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Antinutrients: Lectins, goitrogens, phytates and oxalates, friends or foe?

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ABSTRACT

The intake of foods derived from plants has been proposed as an useful strategy in the prevention of several chronic diseases. However, plants also possess a group of substances known as antinutrients, which may be responsible for deleterious effects related to the absorption of nutrients and micronutrients, or exert beneficial health effects. This review compiles scientific evidence regarding the physiological impact of some antinutrients (lectins, goitrogens, phytates and oxalates) in the human health, their negative effects and the culinary and industrial procedures to reduce their presence in foods. It can be concluded that, the effects of antinutrients on human health could change when consumed in their natural food matrix, and after processing or culinary treatment. Accordingly, some of these compounds could have beneficial effects in different pathological conditions. Future research is required to understand the therapeutic potential of these compounds in humans.

1. Introduction

Rapid population growth worldwide, and changes in the eating behavior are contributing to a massively imbalanced and unsustainable future for the planet. The intake of plant-based or plant-forward eating patterns focus on foods primarily from plants has been proposed as an effective strategy in the prevention of several chronic diseases, mainly those related to an increased oxidative stress (Olaya et al., 2019). The consumption of plant-based foods, that includes not only the consumption of fruits and vegetables, but also nuts, seeds, oils, whole grains, legumes and beans, has shown to have beneficial effects on body weight (E. Tran et al., 2020), glycemic control (Toumpanakis et al., 2018), lipid profile (Yokoyama et al., 2017), inflammatory response (Eichelmann et al., 2016) and cardiovascular disease (Toh et al., 2020). In fact, fruit and vegetable consumption has been associated with a reduction in the risk of all-cause mortality (Olaya et al., 2019), and it has also been suggested that these benefits are partly due to different bioactive compounds mainly present in plants such as phytochemicals and dietary fiber (Kim & Je, 2016; Kris-Etherton et al., 2002). In addition, due to the pandemic situation facing today's society, recent ecological studies have observed a lower coronavirus disease 2019 (COVID-19) death rate in those countries with a higher consumption of vegetables (Bousquet, Anto, et al., 2020). In COVID-19, endoplasmic reticulum stress and Angiotensin-II-AT1R axis pathways are associated to an increased oxidative stress and with the development of insulin resistance, cytokine storm and endothelial damage, complications characteristic of this disease. As mentioned above, fruits and vegetables are rich in antioxidant phytochemicals, and it has been suggested that they could be useful in the prevention and better prognosis of COVID-19 severity through the beneficial effects on these pathways (Bousquet, Cristol, et al., 2020). However, plants also possess a group of substances known as antinutrients with a potential deleterious effect (Alatorre-Cruz et al., 2018; Kim et al., 2020; Tripathi & Mishra, 2007).

Antinutrients such as lectins, glucosinolates, phytates, oxalates, tannins or saponins, among others appear as a result of defence mechanisms with which plants protect themselves from the surrounding environment. Antinutrients are plant compounds which have traditionally been considered harmful to health due to their potential to limit the bioavailability of essential nutrients (Phan, Paterson, Bucknall & Arcot, 2018). For this, different processing and cooking methods have been studied to reduce their quantity in foods (Nugrahedi et al., 2015). However, in recent years, these so-called anti-nutrients have become known to possess beneficial effect and therapeutic potential on several diseases (Petroski & Minich, 2020). The purpose of this study was to examine the scientific literature of some substances classified as antinutrient compounds, providing current evidence of their properties, focus on the potential risks, benefits and clinical implications. This review compiles scientific evidence regarding the role of anti-nutrients lectins, goitrogens, phytates and oxalates in the human health. Moreover, it examines their negative effects and the different procedures or

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approaches to reduce their presence in foods; and, based on the recent research, the new evidences about their potential bioactive properties (Table 1).

