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Phytic acid and its interactions: Contributions to protein functionality, food processing, and safety

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Abstract

Is phytic acid (IP6) an undesirable constituent for vegetables and foods? This question is getting harder to answer. Phytic acid contributes to mineral/protein deficiency, but also brings about potential physiological benefits. Both the positive and negative effects boil down to the interactions among IP6, metal ions, and biopolymers. In the wake of the booming market of plant-based foods, an unbiased understanding of these interactions and their impacts on the foods themselves is a necessity to the smart control and utilization of plant-sourced phytates. This overview presents updated knowledge of IP6-related interactions, with a strong focus on their contributions to food functionality, processability, and safety.

KEYWORDS
food processing, food safety, interactions, phytic acid, protein functionality

1 | INTRODUCTION

Phytic acid (myo-inositol-1,2,3,4,5,6-hexakis phosphate, IP6), discovered in 1903, is a sixfold dihydrogenphosphate ester of myo-inositol (Bedford & Walk, 2016). IP6-derived salts, also known as phytates or phytin, naturally occur in many fiber-rich plants, such as cereals, legumes, and nuts, serving as a phosphorus reservoir. Leafy vegetables and fruits usually contain none or trace amounts of phytates (Schlemmer, Frølich, Prieto, & Grases, 2009). Phytates also comprise 20% to 50% of the organophosphates found in soils (Reinmuth, Pramanik, Douglas, Day, & Bowman-James, 2019), and thus are widely studied in other disciplines of agricultural sciences. The accumulation of phytates in plants starts during seed maturation, which botanists consider a way of "detoxification," as excess inorganic phosphorus is toxic to plants while phytate is a nontoxic remedy (Yang, Huang, Kuo, & Chiou, 2017). It also helps maintain a low inorganic P to promote starch biosynthesis in the endosperm (Iwai, Takahashi, Oda, Terada, & Yoshida, 2012). Upon germination, these phytates are hydrolyzed to release utilizable phosphorus and minerals (Oatway et al., 2001). Many low-phytate mutants reveal undesired characteristics, such as reduced germination rate, yield, and stress sensitivity (Bregitzer & Raboy, 2006; Dong, Echigo, Raboy, & Saneoka, 2020).

Numerous animals live on these fiber-rich grains while humans' daily intakes are greatly affected by culture and dietary regimes. IP6 has drawn massive attention due to its unique chemical structure that facilitates complexation with dietary minerals and proteins. Considering the nutritional importance of metal ions and biopolymers, IP6, together with its salts, has been tagged as an antinutrient since as early as the 1920s (Mellanby, 1949). It has been extensively proved that phytates inhibit the biological functions of trace elements (calcium, magnesium, zinc, iron, etc.), food proteins, and digestive enzymes, causing potential digestive problems for monogastric animals and humans whose diets heavily rely on these plants but cannot produce phytase (Schlemmer et al., 2009). Not only that but the high load of unabsorbed phosphorus excretion

by monogastric animals has also led to increasing environmental pollution (Vats, Bhattacharyya, & Banerjee, 2005). This notoriety as a nutritionally detrimental substance has led to efforts to remove phytate from soy and other plant ingredients. Phytase supplementation to the animal feedstuffs has also become a common practice (Kumar, Sinha, Makkar, & Becker, 2010; Singh, 2008), while the production of some foods and ingredients are also accompanied with phytase treatment (Greiner & Konietzny, 2006). For ruminant animals whose rumen microorganisms produce phytase, phytate is digestible (Shitan & Yazaki, 2013).

Later studies realized that IP6 can provide health benefits because metal ions per se are detrimental under certain circumstances. For instance, Fe^{3+} and Cu^{2+} are critical for mediating oxidation and tumor cell proliferation (Shitan & Yazaki, 2013). Obviously, a chelator is desirable in such cases. More and more research has recognized the antioxidant activity (Kunyanga, Imungi, Okoth, Biesalski, & Vadivel, 2011) and antitumor effects (Fox & Eberl, 2002) of IP6 and phytates, which include but are not limited to preventing pathological calcification, managing blood sugar and cholesterol levels (Kunyanga et al., 2011; Schlemmer et al., 2009), and potential therapeutic effects on Parkinson's (Lv et al., 2015; Xu, Kanthasamy, & Reddy, 2008), Alzheimer's (Anekonda et al., 2011), and other diseases. As a result of the above controversy, the use of the term "antinutrient" should be reconsidered (Murphy, Marques-Lopes, & Sánchez-Tainta, 2018) and the question of whether phytate is an undesired constituent in plant-based food becomes harder to answer (Greiner, Konietzny, & Jany, 2006). Minimizing phytate consumption is unnecessary if there is no potential mineral deficiency in the diet (Belmiro, Tribst, & Cristianini, 2020). In the meantime, this nontoxic and densely charged small molecule has demonstrated great potential in many industries, including dental care, pharmaceutics, and others (Oatway et al., 2001), inspiring the recovery and utilization of unwanted phytate from plant food materials.

Numerous literature reviews have been published in the past 20 years to accumulate findings regarding phytates, including their sources, intake, and digestion (Schlemmer et al., 2009), chemical properties and ligand speciation (Angel, Tamim, Applegate, Dhandu, & Ellestad, 2002; Crea, De Stefano, Milea, & Sammartano, 2008), analytical techniques (Wu, Tian, Walker, & Wang, 2009), phytase applications (Greiner & Konietzny, 2006; Kumar, Sinha, Makkar, De Boeck, & Becker, 2012; Selle, Ravindran, Caldwell, & Bryden, 2000), and most frequently and extensively, their nutritional and bioactive implications (Gibson, Bailey, Gibbs, & Ferguson, 2010; Kumar et al., 2010; Nissar, Ahad, Naik, & Hussain, 2017; Rimbach, Pallauf, Moehring, Kraemer, & Minihane, 2008; Selle et al., 2000; Selle, Cowieson, Cowieson, & Ravindran, 2012; Silva & Bracarense, 2016; Singh, 2008; Singh, Mehra, Bisht, Shekhar, & Kumar, 2018). Readers interested in these aspects can refer to the above review articles.

This work has a different focus from the above, which is introducing updated knowledge of IP6-related interactions and highlighting relevant issues surrounding plant food processing. A comprehensive understanding of IP6 may guide food manufacturers to take smart control over food phytate content and achieve desirable food texture and quality.

2 | IP6/PHYTATE CHEMISTRY AND INTERACTIONS

2.1 | Acid-base properties

The terms phytic acid and phytate in literature are often used interchangeably. Here, for clarity, the term "phytic acid" (IP6) refers to a proton donor that releases H^+ and "phytate" anion, the latter readily forming salts with other cations in the aqueous system. Figure 1(a) illustrates the chemical structure of a fully protonated IP6, featuring six phosphate groups surrounding one inositol ring. Because each phosphate has two dissociable OH groups, IP6 has 12 replaceable protons or reactive sites, among which six are strongly acidic ($pK_a < 3$), two are weakly acidic (pK_a approximately 5 to 6), while the remaining four of them are very weakly acidic ($pK_a > 9$) (Angel et al., 2002). As a result, fully protonated IP6 only exists in an extremely low pH (pH < 1.3). The phosphate groups can be deprotonated stepwise as the pH increases to approximately 10.5 (Figure 1(b)) (Evans, McCourtney, & Shrager, 1982). However, the acid-base properties of IP6 depend on more than just pH. The pKa values of IP6 are also greatly affected by ionic strength, supporting electrolytes, type of cations, and so forth. Increasing ionic strength generally facilitates deprotonation (decreased pKa), whereas some organic salts suppress it (increased pKa) (Crea et al., 2008).

The number of protons also affects the conformation of the inositol ring. Figure 1(b)-insets show the two proposed conformations of an IP6 molecule in a solution: (a) the so-called equatorial conformation in which one phosphate group orients in the axial position and five are in the equatorial (1a5e, Figure 1(b): a); (b) the inverted axial conformation (5a1e, Figure 1(b): b) (Bauman, Chateauneuf, Boyd, Brown, & Murthy, 1999). Solid-state NMR studies also confirmed these conformations. A pH between 9 and 10 is critical for the conformational transition. Lower pH (corresponding to 8 to 10 hydrogen atoms in solid state) is associated with the 1a5e conformation; intermediate pH (corresponding to 2 to 4 hydrogen atoms) results in a mixture of 1a5e and 5a1e conformations; High pH (>9 to

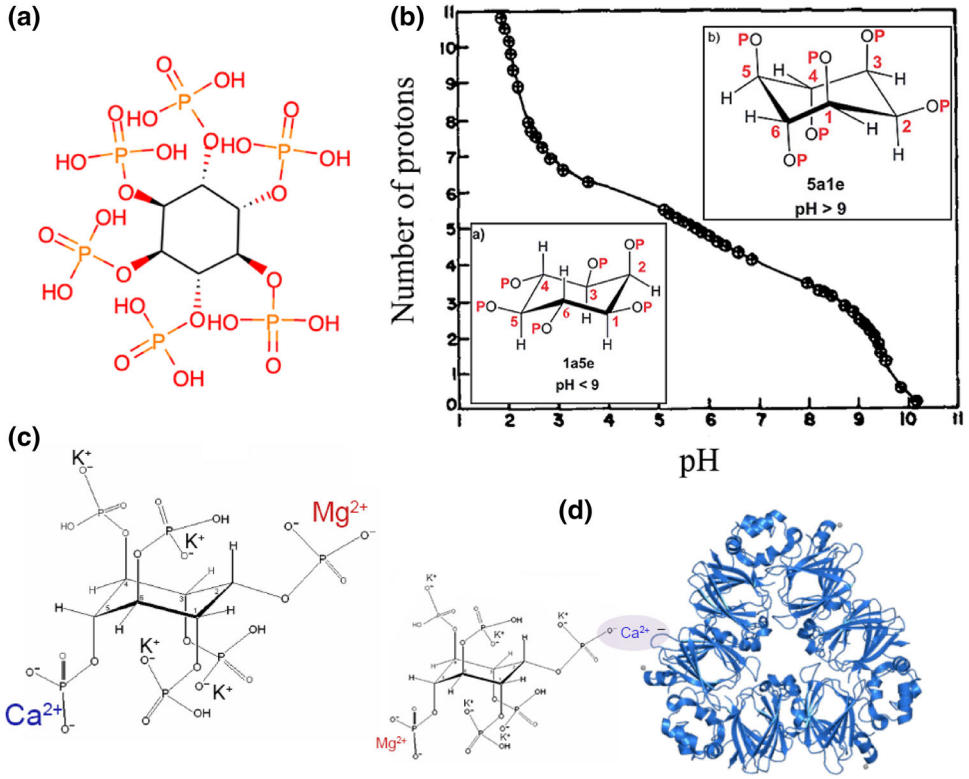

FIGURE 1 Molecular structure of phytic acid (a) (from Protein Data Bank in Europe, PDBe), number of protons bound to a potassium phytate molecule at different pH (Evans et al., 1982 (b)) with two primary conformations of phytate (B-insets) a) 1a5e and b) 5a1e (Reinmuth et al., 2019), one possible form of phytate salt (c) (adapted from Schlemmer et al., 2009)) and protein–metal–phytate complex (d) in plant at neutral pH. The protein (soy β-conglycinin) structure comes from PDBe

10, almost no hydrogen) corresponds to a 5a1e conformation (He, Zhong, & Cheng, 2013). Crystallographic studies have confirmed the IP_6^{12-} in the $[Na]_{12}[IP_6] \cdot 38H_2O$ crystal to be a 5a1e form (Blank, Pletcher, & Sax, 1971), while two other phytate crystals, $[Zn]_{10}[H_2IP_6]_2 \cdot 14H_2O$ and $[K]_3[H_{10}IP_6] \cdot 2H_2O$, are in a 1a5e conformation (Cai et al., 2017; Reinmuth et al., 2019). Metal ion chelation and hydrogen bonding contribute to the stabilization of both conformations (Reinmuth et al., 2019).

