REVIEW

Phytochemicals in quinoa and amaranth grains and their antioxidant, anti-inflammatory, and potential health beneficial effects: a review

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Quinoa (*Chenopodium quinoa* Willd.) and amaranth (*Amaranthus cruentus* L.) are pseudocereal grains rich in both macronutrients and micronutrients including vitamins and minerals. The proteins are particularly of high nutritional quality due to the outstanding balance of essential amino acids. However, recent research strongly suggests that nonessential nutrients such as phytochemicals of quinoa and amaranth may also have potential health beneficial effects. This review focuses on the phytochemical composition of quinoa and amaranth seeds, the antioxidant and anti-inflammatory activities of hydrophilic (e.g. phenolics, betacyanins) and lipophilic (e.g. fatty acids, tocopherols, and carotenoids) nutrients, and how these contribute to the potential health benefits, especially in lowering the risk of the oxidative stress related diseases e.g. cancer, cardiovascular disease, diabetes, and obesity. The gap between current knowledge and future research needs have also been identified.

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1 Introduction

Quinoa (*Chenopodium quinoa* Willd.) and Amaranth (*Amaranthus cruentus* L.) are originally from the Andean region in South America and both belong to the Chenopodiaceae family. Quinoa and amaranth are broad leaf plants (non-grasses) and their seeds have been incorporated into regular cereal-based foods. Quinoa and amaranth seeds as pseudocereal grains are gluten-free, and have received much attention in recent years because of their exceptional nutritional value and potential health benefits. For this reason, the United Nations FAO also declared the year 2013 as "The International Year of Quinoa", promoting the planting, development and research on quinoa, amaranth, and their related products. The high genetic variability of quinoa and amaranth are advantageous for them to be adapted in most of the world's arable regions from tropical to temperate climates, under different environmental conditions [1].

Quinoa and amaranth are rich in macronutrients such as proteins, carbohydrates and fats, as well as micronutrients including vitamins and minerals (Table 1). Extensive reviews of the past decade showed that quinoa and amaranth seeds not only have abundant protein content but outstanding balance of essential amino acids [2–4]. In addition, the two grains are also gluten-free thus offering a variety of nutritious and

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Abbreviations: CAA, cell-based antioxidant assay; **CAT**, catalase; **CD**, celiac disease; **CVD**, Cardiovascular disease; **DPPH**, 1,1-Diphenyl-2-picryl-hydrazyl; **FRAP**, ferric reducing/antioxidant power; **GFD**, Gluten-free diet; **GPx**, glutathione peroxidase; **GSH**, glutathione; **HMF**, hydroxymethylfurfural; **HRV**, heart rate variability; **IGF-1**, insulin-like growth factor-1; **IL-6**, interleukin-6; **L-DOPA**, L-3,4-dihydroxyphenylalanine; **LDL**, low-density lipoprotein; **LDL-c**, LDL-cholesterol; **LPS**, lipopolysaccharides; **MDA**, malondialdehyde; **MPP**, matrix-metalloproteinase; **MUFA**, monounsaturated fatty acids; **NO**, Nitric oxide; **ORAC**, oxygen radical absorbance capacity; **PUFA**, polyunsaturated fatty acids; **ROS**, reactive oxygen species; **SCE**, sister chromatid exchange; **SOD**, superoxide dismutase; **SPE**, solid phase extraction; **TBARS**, thiobarbituric acid-reactive substance; **TCC**, total carotenoids content; **TCI**, total carotenoid index; **TEAC**, trolox equivalent antioxidant capacity; **TNF-α**, tumor necrosis factor-α; **TRAP**, total radical-trapping antioxidant parameter; **TTI**, total tocopherol index; **UFA**, unsaturated fatty acids

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Table 1. Nutrient composition and energy content of quinoa and amaranth seeds as compared with other grains[a)]

	g/kg of edible portion				Kcal/kg		
Grains	Proteins	Total lipids	Carbohydrates	Dietary fibers	Minerals	Water	Energy
Quinoa	141.2	60.7	641.6	70.0	12.8	132.8	3680
Amaranth	135.6	70.2	652.5	67.0	14.9	112.9	3710
Oats	168.9	69.0	662.7	106.0	11.9	82.2	3890
Barley	105.0	16.0	745.2	101.0	11.0	121.1	3450
Buckwheat	126.2	31.0	705.9	100.0	14.7	111.5	3350
Rice	133.5	208.5	496.9	210.0	47.6	61.3	3160
Wheat	74.9	12.7	425.3	11.0	5.0	477.5	2140
Daily requirement							
Male adult	56.0	40.0	130.0	38.0	10.2	3.7	2100
Female adult	46.0	40	130.0	25.0	10.1	2.7	2100

a) Sources: Reference [7]; USDA, National Nutrient Database for Standard Reference Release; USDA, DRI Nutrient Reports) https://ndb.nal.usda.gov/ndb/foods; https://fnic.nal.usda.gov/sites/fnic.nal.usda.gov/files/uploads/DRIEssentialGuideNutReq.pdf)

suitable food products for about 2% of adults and 5% of children estimated to have food allergies such as celiac disease [5]. Other studies have also revealed that they have good quality lipid, starch and mineral compositions and are rich in saponins [6–10].

In addition to minerals, quinoa and amaranth seeds are also rich in vitamins like vitamins B, C and E [11–14]. Phytochemicals such as phenolic compounds, terpenoids and betanins, and their potential health beneficial effects have led to many studies during the last decade [15–17]. Quinoa and amaranth seeds have been processed into breads, Chinese steamed bread, pasta, snacks, biscuits, edible films, beverages and food-grade package materials [18–21]. Distribution of polyphenols and other bioactive compounds in quinoa and amaranth seed is depicted in Fig. 1 [22].

Increasing research has been focused on nonessential nutrients such as phytochemicals of quinoa and amaranth due to their potential role in reducing the risk of chronic diseases beyond basic nutritional functions provided by the macronutrients, minerals and vitamins [6–8, 17, 23, 24]. Different bioactive phytochemicals of quinoa and amaranth seeds including phenolics, betanins, and carotenoids have been shown to possess antioxidant, anti-inflammatory and other health promoting effects based on both in vivo and in vitro studies [1, 18, 25, 26]. However, phytochemicals such as phenolic components are highly complex and can exist in free, conjugated and bound forms, although most studies tend to focus on extractable phenolics only [27, 28]. Recent studies have shown that bound phenolics may play very important role in regulating inflammatory immune responses especially in improving gut health [29, 30]. However, the exact mechanisms as to how the phytochemicals individually or collectively contribute to the overall nutritional value, especially to the health benefits, and the effect of food processing on the bioaccessibility, bioavailability and bioactivity of phytochemicals in quinoa and amaranth seeds are not well studied.

