A Review of Phytic Acid Sources, Obtention, and Applications

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ABSTRACT

Phytic acid (PA), extracted from oilseeds, legumes, cereals, nuts, and pollen by acid solutions under heating and/or stirring and then purified, has shown beneficial health and physiological effects due to its pronounced antioxidant activity and ability to chelate Fe^{3+} ions. Publications on PA have increased, especially the ones reporting its effect on disease prevention and treatment. Moreover, recent studies have suggested the PA efficacy as a foodborne pathogens inhibitor. Therefore, due to its countless proven properties, phytic acid has gained greater attention than its common classification as just an antinutrient. Past and current studies have been reviewed to provide an overview on PA structure, sources, biosynthesis, extraction, purification, and applications.
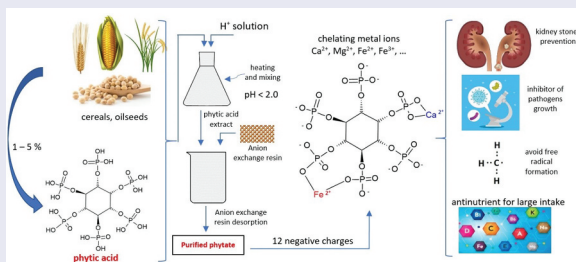
Introduction

Myo-inositol-1,2,3,4,5,6-hexakisphosphoric acid (IP6), commonly known as phytic acid,[1] is a common constituent of plants and the inositol and phosphate main storage form in grains and plant seeds accumulated during the maturation period.[2] Phytic acid has 12 ionizable protons that ensure a unique structure responsible for its characteristic properties, especially the ability to form chelates with polyvalent metal ions such as calcium, zinc, and iron, resulting in insoluble salts called phytates.[3,4] Other compounds such as inositol tri- (IP3), tetra- (IP4) and pentaphosphate (IP5) are also called phytates.[1]

Phytic acid is generally referred to as an anti-nutrient due to the food micronutrients chelating ability, making them unabsorbable and thus low bioavailability.[5] However, this effect is mainly linked to diets that are simultaneously poor in trace elements and high in phytic acid intake. Also, bioavailability may be influenced by the micronutrients binding with other food components and the metal ion: phytic acid molar ratio should also be considered.[6,7] On the other hand, several studies have been done, both *in vitro* and *in vivo*, showing strong anti-cancer activity evidence for phytic acid.[8–12]

Additionally, different studies on beneficial health and physiological effects suggest that phytic acid may have beneficial effects on several other diseases such as diabetes,[13,14] vascular calcifications prevention and consequently reduced risk of cardiovascular events,[15] coronary heart disease,[16] Parkinson's disease,[17] and kidney stones treatment.[18]

Due to its iron binding ability forming a completely inactive chelate, phytic acid shows a pronounced antioxidant activity able to prevent the hydroxyl radical (•OH) formation created by iron catalytic action. This has been demonstrated using *in vitro* biochemical systems as it plays an important role in living systems such as plant seeds, contributing to their preservation.[4,19] In view of this ability and since both phytic acid and its metabolites are non-toxic or reactive, it has been long used as a versatile and unique food preservative often added to several food products for shelf-life extension and/or prevent discoloration.[20] Phytic acid has been granted Generally Recognized As Safe (GRAS) status in the USA, as well as in Japan, China, and the European Union, where it is approved as a food additive under E391 code.[21] Since it is obtained from natural sources, it is an attractive alternative to other synthetic preservatives still in use today. Furthermore, different studies suggest that it may have an antimicrobial effect on food pathogens and natural spoilage fungi.[20–23] Additionally, phytic acid has been used in various industrial applications, such as heavy-metal-contaminated waste treatment,[24] metal coating to prevent rusting and corrosion,[25] and more recently added as a bio-based component in fabrics to confer flame-retardant properties.[26]

Considering the multitude of phytic acid uses and its potential health benefits, different studies and patents have been developed on its extraction and purification. For that, the use phytic-acid-rich food by-products, such as rice bran is suggested due to the need for a circular economy based on sustainable food production and waste recovery. Phytic acid solubility is pH-dependent and a higher solubility is obtained at pH < 2.[27] Therefore, acid solutions are widely used for its extraction, with hydrochloric acid the most commonly used, at concentrations ranging from 0.5 to 2.4 mol L^{-1}.[28,29] For purification, a few studies are found in the literature and some were patented (US Patent No. 3591665A, 1971;[30] US Patent No. 4070422, 1978;[31] US Patent No. 8,012,512 B2, 2011[32]). Phytic acid purification methods are generally based on successive chemical treatments of a phytate acid solution that may be separated using a non-porous anion-exchange resin.[33]

This review aimed at providing an overview of the phytic acid structure, sources, biosynthesis, extraction and purification methods, as well as its use in different fields.

Phytic acid structure and sources

Myo-inositol-1,2,3,4,5,6-hexakisphosphate or phytic acid (Fig. 1a) is one of many myo-inositol (Ins) phosphorylated derivatives,[34] which are characterized as a cyclic alcohol that provides the carbon backbones needed for phytic acid biosynthesis.[35] Phytic acid has a 660.04 g mol^{-1} molar mass and $C_6H_{18}O_{24}P_6$ is its molecular formula. According to X-ray crystallographic analysis, the phosphate groups are axially attached to carbons 1, 3, 4, 5 and 6 and equatorially attached to carbon 2.[36] The phytic acid molecule is inert and highly stable, hence it may be stored in neutral or alkaline aqueous solutions for months or years as a solid before generating any decomposition products.[4]

Phytic acid has a powerful chelating ability due to its structure showing a strong affinity with polyvalent cations in the following descending stability order: Cu^{2+} > Zn^{2+} > Ni^{2+} > Co^{2+} > Mn^{2+} > Fe^{3+} > Ca^{2+}.[4] When the phytic acid chelates such cations, the water-insoluble phytate salts are formed.[37] Mono- and divalent cations K^+, Mg^{2+}, and Ca^{2+} are the ones most commonly present.[1] Phytic acid binds directly or indirectly with starch and protein.[38] Phytic acid was considered an antinutrient for several years. However, various studies in human and animal models have demonstrated the preventive effects of phytic acid on different pathologies.[39]

