Phytic Acid: From Antinutritional to Multiple Protection Factor of Organic Systems

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Abstract: Several studies have shown the benefits of natural antioxidants on health and food preservation. Phytic acid (IP6) is a natural antioxidant that is found mainly in cereals and vegetables and, for a long period of time, was considered an antinutritional factor. However, *in vitro* and *in vivo* studies have demonstrated its beneficial effects in the prevention and treatment of several pathological conditions and cancer. Despite the numerous benefits of IP6, the signs and intracellular interactions mediated by this antioxidant remain poorly understood. This review describes the main chemical and biological aspects of IP6, as well as its actions in the prevention and treatment of various diseases.

Keywords: antioxidant effect, apoptosis, free radicals, natural antioxidants, phytate

Introduction

There is a growing global concern about the quality of food, regarding nutritional aspects as well as contamination by pesticides, toxins, and microorganisms. Studies on so-called nutraceutical foods have demonstrated the importance of a healthy and balanced diet in the prevention and treatment of various diseases (Moraes and Colla 2006).

Phytic acid (IP6) is a natural antioxidant that is found in cereals, vegetables, nuts, and natural oils; IP6 comprises approximately 1% to 5% by weight and 60% to 90% of the total phosphorus present in the seeds used in food and feed (Lolas and others 1976, Graf and Eaton 1990). IP6 has been considered an antinutritional component due to its ability to chelate with such minerals as iron, copper, zinc, and calcium, which hinders its absorption in the gastrointestinal tract (Graf and Eaton 1990). However, several studies in human and animal models have demonstrated the preventive and therapeutic effects of IP6 on different diseases, including inhibition of platelet aggregation (Vucenik and others 1999), reduction of serum lipids (Onomi and others 2004), protective effects in inflammatory bowel disease (Graf and Eaton 1985) and neurodegenerative diseases (Anekonda and others 2011), prevention of cardiovascular diseases (Grases and others 2006), prevention of kidney stone formation (Grases and others 1996) and inhibition of cancer development (Shamsuddin and others 1988, 1993; Vucenik and others 2005).

The protective effect of IP6 has been related to its antioxidant potential in inhibiting radical oxygen species (ROS) production (Graf and Eaton 1985; Vucenik and Shamsuddin 2006). However, little is known about the other possible interactions and signals of this acid in human and animal cells.

In addition to its powerful action in the prevention and treatment of various diseases, IP6 has been studied in the conservation and preservation of the quality of juices and foods, such as meat products (Du and others 2012; Pacheco and others 2012a).

The aim of this review is to present the main chemical and biological aspects of IP6 and to describe its action in the prevention and treatment of various diseases.

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Chemical and Biological Properties

Phytic acid is found naturally in the form of salts, such as phytate Na_2Mg_5, K_2Mg_5 and Ca_2Mg_5 (Plaami 1997). IP6, as an inert and highly stable salt, can be stored in alkaline or neutral solutions at 5 °C for several months at a time (Graf and Eaton 1990). Its chemical structure is composed of 6 phosphate groups linked to an inositol ring (Figure 1); when all 6 carbons are bonded to phosphate groups, the compound becomes known as inositol hexaphosphate (phytic acid, IP6, InsP6, inositol hexaphosphate, or myo-inositol-1 2,3,4,5,6-hexaphosphate). The grouping of phosphates at positions 1, 2, and 3 (axial-equatorial-axial) is unique to IP6, generating a structure that is responsible for specific interactions with iron, which inhibit its ability to catalyze the formation of hydroxyl radicals (Fenton reaction). This inhibition makes, making IP6 a potent physiological antioxidant (Graf and Eaton 1985, 1990). Furthermore, IP6 exhibits a high affinity for polyvalent cations, in the following order of decreasing stability: $Cu^{2+} > Zn^{2+} > Ni^{2+} > Co^{2+} > Mn^{2+} > Fe^{3+} > Ca^{2+}$. Chelation with minerals is dependent on several factors, including the proportion of phytate:metal and the pH (Graf and Eaton 1990).

During the storage, fermentation, germination, and digestion of cereals, IP6 can be dephosphorylated in the smaller phosphoric esters of myo-inositol (IP5, IP4, IP3, IP2, and IP1) by the action of endogenous phytase or by enzymatic hydrolysis with exogenous phytase (Burbano and others 1995). An essential nutrient, inositol is a member of the vitamin B family, which generally conjugates with lipids, and is mainly found in cell membranes as phosphatidylinositol. Mammalian cells respond to various extracellular stimuli from the environment and other cells through the activation of phospholipase C, which hydrolyzes phosphatidylinositol 4,5-bisphosphate to generate inositol 1,4,5-P3 (IP3) and 1,2 diacylglycerol (Berridge and Irvine 1989). Inside the cells, IP3 can serve as a precursor for the formation of other inositol phosphates, such as IP4, IP5, and IP6 (Shamsuddin 1999).