The pH that naturally occurs in plants and food is around 3.5 to 7.0 (Andrés-Bello, Barreto-Palacios, García-Segovia, Mir-Bel, & Martínez-Monzó, 2013). The physiological conditions of human and animal gastric and intestinal tracts cover a pH range of 1.2 to 7.8 and an ionic strength range of 0.051 to 0.166 mol/L (Hamed, 2018). The multiple negative charges an IP6 molecule is supposed to carry under physiological conditions, that is, roughly 0 to 9 charges per molecule according to Figure 1(b), leads to major nutritional concerns about its complexation with food cations and acidic proteins.

Figure 2 illustrates the proposed interactions between IP6/phytate and other food components. It exhibits very high binding capacity with positively charged minerals (Figure 2(a)), proteins (Figure 2(b)), and polysaccharides (Figure 2(e)) via electrostatic interactions. For negatively charged proteins, some studies proposed a sandwich-like mode of binding (metal–protein–phytate, the so-called ternary complex, Figure 2(c)), but its formation is still questionable. The nature and number of charges on a protein surface are dependent on pH and its isoelectric point (pI). Besides, IP6 can interact with starch through either hydrogen bonding (Figure 2(d) or esterification (Oatway et al., 2001). In the following section, these IP6-involved interactions, especially with proteins, are discussed in detail.

2.2 | Phytate as a metal chelator

Having a molecular structure featuring multi-phosphate groups surrounding a central inositol ring (Figure 1(a)), IP6 makes a ligand for strong chelation. It binds with all variety of cations, that is, alkaline and alkaline earth metals, divalent and trivalent inorganic cations, organotin and polyammonium cations, forming complexes. The formation and stability of phytate complexes in solution are determined by pH, ionic strength, supporting electrolyte, temperature, nature, and metal concentrations

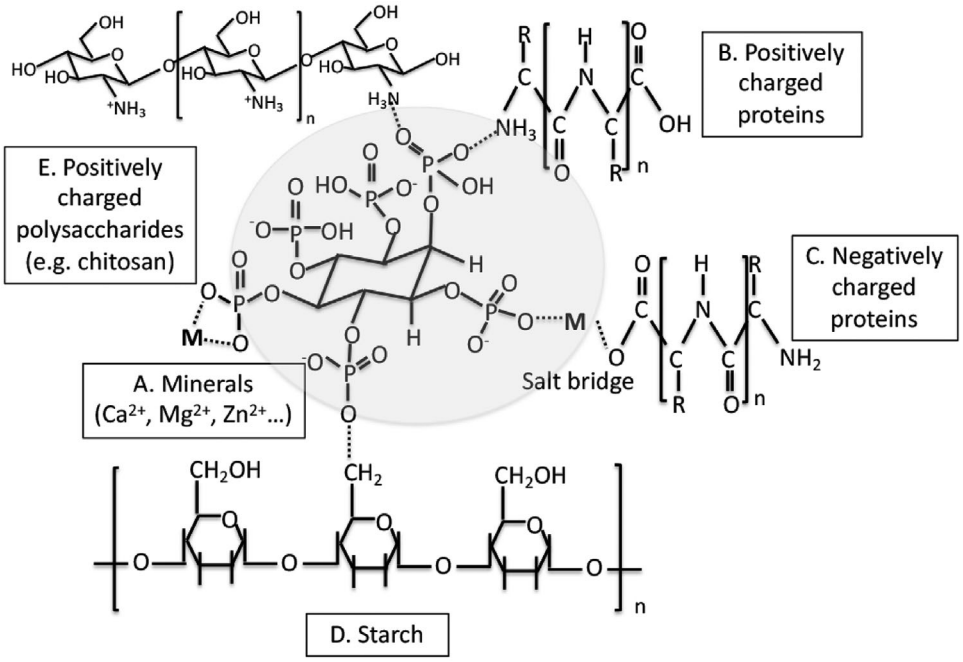

FIGURE 2 Possible interactions of phytic acid with minerals (a), proteins (b) and (c), starch (d), and charged polysaccharides (e) (adapted from Oatway et al., 2001)

(Crea et al., 2008). Chelation is more intensive at medium to higher pHs, as higher pH facilitates deprotonation and increases electronegativity. At neutral pH, the stability order of some metal–phytate complexes follows: $Cu^{2+} > Zn^{2+} > Co^{2+} > Mn^{2+} > Fe^{2+} > Ca^{2+}$ (Angel et al., 2002). According to the crystal lattice structure of $[Zn]_{12}[H_2IP_6]_2 \cdot 14H_2O$ and $[K]_3[H_{10}IP_6] \cdot 2H_2O$, a cation can bind to one or more phosphate groups of a single phytate or bridge two or more phytate molecules (Cai et al., 2017; Reinmuth et al., 2019). Because most phytate–metal complexes are insoluble at physiological pHs (except for some calcium and magnesium phytates), human and animal nutritionists have been concerned about the bioavailability of these elements in phytate-rich diets. Phytate–metal interactions, together with relevant nutritional and environmental consequences, have been discussed for a century and reviewed numerous times, most recently in Silva and Bracarense (2016), and Nissar et al. (2017).

In brief, the coprecipitation between IP6 and metal ions can make both positive and negative contribution to health and the environment such as: (a) inaccessibility of phytase degradation (Angel et al., 2002); (b) hindered absorption of minerals, especially zinc, iron, calcium, magnesium, manganese, and copper (Kumar et al., 2010); (c) an overturn of the adverse effects caused by the above minerals, such as lipid oxidation, kidney stone formation, diabetes mellitus, dental caries, and a variety of cancers (Greiner et al., 2006); (d) recovering the solubility of phytate-precipitated proteins at gastric pH (Gifford & Clydesdale, 1990; Okubo, Myers, & Iacobucci, 1976); (e) remediation of water or soil polluted by heavy metals, such as Hg^{2+} (Crea et al., 2008).

One may wonder where IP6 stands within a spectrum of metal chelators. Phytate–metal complexes are less stable than analogous complexes with diaminetetraacetic acid (EDTA), citrate, and pyrophosphate (Crea et al., 2008), so that these chelators can resume the phytase activity that is suppressed by the metal–phytate complexes (Maenz, Engele-Schaan, Newkirk, & Classen, 1999). Oxalate, on the other hand, exhibits lower chelating capacity than phytate. Thus, phytate reportedly inhibits the formation of calcium–oxalate complexes (Israr, Frazier, & Gordon, 2017) and potentially suppresses kidney stones (Al-Wahsh, Horner, Palmer, Reddy, & Massey, 2005).

IP6 is synthesized at the early stage of plant seed development, followed by association with minerals. Phytates deposit as mixed salts and concentrate in the spherical inclusions (globoids) that reside in the protein storage vacuoles (Cichy & Raboy, 2009). These mixed salts are water soluble (Cheryan & Rackis, 1980), primarily containing K and Mg, and a lesser content of Ca, Fe, Zn, and other minerals (Prattley & Stanley, 1982; Raboy, 2009). Generally, phytates account for 60% to 90% of total phosphorus in mature seeds (Oatway et al., 2001; Wu et al., 2009), while that ratio ranges from 12.3% to 92.9% among some wild plants (Alkarawi, Al-Musaifer, & Zotz, 2018).

How do IP6 and metals coexist while being soluble? Wang, Liu, and Guo (2018) analyzed the existing form of phytates in raw soymilk (water extract of soybean seeds,

unheated), and speculated that around two thirds of the phytates exist as soluble phytate salts, which are most likely formulated as $K_iMg_jCa_mH_nIP6^{(12-i-2j-2\ m-n)-}$, where $j + m \leq 2$ (1 to 2 Ca/Mg per IP6) and $n \approx 4$ (the number of protonated sites at pH 7). Figure 1(c) illustrates one possible molecular structure of naturally occurred phytate. More studies are needed to confirm this speculation, especially in other plants. Interestingly, the remaining one-third soybean phytates, together with about half of the total Ca^{2+} and Mg^{2+}, are bound with proteins (Figure 1(d)), which will be discussed in the following section.

IP6 is not the only inositol phosphate that chelates. Some studies have compared the chelating capacity of IP6 to its hydrolysis products, that is, mono-, di-, tri-, tetra-, and pentaphosphates (IP1 to IP5). Decreased iron-binding ability is found with decreasing numbers of phosphate groups, but they are all effective in preventing iron-induced lipid peroxidation (Miyamoto et al., 2002; Uchida et al., 2001). Lönnerdal, Sandberg, Sandström, and Kunz (1989) reported a strong inhibitory effect of IP6 and IP5 on zinc adsorption in suckling rat pups, which did not happen to IP4 and IP3. Therefore, phytase has been widely used in animal feeds and foods for the recovery of lost solubility of minerals (Greiner & Konietzny, 2006; Kumar et al., 2012; Rimbach et al., 2008).

