7,12-dimethylbenz[a]anthracene (DMBA) is prevented by the oral administration of FA (40 mg dose/kg body weight) in 80% of the studied rats [55]. In addition to these properties, the FA also exhibits antimicrobial activity against both Gram-negative and Gram-positive bacteria and yeasts [56], being an inhibitor of the growth of many pathogens, such as *Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Citrobacter koseri, Pseudomonas aeruginosa, Helicobacter pylori*, and *Shigella sonnei*. Furthermore, amongst PAs, the FA is the most potent antifungal agent against *Sclerotinia sclerotiorum, Fusarium oxysporum, Alternia* sp., *Botrytis cinerea,* and *Penicillium* spp [57]. Finally, several studies report the higher activity of FA in synergism with other PAs; for instance, Cai *et al.* (2012) [58] showed a synergistic effect, especially at high concentrations, of ferulic, *p*-coumaric and caffeic acids on the inhibition of pancreatic lipase, thus suggesting that this association could be a potential therapy for the treatment of obesity. Moreover, a previous study by Yeh *et al.* (2004) [59] investigated the synergistic effect of *p*-hydroxybenzoic, gentisic, ferulic, gallic, and coumaric acids on the phenolsulfotransferases (PSTs), which are important enzymes in the detoxification process of xenobiotics and endogenous compounds and which activities were promoted by all of these combinations of PAs.

2.3. Carotenoids

Wheat is also an important source of carotenoids, which is lower than in fruit and vegetables, but in some populations, even the small increase in carotenoid concentration obtained by the daily consumption of wheat-based products can have a great impact [60]. The carotenoid concentrations significantly differ among cereal species and/or varieties, and small-grain cereals are largely accumulated in germ [61] that contain about 5.5 mg carotenoids/kg [56]. Carotenoids may exist in two main forms: xanthophylls containing oxygen (lutein, β-cryptoxanthin and zeaxanthin, Fig. **3**) and carotenes not containing oxygen (α-carotene and β-carotene). In mammals, β-carotene is converted into vitamin A (retinol); thus, it is also called provitamin A.

The major carotenoid in all wheat varieties is lutein, the major yellow-colored pigment and the higher amounts are found in the einkorn, emmer and durum wheat. The higher content of lutein in ancient wheat varieties could be an essential factor in promoting human health [61].

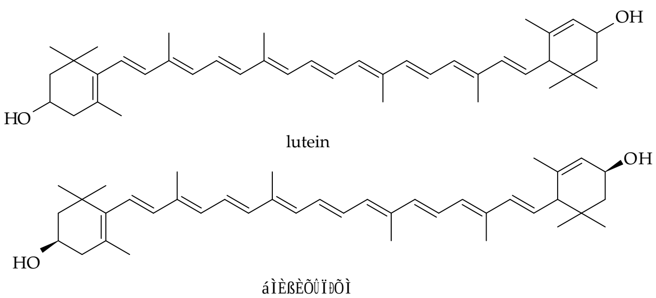


Fig. (3). Chemical structure of lutein and zeaxanthine.

