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Innovations in Health Value and Functional Food Development of Quinoa (*Chenopodium quinoa* Willd.)

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Abstract

Quinoa (*Chenopodium quinoa* Willd., Amaranthaceae) is a grain-like, stress-tolerant food crop that has provided subsistence, nutrition, and medicine for Andean indigenous cultures for thousands of years. Quinoa contains a high content of health-beneficial phytochemicals, including amino acids, fiber, polyunsaturated fatty acids, vitamins, minerals, saponins, phytosterols, phytoecdysteroids, phenolics, betalains, and glycine betaine. Over the past 2 decades, numerous food and nutraceutical products and processes have been developed from quinoa. Furthermore, 4 clinical studies have demonstrated that quinoa supplementation exerts significant, positive effects on metabolic, cardiovascular, and gastrointestinal health in humans. However, vast challenges and

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Practical Application: This work can be used to identify specific research studies necessary to further understand the role that quinoa and its individual chemical constituents play in human health. The information presented also highlights open avenues for technological innovation and quinoa product improvement within the industrial sector.

Author Contributions

BLG and IR conceived of and outlined the manuscript. BLG wrote the manuscript under the supervision of IR with contributions on biochemical aspects from LER (protein and other), MEB (phystosterol), PRS (phenolics), and JHD (saponins). All authors contributed to editing of the final manuscript.

Conflict of Interest

IR owns equity in Nutrasorb, L.L.C., which is involved in quinoa R&D.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

opportunities remain within the scientific, agricultural, and development sectors to optimize quinoa's role in the promotion of global human health and nutrition.

Keywords

biological activity; cereal products; dietary supplements; nutritional quality; quinoa

Introduction

Human health and food security have become increasingly important with the advents of climate change, accelerated human population growth, rise of metabolic disease, and increasing median age of the population. In upcoming years, ecosystems are expected to experience increased year-to-year climatic variation and frequency of extreme events (Perez and others 2010), putting pressure on reliable food production. Meanwhile, food demand is projected to increase between 70% and 100% by 2050 as the human population increases from 6 billion to over 9 billion (Tilman and others 2002; Godfray and others 2010). Today, about 1 in 8 individuals already suffers from chronic undernourishment (FAO, IFAD, WFP 2014), while diabetes, obesity, and other metabolic disorders have reached global epidemic proportions (Nguyen and Lau 2012; Zimmet and others 2014). Furthermore, the median age of the world's population is estimated to increase from 26.6 in 2000 to 31.1 in 2050 (Lutz and others 2008), likely resulting in a mounting prevalence of age-related disorders such as frailty, cardiovascular diseases, and osteoporosis (Lunenfeld and Stratton 2013).

As a strategy to combat metabolic diseases and age-related disorders through affordable, integrative strategies, food can play a stronger role in disease treatment and prevention. Food products that confer specific beneficial health effects, termed “functional foods” in 1984, have made their presence all over the world. The effects of functional foods range from improvement of general well-being to reduction of disease risk to treatment of illness. Functional foods can include conventional foods with specific health-beneficial properties, or foods containing enhanced levels of a particular functional nutrient as a result of natural enrichment, fortification, or processing (Bigliardi and Galati 2013).

Humans currently derive 30% to 70% of their daily energy from cereal-based foods, indicating that innovation of grain or grain-like functional foods plays a “gate-keeping” role in the conversion of agricultural crops to consumables (Poutanen and others 2014). Quinoa (*Chenopodium quinoa* Willd.) (Figure 1) is a grain-like food crop that has provided nutrition and sustenance to Andean indigenous cultures for thousands of years and now plays an increasing role in human diets worldwide. Quinoa has been promoted as an alternative agricultural crop due to its stress-tolerant characteristics and marketed as a “superfood” for its nutritious qualities. A plethora of research has recently emerged on quinoa's chemical constituents and therapeutic properties, depicting the crop as an important resource for functional food development.

However, additional scientific inquiry and modern innovation are necessary to further understand and promote the role that quinoa can play in human health. Quinoa production must also meet demand through sustainable agricultural strategies in order to improve global

access to its health benefits. The objectives of this study were to conduct a comprehensive and up-to-date review of quinoa's ethnobotanical, nutritional, phytochemical, and pharmacological aspects, while outlining recent advancements associated with its use in foods, botanical supplements, cosmetics, and pharmaceuticals.

Ethnobotanical Overview of Quinoa

Botanical distinction from cereal grains

Though quinoa is a dicot crop, it is often mistaken for a cereal grain like rice, corn, and wheat (monocots of the Poaceae family), and has therefore acquired the term “pseudocereal.” However, as a member of the Amaranthaceae family (previously Chenopodiaceae) (APG 1998; Kadereit and others 2003), quinoa is systematically and morphologically distinct from cereal grains. This distinction is especially notable by quinoa's unique fruit and seed anatomy. Quinoa fruits are achenes, comprised of a single seed enclosed by an outer pericarp (FAO 2011). The quinoa seed contains a central perisperm where carbohydrate reserves are localized, surrounded by the circular oil-rich and protein-rich embryo, endosperm, and seed coat (Prego and others 1998). The pericarp of the quinoa fruit is rich in bitter saponins and must be removed via mechanical abrasion or washing before consumption of the seeds (Prego and others 1998; Vega-Galvez and others 2010). This process, termed desaponification (saponin removal), has also been referred to as de-husking (Miranda and others 2012a), pearling (Gomez-Caravaca and others 2014), or milling (Kumpun and others 2011).

From a nutritional perspective, quinoa is included in the “whole grains” category (McKeown and others 2013). However, unlike traditional cereal grains, which are commonly processed to strip away the nutrient-rich germ and bran, quinoa desaponification leaves the nutrient-rich embryo and endosperm intact. The embryo, which constitutes up to 60% of the seed weight, confers a balanced nutritional profile of protein, lipid, and carbohydrate (Valencia-Chamorro 2003).

Traditional use

Quinoa has been traditionally used by several indigenous peoples of South America, including the Quechua, Aymara, Tiahuancota, Chibcha, and Mapuche (Vega-Galvez and others 2010; Bhargava and Srivastava 2013). The seeds have been consumed similarly to rice, prepared in soup, puffed to make breakfast cereal, or ground to flour to produce toasted and baked goods (cookies, breads, biscuits, noodles, flakes, tortillas, pancakes) (Popenoe and others 1989; Bhargava and others 2006). Quinoa leaves have also been eaten similarly to spinach (Oelke and others 1992), and the germinated quinoa seedlings (quinoa sprouts) have been incorporated in salads (Schlick and Bubenheim 1996). Furthermore, quinoa seeds can be fermented to make beer, or a traditional ceremonial alcoholic beverage from South America called “chicha” (Healy 2001; FAO 2011). The whole plant has also been used as a rich nutritional source to feed livestock, including cattle, pigs, and poultry (Bhargava and others 2006).

Records indicate a wide variety of medicinal uses of quinoa, from the treatment of wounds and fractures to the promotion of digestive health (Mujica 1994; Bhargava and others 2006; FAO 2011). Quinoa has widely been considered an invigorating, wellness-promoting, and endurance-enhancing food (Popenoe and others 1989; Lafont 1998; Gorelick-Feldman and others 2008; Kokoska and Janovska 2009; FAO 2011). Pungent ashes prepared from quinoa stems, called “llipta,” have been mixed with coca leaves (*Erythroxylum coca* Lam.) and chewed by Andean farmers to sustain their energy (Martindale 1894). Mixtures of quinoa and fat, called “war balls,” were used to sustain the Incan armies as they marched over the Andes Mountains (Small 2013).