Absorption, Metabolism and Intracellular Functions

Humans and swine have similar characteristics regarding the degradation and absorption of IP6, which occurs mostly in the stomach, upper small intestine and colon (Schlemmer and others 2001). This similarity makes pigs the most suitable experimental model for the study of the effects of IP6 on cancer, inflammatory diseases and other pathologies, especially in comparison with rats and mice.

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In the production of pigs and poultry, it is common to supplement diets with microbial phytase and inorganic phosphorus due to the ability of IP6 to bind minerals that may affect the bioavailability of iron, calcium, and copper in these species (Selle and Ravindran 2007, 2008). On the other hand, studies have indicated that the addition of IP6 to pigs' diets inhibited the oxidation of the meat while inducing no change in growth performance, carcass yield or serum iron (Harbach and others 2007; Monteiro and others 2015). The addition of citric acid to the feed increases the utilization of phytate phosphorus (Rafacz-Livingston and others 1999) and therefore may reduce the need for phytase supplementation with inorganic phosphorus.

Phytic acid has the ability to form insoluble complexes with minerals, proteins, enzymes, and starches. This characteristic may interfere with the absorption of iron, zinc, calcium, and magnesium, especially among people with higher nutritional requirements, inadequate intake or deficiencies of minerals and trace elements (Prynne and others 2010). Nevertheless, some studies have suggested that IP6 has no significant effect on the bioavailability of minerals in subjects eating balanced diets (Forbes and others 1984; Hunt and others 1987). These opposite effects on minerals' absorption occur due to the influence of different factors on IP6 bioavailability. Apparently, both concentration and association of minerals as iron, zinc, cadmium, calcium, and trace elements in the diet seem to be important for the binding effects of IP6 on the minerals' bioavailability and retention (Lopes and others 2002). Moreover, the inhibition of the intestinal metal absorption can be counteracted by many food compounds such as organic acids, ascorbic acid, complexing agents, and food fermentation products that compete with IP6 in the binding of minerals and trace elements (Rimbach and Pallauf 1997; Schlemmer and others, 2001). Therefore, in well-balanced diets, the inhibitory effects of IP6 in the binding of minerals is low and there is little evidence from nutritional surveys that in a well-nourished population, dietary phytate may have a negative effect on the absorption of minerals (Schlemmer and others 2009).

Due to its electrically negative and highly hydrophilic characteristics, IP6 has not been thought to be able to penetrate the cell membrane. However, studies have demonstrated that IP6 can in fact enter cells through dephosphorylation or pinocytosis (Ferry and others 2002). The existence of receptors and binding proteins for inositol polyphosphates indicates their importance in the control of various cellular functions, such as ion channels and protein traffic (Shears 1996), endocytosis (Zi and others 2000), exocytosis (Efanov and others 1997), oocyte maturation (Ji and others 1989), cell division and differentiation (Menniti and others 1993), export of mRNA from the nucleus to the cytoplasm (York and others 1999), DNA repair (Ma and Lieber 2002) and protein enveloping (Macbeth and others 2005). Inositol phosphates show multiple complex patterns of interaction in the phosphorylation and dephosphorylation cycles, renewing the *pools* of intracellular inositol phosphate (Seeds and others 2005). IP5 and IP6 are present inside the cell in higher levels than other phosphoric esters (IP4, IP3, IP2, and IP1), indicating a high capacity for mineral chelation (Sandberg and others 1989). IP3 and IP4 play an important role in cellular signaling and the regulation of cell function, growth and differentiation (Berridge and Irvine 1989).

Anticarcinogenic Effects

In vitro and *in vivo* studies have evaluated the effects of IP6 on various types of cancers, as shown in Table 1. The observed effects of the prevention and inhibition of tumor development are linked mainly to the ability of IP6 to modulate the differentiation, proliferation, and apoptosis of neoplastic cells (Vucenik and others 1998c). This anticarcinogenic protection conferred by IP6 is related to its inhibition of the formation of oxygen free radicals via the prevention of the Fenton reaction in iron chelation (Graf and Eaton 1985). Moreover, studies have shown that IP6 decreases the expression of tumor necrosis factor-α (TNF-α), halts the cell in G0/G1, activates caspase-3, and p53 and inhibits the activation of mitogen-activated protein kinases (MAPKs) (Saied and Shamsuddin 1998; El-Sharbiny and others 2001; Ferry and others 2002; Cholewa and others 2008).