Lutein has several beneficial effects, such as the reduced risk of chronic disease and improved visual function, cognitive function and some cardiovascular and other degenerative diseases [62]. Lutein is the major carotenoid in the endosperm of Triticeae species, such as common wheat (*T. aestivum* L.), durum wheat (*Triticum durum* L.), tritordeum, barley *(Hordeum vulgare* L.) and wild barley (*Hordeum chilense* Roem. and Schult.), even though there are variations in the content and in the ability to produce lutein esters. Indeed, the diploid and hexaploid wheat may synthesize lutein esters, whereas the tetraploid ones cannot produce them. Furthermore, diversity in the same species has also been described in a study of 138 common wheat genotypes, where most of them presented lutein esters in their carotenoid profile, whereas only nine were described as zero-ester genotypes. Carotenoid esters were found in other Triticeae species, such as tritordeum, cultivated and wild barley, spelt (*T. spelta* L.), and einkorn (*T. monococcum* L.) [63]. The carotenoid content in the latter ancient wheat species had previously been demonstrated to be almost 4-fold higher than that in other varieties [64, 65]. Ziegler *et al.* (2015) [66] determined the concentrations of lutein and lutein esters in a collection of 75 wheat genotypes, including old wheat species such as spelt, emmer, and einkorn, grown in diverse environments. The highest total quantities of lutein were found in the einkorn genotypes (4.5-7.8 µg/g dry matter), followed by durum (2.0-4.6 µg/g), spelt (0.9-2.0 µg/g), emmer (0.8-1.9 µg/g), and bread wheat (0.7-2.0 µg/g), suggesting the ancient specie einkorn as a valuable source of lutein in the human diet [66]. The chemical structure of lutein is related to its role in maintaining retinal function and preventing eye diseases. The two hydroxyl moieties enhance the polarity and hydrophilicity if compared to other carotenoids, making them more reactive with oxygen in the serum and acting as ROS scavengers, such as superoxide anion (O_2^{-}), perhydroxyl radical ($HO_2\cdot$), and hydroxyl radical ($OH\cdot$) [67]. Lutein and its isomer zeaxanthin (Fig. **3**) represent 66-77% of the total carotenoids in the brain and in the eyes, where they play an essential role in cognition and are crucial for the neurological connection between the macula and the brain, improve the gap junctional communication needed for light processing and visual system in the retina, increasing the visual processing speed and a reduce the scotopic noise. Lutein may also play a role in reversing diabetic renal injury and inflammation because of its antiapoptotic and free radical scavenging properties [68]. Lutein determines a decrease of serum and urine kidney function tests (urea and creatinine), thus improving diabetes-associated renal damage, reducing the kidney inflammatory responses significantly lowering the tumor necrosis factor-α (TNF-α), interleukins IL-1, and IL-6 levels and enhancing the cytokine IL-10 levels. Supplementation of lutein at high doses seems to attenuate glomerular and tubular diabetes-induced damage by decreasing oxidative and nitrosative stress in renal tissue. The lutein anticancer activity seems to be related to the interaction with the mutagens such as 1-nitro pyrene and aflatoxin B1 and the regulation of specific genes involved in T--cell transformations [68]. Finally, a recent review examined the positive effects of lutein supplementation in pregnant and breastfeeding women, reducing the risk of pregnancy diseases and preterm birth that may derive from enhanced oxidative stress. Besides, carotenoids are among the few nutrients in breast milk, and their content relies upon the mother's dietary intake. Lutein and zeaxanthine are essential in developing the retina and brain in newborns. Accordingly, lutein and zeaxanthin intake in pregnant and breast--feeding women seems to be crucial in preventing disorders affecting preterm infants who are sensitive to oxidative stress, especially retinopathy of prematurity [69].

2.4. Alkyresorcinols