Global production

Quinoa is thought to have been domesticated in the Lake Titicaca region near the Peruvian–Bolivian border and to have been spread through the Andes in parallel with the spread of Incan civilization (Cusack 1984; Dillehay and others 2007). Today, quinoa is cultivated from sea level up to 4500 m in altitude in Argentina, Bolivia, Chile, Colombia, Ecuador, and Peru (Cusack 1984; Fuentes and others 2009; Vega-Galvez and others 2010). An estimated 5000 different accessions of quinoa are currently held in seed banks around the world (Christensen and others 2007). Due to quinoa's water use efficiency, halophytic properties, and wide genetic diversity, the crop can survive in an extreme range of temperatures (−4 to 38 °C), frost, low rainfall (as little as 50 mm/y), nutrient-poor soils with pH ranging from 6.0 to 8.5, and high salinity (40 mS/cm) (Hellin and Higman 2003; Valencia-Chamorro 2003; Bhargava and others 2006; Hariadi and others 2010; Vega-Galvez and others 2010; FAO 2011). In fact, the largest global production region of quinoa is the Salar de Uyuni (salt flats of Oruro and Potosí provinces in Bolivia), where quinoa is the only crop capable of withstanding the extreme environmental conditions (Cusack 1984; FAO 2011; Cusicanqui and others 2013).

Following a long period of marginalized quinoa production and consumption, the demand for quinoa has recently escalated worldwide. However, total production, which is largely limited to small areas in South America, has not been able to meet demand. Therefore, market prices have skyrocketed and access to quinoa's nutritional benefits has become increasingly limited among low-income communities (Jacobsen 2011).

In order to promote quinoa's capacity to improve the livelihoods of diverse communities around the world, improved access to and awareness of quinoa's health value are critical. One key strategy to achieve improved access is the expansion of quinoa cultivation among other continents, especially regions in Africa and Asia where food production is threatened by global climate change and desertification. A second strategy is the dissemination of information regarding quinoa's health value, uses, biodiversity, and sustainable cultivation methods. Recognizing these needs, the United Nations initiated a $2.9 million collaborative program encompassing the public, private, and academic sectors in 2013 entitled “the International Year of Quinoa (IYQ2013)” (FAO 2012, 2014). In upcoming years, generation of further scientific knowledge of quinoa's chemical composition and therapeutic effects, paired by innovation in product development, will facilitate continued steps toward the sustainability of quinoa production and utilization.

Phytochemistry and Nutritional Value of Quinoa

Quinoa has a unique amino acid, carbohydrate, lipid, and micronutrient profile, with nutrient levels often surpassing those in cereal products. Though much of the focus on quinoa's health benefits has centered upon its macro- and micronutrient profiles, quinoa's secondary metabolites may also contribute to the maintenance of human health and wellness. The major groups of secondary metabolites reported in quinoa are triterpenoids (saponins, phytosterols, and phytoecdysteroids), phenolics, beta-lains, and glycine betaine. Representative chemical structures for the major classes of quinoa-derived compounds are depicted in Figure 2.

Protein

The protein quantity and quality of quinoa are generally superior to those of cereal grains, while offering gluten-free property and high digestibility. Quinoa has a higher total protein content (12.9% to 16.5%) than barley (10.8% to 11.0%), oat (11.6%), rice (7.5% to 9.1%), and maize (10.2% to 13.4%), and a total protein content equal to that of wheat (14.3% to 15.4%) (Wright and others 2002; Repo-Carrasco and others 2003; Comai and others 2007; Abugoch James 2009; Jancurová and others 2009; Peiretti and others 2013). The storage proteins of quinoa consist mostly of globulin and albumin, with little to no presence of prolamins, the major storage proteins in many cereal crops. Prolamins, such as gliadin from wheat, secalin from rye, and hordein from barley (collectively referred to as “glutens”), induce autoimmune responses in celiac patients (Zevallos and others 2012; Biesiekierski and others 2013). A recent *in vitro* study of 15 cultivars of quinoa demonstrated that only 2 cultivars showed any detectable levels of celiac-toxic prolamin epitopes (Zevallos and others 2012), while immune responses were not replicated by whole food consumption *in vivo*. These results suggest that quinoa is a safe gluten-free substitutes for cereal grains (Zevallos and others 2014).

Among quinoa total protein, 37% is constituted by chenopodin, a globulin 11S-type protein (Repo-Carrasco and others 2003) that has become a reference source of leucine, isoleucine, and phenylalanine and tyrosine by the FAO (Abugoch James 2009). According to FAO/WHO recommendations, quinoa protein can supply over 180% of the daily recommended intake of essential amino acids for adult nutrition (Wright and others 2002; Abugoch James 2009; Vega-Galvez and others 2010), with adequate proportions of all 10 essential amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, tyrosine, and valine) (Vega-Galvez and others 2010; Miranda and others 2012b). Quinoa's essential amino acid profile is reported to be equivalent to that of casein and dried whole milk by FAO (2011). Furthermore, lysine, one of the limiting amino acids in cereal grains, is found at levels twice as high as those in wheat or maize (Valcárcel-Yamani and Caetano da Silva Lannes 2012).

According to animal feeding experiments, quinoa protein also has high digestibility. Among raw quinoa proteins, 91.6% is absorbable. Heat treatment (cooking) improves protein digestibility to 95.3% (Ruales and others 2002). Quinoa's high bioavailability is partially due to its relatively low content of trypsin inhibitors (1.36 to 5.04 TIU/mg) (Vega-Galvez and

others 2010), which reduce protein enzymatic digestion and absorption (Valencia-Chamorro 2003).

Carbohydrate and fiber

Quinoa starch comprises 58.1% to 64.2% of dry seed weight, but has a low glycemic index (Vega-Galvez and others 2010). The starch is constituted mainly by D-xylose (120 mg/100 g) and maltose (101 mg/100 g) with low glucose (19 mg/100 g) and fructose (19.6 mg/100 g) content (Bhargava and others 2006). The starch is highly branched and consists of small granules (particle size less than 2 μm in diameter), which are smaller than the particle sizes of common cereal grains (Vega-Galvez and others 2010).

According to Lamothe and others (2015), quinoa contains 10% total dietary fiber. Fiber is the carbohydrate fraction which is resistant to enzymatic digestion and absorption in the small intestine, and which usually undergoes full or partial fermentation in the large intestine. Dietary fiber is considered essential for optimal digestive health, and also imparts various functional benefits (Brownawell and others 2012). Dietary fiber can promote satiety, reduce cholesterol and lipid absorption, modulate postprandial insulin response, promote endogenous cholesterol conversion to bile acids, improve intestinal microbiota, and reduce risk and severity of gastrointestinal infection and inflammation (Brownawell and others 2012; De Carvalho and others 2014). Furthermore, epidemiological studies have shown an inverse relationship between dietary fiber consumption and the development of cardiovascular disease, obesity, and type 2 diabetes (Brownawell and others 2012).

Though total fiber content in quinoa is comparable to other cereals, the monosaccharide subunit composition of quinoa fiber more closely resembles that of fruits, vegetables, and legumes. Insoluble quinoa fiber, which is comprised mainly of galacturonic acid, arabinose, galactose, xylose, and glucose subunits, represents 78% of total fiber content in quinoa. Meanwhile, soluble quinoa fiber, comprised mainly of glucose, galacturonic acid, and arabinose subunits, constitutes 22% of total fiber. The soluble fiber content, which is higher than that of wheat or maize (~15% each), may play a role in quinoa's health-promoting potential since the fermentability of soluble fiber by colonic microbiota has been recognized for its functional properties (Lamothe and others 2015). Soluble, well-fermentable fibers, such as inulin, fructooligosaccharides, and galactooligosaccharides, can lead to microbial production of short-chain fatty acids (acetic, butyric, and propionic) that lower luminal pH and increase the colonization of favorable bacteria, thereby serving as “prebiotics” (Biesiekierski and others 2013).