Some clinical studies have suggested that IP6 enhances the action of chemotherapeutic drugs and minimizes side effects in subjects with breast or colon cancer (Druzijanic and others 2004; Bacic and others 2010). The daily intake of 1 to 2 g of IP6 had a prophylactic effect on the development of cancer, and the intake of 8 to 12 g/d may be used in antitumor therapies (Vucenik and Shamsuddin 2006).

Effects in other Pathological Conditions

The protective effects of IP6 in the prevention and treatment of inflammatory and metabolic diseases have been confirmed, as shown in Table 2. The protective effects of IP6 against different pathologies are related to the antioxidant capacities via chelation with iron, suppression of free oxygen radical formation and chelation with Ca^{2+}. Inhibition of lipid peroxidation in the colons of rats (Nelson and others 1989), mice (Singh and others 1997), and pigs (Porres and others 1999) has been reported to have affected the activity of glutathione peroxidase and catalase. Furthermore, IP6 modulates the functions of the immune system by increasing the activity of natural killer cells, regulating the action of neutrophils and decreasing the expression of pro-inflammatory

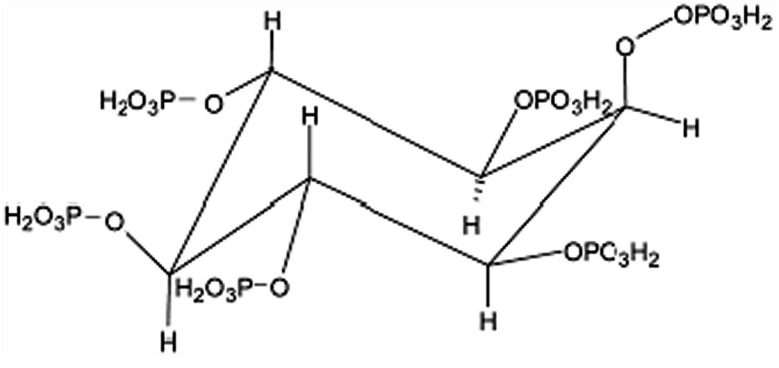

Figure 1–Molecular structure and configuration of IP6 (Carli and others 2006).

Table 1–Antineoplastic action of IP6.

Neoplasia	Model	Effect of IP6	Reference
Adenocarcinoma (pancreatic)	*In vitro*: MIAPaCa and Panc-1 cells	• Inhibition of tumoral growth • Induction of apoptosis • Inhibition of vascular endotelial growth factor (VEGF)	Somasudar and others 2005, McMillan and others 2007
Adenocarcinoma (prostate)	*In vitro*: PC-3, DUI 45 and LNCaP cells	• Inhibition of tumoral growth • Induction of cell differentiation • Increased apoptosis • Decreased cell proliferation	Shamsuddin and Yang 1995, Singh and Agarwal 2004
	In vivo : mouse (drink-water)	• Decreased cell proliferation • Inhibition of VEGF	Singh and others 2004
Cervical cancer	*In vitro*: HeLa cells	• Inhibition of tumoral growth • Induction of apoptosis	Ferry and others 2002
Carcinoma (colon)	*In vitro*: HT-29 cells	• Decreased cell proliferation • Induction of apoptosis • Induction of cell differentiation	Yang and Shamsuddin 1995, Schroterová and others 2010
	In vivo: mouse, rat (diet/drink-water)	• Inhibition of cell proliferation • Inhibition of aberrant crypts formation • Inhibition of tumoral development • Increased natural killer activity	Challa and others 1997, Zhang and others 2005, Norazalina and others 2010
Carcinoma (hepatocellular)	*In vitro*: Hep G2 cells	• Inhibition of tumoral growth	Vucenik and others 1998a
	In vivo: mouse, rat (diet/drink-water)	• Inhibition of tumoral development • Induction of tumoral regression • Inhibition of tumoral growth	Vucenik and others 1998b, Lee and others 2005
Carcinoma (mammary)	*In vitro*: MCF-7 and MDA-MB 231 cells	• Inhibition of tumoral development • Inhibition of adhesion, migration and tumoral invasion	El-Sharbiny and others 2001, Tantivejkul and others 2003,
	In vivo: mouse, rat (diet/drink-water)	• Inhibition of tumoral incidence, size and multiplicity • Inhibition of tumoral development	Hirose and others 1994, Vucenik and others 1993, 1997
Carcinoma (skin)	*In vitro*: JB6 and HEL-30 cells	• Inhibition of tumoral development • Decreased cell proliferation	Huang and others 1997, Nickel and Belury 1999
	In vivo: mouse (topical)	• Prevention of tumoral development	Gupta and others 2003
Fibrosarcoma	*In vivo*: mouse, rat (diet)	• Inhibition of tumoral incidence, growth and pulmonar metastasis	Vucenik and others 1992
Glioblastoma multiforme	*In vitro*: T98 cells	• Induction of apoptosis	Karmakar and others 2007
Leukemia	*In vitro*: K562 cells	• Decreased cell proliferation • Induction of cell differentiation • Induction of apoptosis	Deliliers and others 2002, Bozsika and others 2007
Melanoma	*In vitro*:HTB 68 cells	• Inhibition of tumoral growth • Induction of apoptosis	Rizvi and others 2006
Osteosarcoma	*In vitro*: U20S cells	• Induction of apoptosis	Wang and others 2012
Rabdomiosarcoma	*In vitro*: RD cells	• Inhibition of tumoral growth • Induction of cell differentiation	Vucenik and others 1998c

