Nutritional Advantages and Disadvantages of Dietary Phytates: A Literature Review Part 2

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ANTIOXIDANT, ANTI-CANCER AND PREBIOTIC

The work of Graf and Eaton during the 1980s showed that phytate functions as an antioxidant in the human body, and as such has considerable health benefits as well as potential for dietary therapeutic use. The authors showed that phytate is a stable compound with many binding sites, and its ability to chelate iron is also a health benefit because it prevents iron-catalysed reactions that produce hydroxyl radicals which cause oxidative damage to the body, and slows lipid peroxidation.9

In the form of myo-inositol hexaphosphate (IP6), the phosphate groups at positions 1, 2 and 3 specifically interact with free iron to completely inhibit the formation of hydroxyl radicals, hence phytate's antioxidant power.14 Also, hydrolysis of phytic acid generates several compounds that are effective against iron- and copper-induced lipid peroxidation. IP3, IP4 and IP5 are all able to significantly suppress hydroperoxide decomposition through occupation of iron ion coordination sites.37

Research papers over the last ten years have hypothesised that dietary inclusion of foods with a high phytate content would play a strong preventative role against colon cancer.2,38,39 Subsequent studies have borne this out in both in vitro and in vivo experiments. 40 Phytate has been found to have a role in cell-signalling in its breakdown to the lower inositol phosphates which are important second messengers. IP3 initiates a number of cellular functions including mitosis through mobilisation of intracellular calcium. IP6 therefore has a controlling influence on mitosis through its degradation to lower inositol phosphates, inhibiting the proliferative nature of necrotic activity.43

Phytate-containing foods also have high levels of dietary fibre, fermentation of which by colonic bacteria produces short chain fatty acids (SCFA) which in turn lower colonic pH and precipitate carcinogenic factors such as secondary bile acids.8 In this sense phytate acts as a prebiotic, decreasing bowel transit time, contributing to the lower pH which improves mineral uptake, particularly of calcium. It appears that a calcium-SCFA exchange system may also be located in the colon, and this may provide sufficient calcium to limit depletion from bone.42

Phytates in wheat bran may help to regulate apoptosis, or normal cell death, by mechanical sloughing action of cells from along the tops of intestinal crypts. Dietary phytates also increase butyrate levels in the colon. In various in vitro studies, this has been shown to induce cell differentiation, and promotes apoptosis via a p53-independent pathway.38,39,49 Apoptosis is particularly important in cancer prevention to counter the indiscriminate proliferation of tumour cells.45

A further synergy with docosahexaenoic acid (DHA) has been discovered in mouse studies and this has potentially important ramifications for both colon health and calcium regulation in the body. Fermentable fibre when combined with fish oil containing DHA exhibits an enhanced ability to induce apoptosis and protect against colon tumorigenesis. DHA alters colonocyte mitochondrial membrane composition and function to create a pathway for butyrate and other metabolites to induce apoptosis. An increase in mitochondrial Ca2+ contributes to the induction of apoptosis by DHA and butyrate cotreatment.45

The authors go on to review the current literature regarding the role of Ca2+ as a trigger for apoptosis. Ca2+ concentration inside cells is regulated by a variety of mechanisms that turn cell signalling on or off. Endoplasmic reticulum (ER) is a major storage area for Ca2+, but more recent studies have identified other organelles, particularly the mitochondria, as having a key role through regulation of energy metabolism in determining whether apoptosis or necrosis results. Mitochondria are in close proximity to IP3-gated channels on the ER, and Ca2+ is rapidly taken up into the mitochondria through active pumps.45

Research is showing that mRNA is affected by IP6, which can induce transcriptional activation of p53 and p21 genes in human cancer HT-29 cells. They found that there may be a p53-dependent mechanism which affects the up-regulation of the p21 gene by IP6.47 In another paper, the same authors found that IP6 at a 5mM dose inhibited the growth of colon cancer HT-29 and Caco-2 cells.48 Other studies have yielded very similar results.49,50