While conferring beneficial effects as prebiotics, some readily-fermentable short-chain carbohydrates, referred to as “fodmaps,” can induce symptoms of irritable bowel syndrome. Fodmaps include fructans present in wheat and rye, and foods with fructose content that exceeds glucose content, such as apples. Quinoa, contrarily, does not contain fructans and has a low fructose content. Therefore, quinoa is an integral part of the “low fodmap diet” that has been shown to wield marked beneficial impacts on irritable bowel symptoms in a recent human clinical study (Biesiekierski and others 2013). Further studies are needed to determine the specific types and concentrations of quinoa fibers, paired with their effects on

colonic microbiota, in order to gain a better understanding of quinoa fibers' potential to serve as a prebiotic and prevent disease.

Lipid

The oil content in quinoa ranges from 2% to 10% (average 5% to 7%), which is higher than that of maize (3% to 4%) (Vega-Galvez and others 2010). A recent study found that quinoa seed oil contains 89.4% unsaturated fatty acids and 54.2% to 58.3% polyunsaturated fatty acids (PUFAs). PUFAs are mostly 18:2n-6 and 18:3n-3, with an omega-6/omega-3 ratio of 6/1, which is generally more favorable than that of other plant oils (Tang and others 2015a).

The primary essential fatty acids in quinoa include linoleic acid and linoleneic acid, which are metabolized to arachidonic acid and eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), respectively. These fatty acids are well protected from oxidation by vitamin E and other antioxidant components of quinoa seeds. Essential fatty acids play important roles in brain development, insulin sensitivity, cardiovascular health, prostaglandin metabolism, immunity, inflammation, and membrane function (Kim and others 2006; McCusker and Grant-Kels 2010; Vega-Galvez and others 2010). Essential fatty acids may exert beneficial physiological effects in humans by altering cell membrane phospholipid fatty acid composition, disrupting lipid rafts, inhibiting pro-inflammatory transcription factor activation, and binding to the G protein coupled receptor GPR120 (Calder 2012).

Vitamins

Quinoa seeds are a rich source of vitamins, which are required in the human diet to act as enzymatic cofactors in metabolism, regulate cell growth and development, protect against oxidative damage, improve vision, and play beneficial roles in various other physiological processes (Fitzpatrick and others 2012). Documented vitamins in quinoa include vitamin A precursor β-carotene (0.39 mg/100 g), thiamin/vitamin B_1 (0.4 mg/100 g), riboflavin/vitamin B_2 (0.39 mg/100 g), niacin/vitamin B_3 (1.06 mg/100 g), panthothenic acid/vitamin B_5 (0.61 mg/100 g), pyridoxine/vitamin B_6 (0.20 mg/100 g), folic acid/vitamin B_9 (23.5 to 78.1 mg/100 g), ascorbic acid/vitamin C (4.0 to 16.4 mg/100 g), and tocopherols/vitamin E (3.7 to 6.0 mg/100 g) (Ruales and Nair 1993; Bhargava and others 2006; Vega-Galvez and others 2010; Tang and others 2015a). Quinoa also contains a variety of carotenoids, predominantly luteins and zeaxanthins, with total concentrations ranging from 1.2 to 1.8 mg/100 g (Tang and others 2015a). Concentrations of many of these vitamins and provitamins in quinoa are higher than typical cereal grains (Bhargava and others 2006; Vega-Galvez and others 2010; Tang and others 2015a).

Minerals

Quinoa has a higher total mineral (ash) content (3.4%) than rice (0.5%), wheat (1.8%), and other cereals (Bhargava and others 2006). The micronutrients calcium (275 to 1487 mg/kg), copper (2 to 51 mg/kg), iron (14 to 168 mg/kg), magnesium (260 to 5020 mg/kg), phosphorus (1400 to 5300 mg/kg), potassium (75 to 12000 mg/kg), and zinc (28 to 48 mg/kg) are present in sufficient quantities in quinoa to maintain a balanced human diet (Repo-Carrasco and others 2003; Bhargava and others 2006; Vega-Galvez and others 2010).

Phytic acid (also known as phytate or IP_6) has become a concern among various cereal grain and vegetable crops because it has a strong binding affinity to minerals like iron, thereby reducing their bioavailability (Valencia and others 1999). However, quinoa contains lower levels of phytic acid (1.18 g/100 g seed) than most cereal crops (Valencia-Chamorro 2003), and it has almost twice the soluble iron concentration (Valencia and others 1999). Processing of quinoa by cooking, soaking, and fermentation further reduces phytic acid content and improves iron solubility. Furthermore, germination of quinoa seedlings activates endogenous phytase, an enzyme which hydrolyzes phytic acid–mineral complexes (Valencia and others 1999).

Saponins

Quinoa's outer seed coat (pericarp) is rich in bitter saponins, natural detergent molecules found throughout the plant kingdom (Figure 2A). Saponins are comprised of a steroidal or triterpenoid aglycone (mainly oleanolic acid, hederagenin, phytolaccagenic acid, and serjanic acid), with one or more sugar moieties (Yendo and others 2010). Sugars can be linked to the aglycone at the C-3 and C-28 positions. The major sugar moities include glucose, galactose, arabinose, glucuronic acid, and xylose. Saponin chemistry of quinoa seeds is highly diverse. Madl and others (2006) identified 19 previously reported and 68 novel saponin compounds in quinoa using nano-HPLC electrospray ionization multistage tandem mass spectrometry (nLC-ESI-MS/MS) from a complex triterpene saponin crude extract of quinoa seed coats.

Saponins possess several common properties, including high foaming capacity in aqueous solutions, hemolytic activity when in direct contact with blood cells, and the formation of complexes with cholesterol and other steroidal components of cell membranes (Stuardo and San Martin 2008). Therefore, they are useful for crop protection from microbial infection and insect/bird herbivory, which facilitates organic production of this crop. The synthesis of secondary metabolites, including saponins, is a response to environmental factors and part of an adaptative strategy for abiotic stress tolerance (Ramakrishna and Ravishankar 2011). Triterpenoid saponins are synthesized via the isoprenoid pathway, leading to the formation of triterpenoid skeletons such as oleanane, ursane, lupeol, or dammarane. Subsequent structural modifications, including oxidation, substitution, and glycosylation, are mediated by various enzymes (Cammareri and others 2008).

Since saponins interfere with quinoa's palatability and digestibility, they must be removed before consumption. Some varieties of quinoa have been bred to contain lower saponin content, termed “sweet” quinoa (<0.11% free saponins), though these varieties are often less pest-resistant and experience increased bird herbivory. Despite their unpalatable characteristics, saponins also have a wide range of biological activities relevant to human health, including antifungal, antiviral, anticancer, hypocholesterolemic, hypoglycemic, antithrombotic, diuretic, and anti-inflammatory activities (Madl and others 2006; Vega-Galvez and others 2010). Recently, Yao and others (2014) showed that saponin-rich quinoa seed extracts decreased the production of the inflammatory mediator nitric oxide and inhibited the release of the inflammatory cytokines TNFα and IL-6 in lipopolysaccharide-stimulated RAW 264.7 macrophages.

Phytosterols

Though the phytosterol content of quinoa seeds has not received much attention, quinoa seeds contain phytosterol levels up to 118 mg/100 g quinoa seed, whereby the major constituents were β-sitosterol (Figure 2B), campesterol, brassicasterol, and stigmasterol (Villacrés and others 2013). Ryan and others (2007) found that quinoa seeds contain β-sitosterol (63.7 mg/100 g), campesterol (15.6 mg/100 g), and stigmasterol (3.2 mg/100 g), and these levels were higher than those found in barley, rye, millet, and maize.

