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Review

Food protein-derived chelating peptides: Biofunctional ingredients for dietary mineral bioavailability enhancement

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Minerals such as calcium, zinc, iron and copper are important elements for human health. Deficiencies of dietary minerals can lead to numerous diseases. Mineral chelating peptides have shown potential application in the management of mineral deficiencies. An increasing number of chelating peptides with the ability to facilitate and enhance the bioavailability of minerals are being discovered and identified. This review outlines the current food protein sources, analytical methods and the purification schemes of mineral chelating peptides, and discusses their structure–activity relationship and the bioavailability. The potential of mineral chelating peptides as functional food ingredients is also described.

Metal chelating peptides

Bivalent nutrients such as calcium, zinc, iron and copper possess a wide variety of biological functions. For instance, calcium is known as the most abundant inorganic element in the human body accounting for 1.5–2.2% of total body weight (Daengprok *et al.*, 2003). In addition, calcium is important for intracellular metabolism, bone growth, blood clotting, nerve conduction, muscle contraction and cardiac function (Bass & Chan, 2006). Calcium is also responsible for many important physiological functions such as cell proliferation, responses to hormones and the release of neurotransmitters (Bendich, 2001). Zinc is a catalytic component of a large number of enzymes and has a structural and biological role in many proteins, peptides, hormones, transcriptional and growth factors and cytokines (Bozalioğlu, Özkan, Turan, & Şimşek, 2005). Iron is responsible for oxygen transport within haemoglobin. Meanwhile, iron is a vital substrate for haemoglobin production and sufficient iron stores are necessary to achieve and maintain adequate levels of haemoglobin (Tay *et al.*, 2011). Copper, as an essential element, plays a vital role as a cofactor for a variety of enzymes. However, copper is capable of producing reactive oxygen species inducing DNA strand breaks and oxidation of nucleotide bases (Megias *et al.*, 2007).

Deficiencies of dietary minerals can lead to numerous diseases affecting many bodily organs. For example, low calcium intake leads to a release of calcium from bone and increases the risk of osteoporosis. Zinc deficiencies give rise to alopecia, diarrhoea, delayed sexual maturation as well as eczematous skin rash (Shenkin, 2008). The signs of iron deficiency mainly include microcytic hypochromic anaemia, impaired physical activity and endurance in adults and cognitive impairment in children.

A variety of factors can cause mineral deficiencies. For instance, many staple foods in the diet, such as cereals, corn, rice and legumes, often contain phytate (Miquel & Farré, 2007). Phytate can lead to mineral deficiencies because it acts as an inhibitor of zinc, calcium and iron

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absorption. Lonnerdal (2000) reported that zinc complexes with phytate on entering the duodenum. This impairs zinc absorption in the gastrointestinal tract through complexation and precipitation.

While the phytate content of various foods can be reduced by processing interventions such as adding commercial phytase, by leavening, fermentation, germination and milling (Gibson, Yeudall, Drost, Mtitimuni, & Cullinan, 1998; Sandberg, Hulthen, & Turk, 1996; Türk & Sandberg, 1992), it is not realistic to process all foods in these ways. In addition, metal ions may interact with each other, which in turn may result in a decrease in their bioavailability. Dietary calcium may significantly diminish the absorption of ferrous and ferric iron in a dose-related manner. Individuals consuming a high calcium diet containing marginal amounts of iron can develop an iron deficiency (Barton, Conrad, & Parmley, 1983). The bioavailability of zinc can be markedly affected or reduced by ingestion of large amounts of other elements such as iron and copper (Shenkin, 2008). Iron can interfere with the absorption of calcium, magnesium and zinc if, for example, iron and multivitamins are taken at the same time (Poitou Bernert *et al*., 2007).