2.3 | Phytate–protein interactions

2.3.1 | Phytate-binding in plants

The interaction between phytate and protein starts during the maturation of seeds. Prattley and Stanley (1982) extracted globoids from soybean seeds and used gel filtration to separate the two major fractions, that is, glycinin (11S proteins) and β-conglycinin (7S proteins), at pH 6.8, to maintain their natural states. These authors found that both calcium and phytate coeluted with the 7S fraction but not with 11S, suggesting the existence of 7S-calcium–phytate complexes in soybean seeds (Figure 1(d)). Wang et al. (2018) recently confirmed this observation. Both soy glycinin and whey protein are not bound with phytate, while all the bound phytate and Ca^{2+}/Mg^{2+} reside with β-conglycinin. Because of the intrinsic binding among phytate, metal ions, and the protein, ultrafiltration alone is not able to remove all phytate and minerals from proteins (Omosaiye & Cheryan, 1979; Wang & Guo, 2016)

It is worth mentioning that all soy protein species (i.e., 7S, 11S, and whey) are acidic and carry negative charges at near-neutral pH. The special trait of β-conglycinin being the only soy protein that binds with both metals and phytate during seed development warrants explanation. Further exploring this selective binding, including whether it happens in other plant seeds too, such as cereals and nuts, may help identify more protein resources that are naturally free of phytates.

2.3.2 | Phytate–protein complexes (binary binding)

Just as phytate can chelate cationic metals, cationic amino acids are also affinitive to phytate phosphate groups. The binding between phytate and proteins at different pH conditions are widely studied. Earlier work tracked the solubility of phosphorus and nitrogen in seeds and feedstuffs over a wide pH range and found somewhat parallel solubility profiles, suggesting direct phytate–protein interaction (Champagne, 1988). Ultrafiltration, dialysis, and gel filtration studies confirmed the binding interaction between phytate and extracted or purified proteins, such as bovine serum albumin (BSA), soy proteins, and α-globulin. At acidic pH ranges, these interactions are inclined to causing these proteins to precipitate (Grynspan & Cheryan, 1983, 1989; Okubo et al., 1976; Rajendran & Prakash, 1993; Reddy & Salunkhe, 1981). In general, what have been agreed upon are that a net positive charge (pH < pI) is the prerequisite for strong electrostatic binding to occur (Bye, Cowieson, Cowieson, Selle, & Falconer, 2013), and that the interaction stems from phytate forming salt-like linkages (Figure 2(b)) with the terminal α-amino and ε-amino of lysine, the imidazole groups of histidine, and guanidino groups of arginine. The extent of binding does not appear directly correlated with the percentage of basic amino acids, but may rather depend on the number of unhindered cationic groups of the protein (Selle et al., 2012). Human and animal nutritionists have demonstrated evidence of hindered utilization of both amino acids and phosphorous once phytate precipitates with food proteins and digestive enzymes. Selle et al. (2012) reviewed the protein–phytate interactions in feedstuff while highlighting their implications on poultry and pig nutrition. Still, our understanding of these interactions on a molecular and structural basis is in its infancy.

The formation and stability of phytate–protein complexes are known to be highly dependent on pH, pI, ionic strength, competitors, and amino acid availability. Alkaline pH and increased salt concentration (ionic strength) generally impede the complexation (Prattley, Stanley, & van de Voort, 1982; Tran, Hatti-Kaul, Dalsgaard, & Yu, 2011). In particular, raising the ionic strength, by adding salts, can suppress the interactions between phytate and proteins, but the salt concentration needed for stopping a binding interaction differs among proteins and conditions: BSA (at pH 3.0, 100 mM phosphate buffer) (Kaspchak, Mafra, & Mafra, 2018), lysozyme (at pH 4.0,

TABLE 1 Activity of different commercial phytase on IP6-lysozyme and IP6-soy protein complexes as compared with IP6 as substrate (Tran et al., 2011)

	Relative activity (%)		
Phytase	**IP6-soy protein**	**IP6-lysozyme**	**IP6-Na+**
Escherichia coli phytase variant 1	164.3	229.0	100
Escherichia coli phytase variant 2	137.8	151.8	102.7
Aspergillus niger phytase	31.8	23.1	37.0
Peniophora lycii phytase	24.5	13.0	9.8

Note: Activity of *E. coli* phytase variant 1 (0.096 μmol Pi/mL/min) on IP6-Na+ was set as 100% (control). Activities of phytases on other substrates are reported relative to the activity of the control.

300 mM ammonium acetate buffer) (Darby, Platts, Daniel, Cowieson, & Falconer, 2017), and denatured soy glycinin polypeptides (at pH 6.8, 700 mM NaCl) (Wang et al., 2018).

Some chemicals are able to suppress protein–phytate association through competitive binding. For example, divalent cations (e.g., Ca^{2+}) can preferably bind with phytate and set the proteins free (Okubo et al., 1976). Stronger anionic chelators (e.g., EDTA) and other reagents (e.g., Orange G, a dye that binds ionized basic amino acid residues) reportedly compete with phytate for binding sites and reduce phytate-binding to proteins (Tran et al., 2011; Wang et al., 2018).

For complex globular proteins, many binding sites are hindered within the "hydrophobic core." It is observed that at extreme pHs (<3), native globular proteins denature and dissociate, causing the exposure of all hindered cationic groups that facilitate binding (Okubo et al., 1976; Rajendran & Prakash, 1993). Recently, the exposure of hindered binding sites through heating or chemical denaturation have been found effective in promoting phytate-binding to soy glycinin and BSA, but not in the cases of soy β-conglycinin and whey proteins (Kaspchak et al., 2018; Wang et al., 2018). Succinylation can interrupt the formation of insoluble phytate–protein complexes by turning the positive charges of lysine groups into negative ones (Chung & Champagne, 2007).

Selle et al. (2012) inferred the likelihood of phytate being "shielded" in aggregated proteins and consequently becoming less susceptible to hydrolysis by exogenous phytase. It is also expected that complexes with different proteins may exhibit various extent of phytase inhibition. However, a study by Tran et al. (2011) only showed slightly hindered phytase activity by IP6-proteins when using *Aspergillus niger* phytase, as compared to using IP6-Na^+ as a substrate (Table 1). *Escherichia coli* phytases showed much higher activity toward IP6-Na^+ as compared to fungal phytases, and it turned out that *E. coli* phytases hydrolyzed IP6-protein complexes much faster than they did with sodium phytate and phytate–lysine (not shown). Higher phytase activity with IP6-lysozyme than IP6-soy protein was also reported, which may suggest stronger binding between IP6 and soy protein than that between IP6 and lysozyme. The reason behind the improved accessibility of complexed phytate to *E. coli* phytase remains an enigma, which warrants structural investigation.

Over the decades of studying protein–phytate interactions, researchers relied on the precipitation phenomena to identify binding. Although many studies have explained the binding mechanism and calculated the number of binding sites between phytate and a certain protein, thermodynamic characterization has barely been conducted. Isothermal titration calorimetry (ITC) has been used to successfully characterize a diverse range of binding interactions, including the binding energetics between phytate and proteins. Darby et al. (2017) characterized the binding mechanism between lysozyme and sodium phytate at pH 4, where a lysozyme molecule carries 12 positive charges while one phytate molecule provides 6 negative charges. When sufficient phytate was added to a lysozyme solution dropwise, an initial exothermic binding process occurred, followed by an endothermic crosslinking process at a higher phytate ratio (Figure 3-left column). Using the one binding site model, the calculated stoichiometry (n) of phytate–lysozyme interaction was around 2 (0.5 phytate per lysozyme), which agreed with the hypothesis of two lysozymes being linked together. Through microscopic observation, large numbers of phytate–lysozyme nanoparticles were found at a phytate/lysozyme molar ratio of 0.297 (Figure 3(b), 1:2 crosslinking), which were hardly visible when the phytate/lysozyme ratio was 0.132 (Figure 3(a), 1:1 binding). This suggests the role of phytate as a molecular binder between proteins, promoting aggregation and eventually precipitation (Darby et al., 2017). Similar ITC analysis was done at pH 3 to study the binding between phytate and BSA. Interestingly, based on the stoichiometry, the PA–BSA interaction was favored at 37 °C (physiological temperature) and 80 °C (beyond denaturation temperature) as compared to 10, 25, and 60 °C (Kaspchak et al., 2018).

Gelatin, a type of hydrolyzed animal protein, is widely used as a thickener and gelling agent in the food industry. Type A gelatin (acid treated) is a cationic polymer (pI approximately 7 to 9) that possesses net positive charges and protonated NH_2 groups at acidic or neutral pHs. Recently, several studies have revealed the potential of phytate as a crosslinking agent for cationic gelatin through ionic interaction (Ravichandran et al., 2013; Tashi, Zare, & Parvin, 2020). Type B gelatin

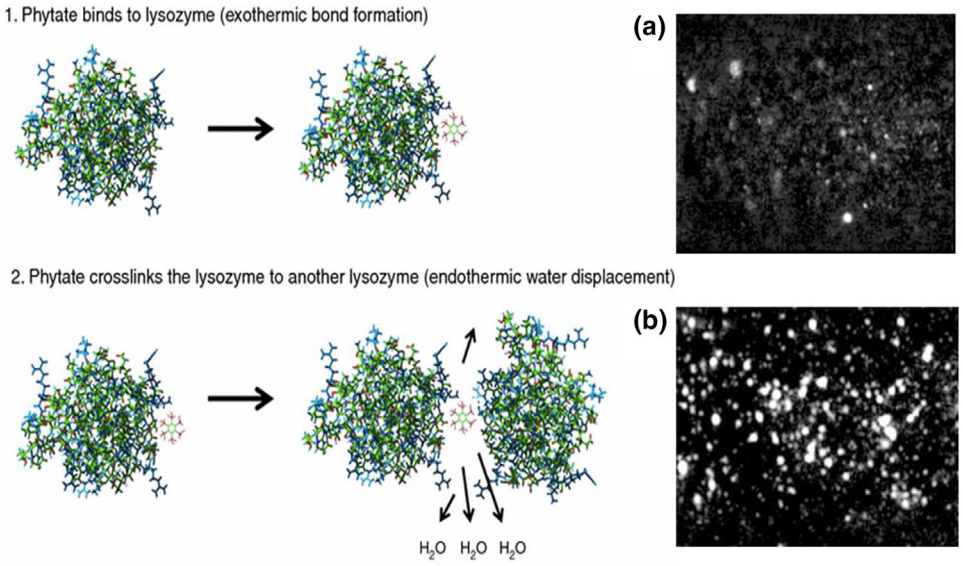

FIGURE 3 Proposed binding events during initial ITC injections of phytate into a lysozyme solution at pH 4.0 and relevant microscopy images of nanoparticle formation at a phytate: lysozyme molar ratio of (a) 0.132, (b) 0.297 (adapted from Darby et al., 2017)

(alkaline-treated), however, has a pI between 4.8 and 5.1 (Djagny, Wang, & Xu, 2001), which does not favor strong ionic attraction except at very low pH range. Shimokawa et al. (2019) investigated the interaction between type B gelatin and IP6 and observed decreased O-H absorbance in the near infrared spectra. However, because these authors did not define the pH of the system, it is uncertain whether the nature of IP6-gelatin binding was ionic or hydrogen bonding, although the authors speculated the latter.