Phytosterols are lipophilic compounds structurally similar to cholesterol. Epidemiological evidence, intervention studies, and meta-analyses have consistently concluded significant hypocholesterolemic effects of phytosterols in humans (Marangoni and Poli 2010). Phytosterols lower serum cholesterol levels by competing for cholesterol intestinal absorption, and possibly also by decreasing atherogenic lipoprotein production in the liver and intestines (Ho and Pal 2005). Furthermore, phytosterols have demonstrated anti-inflammatory, antioxidative, and anticarcinogenic effects (Ryan and others 2007).

Phytoecdysteroids

Among edible agricultural crops, quinoa seeds contain the highest levels of phytoecdysteroids (Table 1), polyhydroxlyated steroids that are structurally related to insect molting hormones involved in plant defense (Dinan 2009) and documented to exert a myriad of biological activities in mammals relevant to human health. Quinoa has been shown to contain a range of 138 to 570 μg/g total phytoecdysteroids (Graf and others 2015b). At least 13 different phytoecdysteroids have been isolated from quinoa seeds, of which 20-hydroxyecdysone (20HE) (Figure 2C) was the most abundant (62% to 90% of total phytoecdysteroids). The second most abundant set of phytoecdysteroids in quinoa include makisterone A, 24-epi-makisterone A, and 24(28)-dehydromakisterone A (Zhu and others 2001; Kumpun and others 2011; Graf and others 2014, 2015b).

Extracts from several phytoecdysteroid-containing plants, especially traditional medicinal Chinese and Siberian herbs (Cheng and others 2008; Kokoska and Janovska 2009; Lafont 1998), have been used as adaptogens, muscle builders, and stress reducers (Báthori 2002). Previous reviews on the bioactivities of phytoecdysteroids highlight their growth-promoting, antidiabetic, immunomodulatory, hepatoprotective, neuroprotective, hypocholesterolemic, wound healing, antidepressive, and antioxidant activities (Lafont and Dinan 2003; Dinan and Lafont 2006; Dinan 2009). Evidence also suggests that phytoecdysteroids may be safe for oral and topical application in humans without inducing the unwanted effects associated with sex hormone supplementation. 20HE has been shown to have very low toxicity (LD_{50} of 6.4 g/kg after intraperitoneal injection; LD_{50} of 9 g/kg after oral application) (Dinan 2009) and is rapidly cleared from the blood following 14-dehydroxylation metabolism (Dinan and Lafont 2006). Furthermore, 20HE does not demonstrate *in vitro* androgen binding (Gorelick-Feldman and others 2008) or *in vivo* estrogenic effects (such as increased uterine weight) in ovariectomized rats (Seidlova-Wuttke and others 2010a).

The most recent studies on the biological effects of 20HE have focused on its potential role in the treatment or prevention of metabolic syndrome and postmenopausal disorders.

Kizelsztein and others (2009) demonstrated that 20HE (10 mg/kg for 13 weeks) reduced adiposity 41%, increased insulin sensitivity, and lowered blood glucose levels in high-fat diet-induced obese, hyperglycemic C57Bl/6J mice. Following that study, Foucault and others (2011, 2014) demonstrated that 20HE (6 mg/kg for 3 weeks) and a 20HE-enriched quinoa extract both induced similar anti-obesity and antidiabetic effects. In a third study among high-fat diet mice, 20HE treatment (25 or 50 mg/kg for 12 weeks) lowered body weight, improved insulin sensitivity, and reduced muscle lipid accumulation (Wang and others 2011). Meanwhile, 20HE administration (18 to 121 mg/d/animal for 12 weeks) prevented fat gain and bone density loss, reduced hot flashes, and improved dermal thickness in ovariectomized rats, the standard rodent model for postmenopausal studies (Seidlova-Wuttke and others 2010a, 2010b; Ehrhardt and others 2011; Seidlova-Wuttke and Wuttke 2012). Future studies are needed to test the effect of 20HE on metabolic markers associated with diabetes, obesity, cardiovascular health, and postmenopausal symptoms in humans.

Due to their steroidal structures, 20HE and other phytoecdysteroids have been investigated for their potential anabolic and performance-enhancing abilities, with mixed results. Studies show that 20HE treatment induces protein synthesis *in vitro* (Gorelick-Feldman and others 2008) and enhances physical performance in rodents, as assessed by forced swim tests and grip strength measurement (Gorelick-Feldman and others 2008; Dinan 2009). However, no significant improvement in performance was found in a double-blind, placebo-controlled human clinical trial among resistance-trained males treated with 20HE (30 mg/d for 8 weeks) (Wilborn and others 2006). This study may have been limited by its small treatment group size (9 individuals in each group) and/or the duration of treatment. Furthermore, the effect of 20HE on performance may be greater among untrained individuals as opposed to trained athletes.

20HE's primary mechanism of action has not yet been determined. 20HE's neuroprotective effects have been attributed to its modulation of $GABA_A$ receptors, and its hypocholesterolemic activity has been explained by its ability to increase the conversion of cholesterol to bile acids (Dinan and Lafont 2006). Studies in high-fat-diet mice have linked 20HE's anti-obesity and antidiabetic activity to reduced dietary lipid absorption, increased glucose oxidation, increased energy expenditure (Foucault and others 2014), and enhanced mitochondrial oxidative phosphorylation (Wang and others 2011). In addition, 20HE has been shown to attenuate oxidative stress in 3 different mammalian cell lines (Hu and others 2010, 2012; Graf and others 2015a). Meanwhile, 20HE may affect mammalian gene expression, resulting in activation of the anabolic P13K/Akt pathway (Dinan and Lafont 2006; Gorelick-Feldman and others 2010), and downregulation of the hepatic gluconeogenesis pathway (Kizelsztein and others 2009). 20HE also modulates cell differentiation, as shown in mesenchymal stem cells and keratinocytes (Detmar and others 1994; Gao and others 2008). 20HE's transcriptional effects are likely mediated by nuclear hormone receptor interaction, although evidence of direct binding has not yet been reported.

Phenolics

Phenolics are a large, diverse class of compounds consisting of hydroxyl group(s) attached to at least one aromatic hydrocarbon ring, a highly stable chemical structure that gives these molecules their well-known antioxidant activity (Harborne and Williams 2000). Phenolics also possess a range of biological activities due to their effects on cell-signaling and metabolism, including anti-inflammatory, anticancer, antidiabetic, anti-obesity, and cardioprotective effects (Harborne and Williams 2000; Da-Silva and others 2007; Kelly 2011; Jeong and others 2012).

Phenolics exist as simple single-ringed structures called phenolic acids (Figure 2D), or multiringed structures termed polyphenols (Figure 2E). Phenolic acids can exist in free form or as bound phenolics, associated with pectins in the cell wall (Renard and others 1999; Gomez-Caravaca and others 2011). Several phenolic acids, including derivatives of hydroxycinnamic acid and hydrobenzoic acid, have been identified in quinoa seeds and leaves (Supp. Table 1). Individual phenolic acids have been reported in quinoa seeds at concentrations as high as 251.5 μg/g dry weight (Gorinstein and others 2008).

Polyphenols are divided into several subgroups, among which the flavonoids (including flavonol glycosides and isoflavones) have been most extensively investigated (Tsao 2010). Flavonol glycosides constitute the most abundant phenolics in quinoa seeds and leaves (Gomez-Caravaca and others 2011). More than a dozen different flavonol glycosides have been identified in this plant, constituted mainly by quercetin and kaempferol derivatives, with concentrations of individual compounds occurring at levels as high as 839 μg/g dry weight (Dini and others 2004; Hirose and others 2010).