The alkylresorcinols are another class of potent antioxidant polyphenols present in whole grain wheat products (ARs, Fig. **4**, Alk = alkyl). In cereals, they may be found only in the intermediate outer layer of the kernels and only in small amounts in refined flours. *in vitro* studies suggested the anti-mutagenic properties of ARs, as well as the prevention of colon cancer and the anti-inflammatory activities. Moreover, the antifungal activity of ARs against plant pathogenic fungi has been shown [22].

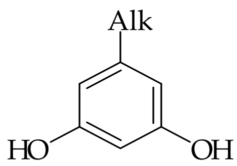


Fig. (4). The basic structure of alkylresorcinols (ARs).

The HEALTHGRAIN study demonstrated higher alkylresorcinol contents in small-seeded ancient wheat (einkorn, emmer, and spelt) than in large-seeded modern wheat (durum and bread wheat) [15]. Andersson *et al.* (2008) reported ARs mean values of 581, 595, and 605 µg g^{-1} in the dry matter of the emmer, einkorn, and spelt, respectively (*versus* 432 µg g^{-1} for the modern wheat, see Table **1**) [43]. Cereal ARs are 1,3-dihydroxy-5-alkyl-benzenes bearing a long alkyl chain usually between 17 and 25 carbon atoms (Fig. **4**), and the polar dihydroxyphenyl ring and the hydrophobic alkyl chain give amphiphilic properties to ARs so that they can fit themselves at the interface water/oil, a characteristic that is fundamental for their bioactivity. ARs are named based on the length of the alkyl chain, as for fatty acids, and, for instance, an AR with a 17-carbon long alkyl chain (heptadecyl resorcinol) is referred to as C17:0 or AR17:0 [70]. The composition of ARs differs among cereals; the amounts of the two homologues C17:0 and C21:0 are similar in the rye (C17:0/C21:0 ~ 1.0), whereas the ratio is ~0.1 in the common and spelt wheat, ~0.04 in the einkorn and emmer wheat and in the durum wheat the amount of C21:0 is about 100-fold higher than the amount of C17:0 [71]. Differences in chain length in the structure of ARs, *i.e.,* the presence of unsaturations and keto groups, play an important role in their activity, and their anti-inflammatory, antioxidant and antitumor properties have attracted scientific interest. In a recent study, Liu *et al.* (2018) [72] reported the anti-inflammatory activity of ARs from 21 different wheat varieties, which molecular mechanisms may derive from the suppression of the NF-κB p65 nuclear translocation and inhibition of the κB (IκBα) kinase and JNK phosphorylation. In male mice, wheat ARs suppress the high-fat, high-sucrose diet-induced obesity and glucose intolerance by increasing insulin sensitivity and cholesterol excretion [73]. Moreover, Wang *et al.* (2019) investigated the protective effect of wheat ARs on human retinal pigment epithelium cells (ARPE-19) against H_2O_2-induced oxidative damage. The results suggest that ARs treatment activates the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling and enhances the transcription of antioxidant-responsive genes (GCL, NQO1 and HO-1) [74]. A later study by Fan *et al.* (2020) investigated the connection between the neuroprotective effect of wheat bran ARs and the Nrf2/antioxidant-response element (ARE) pathway. The neuroprotection effect seemed driven by the increase of the Nrf2 nuclear location and the up-regulation of mRNA and protein expressions of heme oxygenase-1, NAD(P)H quinone dehydrogenase 1, glutamate-cysteine ligase catalytic subunit, and glutamate-cysteine ligase modifier subunit l [75]. Fu *et al.* (2018) suggested that ARs can inhibit the growth of human colon cancer cells, probably by inducing apoptosis and cell-cycle arrest *via* activation of the p53 pathways [76]. Nowadays, by-products and waste originating from agro--food processes are considered an important source of bioactive molecules [77, 78], and in a recent study, intact kernels of durum and einkorn wheat, submitted to three different thermal pre-treatments (hydrothermal, hot air-drying at three different temperatures and freeze drying), were studied to investigate the effects on the recovery and composition of ARs, the total soluble phenolic (TSP) compounds and antioxidant capacity (TAC). Thermal processing generally seems to enhance the possibility of extraction of ARs but causes changes in ARs homologue chain compositions; a lowering in TSP content was shown in both wheat species, while the treatments did not change TAC. Thus, the authors suggested that other antioxidant compounds might probably contribute to wheat's TAC [79].