2. Lectins

Lectins are a type of glycoprotein with noncatalytic carbohydrate-binding sites grouped according to their species of origin in animal, algal, bacterial, fungal and plant lectins (Mishra et al., 2019). This binding occurs through a carbohydrate recognition domain (CRD), present in the peptide structure of the lectins. Depending on their origin, each type of lectin has a characteristic structure and specificity. Animal lectins have higher specificity for hydrocarbon complex structures, algal lectins for glycoproteins, bacterial lectins for glycans, fungal lectins for N-acetyl galactosamine and plant lectins for monosaccharide and oligosaccharide (Fig. 1) (Hooper & Gordon, 2001; Kilpatrick, 2002; Kobayashi & Kawagishi, 2014; Van Damme et al., 2007). In particular, plant lectins are found in nuts, cereals and mainly in the seeds of leguminous (El-Araby, El-Shatoury, Soliman & Shaaban, 2020). Lectins have the capacity to agglutinate red blood cells through their reversible binding to specific mono-oligosaccharides and oligosaccharides present in glycoproteins and glycolipids (Sharon, 2007). Among their main characteristics, it is worth highlighting that they are relatively resistant to the activity of enzymes in the digestive tract. Thus, lectins may interact with intestinal epithelial cells, modifying intestinal permeability (Muramoto, 2017). In addition, it has been demonstrated in animal models that the intake of high doses of isolated lectins, produced alterations in the integrity of the intestinal mucosa, leading to increased permeability, the activation of the immune system and the alteration in the absorption of nutrients (Alatorre-Cruz et al., 2018; Gong et al., 2017). However, using different conventional processing or cooking techniques, the lectin content can be reduced. In this sense, boiling processes (95 °C for 1 h) reduce the hemagglutinating activity of the pulses between 94% and 100% (Shi, Arntfield & Nickerson, 2018). In the same way, germination and fermentation have also proved capable of reducing the lectins content (Cuadrado et al., 2002). Moreover, cooked pulses have been used in human intervention studies and no harmful effects have been observed (Nciri et al., 2015). As mentioned above, different culinary treatments reduce the lectin content of foods, which modulates the potential health effects. To date, no human studies have been conducted to assess whether cooked foods are a practical source of lectins, which confer positive health benefits. The potential health benefits of lectins described in scientific reports correspond to purified compounds intended to develop pharmaceutical products. Administration is not associated with the consumption of foods of plant origin because the dose must be controlled.

In last years, and despite of the unwanted effects associated to the consumption of unprocessed foods which contain lectins, different studies are suggesting the therapeutic utility of lectins in the diagnosis and treatment of several diseases. In this context, it has been described that lectins could be helpful for cancer because of their potential anti-angiogenic (Bhutia et al., 2016), antimetastatic (Sinha et al., 2019) and antiproliferative activity (Panda et al., 2018), both *in vitro* and *in vivo*. At the clinical level, a few studies have evaluated the usefulness of lectins as a possible antitumour agent. A complete remission of a colon adenoma was observed after intratumoral injection with a lectin-rich extract obtained from mistletoe (*Viscum album* L.) (von Schoen-Angerer et al., 2014). Also, the coadjuvant administration of mistletoe with standard chemotherapy in patients with stage IV non-small cell lung cancer has shown an improvement in survival rates (Schad et al., 2018). Apoptosis and autophagy pathways by stimulating the synthesis of caspases and other proteins have been suggested as the potential mechanism of actions of antiproliferative properties of lectins on cell lines of human cancer (Gautam et al., 2020). Although further studies are needed to corroborate these promising results and to assess the potential issue of toxicity (Mazalovska & Kouokam, 2020).

Furthermore, the possible effects of plant lectins on metabolic complications have also been investigated. Thus isolated lectins from seeds of *Abrus precaterius* L., known as Gunja or Jequirity, have reported antidiabetic and hyperlipidemic activity for the treatment of diabetes in alloxan monohydrate induced diabetic rats (Sawant, Randive & Kulkarni, 2017). Similarly, purified lectins from *Cratavea tapia* bark, used at a fixed dose by intraperitoneal administration, have shown hypoglycemic activity as well as have improved renal liver complications in alloxan monohydrate induced diabetic mice (da Rocha et al., 2013). Purified lectin-like proteins from *Agaricus bisporus,* the common "button mushroom", have revealed a potential in different pharmaceutical applications such as antidiabetic and antiproliferative properties, both *in vitro* and *in vivo* (Ismaya, Tjandrawinata & Rachmawati, 2020).

The potential immunomodulatory activity of lectins has also been well documented and lectins have also shown antimicrobial, antibacterial, antifungal and antiviral properties (Mishra et al., 2019). Legume lectins have demonstrated antimicrobial and antifungal activities against *Candida albicans.* The inhibition of microbial growth might be due to the agglutination effect observed on microbial cells (El-Araby et al., 2020). The antiviral activity against a variety of viruses has been studied (Mazalovska & Kouokam, 2018; Mishra et al., 2019). In fact, the antiviral effect of lectins on Herpes simplex virus, Ebola or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been recently

Table 1
Potential biological activities of different anti-nutrients.

