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# Exploring the health benefits of quinoa (*Chenopodium quinoa* Wild): a review of the recent literature

**Short title:** Health benefits of Quinoa (*Chenopodium quinoa* Wild)

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# Exploring the health benefits of quinoa (*Chenopodium quinoa* Wild): a review of the recent literature

Quinoa is a particularly nutrient-rich grain crop, which is abundant in micronutrients, fibre and essential amino acids, making it an excellent staple food source. The current review provide an outline of the antioxidant and anti-inflammatory properties of quinoa and a critical evaluation of health benefits following its consumption focusing on diabetes and diabetes risk factors, non-alcoholic fatty liver disease, hypertension, cancer risk, body weight regulation and obesity and cardiovascular disease risk factors. Quinoa has been demonstrated to have as hypoglycaemic effect and inducing favourable changes in cholesterol, HDL, and LDL levels, inflammatory markers as well as body weight in humans.

Keywords: obesity, diabetes, hypertension, NAFLD, cancer, CVD

## Introduction

Good nutrition can play a role in the prevention of many chronic diseases. Diseases such as ischaemic heart disease, stroke, dementia and diabetes are among the leading cause of death globally.[1] With the cost of chronic disease worldwide is estimated to reach $47 trillion by 2030,[2] people are searching for food related solutions to ameliorate the impact of current lifestyles on health.

*Chenopodium quinoa W.* is a plant originating from the Andes in South America. Processed quinoa grain, ready for preparation and subsequent consumption, is recognised as a particularly nutrient-rich grain crop, which is richer in micronutrients including riboflavin, thiamine and folic acid than many other grains such as oats, wheat, barley, rye, rice, and corn,[3, 4] Quinoa is considered a whole-grain product and as such a good source of, primarily insoluble, dietary fibre[5] which we know is lacking in diets across developed countries.[6, 7] It has a good composition of essential amino acids, with a Protein Digestibility Corrected Amino Acid Score (PDCAAS) higher than that of other plant protein sources

such as chickpeas and lentil.[8] Quinoa is also rich in bioactive compounds such as saponins, phenolic compounds, phytosterols, phytoecdysteroids, betalains, and peptide which can play potentially essential roles in the prevention of diseases. As well as being consumed as a whole grain, quinoa, through innovative food processing, can be utilised in a diverse range of food products including yogurt, bread, noodles, biscuits, ice cream and porridge providing an innovation nutritious food ingredient with positive potential for health.[9]

In the past number of years, there has been an increase in research into quinoa, particularly in the nutrition and food technology space, resulting in several reviews of the literature.[4, 10] Research assessing the application of quinoa in the prevention and treatment of chronic non-communicable diseases has also increased, however, there is lack of reviews in this area. While some reviews in the literature discuss the health benefits of quinoa [11, 12], they primarily focus on its nutritional profile and constituents, with little or no reference to its effects on specific diseases. The current review focuses on providing a critical evaluation of the antioxidant and consequent anti-inflammatory properties of quinoa and impact of quinoa consumption on diabetes and diabetes risk factors, non-alcoholic fatty liver disease, hypertension, cancer risk, body weight regulation and obesity and cardiovascular disease risk factors. The review describes the underlying mechanisms for improvement in health following the consumption of quinoa, as such, mechanistic cell, animal and human data has been included focusing on recent research published between 2019 and 2024.

## *Antioxidant properties*

The redox balance, in which oxidative species are rapidly counteracted by antioxidant defence mechanisms, is an essential factor in maintaining health in the organism.[13] The consumption of food products with high contents of antioxidants could lead to an increase in the body's antioxidant defence systems and plasma antioxidant status.[14] These antioxidant compounds have different mechanisms of action, such as activation of antioxidant enzymes, chelation of metals, blocking lipid peroxidation or elimination of superoxide radicals.[15] Quinoa seeds are an interesting field of investigation due to the high content of both macromolecules and phytochemicals[16] with antioxidant properties such as

triterpenoid saponins, phytoecdysteroids, phenolic compounds, betalains and bioactive peptides.[17] The phenolic compounds can act as antioxidants and eventually prevent many diseases.[18]

In an experiment involving forty-two rats under various conditions, antioxidant genes (GPX1, SOD1) increased nine to tenfold after quinoa administration (35 g/kg/day).[19] The bound polyphenols extracted from red quinoa demonstrate stronger DPPH and ABTS antioxidant activities in comparison to their free counterparts.[20] Conversely, in commercial samples, it has been observed that free phenolics exhibit higher ABTS and FRAP values.[21] In terms of quinoa varieties, Temuco, Rainbow, Nariño, and Titicaca are noted for their high antioxidant activity, with the Baer and Temuco cultivars characterized by high reducing power.[22, 23] Notably, Red Bolivian Real quinoa and Black Bolivian Real quinoa, both sourced from organic farming, exhibit substantial antioxidant activities, whereas Peruvian quinoa shows lower levels.[24]

Quinoa sprouts show better antioxidant activity than fully grown parts of the quinoa plant. Generally, the root and sprout manifest a superior antioxidant capacity compared to other plant components, suggesting their potential application as nutraceutical ingredients in the health food industry.[25] In an evaluation of sprouts' antioxidant activity during *in vitro* gastrointestinal digestion, significant increases were noted during the gastric stage, as measured by DPPH and ABTS, implying the release of bioactive compounds post-digestion.[26]

Research indicates that as the degree of quinoa seed milling increases (from 0% to 27.23%), the total ORAC and FRAP antioxidant activities decrease by 39.6% and 40.7%, respectively.[27] This is due to the milling process that results in a loss of phenolic compounds along with their antioxidant activity.[28] In protein hydrolysates, proteins are broken down into smaller peptides and amino acids. Quinoa protein hydrolysate exhibits superior emulsifying, foaming, and antioxidant properties compared to quinoa protein concentrate following hydrolysis by pancreatic enzyme.[29] Given the differences in antioxidant activities found in the different varieties, parts of the plant and processing levels (whole, milled, hydrolysates, concentrates), comparative studies should be conducted to optimize these parameters and maximise antioxidant properties.

The ethyl acetate fraction of quinoa extract has been found promising with high antioxidant activity, including DPPH and ABTS radical scavenging abilities, FRAP, ORAC, as well as potent α-glucosidase and acetylcholinesterase inhibitory effects.[30] Furthermore, crude polysaccharides from quinoa showcase notable antioxidant activities, with an increase observed as the molecular weight of quinoa polysaccharides decreases.[31]

Both the starter strains and fermentation time of quinoa can significantly influence its antioxidant activities. Fermentation with *Helvella lacunose* X1 results in high DPPH radical scavenging capacity and reducing power, while fermentation with *Fomitiporia yanbeiensis* G1 yields high superoxide anion radical scavenging ability.[32] Quinoa fermented by *B. breve* and *B. longum*, have significant antioxidant activity as well.[33] A recent study explored the impact of enzymatic hydrolysis on the antioxidant activity of white, red, and black quinoa varieties, along with the *in vivo* antioxidant capacity of the most promising quinoa hydrolysate, utilizing *Saccharomyces cerevisiae* BY4741 as an experimental model. The *in vitro* oxygen radical scavenging capacity was higher for the red quinoa hydrolysate produced with Alcalase 2.4 LFG. *In vivo*, the red quinoa hydrolysate significantly enhanced yeast cell growth rate, comparable to the recovery achieved with vitamin C or resveratrol. Moreover, in hypertensive rats the survivors after oxidative insult were significantly higher for the red quinoa hydrolysate than for known antioxidant compounds like vitamin C or resveratrol.[34] When quinoa flour is fermented with lactic acid bacteria strains to exploit its antioxidant potential, the scavenging activity of water/salt-soluble extracts from fermented doughs is notably higher than that of non-inoculated doughs.[35]

Lastly, as the roasting duration of quinoa seeds increases from 5 to 15 minutes, a reduction in antioxidant activity is generally observed, except at 300 W for 15 minutes, where the maximum antioxidant activity is found.[36] This might suggest that the cooking process (type of cooking, temperature and duration) should be taken under consideration in order to maximise the antioxidant activity of quinoa while preserving palatability. These findings are summarized in Table 1.