Phytic acid is ubiquitous in eukaryotic species[40] and lower amounts of myo-inositol with fewer phosphate groups (IP1-5) are relevant for regulating vital cellular functions such as cell division, cellular differentiation, exocytosis, and endocytosis.[41]
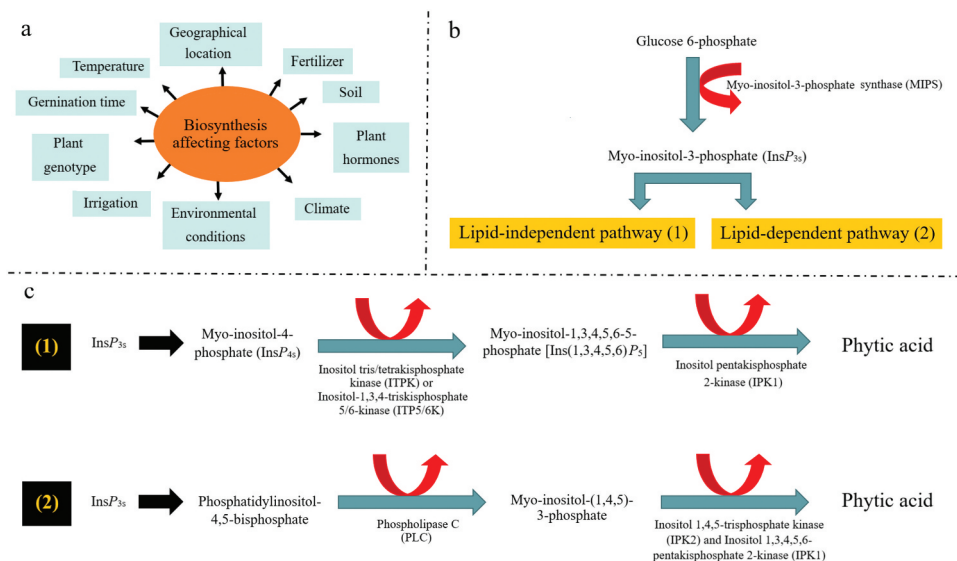
Figure 1. (a) Factors that affect phytic acid biosynthesis; (b) first step of phytic acid biosynthesis; and (c) lipid-independent and lipid-dependent biosynthesis route for phytic acid biosynthesis.

Phytic acid constitutes 1% to 5% (w w^{-1}, dry weight basis) from most oilseeds, legumes, cereals, nuts, and pollen[4] and it represents from 50% to 80% of total phosphorus level in seeds.[5] Phosphorus accumulation in developing seeds is higher than that needed for nominal cellular functions. Several plants use the excess phosphorus to synthesize phytic acid.[35] The phytic acid contents for some foods is summarized in Table 1. It is noted a lower phytic acid content in fruits and vegetables, such as bananas (0.017–0.036%) and carrots (0.015–0.09%). On the other hand, the ground cereal fractions have the highest phytic acid concentrations, especially in rice bran, where the phytic acid contents is significantly higher when compared to brown and polished rice.

Whole grains, such as brown rice, are composed of germ, endosperm, and bran.[54] The bran represents 5% to 8% of total rice grain weight[55] and is comprised of starchy endosperm, germ, aleurone, testa, mesocarp, and epicarp.[56] About 80% of rice bran organic phosphorus is found in the pericarp and aleurone, 7.6% in the germ, and 1.2% in the endosperm.[57] When analysing other cereals such as corn, phytic acid is predominantly found in the germ (88%), endosperm (3.20%), and hull (0.40%); for wheat, it is found in the germ (12.9%), endosperm (2.20%), and aleurone (87%).[57] The milling by-products of these cereals for human consumption, such as rice bran, corn germ-bran and wheat bran are used as feed and as an ingredient on food products formulation due to their protein, lipid, mineral, and antioxidant contents[58–60] Only a small portion is used to recover active ingredients, causing large wastage of resources.[58]

Phytic acid biosynthesis

Various factors such as the geographical location of cultivated crop, climate and environmental variations, type of soil, fertilizer use, irrigation conditions, and plants genotypic variation[2,5] may affect the phytic acid biosynthesis in grains and seeds (Fig. 1a). The effects of temperature on seed phytic acid in 11 lentil genotypes during grain filling period were reported by Thavarajah et al. (2010)[5] where the phytic acid concentration during seed maturation was significantly greater at higher temperatures than at lower ones, 8.8 mg kg^{-1} and 6.7 mg kg^{-1}, respectively. Furthermore, germination time may cause changes in phytic acid content, as reported by Khattak, Zeb, Bibi, Khalil, & Khattak (2007),[61] who reported that phytic acid content in chickpea seeds decreased from 1.01% to

Table 1. Phytic acid content in food (dry basis).

Products		Phytic acid (%)	Reference
Cereals	Polished rice	0.60	[42]
	Brown rice	0.99	[42]
	Oat	0.79–1.01	[43]
	Corn	0.78–1.05	[44]
	Wheat	0.39–1.35	[45]
Milled cereal fractions (brans and flours)	Rice bran	5.90–6.48	[46,47]
	Wheat bran	5.38	[44]
	Whole wheat flour	2.22	[48]
	White wheat flour	0.404	[48]
Fruit	Avocado	0.05	[49]
	Banana	0.017–0.036	[50]
	Mango	0.14	[49]
Tubers and vegetables	Carrot	0.09	[45,51]
	Spinach	0.07	[42]
Legumes	Peanut	1.86–2.31	[50]
	Lentil	0.71	[42]
	Pinto bean	0.61–0.64	[52]
	Navy bean	0.75–1.58	[52]
	Soy	1.01–1.47	[43]
Nuts	Almond	2.11	[53]
	Cashew nut	1.23	[53]

0.60% after 48 h of germination. Other factors, such as variations on plant hormones concentration during seed maturation, may also influence the phytic acid concentration in plants. Matsuno and Fujimura (2014)[37] cultured rice cells with different abscisic acid (ABA) concentrations and showed that ABA is a phytic acid production regulating agent since, compared to control cells, the phytic acid content in rice cells increased as the ABA concentration increased, while no effect was found on either sucrose or inorganic phosphate.