Isoflavones were identified for the first time in quinoa by Lutz and others (2013), who reported the presence of genistein (0.05 to 0.41 mg/100 g) and daidzein (0.70 to 2.05 mg/100 g) among 10 different seed varieties. However, compared to soybean isoflavone concentrations (genistein, 83.8 mg/100 g; daidzein, 58.3 mg/100 g), the concentration of isoflavones in quinoa is very low (Lutz and others 2013).

Total flavonoid, phenolic, and antioxidant contents have been assessed by spectrometry among several quinoa varieties, indicating that differences in phytochemical content may be due to genotypic or environmental factors (Supp. Table 2). However, spectrophotometric analysis methods are often influenced by interfering compounds, such as vitamins, amino acids, and sugars, which make reliable quantification difficult (George and others 2005). There is need for further studies on specific phenolics in quinoa using HPLC or MS (Gomez-Caravaca and others 2012).

Betalains

There are not many reports regarding the content of betalains (Figure 2F) in quinoa. These molecules give quinoa seeds and vegetative parts their varied yellow, red, and black colors (Figure 1) (Bhargava and others 2006). Betalain pigments, including red-violet betacyanins and yellow-orange betaxanthins, are nitrogen-containing aromatic indole derivatives synthesized from tyrosine (Tang and others 2015b). They are structurally and

biosynthetically distinct from phenolics and are restricted to the order Caryophyllales, to which Amaranthaceae crops belong (Moreno and others 2008).

The most abundant betalains in quinoa seeds are betanin and isobetanin, which possess a range of health-promoting properties similar to those of phenolic compounds, including antioxidant and anti-inflammatory effects (Tang and others 2015b). However, studies have shown that some betalains possess antioxidant activity higher than that of polyphenols (Neagu and Barbu 2014).

Betalains are stable between pH 3 and 7, and can therefore be used as a natural dye. There is a growing consumer and industrial demand for natural, safe, stable alternatives to synthetic color ingredients in foods (Neagu and Barbu 2014). Today, betalains are approved for use as colorants in dairy products, sauces, soups, cosmetics, and pharmaceuticals by the U.S. FDA and European Union (E-162) (Esatbeyoglu and others 2015). Quinoa is a candidate crop for the extraction of natural color ingredients, particularly from the nonconsumed vegetative parts. However, additional research is needed to determine the concentration, extractability, and stability of quinoa-derived betalains in order to develop value-added products for use in food coloring.

Glycine betaine

Glycine betaine (Figure 2G), also known as betaine or *N,N,N*-trimethylglycine, is an *N*-trimethylated amino acid. Betaine and its precursor, choline, are important for homocysteine regulation and have been implicated in the treatment and prevention of diabetes, obesity, and cardiovascular disease (Olthof and Verhoef 2005). Cereal crops are the largest contributing source of betaine in the Western diet. However, quinoa contains a higher amount of betaine (3930 to 6000 μg/g) compared to other cereal and cereal-like crops (174 to 706 μg/g among wheat products, 50 to 150 μg/g for millet and teff, less than 20 μg/g in buckwheat, 646 μg/g in amaranth) (Ross and others 2014).

Clinical Evidence of Health Benefits of Quinoa-Derived Products

The high nutritional value, medicinal properties, and gluten-free quality of quinoa may benefit several at-risk consumer populations, including children, the elderly, high-performance athletes, lactose-intolerant consumers, osteoporosis-prone women, and people with anemia, diabetes, dyslipidemia, obesity, or celiac disease (Bhargava and others 2006; Vega-Galvez and others 2010). Though the number of animal and human clinical trials on quinoa's therapeutic potential is limited, several studies indicate various benefits associated with quinoa consumption (Table 2).

In a childhood nutrition study among boys aged 50 to 65 months from low-income families in Ecuador, the consumption of infant food formulated with quinoa (100 g twice per day for 15 days) significantly increased plasma IGF-1 levels, whereas IGF-1 levels were unchanged in the control group. IGF-1 is a hepatic peptide that promotes growth, increasing body weight and bone length. IGF-1 has been suggested as a marker of malnutrition or a measure of response to nutritional therapy. The positive effects observed for the quinoa-treated group were attributed to the complete essential amino acid profile of the quinoa-formulated baby

food, as well as its high digestibility (95.3%), which was higher than that of 5 commercially available infant foods derived from milk and soy. This study indicates that infant food derived from quinoa provides sufficient protein and other essential nutrients crucial for reducing child malnutrition (Ruales and others 2002).

The use of quinoa seeds as a safe, gluten-free alternative to cereal grains was evaluated in a human clinical trial among celiac patients. Nineteen celiac patients consumed 50 g quinoa daily for 6 weeks. Gastrointestinal parameters (villus height:crypt depth, surface-enterocyte cell height, and number of intra-epithelial lymphocytes per 100 enterocytes) and serum lipid levels were evaluated before and after intervention. The study found that gastrointestinal parameters improved following the quinoa diet, while serum lipid levels remained within a normal range, with small decreases observed in total cholesterol, LDL, HDL, and triglycerides (Zevallos and others 2014).

The hypolipidemic potential of quinoa products has been further demonstrated in human trials. Daily consumption of a quinoa cereal bar for 30 days significantly lowered triglyceride, total cholesterol, and LDL levels among 22 students aged 18 to 45 years. Meanwhile, blood glucose levels, body weight, and blood pressure each decreased, though nonsignificantly (Farinazzi-Machado and others 2012).

In a prospective, double-blind human clinical trial among post-menopausal women with excess weight, quinoa flake consumption (25 g/d for 4 weeks) also modulated metabolic parameters posttreatment compared to baseline. In this study, serum triglycerides (112.3 ± 35 to 107.9 ± 33.1 mg/dL) and TBAR values (3.06 ± 0.6 to 2.89 ± 0.5 μmol/L; TBARs are substances produced in response to lipid peroxidation-induced oxidative stress) were both significantly reduced. Furthermore, quinoa intervention nonsignificantly reduced total cholesterol (191 ± 35 to 181 ± 28 mg/dL) and LDL-cholesterol (129±35 to 121±26 mg/dL), while glutathione (GSH, a marker of antioxidant defense) was increased (1.78 ± 0.4 to 1.91 ± 0.4 mmol/L). In a parallel intervention group that consumed corn flakes, similar decreases in triglycerides and TBAR values were observed, but total cholesterol, LDL, and GSH levels were not affected, indicating a possible unique benefit from quinoa consumption (De Carvalho and others 2014).

Though the antidiabetic effects of quinoa have not been studied in humans, co-administration of quinoa seeds (310 g/kg feed for 5 weeks) significantly reduced plasma glucose levels and oxidative stress in Wistar rats fed a high-fructose diet (31% fructose) compared to the control group (Pasko and others 2010a, b). Secondly, phytochemically enriched products derived from quinoa seeds (described in detail below) significantly lowered levels of fasting blood glucose, adiposity, and cholesterol *in vivo* (Foucault and others 2011, 2014; Graf and others 2014).

The present evidence for quinoa's health benefits warrants future studies on this crop's role in the treatment and prevention of complex human diseases. Randomized, controlled trials are the gold standard for determining the effect of diet on health outcomes, though optimal study design and length of the study are crucial factors in determining trial outcomes. Epidemiological studies and observational cohort studies, which have not yet been

conducted on quinoa consumption, can also be useful to generate hypothesis-driven research questions.