### *Anti-inflammatory property*

Inflammation is a protective nonspecific response of the immune system that can be triggered by a variety of factors.[37] Chronic inflammation is considered a plausible biological mechanism in the development of cancer in humans triggering the progression of inflammatory cytokines and chemokines and facilitating tumor growth (Reuter et al., 2010). Utilizing natural compounds can be a fundamental mechanism for altering gene expression, mitigating oxidative damage, and diminishing inflammation.[38]

Quinoa provides immunonutritional ingredients, including low-molecular-weight protein fractions and lipid fractions that promote hepatic innate immunity by regulating major lipid profiles. These effects are beneficial in counteracting immune and metabolic imbalances and liver dysfunction resulting from a high-fat diet.[39] The major O-prenylated phenylpropanoid phytochemical in ethanolic extracts from quinoa seeds, 40-Geranyloxyferulic acid, counteracts oxidative stress and restores redox balance by activating defensive antioxidant enzymes. It can be considered a new candidate for reducing intestinal mucosal inflammation.[40] The ethanol extraction process yields high rutin and antioxidative agents from red quinoa bran, exhibiting strong effects in preventing alcoholic fatty liver disease and liver injury by increasing the superoxide dismutase/catalase antioxidative system and repressing the expression of the fatty acid synthesis enzyme acetyl-CoA carboxylase.[41] Quinoa consumption has been shown to alleviate clinical symptoms of colitis and reduce the degree of histological damage in mice. Compared to mice fed a standard diet, those consuming quinoa experienced remarkable alleviation of dextran sulfate sodium (DSS)-induced dysbiosis.[42] In the form of quinoa yogurt (20 μL/g), it can reduce proinflammatory cytokine levels and inhibit endotoxemia and systemic inflammation.[43]

In an experiment with forty-two rats subjected to different conditions, apoptotic (BCL2 5, BAX 9, CAS 3), autophagic (SQSTM1 7, ATG5), and inflammation-related (IL-1β, TNF-α) genes were upregulated by 5–11-fold in the insulin resistance-created group. However, in the groups receiving quinoa (35 g/kg per day) for treatment and protection, these genes were upregulated to a lower extent.[19] The most potent fraction of quinoa bran saponins (100 mg/kg) was found to reduce levels of uric acid, serum urea

nitrogen, creatinine, and lipids in mice with hyperuricemia, decreasing renal inflammation and damage.[44]

Tested on animals, a synergistic anti-inflammatory drug (quercetin/Epigallocatechin-3-gallate)-loaded micelle, developed using hydrolytic quinoa protein and cationic lotus root starch, efficiently accumulated in the colonic inflammatory region and enabled sustained release of drugs for more than 24 hours, notably alleviating symptoms of ulcerative colitis.[45] Similarly, quinoa protein hydrolysates prepared using different enzymes (papain, pepsin, and pancreatin) and total protein from quinoa possess high anti-inflammatory activity.[46] The protein hydrolysate from quinoa prepared using pepsin for 120 minutes exhibited high solubility and significantly suppressed 3T3-L1 cell differentiation through the PPARγ pathway.[46] Moreover, when quinoa protein isolate is combined with mannose and xylose and reacted at 65 °C, structural changes enhance its anti-inflammatory and antiproliferative activities, as observed in *in vitro* studies.[47] Regarding chenopodin, the major protein component of quinoa seeds, both low and high charge chenopodin show potential anti-inflammatory activities in an undifferentiated Caco-2 cell model, acting differently depending on their structural features. Low charge chenopodin likely binds to IL-1, preventing cytokine interaction with the target membrane receptor, while high charge chenopodin interacts directly with cells, possibly reducing the accessibility to IL-1.[48] These findings are summarized in Table 2.

## ***Impact of quinoa consumption on chronic disease risk factors***

### *Body weight regulation and obesity*

Obesity is caused by the interaction of many factors such as diet, environment, and genetics.[49] It is a complex disorder caused where adipose tissue is accumulated due to increasing and enlarged fat cells.[50] Obesity is related not only to higher mortality, but also to an increased risk of cardiovascular disease, diabetes, gallbladder disease, and various cancers.[51] Foods containing natural products could be an alternative approach for obesity management.[52] Quinoa phytochemicals include a balanced combination of compounds which may contribute to lower the risk of obesity-related chronic diseases.[53–55]

Furthermore, a quinoa diet (2 g quinoa/day) has been shown to reduce body weight and body fat mass while improving serum glucose and lipid distribution in a mouse model of high-fat diet-induced obesity. The underlying mechanisms involve the regulation of endoplasmic reticulum stress through eIF2α, GRP78, and CHOP in liver tissues by quinoa.[56] Even in the form of quinoa yogurt (20 μL/g), it demonstrated a significant reduction in body weight gain and fat tissue weight in high-fat diet-fed obese mice.[43] The body weight gain of obese-diabetic (db/db) mice under a quinoa-supplemented diet was delayed during the first five weeks of dietary intervention. Hepatic steatosis and total fat accumulation in the liver were reported to be similar between those under a lean diet and a quinoa diet, both lower than the obese diet.[57]

Supplementation of quinoa seed (200 mg/kg b.w./day) in obese rats was found to reduce adipogenesis by downregulating adipogenesis transcription factors and lipogenesis mediators. Additionally, it exhibited an upregulatory effect on oxidative-encoding genes and a downregulatory effect on lipogenic-related genes.[58] Separated and purified bioactive polysaccharides from quinoa were shown to have inhibitory effects on 3T3-L1 adipocyte differentiation, a process linked to obesity. The proliferation was inhibited through the promotion of PPARγ, C/EBPα, C/EBPβ, C/EBPδ, SREBP1C, and AP2 expression.[59, 60]

Quinoa seeds have been reported to contain significantly higher saponin content than other parts such as quinoa stem, leaves, and roots.[25] Saponins extracted from quinoa bran were capable of reducing body weight gain and visceral fat accumulation in obese rats. Trends in ameliorating insulin resistance and improving glucose tolerance were also observed.[61] Quinoa, especially when combined with saponin, has shown significant improvements in high-fat diet-induced obesity rats. It not only alleviates abnormal glycolipid metabolism but also reverses gut microbiota dysbiosis and functional profiling of microbial communities, particularly in lipid metabolism and carbohydrate metabolism. Furthermore, it upregulates the expression of TGR5 in the colon and brain, as well as GLP-1 in the colon, liver, and brain. Simultaneously, it downregulates the expression of TLR4 in the colon and liver, along with markers of endoplasmic reticulum stress and oxidative stress in livers and sera.[62]

In an experiment with human subjects, where participants aged 65 years adopted a quinoa-based diet, replacing foods rich in complex carbohydrates, a decrease in body weight, BMI, and waist circumference was observed. Nutrient intake during the quinoa diet showed changes, including a decrease in carbohydrates and an increase in lipids and some amino acids.[63] These findings are summarized in Table 3.