A few days after flowering, phytic acid biosynthesis and accumulation may be detected, and it continues during seed development to maturity.[62] The synthesized phytic acid, as well as its salt and protein complexes are stored in globoids located inside protein bodies.[63] Fig. 1b summarizes the phytic acid biosynthesis. The first step of the synthesis process is the glucose 6-phosphate conversion into myo-inositol-3-phosphate ($InsP_{3s}$) catalysed by myo-inositol-3-phosphate synthase (MIPS).[62] In the steps that follow (Fig. 1c), phytic acid may be synthesized by two pathways, one lipid-independent and one lipid-dependent,[37] with the former the most common one and occurring in cereal and legumes.[62] In this pathway, after $InsP_{3s}$ formation, $InsP_{3s}$ and myo-inositol-4-phosphate ($InsP_{4s}$) are converted into myo-inositol-1,3,4,5,6-5-phosphate [$Ins(1,3,4,5,6)P_5$] catalysed by inositol tris/tetrakisphosphate kinase (ITPK), also known as inositol-1,3,4-triskisphosphate 5/6-kinase (ITP5/6 K).[62] Suzuki, Tanaka, Kuwano, and Yoshida (2007)[64] suggested that the genes *OsITP5/6 K-4* and *OsITP5/6 K-6*, which encode the ITPK enzyme in developing rice seed, may have multi-kinase activities, indicating the existence of multiple intermediate pathways for creating $Ins(1,3,4,5,6)P_5$ from $InsP_{3s}$ during the phytic acid biosynthesis process. Finally, in the final phytic acid synthesis step, $Ins(1,3,4,5,6)P_5$ is converted into phytic acid by the enzyme inositol pentakisphosphate 2-kinase (IPK1).[62]

In the lipid-dependent pathway, phospholipase C (PLC) catalyses the myo-inositol-(1,4,5)-3-phosphate synthesis from phosphatidylinositol-4,5-bisphosphate, and the subsequent catalytic action of enzymes inositol 1,4,5-trisphosphate kinase (IPK2) and inositol 1,3,4,5,6-pentakisphosphate 2-kinase (IPK1) to produce phytic acid occurs.[64]

Phytic acid extraction methods and yield

Phytic acid extraction methods may be applied to various types of grain, as well as to other vegetable sources and biological samples. The extraction includes phytic acid solubilization and acidic dissociation from related proteins or mixed salts.[65] As mentioned earlier, according to

dissociation constants obtained by ^{31}P nuclear magnetic resonance spectroscopy at 28°C, phytic acid has 12 ionizable hydrogen atoms.[66] From the acidic groups, three are weak acid (pKa 5.7–7.6), three are very weak acid (pKa 10.0–12.0),[67] and the remaining six one from each phosphate, are heavily acid (pKa 1.1–2.1). Therefore, phytic acid is largely ionized under physiological pH conditions, becoming negatively charged, thus reacting easily with positively charged substances such as proteins.[38,68,69] A study on rice bran phytic acid solubility behaviour showed a pH-dependent phytic phosphorus solubility; a distinct solubility increase occurred in the 6.2–5.0 pH range, which decreased to a minimum at pH 2.0 before increasing to pH < 2.0.[27] Rice bran phytic acid solubility had a high pH value increase below 2.0 due to the complete phytic acid displacement from protein molecules caused by hydrochloric acid chloride ion.[68] At above 11 pH values, the phytic acid and protein interaction was disrupted and consequently phytic acid was extracted as an insoluble potassium, calcium, and magnesium salts mixture, which precipitate as phytates.[27]

Based on the aforementioned, different phytic acid extraction conditions have been studied using different acid solutions. The first studies were carried out by Wheeler & Ferrel (1971)[70] who investigated the organic phosphorus extraction from wheat and wheat fractions. They found that 0.3 mol L^{-1} trichloroacetic acid (50 mL), under mechanical shaking for 30 min or occasional manual swirling for 45 min, was more extraction-efficient than 6 mol L^{-1} hydrochloric acid, extracting 88% of total phosphorus.

The effects of different treatments on phytate extraction from soybean and cottonseed bran were described by Han (1988).[71] The results showed an 87% phytate extraction yield using 1.0 mol L^{-1} hydrochloric acid under shaking for 1 h at room temperature, higher than that using 0.01 mol L^{-1} hydrochloric, phosphoric, formic, and sulphuric acid solutions, which achieved only a 67% extraction yield. However, it is noteworthy that no clear link between the acid concentration used and the amount of extracted phytate was noted, since hydrochloric acid and sulphuric acids (strong acids) at 1.0 and 0.01 mol L^{-1} extracted more phytate than at 0.1 mol L^{-1}. Moreover, phosphoric and formic acids (weak acids) at high concentration (1 mol L^{-1}) had a negative effect on the phytate extraction yield.

Fuh & Chiang (2001)[68] when evaluating different parameters and using hydrochloric acid on the rice bran phytic acid extraction, namely pH range (1 to 6), extraction time (1, 3 and 5 h) and extraction temperature (25, 40 and 55°C) found pH 2, at 25°C for 30 min as the optimal extraction conditions. At such conditions and at a 1: 5 solvent/rice bran ratio, approximately 94% of the total phytic acid could be removed from rice bran obtaining 30.5% phytic acid in the extract. On the other hand, Champagne et al. (1985)[27] stated that the phytic acid solubility decreased to a minimum at pH 2.0 before increasing at pHs <2.0.

Canan et al. (2011)[47] developed a technique to phytic acid extraction and purification from rice bran. The results showed that optimal extraction was achieved using 1 mol L^{-1} hydrochloric acid with a 0.1 g mL^{-1} rice bran under stirring for 1 h at 25°C. Also aiming for phytic acid extraction from rice bran, Saad et al. (2011)[65] proposed using different acid conditions, namely 0.9 mol L^{-1} sulphuric acid at pH 6 and a 30 min extraction time. Such conditions resulted in an 82.73% extraction yield and were considered more effective than 0.8 mol L^{-1} hydrochloric acid and 1.0 mol L^{-1} trichloroacetic acid, both used at pH 1 and with 3 h extraction.

The conditions for the phytic acid extraction from peanut meal were optimized by Hong, Ting, & Huijie (2017).[72] In their study, proteins were removed to improve the extraction yield and purity. The best extraction conditions were 0.02 mol L^{-1} HCl for 105 min at 30°C allowing a 6.12 ± 0.51% extraction rate and a 182.70 ± 2.35 mg g^{-1} dry PA extract yield.

Despite the different approaches found in the literature for phytic acid extraction and the some-times-divergent results obtained, the overall studies were based on acidic solutions use for solubilization and extraction yield optimization. However, further systematic studies are needed to scale-up the process enabling its industrial application.