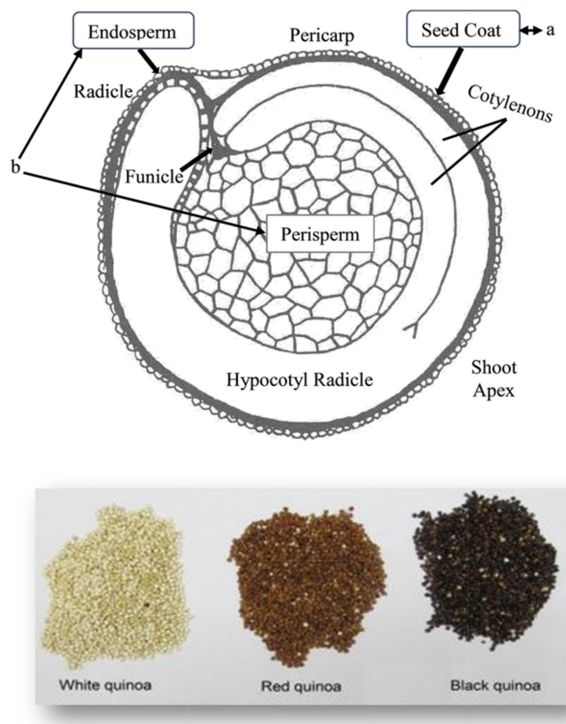

Figure 1. Seeds structure of quinoa and amaranth (a, Source of polyphenols, saponin and starch; b, Source protein and lipids), adapted from Prego et al. [22]

This review aims to summarize scientific evidence concerning the most current advances in the phytochemical composition of quinoa, amaranth and related food products, and their contribution to the antioxidant and anti-inflammation activities, the underlying mechanisms of these activities, and to discuss about the potential health benefits and/or issues related to the various phytochemicals of quinoa and amaranth seeds.

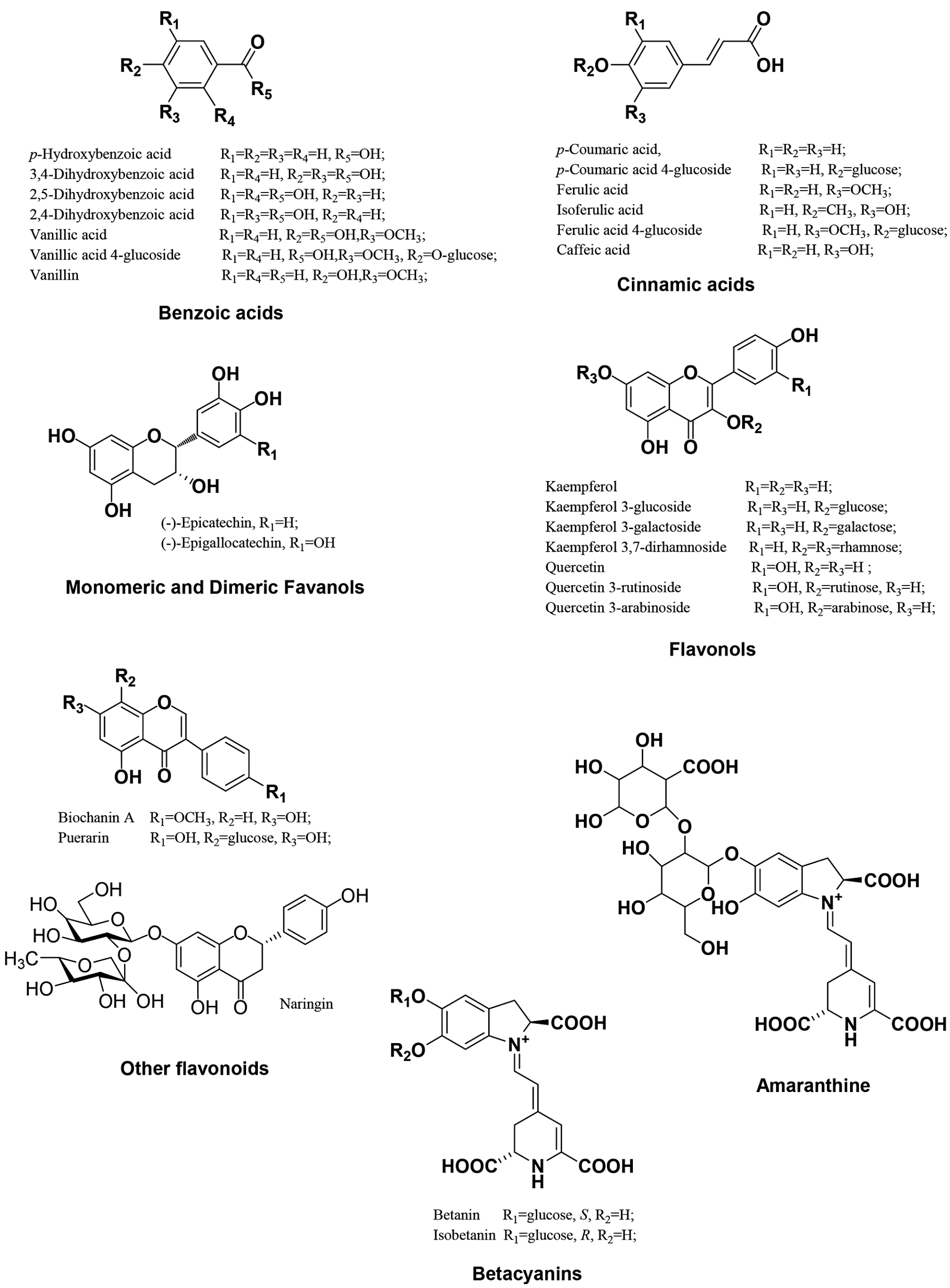

Figure 2. Chemical structures of the main hydrophilic phytochemicals in quinoa and amaranth seeds

2 Main bioactive components in quinoa and amaranth seeds

2.1 Phenolic compounds in quinoa and amaranth

Bioactive phytochemicals of quinoa and amaranth are found mainly in the outer layers of the seeds, functioning as a chemical defense against insects and microorganisms (Fig. 1). These compounds may be hydrophilic (Fig. 2) or lipophilic in nature (Fig. 3). Phenolic compounds, especially phenolic acids are located primarily in the seed coat of the quinoa and amaranth seeds (Fig. 1). Phenolics are relatively hydrophilic and may include phenolic acids, flavonoids and tannins, and they make up the majority of the secondary metabolites of plants that contribute to diverse physiological effects. Characterization of phenolics has mainly been carried out for the extractables. Two kaempferol glycosides and other free phenolics have been reported in polar extract of quinoa [31]. In recent studies, however, other forms of phenolics such as extractable conjugated phenolics and unextractable or bound