2.5. Steryl ferulates

Steryl ferulates (SFs) are esters of ferulic acid and phytosterol present in wheat bran (Fig. **5**) [80]. Nurmi *et al.* (2008) [81] investigated the contents of phytosterol in 130 winter wheat, 20 spring wheat, 10 durum wheat, 5 spelt, 5 einkorn, and 5 emmer wheat genotypes, grown in the same place and year. The highest sterol contents were found in the spelt, durum wheat, and einkorn wheat and the total phytosterol contents of the durum, spelt, einkorn, and emmer wheat genotypes were 871–1106, 893–963, 976–1187 and 796–937 µg/g, respectively. Approximately 10% of the total phytosterols in wheat occur as SFs, which possess several health benefits, such as lowering cholesterol, inhibiting melanogenesis, and exhibiting anti-inflammatory and antioxidant activities [82]. Up to now, at least 21 different SFs, only differing for the type of sterol moiety, have been identified [83], and the total content and composition of individual SFs depend on the genotype, the grain source, and environmental factors. The SFs prevent oxidation in various biological systems and seem to be related to the presence of 4-desmethylsteryl ferulates, which may be found in wheat bran.

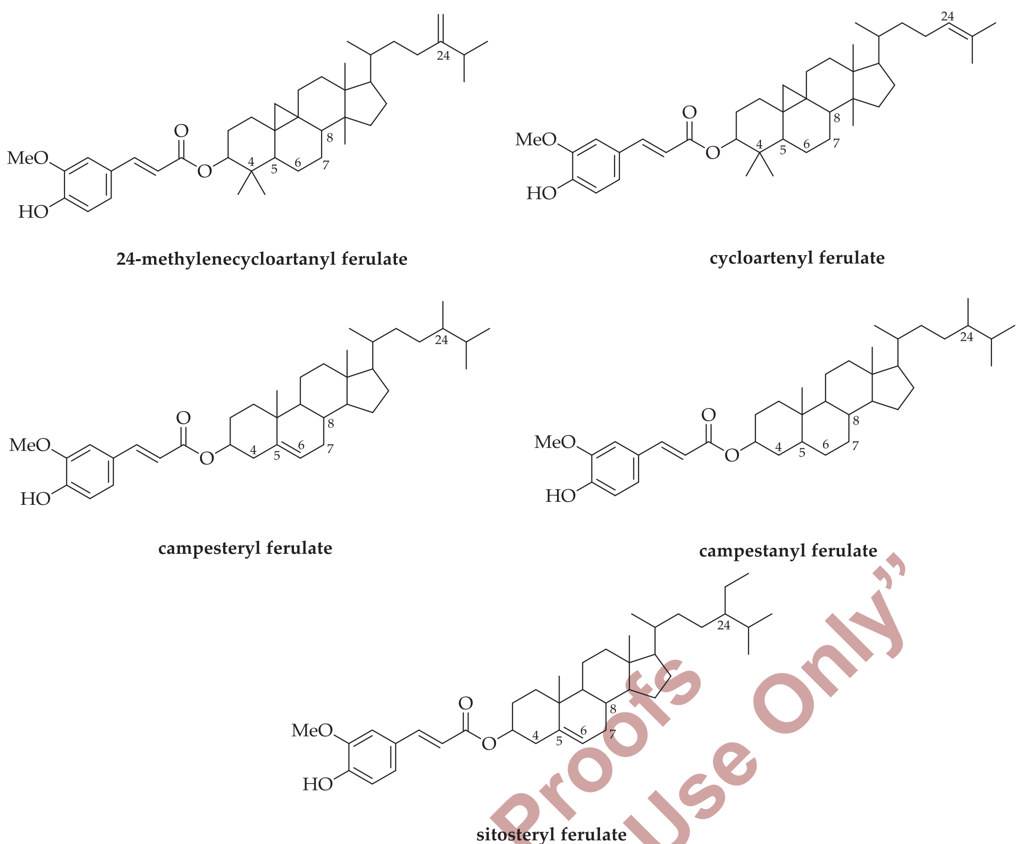


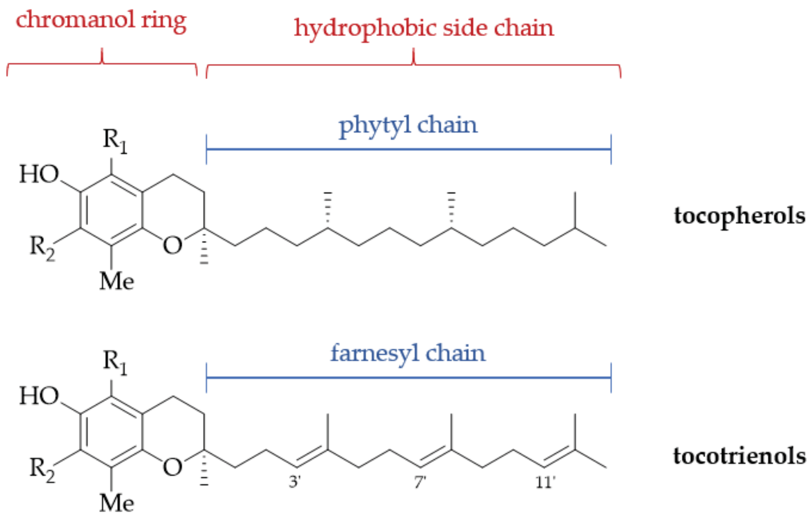
Fig. (5). Chemical structures of the most relevant steryl ferulates.

The mechanism of the antioxidant activity is due to the presence of the phenolic moiety in the ferulic acid group, which can withdraw radicals and the resonance obtained by the π-electron system of the aromatic ring and the carboxylate group stabilizes the resulting SF radical [80].

2.6. Vitamin E

Wheat grains are also a wealthy source of the vitamin E [84, 85], a group of eight fat-soluble vitamins consisting of four tocopherols, bearing a phytyl side chain, and four tocotrienols, bearing a side chain with double bonds at positions 3',7', and 11' carbon atoms, *i.e.,* a farnesyl chain (Fig. **6**). These groups have four isomers (each with α- β-, γ-, and δ-isomers), commonly known as tocochromanols [86], which may be incorporated into the amphipathic phospholipid bilayer of cell membranes and protect membrane lipids and organs in plants from oxidative stress. All the isoforms of vitamin E are biologically active, but only α-tocopherol is present at higher levels in tissues and plasma [87]. The tocochromanol contents in ancient and modern wheat species are often compared.

Particularly, Lampi *et al.* (2008) [88] found that, amongst the *Triticum* spp., the highest amount of tocochromanols was found in the einkorn (42.7-70.2 μg/g, on average = 57) followed by durum wheat (40.1-62.7 μg/g, on average = 48.1). In another study by Hidalgo *et al.* (2006) [89], it was reported that tocol concentrations in ancient wheat, particularly the einkorn (61.80-115.85 μg/g), emmer (62.7-67.9 μg/g), and spelt (62.7-67.5 μg/g) were slightly higher than those found in the durum (38.8-57.27 μg/g) and common (53.2-74.9 μg/g) wheat. In 2010, a work by the same research group [90] reported the stability of tocols from the einkorn and modern wheat during the production of bread, pasta and water biscuits, indicating that the einkorn contained more tocols than the durum and modern wheat [91]. The effects of vitamin E on human health are related to both antioxidant and non-antioxidant properties, and besides, antiproliferative, antiangiogenic, pro-apoptotic and anti-inflammatory activities have been also demonstrated [92, 93].