Metal salts and multi-mineral supplements have previously been used in the food industry to overcome the issue of mineral deficiencies. However, these have been shown to cause adverse effects on foods. Food fortification with various metal salts may result in a change in the physical and sensory properties of foods. For example, ferrous sulphate has been reported to cause unacceptable colour changes when added to infant cereals and tortillas, caused a metallic taste in fruit drinks and it also causes precipitates to form in fish sauce and tea infusions (Hurrell, 2002). Multimineral supplementation can be limited due to their instability and ability to cause intestinal disorders. Mineral deficiencies may also occur despite regular use of multimineral supplementation as a consequence of reduced bioavailability (Poitou Bernert *et al*., 2007). Therefore, nutritional authorities encourage consumers to include metal element-rich food in their daily diets (Keller, Lanou, & Barnard, 2002).

Amino acid chelators, such as ferrous bisglycinate, have been developed commercially and have been reported to protect iron from dietary inhibitors and to have a fourfold higher iron absorption than ferrous sulphate (Bovell-Benjamin, Viteri, & Allen, 2000). Amino acids, such as histidine (His) and methionine (Met), have been used in an effort to enhance zinc bioavailability due to their ability to increase zinc solubility (Lonnerdal, 2000). However, these amino acids were gradually replaced due to their high cost, tendency to cause unwanted colour reactions and to provoke fat oxidation.

Food-derived nutritional supplements are more acceptable from general health considerations and dietary preferences. Studies in this area have risen significantly in recent years. CPPs derived from milk protein are mineral absorption enhancing peptides. CPPs have been shown to chelate calcium (McDonagh & FitzGerald, 1998; Park, Swaisgood, & Allen, 1998; Tsuchita, Goto, Yonehara, & Kuwata, 1995), zinc (García-Nebot, Barberá, & Alegría, 2013), and iron (Aït-oukhatar *et al*., 1997; Pérès *et al*., 1999). The mechanism by which CPPs act as calcium chelating peptides has been extensively investigated. CPPs contain highly polar acidic sequences consisting of three phosphoserines followed by two glutamic acid residues, which are the binding sites for calcium (García-Nebot *et al*., 2013). Briefly, the binding strength between CPPs and calcium plays an important role in their biological function. On the one hand, CPPs protects calcium against precipitation during gastrointestinal digestion, while supporting the transport of calcium from food to the intestinal mucosa. On the other hand, the calcium is released from the calcium-peptide complexes when it reaches the small intestinal prior to uptake. CPPs were found to increase the concentration of soluble calcium in the lumen of the distal ileum, enabling the enhancement of passive calcium absorption (Lee, Noguchi, & Naito, 1980). CPP binding to Ca^{2+} enhances the absorbability of calcium from milk and dairy products (Sato, Shindo, Gunshin, Noguchi, & Naito, 1991). CPPs and the mechanism by which they exert their biological activity have been reported elsewhere (Cross, Huq, & Reynolds, 2007; Kitts, 2005; McDonagh & FitzGerald, 1998; Meisel *et al*., 2003; Miquel & Farré, 2007). To date, the application of CPPs as mineral enhancing agents has been extensively developed in food products such as milk powder, biscuits and oatmeal.

Mineral chelating peptides derived from a variety of other food protein sources have been reported in last decade. These include chelating peptides from sesame (Wang, Li, & Ao, 2012), chickpea (Megias *et al*., 2007; Torres-Fuentes, Alaiz, & Vioque, 2011, 2012), sunflower (Megías *et al*., 2008), oyster (D. Chen *et al*., 2013), anchovy (Wu, Liu, Zhao, & Zeng, 2012), hoki (Jung & Kim, 2007) and porcine blood plasma (Lee & Song, 2009a, 2009b) proteins. Metal chelating peptides have been identified as potential functional ingredients to improve bivalent mineral bioavailability. This review summarized the metal chelating peptides reported from a wide variety of food protein resources. It outlines the main peptide purification techniques used. Furthermore, it summarizes the currently available *in vivo* animal and human study data and the potential applications of food protein-derived metal chelating peptides.

Food protein derived metal chelating peptides

Bioactive peptides are encrypted within the primary structures of protein molecules but can be released by proteolysis. Depending on their amino acid sequence, bioactive peptides can exhibit diverse activities in the gastrointestinal tract or in target organs and tissues after absorption into the bloodstream. Biological activities associated with food protein-derived peptides include antimicrobial, immunomodulatory, anticarcinogenic, antitumoral, antithrombotic,

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