Phytic acid purification methods

Several studies on phytic acid extraction and quantification from different vegetable sources and biological samples have been carried out. However, research data on its isolation as a purified compound are scarce. A few purification techniques for phytic acid or its phytate salts from different vegetable sources have been reported in patents. In the 1970s, US Patent 3591665A (1971)[30] claimed a concentrated phytic acid production method from whole bran, defatted rice bran, defatted wheat gluten, and wheat bran. In this method, the phytic acid extraction was performed using different sulfuric acid (0.25 to 0.5%), acetic acid (1.0 to 2.0%), and hydrochloric acid (1.5%) concentrations. After that, either ammonia water, sodium hydroxide or potassium hydroxide was added for pH correction from 8.6 to 9.2. The generated waste was suspended in distilled water and eluted using a column filled with a potent acid cation exchange resin to remove ammonia, calcium, and magnesium cations. The obtained eluate was concentrated and eluted using a column filled with a weak anion exchange resin to obtain a 72% to 76% phytic-acid-containing solution. The purified phytic acid yield was between 94% and 97%.

In 1978, another patent (US Patent 4070422)[31] proposed a phytin or phytic acid (from rice bran) production technique. For that, the extraction was carried out with 0.1 mol L^{-1} hydrochloric acid at pH 1 for 2 h. The obtained precipitate was washed and the filtrate treated with sodium bicarbonate to obtain a precipitate, which was dissolved in 0.1 mol L^{-1} hydrochloric acid. Ether was added to this solution under stirring for 1 h. The aqueous layer was separated and a pharmaceutical-grade phytic acid precipitate was obtained after adding sodium bicarbonate, and then the phytin precipitate was dried. The author did not cite the phytin or phytic acid purity obtained.

More recently, there has been a significant increase in patents and studies on obtaining phytic acid from different vegetable matrices. In 2010, Patent CN102010441A[73] disclosed a technique for obtaining phytic acid/sodium phytate and proteins from corn. For phytic acid extraction, the corn was immersed in water with 0.2% of corn weight in diatomite to remove soluble protein and starch, followed by heating, protein separation by thermocoagulation and suction filtration. The washing water containing phytin was pH adjusted, and followed by solution concentration and ion exchange resin adsorption for phytic acid extraction. The collected phytate solution was concentrated and dried to obtain the final sodium phytate product (over 96% yield).

Newkirk et al. (2011)[32] put forward a patented inositol production process from plant materials. An aqueous-slurry plant material was partially hydrolysed with phytase at a suitable pH and temperature. The partially hydrolysed slurry was separated using a physical separation process, either by filtration or centrifugation, creating an inositol phosphate-containing a soluble and an insoluble fraction. The obtained phytic acid purity was not mentioned in this patent.

Canan et al. (2011)[47] developed an analytical method for phytic acid purification from defatted rice bran. Phytic acid was extracted using hydrochloric acid. The obtained extract pH was adjusted to 4.5 and the precipitate was discarded after centrifugation. The supernatant pH was adjusted for phytic acid precipitation. The supernatant was discarded and the precipitate was resuspended in hydrochloric acid, formaldehyde and diatomaceous earth. A precipitate was formed after decantation, filtration and pH adjustment, which was dehydrated in a laboratory oven to obtain purified phytic acid. The obtained phytic acid reached a maximum 42.3% purity.

Kumar, Makkar, Devappa, and Becker (2011)[74] studied the phytate isolation from defatted jatropha flour using a method based on chemical treatment and differential centrifugation by adding organic solvents. The sample was initially treated with 0.36 mol L^{-1} hydrochloric acid and the obtained solution was freeze-dried and then suspended in an acetone and carbon tetrachloride solution. The suspension was centrifuged, the supernatant discarded and the precipitate fractionated by differential centrifugation into five fractions that were treated with an acetone and carbon tetrachloride solution at different densities. Fractions III and IV were joined due to their high phytate and protein content, solubilized in Tris base, centrifuged and washed sequentially with water and acetone, and a 66% concentrated phytate phase was obtained.

More recently, phytic acid, synaptic acid, and proteins isolation from defatted rapeseed meal using a non-porous anion exchange resin and zeolite was investigated by Thiel et al. (2015).[33] The authors described an efficient sequential phytic acid recovery process (32.24 mg g^{-1}), which involved obtaining phytic acid by adsorption on a chromatography column filled with resin after protein and synaptic acid isolation. The resin was desorbed using 1.0 mol L^{-1} sodium chloride acidified with 0.5 mol L^{-1} hydrochloric acid.

As for extraction procedures, distinct methods aiming at phytic acid purification have been described with significant differences on the purity achieved. In this case, further studies are needed to scale-up the process. Ultimately, it is worth mentioning the shortage of available information on phytic acid purification compared to that concerning extraction.

Phytic acid application

Phytic acid interaction with food components

Phytic acid has chelating properties on food micronutrients such as zinc and iron during intestinal digestion, producing insoluble complexes not absorbed by the intestinal mucosa, thus reducing the micronutrients bioavailability.[5] However, a low nutritional impact of phytic acid inhibitory effect has been suggested in well-balanced diets, whereas the opposite is observed mainly in poor trace element diets with simultaneously high phytic acid intake.[39,41,75] In this way, the high content of phytic acid present in the diet of the Asian population, which is basically composed of cereals, may be one of the causes of malnutrition in these people.[75] However, it should be mentioned that different strategies may be put in place to reduce the antinutritional effects of phytic acid, such as cooking, fermentation, germination and more recently proposed, the use of enzymatic approaches such as the addition of phytases, including those from microbial sources.[75] Additionally, other food components such as vitamins, fats, and polyphenols may also interact with minerals, reducing their bioavailability. Moreover, other factors such as fermentable fibre content, phytase vegetable activity and phytate : mineral intake ratio also affect mineral absorption.[7,76] Some studies have shown that a legume-based diet, despite having a high phytic acid content, may foster a zinc absorption comparable to animal-protein-containing-diets.[77] Furthermore, oat-bran-containing-diets, which have a high phytate content, associated with a low-fiber animal-based-protein diet, do not affect zinc absorption.[78] Therefore, the phytic acid effect analysis on mineral absorption should take into account all dietary components.

On the other hand, oral co-administration of phytic acid with bioactive compounds, such as flavonoids and curcumin, has been suggested to enhance the compounds' bioavailability. Matsumoto et al. (2007),[79] when studying the effects of phytic acid on blackcurrant anthocyanins absorption, both in rats and humans, noted a distinct anthocyanins absorption improvement, with anthocyanins increased recovery in the rat urine dependent on the phytic acid dose. The increased absorption effect was also evidenced by their increased levels in plasma and urine from six healthy human volunteers. The authors suggested that such effect might be due to a longer transient time caused by a gastrointestinal motility decrease. Other flavonoids, such as isorhamnetin, kaempferol and quercetin from *Hippophae rhamnoides* L. were also increasingly absorbed when orally administrated to rats together with phytic acid.[80] The compounds solubility was found to increase with higher phytic acid concentrations due to intermolecular interactions formation between flavonoid's carbonyl groups and phytic acid phosphate groups, increasing their hydrophilicity. Another plausible mechanism supporting the *in vivo* increased absorption could be enhanced cell permeability via a transcellular pathway caused by phytic acid. Due to the strong ability of phytic acid to chelate metal ions, the membrane fluidity could be impacted, thus increasing the transport of these flavonoids. The authors also showed that phytic acid cytotoxic effects were non-existent, both when Caco-2 cells were treated at a 400 μg mL^{-1} concentration and when administrated to rats at a 200 mg kg^{-1} dose, demonstrating its safety when used as a nutraceutical oral absorption enhancer.