Tocopherols/ Tocotrienols	R_1	R_2
α-	Me	Me
β-	Me	H
γ-	H	Me
δ-	H	H

Fig. (6). Structure of tocopherols, tocotrienols and their isoforms.

3. WHEAT AND GLUTEN

Gluten is a mixture of protein stored in grains, including wheat, rye, barley and oat [94]. The main component of wheat grains is represented by starch (60-75%). However, grain proteins (9-18%) are crucial for bread-making quality. Wheat prolamins were firstly identified as gluten proteins and are usually divided into two classes, according to their solubility, the alcohol-soluble fraction, named gliadins (GLIA, mainly monomeric proteins with molecular weights around 28,000-55,000, including α-, β-, ω-, and γ-gliadins) and the insoluble fraction, named glutenins (GLUT, generally polymeric, soluble in dilute acids and bases), divided into high molecular weight glutenin subunits (HMW-GS) and low molecular weight glutenin subunits (LMW-GS) [95]. Only after reduction of the disulfide bonds does GLUT become soluble in aqueous alcohol. The complete digestion of gluten proteins is difficult due to the high content of proline and glutamine residues [96], and the presence of gluten in most cereals is the cause of gluten-related disorders (GRDs), which have gradually emerged, amongst them the main Celiac (or Coeliac) Disease (CD) [97], Non-Celiac Gluten Sensitivity (NCGS) [98] and Wheat Allergy (WA) [99]. The CD is a chronic immune-mediated enteropathy of the small intestine that evolves in genetically susceptible individuals by the exposure to gluten proteins present in cereals such as wheat, rye and barley [100]. The WA is an allergic reaction involving the immune system and mediated by immunoglobulins E (IgE), whereas the NCGS is a syndrome characterized by intestinal and extra-intestinal symptoms associated with the ingestion of gluten-containing foods in subjects who are not affected by CD or WA [101]. The wheat species highly differ in the gluten composition and GLIA/GLUT ratios, and in a recent study analysing GLIA and GLUT, it was found that the einkorn, emmer and spelt had higher protein and gluten contents than the common wheat. This is contrary to consumer expectations, who usually believe that ancient wheat has lower gluten contents [102]. However, ancient wheat's celiac antigenicity has been debated at length because different studies show different results [103]. The diploid wheat species *T. monococcum* has a less toxic and more digestible gluten content. However, it remains still inadmissible for celiacs [6]. In contrast, studies on the ancient tetraploid wheat species demonstrated that the ancient durum wheat found in Italy, such as Graziella Ra and Capelli, is toxic for CD patients [104]. Although some wheat-related ancient grains, such as the *T. monococcum*, *T. aestivum* ssp., *T. spelta* and Kamut®, have shown low *in vitro* toxicity, they are also considered toxic for CD patients [101]. It has been suggested that some varieties, with a reduced ability to activate the immune response in CD mucosa, may be useful in reducing the incidence of CD [96, 102]. Besides gluten, the amylase/trypsin inhibitors (ATIs) account for about 4% of wheat protein and are implicated in causing NCGS and worsening other inflammatory conditions. An ATI content analysis in eight cultivars of modern species (the common and durum wheat) and ancient species (the spelt, emmer and einkorn) grown in three different locations in Germany was recently carried out [105], and only a few ATIs were found in the einkorn, whereas the spelt had the greatest total ATI contents, the Emmer and common wheat had similar total ATI contents, and the durum wheat had lower ATI content.