Just as metal ions can be a double-edged sword, some proteins are known as "harmful" too, such as allergens, oxidase, and pathogenic proteins. If bound with phytate, the negative effects of these proteins may be avoided. There are several such interesting findings. For example, Chung and Champagne (2007) revealed the antiallergenic ability of phytate by binding with major peanut allergens (Ara h 1 and Ara h 2). Insoluble complexes were formed at neutral or acidic pH, resulting in reduced level of soluble allergens and IgE binding. Polyphenol oxidase (PPO) is responsible for the browning of vegetable and fruits. Phytate can inhibit the activity of PPO at pH 6.0, exhibiting a greater antibrowning effect than ascorbic acid, sodium sulfite, and citric acid (Du, Dou, & Wu, 2012). Moreover, IP6 and phytate have been found therapeutic toward Alzheimer's disease, reducing amyloid β plaque and tau protein (Anekonda et al., 2011). More beneficial effects of phytate may be discovered in future studies.

When the environmental pH equals to or is higher than the pI of the protein, it is theoretically impossible for direct ionic complexation to happen between phytate and protein. However, there is still evidence of weak interaction. For example, Prattley et al. (1982) reported weak binding between phytate and native soy protein at pH 5 to 9. Bye et al. (2013) also observed very weak interaction between phytate and negatively charged proteins (human serum albumin and myoglobin), possibly through ion–dipole interaction or hydrogen bonding. The nature and impact of these weak interactions still deserve further investigation.

2.3.3 | Protein–metal–phytate complex (ternary binding)

Another type of interaction that researchers have proposed is what may happen at a pH higher than the pI of the protein and in the presence of divalent or multivariant cations: a ternary protein—metal–phytate (Figure 2(c)). In this case, a protein and a phytate molecule are connected via a cationic bridge, usually Ca^{2+}. The suggested binding sites include the ionized carboxyl groups, as well as the unprotonated imidazole groups of histidine (Cheryan & Rackis, 1980). Nutritionists consider that ternary protein–phytate complexes are formed de novo in the small intestine and that this ternary binding is not a major concern for protein availability (Selle et al., 2012).

The speculations supporting the formation of ternary complexation are made simply based on the solubility profiles. Nosworthy and Caldwell (1988) indicated that 1 mole of soy glycinin bound with 15 M Zn^{2+} at pH 6.2 in the absence of IP6. On the contrary, more Zn^{2+} (39 M) bound to the protein in the presence of 7 M IP6 while the

protein was still soluble. These authors assumed the formation of ternary complexes via Zn^{2+} salt bridges. Grynspan and Cheryan (1989) conducted a study where Ca^{2+}, phytate, and soy protein were mixed at different ratios. They also suggested the formation of both insoluble calcium phytate and soluble phytate–calcium–protein complexes at an intermediate pH range (4.5 to 6.5). A later study observed similar solubility trends at pH 5 to 7, but the authors ascribed this to the formation of both soluble and insoluble Ca^{2+}-phytate complexes (Pontoppidan, Pettersson, & Sandberg, 2007), which is also possible now that we know calcium phytates can be both soluble and insoluble.

Ternary complexes may be present in the seeds, but whether a similar reaction will occur when phytate and divalent cations are added to a protein solution is still an open question until molecular and thermodynamic characterization are carried out. Some doubts may be raised regarding this hypothesis of electrostatic ternary binding if we further look at the possibilities. Four types of binding can occur in a ternary system (pH > pI) when divalent ions (M^{2+}) are added to a solution with proteins and phytate:

1. phytate + M^{2+} → phytate – M^{2+}
2. protein + M^{2+} → protein – M^{2+}
3. phytate + M^{2+} + protein → protein – M^{2+} – phytate
4. phytate + M^{2+} + protein → protein -- phytate – M^{2+}

Here the "–" suggests ionic bonding, while "--" denotes hydrogen bonding or physical absorption. The carboxyl groups on the proteins can bind with divalent cations, such as Zn^{2+} and Ca^{2+}, in the absence of phytate (Clydesdale & Camire, 1983). Ca^{2+} have been found to dissociate protein–phytate precipitates by preferentially binding with phytate (Prattley et al., 1982), which indicates greater affinity and complex stability of M^{2+}–phytate than protein–phytate. Wang, Xie, and Guo (2015) also pointed out that the formation of unionizable calcium phytate is the first step in tofu curding when Ca^{2+} is added to soymilk, an aqueous system with both proteins and phytates. It is potentially the case that phytate – M^{2+} is preferably formed but somehow absorbs to the protein surface before protein precipitates at higher Ca^{2+} concentration.

In other words, the formation of a ternary protein–metal–phytate structure requires further confirmation, probably through ITC, Fourier Transfer Infrared Spectroscopy (FTIR), and other techniques. Moreover, the order of salt addition (phytate or metal ions first) to a protein solution, and their relative ratio should also manipulate the binding mechanism.

2.4 | Interactions with polysaccharides and other polymers

With multiple reactive phosphate groups, phytate could not only interact with cations, charged amino acids, but also bind to charged and uncharged groups of polysaccharides through electrostatic interaction, hydrogen bonding, or an esterification reaction (Figure 2(d) and (e)). Yonekura and Suzuki (2003) found that by adding chitosan, alginic acid, and raw potato starch to rats' phytate-containing diets, the inhibitory effects of phytate on zinc bioavailability were effectively alleviated, which implied certain interactions between these polysaccharides and phytate.

Chitosan is a cationic polysaccharide with multiple industrial applications (Bugnicourt & Ladavière, 2016). It has been shown that IP6 interacts with chitosan at acidic pHs through a combination of electrostatic interactions and hydrogen bonding, forming heat-stable spherical nanoparticles, but this only happens with low molecular weight and medium molecular weight chitosan (Yang et al., 2017). At pH 1.5, the ionic interaction between IP6 and chitosan results in precipitation, while at pH < 1.5, as IP6 is almost unionized, the chitosan–IP6 mixture remains stable and homogeneous (Cheng, Guan, Yang, Tang, & Yao, 2019). Increasing pH also results in an increasingly compact chitosan conformation, thus altering the structure formed between IP6 and chitosan (Laufer, Kirkland, Morgan, & Grunlan, 2012).

Starch does not carry any charges, thereby not facilitating electrostatic interactions with phytate. It is considered that phytate indirectly affects starch digestibility through its association with glycosidase enzymes and catalyzing minerals (Juanpere, Pérez-Vendrell, Angulo, & Brufau, 2005; Yoon, Thompson, & Jenkins, 1983), but very little evidence has shown a direct association between phytate and starches. One recent study by Sun et al. (2017) indicated the potential of phytate as a modifier to prepare crosslinked starch, in which a 30% wheat starch solution was mixed with 2% sodium phytate (on a dry basis), followed by a 6-hr incubation at 50 °C and pH 7. FTIR and morphological observation suggested that two (or more) phosphate groups formed phosphodiester bonds between individual starch molecules. Although hydrogen bonding is also likely to happen between phytate and starch, it has not been confirmed yet.

Recent years witnessed the creative synthesis of a wide variety of IP6-polymer complexes, where IP6 forms hydrogen bonding with cellulose (Jiang, Qiao, & Hong, 2012), ester bonds with polyhydric alcohols (Cai et al., 2017; Li,

Li, Song, Niu, & Li, 2017), and ionic bonding with conductive polymers (Zhang et al., 2014). These modified polymers have exhibited great potentials in an array of novel applications in multiple fields, contributing to the innovation of fire retardant, batteries, drug-delivery vehicles, and more.

3 | PHYTATE AND FOOD PROCESSING

3.1 | Phytates in processed foods and phytate removal

Food processing covers a wide range of physical and chemical operations, many of which change the level of phytate consumers take in. Back in the days when phytate's health hazard was the mainstream concern, much attention was paid to finding a simple method to remove food phytates, to enhance the bioavailability of micronutrients in plant-based diets (Hotz & Gibson, 2007). In the cases where plant-based alternative infant formula and weaning foods are fed to infants as the daily staples, extra attention to the phytate level is in demand. According to a survey with 82 commonly consumed plant-based foods, mildly processed materials (nuts and whole wheat flour) and soy protein isolates have relatively high phytate levels, while deep-processed categories including bread, cakes, cookies, coffee, grain cereals contain very little phytate (not detected) (Harland, Smikle-Williams, & Oberleas, 2004). This indicates phytate loss during food processing, such as cereal refining. The effects of processing on phytate removal have been reviewed several times (Anderson & Wolf, 1995; Haileslassie, Henry, & Tyler, 2016; Oghbaei & Prakash, 2016; Schlemmer et al., 2009). Milling (mainly for cereals), soaking, and cooking all result in a certain degree of phytate removal. However, by discarding the phytate reservoirs (e.g., cereal bran) or soaking water, nutritionally important minerals and proteins are also sacrificed, adding to the cost in subsequent fortification.

Hydrothermal treatment does not induce phytate hydrolysis (dephosphorylation) until it is heated up to 130 °C for 1.5 h, or 140 °C for 45 min (Schlemmer et al., 2009). γ-irradiation reportedly degrades phytate in foods (Park et al., 2004; Sattar, Neelofar, & Akhtar, 1990), but enzymatic degradation is the most effective and applicable way to hydrolyze phytates. Phytates are enzymatically dephosphorylated by: (a) isolated phytases from microorganisms; (b) intrinsic plant phytases that can be activated through certain bioprocesses. Greiner and Konietzny (2006) and Kumar et al. (2010) both reviewed the application of phytase in food processing. It is worth mentioning here that microbial phytases have versatile in pH optimum (2.2 to 8.0) and temperature optimum (40 to 80 °C), while acidic phytases are more common. They are often used in animal feed to assist digesting in an acidic gastric environment. It is said that in modern processing of soy-based infant formula, phytase is used to hydrolyze phytate (Vandenplas, De Greef, Devreker, & Hauser, 2011). Jovani et al. (2000) surveyed the phytate levels of 8 soy-based formulas from the market in Spain and found them to be as low as 1.3 to 4.8 mg/100 mg.

Plant phytases are often activated at pH 5 to 6, at 35 to 50 °C, but not in gastric conditions. These mild conditions for optimum phytase activity can be realized through warm-temperature soaking, germination, and fermentation, leading to sufficient reduction of phytate level (Kumar et al., 2010; Hurrell, 2004; Ijarotimi 2012& Keshinro, 2019; Oyarekua, 2010; Rasane, Jha, Kumar, & Sharma, 2015; Wakil & Kazeem, 2012). One can also achieve sufficient phytate degradation when a cereal legume–based food contains a certain level of high-phytase whole grains (rye, wheat, or buckwheat). Simply through warm temperature incubation, these grains provide high phytase activity to break down phytates (Egli, Davidsson, Juillerat, Barclay, & Hurrell, 2003).