Table 2–Action of IP6 on several pathological conditions.

Pathological condition	Model	Efect of IP6	Reference
Alzheimer's disease	*In vitro*: MC65 cells	Protection against cytotoxicity caused by β amyloid precursor	Anekonda and others 2011
	In vivo: mouse (drink-water)	Decreased lipidic peroxidation	Anekonda and others 2011
Cholesterol	*In vivo*: rat (diet)	Decreased serum triglyceride	Onomi and others 2004
Cardiovascular disease	*In vivo*: rat (diet)	Decreased arterial and cardiac calcification	Grases and others 2006
Diabetes	*In vitro*: HITT15 cells	Stimulates insulin secretion -Regulation of Ca^2 channels	Efanov and others 1997
	In vivo: mouse,rat (diet)	Insulin secretion regulation -Reduction of hyperglycemia	Kim and others 2010
	Clinical: human prospective diet study	Decreased kidney stone development	Curhan and others 2004
Gastric ulcer	*In vivo*: rat (diet)	Decreased erosion, necrosis, congestion and hemorrhage	Sudheer and others 2004
Intestinal inflammation (colon)	*In vitro*: Caco-2 cells	Regulation of IL-8 and IL-6 expression	Weglarz and others 2007
Parkinson's disease	*In vitro*: mesencephalic/dopaminergic cells from mice	Decreased apoptosis - Increased cell viability	Xu and others 2008
Pulmonary inflammation and fibrosis	*In vivo*: rat (tracheal instillation)	Decreased inflammation -Decreased fibrosis	Kamp and others 1995
Intestinal inflammation (colon)	*In vitro*: Caco-2 cells	Regulation of IL-8 and IL-6 expression	Weglarz and others 2007
Soft tissue calcification	*In vivo*: rat (diet)	Decreased soft tissue calcification	Grases and others 2008
Thrombosis and Atherosclerosis	*In vitro*: human blood cells	Decreased platelet agregation	Vucenik and others 1999

cytokines and interleukins (Cholewa and others 2008). Interestingly, in Parkinson's disease patients, IP6 decreases the apoptosis of neurons, as distinct from its action on tumor cells (Xu and others 2008). These results demonstrated that IP6 modulates apoptosis to protect cells and to prevent the development of disease. In a previous study, our group showed a protective effect of IP6 against the cellular hypoxia-induced intestinal morphological changes of pigs (Silva and others 2014aa). In addition, we were able to demonstrate decreases in cell proliferation, apoptosis, and the expression of cyclooxygenase-2 (Cox-2) (Silva and others 2014b).

Effects on Mycotoxins

Mycotoxins are contaminants of food, mainly cereals, that cause significant economic losses and risks to the health of humans and animals (Rodrigues and others 2012). Abu-Saad El and Mahmoud (2009) observed that the addition of phytic acid to the diet of rats significantly decreased the histological and reproductive disorders caused by aflatoxin B1 in the testis. Pacheco and others (2012b) showed that phytic acid protected the integrity of the cytoplasmic membrane of intestinal cells against the harmful effect of deoxynivalenol (DON).