*Diabetes and glycaemic control*

According to the Centers for Disease Control and Prevention, 14.7% (38.1 million) of all adults in the United States (U.S.) had diabetes in 2021.[64] The liver is an organ that plays a key role in regulating metabolism and maintaining blood sugar levels. Metabolism is usually disturbed due to diabetes which may affect the function of liver cells, preparing them for various liver disorders as well as causing disturbance in renal function.[65, 66] Several studies suggest that quinoa, high in nutrients, fibre, and phytochemicals , may be a prime candidate for dietary intervention to prevent and counteract type 2 Diabetes.[53]

Quinoa appears to exert hypoglycemic effects through the gut microbiota and the TAS1R3/TRPM5 taste signaling pathway. In type 2 diabetes mellitus mice, quinoa (2 g per day) significantly improves abnormal glycolipid metabolism and positively contributes to the enhancement of gut microbiota composition. Notably, it downregulates the expression of TAS1R3 and TRPM5 in the colon.[67] Quinoa's regulation of microbiota in the colon primarily impacts Bacteroidetes, Actinobacteria, and Desulfovibrio, leading to a decrease in the Firmicutes/Bacteroidetes ratio and the abundance of Blautia.[67] When administered to diabetic rats (25 % of total feed), quinoa seeds demonstrate a hypoglycemic effect and induce favourable changes in cholesterol, HDL, and LDL levels.[68]

Although glucose levels significantly decrease with quinoa administration to rats (35 g/kg/day), insulin levels and the Homeostatic Model Assessment of Insulin Resistance show no significant changes. However, other biochemical parameters, including alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total cholesterol, total protein, urea, and creatinine, undergo significant alterations in insulin resistance-created rats following quinoa administration.[19] A study

involving male Wistar rats with cafeteria diet-induced obesity reveals that feeding 315g of quinoa seeds per 1000 g of chow diet can lead to reduced energy intake, differentiated macronutrient intake, regulated glucose homeostasis, attenuated microvesicular steatosis, hepatocyte degeneration, and increased IRS-1 and AMPK in the liver. Additionally, there is a potential attenuation of insulin immunoreactivity in pancreatic β-cells.[69]

The sprouting and/or fermentation of quinoa enhances its ability to reduce the glycemic index of diets high in simple carbohydrates. This effect is associated with the chemical changes occurring in quinoa as a result of processing. Regarding fermentation, this could be related with the formation of lactic acid that increases starch retrogradation, and therefore, increases resistant starch formation. Consequently, food intake, blood glucose and lipid levels, and the accumulation of epididymal adipose tissue can be reduced in rats fed diets supplemented with quinoa.[70] However, in obese-diabetic (db/db) mice, quinoa intake increases plasma insulin without offering protection from other pathophysiological manifestations.[57]

Molecular weight is closely related to the structure and biological activity of polysaccharide. Crude polysaccharides from quinoa exhibit certain antidiabetic activities, with the activity increasing as the molecular weight decreases. The glycemic index of quinoa polysaccharides shows a significant correlation with α-glucosidase inhibitory activity.[31] Furthermore, bound polyphenols from red quinoa demonstrate a lower $IC_{50}$ value in inhibiting α-glucosidase activity compared to free polyphenols. Both free and bound polyphenols can inhibit α-glucosidase in a non-competitive mode and an uncompetitive mode, respectively. The effective delay in starch digestion and suppression of postprandial hyperglycemia by bound polyphenols is more pronounced than that achieved by free polyphenols. In Institute of Cancer Research (ICR) mice, bound polyphenols at a level of 50 mg/kg have been found to reduce postprandial glucose increases comparably to acarbose at 20 mg/kg.[20] The ethyl acetate fraction of quinoa extract has been reported to possess the strongest α-glucosidase and acetylcholinesterase inhibitory abilities among various fractions.[30]

Dipeptidyl peptidase IV (DPP-IV) inhibitors, used to manage type 2 diabetes mellitus, have been explored in quinoa protein-derived peptides (IPI, IPV, VAYPL, and IPIN), showing competitive

inhibition of DPP-IV.[71, 72] Quinoa protein, especially globulin, emerges as a potential source of peptides with dipeptidyl peptidase-IV (DPP-IV) and angiotensin-I-converting enzyme (ACE) inhibitory activities.[73] You et al, (2022), reported that hydrolysates with a molecular weight below 1 kDa demonstrate *in situ* DPP-IV inhibition on Caco-2 cells.[72] Papain has a relatively strong potential as an enzyme releasing DPP-IV and ACE inhibitory peptides, although it exerts a lower degree of hydrolysis than stem bromelain.[73]

Quinoa protein-rich flour significantly increases microbial activity in the caecum, enhancing the activity of α-glucosidase, β-glucosidase, and α-galactosidase, as well as the production of short-chain fatty acids, primarily butyric acid.[74] Incorporating quinoa as a staple dietary food (100 g of quinoa replaced the same amount of the daily staple food) can regulate glucose tolerance and reduce blood glucose and lipid levels in patients diagnosed with impaired glucose tolerance.[75] In the elderly population at risk of developing type 2 diabetes, a diet rich in quinoa as a substitution for other foods high in complex carbohydrates shows promise as a type 2 diabetes preventive strategy. A reduction in postprandial glycemia has been observed in participants aged 65 years following a quinoa-rich diet, owing to the combined action of different nutrients and the suppression of others consumed regularly.[63] These findings are summarized in Table 4.

### *Non-alcoholic fatty liver disease*

The accumulation of triglycerides in liver cells leads to non-alcoholic fatty liver disease (NAFLD), a liver manifestation of obesity and metabolic syndrome.[76] NAFLD is the most common liver disease worldwide and the leading cause of liver-related morbidity and mortality.[77] possessing a heightened risk for the development of type 2 diabetes and other key components of the metabolic syndrome.[78]

Quinoa emerges as an effective preventive measure against NAFLD, demonstrating its efficacy through the control of body weight, attenuation of oxidative stress, regulation of the lipid metabolic profile, and modulation of gene expression related to lipid metabolism and the immune response.[43, 79] Even in relatively low amounts (equivalent to 100 g/d of human intake), quinoa has been found to exert control over the weight of rats fed a high-fat diet. Moreover, it inhibits the increase in triglyceride and total

cholesterol levels, mitigates pathological injury, and promotes increased activities of superoxide dismutase and glutathione peroxidase, and decreases malondialdehyde levels. Quinoa also regulates lipid metabolites in both the circulation system and the liver, such as LysoPC and PC. Transcriptomic analysis (RNA-Seq) and subsequent RT-PCR verification reveal that a higher quantity of quinoa more effectively upregulates genes related to lipid metabolism and downregulates genes associated with the immune response.[79]

In a comparison of the effects of immunonutritional bioactives from quinoa when used to partially replace (25%) wheat flour in bread formulations, it was observed that feeding animals with quinoa formulations (14 mg bread per day) influenced the expression of lipogenic and coronary risk markers. This led to better control of hepatic lipid accumulation, and quinoa products also demonstrated improved glucose homeostasis compared to wheat flour, normalizing the HOMA-IR in animals with altered glucose and lipid metabolism.[80] Additionally, addressing endotoxemia and systemic inflammation in high-fat diet-fed mice is achievable by restoring normal levels through the consumption of yogurt containing quinoa (20 μL/g). This combination effectively alleviates symptoms of non-alcoholic fatty liver disease and may exert its effects via mechanisms associated with the microbiome-gut-liver axis. Quinoa yogurt has been shown to significantly reduce liver steatosis, enhance glucose homeostasis, and improve insulin sensitivity in mice.[43] More work, though, is required incorporating human subjects to explore the potential effect of quinoa to NAFLD. These findings are summarized in Table 5.

*Hypertension*

Hypertension is the leading cause of cardiovascular diseases and premature death worldwide.[81] There are several risk factors that can increase the likelihood of developing hypertension such as family history, age, race, physical inactivity, sleep apnea, smoking, stress, regular consumption of a diet rich in salt, fat and alcohol.[82] Changes in lifestyle is the most relevant approach in the treatment of hypertension.[83]

As prolonged hypertension is known to contribute to the development of type 2 Diabetes Mellitus, recent research has been focused on identifying natural products with the ability to inhibit enzymes that cause hypertension, such as angiotensin-converting enzyme (ACE).[84] In many diabetic cases, ACE inhibitors are commonly prescribed to reduce the risk of other complications (Konrad et al., 2014). Quinoa protein emerges as a promising natural source of ACE inhibitory peptides, capable of lowering blood pressure in spontaneously hypertensive rats.[85, 86]

In a study involving the administration of quinoa protein (400 mg/kg body weight) to spontaneously hypertensive rats, a significant decrease in blood pressure was observed, accompanied by a notable increase in alpha diversity and alterations in microbial structure towards that seen in non-hypertensive rats. Blood pressure was found to be highly negatively correlated with the elevated abundance of genera in quinoa protein-treated spontaneously hypertensive rats, such as Turicibacter and Allobaculum. Interestingly, the fecal microbiota in quinoa protein-treated spontaneously hypertensive rats shared more features in the composition of genera with non-hypertensive rats than with the captopril-treated group.[86] López-Moreno et al. (2023) reported an *in vivo* antioxidant effect of quinoa hydrolysate and its ability to ameliorate hypertension and its associated complications. Quinoa hydrolysate demonstrated a protective effect against oxidative stress, which may be related to the antioxidant effect demonstrated *in vitro*. In terms of lipid peroxidation in the kidney of spontaneously hypertensive rats, quinoa hydrolysate at a dose of 1000 mg/kg/day induced a significant decrease in kidney malondialdehyde levels.[87]