Compound	*Biological activity*	*Experimental model*	*Reference*
Lectins	Antiangiogenic	*In vitro,* Murine Models	(Bhutia et al., 2016)
	Antimetastatic	*In vitro*	(Sinha et al., 2019)
	Antiproliferative	*In vitro*	(Panda et al., 2018)
	Antitumoral	*Case report*	(von Schoen-Angerer et al., 2014)
	Antidiabetics	Murine models	(Sawant et al., 2017)
	Immunomodulatory	*In vitro,* Murine Models	(Mazalovska & Kouokam, 2018)
	Antimicrobial	*In vitro*	(El-Araby et al., 2020)
Glucosinolates	Antiproliferative	*In vitro*	(Chatterjee et al., 2018)
	Chemopreventive	*In vitro*, Humans	(Tahata et al., 2018; Traka et al., 2019)
	Anticholesterolemic	Murine models	
	Antiinflammatory	*In vitro*, Murine models	(Valdivia et al., 2020)
	Antiasthmatic	Humans	(Miękus et al., 2020)
	Neuroprotective	Murine models, Humans	(Brown et al., 2015) (Schepici et al., 2020; Shiina et al., 2015)
Phytates	Antioxidant	Humans	(Sanchis et al., 2018; Zajdel et al., 2013)
	Anticholesterolemic	*In vitro,* Murine models	(Onomi et al., 2004)
	Antidiabetics	*In vitro,* Murine models, Humans	(Omoruyi et al., 2020)
	Neuroprotective	*In vitro*, Murine models	(Anekonda et al., 2011; Xu et al., 2011)
	Chemopreventive	*In vitro*	(Abdulwaliyu et al., 2019)
	Antiosteoporotic	Epidemiologic	(Fernández-Palomeque et al., 2015)

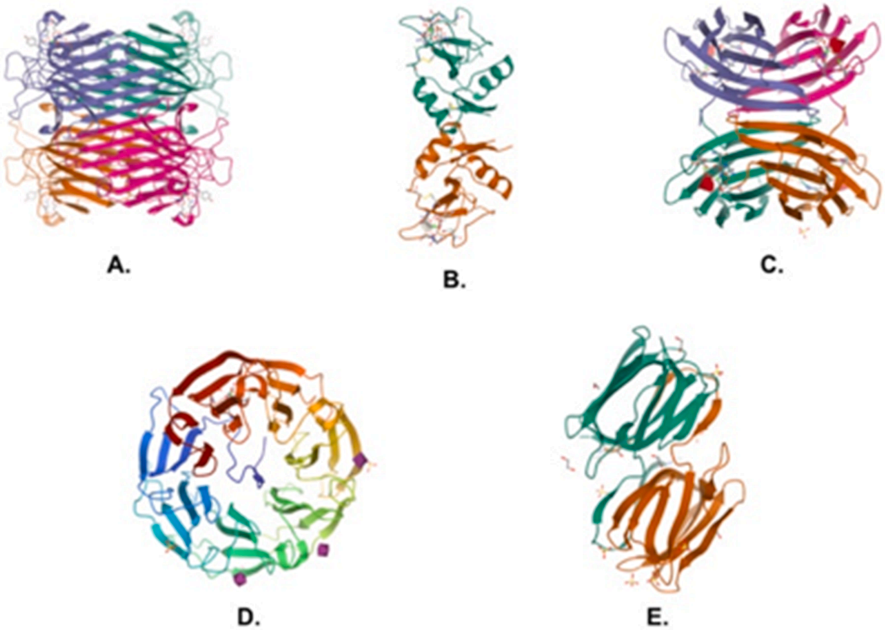

Fig. 1. Types of lectins according to their origin. (A) Plant lectins derived from *Canavalia ensiformis*, PBD code 1VLN. (B) Animal lectins derived from *Rattus rattus*, PBD code 1RDJ. (C) Bacterial lectins derived *Pseudomonas aeruginosa*, PBD code 1UZV. (D) Fungal lectins derived *Lacrymaria velutina*, PBD code 2C25. (E) Algal lectins derived *Griffithsia*, PBD code 2GTY. (Taken from Protein Data Bank).

described *in vitro* (Mani et al., 2020). Although the exact mechanisms are unknown, these compounds appear to act at the viral attachment stage or at the end of the viral cycle of infection (Mani et al., 2020).