4. ANCIENT WHEAT IN CLINICAL STUDIES

So far, there are some interesting studies carried out on human beings aimed at testing the effect of consumption of ancient wheat on diabetes, cardiovascular diseases, Nonalcoholic Fatty Liver Disease (NAFLD) [106], and gastroenteric disorders, such as Irritable Bowel Disease (IBD) [107], CD and NCGS. In these studies, the enrolled patients were asked to substitute the generally ingested grains with those selected for the study, most of which were the Khorasan (KAMUT® brand) [6]. Interestingly, a study on 21 patients with type 2 diabetes mellitus (T2DM) showed that replacing modern wheat with the Khorasan for eight weeks markedly lowered insulin and glucose levels compared to modern wheat [108]. The antioxidant and diabetes-preventive properties of the Khorasan were confirmed by a second study on 30 healthy volunteers recruited to follow a Khorasan or a modern durum wheat-based diet. After 16 weeks, the group eating the KAMUT® Khorasan food showed a high increase in serum docosahexaenoic acid (DHA) concentration, a significantly lower fasting insulin concentration and a statistically significant decrease in Fat Mass [109]. Recently, a randomized controlled study was carried out by Dell'Asta *et al.* [110] on healthy subjects, aimed at evaluating if bread made with the wheat evolutionary populations (EPs), of which one originating from historical wheat varieties, could differently affect postprandial glucose (PGG) and insulin responses, compared with a modern variety. The results, obtained after comparison of acute blood glucose and plasma insulin concentration in the postprandial phase, demonstrate a similar effect produced by consuming bread baked with the EPs and the modern variety. In another study, the effects of consumption of three heritage cultivars (Verna, Gentil Rosso, and Autonomia B) were compared to those based on a modern wheat (Blasco) and suggested that the consumption of the heritage varieties may lead to a substantial blood reduction of total cholesterol, low-density lipoprotein (LDL) cholesterol, and glucose, while these modifications were not observed in the consumption of the modern variety. Moreover, a significant enhancement in circulating endothelial progenitor cells was described after consuming products containing the ancient "Verna" variety [111]. In 2021, an interesting study compared the effect of consumption of the ancient grain Verna bread, obtained by two different fermentation agents, Sourdough (SD) and Baker's Yeast (BY), on inflammatory and cardiometabolic parameters. This study was run on 17 clinically healthy subjects who consumed the SD or BY bread for 4 weeks each. The consumption of the "Verna" bread led to a substantial decrease of the LDL cholesterol of about 10% after replacing SD and BY bread. After the administration with BY bread, a significant enhancement in fasting blood glucose (6%) was observed, whereas a 10.7% decrease in VEGF was observed after the SD bread replacement period. The consumption of the Verna bread determined an improvement in cardiometabolic and inflammatory parameters, and a significant increase in blood glucose levels was observed only after the consumption of the BY bread [112]. A previous study reports the effect of pasta consumption, produced from an old Italian durum wheat variety (Senatore Cappelli), on parameters related to atherosclerosis in 20 subjects. A diet containing 70 g/die of test pasta determined a significant improvement of total cholesterol levels concerning the placebo, and the whole blood viscosity was significantly ameliorated, as well as erythrocytes' deformability [113]. Next, some human studies evaluated the safety of ancient strains of wheat in CD. One clinical study involved eight CD patients. and confirmed the toxicity of *T. monococcum* for patients with CD from a histological and serological point of view [114]. These results were in line with the results subsequently obtained, in 2020, by Picascia *et al.* [115], who used the same ancient variety of wheat. It should be noticed that the gluten from *T. monococcum* has a low content of immunostimulatory sequences and a high gastrointestinal digestibility [93]. Table **4** summarizes some clinical trials conducted on ancient wheat cultivars, demonstrating that wheat varieties possess antioxidant and anti-inflammatory activities that benefit metabolic and clinical parameters in healthy or unhealthy subjects.

Table 4. Human intervention trials on ancient cultivars were performed on healthy or unhealthy subjects.

Inclusion Criteria	Experimental Design	No. of Subject Enrolled	Ancient/Heritage Wheat Varieties	Duration of Intervention	Recorded Effects (Ancient/Heritage vs. Control)	Refs.
Type 2 Diabetes Mellitus	Randomized, double-blind, crossover. Enrolled patients switched from ancient/heritage grain-based diet to modern grain-based diet.	24 (14 m, 7 f, mean age 64.4 ± 10.9 years)	Semi-whole grain: *T. turgidum* Khorasan	8 weeks diet	Decrease of blood total and LDL cholesterol, insulin, fasting glucose, ROS, VEGF and IL-1Ra	[108]
Healthy subjects	Randomized, non-blind, parallel arm study	30 (age ranging between 25 and 60 years)	Semi-whole grain: *T. turgidum* Khorasan	16 weeks diet	Decrease of fat mass, insulin and significant increase of DHA	[108]
Healthy subjects	Randomized controlled trial	13 (mean age 24 ± 3 years)	*T. aestivum*	7 visits of 2 h	The comparison of incremental curves, IAUC, and maximum postprandial peaks after consumption of bread formulated with EPs and control bread showed no differences among samples	[109]
Healthy subjects	Randomized, double-blinded, crossover trial. Enrolled patients switched from heritage grain-based diet to modern grain-based diet. Three diet interventions were studied: 1. Verna 2. Blasco 3. Gentil Rosso or Autonomia B	45 (32 m, 13 f, the median age 50.1 (25-75) years)	*T. aestivum*: Verna, Gentil Rosso, Autonomia B	8 weeks diet	Decrease of blood total cholesterol, LDL-cholesterol and fasting glucose	[111]
Healthy subjects	Randomised, double-blinded cross-over trial	17 (7 f, 10 m, mean age of 34.6 ± 9.1 years)	*T. aestivum; T. Verna*	4 weeks diet	Decrease of LDL-cholesterol and VEGF	[112]
Healthy subjects	Randomized, single-blinded, crossover trial. Enrolled patients switched from heritage grain-based diet to modern grain-based diet.	20 (11 m, 9 f, age: 21-61 years. Mean BMI: 26.1 ± 2.5 (m) 24.8 ± 4.9 (f))	*Semi-whole grain: T. durum; Senatore Cappelli*	10 weeks diet	Decrease of total cholesterol, whole blood viscosity and red blood cell deformability	[113]
CD patients in remission	Phase II, open-label	7 (1 m, 6 f, median age 37 ± 7.3 years)	*T. monococcum*	60 days	Increase in villous atrophy and recurrence of dermatitis herpetiformis.	[114]
CD patients	Randomized trial	17 (10 f, 7 m; median age 13, range 11-71 years)	*T. monococcum*	3 days	Reduce mobilization in the blood of gliadin-reactive T cells; reduce the number of T cells reactive to immunodominant gluten peptides	[115]