Quinoa yoghurt beverage, optimized by germination-influenced hydrolysis, exhibits a dual inhibitory action on α-glucosidase and ACE through bioactive peptides. The quinoa yoghurt beverage fermented with *Lactobacillus casei* SY13 demonstrated the highest inhibitory activities, likely attributed to its relatively higher amino acid contents and hydrophobicity. Notably, both LAHMIVAGA and VAHPVF, identified as potent inhibitory peptide sequences, significantly exhibited α-glucosidase and ACE inhibitory activities.[85] Additionally, a bioactive peptide produced by quinoa albumin (RGQVIYVL, 946.6 Da) has shown high ACE-inhibitory activity with a competitive mode of inhibition and a significant antihypertensive effect in spontaneously hypertensive rats at a concentration of 100–150

318 mg/kg body weight.[88] Lastly, quinoa fermented in vitro by *B. breve* and *B. longum* demonstrated
319 markedly increased ACE-inhibition and antihypertensive activities.[33] These findings are summarized
320 in Table 6.

321 *Cardiovascular disease risk factors*

322 Cardiovascular diseases continue to be the major cause of morbidity and death across the globe of all
323 the non-communicable diseases (approx. 17.9 million).[89] Excess body weight, and diet are considered
324 the most potent risk factors for cardiovascular diseases.[90, 91] The consumption of plant-based
325 ingredients with a high content of antioxidant compounds and phytosterols play an important role in
326 lowering total and LDL cholesterol and regulating cardiovascular diseases.[14, 92]

327 A diet enriched with quinoa protein-rich flour in male Wistar rats has been observed to positively affect
328 the plasma lipid profile by reducing total cholesterol and LDL cholesterol levels. However, it was noted
329 to increase the level of plasma inflammatory markers.[74] Additionally, a quinoa diet (2 g quinoa/day)
330 has shown significant reductions in blood glucose, triglyceride, cholesterol, and low-density lipoprotein
331 levels, along with improvements in glucose tolerance and positive changes in liver tissue histology in
332 obese mice.[56] In obese-diabetic mice fed a quinoa-supplemented diet, plasma levels of total cholesterol,
333 LDL cholesterol, oxidized-LDL, protein carbonyls, and interleukin (IL)-6 were reduced to levels similar
334 to lean mice.[57] Quinoa seeds (200 mg/kg b.w./day) administered to a High-Fat Diet–Induced Obesity
335 Rat Model demonstrated hepatoprotective effects, anti-inflammatory and antioxidant activities, and
336 modulation of leptin, adiponectin, serum lipid, and glycemic profiles.[58]

337 A dietary intervention with extracted soluble and insoluble quinoa bran dietary fibre was found to
338 reduce body weight, liver weight, blood glucose levels, and serum levels of total cholesterol and
339 triglycerides. It also decreased plasma transaminase (AST and ALT) levels, improved liver
340 morphology, and inhibited lipid deposition in obese rats. Aspartate aminotransferase and alanine
341 aminotransferase was reduced after the intervention with insoluble quinoa bran dietary fibre,
342 demonstrating that it improves liver injury more significantly than soluble dietary fibre. Insoluble
343 quinoa bran dietary fibre supplementation significantly improved the oxidation resistance of obese rats

by decreasing malondialdehyde and increasing superoxide dismutase and glutathione peroxidase levels.[93] Additionally, both red quinoa bran ethanol and water extracts were reported to decrease alcoholic diet-induced activities of aspartate aminotransferase and alanine aminotransferase, as well as levels of serum triglycerides, total cholesterol, and hepatic triglycerides.[41]

Studies by Pourshahidi et al. (2018) and Pourshahidi et al. (2020) suggested that regular quinoa consumption (2 × 15 g quinoa-enriched biscuits (60 g quinoa flour/100 g) and 9 g quinoa/day respectively), in the form of quinoa biscuits, could contribute to a lower cardiovascular diseases risk in older adults. Consumption of quinoa biscuits led to decreases in circulating total and LDL cholesterol concentrations, body weight, BMI, and TC:HDL ratio. No significant differences were observed in the change in triglycerides, HDL cholesterol, total PUFA, or CRP concentrations between treatment groups.[94, 95] However, contrasting results were reported for quinoa-enriched bread (20 g quinoa flour/day) in healthy overweight men. After a 4-week intervention, blood glucose and low-density lipoprotein (LDL) cholesterol were significantly lower than baseline in both groups, but no significant difference was observed between the quinoa and control groups. This indicates that the consumption of 20 g of quinoa per day in the form of a wheat-quinoa bread roll might not affect markers of cardiovascular disease risk.[96] These studies highlight the need for future research to focus on understanding the most beneficial daily intake amounts of quinoa in humans. These findings are summarized in Table 7.

### *Cancer risk*

Cancer is a complex and heterogeneous disease where genetic and environmental factors contribute to initiation, progression, and resistance to treatments.[97] Tumor cells frequently upregulate aerobic glycolysis (Warburg effect) and glutaminolysis to sustain cell proliferation.[98, 99] The World Health Organization estimates that 30 to 50% of all cancer cases are preventable by adopting healthy lifestyles.[100] A big variety of medicinal aspects of plant extracts can have successful anticancer effects.[101] Plant extracts possessing anti-inflammatory, antioxidant, anti-proliferative, and anti-

angiogenic properties, are able to block, reverse, or prevent tumor growth. Thus, they have been investigated as part of anticancer therapies.[102]

Quinoa bran terpenoids (0.6 mg/mL applied on adherent cells) exhibit a remarkable ability to suppress tumor growth in nude mice. They significantly inhibit the proliferation of colorectal cancer cells DLD-1 and HCT-8 in a concentration-dependent manner. These terpenoids reduce mitochondrial membrane potential, promote the expression of the pro-apoptotic protein Bax, and inhibit the antiapoptotic protein Bcl-2.[103] In an azoxymethane/dextran sulfate sodium (AOM/DSS)-induced mouse model of colorectal cancer, quinoa protein (100 to 400 mg/kg/day) and its hydrolysate (100 to 400 mg/kg/day) demonstrated ameliorative effects by altering intestinal flora and increasing the production of beneficial short-chain fatty acids. The administration of quinoa protein or its hydrolysate mitigated clinical symptoms of colorectal cancer and increased short-chain fatty acids contents in colon tissues. Moreover, it partially alleviated gut microbiota dysbiosis in colorectal cancer mice by decreasing the abundance of pathogenic bacteria and increasing the abundance of probiotics.[104] Contrary to these findings, quinoa saponin-rich extracts did not show relevant activities in inhibiting colorectal cancer cell lines, unlike fenugreek saponin-rich extracts.[105]

Quinoa protein hydrolysate demonstrated the potential to inhibit the proliferation of colon cancer cells, particularly in Caco-2 cells. Peptides identified from the hydrolysate, including FHPFPR, NWFPLPR, and HYNPYFPGGA, displayed promising antiproliferative activity. Specific amino acids in the peptide sequence were suggested to contribute to the binding mode between peptides and HDAC1, potentially inhibiting HDAC1 activity and modulating cancer-related gene expression.[106] Peptides with chemopreventive potential from quinoa protein showed the highest inhibitory effects on colon cancer cell viability during the intestinal phase, with fractions containing peptides > 5 kDa exhibiting the greatest anti-cancer effects.[107]

In an *in vitro* digestion experiment, the addition of olive leaf polyphenolic extract (OLE) to quinoa protein isolate (QPI) solution promoted the production of bioactive peptides. Hydrolyzed QPI/OLE complexes exhibited significant reductions in cell survival compared to OLE alone.[108] Purified quinoa

husk peptides demonstrated the ability to reduce melanin content in cultured cancer cells and rats, as well as accelerate A375 cell apoptosis, contributing to the reduction of melanin content.[109]