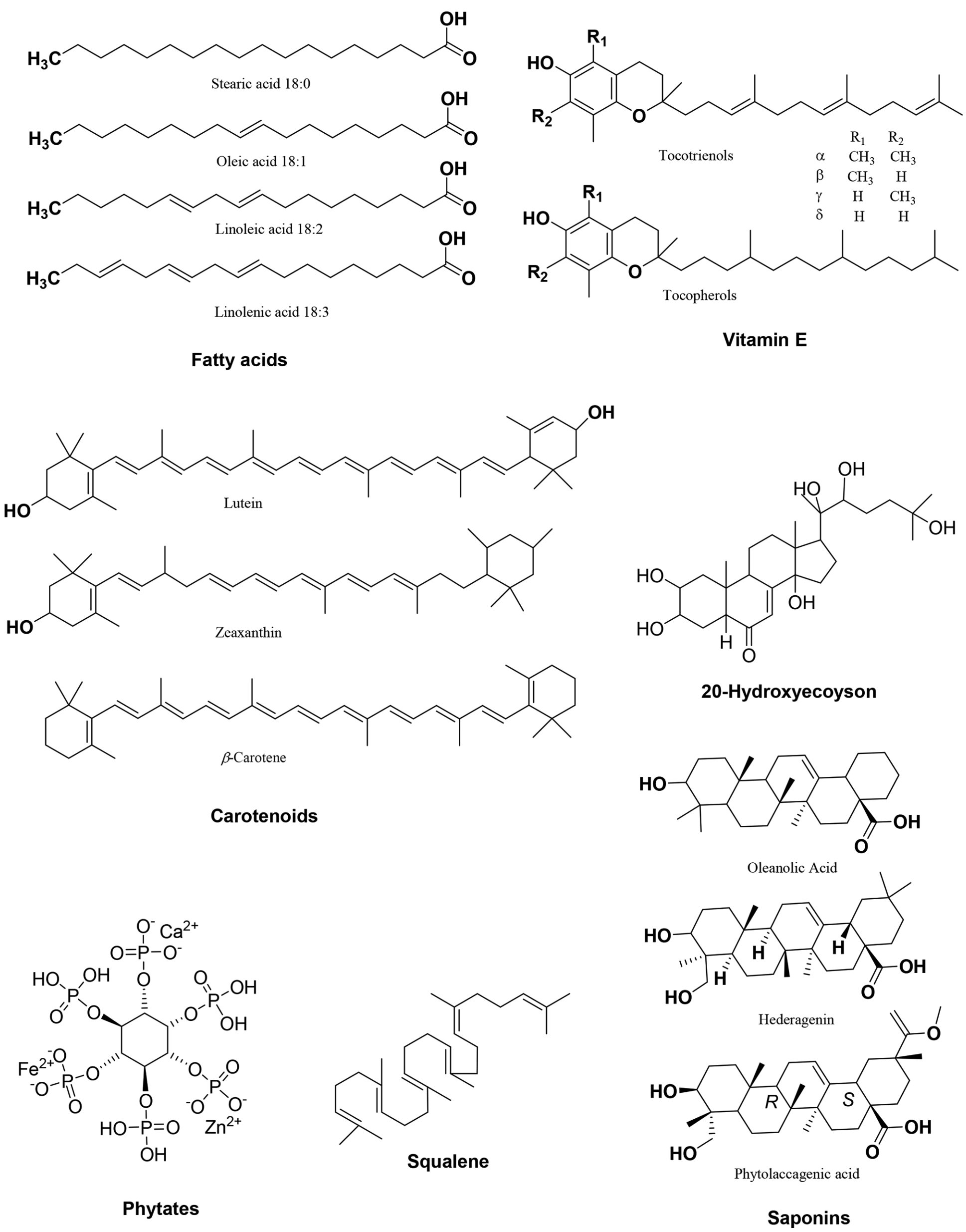

Figure 3. Chemical structures of the main lipophilic phytochemicals in quinoa and amaranth seeds (continued)

phenolics have also been identified and their significance in health, especially in gut health recognized [32–34]. Extractable phenolics may be in free and conjugated forms. Free phenolics are normally detected and characterized after chromatographic separation, whereas conjugated phenolics are associated with soluble biopolymers such as peptides or polysaccharides and can be released by acid or alkaline hydrolysis. Bound phenolics are those attached to cell wall structures such as cellulose, hemicellulose (e.g. arabinoxylans), lignin, pectin and rod-shaped structural proteins [34–36]. Bound phenolics in quinoa leaves but not seeds have been previously studied by alkaline hydrolysis and five hydroxycinnamic acid monomers and six dehydrodiferulic acids were identified [37]. Most recent studies on quinoa seeds led to the identification of 23 phenolic compounds in either free or conjugated forms, the majority of which were phenolic acids consisting of vanillic acid, ferulic acid and their derivatives, along with flavonoids quercetin, kaempferol and their glycosides. Ferulic acid-4-glucoside was the predominant free phenolic compound at 132–161 mg/kg quinoa seeds, while vanillic acid and ferulic acid were the two overwhelmingly dominant extractable phenolics in conjugated forms, at around 207–250 mg/kg quinoa seeds. Ferulic acid and its derivatives were also the predominant phenolics in bound form, at 169–231 mg/kg of quinoa seed. The total of conjugated and bound phenolics in quinoa were at comparable level as that of free phenolics, suggesting that conventional solvent extraction and chromatographic analysis of extractable phenolics might have significantly underestimated the total phenolic content in quinoa or other grains, as such methods only detect free phenolic compounds [17, 34]. Complete assessment of all three forms of phenolics help better understand and explain the overall health effects of whole grain consumption.

Similar to quinoas, several phenolic acids, flavonoids and their glycosides have been identified in Amaranthus species in previous studies. The total amount of phenolic acids in amaranth seeds varied from 168 to 329 mg/kg, whereas the proportion of extractable phenolic acids ranged from 7 to 14% of the total phenolic acids (in free, conjugated and bound forms). Rutin and phenolic acids including gallic acid, *p*-hydroxybenzoic acid and vanillic acid were found in amaranth seeds and sprouts [38–40]. Gallic, protocatechuic and *p*-hydroxybenzoic acid are three primary free phenolics in seeds at 11.0–440, 4.7–136, and 8.5–20.9 mg/kg dry seed, respectively [39, 40]. Bound ferulic acids, mainly *trans*-ferulic acid (620 mg/kg) and *cis*-ferulic acid (203 mg/kg) were found in amaranth seeds after alkaline and enzyme hydrolyses [41]. The higher content of bound phenolics that give place to free phenolics in amaranth seeds warrants further study and reevaluation of the role of these phytochemicals in potential health benefits. The major phenolics identified in quinoa and amaranth seeds are listed in Table 2.