3. Glucosinolates

Glucosinolates are a series of compounds belonging to the family of the goitrogens mainly found in cruciferous plants such as broccoli, cauliflower or cabbage, among others (Felker, Bunch & Leung, 2016). They are secondary plant metabolites constituted of a core structure with a β-D-thioglucose group linked to a sulfonated aldoxime moiety and a variable chain derived from amino acids (Fig. 2) (Redovniković, Glivetić, Delonga & Vorkapić-Furač, 2008). During the mastication process, glucosinolates are converted into a series of derivatives such as thiocyanates, isothiocyanates or epithionitriles by the enzyme myrosinase (Prieto et al., 2019). Traditionally, the intake of glucosinolates and derived compounds have also been linked to harmful properties for the human body, and it has been described that their consumption cause an altered thyroid function and an increased risk of various thyroid diseases (Tripathi & Mishra, 2007). The reason for this association is because these compounds may reduce the release of iodine from the thyroid gland by acting as a competitive inhibitor of the sodium/iodide symporter of follicular thyroid cell (Di Bernardo et al., 2011; Tonacchera et al., 2004). However, this association is controversial when evaluating the scientific literature on the toxic potential of glucosinolates. On the one hand, an iodine-deficient diet combined with the intake of thiocyanates led to a reduction in thyroxine levels with the consequent thyroxine deficiency in animal studies (Rao & Lakshmy, 1995). However, the results are heterogeneous and the adverse effects of goitrogen-rich foods are only observed in diets with low iodine intake in epidemiological studies (Hassen, Beyene & Ali, 2019; Knight et al., 2018). Therefore, taking into consideration all this evidence, it seems cautious that in people with thyroid disease or risk of it, the consumption of this type of food cooked with iodized salt should be prioritized to reduce the possible adverse effect on iodine bioavailability (Petroski & Minich, 2020).

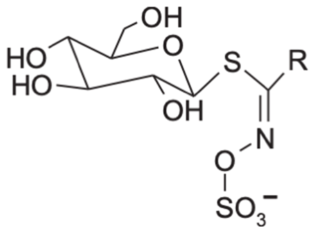

Fig. 2. Generalized structure of glucosinolates. R indicates the variable side chain of amino acids (Taken from Redovniković et al., 2008).

In the same way as lectins, after food processing or cooking the concentration of glucosinolates is significantly reduced. Thus, after 5 min of boiling process, a 51% of reduction in total glucosinolates has been observed as a result of cell lysis and diffusion, which triggers the action of endogenous myrosinase activity on glucosinolates (Hwang & Kim, 2013). Pre-processing associated with freezing may also influence the glucosinolate content, thus in frozen Brassica vegetables a greater reduction of total glucosinolates after cooking has been observed compared to the same treatment on fresh vegetables (Pellegrini et al., 2010). This may be due to blanch-freezing prior to boiling which causes a softening of the vegetable matrix. Other techniques such as microwaving appear to be able to reduce the glucosinolate content between 17.3% and 27.4% (López-Berenguer, Carvajal, Moreno & García-Viguera, 2007; Rungapamestry, Duncan, Fuller & Ratcliffe, 2007). On the other hand, steaming has been shown to cause a lower loss of glucosinolates than those observed with boiling and blanching mainly due to differences in leaching losses (Nugrahedi et al., 2015). In the case of fermentation, the bioconversion has been described of these compounds into derivates such as isothiocyanates and ascorbigen (Nugrahedi et al., 2015). Moreover, it has recently been also shown that the absorption and bioavailability of glucosinolates are influenced by the activity and composition of the gut microbiota and therefore determines the final effect of these compounds in the organism (Sikorska-Zimny & Beneduce, 2020).

However, these results are controversial and other epidemiological studies have found a link between the consumption of crucifers and a reduced risk of thyroid cancer (Peterson et al., 2012). It is also striking that higher urinary levels of thiocyanates and lower iodine levels were observed and a thyroid function was not further altered in vegan population (Leung, LaMar, He, Braverman & Pearce, 2011). Regarding that foods classified as goitrogenic contain different bioactive compounds, they could be responsible of the protective effect against thyroid cancer observed in some studies (Fiore et al., 2020). In fact, sulforaphane, an isothiocyanate from the crucifers, have shown to have an apoptotic and anti-proliferative effect in thyroid cancer cells (Chatterjee, Rhee, Chung, Ge & Ahn, 2018). It has even been related a low intake of glucosinolates or isothiocyanates with an increased risk of breast cancer (Zhang et al., 2020). Similarly, the usefulness of sulforaphane as a chemopreventive agent for melanoma was also reported in a pilot study in melanoma patients with multiple atypical nevi (Tahata et al., 2018). Glucoraphanin, an glucosinolate from broccoli whose hydrolysis product is the isothiocyanate sulforaphane, appears to be able to modulate the expression of oncogenes related to inflammation processes and inhibit prostate cancer progression in men on active surveillance (Traka et al., 2019).