Ethanolic extracts of red and white quinoa, rich in hederagenin, a type of quinoa saponin, demonstrated higher caspase-3 activity than staurosporine in HeLa cancer cells, suggesting an anti-cytotoxic activity via a caspase-dependent apoptosis pathway. However, the ethanolic extracts did not exhibit cytotoxic activity.[110] The O-prenylated phenylpropanoid phytochemical 40-geranyloxyferulic acid, found in ethanolic extracts from quinoa seed, interfered with the expression of the CAT-2B transporter in human cancer colon cells, leading to a reduction in phlogistic mediators NO.[40] Low-polarity fractions of quinoa, such as CHCl3 and nonsaponifiable fractions, exhibited cytotoxic potential against A549 human lung cancer cells. The lipoidal components and different fractions of quinoa demonstrated cytotoxic activity against lung cancer cell line A549, with varying responses in human colon cancer cell (Caco-2) and human hepatocellular carcinoma cells (HepG2).[111]

Quinoa's oils nanocapsules (100 and 200 mg/kg body weight) in rat models repressed the activation of cancer-associated genes MYC and PIK3CA, modulated liver enzymes, and mitigated kidney function alterations induced in mammary tumor animals. Notably, healthy rats' livers and kidneys were not impacted. The inhibition of tumors in response to quinoa nanocapsules was associated with a reduction in tumor necrosis factor-α (TNF-α) levels, proliferation capability, and induction of apoptosis.[112] Quinoin, a type 1 ribosome-inactivating protein found in quinoa, has shown the ability to strongly reduce glioblastoma cancer cells' growth. When used in combination with temozolomide, a standard treatment for glioblastoma, quinoin enhances the sensitivity of primary cells to the treatment.[113] These findings are summarized in Table 8.

## *Conclusion and Future perspectives*

Quinoa is recognized for its rich nutrient profile and potential health benefits, making it a valuable dietary component in the prevention and management of chronic diseases. Various components contribute to its potent antioxidant and anti-inflammatory properties, which are crucial in maintaining health.

Quinoa consumption has been linked to weight loss and reduced fat mass. It influences metabolic pathways and gut microbiota, contributing to improved weight management and metabolic health. This makes quinoa a promising dietary intervention for managing and preventing type 2 diabetes. Moreover, recent research has demonstrated reductions in blood pressure following quinoa administration in rats, as well as, protective effect in managing hypertension and its associated complications. Quinoa consumption can positively affect the plasma lipid profile, reduce inflammatory markers, and improve overall cardiovascular health. There is also evidence that quinoa protein and its hydrolysates can inhibit cancer cell proliferation, particularly in colorectal and colon cancer models.

As we graphically summarize in figure 1, the effects of processing and cooking methods used to incorporate quinoa into foods versus more direct methods (intake of cooked quinoa on its own or plain) on the bioavailability of quinoa's health markers should be investigated using both *in vitro* and *in vivo* approaches. Moreover, future studies should focus on understanding the effects of the food matrix on quinoa's health benefits by incorporating it into different food formulations. Only a few of the reported studies used different food matrices (bread, biscuits and yogurt); therefore, comparisons among those are necessary. Lastly, and most importantly, more research data from studies involving human subjects are crucial for having a clear picture of how quinoa incorporation in our diets affects health. This will contribute to a holistic approach towards nutrition as part of public health interventions, where good health and well-being is achieved through dietary changes to prevent nutrition-related illnesses in the population.

## *Disclosure statement*

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Tables

844 Table 1. Studies evaluating the antioxidant action of quinoa (*Chenopodium quinoa* W.).

| Form of quinoa | Model* | Intervention | Key results | Reference |
|---|---|---|---|---|
| Quinoa seeds | IVV (R**) | The control group, the quinoa administered group, the insulin resistance-created group, the insulin resistance-created + metformin group, the insulin resistance-created + quinoa for treatment group and the quinoa + insulin resistance-created for prophylaxis group. | Antioxidant genes (GPX1, SOD1) increased nine to tenfold after quinoa administration (35 g/kg per day). | [19] |
| Free polyphenols and bound polyphenols extracted from red quinoa | IVT | N/A | The bound polyphenols extracted from red quinoa demonstrate stronger DPPH and ABTS antioxidant activities in comparison to their free counterparts. | [20] |
| Quinoa seeds | IVT | N/A | Antioxidant activities measured by FRAP, ABTS+• and DPPH of free, conjugated and bound extracts were broadly similar, except for free antioxidants when determined by FRAP, which were higher. | [21] |
| Different quinoa seeds varieties | IVT | N/A | According to the DPPH technique, Nariño had the highest value. Based on the FRAP technique, Titicaca and, on the ABTS method, both cultivars had the greatest values. | [22] |
| Different quinoa seeds varieties | IVT | N/A | The best antiradical properties were determined for Temuco and Rainbow quinoa varieties, while the Baer and Temuco cultivars were characterized by the highest reducing power. | [23] |
| Various parts of quinoa plants | IVT | N/A | Quinoa sprouts showed better antioxidant activity than fully grown parts of the quinoa plant. | [25] |
| Quinoa sprouts | IVT | N/A | The antioxidant capacity significantly increased during the gastric stage relative to the oral stage. | [26] |
| Quinoa seeds | IVT | N/A | As the degree of quinoa seed milling increased the total ORAC and FRAP antioxidant activities decreased. | [27] |
| Quinoa protein hydrolysate | IVT | N/A | Quinoa protein hydrolysate exhibited superior emulsifying, foaming, and antioxidant properties compared to quinoa protein concentrate. | [29] |
| Quinoa extract and its fractions | IVT | N/A | The ethyl acetate fraction of quinoa extract found promising with high antioxidant activity. | [30] |

| | | | | |
|---|---|---|---|---|
| Crude polysaccharides from quinoa | IVT | N/A | Crude polysaccharides from quinoa showed notable antioxidant activities, with an increase observed as the molecular weight of quinoa polysaccharides decreases. | [31] |
| Quinoa after solid-state fermentation | IVT | N/A | Both the starter strains and fermentation time of quinoa can significantly influence its antioxidant activity. | [32] |
| Quinoa fermented by three species of *Bifidobacterium* spp. | IVT | N/A | Quinoa fermented by *B. breve* and *B. longum*, had significant antioxidant activity. | [33] |
| Hydrolysate from white, red and black quinoa varieties | IVT and IVV (R) | Control (tap water; n = 8), vitamin C (a vitamin C solution 250 mg/kg/day; n = 8) and QrHH (a red quinoa hydrolysate solution 1000 mg/kg/day; n = 8). | The IVT oxygen radical scavenging capacity was higher for the red quinoa hydrolysate produced with Alcalase 2.4 LFG. IVV, the red quinoa hydrolysate significantly enhanced yeast cell growth rate, comparable to the recovery achieved with vitamin C or resveratrol. | [34] |
| Fermented quinoa flour | IVT | N/A | The scavenging activity of water/salt-soluble extracts from fermented doughs was notably higher than that of non-inovulated doughs. | [35] |
| Microwave treated quinoa | IVT | N/A | As the roasting duration of quinoa seeds increased from 5 to 15 minutes, a reduction in antioxidant activity was generally observed, except at 300 W for 15 minutes, where the maximum antioxidant activity was found. | [36] |