The anti-cancer effects of IP6 are not limited to colon cancer. Vucenic et al list human in vitro experiments on blood, liver, mammary tissue, uterine cervix, prostate and soft tissue, along with murine studies of skin and lung, all of which have found an anti-tumour effect for IP6.51 They further note that leukemic cell lines have a very high susceptibility to IP6, which may suggest that some tissues are more responsive to this effect than others. In a later study, the same authors found that IP6 also induces differentiation of malignant cells, enhances chemotheraphy and helps to prevent metastasis.40

Studies of IP6 and breast cancers in vitro and in biopsied human cells have shown that IP6 alone at concentrations between 0.91-5.5mM shows anti-tumour effects, and when combined with Tamoxifen and other breast cancer drugs, show a synergistic effect.51 The same authors have moved on to examining the effects of enzymes — particularly protein kinase C and others — on breast cancer cells, showing that IP6 can arrest their growth by upregulation of p27/Kip1, which causes inhibition of retinoblastoma protein 1. However, as yet the mechanism by which this
happens is not understood.\textsuperscript{52}

Prostate cancer is another disease where IP6 has shown useful therapeutic results. In an in vitro study, results suggest that IP6 could be a potent dietary agent in controlling the growth of advanced prostate cancer cells and inducing their apoptotic death, in part, by its inhibitory effect on the NF-kappa B signalling pathway.\textsuperscript{53} The same authors also found that IP6 was capable of inhibiting the G1 phase of the cell cycle, increasing its arrest in prostate cancer cells, as well as upregulating p27/Kip1 and p21/Cip1 which contribute to this effect. However, this effect is unlikely to be produced with normal dietary levels of phytate, and that higher levels are needed for efficacy.\textsuperscript{54}

Pancreatic cancer has also been tested with IP6. A US team has carried out in vitro studies, one with IP6 alone,\textsuperscript{55} and another with IP6 and catechins found in green tea and grape seeds. The first study showed that 2.5 mM of IP6 significantly increased early apoptosis. In the later study both substances were found to show significant results in reducing cellular proliferation and when they were combined the synergy produced considerably higher benefits.\textsuperscript{56}

Melanoma studies have demonstrated that dietary phytate has across the board implications for inhibiting cancer cell growth.\textsuperscript{57} The melanoma studies are still at the in vitro stage, with significant reductions in cellular proliferation observed in the HTB68 melanoma cell line. Some animal experiments have also commenced that show that topical administration of IP6 can significantly inhibit skin tumour development.\textsuperscript{58} A study of the topical use of IP6 has shown that it can achieve important concentrations in tissues and biological fluids, which demonstrates that it is possible to propose the topical use as a new InsP(6) administration route, which might be useful in skin cancer treatment or prevention.\textsuperscript{59} Further study is needed on this application.

Lung cancer has so far only been studied in mice. Mice were fed dietary phytate after administration of benzoyl peroxide or methyl nitrinosamine 1-(3-pyridyl)-1-butanone (NNK). A significant inhibitory effect was found.\textsuperscript{60}

An in vitro study has shown that the chelation effect of phytate on iron inhibited asbestos-induced decreases in epidermal growth factor receptor (EGFR) phosphorylation in human lung epithelial (A549) cells, human pleural mesothelial (MET5A) cells, and normal human small airway epithelial (SAEC) cells. This shows phytate's potential as a treatment for asbestos-related lung damage, but further study is required in vivo.\textsuperscript{61}

OTHER PHYTATE HEALTH BENEFITS

Renal lithiasis

As early as the 1980s, the possibility of phytate having preventative activity against renal lithiasis was proposed.\textsuperscript{62} More recent studies have borne this out, with 96,245 younger women who took part in the Nurses Health Study II, demonstrating a strong inverse association between phytate intake and the risk of stone formation. The women in the highest quintile of phytate intake had a 36% lower risk of forming kidney stones.\textsuperscript{63} Phytate exhibits a strong inhibitory effect on the crystallisation of calcium salts such as calcium oxalate and calcium phosphate. Research found that people who form calcium oxalate stones have an abnormally low level of urinary phytate, which would be a direct result of low dietary phytate intake.\textsuperscript{64}