5. KAMUT® KHORASAN WHEAT

The KAMUT® khorasan wheat emerged as one of the most important grains for its specific nutritional and nutraceutical properties, such as its positive effect on circulatory blood parameters [116]. KAMUT® is a registered trademark used in marketing foodstuffs of the ancient cultivated Khorasan wheat variety called 'QK-77', registered by the USDA in 1990. The cultivation of KAMUT® khorasan wheat is managed exclusively by a license agreement, which requires certification of the crop and some quality specifications of nutritional characteristics and growing conditions [117]. The grain must descend unmodified from the original seed stock used under the KAMUT® brand; the protein content must be between 12 and 18/100 g and contain selenium between 400 and 1000 ppb, which is present in the active site of enzymes involved in cellular protection from oxidative damage, including glutathione peroxidase and other selenoproteins [118]. The selenium content in KAMUT® Khorasan bread was ten-fold higher than that found in modern durum bread [98]. The KAMUT® khorasan wheat is very versatile as a raw material because it is suitable for several consumer uses, including the production of bread, tortillas and cookies. The total phenols, flavonoids, and carotenoids associated with the antioxidant capacity were higher in the KAMUT® flakes and muesli than in the conventional products [24]. The main carotenoid was lutein (5.77 mg/g), compared with a mean of 2.06 mg/g in four common wheat cultivars [64]. Different intervention trials on the Kamut involving human volunteers have been reported in the literature; for instance, Sofi *et al.* (2013) described a study on 22 healthy subjects with two intervention phases. The participants had to consume the Kamut products (bread, pasta and crackers) or control semi-whole-grain wheat for 8 weeks randomly. People consuming the Kamut products showed a significant reduction of metabolic risk factors, such as total cholesterol, LDL cholesterol and blood glucose, and improvement in the redox status. A significant lowering in the levels of pro-inflammatory cytokines, such as TNFα (-34.6%), IL6 (-23.6%), IL12 (-28.1%) and VEGF (−10.5%), was also demonstrated [119]. In the following paper, the same research group compared the organic Kamut grown in Canada with mixtures of organic durum and bread wheat grown in Italy to determine the effects on IBS. Twenty participants with moderate IBS were divided into two groups: the first received the KAMUT® Khorasan products, and the second was supplied with the modern wheat products for 6 weeks. According to the IBS-GAI (Global Assessment of Improvement) and the IBS-SSS (Symptom Severity Scale), significant health amelioration in patients consuming the KAMUT® Khorasan products was evidenced. A simultaneous substantial reduction of IL-6, IL-17, interferon γ and VEGF (-36.2%; -23.3%; -33.6% and -23.7%, respectively) was detected after the KAMUT® Khorasan wheat intervention phase [120]. Whittaker *et al.* (2015, 2017) [121, 108] compared the organically grown Kamut with the Italian durum and bread wheat. Even in these studies, blood glucose, insulin, total cholesterol and LDL cholesterol levels were significantly reduced. Moreover, in both studies, a significant reduction in ROS production was observed. Interestingly, the first study detected reduced lipoperoxidation of circulating monocytes, lymphocytes, and TNF-α. The second study showed a significant decrease in the VEGF and interleukin 1 receptor antagonist (IL-1Ra) levels.