Special attention has been paid to obtaining low-phytate plant-protein ingredients. The global market size of plant protein ingredients was over $5.5 billion in 2019, which is projected to expand to $8 billion in 2025. Plant protein ingredients, for example, texturized plant proteins, protein concentrates, and isolates, are widely used in plant-based meats, energy beverages, functional foods, bakery, milk alternative formula, and other products. Protein ingredients from pea and soy are the most available. As phytate and proteins are bound in the raw materials, the proteins extracted from plants are bound with phytates, and the level of phytates in the final products is governed by plant species and the method of extraction (Deak & Johnson, 2007; Fredrikson, Biot, Alminger, Carlsson, & Sandberg, 2001).

Researchers put much effort into preparing low-phytate or phytate-free plant protein ingredients as an approach to eliminating potential health concerns. Because of the intrinsic occurrence of phytate–protein complexes and the binding induced by acidification, protein isolates prepared by conventional isoelectric precipitation usually contain 60% to 70% of the original phytates of raw soybeans (Omosaiye & Cheryan, 1979). It is found that removal of phytate is the most efficient around pH 5.5 (Ford, Mustakas, & Schmutz, 1978; Siy & Talbot, 1981), which agrees with the lowest extent of phytate–protein association observed around this pH (Grynspan & Cheryan, 1989). Alkaline extraction (pH 11.5) can remove 62% of bound phosphorus from soy protein, but it is not an ideal method as it causes major aggregation of proteins (Brooks & Morr, 1985).

Table 2 lists a number of documented methods of phytate removal from plant proteins, including pH adjustment, membrane technology, ionic exchange, phytase treatment, bioprocesses, γ-irradiation, and so on. Genetic modification and breeding are also promising approaches to obtaining low-phytate grains for the production of low-phytate food and feedstuff (Freed, Adepoju, & Gillaspy, 2020; Raboy, 2007).

As mentioned earlier, soy globulin, as a phytate-free protein per se, can be of great value when a low-phytate content is desirable, such as formulating infant foods or nutritional regimes for mineral deficiency. Comparing to the 7S protein, the 11S protein is also a hypoallergenic component (Bittencourt et al., 2007). It is relatively easy to isolate glycinin fraction from defatted soy flour by cryoprecipitation (Nagano, Hirotsuka, Mori, Kohyama, & Nishinari, 1992; Xu, Ren, Ye, & Guo, 2010), and it contains a very low level of phytate (approximately 3 mg/g protein) (Deak & Johnson, 2007; Wang et al., 2018). More and more such protein sources may be discovered if research goes on. However, before pursuing a low-phytate protein ingredient, food manufacturers should be aware of the possible functionality changes and consider whether it is imperative to remove phytate.

3.2 | Effect of phytate on protein functionalities

Among different genotypes of soybean, barley, common beans, and others, phytate and protein concentrations are found to be positively correlated (Coelho, Bellato, Santos, Ortega, & Tsai, 2007; Dai, Wang, Zhang, Xu, & Zhang, 2007; Raboy, Dickinson, & Below, 1984). As there are both protein-bound phytates and free phytates, it is likely that phytates are attached to or surrounding proteins because they contribute positively to protein functionalities, such as solubility. Proteins contribute substantially to food texture and quality due to its thickening, emulsifying, and gelling properties. What are the impacts of pursuing low-phytate grains or protein ingredients on the manufacturing of foods? Although the number of studies is limited regarding this topic, mostly surrounding soy proteins, it is meaningful to collect available information on how IP6 and phytates affect protein functionalities and food processing.

Solubility is the most important functionality of proteins, as it is also critical to other functionalities such as viscosity, interfacial properties, and gelling capacity. As discussed, many studies have agreed that phytate aggregates proteins, resulting in visible precipitates or turbidity (Darby et al., 2017; Tran et al., 2011). As compared to phytate-free rapeseed protein, proteins with increasing phytate content exhibited lowered pI and a greater extent of protein solubility loss at acidic pHs (Kroll, 1991). However, when the environmental pH > pI, numerous studies in the past years have pointed out that phytate is not always detrimental to protein solubilities. Instead, it promotes protein dissolution at neutral conditions.

According to Cowieson and Cowieson (2011) and Bye et al. (2013), in a lysozyme (pI 11.0) solution (pH 6.5 and 7.0), lower concentrations of phytate resulted in a significant reduction of protein solubility. However, this solubility loss was resumed at higher phytate concentrations. For proteins that have acidic or neutral pIs (such as human serum albumin, pI = 4.8, and myoglobin, pI approximately 6.8 to 7.3), phytate continuously increased their solubilities in a "salting-in" manner. For all the three proteins, adding a low level of phytate resulted in lowered denaturation temperature, namely, reduced thermal stability.

Some proteins are less hydrophilic than others, and therefore more difficult to hydrate. Soy glycinin is such a globular protein that has a high molecular weight (320 to 363 kDa) and a hydrophobic core inside its structure (Kinsella, 1979). Wang et al. (2018) studied the interactions between sodium phytate and soy glycinin solution at neutral pH (6.60). They had several findings that support phytate's positive contribution to glycinin functionalities (Figure 4). First, hydrating powdered glycinin in the presence of 0.1% phytate led to increased soluble protein content and decreased mean particle size after hydration (Figure 4(c) and (g) in comparison to Figure 4(a) and (e)). Second, in the presence of phytate, the cryoprecipitation of the 2% glycinin solution after a 1-day storage at 4 °C (Figure 4(i), control) did not happen (Figure 4(k)). Third, after thermal denaturation, the phytate-free glycinin solution went through self-aggregation and became turbid (Figure 4(b) and (f)), while the sample with 0.1% phytate exhibited lower turbidity and particle size (Figure 4(d) and (h)). Before heating, there was no electrostatic interaction between native glycinin (pI approximately 5.0 to 5.5) and phytate, but phytate was able to stabilize the protein. After thermal denaturation, phytate interacted with the hydrophobic basic polypeptides (pI approximately 8.0 to 8.5) that are susceptible to self-aggregation. This interaction stabilized the basic polypeptides and limited the aggregation. These effects may also apply to proteins with similar molecular structures, such as legumin.

A protein can serve as an emulsifier and a stabilizer due to its amphiphilic nature and the ability to form a viscoelastic film around fat globules to prevent coalescence (Lam & Nickerson, 2013). Recently, Pei et al. (2019) investigated the interactions between whey protein isolates (WPIs) and sodium phytate within pH 2 to 8. As compared with WPI solution without phytate, the one with phytate exhibited a lower pI (decreased from 5.1 to 4.5) (Figure 5(a)) and

TABLE 2 Methods to prepare plant protein-based ingredients with reduced phytate level

Approaches	Brief description	Product	Phytate content in the product (mg/g)	Phytate content in control (mg/g)[a]	References
pH adjustment	■ 2.5 mM $CaCl_2$ added to soy flour dispersion at pH 5.5, heating, cooling, and centrifugation	Soybean lipid protein concentrate	1.42	14.2	Ford et al. (1978)
	■ Extraction (75 to 88 °C, pH 8 to 10), precipitation (pH 5.3 to 5.5)	SPI	0.2 to 2	19.6	Puski, Hartmen, and Talbott (1987)
	■ Extraction (pH 11.5), precipitation (pH 5.5)	SPI	1.8	18.4	Rham and Jost (1979)
Membrane technology	■ Ultrafiltration performed at pH 5.5 with 4% sodium chloride	Rapeseed protein isolates	NA (approximately 85% removal rate)		Siy and Talbot (1981)
	■ Extraction (pH 9, 50 °C), electro-acidification (pH 6), tangential ultrafiltration/diafiltration	SPI	12.4	23.4	Ali, Ippersiel, Lamarche, and Mondor (2010)
	■ Extraction (pH 8.0, 8.5% to 15% NaCl), dialysis or ultrafiltration	SPI	0.5 to 0.9	18.4	Rham and Jost (1979)

(Continues)

TABLE 2 (Continued)

Approaches	Brief description	Product	Phytate content in the product (mg/g)	Phytate content in control (mg/g)[a]	References
Phytase	■ Extraction (pH 7.5), phytase treatment (pH 6.0, 40 °C), separation	Glycinin, β-conglycinin	Almost 0	NA	Saito et al. (2001)
	■ Extraction (pH 7.0, 25 °C), phytase treatment (pH 5.0), precipitation	SPI	0.11	19.86	Wang et al. (2014)
	■ Phytase treatment (pH 5.5, 55 °C), drying, milling, and fortification.	Infant cereals	0.10 to 0.40	0.73	Sanz-Penella et al. (2013)
	■ Extraction and phytase degradation (pH 5.5, 40 °C), centrifugation (pH 4.5)	SPC	4.2	9.4	Qasim, Shakir, and Al-Shaibani (2012)
	■ Phytases treatment at pH5.5, 55 °C and ultrafiltration,	Pea protein isolates	0	12.1 to 19.5	Fredrikson et al. (2001)
	■ Extraction and phytase degradation (pH 5.5, 40 °C), alkaline-extraction (pH 8.5) and separation (pH 4.5)	SPI	3.9	11	Qasim, Shakir, and Al-Shaibani (2012)
Ion exchange	■ Extraction (pH 8 to 9), cation and anion exchange, dialysis	SPI	<0.011	2.03	Brooks and Morr (1982)
	■ Extraction (pH 8.0), cryoprecipitation, anion-exchange resins	Soy globulin	Approximately 2.2	Approximately 4.95	Kumagai, Ishida, Koizumi, Sakurai, and Kumagai (2002)
Fermentation	■ Fermentation (30 °C, 72 hr) by *Aspergillus niger*	Lupin flour	2.3 to 3.3	5.5 to 6.7	da Silva, Trugo, da Costa Terzi, and Couri (2005)
Radiation	■ 10 MeV electron beam (30 kGy)	Canola meal	0	0.42	Taghinejad-Roudbaneh, Ebrahimi, Azizi, and Shawrang (2010)

[a]The control refers to products without phytate removal. Calculation is done in some cases to standardize the unit.