On the other hand, it has also been suggested that the previous catalogued compounds as antinutrients could also exert beneficial biological properties for the organism improving metabolic and neurodegenerative diseases. These health benefits of glucosinolates can be attributed in part to the regulation of pro-inflammatory signaling pathways such as the inhibition of Tumor Necrosis Factor (TNF-α) and the reduction of reactive oxygen species confirmed by both *in vitro* and *in vivo* studies (Miękus et al., 2020). Moreover, sulforaphane is considered one of the most potent natural activators of the Nuclear factor erythroid 2-related factor 2 – Kelh like ECH associated protein 1 (Nrf2-Keap1) signaling pathway, a basic leucine zipper transcription factor that binds to the promoter region of the antioxidant response element, inducing the coordinated up-regulation of antioxidant and detoxification genes implicated in several diseases (Dinkova-Kostova et al., 2017; Houghton, 2019). Recently, it has been observed that a supplement with glucosinolates caused a reduction in weight gain and plasma total cholesterol levels in a menopausal murine model (Valdivia et al., 2020), and also possess beneficial effects on insulin resistance (Houghton, 2019). This effect could be due to attenuation of oxidative stress and activation of the peroxisome proliferator- activated receptors (PPAR), involved in glucidic and lipid metabolism (Melrose, 2019). Sulforaphane has also been suggested as a potential adjuvant treatment moderate asthmatics patients because of its bronchoprotective response through regulation of the Nrf2 signaling pathway (Brown, Reynolds, Brooker, Talalay & Fahey, 2015). This compound has even been shown to be useful in improving cognitive deficits in patients with mental disorder such as schizophrenia (Shiina et al., 2015). Moreover, a neuroprotective effect of sulforaphane through inhibition of mammalian Target of Rapamycin (mTOR) in a Nrf2-independent manner has also been reported (Schepici, Bramanti & Mazzon, 2020). Such is the relevance of this goitrogen that its therapeutic role has been suggested in the treatment of COVID-19 through the activation of Nrf2-Keap1 and counteracting the COVID-19 induced cytokine storm (Bousquet, Anto, et al., 2020; Singh et al., 2021).

4. Phytates

Phytates or myo-inositol hexaphosphate or IP6 are another such “anti-nutrient” found in cereals, pulses, nuts and seeds. Phytates consist of a ring with 6 carbon atoms esterified with a phosphate group, which is dephosphorylated by phytases into smaller phosphoric esters of phytates (IP1-IP5) (Silva & Bracarense, 2016). Oats, dry fava beans and amaranth stand out among the foods with higher quantities of phytates, with 2.618 mg, 2.248 mg and 1.382 mg phytate/100 g dry matter, respectively (Castro-Alba, Lazarte, Bergenståhl & Granfeldt, 2019). These compounds are a storage form of phosphorus and inositol in plants (Fig. 3). Phytates can form soluble complexes with divalent cations such as zinc, iron and calcium under the acidic pH in the stomach and precipitate at physiological pH in the intestine, reducing their bioavailability in the digestive tract (Lesjak & K S Srai, 2019; Schlemmer et al., 2009). In fact, the bioavailability of these minerals can be calculated according to the phytate:mineral ratio (Castro-Alba, Lazarte, Bergenståhl et al., 2019). Previous studies have reported that a phytate/iron ratio greater than 1:1 has a negative effect on iron bioavailability, with an optimal molar ratio of less than 0.4:1 (Hurrell & Egli, 2010). A negative effect has also been seen with a phytate:zinc ratio and phytate:calcium ratio, higher than 15:1 and 0.17:1, respectively (Castro-Alba, Lazarte, Bergenståhl et al., 2019). Also, phytates can form complexes with proteins, however, this interaction is dependent on pH, isoelectric point, ionic strength and amino acid availability (Kaspchak et al., 2018; Prattley et al., 2007; T. T. Tran et al., 2011). A net positive charge (pH < isoelectric point) seems to be necessary for the formation and stability of phytate-protein complexes (Wang & Guo, 2021).