Pei et al. (2019)[81] evaluated the *in vitro* impact of phytic acid on the curcumin bioaccessibility in oil-in-water nanoemulsions. After passing through simulated mouth, stomach, and small intestine stages, the total free fatty acids contents decreased when increasing the curcumin fraction released in a soluble form. The results suggest that phytic acid may affect curcumin bioaccessibility by numerous mechanisms such as affecting droplet flocculation at different pH and decreasing the free calcium ions level, while the inverse relation with lipolysis may be due to digestive enzymes inhibition. Even though further studies would be needed to evaluate if phytic acid could have a positive impact on the curcumin absorption by intestine cells, the authors suggested that phytic acid could be used as a multifunctional ingredient, acting as a lipid-reducing agent, while simultaneously boosting nutraceutical bioavailability.

Based on the ability of phytic acid in forming complexes with some proteins, reducing their solubility and affecting their function, another suggested application is its use in allergenic foods. Chung & Champagne (2007)[82] demonstrated that phytic acid was able to form insoluble complexes with major peanut allergens (Ara h 1 and Ara h 2), causing a 6-fold reduction in IgE binding, thereby reducing the extracts allergenicity. Furthermore, more insoluble complexes have been formed in raw peanut extract than in roasted peanut. The authors also suggested that phytic acid may be used to develop hypoallergenic peanut products as the use of phytic acid in a non-hydrogenated peanut butter slurry reduced its allergenicity.

Phytic acid disease prevention potential

Several studies have been done to evaluate the beneficial health and physiological effects of phytic acid on pathologies such as cancer, diabetes, coronary heart disease, Parkinson's, and kidney stones.

Cancer

The importance of phytic acid as a dietary component is not yet fully clarified, although its protective effects against cancer have been widely studied and proven, using cell lines, such as hepatocellular carcinoma (HepG2) and Caco-2 cells, and *in vivo* studies mainly performed with rats.[9,83–85] In the first case, after a 48-hour-treatment, HepG2 viability was 23.8% in succinate dehydrogenase activity (3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide (MTT)) assay, and 32.4% in lactate dehydrogenase (LDH) assay, at 3.5 mM phytic acid.[85] For Caco-2 cells, the phytic acid decreased the effective permeability of the typical *P*-glycoprotein (*P*-gp) substrate rhodamine 123 (R123) by 50% in the colon, also at the 3.5 mM phytic acid.[84]

Khatiwada et al. (2006)[86] studied the effect of phytic acid and inositol on the induced colon tumor reduction in male rats. The results showed that 2 g 100 mL^{-1} phytic acid added to drinking water significantly reduced the occurrence of colon tumor in rats. When evaluating the effects of commercial phytic acid and phytic acid extracted from rice bran on the induced colon cancer suppression in rats, it was found that 0.20% (w v^{-1}) phytic acid from rice bran added to drinking water greatly reduced (52%) total aberrant crypt foci (ACF) in the colon.[12] The results suggest that phytic acid could be a powerful chemo-preventive agent on neoplastic changes suppression caused by colon cancer as well as inhibiting colon tumor formation. It has been demonstrated either in cell lines (CaCo-2 and HT-29 colorectal cancer cell lines) or animal studies that IP6 can regulate cell cycle progression, cell proliferation, and apoptosis by different malignancy pathways such as TGF-beta, NF-κB, EGF/EGFR, IGF-1 R and I3K/Akt.[8,10] Another feasible mechanism by which phytic acid (IP6) suppresses cancer is that IP6 has iron chelating properties, suppressing the iron-catalyzed hydroxyl radicals production and reducing the pH in the colon.[1,9] This effect was also noted when studying cells treated with 1 to 5 mmol L^{-1} IP6. However, such a large amount of IP6 binds metals and changes the pH in cell culture medium. Aiming at overcoming this issue, Masunaga et al. (2019)[9] synthesized an IP6 prodrug (Pro-IP6) and clarified the IP6 creation from Pro-IP6 in cells. Cellular experiments using up to 10 μM Pro-IP6 concentrations showed selective anti-cancer effects, including apoptosis and Akt (Kinase B protein) activation inhibition. Furthermore, an *in vivo* study using Pro-IP6 (μmol kg^{-1}) compared to a control group

with an intraperitoneal vehicle once daily in rats with adult T-cell leukemia, showed that Pro-IP6 reduced the tumor size. Colorectal cancer cell proliferation suppression was demonstrated by Yu et al. (2018)[10] who evaluated the underlying possible mechanisms linked to the chemopreventive process. The use of IP6 reduced four tumour indexes, in terms of tumour incidence, number, weight and volume, in 1.2-dimethy-hydrazine dihydrochloride (DMH)-induced colorectal cancer model in rats that received 0.25 g kg^{-1}, 0.5 g kg^{-1} and 1.0 g kg^{-1} body weight of IP6 respectively, by gavage daily during a 39-week-period experiment. Furthermore, the study verified changes in different pathways demonstrated by a significant Akt and c-Myc mRNA levels decrease and protein changes. Thus, it was shown that IP6 down-regulates Akt, pAkt, pGSK-3β, and c-Myc protein expression and up-regulates β-catenin protein expression. Moreover, tumour tissues from IP6-treated rats showed decreased proliferation. The authors concluded that the IP6 anti-proliferative effect may be related to the crosstalk between PI3K/Akt and Wnt pathways, revealing a potential CRC inhibition mechanism by IP6.[10] Further details on the uptake mechanisms and intracellular involvement in IP6 pathways signalling in cancer cells may be found on a recent review paper on the subject.[8]

Phytic acid has been used in ingenious biocompatible nanocomposites for drug administration improving the drugs biodistribution and selectively targeting diseased tissues while protecting healthy ones. Barahuie et al. (2017)[11] used phytic acid to coat chitosan iron oxide magnetic nanoparticles and form phytic acid-chitosan-iron oxide nanocomposites to improve the thermal stability of the anti-cancer nanocomposite obtained. The drug loading was estimated at 12.9% in the designed nanocomposite and approximately 86% and 93% of phytic acid from nanocomposite could be released within 127 and 56 h by a phosphate buffer solution at pH 7.4 and 4.8, respectively. MTT assay was used to evaluated cytotoxic effects of the compounds on a colon cancer cell line (HT-29). The results indicated that the phytic acid-chitosan-iron oxide nanocomposite may inhibit the colon cancer cells proliferation without damaging healthy cells.