In studying bound phenolics, alkaline, acid and enzymatic hydrolyses are performed to release these compounds from the glycosidic and ester bonds [42–44]. However, acidic hydrolysis at elevated temperatures results in the loss of some phenolics and generation of furfural and its derivatives hydroxymethylfurfural (HMF) [32, 35, 44]. HMF and related hydrolysis by-products have been misidentified as phenolics due to similar UV absorbance at 280 nm and 360 nm. This not only overestimates the total phenolic concentration, but also the in vitro antioxidant activities [34]. Hydrolysates containing acid hydrolysable bound phenolics are therefore recommended to go through solid phase extraction (SPE) to remove these by-products and free sugars before quantitative analysis and bioassays [45, 46]. Alkaline hydrolysis using sodium hydroxide at different concentrations (1–4 M) for various lengths of time has been proven effective in releasing conjugated and bound phenolics [35,42,43,47]; however, some phenolic acids such as caffeic acid and chlorogenic acid are not stable under these conditions [48]. High temperature and harsh acidic and alkaline conditions used in chemical hydrolyses are also disadvantageous as they are irrelevant to human digestive system. Recently, carbohydrase enzymes such as pectinase, cellulase, feruloyl esterase, and glucanase have been studied as a more specific and milder approach to releasing bound phenolics [34,35]. While many of these enzymes are known to be secreted by different colonic bacteria of humans e.g. probiotics of the *Lactobacillus* and *Bifidobacterium* genera [49], using these enzymes to liberate bound phenolics is generally less effective as acid and alkaline hydrolyses. Various novel techniques including ultrasound-assisted, microwave-assisted, supercritical fluid and accelerated solvent extraction have been developed for increased extraction efficiency of phenolic compounds; however, it is not known if these physical actions are sufficient in breaking the ester or ether bonds of bound phenolics [50].

2.2 Betalains

Betalains are nitrogen-containing pigments synthesized from tyrosine then L-3,4-dihydroxyphenylalanine (L-DOPA), and are divided into two subgroups: the red-violet betacyanins and the yellow-orange betaxanthins [51] (Fig. 2). Betanin is used as a natural food colorant, but it also acts as an efficient scavenger of the reactive oxygen species (ROS) which is an inhibitor of low-density lipoprotein (LDL) oxidation and DNA damage, and inducer of phase II enzymes and antioxidant defense mechanisms [51]. Betacyanins, mainly betanin and isobetanin, were confirmed to be the pigments of the red and black quinoa seeds instead of anthocyanins based on UV/Vis spectrum and LC-MS fragments referenced with beets betanin extracts [17, 52]. The main betacyanins in *Amaranthus* were amaranthine and isoamaranthine. Due to the lack of standard references for individual betanin and isobetanin, the contents of total betanins in quinoa (1.5–61 mg/kg) and amaranth (19 mg/kg) seeds have been estimated based on UV/Vis absorbance data [53, 54]. These estimates are useful for general discussions, however, for specific roles of the individual compounds, HPLC, LC-MS, and NMR spectroscopy are used for separation and identification of the various compounds, including the positional isomers or homologs of different polyphenols [55].

2.3 Fatty acids and lipids

The main lipophilic bioactives in quinoa and amaranth seeds are listed in Fig. 3. Compositional analysis of lipophilic phytochemicals in quinoa was first reported by Wood [6]. Quinoa seed was found to contain 9.7% fat content, majority of which were unsaturated fatty acids (UFA) (84.83–89.42%), and approximately two thirds of UFA were polyunsaturated fatty acids (PUFA), and one-third monounsaturated fatty acids (MUFA). The UFAs in quinoa are mainly linoleic (52%), oleic (25%) and α-linolenic (4%) acids [7]. The PUFA were mainly from two essential fatty acids, linoleic acid (18:2n-6, an omega-6 fatty acid) and α-linolenic acid (18:3n-3, an omega-3 fatty acid). Lipids in amaranth are slight higher than in quinoa seeds, averaging 6–9%, but some species such as *A. spinosus* and *A. tenuifolius* have been reported to contain as much as 19.3%. The major fatty acids in amaranth seeds were linoleic acid (39.4–49.1%), oleic acid (22.8–31.5%), and palmitic acid (21.4–23.8%), and the total UFAs was as high as 71.4–73.2% of oils [8]. Both quinoa and amaranth seeds have higher lipid yield in comparison with cereal grains including wheat (2.0%), rice (1.9%), millet (2.9%), corn (3.9%), and sorghum (3.3%) [56]. The linoleic, oleic and linolenic acids are defined as essential fatty acids since they

Table 2. Major bioactive phytochemicals and concentrations in quinoa and amaranth seeds (mg/kg)