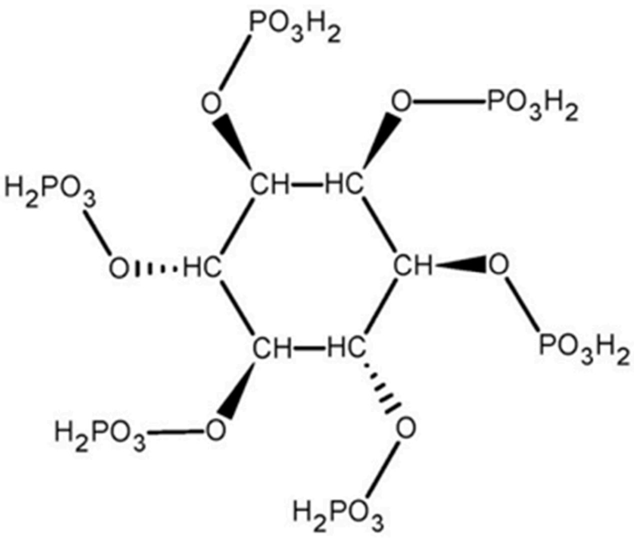

Fig. 3. Generalized structure of phytates, which are the main phosphorus storage molecule in plants seeds (Lesjak & Srai, 2019).

With regard to the possible adverse effects discussed above, several studies have shown that the bioavailability of zinc is reduced when isolated phytates are ingested (Fredlund, Isaksson, Rossander-Hulthén, Almgren & Sandberg, 2006), but no significant effects have been observed when phytates are consumed in a matrix (Miller, Hambidge & Krebs, 2015). Traditionally, phytates have also been linked to disruption of calcium and phosphate homeostasis in animals and it has been suggested that phytate intake may be associated with a reduced risk of stone formation (Kim et al., 2020). However, there is insufficient evidence in humans to support that dietary phytates act as inhibitors in formation of renal calculi (Fakier & Rodgers, 2020). This underlines the importance of the food matrix on the effect of dietary phytates. On the one hand, phytate-rich foods also contain fermentable fiber which is able to reduce the pH of the caecum, leading to reduction of ferric iron to ferrous iron, and an increase in the absorption of these minerals (Baye et al., 2017; Chen et al., 2020). This suggests that some dietary components such as fiber present in the food may minimize the negative impact of phytates on the bioavailability of different minerals. Similarly, vitamin C has been shown to counteract the inhibitory effects of phytates on mineral absorption (Hallberg, Brune & Rossander, 1989). In studies with Caco-2, a cell line of human colorectal adenocarcinoma, a molar ratio Iron: Ascorbic Acid:Phytates higher than 1:20:1 has been proposed as optimal to counteract the effect of phytic acid on iron bioavailability (Engle-Stone et al., 2005). Human studies have shown that iron absorption from a maize bran with 58 g of phytates doubled when a dose of 50 mg of vitamin C was added (Siegenberg et al., 1991). Ascorbic acid forms a soluble complex with iron, which would facilitate the reduction of Fe^{3+} to Fe^{2+} by preventing the formation of non-absorbable iron complexes. However, the biochemical pathway of the effect of ascorbic acid on iron absorption are not fully described (Milman, 2020). It has also been postulated that regular consumption of phytate can trigger an inhibition of the negative effect of this compound on iron absorption in women with suboptimal iron store, a phenomenon known as phytate adaptation (Armah, Boy, Chen, Candal & Reddy, 2015). This is because a regular diet high in phytate-rich foods, increase the potential of the intestinal microbiota to degrade phytates (Markiewicz, Honke, Haros, Świątecka & Wróblewska, 2013).

In the same way as the previous compounds, the concentration of phytates is significantly reduced with techniques such as cooking, soaking, fermentation and germination. Thus with cooking at 95 °C for 1 h, the phytate content of different legumes is reduced between 11% and 80% (Shi et al., 2018). In the same way, soaking reduces the phytate content of different cereals from 17% to 28% (Lestienne, Icard-Vernière, Mouquet, Picq & Trèche, 2005), while sprouting reduces the phytate content of legumes by more than 60% (Duhan, Khetarpaul & Bishnoi, 2002; Lestienne et al., 2005). This situation seems to be due to the enzymatic action on phytates released during germination of the seed, leading to the formation of myo-inositol phosphate derivative and inorganic phosphate (Pramitha et al., 2021). Fermentation has been shown to be an effective method in reducing the phytate content of pseudocereals, especially in the form of flour (Castro-Alba, Lazarte, Perez-Rea, et al., 2019). Interestingly, the intake of fermented vegetables with a high phytate content has been shown to increase the bioavailability of dietary iron (Scheers, Rossander-Hulthen, Torsdottir & Sandberg, 2016). Fermentation can achieve a reduction of phytic acid by the action of both microbial and grain phytases (Gupta et al., 2015).