Diabetes

The consumption of high-phytic-acid diets has also been linked to changes in blood glucose response.[87] Phytic acid, due to its binding ability, can chelate Ca^{2+} ions, which are a co-factor for α-amylase, but can also bind to certain amino acids in proteins, thus inhibiting digestive enzymes. Such effects may result in slower starch digestion leading to a lower glycemic response (consequently, high-phytic-acid diets are usually linked to a lower glycemic index).[87,88] Phytic acid intake has been linked to lower blood glucose levels and improved insulin response, both in rodents and humans.[14,89] In diabetic mice fed a diet containing 0.5% and 1.0% phytic acid, a significant fasting glucose levels reduction occurred.[14] Similarly, Kim, Rico, Sang, and Kang (2010)[13] reported that mice fed a high-fat diet supplemented with rice bran or phytic acid had considerably lower glucose levels compared to the diet-only-fed group. Furthermore, rice bran and phytic acid increased the glucokinase enzyme and decreased hepatic enzymes activity involved in gluconeogenesis, improving glucose metabolism. Kim et al. (2014)[88] studied the effects of phytic acid on differentiation, insulin-stimulated glucose uptake, and adipocytes lipolysis obtained from mouse embryo fibroblasts cell line (3T3-L1) differentiation treated with 10, 50, or 200 μmol L^{-1} of phytic acid or myo-inositol. Phytic acid was found to increase mRNA levels in the insulin receptor substrate 1 and the glucose transporter 4 while reducing basal lipolysis, suggesting that it may increase insulin sensitivity into adipocytes in a dose-dependent manner. For rats fed a high-sucrose diet with or without 1.02% phytic acid for 12 days, dietary phytic acid reduced hepatic lipogenic enzymes activity and expression, thus ameliorating sucrose-induced fatty liver, as well as modulating gut microflora, by increasing fecal *Lactobacillus* sp. and decreasing *Clostridium coccoides*.[90]

Coronary heart diseases

An *in vivo* study reported the phytic acid attenuation effects on ischemic reperfusion induced by hydroxyl radicals in rats' myocardium. Obata & Nakashima (2015)[16] observed that rats with induced ischemic-reperfusion previously treated with phytic acid (20 mg kg^{-1} intraperitoneal (ip)), showed no

increase on hydroxyl radicals. Furthermore, phytic acid may significantly reduce the creatine phosphokinase (CPK) content generated during myocardial injury, while in the control animals serum, a CPK increase was observed (131 ± 25 *versus* 233 ± 38 U mL^{-1}). Moreover, Kang et al. (2012)[91] reported that rice bran and phytic acid may have anti-hyperlipidemic activity in mice fed a high-fat diet containing 30% rice bran or 0.5% phytic acid, mainly by increasing cholesterol and triacylglycerols fecal excretion and by regulating lipogenic and antioxidant enzymes activity. Improvements in serum lipids level and profile may indirectly add to cardiovascular health benefits.

Parkinson's disease

Parkinson's disease is characterized by an irreversible motor dysfunction caused by a degeneration of dopaminergic neurons in the substantia nigra.[17] The discovery of excessive iron accumulation in substantia nigra in Parkinson's disease patients has led to questioning on the role of iron in the disease occurrence. The iron-regulatory mechanisms imbalance can lead to its accumulation, causing oxidative stress with the free radical formation and induced cell damage.[92] In this respect, Xu et al. (2008)[17] established the protective effect of phytic acid on 1-methyl-4-phenylpyridine (MPP$^+$) molecule, which induces dopaminergic neuron loss and is susceptible to chelating activity molecules. The results showed that phytic acid could protect dopaminergic neurons from apoptosis caused by MPP$^+$ action, as the cell survival rate increased by 18% and 42% with 30 and 100 µmol L^{-1} IP6 respectively, under iron-excess conditions. In a similar way, a 45% reduction in DNA fragmentation was found with 100 µmol L^{-1} of phytic acid. Also, Hoechst nuclear staining results confirmed the protective effect of IP6 on apoptosis.

Kidney stones

Saw et al. (2007)[18] studied the calcium oxalate crystallization inhibition by phytic acid by a turbidimetric method with artificial and whole urine. Effects on stone growth were measured using an *in vitro* system with 12 stones grown simultaneously using artificial urine only or supplemented with urinary macromolecules. The authors noted an ionized calcium decrease, a metastable limit increase, a crystallization turbidity rate index decrease and *in vitro* stone growth rate decrease using 120 µmol phytic acid. Experimental studies in animals and observational studies in humans suggest that IP6 may prevent lithiasis, vascular calcification as well as osteoporosis.[15] In this sense, IP6-containing food supplements have been marketed in several countries to prevent calcium stones and plaque.[15] Various studies indicate that phytic acid may interfere with calcium availability, which is an important micronutrient for bone formation and maintenance,[93] Kumar et al. (2010)[1] reported that during consumption of phytic acid- and phytase-rich cereals, phytase not only releases phosphorus from vegetable-based diets but also makes calcium, magnesium, protein and lipid available. Thus, by releasing bound phosphorus in vegetable-based feed ingredients, phytase provides more phosphorus for bone growth.