Phytochemicals	Quinoa	Amaranth	References
Benzoic acid	19–21	n.d.	[85, 140]
p-Hydroxybenzoic acid	15.84–275	8.5–20.9	[16, 17, 53]
3,4-Dihydroxybenzoic acid	29.82–97	4.7–136	[17, 141]
3,4-Dihydroxybenzoic acid-4-O-glucoside	10.5–14	n.d.	[140, 142]
2,5-Dihydroxybenzoic acid	0.28–0.73	trace	[17, 143]
2,4-Dihydroxybenzoic acid	5.35–21.06	4.68–5.11	[17, 104]
Vanillic acid	14–523.92	15.5–69.5	[16, 17, 53, 140]
Vanillic acid glucoside	13.6–60.92	n.d.	[17, 80, 85]
Vanillin	2.21–23.89	n.d.	[17, 142]
Gallic acid	3.7–320	11.0–440	[16, 53]
p-Coumaric acid	1.1–275	1.2–17.4	[16, 122, 140]
p-Coumaric acid 4-glucoside	19.34–31.31	n.d.	[17]
Ferulic acid	76–251.5	120–620.0	[41, 53, 122, 140]
Ferulic acid 4-O-glucoside	14.3–161.39	n.d.	[17, 140, 142]
Isoferulic acid	8.21–19.44	n.d.	[17]
Caffeic acid	6.31	6.41–6.61	[122]
Epigallocatechin	1.55–120	n.d.	[17, 140, 142]
Epicatechin	3.89–4.62	n.d	[17]
Daidzein	0.11–20.5		[144, 145]
Genistein	0.4–4.1	n.d	[144]
Quercetin	18.41–680	214–843	[53, 140, 145]
Quercetin 3-rutinoside	50.8–360	7–592	[16, 142, 146]
Quercetin 3-o-glucoside	72.1	trace	[142, 147]
Quercetin 3-arabinoside	5.79–18.97	trace	[17, 147]
Kaempferol	0.25–542	22.4–59.7	[17, 53, 140, 145]
Kaempferol dirhamnoside	4.61–14.0	70	[17, 148]
Kaempferol 3-galactoside	32.02–41.56	n.d.	[17]
Kaempferol 3-glucoside	16.58–28.16	n.d.	[17]
Naringin	18.37–29.83	trace	[104, 149]
Myricetin	0.26–12.4	1.8	[53, 145]
Isorhametin	4.0–20.8	142–600	[53]
Amaranthine	–	151.3	[148]
Isoamaranthine	–	58.7	[148]
Betanin	0.15–6.10	17.7	[17, 52, 148]
Isobetanin	trace	5.0	[17, 148, 150]
Ascorbic acid	40–493	41.3–70.5	[96, 150, 151]
Thiamn (B1)	3.49–8.3	0.72–2.4	[96, 151–153]
Riboflavin (B2)	0.56–3.9	1.8–2.7	[96, 151–153]
Niacin (B3)	5.62–22.6	8.9–10	[96, 151–153]
α-Tocopherol	8.03–26	2.97–34.81	[7, 23, 24, 60, 154, 155]
β-Tocopherol	0.41–2	5.92–211.8	[7, 23, 24, 60, 154, 155]
γ-Tocopherol	25.89–53	0.95–57.07	[7, 23, 24, 60, 154, 155]
δ-Tocopherol	0.93–3	0.01–48.79	[7, 23, 60, 154, 155]
α-Tocotrienol	0.40-	10.2–20.6	[23, 60, 154, 155]
β-Tocotrienol	0.78–3	35.4–48.5	[7, 23, 60, 154, 155]
γ-Tocotrienol	n.d.	2.0–4.0	[60, 154, 155]
δ-Tocotrienol	n.d.	15.5–18.4	[60, 154, 155]
Lutein	3.96–12.42	3.55–4.29	[23, 24]
Zeaxanthin	0.28–5.37	0.14–0.32	[23, 24]
β-Carotene	0.26–1.07	–	[23, 24]
20-Hydroxyecdysone	8.6–760	–	[80, 121]

are not being synthesized in the human body. Linolenic and linoleic acids are precursors of different classes of pro-inflammatory or anti-inflammatory eicosanoids that are useful biomarkers to justify risks and benefits of PUFA consumption. Extremely large amount of omega-6 PUFA results in a very high omega-6/omega-3 ratio, which would stimulate the pathogenesis of many diseases, including cardiovascular disease, cancer, and autoimmune diseases [57]. The ratio in quinoa seeds varied from 5.3 to 10.6, significantly lower than it in amaranth seeds (33.0–69.0) [4, 24]. Quinoa seed oil has better nutrition quality than that of amaranth seeds based on the omega-6/omega-3 ratio [57, 58].

2.4 Tocopherols

Tocopherols and tocotrienols are vitamin E homologs (Fig. 3). All four tocopherol isoforms (α, β, γ, and δ) have been detected in quinoa and amaranth seeds, with γ-tocopherol (47–53 mg/kg dry weight (DW)) to be the most abundant followed by α-tocopherol (17–26 mg/kg DW), β- and δ-tocopherols in trace amount (<5 mg/kg DW) [7, 59] (Table 2). The most common tocols in amaranth seeds were α-tocopherol (1.40–31.6 mg/kg) and β-tocotrienol (0.53–43.86 mg/kg), γ-tocotrienol (0.06–8.69 mg/kg), and δ-tocopherol (0.01–48.79 mg/kg) [24, 60, 61]. Trace amount of the other vitamin E isomers, α- and β-tocotrienol were also found in quinoa seeds [23].

Vitamin E analogs are strong antioxidants and have many essential physiological functions such as anticoagulation, regulation of the metabolic, inflammatory and anticancer processes in humans [62, 63]. Tocotrienols have received renewed recognition in recent years for their roles in human health, particularly for their hypocholesterolemic, anticancer and neuroprotective properties [64, 65]. Tocotrienols are less studied in quinoa and amaranth seeds, due mainly to the lack of positive detection [7, 59].

2.5 Carotenoids

In addition to be an essential photosensitizer for plants' photosynthesis, carotenoids are also known to be provitamin A and strong antioxidants, to regulate cellular gene transcription, to enhance gap junction communication, phase II enzyme-inducing activity and immune functions (Fig. 3). The total carotenoids content (TCC) ranges from 1.69 mg/kg to 17.61 mg/kg in quinoa seed oils [23, 66–68]. Individual carotenoids in quinoa seed were mainly lutein (3.96–12.01 mg/kg), followed by zeaxanthin (0.31–5.37 mg/kg) and β-carotene (0.26–1.07 mg/kg). Only lutein (3.55–4.44 mg/kg) and zeaxanthin (0.14–0.30 mg/kg) were found at lower concentrations in amaranth seeds [24]. Apart from being provitamin A, many carotenoids of food origin offer a number of potential health benefits, including antioxidant, anti-inflammatory and anti-cancer activities and as chemoprotective agents [69–72] (Table 2). TCC and lutein in amaranth seeds are similar to those of common cereal grains, but those in quinoa seeds are significantly higher, suggesting consumption of quinoa and amaranth seeds may have added nutritional and health benefits over other cereals (Table 2).

Individual lipophilic components in quinoa and amaranth seeds are analyzed using chromatographic techniques. Gas chromatography and thin-layer chromatography (TLC) are important tools for the analysis of lipids, and with the help of Ag-Ion SPE application could provide resolution determined by chain length and number of double bonds, as well as resolve these geometric FAME fractionations and *cis/trans* separations [73]. Both reversed and normal phase HPLC coupled with different detectors have been used for the separation and detection of tocopherols and carotenoids [74, 75].

2.6 Other lipophilic compounds

Squalene, a 30-carbon isoprenoid (Fig. 3), is a key intermediate in cholesterol biosynthesis. In quinoa and amaranth seeds, the concentration of squalene can be as high as 584 and 620 mg/kg, respectively, significantly higher than buckwheat, barley and maize [76, 77]. The squalene may serve as an antioxidant through quenching singlet oxygen and protection against H_2O_2-induced sister chromatid exchange (SCE) in Chinese hamster V79 cells and animal models [78].