845 * IVT: *in vitro* and IVV: *in vivo*

846 ** R: rats and M: mice

847

848 Table 2. Studies evaluating the anti-inflammatory action of quinoa (*Chenopodium quinoa* Wild).

| Form of quinoa | Model* | Intervention | Key results | Reference |
|---|---|---|---|---|
| Quinoa's germen | IVV (M**) | Six week old Rag2-/- and Rag2-/-Il2-/- mice received (12 days) a low-molecular-weight protein fraction or the lipid fraction obtained from the cold pressing of quinoa's germen. | Quinoa provides immunonutritional ingredients, including low-molecular-weight protein fractions and lipid fractions that promote hepatic innate immunity by regulating major lipid profiles. | [39] |
| Quinoa seeds | IVT | N/A | The major O-prenylated phenylpropanoid phytochemical in ethanolic extracts from quinoa seeds, 40-Geranyloxyferulic acid, counteracted oxidative stress and restored redox balance by activating defensive antioxidant enzymes. | [40] |
| Red quinoa bran | IVV (M) | The mice were given whole grain powder of red quinoa, red quinoa bran ethanol extract, red quinoa bran water extrac, and rutin orally for 6 weeks. | The ethanol extraction process yielded high rutin and antioxidative agents from red quinoa bran, exhibiting strong effects in preventing alcoholic fatty liver disease and liver injury. | [41] |
| Yogurt containing quinoa | IVV (M) | Yogurt with addition of polymerized whey protein was used as the control yogurt sample. The other samples were supplemented with different levels of quinoa (0, 1, 2, 3, and 5%, wt/wt) on the basis of milk. | Quinoa consumption showed to alleviate clinical symptoms of colitis and reduce the degree of histological damage in mice. | [43] |
| Quinoa seeds | IVV (R) | The control group, the quinoa administered group, the insulin resistance-created group, the insulin resistance-created + metformin group, the insulin resistance-created + quinoa for treatment group and the quinoa + insulin resistance-created for prophylaxis group. | Genes were upregulated by 5–11-fold in the insulin resistance-created group. However, in the groups receiving quinoa (35 g/kg per day) for treatment and protection, these genes were upregulated to a lower extent. | [19] |
| Quinoa bran saponins | IVV (R) | Control, Model, total saponins of low-dose (Quinoa bran saponins 4-25 mg/kg), medium-dose (Quinoa bran saponins 4-50 mg/kg), and high-dose groups (Quinoa bran saponins 4-100 mg/kg). | The most potent fraction of quinoa bran saponins (100 mg/kg) was found to reduce levels of uric acid, serum urea nitrogen, creatinine, and lipids in mice with hyperuricemia, decreasing renal inflammation and damage. | [44] |
| Hydrolytic Quinoa Protein | IVV (M) | Mice were divided into seven groups (n = 6/group): normal group (water), model group (water), control group (dexamethasone: 25 μg/kg/day), low quercetin /EGCG group (free Que/EGCG: 20 mg/kg/day), high quercetin /EGCG group (free Que/EGCG: 50 | The synergistic anti-inflammatory drug (quercetin/Epigallocatechin-3-gallate)-loaded micelle, efficiently accumulated in the colonic inflammatory region and enabled sustained release of drugs for more | [45] |

| | | | | |
|---|---|---|---|---|
| | | mg/kg/day), low quercetin - Hydrolytic Quinoa Protein-EGCG- cationic lotus root starch group (encapsulated quercetin /EGCG: 20 mg/kg/day), and high quercetin -Hydrolytic Quinoa Protein-EGCG-cationic lotus root starch group (encapsulated Que/EGCG: 50 mg/kg/day). | than 24 hours, notably alleviating symptoms of ulcerative colitis. | |
| Quinoa protein hydrolysates | IVT | N/A | Quinoa protein hydrolysates prepared using different enzymes (papain, pepsin, and pancreatin) and total protein from quinoa possessed high anti-inflammatory activity. | [46] |
| Quinoa protein isolate | IVT | N/A | When quinoa protein isolate was combined with mannose and xylose and reacted at 65 ℃, structural changes enhanced its anti-inflammatory and antiproliferative activities. | [47] |
| Purified protein | IVT | N/A | Regarding chenopodin, the major protein component of quinoa seeds, both low and high charge chenopodin showed potential anti-inflammatory activities in an undifferentiated Caco-2 cell model, acting differently depending on their structural features. | [48] |

849 * IVT: *in vitro* and IVV: *in vivo*

850 ** R: rats and M: mice

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854 Table 3. Studies evaluating the effect of quinoa (*Chenopodium quinoa* Wild.) on body weight regulation and obesity.

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| Form of quinoa | Model | Intervention | Key results | Reference |
|---|---|---|---|---|
| Quinoa seeds | IVV* (M**) | Six-week-old C57BL/6J female mice received a high-fat diet to induce obesity and subsequently were treated with a quinoa diet for 12 weeks. | 2 g quinoa per day reduce body weight and body fat mass while improving serum glucose and lipid distribution in a mouse model of high-fat diet-induced obesity. | [56] |
| Yogurt containing quinoa | IVV (M) | Yogurt with addition of polymerized whey protein was used as the control yogurt sample. The other samples were supplemented with different levels of quinoa (0, 1, 2, 3, and 5%, wt/wt) on the basis of milk. | With 20 μL/g, demonstrated a significant reduction in body weight gain and fat tissue weight in high-fat diet-fed obese mice. | [43] |
| Quinoa seeds | IVV (M) | The Obese-diabetic mice fed quinoa-supplemented or AIN-93G diet were compared to lean control fed AIN-93G diet. | The body weight gain was delayed during the first five weeks of dietary intervention. | [57] |
| Hydroalcoholic extract of quinoa seeds | IVV (R) | Group I: normal food diet were fed normal food diet and saline. Group II: high-fat diet animals were fed high fat diet and saline. Group III: animals on high-fat diet, received green tea extract in dose 250 mg/kg/day. Group IV: animals on high-fat diet, received quinoa in dose 250 mg/kg/day dissolved in saline, and Group V: animals on high-fat diet, received chia in dose 250 mg/kg/day dissolved in saline. | Supplementation of quinoa seed (200 mg/kg BW/day) in obese rats reduced adipogenesis by downregulating adipogenesis transcription factors and lipogenesis mediators. | [58] |
| Separated and purified bioactive polysaccharides from quinoa | IVT | N/A | They found to have inhibitory effects on 3T3-L1 adipocyte differentiation, a process linked to obesity. | [60] |
| Saponins extracted from quinoa bran | IVV (R) | All rats, except those of the normal control group, were fed with high fat diet consisting of 24% total fat, 24% protein, and 48% carbohydrates, 45% calories from fat for a total of 11 weeks. | Saponins extracted from quinoa bran were capable of reducing body weight gain and visceral fat accumulation in obese rats. | [61] |

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| Quinoa with saponin and quinoa without saponin | IVV (R) | Mice were randomly divided into the high fat diet induced obesity group, positive control group, the Quinoa with saponin group and Quinoa without saponin group. | Quinoa, especially when combined with saponin, showed significant improvements in high-fat diet-induced obesity rats. | [62] |
| Quinoa seeds | IVV (H) | A cross-over design pilot clinical study with a nutritional intervention for 8 weeks was performed: 4 weeks on a regular diet and 4 weeks on a quinoa diet. | When participants adopted a quinoa-based diet, replacing foods rich in complex carbohydrates, a decrease in body weight, BMI, and waist circumference was observed. | [63] |

* IVT: *in vitro* and IVV: *in vivo*

** H: humans, R: rats and M: mice

860 Table 4. Studies evaluating the effect of quinoa (*Chenopodium quinoa* Wild) on diabetes and glycaemic control.

| Form of quinoa | Model | Intervention | Key results | Reference |
|---|---|---|---|---|
| Quinoa seeds | IVV* (M**) | A T2DM mice model was induced with a high-fat diet combined with streptozotocin, followed by treatment with a quinoa diet. | In type 2 diabetes mellitus mice, quinoa (2 g per day) significantly improved abnormal glycolipid metabolism and positively contributed to the enhancement of gut microbiota composition. | [67] |
| Quinoa seeds | IVV (R) | Rats were split into three groups, the first group was the normal control, the second group was the diabetic control, and the third group was diabetic rats treated with quinoa seeds. | Quinoa seeds demonstrated a hypoglycemic effect and induced favourable changes in cholesterol, HDL, and LDL levels. | [68] |
| Quinoa seeds | IVV (R) | The control group, the quinoa administered group, the insulin resistance-created group, the insulin resistance-created + metformin group, the insulin resistance-created + quinoa for treatment group and the quinoa + insulin resistance-created for prophylaxis group. | Although glucose levels were significantly decreased with quinoa administration to rats (35 g/kg/day), insulin levels and the Homeostatic Model Assessment of Insulin Resistance showed no significant changes. | [19] |
| Quinoa seeds | IVV (R) | Male Wistar rats were randomly allocated to be fed by; control chow, quinoa, cafeteria, or quinoa and cafeteria for 15 weeks. | Feeding 315g of quinoa seeds per 1000 g of chow diet led to reduced energy intake, differentiated macronutrient intake, regulated glucose homeostasis, attenuated microvesicular steatosis, hepatocyte degeneration, and increased IRS-1 and AMPK in the liver. | [69] |
| Toasted quinoa flour, sprouted and toasted quinoa flour, fermented and toasted quinoa flour or sprouted/fermented and toasted quinoa flour | IVV (R) | Animals were divided into 6 groups and were fed different diets that can be found in Table 6 in the cited research article. | The sprouting and/or fermentation of quinoa enhanced its ability to reduce the glycemic index of diets high in simple carbohydrates. | [70] |
| Quinoa seeds | IVV (R) | The Obese-diabetic mice fed quinoa-supplemented or AIN-93G diet were compared to lean control fed AIN-93G diet. | Quinoa intake increased plasma insulin without offering protection from other pathophysiological manifestations. | [57] |