Phytic acid antioxidant properties

Varied studies have long demonstrated the pronounced antioxidant activity of phytic acid, which is closely linked to its high affinity to bind iron (Fig. 2). [4,75,94,95] If only one of the six iron coordination sites is open or bound to a readily dissociable ligand such as water, it acts as a potent iron-catalyzed hydroxyl radicals formation (•OH) inhibitor.[19]

A consistent observation in studies involving iron, regardless of the radical-generating system used or the nature of the lipid substrate, has indicated that ferric ion (Fe^{3+}) reduction or ferrous ion (Fe^{2+}) oxidation is mandatory for the lipid peroxidation initiation.[96] Minotti and Aust (1987)[97] investigated lipid peroxidation systems involving Fe^{2+}, H$_2$O$_2$, and phospholipid liposomes. The results showed that lipid peroxidation onset is not dependant on radical •OH generation and it occurs only when both Fe^{3+} and Fe^{2+} are present, not occurring in the presence of either Fe^{3+} or Fe^{2+} alone. Also, lipid peroxidation is not induced by Fe^{2+} ions or H$_2$O$_2$ alone, demonstrating that H$_2$O$_2$ has virtually
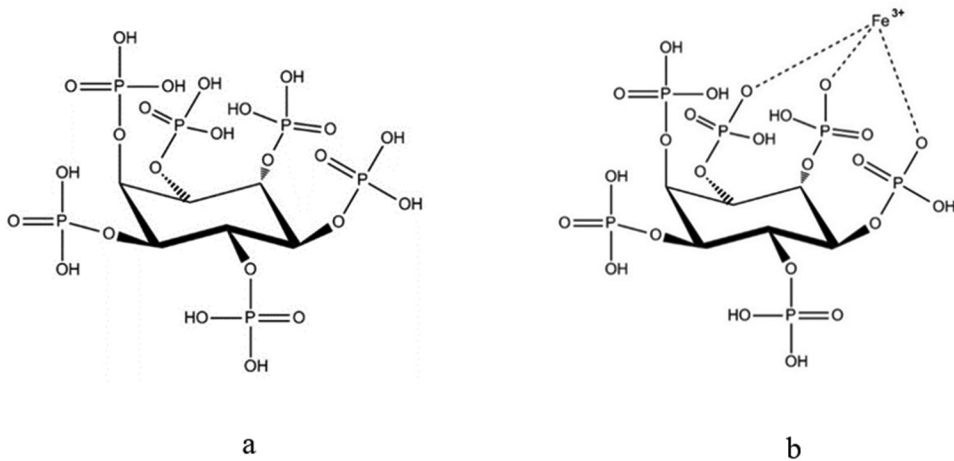
Figure 2. (a) Phytic acid chemical structure and (b) phytic acid connected with the six coordination sit.

no reactivity against phospholipids, and both iron ions are required for the initiator species generation.

Phytic acid is the only element which, when linked to the six coordination sites of iron (Fig. 1b), generates a totally inactive chelate, thereby inhibiting the hydroxyl radicals production and the iron oxidising from Fe^{2+} to Fe^{3+}.[4,19] Fe^{3+} is relatively inert even with polyunsaturated fatty acids and oxygen, whereas Fe^{2+} causes lipid peroxidation and oxyradicals production.[98] By binding with the six Fe^{3+}coordination sites, phytic acid prevents the reaction between H_2O_2 and chelated Fe^{3+} ion, avoiding iron hydroxyl radical formation.[19] The study of the phytic acid effect on oxidation reactions in a linoleic acid micellar system showed that Fe^{2+} to Fe^{3+} oxidation was eased by the addition of phytic acid, which is dose- and time-dependent. Furthermore, the inhibition of thiobarbituric acid reactive substances (TBARS) formation was also dose-dependent and phytic acid could reduce deoxyribose degradation by 78%, 81% and 88% when used at 0.1, 1.0 and 5.0 mmol L^{-1} concentrations, respectively.[99]

Before its recognition as GRAS by the FDA (Food and Drug Administration) in 1997, phytic acid had been widely used as a food additive in several countries.[4] Considering that phytic acid and its metabolites are neither toxic nor reactive, its use as a food additive to replace other commonly used preservatives becomes attractive.[100] In this regard, several studies have been performed to evaluate the antioxidant effects of phytic acid, especially in meat foods.

The effect of sodium phytate (SPT) on restructured beef`s physicochemical characteristics, including TBARS formation inhibition, when compared to traditional meat phosphate additives (sodium pyrophosphate (SPP) and sodium tripolyphosphate (STP)) were studied by Lee, Hendricks, & Cornforth (1998).[101] The results showed that all tested compounds avoided lipid peroxidation after one day of raw restructured beef storage. For cooked meats, SPT was the most effective on inhibiting lipid peroxidation, even at a much lower concentration (4.5 mmol L^{-1} compared to 11.2 mmol L^{-1} SPP and 13.6 mmol L^{-1} STP). Other studies have also proved the ability of phytic acid to inhibit lipid oxidation in meat-based foods.[102–104] The use of phytic acid as a suitable alternative for the meat industry to improve industrialized meat products stability and quality, was also established by Stodolak et al. (2007)[105] who when evaluating phytic-acid-containing solutions as stability extenders for raw and cooked beef and pork meat kept under refrigeration, it found that metmyoglobin production was inhibited in the presence of phytic acid in raw meat.

Besides using phytic acid as an additive added to meat foods, further studies have been done to evaluate a possible indirect effect on meat products obtained from animals fed with phytic-acid-rich diets. The endogenous effects of defatted corn germ phytic acid added to pig diets were studied by

Harbach et al. (2007).[106] The results showed that adding 0%, 10%, 20%, and 40% defatted corn germ to feed did not affect feed conversion, weight gain or carcass characteristics. Furthermore, the *Longissimus dorsi* muscle from animals fed with diets containing 40% defatted corn germ inhibited 63% lipid oxidation. Chicken nuggets added with defatted rice bran replacing soy protein and sodium erythorbate antioxidant showed the same lipid stability and sensory acceptance as chicken nuggets added with soy protein and sodium erythorbate. This result may be due to rice bran high phytic acid content.[107]

Due to its inhibiting polyphenol oxidase and oxygen reduction abilities, phytic acid was suggested as a possible enzymatic browning control agent in different foods including apple and bur fruit juices, green bracken, and pickled leaf mustard.[108]