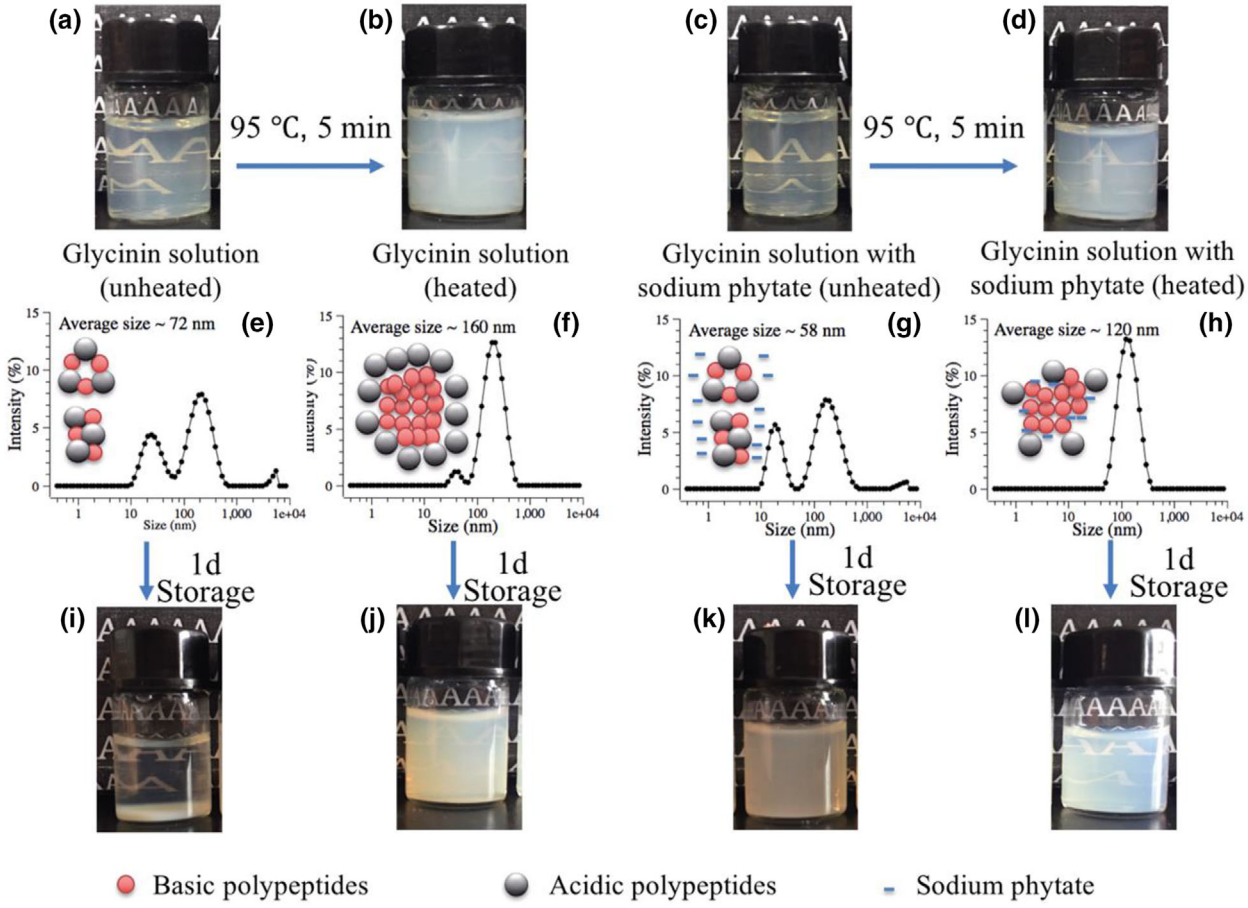

FIGURE 4 Effect of sodium phytate (0.1%) on the solubility and the stability of soybean glycinin (2%) after heat treatment and a 1-day 4 °C storage (adapted from Wang et al., 2018)

obvious turbidity and precipitation at acidic pH range (Figure 5(c)). At pH higher than pI, phytate addition resulted in increased ζ-potential, suggesting greater physical stability (Figure 5(a)). When phytate was added to a 1% WPI solution at pH 3.5, turbidity increased with phytate concentration, while the absolute ζ-potential first increased (0.01% to 0.05% phytate) but then dropped until precipitation occurred when the phytate concentration was higher than 0.15% (Figure 5(d)). With the highest ζ -potential, as well as the maximum viscosity, the W/O emulsion, stabilized with 1% WPI and 0.05% phytate, was prevented from creaming (Figure 5(f)). It was suggested that the phytate–WPI complexes accumulated around the fat globules, with additional positive charges and electrostatic repulsion to prevent coalescence (Figure 5(g)).

As there is a difference between natural plant phytates and sodium phytate, removing plant phytates with phytase will not only diminish the protein stabilizing effects of phytate but also release the bound Ca^{2+} and Mg^{2+} that further destabilize proteins. Saito, Kohno, Tsumura, Kugimiya, and Kito (2001) used phytase to treat defatted soymilk at pH 6 and observed the precipitation of soy glycinin, which should not have precipitated at this pH. Although the authors ascribed the observation to the removal of phytate from glycinin–phytate complexes, which do not exist, the possible reason behind the precipitated glycinin at pH 6 might be related to the released Ca^{2+} and Mg^{2+} that neutralize the surface charges of glycinin. Wang, Chen, Hua, Kong, and Zhang (2014) reported a series of functionality changes when SPI was prepared using a phytase-assisted method. At neutral pH, the phytate degradation brought about decreased protein solubility, heat stability, and absolute ζ-potential values, together with a secondary structure with lessened molecular flexibility. The solubility and molecular structure changes resulted in poor emulsion stability and foaming capacity, as well as hardened thermal-induced gel texture.

All the above evidence confirms that phytate is essential in maintaining the solubility, stability, and interfacial properties of soy proteins, especially at physiological pH. This is potentially true for other proteins too. The following section will continue to discuss the implications of metal–phytate–protein relationship on the quality of selected plant foods.

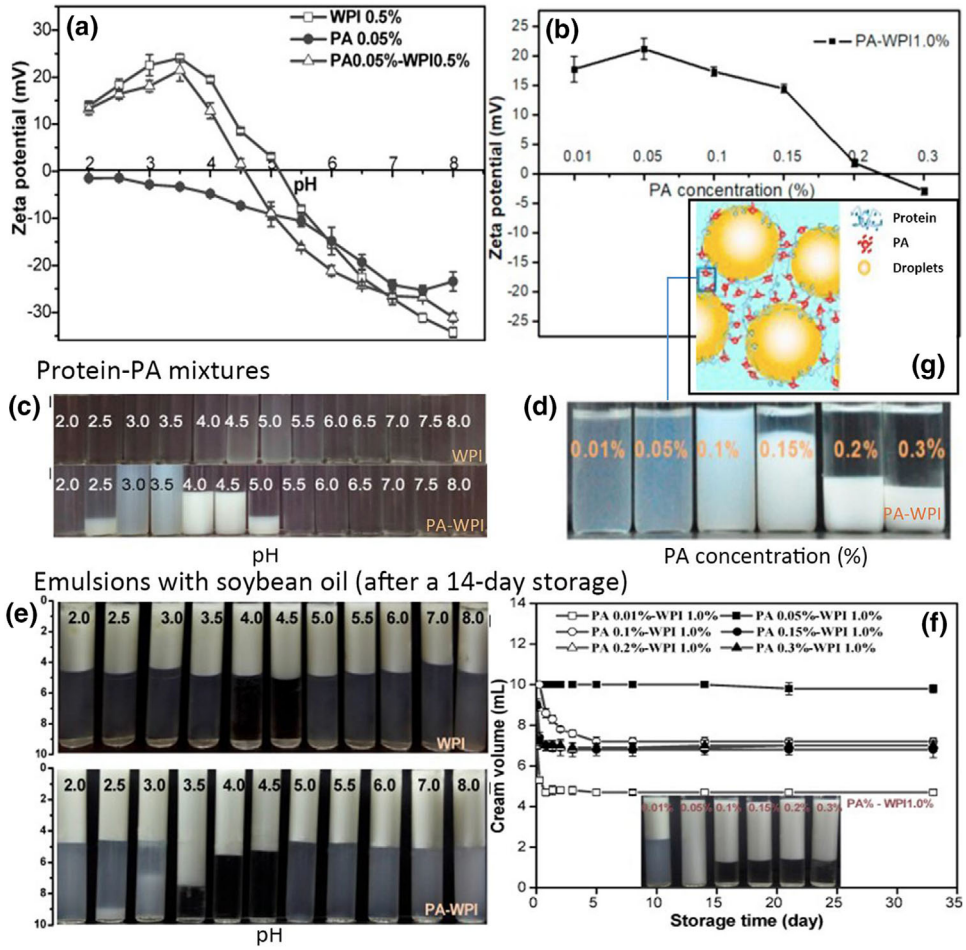

FIGURE 5 Zeta potential and images of whey protein isolate (WPI) dispersions at different pH with and without 0.05% phytic acid (PA) (a and c, 0.5% WPI) and at different PA concentrations (b and d, pH = 3.5, 1% WPI); images of emulsions stabilized by 0.5% WPI dispersions at different pH (with and without 0.05% PA) after a 14-day storage (e); changes of cream volume with time for WPI–oil emulsions with increased PA concentration (f, pH = 3.5, 1% WPI); proposed illustration of oil droplets stabilized by WPI–PA dispersion (g, 0.05% PA+1% WPI) (adapted from Pei et al., 2019)

3.3 | Effect of phytate on food quality

Plant-based foods have long been known to play a crucial role in basic human nutrition and health. Renewed global interests in the health-benefiting properties of plants are making plant-based food a new booming business, especially dairy and meat alternatives. Associated with the chelating power, it has been recognized since the 1960s that phytate is responsible for food texture and other quality attributes, such as soymilk, tofu, bread, and beans (Figure 6). Since 1997, sodium phytate has been listed as a Generally Recognized As Safe (GRAS) substance and has been used as a preservative for baked goods in the United States (Oatway et al., 2001). Outside the United States, phytic acid is extensively added to meats, fishmeal pastes, canned seafoods, fruits, vegetables, cheese, noodles, soy sauce, juices, bread, and alcoholic beverages to prevent product discoloration and prolong shelf-life (Zhang et al., 2013). In this section, we introduced the mechanisms related to how phytates play a positive or negative role in the processing of traditional plant-based foods, which may inspire knowledge toward the significance of phytates in other conventional and emerging plant-based and whole foods.