Within clinical intervention studies, it is important to utilize quinoa products with well-characterized and standardized phytochemical contents so that observed effects can be linked to specific constituents. Previous clinical studies collectively suggest that the major cholesterol-lowering and antioxidant components of quinoa were proteins, fiber, vitamins (tocopherols and carotenoids), minerals (iron, zinc, magnesium), saponins, phytosterols, phytoecdysteroids, and phenolics (Ruales and others 2002; Farinazzi-Machado and others 2012; De Carvalho and others 2014; Zevallos and others 2014). However, other quinoa phytochemicals, such as polyunsaturated fatty acids and betalains, may also play an important role. Furthermore, individual quinoa constituents may positively interact with each other, leading to enhanced bioactivity through a phenomenon referred to as synergy or potentiation (Schmidt and others 2008). Many studies on whole grains have shown that their health benefits are likely the result of the “whole-grain package” rather than single constituents (McKeown and others 2013). A single serving of quinoa (approximately 40 g) will deliver a large portion of the Recommended Daily Allowance (RDA) of key nutrients and health-beneficial compounds to the consumer (Supp. Table 3). Given the complex nature of quinoa's phytochemical profile, it is important to consider the “whole-grain package” hypothesis when designing or analyzing the results of future clinical studies.

Patient compliance is another factor to consider when drawing conclusions from human clinical trials. Quinoa products used in feeding studies should be appealing and convenient for consumption, such as packaged snacks and energy bars. Biomarkers of quinoa consumption should also be used as tools to measure compliance. De Carvalho and others (2014) utilized urinary enterolignan concentration as a biomarker of quinoa intake. Enterolignans (enterodiol and enterolactone) are the compounds that result from the metabolism of plant lignans by gut microbiota. However, enterolignan concentration may not be a robust measure of quinoa intake since many plant-based foods (various whole grains, vegetables, tea, and coffee) are also rich in lignans and several variables affect the efficiency of gut microbiota conversion of lignans to enterolignans (intestinal integrity, stress, genetics, antibiotic intake) (van Dam and Hu 2008; De Carvalho and others 2014).

A recent study found that alkylresorcinols, phenolic lipids previously thought to be present only in the bran of cereal grains, were also present in quinoa (Ross and Savolainen 2014). Alkylresorcinols have been suggested to be a better measure of whole grain intake in humans (van Dam and Hu 2008). Furthermore, in this study on quinoa, the alkylresorcinol homologs C18:0, C22:0, and C24:0 were identified for the first time in nature. Therefore, specific alkylresorcinol homologs may serve as unique biomarkers of quinoa intake for future clinical intervention and epidemiological studies.

Technological Innovations in Quinoa Processing and Applications

Technological innovations that speed cooking time, generate ready-to-eat packaged products, or deliver phytochemicals in concentrated form can facilitate the intake of health-beneficial phytochemicals in today's fast-paced society. With the growing interest in quinoa's

nutritional and medicinal value, methods for producing, concentrating, and/or utilizing several value-added products from quinoa have been developed over the past 25 years. This phenomenon has been demonstrated by the steady rise in publications generated over this time period, especially patents and patent applications (Table 3, Figure 3). Within the functional food, botanical supplement, cosmetic, and pharmaceutical sectors, quinoa-based technologies have been developed to target the following therapeutic areas of human health: (1) celiac disease, (2) sports performance and fitness enhancement, (3) weight loss and/or metabolic parameters associated with diabetes, obesity, hypertension, hyper-lipidemia, and postmenopause, (4) skin and hair care, and (5) drug absorption.

Food processing, packaging, and formulation

Superheated steam treatment has been optimized to remove quinoa saponins while also expanding the seeds so as to reduce cooking time for the consumer (Thomas 1995). Tempe production from quinoa seeds has been developed via solid-state fermentation with *Rhizopus oligosporus* Saito, thereby producing a tempe product which contains all essential amino acids and lower levels of the estrogenic isoflavone compounds than those found in traditional soy-based tempe (Penaloza and others 1992).

The small size and thermostability of quinoa starch granules make them useful in frozen food packaging, emulsion-type products (thickeners), and malted beverages (Bhargava and others 2006). Recently, an antimicrobial biofilm comprised of gold nanoparticles incorporated in quinoa starch has been suggested for use in food packaging to prevent food-born pathogens *Escherichia coli* and *Staphylococcus aureus* (Pagno and others 2015). Furthermore, quinoa maltodextrins, derived from the hydrolysis of quinoa starches, possess a gel-like consistency for the delivery of performance-enhancing nutrients or use as a fat/cream substitute (Singer and others 1990; Enrione and others 2013).

Methods to improve the quality of baked goods via substitution of cereal grains for quinoa flour have been investigated. Up to 10% quinoa flour was used in wheat-based bread to improve nutritional quality without negatively affecting loaf volume. Gluten-free spaghetti made from quinoa flour instead of wheat flour had reasonable physical properties and acceptable taste. Gluten-free bread made from quinoa flour as opposed to potato starch had improved bread volume, softer crumb structure, and higher contents of protein, fiber, vitamins, minerals, polyphenols, and antioxidants (Valcárcel-Yamani and Caetano da Silva Lannes 2012). Loaf volume and texture were also improved by the substitution of quinoa flour for rice or corn flour in gluten-free bread production (Elgeti and others 2014). Considering the low nutritional value of gluten-free products currently available in the market, further work on the behavior of quinoa proteins and carbohydrates in bread- and pasta-making is warranted.

Concentration/purification of chemical constituents

Various methods to concentrate or purify quinoa proteins, oils, saponins, and phytoecdysteroids have been developed for food and pharmaceutical applications. One of the most highly studied quinoa extraction methods has been the production of quinoa protein concentrate via alkali or enzyme hydrolysis and precipitation. Hydrolyzed quinoa protein

showed higher protein solubility and may be useful for the treatment of protein deficiency, enhancement of sports performance, promotion of exercise recovery, and skin/hair care (Scanlin and Stone 2009; Kruger 2012; Enrione and others 2013; Pouvreau and others 2014). Quinoa protein isolate also demonstrated a hypocholesterolemic effect *in vivo* by inhibiting bile acid re-absorption in the small intestine and regulating cholesterol synthesis and catabolism (Takao and others 2005).

Extraction methods and uses of quinoa-derived lipids and triterpenoids have also been studied. For example, refined quinoa seed oils have been proposed for dermatological applications (Msika 2012). Quinoa-derived saponins may enhance the mucosal absorption of pharmaceutical drugs and vaccines due to their interactions with cell membranes (Estrada and others 1997). Lastly, quinoa extracts enriched in phytoecdysteroids (1.0% to 2.0% 20HE w/w) lowered adiposity and blood glucose levels associated with metabolic syndrome *in vivo* (Foucault and others 2011; Veillet and Lafont 2012; Graf and others 2014).

Rapid determination and breeding of improved crop qualities

Quinoa breeding programs in the Americas, Asia, and Europe have successfully improved quinoa crop qualities to facilitate seed production and mechanical harvesting, while improving protein content and minimizing saponin levels (Cusack 1984; Jancurová and others 2009; Bhargava and Srivastava 2013; Bendevis and others 2014). Quinoa is a challenging crop to breed via mass selection or hybridization because the small, tightly clustered flowers are difficult to manually emasculate and are mainly self-pollinating. Nonetheless, outcrossing occurs at rates of 0.5% to 9.9%, and both mass selection and hybridization have been practiced (Bhargava and Srivastava 2013). An alternative method for quinoa hybrid production is the use of cytoplasmic and genetic male sterile lines as maternal parents (Ward and Johnson 1994; Bhargava and Srivastava 2013).