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| Crude polysaccharides from quinoa | IVT | N/A | Crude polysaccharides from quinoa exhibited certain antidiabetic activities, with the activity increasing as the molecular weight decreases. | [31] |
| Free polyphenols (FPE) and bound polyphenols (BPE) extracted from red quinoa | IVT | N/A | Bound polyphenols from red quinoa demonstrated a lower $IC_{50}$ value in inhibiting α-glucosidase activity compared to free polyphenols. Both free and bound polyphenols inhibited α-glucosidase in a non-competitive mode and an uncompetitive mode, respectively. | [20] |
| Quinoa extract and its fractions | IVT | N/A | The ethyl acetate fraction of quinoa extract possessed the strongest α-glucosidase and acetylcholinesterase inhibitory abilities among various fractions | [30] |
| Quinoa-derived protein hydrolysates | IVT | N/A | Dipeptidyl peptidase IV (DPP-IV) inhibitors, were explored in quinoa protein-derived peptides (IPI, IPV, VAYPL, and IPIN), showing competitive inhibition of DPP-IV. | [72] |
| Quinoa protein | IVT | N/A | Quinoa protein, especially globulin, emerged as a potential source of peptides with dipeptidyl peptidase-IV (DPP-IV) and angiotensin-I-converting enzyme (ACE) inhibitory activities. | [73] |
| Quinoa protein rich flour | IVV (R) | Animals were divided into 4 groups and were fed different diets that can be found in Table 1 in the cited research article. | Quinoa protein-rich flour significantly increased microbial activity in the caecum, enhancing the activity of α-glucosidase, β-glucosidase, and α-galactosidase, as well as the production of short-chain fatty acids, primarily butyric acid. | [74] |
| Quinoa seeds | IVV (H) | 138 patients with impaired glucose tolerance were randomly divided into quinoa intervention and control groups, according to the digital table method. | Incorporating quinoa as a staple dietary food (100 g of quinoa replaced the same amount of the daily staple food) regulated glucose tolerance and reduced blood glucose and lipid levels in patients diagnosed with impaired glucose tolerance. | [75] |
| Quinoa seeds | IVV (H) | A cross-over design pilot clinical study with a nutritional intervention for 8 weeks was performed: 4 weeks on a regular diet and 4 weeks on a quinoa diet. | In population at risk of developing type 2 diabetes, a diet rich in quinoa as a substitution for other foods high in complex carbohydrates found promising as a type 2 diabetes preventive strategy. | [63] |

861 * IVT: *in vitro* and IVV: *in vivo*

862 ** H: humans, R: rats and M: mice

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865 Table 5. Studies evaluating the effect of quinoa (*Chenopodium quinoa* Wild) on non-alcoholic fatty liver disease (NAFLD).

| Form of quinoa | Model | Intervention | Key results | Reference |
|---|---|---|---|---|
| Yogurt containing quinoa | IVV* (M**) | Yogurt with addition of polymerized whey protein was used as the control yogurt sample. The other samples were supplemented with different levels of quinoa (0, 1, 2, 3, and 5%, wt/wt) on the basis of milk. | Yogurt containing quinoa effectively alleviated NAFLD symptoms and may exert its effects via microbiome-gut-liver axis mechanisms. | [43] |
| Quinoa seeds | IVV (R) | Male rats were simultaneously administered a high fat diet and different amounts of quinoa (equivalent to 100 g/day and 300 g/day of human intake, respectively). | Quinoa regulated lipid metabolites in both the circulation system and the liver, such as LysoPC and PC. Transcriptomic analysis (RNA-Seq) and subsequent RT-PCR verification revealed that a higher quantity of quinoa more effectively upregulates genes related to lipid metabolism and downregulates genes associated with the immune response. | [79] |
| Immunonutritional bioactives from quinoa | IVV (M) | Different bread formulations were administered (14 mg/day/animal) to the different animal models. | Feeding animals with quinoa formulations (14 mg bread per day) influenced the expression of lipogenic and coronary risk markers. This led to better control of hepatic lipid accumulation, and quinoa products also demonstrated improved glucose homeostasis compared to wheat flour, normalizing the HOMA-IR in animals with altered glucose and lipid metabolism. | [80] |

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867 ** H: humans, R: rats and M: mice

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870 Table 6. Studies evaluating the effect of quinoa (*Chenopodium quinoa* W.) on hypertension.

| Form of quinoa | Model | Intervention | Key results | Reference |
|---|---|---|---|---|
| Quinoa protein | IVV* (R**) | In the short-term study, rats were randomly divided into five groups that received a saline solution, 10 mg/kg body weight captopril, 100 mg/kg, 200 mg/kg, and 400 mg/kg BW quinoa protein, respectively, through oral administration, using syringes. In the long-term study, spontaneously hypertensive rats were assigned into three groups of spontaneously hypertensive rats, spontaneously hypertensive rats, and spontaneously hypertensive rats. These groups were orally administered once daily for five weeks by saline, 200 mg/kg BW quinoa protein, and 10 mg/kg BW captopril, respectively. | A significant decrease in blood pressure was observed, accompanied by a notable increase in alpha diversity and alterations in microbial structure towards that seen in non-hypertensive rats. | [86] |
| Quinoa yoghurt beverage | IVT | N/A | Quinoa protein emerged as a promising natural source of ACE inhibitory peptides, capable of lowering blood pressure. | [85] |
| Hydrolysate from white, red and black quinoa varieties | IVT and IVV (R) | Control (tap water; n = 8), vitamin C (a vitamin C solution 250 mg/kg/day; n = 8) and QrHH (a red quinoa hydrolysate solution 1000 mg/kg/day; n = 8). | The authors reported an *in vivo* antioxidant effect of quinoa hydrolysate and its ability to ameliorate hypertension and its associated complications. | [34] |
| Albumin extracted from quinoa bran | IVV (R) | 5 groups with physiological saline as the negative control and captopril as the positive control. High dosage group, middle dosage group, and low dosage group were orally given the peptide dissolved in 0.9% saline solution via gastric intubation. | RGQVIYVL, 946.6 Da showed high ACE-inhibitory activity with a competitive mode of inhibition and a significant antihypertensive effect at a concentration of 100–150 mg/kg body weight. | [88] |
| Quinoa fermented by three species of *Bifidobacterium* spp. | IVT | N/A | Quinoa fermented by B. *breve* and B. *longum* demonstrated markedly increased ACE-inhibition and antihypertensive activities. | [33] |