CONCLUSIONS

Wheat is one of the major staple food crops grown worldwide, and for about 8000 years, it has been the fundamental domesticated crop food of the main civilizations of West Asia, Europe and North Africa. To date, wheat grows on more land areas than any other commercial crop and remains the major food grain source for humans. It is worth noting that the traditional Mediterranean diet, recognized as a highly healthy dietary pattern, is characterized by a regular intake of whole grain derivates, which provide 55-60% of the total caloric intake and are placed at the bottom of the food pyramid. Most of the wheat species grown today are hybrids produced from ancient wheat. The latter contains high amounts of phytochemicals, which are secondary metabolites of plants with biological activity, and the main components are represented by polyphenols, carotenoids, phytosterols, vitamin E, steryl ferulates, phenolic compounds, such as organic acids, amines, lipids, carbohydrates and other phenols or glycosides. The grains of ancient wheat also represent a dietary source of minerals such as zinc, calcium, magnesium, and vitamin E. The content of macro- and micro-elements in the grain is mainly determined by genetics, the growing environment and the climate. Ancient wheat species are interesting for healthy food production, as several studies have suggested their role in a better nutritional profile than modern wheat. Recent studies have shown its usefulness in dyslipidemia, type 2 diabetes, dermatitis, CD, cardiovascular disease and cancer prevention. The antioxidant and anti-inflammatory activities of nutraceuticals present in an ancient wheat highlight that they are useful in ameliorating the profile of significant biomarkers in consumers, especially when cardiometabolic diseases occur. Indeed, a marked improvement of these parameters, including total and LDL cholesterol levels, was obtained after the consumption of ancient wheat concerning modern varieties. However, it is unclear if the ancient wheat is preferable to the modern one as the scientific literature is very controversial about this topic. Generally, the differences in nutraceutical content and the potential benefits of the ancient varieties are described in comparison with modern grains. Further, follow-up clinical trials are needed to confirm if the ancient wheat's positive impact on human health is greater than the modern wheat. Another aspect to consider is the sustainability of wheat cultures, as intensive agriculture produces an impoverishment in terms of physicochemical properties and the use of agrochemicals, such as pesticides, fertilizers, herbicides, insecticides, and so on, which have negative effects on the environment, may also contaminate the products. It should be worth wishing to step a bit backward to preserve the nutraceutical features of wheat and try to avoid possible pollution, which is feasible, for instance, by improving the agricultural techniques, the food supply chain and the reuse of by-products. Overall, returning to ancient wheat cultivation in a sustainable way is a charming challenge and may better contribute to diminishing or preventing the onset of chronic diseases. Finally, it has to be considered that particularly in crises like the actual COVID-19 pandemic, the relaunch of the cultivation and use of ancient wheat and the strengthening of short supply chains and local productions could be fundamental to take a step forward in the safeguarding of the right of access to healthy and sustainable food.

LIST OF ABBREVIATIONS

ALPs	=	Avenin-like proteins
ARE	=	Antioxidant-response element
ARs	=	Alkylresorcinols
ATI	=	Amylase/trypsin inhibitor
BY	=	Baker's yeast
CD	=	Celiac (or Coeliac) Disease
CV	=	Coefficient of variation
DHA	=	Docosahexaenoic acid
EPs	=	Evolutionary populations
FA	=	Ferulic acid
GLIA	=	Gliadins
GLUT	=	Glutenins
GRDs	=	Gluten-related disorders
GSH	=	Reduced glutathione
HEALTH-GRAIN	=	Exploiting Bioactivity of European Cereal Grains for Improved Nutrition and Health Benefits
HMW-GS	=	High molecular weight glutenin subunits
IBD	=	Irritable Bowel Disease
IBS	=	Irritable Bowel Syndrome
IBS-GAI	=	Irritable Bowel Syndrome Global Assessment of Improvement
IBS-SSS	=	Irritable Bowel Syndrome Symptom Severity Scale
IgE	=	Immunoglobulins E
IL	=	Interleukin
IL-1Ra	=	Interleukin 1 receptor antagonist
JNK	=	c-Jun NH2-terminal kinase
LDL	=	Low-density lipoprotein
LMW-GS	=	Low molecular weight glutenin subunits
MAPK	=	Mitogen-activated protein kinase
NAFLD	=	Nonalcoholic Fatty Liver Disease
NCGS	=	Non-Celiac Gluten Sensitivity
NF-κB	=	Nuclear factor-κB
Nrf2	=	Nuclear factor erythroid 2-related factor 2
PAs	=	Phenolic acids
PGG	=	Postprandial glucose
PSTs	=	Phenolsulfotransferases
RDA	=	Recommended daily allowance
ROS	=	Reactive oxygen species
SD	=	Sourdough
SFs	=	Steryl ferulates
SOD	=	Superoxide dismutase

TAC	=	Compounds and on total antioxidant capacity
TBARS	=	Thiobarbituric acid reactive substances
TNF-α	=	Tumor necrosis factor-α
TSP	=	Total soluble phenolic
T2DM	=	Type 2 diabetes mellitus
USDA	=	U.S. Dept. of Agriculture
VEGF	=	Vascular endothelial growth factor
WA	=	Wheat allergy

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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