These breeding approaches, combined with efficient methods of biochemical analysis, may facilitate the development of quinoa varieties with enhanced nutritional and medicinal properties. Researchers have begun to investigate variation in carbohydrate, lipid, vitamin, mineral, total polyphenol, and antioxidant contents among quinoa varieties using traditional biochemical analysis technologies (Bhargava and others 2006; Christensen and others 2007; Shen and others 2009; Gonzalez and others 2012; Miranda and others 2012a, 2012b; Yousef and others 2013). However, rapid, simple, low-cost techniques that require no sample preparation and generate no waste are preferable to traditional methods of sample analysis.

Near-infrared spectroscopy (NIRS) is a rapid technology that may be applicable for quinoa quality analysis. Previously used to monitor quality of cereal grains and beans, NIRS has been optimized to accurately determine protein, carbohydrate, lipid, ash, and moisture contents in quinoa seeds, as well as the concentrations of 12 specific amino acids (Escuredo and others 2014; Ferreira and others 2015). NIRS can also be developed to assess concentrations of fiber, fatty acids, vitamins, and minerals (Ferreira and others 2015).

Though NIRS may not be applicable for the determination of secondary metabolite concentration in quinoa seeds, a method to rapidly leach the total amount of phytoecdysteroids and flavonol glycosides available in quinoa seeds, without sample

destruction, has recently been developed by Graf and others (2014, 2015b) for application in phytochemical analysis of quinoa varieties. Further work is needed to determine the variation in phytosterols, phenolic acids, betalains, and glycine betaine among quinoa sources, as well as the genetic and environmental factors that influence their concentrations.

Conclusion

Quinoa is a culturally important, stress-tolerant crop with high nutritional value and unique phytochemical composition. Quinoa-derived products and their individual chemical constituents have demonstrated biological activities with various applications to benefit human health. Quinoa therefore has the potential to provide nutrition and medicine to millions of malnourished or health-impaired people worldwide. Further research, including additional human clinical trials, is required to understand quinoa's functional benefits, mechanisms of action, and phytochemical interactions. Lastly, integrative strategies to improve access to, awareness of, and deliverability of quinoa's health benefits among the scientific, agricultural, and industrial sectors are critical.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AFLPs	amplified fragments length polymorphisms
CE	catechin equivalents
CF	corn flakes
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
FAO	Food and Agriculture Organization of the United Nations
FRAP AA	ferric-reducing ability of plasma antioxidant activity
GAE	gallic acid equivalents
GSH	glutathione

HDL	high-density lipoprotein
20HE	20-hydroxyecdysone
HPLC	high-performance liquid chromatography
HPLC-DAD-ESI-TOF-MS	HPLC-photodiode array coupled with electrospray ionization time-of-flight mass spectrometry
IGF-1	insulin-like growth factor-1
IL-6	interleukin-6
IYQ2013	International Year of Quinoa 2013
LDL	low-density lipoprotein
MS	mass spectrometry
NIRS	near-infrared spectroscopy
nLC-ES-MS/MS	nano-HPLC electrospray ionization multistage tandem mass spectrometry
PUFAs	polyunsaturated fatty acids
RDA	recommended daily allowance
QF	quinoa flakes
SD	standard deviation
TAE	tannic acid equivalents
TBARs	thiobarbituric acid-reactive substances
TE	trolox equivalents
TNFα	tumor necrosis factor alpha
WHO	World Health Organization of the United Nations

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Figure 1.
Photograph of *Chenopodium quinoa* plants with varying fruit colors. Courtesy of David Wu, Jiaqi Agri, China.

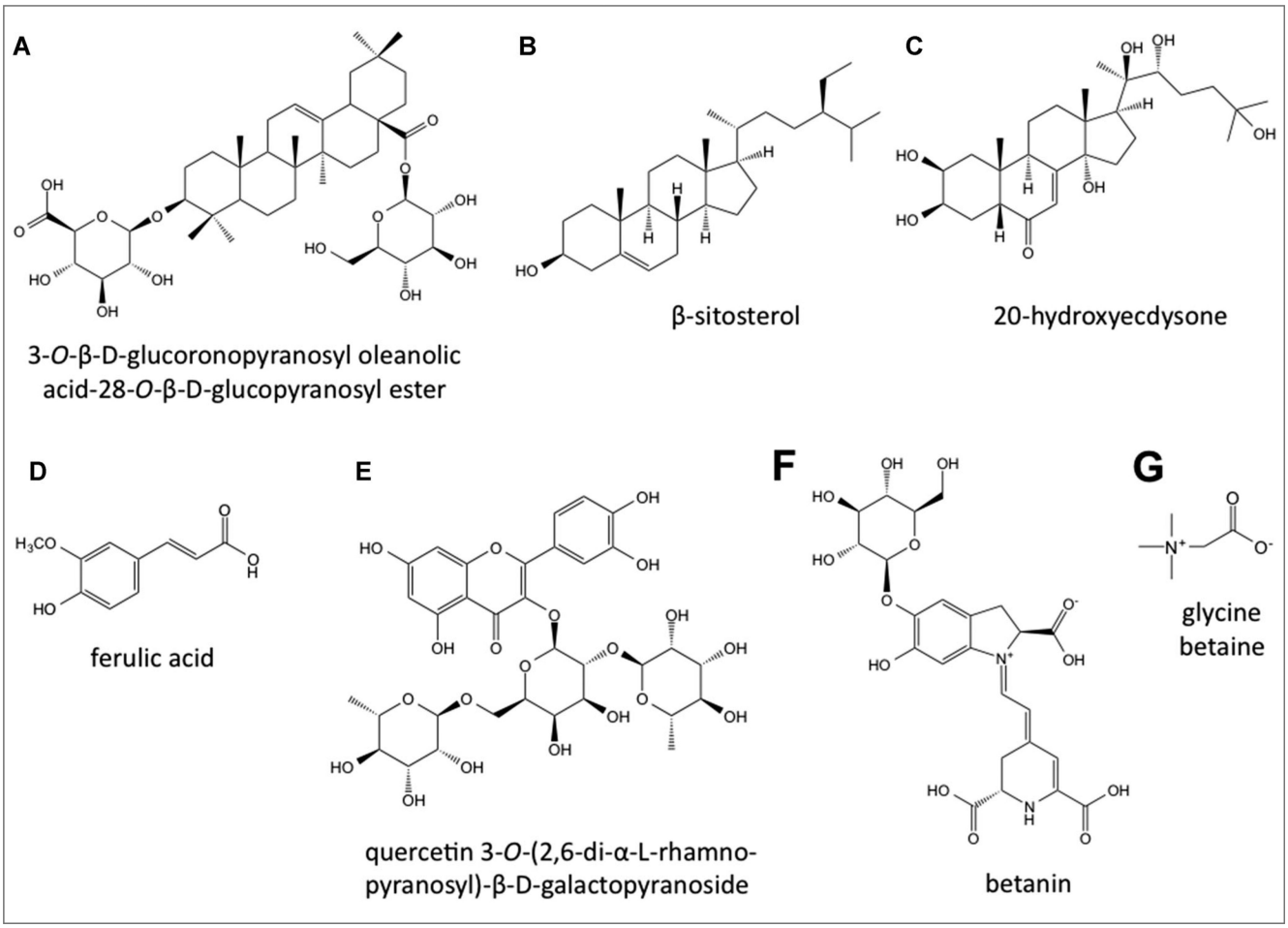

Figure 2.

Representative chemical structures of the major pharmacologically active secondary metabolites present in quinoa seeds. A: triterpene saponin, B: phytosterol, C: phytoecdysteroid, D: phenolic acid, E: flavonol glycoside, F: betalain, G: glycine betaine.