871 * IVT: *in vitro* and IVV: *in vivo*

872 ** H: humans, R: rats and M: mice

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874 Table 7. Studies evaluating the effect of quinoa (*Chenopodium quinoa* Wild) on cardiovascular disease risk factors

| Form of quinoa | Model | Intervention | Key results | Reference |
|---|---|---|---|---|
| Quinoa protein rich flour | IVV* (R**) | Animals were divided into 4 groups and were fed different diets that can be found in Table 1 in the cited research article. | A diet enriched with quinoa protein-rich flour positively affected the plasma lipid profile by reducing total cholesterol and LDL cholesterol levels. However, it was noted to increase the level of plasma inflammatory markers. | [74] |
| Quinoa seeds | IVV (M) | Six-week-old C57BL/6J female mice have received a high-fat diet (HFD) to induce obesity and subsequently were treated with a quinoa diet for 12 weeks. | Significant reductions were observed in blood glucose, triglyceride, cholesterol, and low-density lipoprotein levels, along with improvements in glucose tolerance and positive changes in liver tissue histology. | [56] |
| Quinoa seeds | IVV (M) | Obese-diabetic mice fed quinoa-supplemented or AIN-93G diet were compared to lean control fed AIN-93G diet. | In mice fed with quinoa, plasma levels of total cholesterol, LDL cholesterol, oxidized-LDL, protein carbonyls, and interleukin (IL)-6 were reduced to levels similar to lean mice. | [57] |
| Hydroalcoholic extract of quinoa seeds | IVV (R) | Group I: normal food diet were fed normal food diet and saline. Group II: high-fat diet animals were fed high fat diet and saline. Group III: animals on high-fat diet, received green tea extract in dose 250 mg/kg/day. Group IV: animals on high-fat diet, received quinoa in dose 250 mg/kg/day dissolved in saline, and Group V: animals on high-fat diet, received chia in dose 250 mg/kg/day dissolved in saline. | Quinoa seeds demonstrated hepatoprotective effects, anti-inflammatory and antioxidant activities, and modulation of leptin, adiponectin, serum lipid, and glycemic profiles. | [58] |
| Soluble and insoluble dietary fibre from quinoa bran | IVV (R) | Two groups: the blank group (n = 8) was fed a basal diet, and the diet-induced obesity group (n = 40) was fed a high-fat diet. | The intervention reduced body weight, liver weight, blood glucose levels, and serum levels of total cholesterol and triglycerides. | [93] |
| Red quinoa bran | IVV (M) | The mice were given whole grain powder of red quinoa, red quinoa bran ethanol extract, red quinoa bran water extract, and rutin orally for 6 weeks. | Both red quinoa bran ethanol and water extracts were reported to decrease alcoholic diet-induced activities of aspartate aminotransferase and alanine | [41] |

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| | | | aminotransferase, as well as levels of serum triglycerides, total cholesterol, and hepatic triglycerides. | |
| Quinoa-enriched biscuits | IVV (H) | Healthy adults aged 50–75 years (n 40) consumed 2 × 15 g quinoa-enriched biscuits (60 g quinoa flour/100 g) or control iso-energetic biscuits (made using wheat flour) daily for 28 days, in addition to their normal diet. | A significantly greater decrease in body weight, BMI, total and LDL cholesterol concentrations, and TC: HDL ratio were apparent following consumption of the quinoa-enriched biscuits compared to the control biscuits. | [94] |
| Quinoa-enriched biscuits | IVV (H) | Healthy adults aged 50–75 years (n = 40) consumed 15 g quinoa biscuits (60 g quinoa flour/100 g) or control iso–energetic biscuits (made using wheat flour) daily for 28 days, in addition to their normal diet. | Consumption of quinoa biscuits, decreased circulating total and LDL cholesterol concentrations, body weight and BMI compared to control (wheat) biscuits, without concomitant changes in PUFA concentrations. | [95]. |
| Quinoa-enriched bread | IVV (H) | Thirty-seven healthy overweight men (35–70 years, body mass index >25 kg/m2) completed a 4-week cross-over intervention, separated by a 4-week washout period. | After a 4-week intervention, blood glucose and low-density lipoprotein (LDL) cholesterol were significantly lower than baseline in both groups, but no significant difference was observed between the quinoa and control groups. | [96] |

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876 ** H: humans, R: rats and M: mice

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879 Table 8. Studies evaluating the effect of quinoa (*Chenopodium quinoa* Wild) on cancer.

| Form of quinoa | Model | Intervention | Key results | Reference |
|---|---|---|---|---|
| Quinoa bran | IVT* | N/A | Quinoa bran terpenoids (0.6 mg/mL applied on adherent cells) exhibit a remarkable ability to suppress tumor growth in nude mice. They significantly inhibit the proliferation of colorectal cancer cells DLD-1 and HCT-8 in a concentration-dependent manner. | [103] |
| Peptides from quinoa protein hydrolysate | IVV (M**)) | The mice were randomly divided into the control group, the AOM/DSS-induced group, the AOM/DSS + low quinoa protein group, the AOM/DSS + high quinoa protein group, the AOM/DSS + low quinoa protein hydrolysate group, and the AOM/DSS + high quinoa protein hydrolysate group. | The administration of quinoa protein or its hydrolysate mitigated clinical symptoms of colorectal cancer and increased short-chain fatty acids contents in colon tissues. | [104] |
| Saponin-rich extracts from quinoa | IVT | N/A | Quinoa saponin-rich extracts did not show relevant activities in inhibiting colorectal cancer cell lines, unlike fenugreek saponin-rich extracts. | [105] |
| Quinoa protein hydrosylate | IVT | N/A | Specific amino acids in the peptide sequence were suggested to contribute to the binding mode between peptides and HDAC1, potentially inhibiting HDAC1 activity and modulating cancer-related gene expression. | [106] |
| Peptides from quinoa protein | IVT | N/A | Peptides with chemopreventive potential from quinoa protein showed the highest inhibitory effects on colon cancer cell viability during the intestinal phase. | [107] |
| Quinoa protein isolate | IVT | N/A | The addition of olive leaf polyphenolic extract (OLE) to quinoa protein isolate (QPI) solution promoted the production of bioactive peptides. Hydrolyzed QPI/OLE complexes exhibited significant reductions in cell survival compared to OLE alone | [108] |

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| Purified quinoa husk peptides | IVT | N/A | Purified quinoa husk peptides demonstrated the ability to reduce melanin content in cultured cancer cells and rats, as well as accelerate A375 cell apoptosis, contributing to the reduction of melanin content. | [109] |
| Quinoa extract | IVT | N/A | Ethanolic extracts of red and white quinoa, rich in hederagenin, a type of quinoa saponin, demonstrated higher caspase-3 activity than staurosporine in HeLa cancer cells. | [110] |
| Quinoa seeds | IVT | N/A | The O-prenylated phenylpropanoid phytochemical 40-geranyloxyferulic acid, found in ethanolic extracts from quinoa seed, interfered with the expression of the CAT-2B transporter in human cancer colon cells, leading to a reduction in phlogistic mediators NO. | [40] |
| Low-polarity fractions of quinoa | IVT | N/A | The fractions exhibited cytotoxic potential against A549 human lung cancer cells. | [111] |
| Quinoa's oils nanocapsules | IVV (R) | Six groups: distilled water and considered a negative control; 100 mg/kg body weight (BW) corn oil as a vehicle; 100 and 200 mg/kg BW. Quinoa oil nanocapsules; 100 and 200 mg/kg BW chia oil nanocapsules. Then, 16 female rats were injected subcutaneously into the mammary region with a single dose of 80 mg/kg BW. DMBA dissolved in 0.5 ml corn oil. Four months later of the treatment, rat breast cancer models were divided into six groups: DMBA group animals (without treatment); 5-Flu group animals (with a dose of 20 mg/Kg BW /day 5-fluorouracil); chia oil nanocapsules two groups (with chia oil nanocapsules 100 and 200 mg/kg BW /day); and two more groups (with quinoa oil nanocapsules at a dose of 100 and 200 mg/kg BW /day). | Repressed the activation of cancer-associated genes MYC and PIK3CA, modulated liver enzymes, and mitigated kidney function alterations induced in mammary tumour animals. | [112] |

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| Quinoin, a type 1 ribosome-inactivating protein | IVT | N/A | The ability to strongly reduce glioblastoma cancer cells' growth was observed. When used in combination with temozolomide, a standard treatment for glioblastoma, quinoin enhanced the sensitivity of primary cells to the treatment. | [113] |

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882 ** H: humans, R: rats and M: mice

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