Our research group seeks to elucidate the mechanisms of action of the toxic effects of DON and fumonisin B1 (FB1); therefore, we are also interested in evaluating the mechanisms or substances that inactivate or minimize the harmful effects of mycotoxins on animal health. In a recent study, we observed that phytic acid significantly decreased the morphological changes induced by mycotoxin FB1 and DON in the jejunum of pigs (Figure 2). Furthermore, we showed that IP6 intestinal exposition reduced cell proliferation, apoptosis, and the expression of Cox-2, contributing to tissue homeostasis (Silva and others 2014b).

Effects on Food

Worldwide, interest in food quality has been increasing. Natural antioxidants, such as vitamin E (tocopherol), selenium, vitamin C (ascorbic acid), and IP6, have become objects of increasing interest

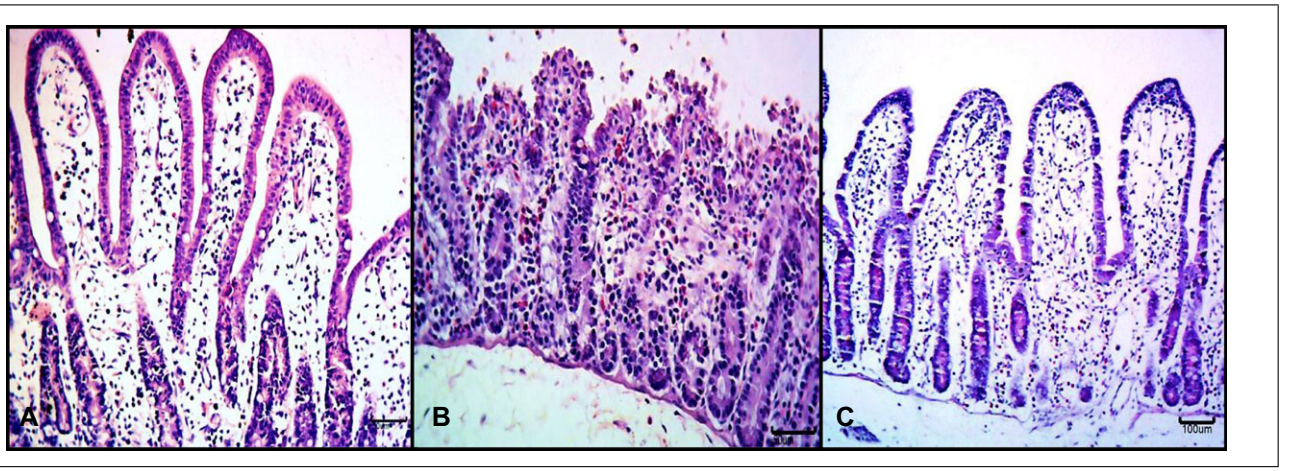

Figure 2–Effect of IP6 on the histological morphology of jejunal explants exposed to DON. (A) Control treatment with normal morphology. HE, bar 100 μm. (B) DON treatment, villi atrophy and loss of the apical enterocytes. HE, bar 50 μm. (C) DON plus 5 mM IP6 treatment, morphology similar to the control. HE, bar 100 μm.

to the food industry (Ramalho and Jorge 2006; Pacheco and others 2012a). Phytic acid has been established as an excellent preservative of juice (Du and others 2012) and meat products (Ghiretti and others 1997; Costa and others 2011; Pacheco and others 2012a).

Apple juice treated with IP6 during processing and storage showed a significant reduction in browning formation due to polyphenol oxidase inhibition by IP6 (Du and others 2012), whereas pigs fed diets containing IP6 showed an increase in meat shelf life (Ghiretti and others 1997; Costa and others 2011). In addition, preservation of color, odor, nutritional value, and other specific characteristics of the meat and derivative products (mortadella, salami, ham, and frescal sausage) during storage were reported (Ghiretti and others 1997; Costa and others 2011; Pacheco and others 2012a). The effect of IP6 on unsaturated fatty acids contributed to the preservation of meat quality and increased shelf life by the inhibition of lipid peroxidation (Ghiretti and others 1997; Costa and others 2011; Monteiro and others 2015).

Conclusion

The protective effects of phytic acid have been demonstrated for various pathological conditions, intoxications, and cancers. The antioxidant effect of IP6 on free radical inhibition by iron chelation is also well established. Although new studies have described the intracellular actions of IP6, little is known about the modulation of the intracellular signals propagated by this antioxidant. Therefore, further studies are needed to elucidate the protective functions of IP6 and its application in the prevention and therapy of pathological conditions.

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Author Contributions

E. O. Silva and A. P. F. R. L. Bracarense conceived and wrote the manuscript.

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