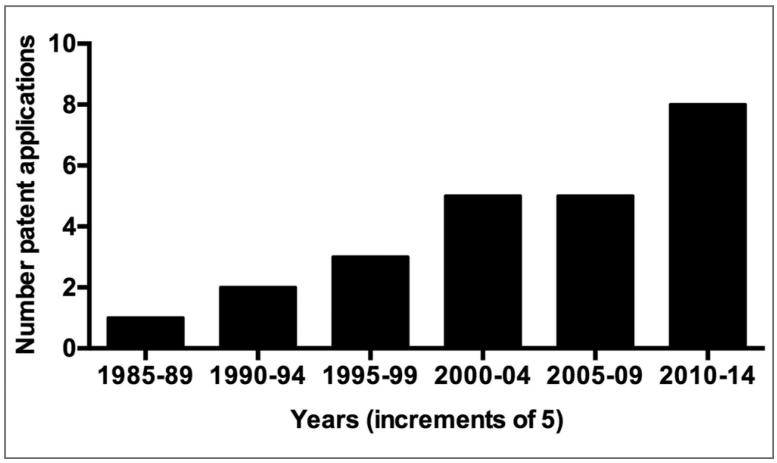

Figure 3.
Incremental increase in quinoa-related patent applications from 1985 to 2014.

Table 1

Phytoecdysteroid content among edible agricultural crop plants.

Common name	Scientific name	Plant part	Phytoecdysteroid content	Reference
Quinoa	*Chenopodium quinoa* Willd.	Seed	138 to 570 μg/g total phytoecdysteroids; 109 to 497 μg/g 20HE	Graf and others 2015a, 2015b; Kumpun and others 2011
Spinach	*Spinacia oleracea* L.	Dry leaves	40 μg/g 20HE	Gorelick-Feldman and others 2008
		Fresh whole plant	100 to 200 μg/g total phytoecdysteorids	Bakrim and others 2008
		Fresh leaves	≤40 μg/g total phytoecdysteroids	Dinan 1995
		Fresh roots and stem	≤100 μg/g total phytoecdysteroids	Dinan 1995
Beets	*Beta vulgaris* L.		nd	Báthori and others 1984
Bitter yam	*Dioscorea dumetorum* Kunth (Pax)	Dried rhizome	22 μg/g (20)-5β,11α,20-trihydroxyecdysone; 266 μg/g ajugasterone C; 32 μg/g herkesterone	Sautour and others 2008

nd, not determined, but the presence was confirmed.

Table 2

Clinical trials on the effect of quinoa products in human health.

Therapeutic application	Study participants and location	Treatment	Endpoints (measured before and after intervention) and outcomes	Conclusions	Reference
Child growth and development	Boys aged 50–65 months from low-income families in Ecuador	Infant food formulated from quinoa (100 g × 2/d for 15 days) compared with no treatment	↑ Plasma levels of IGF-1, a marker of malnutrition, known to increase body weight gain	Quinoa-based infant food may play a role in reducing childhood malnutrition	Ruales and others 2002
Celiac disease	19 celiac patients	Cooked quinoa (50 g/d for 6 weeks)	All gastrointestinal parameters (villus height:crypt depth), surfacen-enterocyte cell height, number of intra-epithelial lymphocytes per 100 enterocytes) improved following quinoa diet; serum lipid levels remained normal with small decrease in total cholesterol, LDL, HDL, and triglycerides	Quinoa is safe for consumption by celiac patients	Zevallos and others 2014
Risk of cardiovascular disease	22 students aged 18 to 45 years	Quinoa cereal bar daily for 30 days	↓ Triglycerides ↓ Cholesterol ↓ LDL	Quinoa intake may reduce risk of developing cardiovascular disease	Farinazzi-Machado and others 2012
Postmenopausal symptoms	35 postmenopausal women with excess weight (menopasual for ≥2 years, waist circumference > 80 cm, serum estradiol 10–20 pg/mL, follicle-stimulating hormone ≥35 mIU/mL, not undergoing hormone therapyor isoflavone supplements in the past 6 months, not taking lipid lowering drugs in the last 2 weeks)	Quinoa flakes (QF) compared with corn flakes (CF), 25 g/d for 4 weeks	QF consumption increased protein and fiber intake but not total caloric intake ↓ Triglycerides, ↓ TBARS ↓ Cholesterol, ↓ LDL, ↑ GSH	Quinoa intake beneficially modulates metabolic parameters	De Carvalho and others 2014

IFG-1, insulin-like growth factor 1; TBARS, thiobarbituric acid reactive substances; GSH, glutathione; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 3

Patents and patent applications related to quinoa.

Quinoa-derived product	Production method and/or use	Year(s) filed	Reference(s)
Treated seeds	Superheated steam treatment to expand the seeds and reduce cooking time	1992	Thomas 1995
	Mechanical abrasion, washing, or a combination to debitter seeds for use as flavoring or texturizing agents in food products	2010[a]	Scanlin and Burnett 2010
Flour	Substitute for food additives	2010[a]	Weinreich and Konecny 2011
Vegetative portion	Dried and heat treated for incorporation into animal foodstuffs	1996	Haaber 1999
Beverages	Boiling of quinoa seeds with other ingredients, including buckwheat, for production of a milk/tea/wine with a balanced and easily absorbable nutritional profile to promote human health; organic quinoa buckwheat tea production using certified organic quinoa	2013[a]; 2013	余磊 2014; 谢振文 2014
	Seeds are soaked, malted, kilned, mashed, cooled, and fermented with yeast to produce a gluten-free (and Kosher, optionally) fermented alcoholic beverage	2011[a]	Kamelgard 2013
	Mixing of quinoa extract, tiger nut (*Cyperus esculentus*), and α-amylases for hydrolysis of starches to thermostable maltodextrins within a beverage formulation that can act as a substitute for animal or plant-derived milk	2001[a]	Felipe and others 2003
	Seeds milled to specific particle size, mixed with liquid in specific ratio, and heated within specific temperature range for automated commercial-scale beverage production	2006[a]	Edwards 2007
Protein concentrate	Extraction and precipitation via alkali or enzyme treatment for use in foods, cosmetics, animal food, or sports performance and recovery	2012[a]; 2011[a]; 2012[a]; 2004	Enrione and others 2013; Kruger 2012; Pouvreau and others 2014; Scanlin and Stone 2009
	Incorporation in formulation for hair treatment	2011[a,b]	Kruger 2012
Lipid	Extraction and molecular distillation to obtain a refined oil for dermatological use	2007[a]	Msika 2012
Carbohydrate	Extraction of maltodextrin via alkali or enzyme treatment of quinoa flour to produce a gel-form to deliver quinoa-derived peptides for sports performance and recovery	2012[a,b]	Enrione and others 2013
	Use of quinoa starches of specific shape and particle size to act as cream substitute that mimics the mouth feel of fat/cream in foods	1988	Singer and others 1990
Saponins	Extraction and precipitation of saponins	1999; 2007[a]	Gamboa 2008; Muir and others 2002
	Protection of crop plants, especially potatoes, tomatoes, and rice, from fungal, bacterial, and mollusk pathogens	2007[a]; 2003; 2004[a]; 2001; 2008[a,b]	Bengtsson and others 2008; Dutcheshen 2004, 2005; Dutcheshen and Danyluk 2002; Gamboa 2008
	Growth promotion of crop plants	2007[a,b]	Bengtsson and others 2008
	Enhancement of mucosal absorption of pharmaceutical drugs/vaccines	1995	Estrada and others 1997
Phytoecdysteroids	Reduction of fat associated with metabolic syndrome	2008	Veillet and Lafont 2012
Cytoplasmic male sterile plants derived from Apelawa quinoa variety	Breeding of new high-yielding quinoa varieties	1992	Ward and Johnson 1994

[a] indicates application status (not granted).

[b] Patent was listed earlier in the table.