20-Hydroxyecdysone (20HE) (Fig. 3) is a phytochemical that has been reported to regulate protein synthesis in murine muscular cells and blood glucose levels in vitro, and to have anti-diabetic and anti-obesity effect in a high-fat (HF) diet mouse model [79]. However, 20HE is better known as an ecdysteroid hormone used by insects. Its content is reported to be 184 - 484 mg/kg in quinoa [80]. A recent study showed that quinoa seed leachate containing 20HE inhibited matrix metalloproteinase (MPP) activity and production of intracellular ROS [81]. No data is available for amaranth seed, however, *Gomphrena haageana*, a plant that belongs to the same family as quinoa and amaranth contained as high as 2580 mg/kg seed [82]. Although 20HE is ingredient of some nutritional supplements for several physiological benefits, most of its human health benefits are yet to be validated, and further studies are necessary, especially for the effect of quinoa and amaranth on the prevention and treatment of diabetes, obesity and the associated disorders.

2.7 Saponins and phytates

Quinoa and amaranth seeds contain high amount of saponins. Saponins are triterpenoids and are glycosides of sapogenins, the aglycones (Fig. 3). Saponins are bitter and depending on the structure, some may have negative impact on animals and humans, therefore they are eliminated or significantly reduced before cooking or industrial processing [83]. Quinoa seed contains 6.27 to 692.49 mg/kg total saponins, whereas saponin content in amaranth seed is significantly lower at 0.9 to 4.91 mg/kg [84–86]. At least 16 and 6 saponins have been identified in quinoa and amaranth seed, respectively, which can be divided into three different subgroups containing either oleanolic acid, hederagenin or phytolaccagenic acid as the aglycone [87–93].

Quinoa saponins have been reported to have substantial antifungal activity against *Candida albicans* [90]. *3-O-β*-D-Glucopyranosyl oleanolic acid, a sapogenin found in quinoa seeds, showed significant anti-inflammatory activity [94]. Quinoa saponin fractions also dose-dependently reduced the production of inflammatory mediators and inhibited the release of inflammatory cytokines including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in lipopolysaccharide-induced RAW264.7 cells [84]. Saponins can enhance drug absorption through mucosal membranes due to its surfactant property. Some saponins may form insoluble complexes with minerals, such as zinc and iron, which negatively affect the absorption and bioavailability of these minerals in the gut [95]. However, dietary saponins are generally safe and not a concern for human health [86].

Phytic acid (myoinositol hexaphosphoric acid) in quinoa and amaranth ranges from 10.5 to 13.5 g/kg and 2.9 to 7.9 g/kg, respectively [96, 97] (Fig. 3), lower than many food items such as sesame seeds (toasted), soy protein concentrate, rice (unpolished and cooked), maize bread (unleavened) and peanuts [98]. The unique structure of phytic acid allows it to strongly chelate with cations such as calcium, magnesium, zinc, copper, iron and potassium to form insoluble salts (these are collectively called phytates), thus high phytate content adversely affects the absorption, digestion and availability of these minerals in animals [98]. Phytates also form complexes with proteins in a relatively broad pH range, resulting in decreased protein solubility, enzymatic activity and proteolytic digestibility. Despite these potential negative impacts, studies also indicate that phytates may have anti-carcinogenic and antioxidant activities by inhibiting the production of hydroxyl radicals and normalizing cell homeostasis [98–101]. The positive or negative impact of quinoa or amaranth originated phytic acid on nutritional quality is yet to be systematically investigated.

3 Nutritional attributes and health benefits

3.1 Antioxidant activities

Many non-essential nutrients such as phenolics and carotenoids have diverse health beneficial activities including antioxidant, antiviral and anti-inflammatory properties [102]. Oxidative stress resulted from imbalance between the production of ROS and antioxidant defense may lead to oxidative damage (Fig. 4). Antioxidant activity is a measurement that assesses the ability of a compound in reducing the impact of ROS. Many chemical-based assays have been developed to evaluate the antioxidant activity of food or its derivatives, including the oxygen radical absorbance capacity (ORAC), total radical-trapping antioxidant parameter (TRAP), Trolox equivalent antioxidant capacity (TEAC), ferric reducing/antioxidant power (FRAP) assay and the DPPH free radical assay [17, 23, 32, 34, 68, 103, 104].

Seeds of quinoa and amaranth are an excellent source of antioxidants. The antioxidant activities as measured by the DPPH, FRAP and ORAC assays were highly positively correlated with TPC of quinoa and amaranth seeds [103,105]. Similarly, lipophilic antioxidants in quinoa and amaranth such as fatty acids, tocopherols and carotenoids also contributed to the antioxidant activity of these grains. In general, the antioxidant activities of the lipophilic extracts in quinoa seeds as measured by DPPH, FRAP and ORAC were higher than those in amaranth seeds, but similarly highly correlated with unsaturated fatty acids (UFAs), total carotenoid index (TCI), and total tocopherol index (TTI) of the seeds [24].

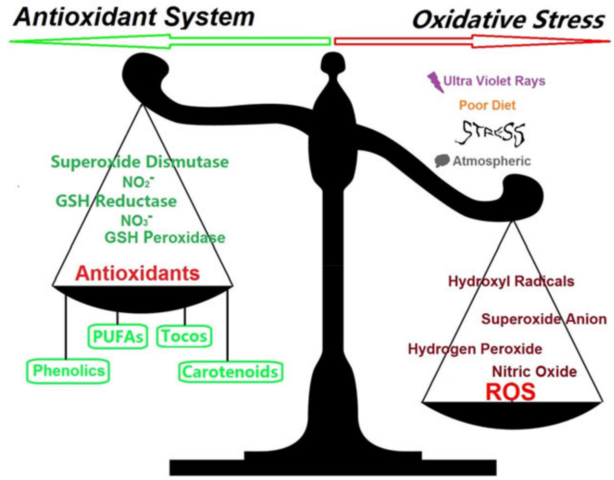

Figure 4. Phytochemical nutrients in quinoa and amaranth may help restore the balance between oxidative stress and antioxidant defense

Despite the wide usage of these chemical-based antioxidant activity assays, they lack the in vivo physiological relevance in pH and temperature, and more importantly in bioavailability, uptake, and metabolism of the antioxidant compounds [106, 107]. Cell-based antioxidant assay (CAA) is a recently developed method to compensate these shortcomings. The innate antioxidants or enzymes such as glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) are also chief defense against ROS and ex vivo measurement of their activities is another valid way to assess the antioxidant effect of phytochemicals [106, 108]. The free phenolic and PUFA fractions of cooked quinoa showed strong antioxidant ability based on Caco-2 cell-based antioxidant activity assay. In addition, the phenolics and UFAs exhibited protective effects on H_2O_2-induced Caco-2 cell oxidative injury, and positively correlated with dosage [109].