3.3.1 | Soymilk and tofu

Soymilk and tofu are the two traditional forms of soy-based foods. In East Asian cultures, soymilk production involves soaking, grinding, separation, and heat processing. In Western cultures, where the beany flavor is unwelcomed, the beans are often blanched before grinding to inactivate lipoxygenase and minimize beany flavor (Wang, Xing, Wang, & Guo, 2017). Tofu, also known as bean curd, is a soy-based hydrogel food whose

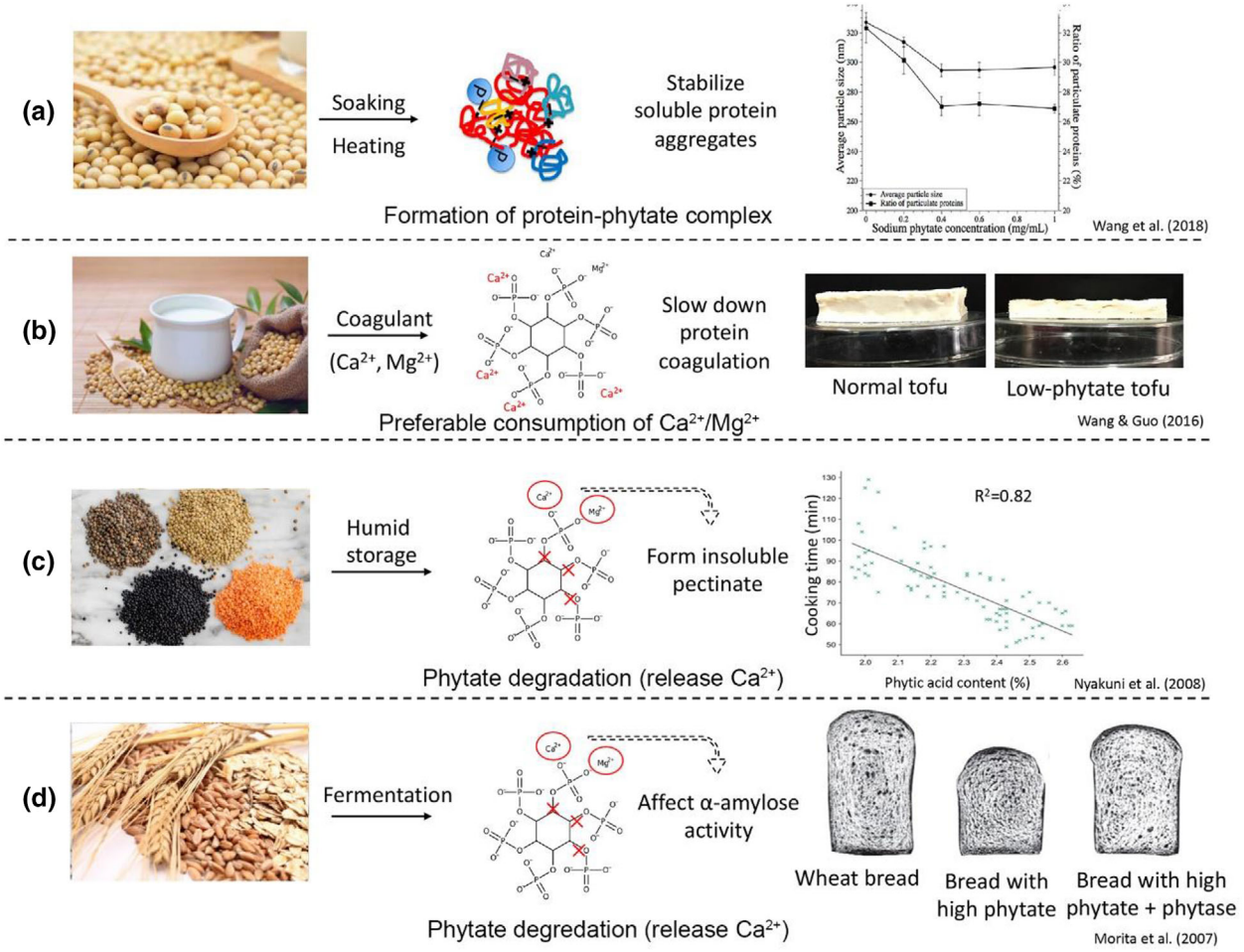

FIGURE 6 Effects of phytate on the processing and quality of traditional plant-based foods (a) soymilk, (b) tofu, (c) cooked beans, (d) bread

formation is attributed to the gelling behavior of soymilk in presence of chemical coagulants (e.g., acids, salts, and enzymes). The most widely used coagulants are $CaSO_4$, $MgCl_2$, and gluco-δ-lactone (GDL). Upon heating, native soy proteins go through a series of changes, resulting in covalent (e.g., isopeptide and disulfide bonds) and non-covalent (e.g., hydrophobic interaction, hydrogen, and ionic bonds) interactions, which comprise the building blocks of tofu (Zhang et al., 2017). Many studies have revealed the critical roles of phytate in soymilk and tofu production.

Due to the solubilizing effect of phytate on proteins, as discussed, the presence of phytate in soybeans likely assists proteins to hydrate during soaking. The fact that phytate is naturally bound with β-conglycinin may contribute to the protein's hydrophilicity. During heat treatment, phytate interacts with denatured soy glycinin, resulting in a reduced level of hydrophobic aggregation. As a result, the proteins exhibit greater ζ-potential and smaller mean particle size, both of which indicate improved stability against precipitation (Wang et al., 2018). Tsumura, Saito, and Kugimiya (2004) applied phytase treatment to soymilk, and the resultant soymilk became a gel after heat treatment, potentially by releasing Ca^{2+} and Mg^{2+} to crosslink proteins. In other words, phytase can function as a potential tofu coagulant.

Similarly, when soybean is stored at a high-temperature high-moisture condition, or germinated before subsequent processing, the phytates are degraded by endogenous phytase and the resultant soymilk exhibits reduced total solids content, soluble protein level, and viscosity. The pH of soymilk also drops, probably due to the lost pH-buffering ability of phytates (Jiang, Cai, & Xu, 2013; Kong et al., 2008).

Saio, Koyama, Yamazaki, and Watanabe (1969) first recognized that tofu hardness is closely related to its phosphorus content and that phytic acid is effective in slowing the coagulation of soy protein with calcium. This finding has inspired numerous later studies on understanding the relationship between phytate, Ca^{2+} (or Mg^{2+}), and soy proteins during tofu-making. Phytate content, as affected by soybean cultivar differences, is positively related to

the required coagulant ($MgCl_2$ and $CaSO_4$) concentration (Liu & Chang, 2004) and negatively correlated with the firmness of tofu (Toda, Takahashi, Ono, Kitamura, & Nakamura, 2006). As the soymilk phytate level increases, a higher amount of coagulant is required to form a gel, and the maximum gel hardness decreases (Ishiguro, Ono, & Nakasato, 2008; Ishiguro, Ono, Wada, Tsukamoto, & Kono, 2006; Wang et al., 2015). Phytate reduction treatments, including ultrafiltration, phytase treatment, germination, and high-temperature high-humidity storage, all reportedly decrease tofu yield and harden product texture (Kong et al., 2008; Ojha, 2014; Tsumura et al., 2004; Wang & Guo, 2016).

The mechanism behind the above buffering effect comes down to its metal-chelating ability. When Ca^{2+} is added to soymilk, it preferably interacts with free and bound phytate, forming stable complexes. This competitive consumption of protein crosslinker decelerates the gelling process. Gelation rate, namely the speed at which proteins fabricate into a network, plays a vital role in the quality of soymilk gels. Fast gelation gives rise to a coarse gel network with syneresis, while slower gelation, due to phytates, contributes to a compact structure that holds more water and shows a softer texture (Wang, Jin, Su, Lu, & Guo, 2019). Low-phytate soymilk gels barely retain water (Figure 6(b)) (Wang & Guo, 2016).

In addition to tofu made with Ca^{2+} and Mg^{2+}-based coagulants, GDL-solidified products are also affected by phytate content. Similarly, GDL-tofu with higher phytate content exhibits higher final pH and is softer than the ones with lower phytate levels (Ishiguro et al., 2006). The higher final pH, probably due to the pH-buffering capacity of phytate, facilitates electrostatic repulsion and weakens hydrophobic interaction.

Tofu products come in all types, and there is nothing wrong with a softer or harder texture. In China, consumers enjoy both hard and soft tofu, while Japanese cuisine prefers silken tofu. In the U.S. grocery stores, tofu is labeled according to its firmness, classified into extra firm, firm, and soft products. However, in industrial production, the product yield and texture are greatly affected by soybean cultivars, leading to great batch-to-batch differences. Manufacturers need to understand the relationship between gelation rate and gel properties, so that they can make a flexible adjustment when needed. Phytate can be used as a gelation rate controller when a softer texture is desired.

There are certainly many other kinds of gel foods that can be affected by the presence of phytate or phytase. It would be interesting to see future work on the effects of phytate on gels induced by transglutaminase, soy yogurt fermented by bacteria, emerging plant-based meat alternatives, and many other variants.

3.3.2 | Hard-to-cook beans

Many cultures love beans and lentils and appreciate the versatile health benefits associated with these legumes. They are usually served after soaking and cooking, by which the seeds take up water and become soft. However, some beans refuse to soften and are hard-to-cook (HTC). Severe storage conditions, particularly with high temperatures and relative humidity, give rise to an increase in the cooking time that is required to soften legumes. As compared to normal beans, HTC beans exhibit harder texture and have a much thicker seed coat with a highly structured palisade layer. Gonzalez and Paredes-Lapez (1993) summarized the proposed hypotheses regarding the hardening: (a) lipid oxidation and/or polymerization, (b) formation of insoluble pectates, (c) lignification of the middle lamella, and (d) a combination of multiple mechanisms.

Phytate is found responsible for the second mechanism. After storage at elevated temperature and humidity, phytase is activated and hydrolyzes phytates inside the cotyledon cell. In the middle lamella, pectin methyl esterase hydrolyzes pectin to pectic acid. As Ca^{2+} and Mg^{2+} are set free from the phytate enzymolysis, they migrate to the middle lamella, reacting with pectic acid and forming insoluble pectinate that serves as a physical barrier against water (Jones & Boulter, 1983; Moscoso, Bourne, & Hood, 1984). Besides, the released Ca^{2+} and Mg^{2+} may crosslink the hydrated bean proteins, adding to the hardness.

In agreement with this mechanism, any conditions that promote phytase activity or Ca^{2+}/Mg^{2+} availability are in favor of turning easy-to-cook (ETC) beans into HTC beans. Galiotou-Panayotou, Kyriakidis, and Margaris (2008) found that by soaking ETC beans and lentils in the water at 50 °C for 5 hr and drying for 48 hr at 20 °C, HTC features were developed, with decreased concentrations of soluble pectin, protopectin, and phytate but higher levels of calcium pectate. Moreover, increasing calcium content resulted in reduced phytate content and increased bean hardness in both ETC and HTC beans. Phytate content is negatively correlated to bean hardness and cooking time (Figure 6(c)) (Galiotou-Panayotou et al., 2008; Nyakuni et al., 2008).