At the same time, phytate may also have beneficial roles mainly as antioxidants by acting as a regulator of possible excess of heme iron, and by reducing the occurrence of advanced glycation end products (AGEs) in patients with type 2 diabetes mellitus (Sanchis et al., 2018). Animal studies have postulated that phytates may reduce the toxicity produced by free radicals and the oxidative stress caused by chemical agents, such as aflatoxin B1 (Abu El-Saad & Mahmoud, 2009). Regarding oxidative stress, *ex vivo* models have found that compounds such as phytates can attenuate lipid peroxidation through scavenging free radicals and increasing intracellular glutathione concentration (Da Silva et al., 2019). Phytate was also capable of reducing linoleic acid autoxidation and lipid peroxidation in human colonic epithelial cells (Zajdel, Wilczok, Węglarz & Dzierżewicz, 2013). These effects appear to be linked to the chelating properties of phytates identified *in vitro* and *in vivo* studies, as they are able to scavenge free radicals caused by the autoxidation of linoleic acid (Anekonda et al., 2011).

Furthermore, different studies have suggested the usefulness of phytates in regulating some metabolic disorders or related complications. In rats fed with high-sucrose diet, phytates were able to reduce the levels of triglycerides and cholesterol, as well as lipogenic enzymes in liver (Onomi, Okazaki & Katayama, 2004). This consequence may be due to the inhibitory effect of phytate on 3-hydroxy-3methylglutaryl-co-enzyme A (HMG-CoA) reductase activity involved in hepatic cholesterol synthesis (Lee et al., 2007). It has also been observed that a high phytate intake was associated with lower levels of C-reactive protein through its ability to inhibit the formation of iron-mediated free radicals and the prevention of lipid peroxidation, especially among overweight or obese individuals (Armah, 2019).

The usefulness of phytates has also been reported on insulin response, leptin secretion, vascular damage and food intake in prediabetic and diabetic situations (Omoruyi, Stennett, Foster & Dilworth, 2020). These improvements have been associated with the reduction of protein glycation by the chelation of Fe^{3+} which, in turn leads to a decrease in glycated hemoglobin HbA1c, used as a screening, diagnosis and monitoring marker of diabetes (Sanchis et al., 2018).

Phytate consumption has also been associated with neuroprotective properties. These compounds could be a novel protective treatment for Alzheimer's disease through the improvement in autophagy and mitochondrial functions in a model of Alzheimer's disease, Tg2576 mouse (Anekonda et al., 2011). In Parkinson's disease phytates may have a neuroprotective role identified in a cell culture model through decreasing caspase-3 activity as well as DNA fragmentation in normal and iron-excess conditions (Xu, Kanthasamy & Reddy, 2011).

Phytates have also demonstrated beneficial effects in other disorders. It has been observed a chemopreventive potential *in vitro* and *in vivo* of phytates on different carcinogenic processes (Abdulwaliyu et al., 2019). New areas of research are also emerging because of the possible beneficial effects of these compounds on the risk of osteoporosis or age-related cardiovascular calcifications (Fernández-Palomeque et al., 2015; Gonzalez, Grases, Mari, Tomas-Salva & Rodriguez, 2019).

5. Oxalates

Oxalates are antinutrient compounds present in vegetables such as spinach, chard, beet or rhubarb. These compounds are a strong organic acid with the ability to form water-soluble salts by binding to minerals such as sodium or potassium, as well as water-insoluble salts by binding to calcium, iron or zinc (Fig. 4) (Lo, Wang, Wu & Yang, 2018). Traditionally, dietary oxalate intake has been associated with the pathophysiology of kidney stone disease risk (Crivelli et al., 2021), and a relationship between dietary oxalates and kidney stone formation has been observed in human studies (Curhan, Willett, Knight & Stampfer, 2004). In relation to oxalate content, it is important to take into consideration that soluble oxalates have a greater impact on bioavailability and the risk of stone formation than insoluble oxalate (Chai & Liebman, 2005). Thus spinaches contain an average of 1145 mg total oxalate/100 g fresh weight, with 803 mg being soluble oxalate (Petroski & Minich, 2020). Almonds also stand out with 469 mg/100 g of product, with 153 mg being soluble oxalate (Petroski & Minich, 2020). Moreover, it has being observed that the kidney stone formation risk was higher among subjects with lower dietary calcium intake while those with optimal calcium intake did not show an increased risk. Therefore, it has been postulated that dietary oxalate has little impact on kidney stone formation and the priority should be to ensure adequate calcium intake (Curhan, Willett, Knight & Stampfer, 2004). Several studies have reported a greater influence of dietary calcium than dietary oxalate on the risk of kidney stone (Mitchell et al., 2019). In a prospective study of the chronic renal insufficiency cohort was found that higher levels of urinary oxalate excretion were independently associated with an increased risk of chronic kidney disease progression and end-stage renal disease (Waikar et al., 2019). However, in the subgroup analysis, an increased risk of end-stage renal disease was observed only in those participants with plasma calcium levels below 9.3 mg/dl.