Phytic acid antimicrobial properties

Recent studies have suggested that phytic acid may effectively inhibit the growth of foodborne pathogens such as *Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Salmonella* Typhimurium, and *Clostridium perfringens*.[21–23,109] Zhou et al. (2018),[21] after observing that phytic acid exhibited antimicrobial activity against two *E. coli* and *S. aureus* strains, studied the mechanism underlying such activity. The authors reported that phytic acid caused morphological modifications on both Gram-positive and Gram-negative bacteria, inducing an increased cell membrane permeability, which caused intracellular ATP losses. Increases in cell permeability and outer membrane damage were also noted by Kim et al. (2015)[110] when evaluating the antimicrobial activity of phytic acid alone and combined with sodium chloride, against *E. coli* O:157: H7. The results showed that adding phytic acid to the hyper-salting stage in kimchi production from napa cabbage significantly reduced the inoculated *E. coli* O157: H7 population. The treatment was successfully applied on an industrial scale in a commercial kimchi processing plant, allowing the full elimination of total and thermotolerant coliforms and initial aerobic plate counts reduction. According to the authors, phytic acid may sequester polyvalent cations that stabilize the molecular interaction in the outer membrane, permeating it, thus allowing a rapid ions penetration leading to increased osmotic pressure and ultimately, to lysis. Afterwards, the same group reported that the bactericidal effects of phytic acid against *E. coli* O157: H7 were much greater than those of organic acids, such as acetic, citric, lactic, and malic acids, under the same experimental conditions. It confirms once again the synergistic effect of phytic acid when used in conjunction with sodium chloride.[111] Phytic acid activity (0.4%) added with sodium chloride (2–4%) further tested against *E. coli* O157: H7 biofilms showed a synergetic effect and the effectiveness of the approach as an alternative to eliminate biofilm formation in food processing environments.[110] Phytic acid also combined with lysozyme significantly reduced the amount of genus *Pseudomonas* bacteria in herbivorous carp spoiled fillets.[112] Phytic acid has also enhanced the antibacterial effect of nisin against *Listeria monocytogenes* on cabbage and broccoli, significantly reducing bacteria.[113] Besides that, treatment with exogenous phytic acid has been reported to improve the oral S-nitrosothiols protection mechanism in rat models with *Clostridium difficile* infection, one of the major microorganisms causing intra-hospital infections.[114]

In addition to presenting antibacterial activity, *in vitro* tests and assays on strawberries have shown that phytic acid may enhance *Rhodotorula mucilaginosa* biocontrol activity against gray mold spoilage caused by *Botrytis cinerea*, a natural spoilage fungi often found in strawberries causing postharvest economic losses.[20]

Phytic acid and different industrial applications

Phytic acid has great potential for use in other fields, such as heavy-metal-contaminated waste treatment,[115–117] radionuclides recovery from contaminated water,[118,119] new modified electrodes development for cadmium and lead detection,[120] and metal coating for inhibiting of rust formation and corrosion.[121]

Iemma et al. (2008)[24] synthesized a chelating resin with phytic acid immobilized in its structure aiming at copper (II), iron (III), and nickel (II) removal from aqueous solutions. The results showed that the resin was successfully synthesized, exhibiting powerful chelating activity. Ali et al. (2020)[115] synthesized a novel phytic acid-functionalized poly-phenylglycine material with great heavy-metal-removing-capacity (Cu, Pb, and Cd) from water and its four-cycle-reuse aiming for environmental remediation.

Other phytic acid applications include its use as a metallic anticorrosion coating constituent due to the economic losses involved. Therefore, Tang, Wang, Xu, and Li (2010)[25] coated a silica nanoparticle with phytic acid to obtain an environmentally friendly anti-corrosion coating. The results showed that the surface coated with nanoparticles showed no visible corrosion signs, while the surface without a phytic acid anticorrosion coating showed several flaws on the metal surface. Gao, Zhao, Lu, Gao, and Ma (2014)[122] when studying the effect of phytic acid as an anticorrosion agent in iron surfaces under acidic and neutral conditions reported that phytic acid and its anions bind with iron (II) ions at a pH around 7.0 producing phytate salts. Such phytate salts form a protective film on an iron-coated surface. In an acidic environment, phytic acid inhibits corrosion by forming phytic acid layers adsorbed onto the iron surface.

Another recent potential industry application, is the use of phytic acid for imparting long-lasting flame-retardant properties to fabrics.[123–125] Different approaches based on the use of phytic acid as a bio-based phosphorus flame retardant have been applied to develop fabrics such as cotton,[123] wool,[126] silk,[127] cellulosic fibers,[128] and nonwoven fabric with flame retardant properties or heat and smoke suppressing ability.[129]

Future directions

Phytic acid has demonstrated a high potential for a wide range of applications. In the health field, there are growing evidences of a beneficial effect in the prevention of numerous diseases. However, more intensive studies are needed to gain a better understanding of the mechanisms of action. Moreover, further *in vitro* and *in vivo* research is required towards phytic acid application. Its application in the form of biocompatible nanocomposites for drug administration has already been evaluated, improving biodistribution and selective targeting of diseased tissues.[11] Yet, information on the dosage to be used to obtain positive effects without causing damage to health is limited and the ideal dosage for clinical applications has not yet been determined.

Regarding food industries, currently they are looking for natural, viable and safe antioxidants and antimicrobials agents, and phytic acid meets these needs. Studies indicate that phytic acid has no cytotoxic effect,[79] and its application is even suggested in allergenic foods,[81] due to its ability to form complexes with some proteins, reducing its solubility and affecting its function. Despite its high potential in this sector, the interaction of phytic acid with food components cannot be disregarded in order not to compromise the absorption of micronutrients from the diet. While for populations in developed countries, that generally do not suffer from mineral deficiencies, the beneficial health effects of phytate overpass its possible impact on mineral absorption, in underdeveloped or developing countries having high intake of foods rich in phytic acid, this aspect should be considered. In order to minimize this problem, the application of phytases has been evaluated to reduce the content of phytic acid and its derivatives.[75]

Finally, in the current context of increasing demand for solutions towards circular economy and zero waste, the fact that phytic acid is present in a significant amount in different agro-industrial wastes, becomes an alternative to aggregate value to these by-products.

Conclusion

Phytic acid is a plant-based component obtained from different grain by-products such as rice and wheat with a powerful chelating activity responsible for its functional properties. Since it has a high

affinity with polyvalent cations it may form chelates with food micronutrients, reducing mineral bioavailability. However, such phenomenon impacts only poor-trace elements diets combined with a high phytic acid intake. In contrast, phytic acid has been associated with several health and physiological benefits, also having practical application in industrial fields. In view of its pronounced antioxidant activity, it may be used as a natural food preservative, replacing the artificial ones commonly used. In addition, recent studies have shown its potential as an antimicrobial agent. Therefore, regulatory bodies from countries that have not yet allowed its use as a food additive ought to offer alternatives, mainly for lipid-rich animal protein such as processed meat products. This could improve the food stability and quality and, at the same time, draw consumer attention by replacing artificial preservatives with a natural compound. Furthermore, the pharmaceutical and food supplements industries could take advantage of its well-reported benefits, mainly with regards to its anti-cancer protection. The wide use of phytic acid in other industrial applications has also been demonstrated. In view of the growing interest of governments, industries and the overall society for implementing a circular economy, a future upward trend in the use of this natural compound is expected. For this purpose, further studies are needed for improving its extraction and purification yields from food industry by-products, such as rice and wheat bran scaling-up processes at an industrial level.

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Declaration of interest

The authors declare that they do not have any conflicts of interest.

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