The hydrophilic and lipophilic fractions of quinoa seed significantly inhibited MMP, catalase and glutathione and tyrosinase activities and intracellular ROS production in cultured cells and were suggested to play a role in preventing skin aging, an oxidation process [106, 110]. Diet supplemented with quinoa seeds reduced oxidative stress in plasma, heart, kidney, liver, spleen, lung, testis and pancreas of fructose administered rats and inhibited plasma lipid peroxidation as seen in significantly lowered plasma malondialdehyde (MDA) concentration. Co-administration of quinoa seeds maintained normal activities of some antioxidant enzymes including SOD, CAT, and GPx [106]. Aqueous methanol extract of quinoa extracts was found to increase

SOD and GPx activities of the liver, and to enhance the production of 12-hydroxy-eicosatetraenoic acid (12-HETE) in the lung of treated rats [104]. The thiobarbituric acid-reactive substance (TBARS) value and the serum GPx and SOD activity of the rats were similar to the positive control fed with vitamin E-supplemented diet [104].

Nitric oxide (NO) is another signaling molecule that acts against oxidative stress thus important in repairing damages caused by ROS. Extracts of amaranth seeds showed strong antioxidant activity in cell models, particularly against the superoxide radical and inhibited the production of NO in lipopolysaccharides (LPS)-stimulated RAW 264.7 macrophages. Composition of the extracts were reported, and some compounds such as quercetin and betanins were known antioxidants and anti-inflammatory agents, but the study did not establish an association between these compounds and the antioxidant effects [111]. Currently, while many studies have suggested the strong antioxidant activity of phytochemicals e.g. saponins, flavonoids of quinoa, in vivo effects of these compounds are still not well documented and further in vivo studies are necessary to especially focus on the modulatory effects at physiologically relevant concentrations of the bioactive components of quinoa and amaranth seeds [112].

3.2 Anti-inflammatory activities

Polyphenols extracted from quinoa have been reported to downregulate IL-1β, IL-8, and TNF cytokines in cultured colonic epithelial Caco-2 cells, and to prevent obesity-induced inflammation and promote gastrointestinal health in mice [113]. A group of overweight postmenopausal women served with quinoa flakes for 4 weeks reversed the IL-6 level whereas those served with corn flakes did not. IL-6 is a pro-inflammatory marker thus lowered plasma expression of IL-6 by quinoa consumption suggests a potential treatment of inflammatory process of postmenopausal women [114]. Saponins in quinoa seeds have also been associated with the inhibition of inflammatory mediator overproduction, including NO, TNF-α, and IL-6, suggesting quinoa saponins may be a good functional food ingredient for the prevention and treatment of inflammation [115]. Anti-inflammatory effects of other specific bioactives of quinoa such as the hydrophilics (phenolics and betanins) and lipophilics (fatty acids, tocopherols and carotenoids) have not been reported. Our recent studies have shown that extractable phenolics and PUFA of cooked quinoa significantly inhibited the release of pro-inflammatory factor IL-8, and significantly downregulated the mRNA expression of IL-6, IL-8, TNF-α, IL-1β and COX-2, but up-regulated the mRNA expression the anti-inflammatory cytokine IL-10, all in a dosage dependent manner [109].

The hydromethanolic extract of amaranth seeds was found to decrease NO production in mouse macrophage-like cell line RAW264.7, and to increase the levels of NO_3^- and NO_2^- in the mouse body eight hours after a single oral dose of amaranth extract [116, 117]. Decrease of NO and increases in NO_3^- and NO_2^- levels are indications of the overall performance of people involved in vigorous physical activities or sports. Selenium and betacyanins in edible amaranth seed sprouts were found to prevent NFκB translocation to the cell nucleus and showed anti-inflammatory effect by significantly decrease the pro-inflammatory cytokine IL-6 in RAW 264.7 macrophages [118]. Effect of phytochemicals on the major inflammatory cytokines is shown in Fig. 5.

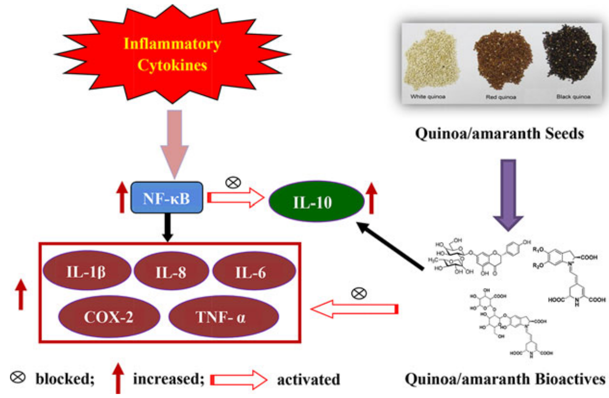

Figure 5. Anti-inflammatory effects of phytochemical nutrients in quinoa and amaranth.

3.3 Anti-obesity and anti-diabetic activities

Diabetes mellitus is becoming increasingly prevalent, 8.3% of the U.S. population has diabetes and an estimated 35% have pre-diabetes according to the report of the Centers for Disease Control and Prevention [119]. More than 1.9 billion adults were overweight worldwide in 2014, and over 600 million of them were obese. Increased intake of energy-dense foods that are high in fat is the main cause of obesity and overweight [120].

Type 2 diabetes is a metabolic disorder typified by hyperglycemia causing subsequent defects in insulin secretion, insulin action or both, whereas obesity is characterized by low-grade chronic inflammation in adipose tissue, liver, and skeletal muscle leading to areas of adipose tissue hypoxia [121]. Nutrition therapy and glucose monitoring including diet control are suggested as fundamental approaches to type 2 diabetes management. Quinoa and amaranth have been evaluated for their potential in lowering risk of type 2 diabetes by assessing the antihyperglycemia and antihypertension activities using in vitro enzyme assays and the anti-obesity effect by using obese, hyperglycemic mice model [34, 79, 122–124]. α-Glucosidase and pancreatic lipase are important enzymes for the digestion of complex carbohydrates and the absorption of triglyceride lipids, respectively. Inhibition of these two enzymes by food bioactive is suggestive of potential benefits in blood sugar and weight management, thus, ultimately in obesity and type 2 diabetes. Phenolic contents of quinoa showed strong inhibition of α-glucosidase and pancreatic lipase activities [34].