It is important to note that other compounds present in these oxalate-rich foods such as magnesium and potassium are associated with a reduced risk of kidney stones. It explains why diets predominantly rich in oxalate sources, such as the dietary approaches to stop hypertension (DASH diet) with a high consumption of vegetables, fruits, whole grains, beans, nuts, low-fat dairy, fish and poultry, have been shown to reduce the risk of this condition (Taylor, Fung & Curhan, 2009). In the same way, a balanced vegetarian diet with high content of vegetables, has been suggested as one of the most useful dietary strategies for kidney stone patients (Ferraro, Bargagli, Trinchieri & Gambaro, 2020). On the other hand, low calcium diets have been associated with increased

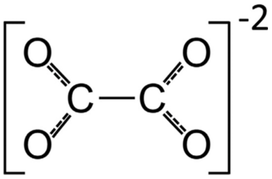

Fig. 4. Generalized structure of oxalates, an organic acid produced in both plants and animals with the ability bonds with different minerals (Lo et al., 2018).

absorption of dietary oxalate (Israr, Frazier & Gordon, 2013). These findings call into question the effect of reduced oxalate intake on renal function in chronic kidney disease patients and on the risk of acute kidney injury (Bargagli, Tio, Waikar & Ferraro, 2020). Recent research has suggested that the gut-kidney axis is a determinant in the metabolism of oxalates and thus dysbiosis is a risk factor in the formation of kidney stones (Ticinesi, Nouvenne & Meschi, 2019). Furthermore, in the intestinal tract are found some anaerobic bacterial species like *Oxalobacter formigenes,* which have been shown to be related to oxalate degradation (Chamberlain, Hatch & Garrett, 2020). Similarly, short-chain fatty acids (acetate, propionate and butyrate) produced in the gut microbiota have shown to be negatively associated in animal studies with the risk of kidney stone disease (Liu et al., 2020). Previous studies in rat models have suggested that acetate is involved in urinary citrate and calcium excretion through regulating histone acetylation, attenuating the formation of renal CaOx crystals (Zhu et al., 2019).

Due to the solubility of oxalate in water, culinary processes, such as boiling and steaming allow to reduce considerably the content of these compounds. A boiling process for 12 min resulted in a reduction between 30% and 87% of soluble oxalates. Whereas, in steam cooking the reduction in oxalates is around 42% to 46% (Chai & Liebman, 2005). Similarly, with soaking a loss of oxalate content between 40.5% and 76.9%, can be achieved (Akhtar, Israr, Bhatty & Ali, 2011). In the fermentation process, oxalate reduction can also occur through the action of enzymes that degrade oxalate, such as oxalate oxidase, oxalate decarboxylase and oxalyl-CoA synthetase (Lo et al., 2018).

In contrast to the other antinutrients, in the case of oxalates there are not published clear evidences of a possible therapeutic role in the scientific literature. However, oxalates are found in vegetables that contain a number of bioactive compounds with health benefits, suggesting the suitability of consumption of this food group.

6. Conclusions

After analyzing in depth the bibliography published related to these antinutrients, it can be observed that, when foods rich in these compounds are consumed without culinary treatment or isolated, they can cause a negative effect on human health. However, in the context of a regular diet when they are consumed in a food matrix and with a culinary treatment or processing such germination, fermentation or milling, in which they are reduced in concentration or are found a synergy with other compounds beneficial to health, the negative effects are greatly minimized. Even if we go one step further, some of these compounds mainly as purified molecules seem to have beneficial effects in different pathological conditions. However, most of this evidence comes from studies carried out in animal models, with the limitations that this implies to extrapolate the results obtained to human beings. In the other hand, epidemiological studies show promising results, but this characteristic design makes difficult to discern between the real effects from these compounds and the ones derived from other molecules present in the food matrix in which these antinutrients are found. Currently, there are few human clinical trials that evaluate these effects, so future research is required in this area to understand the therapeutic potential of these compounds.

Declaration of Competing Interest

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

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