These studies give valuable guidance to bean breeding, storage, and cooking. Hard water, with a high level of Ca^{2+} and Mg^{2+}, may not be suitable for quick cooking or desired bean quality. Both phytate or EDTA are found to shorten the cooking time of beans (Kon & Sanshuck, 1981). High-phytate beans might be more resistant to phytase degradation and are able to chelate divalent ions from the water. HTC beans, in spite of the defect, can still be used for extrusion, fermentation, and the production of starch and low-phytate protein concentrates and isolates (Gonzalez & Paredes-Lapez, 1993).

3.3.3 | Breadmaking

Bread made from refined wheat flour has a low phytate content, but a supplement of whole wheat flour, rice bran, or soy flour results in bread with a much higher amount of phytate (Garcıá-Estepa, Guerra-Hernández, & Garcıá-Villanova, 1999). The enriched recipes are believed to increase the nutritional values but often fail in good quality. The addition of 1% phytate to refined flour resulted in a prolonged mixing time, delayed dough development, and decreased loaf volume (Park, Fuerst, & Baik, 2016), similar to the "symptoms" found in the bread substituted with phytate-containing fortifying ingredients (e.g., wheat/rice bran, brown rice, amaranth flour) (Morita, Maeda, Watanabe, & Yano, 2007; Sanz-Penella, Wronkowska, Soral-Smietana, & Haros, 2013).

There are a couple of potential reasons why phytate is to blame for inferior bread quality. First, α-amylase is a type of calcium metalloenzyme that requires a specific amount of calcium for activity at neutral pH. Endogenous phytase is activated during the fermentation process, resulting in partial degradation of phytate and the release of Ca^{2+} for the starch hydrolysis to proceed. However, the phytase activity (optimum pH 5.15) during fermentation is often inadequate, where only about 15% to 25% of phytate is degraded during proofing (Haros, Rosell, & Benedito, 2001a), and a total reduction of 30% to 48% is achieved in the bread (McKenzie-Parnell & Davies, 1986). Adding phytate or phytate-rich grains will obviously immobilize Ca^{2+} and suppress dough development (Haros et al., 2001b; Yoon et al., 1983).

Second, the formation of bread also relies on the crosslinking among gliadin and glutenin molecules during heat treatment, which involves an oxidation-induced sulfhydryl–disulfide exchange process (Lagrain, Thewissen, Brijs, & Delcour, 2008). The antioxidant property of phytate reportedly lessens the disulfide bonding during breadmaking, thereby weakening the bread network (Park et al., 2016). Third, the charges of phytate may also suppress the hydrophobic interaction of proteins during heat treatment, further weakening the structure. Therefore, the presence of phytate affects fermentation time and the quality of dough and bread.

To reduce or eliminate phytate, attempts have been made to increase fermentation time, reduce pH, or use enzymes. Moderate pH decrease (to around 5.5) by sourdough fermentation is sufficient to reduce phytate content of white and whole wheat flour (Frontela, Ros, & Martínez, 2011; Leenhardt, Levrat-Verny, Chanliaud, & Rémésy, 2005). Additional phytase could accelerate and intensify phytate hydrolysis, which is reported to improve bread shape (width/height ratio), increase specific volume, and decrease textural hardness (Figure 6(d)) (Haros et al., 2001a; Morita et al., 2007). As certain grains have higher phytase activity (rye and buckwheat) (Egli et al., 2003), they may be valuable sources to achieve a win–win situation where nutrients are fortified while phytates can be sufficiently degraded.

3.3.4 | Phytate and food safety

As early as 1953, Evans, Cooney, Moser, and Schwab (1953) recognized the potential of IP6 in inactivating iron-driven oxidation and preserving the flavor of soybean and other edible oils. Phytic acid is a powerful inhibitor of iron-driven hydroxyl radical formation because it can form a unique iron chelate that becomes catalytically inactive. Thereby, it can protect tissues against oxidative reactions and suppress oxidant damage to human/animal organs and foods. It can be added to juice, soybean oil, and meat products to prevent both autoxidation and hydrolysis, preventing product discoloration, maintaining food safety, and extending shelf-life (Silva & Bracarense, 2016). Furthermore, phytate exhibits strong antibacterial activities, inhibiting the growth of *E. coli*, *Salmonella trphimrium*, and others (Narayanaswamy & Esa, 2018).

Regarding antioxidant properties, purified sodium phytate solution does not show 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging activity but has certain ferric reducing/antioxidant power (FRAP), despite not being as high as those of ascorbic acid, tocopherol, and butylated hydroxyl anisole. As a result of γ-irradiation (20 kGy), phytate goes through radiolysis and starts to show DPPH radical-scavenging capacity that is comparable to ascorbic acid and tocopherol, as well as increased FRAP (Ahn, Kim, Yook, & Byun, 2003; 2004; Song et al., 2006). Phytates extracted from rice bran show certain DPPH radical-scavenging activity (Zhang & Bai, 2014). The reason why there is a DPPH-scavenging activity difference between plant phytates and purified sodium phytate is unclear.

The pronounced chelating powder makes IP6 an effective antioxidant against both iron-induced and noniron-induced lipid peroxidation. It can completely shut off the Fe^{3+}-mediated redox reaction but not as effective for the Cu^{2+}-mediated reaction (Empson, Labuza, & Graf, 1991). A number of studies have revealed its effectiveness in preventing meat oxidation. Lee and Hendricks (1995) investigated the protective role of IP6 against beef round muscle lipid peroxidation. The inhibitory rate was affected by the buffering system and increased with pH and IP6 concentration. At pH 7.0, IP6 exhibited a higher inhibitory rate than EDTA, butylated hydroxytoluene, and ascorbic acid (vitamin C). In slowly cooked chicken, IP6 substantially inhibited oxygen uptake, malondialdehyde formation, and the warm-over flavor development. With a

5 mM IP6 concentration, significant antioxidant effects were observed in both raw and cooked meat, but the effect was more pronounced in cooked meat than in raw meat, and more in cooked beef homogenates than in pork (Stodolak, Starzyńska, Czyszczoń, & Żyła, 2007). Harbach et al. (2007) demonstrated that phytate prevents meat rancidity without endangering health when administered in a swine diet.

As a chemical preservative, IP6 is able to change the cell morphology of foodborne pathogens and disrupt the intercellular adhesion. It retards bacterial growth and causes bacteria cell membrane damage (Zhou, Zhao, Dang, Tang, & Zhang, 2019). It is reported that phytate was not as effective as antagonistic yeast (*Rhodotorula mucilaginosa*), a biocontrol approach, in controlling strawberry gray mold spoilage (caused by *Botrytis cinerea*), but when they were applied together, the growth of *R. mucilaginosa* was promoted as that of *B. cinerea* was suppressed by phytate, thereby giving a synergic benefit (Zhang et al., 2013).

Browning and the formation of hazardous chemicals are among the major safety concerns for fruit products. Du et al. (2012) studied the effects of IP6 (0.1 mM) on the enzymatic and nonenzymatic browning in apple juice. As mentioned, IP6 can bind to polyphenol oxidase (PPO), inhibiting enzymatic browning by 99.2%, and can also suppress nonenzymatic browning for 6 months. Nonenzymatic browning is often associated with the Maillard reaction, but it also includes other reactions such as caramelization, phenol oxidation, and maderization (Jeantet, Croguennec, Schuck, & Brulé, 2016). Regarding the Maillard reaction, in particular, Wang, Zhou, Ma, Zhou, and Jiang (2013) observed a promoted Maillard reaction between glucose and β-alanine, upon the addition of 0.1 M IP6 or 0.6 M sodium phosphate, as indicated by the formation of brown color and acrylamide. Interestingly, with the same P content, phytate was not as promotive to Maillard browning as phosphate. Based on this study, the inhibitory effect of nonenzymatic browning observed by Du et al. (2012) may either be a non-Maillard reaction or indicate a dosage-dependent effect.

To sum up, current knowledge indicates that phytate makes positive contributions to the solubility and thermal stability of proteins when they are not carrying the opposite type of net charges. When carrying opposite charges, on the contrary, whether phytate stabilizes or destabilizes proteins and protein-stabilized emulsions depends on the ratios between phytate and protein. Because phytate is naturally complexed with minerals (especially Ca^{2+} and Mg^{2+}), it affects some bioprocesses that require the aid of Ca^{2+} or Fe^{3+}, such as starch hydrolysis and oxidation. Once these phytate–metal complexes are degraded by endogenous or exogenous phytase, the released Ca^{2+} and Mg^{2+} can promote breadmaking, but they can also complex with pectin and proteins to deteriorate legume cookability. One can expect accordingly that the processing of other plant-based foods and beverages, such as beer, meat analog, and spaghettis, may also be affected by the presence of phytate or phytase, which warrants further investigation. The existence of endogenous phytates in plants is generally beneficial to food processing (except bread), shelf-life, and microbial safety. Plant-based food manufacturers needs to balance processing benefits and health concerns when considering whether to remove or keep phytates in their produces.

4 | CONCLUSION AND PROSPECTS

Phytate is a highly reactive ligand that is inclined to interact with various cations, small molecules, and polymers. Its chelating capacity has detrimental effects on nutrient utilization but also provides potential benefits by inhibiting oxidation, calculus formation, and other unfavorable reactions that require metal ions. An in-depth understanding of the chemical and structural properties of phytate as well as how and when interactions occur is essential in understanding the roles phytate can play in human/animal digestion, food processing, polymer functionalities, and many other fields. The present work provides a comprehensive and detailed summary on how phytate interacts with other molecules and affects protein functionalities, food processing, and safety.

It is concluded that in terms of food processing, phytate is not an undesired constituent for plant-based foods. Instead, its presence is essential for the processability of certain crops and contributes to desired quality of food products. In future studies, our knowledge of phytate–protein interactions will further expand, with more and more critical roles uncovered. There is still a long way to go before we address the general bias toward phytate as an antinutrient. The judgment on whether or not phytate presence is desirable in a specific application should be made based on the nutritional or processing needs of the product. The untapped beneficial effects of phytate on food polymer functionality should be further explored, together with a reappraisal of phytate's potential to be listed as a desirable food additive.

In particular, as phytate becomes increasingly popular in other industries, as a molecular binder and functional ingredient, discharging phytate-rich agricultural waste into the water or landfills becomes unwise and environmentally detrimental. Food scientists may come up with sustainable approaches to recover IP6 or phytates from a wide variety of agricultural byproducts. These include but are not limited to defatted rice and wheat bran (Canan et al., 2011; Ebrahimian & Motamedi, 2016), corn

steep water, soy whey fraction, and animal waste. Food academics, manufacturers, regulators, and researchers from other fields should encourage interdisciplinary collaboration to achieve safe and efficient applications of phytate.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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