Dental caries prevention

Observation of the lower incidence of dental caries in native tribes with high plant-food intake has given rise to research in this area. While the reason for the lower incidence of dental caries may be multifactorial, past in vitro experiments have shown a strong affinity for phytate and calcium hydroxyapatite in tooth enamel, forming a physical barrier that protects against acid attacks.\textsuperscript{65} However, as phytate is only processed within the colon, it would need to be used as a food additive to have a protective effect within the mouth, although the accompanying fibre in the food may also help to protect teeth by stimulating saliva secretion which is alkaline, and may therefore help to resist acid attack.\textsuperscript{66}

Benefits in post-menopausal conditions

Higher homocysteine (Hcy) levels, higher cholesterol and progression of cardiovascular disease are all more common after menopause and, in particular, women's homocysteine levels increase by 7-20% after menopause.\textsuperscript{67} Studies of soy products (which include high levels of phytate) have shown some benefit for older people in reducing iron absorption. This relates to its anti-nutritional role of chelating divalent ions, but in this case it is beneficial for older women who may be at risk of oxidative damage from elevated iron levels once menstruation has ceased.\textsuperscript{68}

In general, studies in this area have revealed mixed results, with some findings showing that phytates and isoflavones (from soy products) have mostly insignificant results on cholesterol,\textsuperscript{69} and C-reactive protein and Hcy.\textsuperscript{70} However the authors raise the possibility that their use of healthy human volunteers meant that there was not room for a significant improvement to be made. Their results contrast with another study where 42 healthy postmenopausal women were given three daily servings of soy foods for 12 weeks. A significant increase in HDL cholesterol and a decrease in total cholesterol were found, while levels of serum osteocalcin, a sensitive and specific marker of osteoblastic activity, were boosted.\textsuperscript{71}

Earlier studies have found positive benefits for inclusion of soya and other phytate-rich plant foods. One study of 25 people with hyperlipidaemia who consumed a soy-rich breakfast cereal did not find a reduction in overall LDL levels, but did find a significant reduction in oxidised LDL in the test group compared to the control. This could assist in reduction of cardiovascular risk.\textsuperscript{72} Further study particularly on symptomatic volunteers, and with clear delineation of the different risk factors and the food source (i.e. whether dietary phytate, isoflavones and/or other components), needs to be done in this important area.

Blood glucose management in diabetes and hyperlipidaemia

Research in the 1980s showed that a diet high in legumes resulted in a slower rate of digestion in vitro and a lower blood glucose response in vivo compared to a diet high in breads and cereals. Phytic acid is present in higher concentrations in legumes than in cereals and bread. This was confirmed in a study of navy bean flour that examined
results of addition and removal of phytic acid on digestion. Removal of phytate and addition of calcium speeded up digestion and glycemic response, while adding phytate to the flour did the opposite. These results show promise for the use of phytate-rich foods such as legumes in the diet of patients with glycemic conditions such as diabetes.

More recent research has shown a further benefit of IP6 in type II diabetes, where loss of glucose-stimulated insulin exocytosis from the pancreatic beta-cell is an early pathogenetic event. IP6 dose-dependently and differentially inhibited enzyme activities of ser/thr protein phosphatases in physiologically relevant concentrations. This may be a novel regulatory mechanism linking glucose-stimulated polyphosphoinositide formation to insulin exocytosis in insulin-secreting cells.73

NOVEL USES OF PHYTATE

In recent research, phytate's chelating ability has been hypothesised as a potential chelate for uranium contamination in humans. Once deposited in the body, uranium is retained in various organs, particularly the kidneys, and in the bones, with highly toxic effects. Sodium bicarbonate is one standard treatment for uranium poisoning, but has its limits. In an in vitro assay phytic acid's ability to chelate uranium was found to be twice as high as ethane-1,2-diol and 1-bisphosphonate (EHBP), 2.6 times higher than citric acid, and 16 times higher than Diethylene triamine penta-acetic acid (DTPA), which have all been examined in animals as potential chelating agents for humans. The authors suggest that further in vivo study is required.74