The most prevalent phytoecdysteroid, 20HE, extracted from quinoa seed was found to significantly lower fasting blood glucose in obese, hyperglycemic mice. Furthermore, 20HE enriched quinoa fed mice exhibited reduced mRNA levels of several inflammation markers (monocyte chemotactic protein-1, CD68) and insulin resistance. Dietary quinoa also reversed the effects of HF-induced down-regulation of the uncoupling proteins in mouse muscle. Male Wistar rats fed with amaranth seeds had significantly lower plasma MDA and higher activities of antioxidant enzymes. Amaranth seeds can act as a moderate protective agent against fructose-induced obesity and diabetes mellitus [122]. The amaranth grain and its oil fraction significantly decreased the serum glucose and increased serum insulin level in diabetic rats, thus amaranth seeds are beneficial for correcting hyperglycaemia and preventing diabetic complications. The exact components behind amaranth's anti-obesity and anti-diabetic activities have not been clearly identified. Majority of the anti-obesity and anti-diabetic activities of quinoa and amaranth have been investigated in vitro and in animals in vivo, and future human trials on the effect of quinoa and amaranth diets are necessary.

3.4 Gluten free (celiac disease safety)

Celiac disease (CD), also known as gluten-sensitive enteropathy and nontropical sprue, is a condition that generates inflammation in the small intestine and is characterized by damage of the mucosa layer caused by the ingestion of gluten, the major storage protein of wheat and similar grains of barley and rye in genetically susceptible subjects. The gluten protein is enriched in glutamine and proline and is poorly digested in the human upper gastrointestinal tract. Gluten-free diet (GFD) is the recommended therapy; however, adhering to the special diet is difficult for CD patients. The growth rate of the gluten-free foods market has extended 28% over the 2008–2012 period, and reached $ 4.2 billion in 2012 in the US market [125].

Quinoa and amaranth are highly nutritive pseudocereal grains. Recent in vitro studies suggest that quinoa complies with the Codex Alimentarius nomenclature of gluten-free products (gluten < 20 mg/kg), and is potentially suitable for patients with CD, although other in vitro studies indicated that some quinoa cultivars may trigger celiac toxic epitopes that could activate the adaptive and innate immune responses in some patients with celiac disease [126–128]. However, in vivo test in celiac patients showed that addition of quinoa to the GFD was well tolerated and did not exacerbate the condition [125]. Further studies are needed to validate the long-term effects of quinoa consumption and CD. A study on 11 female diabetic patients with celiac disease showed that diets containing amaranth seeds are beneficial and should be recommended [129].

3.5 CVD and other chronic diseases

Cardiovascular disease (CVD) is the world's number one cause of death and disability, and diet is one of the most important risk behaviors [130, 131]. Total cholesterol and LDL-cholesterol (LDL-c), triglyceride concentrations are the risk markers of CVD. The effects of dietary quinoa on parameters for risk of cardiovascular diseases were evaluated after 30 d consumption in twenty-two 18 to 45-year-old students. Around 42.2 and 40.7% of the individuals were found reduced blood pressure and body weight, respectively [132]. The extruded amaranth diet and diet with amaranth oil were found to reduce approximately 50% of the total cholesterol, LDL-c, triglycerides and very low-density lipoprotein cholesterol (VLDL-C) concentrations in hypercholesterolemic rabbits than rabbits fed the control diet [133]. Among them those with dramatically low heart rate variability (HRV) (Total Power (TP) ≤ 400 ms^2) were assigned into very low resistance group 1, while low resistance group 2 comprised the individuals with slightly higher HRV (TP > 400 ms^2). Regional and national level athletes with TP ranging from 3500 to 7000 ms^2 formed group 3 [134]. Amaranth oil was found to lower total cholesterol, triglycerides, LDL and VLDL cholesterols significantly in human subjects who took 18 mL per day for 3 weeks. LDL above 130 mg/dL, high-density lipoprotein (HDL) cholesterol below 35 mg/dl and total blood cholesterol above 200 mg/dl are indicators of problematic cholesterol [135]. Both quinoa and amaranth seeds contain good quality of polyunsaturated fatty acids, lutein and tocopherols [23, 24], but further investigation is necessary to validate the effect of these components on potential CVD preventing benefits in humans. Daily intake of 25 grams of quinoa flakes, not the corn flakes, in postmenopausal women was shown to reduce total cholesterol and LDL-c and to increase in GSH in a prospective and double-blind study [136]

3.6 Other nutritional and health values

Undernourished pre-school children (of 5 years of age) showed significantly increased plasma level of insulin-like growth factor-1 (IGF-1) when consumed a supplementary portion of quinoa meal after a period of 15 days, while children of the control group as well as the reference group did not [137]. IGF-1 is a hormone that plays an important role in childhood growth and continues to have anabolic effects in adults.

Components of quinoa and amaranth may also contribute to skin health. Phytoecdysteroids isolated from the seeds of quinoa were demonstrated to be potent protective agents to prevent or delay both collagenase-related skin damages and oxidative stress [138]. The oil and phytoecdysone, and other phytochemicals of quinoa significantly inhibited MMP-1 mRNA expression and MMP-9 and tyrosinase enzymatic activities, and reduced intracellular ROS production in a human dermal fibroblasts cell model, suggesting quinoa phytochemicals may play a role in the treatment and prevention of skin ageing through a multiplicity of effects [110]. Squalene in amaranth seed oil was also found to help reduce oxidative damage to the skin [139].

Phenolic extracts of quinoa seeds from Chile showed antimicrobial activity against *E. coli* and *Staphylococcus aureus* [140]. Methanol extracts of the dried leaves and seeds of amaranth were effective against pathogenic bacteria *S. aureus* and *E. coli* and fungi *Fusarium solani* and *Rhizopus oligosporus* [141].

4 Summary

Quinoa and amaranth grains have been recognized as a complete food due to their excellent essential nutrients especially the amino acid balance and an array of phytochemical nutrients. They contain high quality fatty acids especially the PUFAs, and other lipophilic phytochemicals including carotenoids and tocopherols. The majority of the phytochemicals in quinoa and amaranth grains are however, the various polyphenols, mainly phenolic acids and flavonoids, and betanins in colored varieties. These compounds possess additional health benefits beyond the high nutritional value of the two grains, especially the antioxidant and anti-inflammatory activities, which are critical in reducing risk of oxidative stress related chronic diseases including cancer, cardiovascular diseases, diabetes and aging. Quinoa and amaranth are generally safe for people with celiac disease. The potential antinutritional compounds in quinoa and amaranth grains including saponins and phytates can be carefully removed during processing or cooking, but review of the literature suggests even these compounds may have beneficial effects. All these make quinoa and amaranth grains not only a highly valued food, but also ingredients of specialty foods such as gluten-free foods and novel functional foods. Current findings also suggest future research needs in identifying quinoa and amaranth seed bioactives related to the observed effects, in validating the effects in humans, and the mechanisms of such effects. New varieties rich in these bioactive components and incorporation into functional foods are also important areas of future research.

The authors have declared no conflict of interest.

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