MANAGING PHYTATE

Phytate clearly has both advantages and disadvantages for human health. However, it is clear that in communities where phytates are responsible for widespread mineral deficiencies means have to be found to overcome these problems. A number of traditional communities have done that, through means such as fermentation, soaking in water, germination, mechanical pounding, and combinations of these processes. The use of enzymes to break down phytate has also been studied.75

Fermentation and germination of grains have been shown to activate endogenous phytases to convert phytate to the lower inositol phosphates. When phytate was completely hydrolysed after fermentation and germination of white sorghum, the amount of soluble iron was strongly increased.76 Cooking will produce moderate phytate losses of between 5-15%, depending on the type of plant species, temperature and pH.78

In many African countries, traditional processing of grains is frequently achieved by fermentation of gruels. Fermentation, as well as degrading phytates, has sanitation benefits in that the reduction in pH inhibits growth of microorganisms. A study carried out in Burkina Faso which examined the lactic acid fermentation of pearl millet (ben-saalgo), a food that is regularly consumed by up to 49% of the population, showed that phytate degraded naturally with a 75% reduction.77

Anemia is a common problem for pregnant women in South America. Quinoa, a pseudocereal species of chenopodium common in Andean countries, is a good source of minerals, but also of phytate. Soaking, germination and lactic acid fermentation of quinoa were found to enhance iron solubility and degrade phytate. Fermentation of germinated quinoa flour was found to yield almost 98% phytate hydrolysis.78

However, germination and fermentation do not always result in higher mineral bioavailability. In a study of zinc and iron in food grains, germination of finger millet and green gram (mung bean) did not result in higher zinc availability but did assist iron availability. A fermented batter of rice and black gram did provide higher levels of zinc, and much higher levels of iron. Bioavailability did not improve after fermentation of a combination of chickpea, green gram, black gram and rice.79

Magnesium absorption is also affected by dietary phytates. A study of the addition of phytic acid to white bread showed that fractional magnesium absorption is significantly impaired by the addition of phytic acid, in a dose-dependent manner, at amounts similar to those naturally present in whole-grain and brown bread.80 But fermentation of dietary fibre has been shown to have a beneficial effect on magnesium absorption in the presence of phytate-rich foods. Inulin was one substance studied, where magnesium absorption was increased by up to 10% above that of the control group when the study group consumed 40 mg inulin for 28 days.81

It appears that a combination of methods shows the greatest efficacy for phytate degradation. Simply soaking grains and legumes with no other intervention does not reduce phytate levels sufficiently to make a difference to nutrition. Soaking also has different outcomes for various metals. A French study found that some iron leaches into the soaking medium, while zinc does not. They found that soaking grains and legumes may have a slightly beneficial effect on zinc bioavailability, but not on iron.82 More studies are needed to better understand the mechanisms involved.

CONCLUSION

It is clear from published research that phytates have many advantages for human health, despite earlier studies suggesting that they should be avoided due to their effects on mineral status. There are methods, such as soaking, fermentation, germination and mechanical processes available to all communities that allow them to mitigate the disadvantages of high-phytate consumption. Diseases such as anemia, rickets and birth defects do not need to occur in future in these communities as long as education is provided to help people to maximise the benefits of phytate, and to counteract the effects of mineral chelation.

Given the abundant health advantages of phytate-rich foods, it would appear that the breeding of low phytate crops for human consumption is a less than profitable route to pursue. They may have some advantages for animal consumption in the prevention of phosphorus imbalance in the environment of feedlots.

In order to benefit human populations phytate-rich foods need to be available and utilised in diets, particu-
larly in first world countries where cancer, diabetes, renal lithiasis and other diseases are rife. The inclusion of greater amounts of plant-based foods in the diet provides many phytochemicals, including phytate, a high fibre content, and a balance to animal foods. However, it is clear that more education is required in the community regarding these foods and how to balance them to avoid mineral deficiencies.

It is also clear that phytate also has therapeutic uses in higher dosages than would be consumed in a normal diet. Further testing to refine optimum dosages and methods of administration is required, as well as education of medical professionals in the potential of phytate or IP6 as a therapeutic substance.

REFERENCES


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