Phytic acid (IP6), novel broad spectrum anti-neoplastic agent: a systematic review

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SUMMARY. Introduction: Phytic acid or IP6 has been extensively studied in animals and is being promoted as an anti-cancer agent in health food stores. It is naturally found in legumes, wheat bran, and soy foods. It is believed to be the active ingredient that gives these substances their cancer fighting abilities. Proposed mechanisms of action include gene alteration, enhanced immunity, and anti-oxidant properties. Methods: A Medline search from 1966 to May 2002 using the keywords phytic acid and cancer, and limiting the search to the subheadings of therapeutic uses, prevention, and adverse effects revealed 28 studies. These studies were included in the review. Results: A great majority of the studies were done in animals and showed that phytic acid had anti-neoplastic properties in breast, colon, liver, leukemia, prostate, sarcomas, and skin cancer. There were no human studies. Side effects included chelation of multivalent cations, and an increase in bladder and renal papillomas. This increase in papilloma formation only occurred with the sodium salt of phytic acid. It did not occur with either the potassium or magnesium salts. Conclusions: There is a large body of animal evidence to show that phytic acid may have a role in both the prevention and treatment of many forms of cancer. There is clearly enough evidence to justify the initiation of Phase I and Phase II clinical trials in humans.

BACKGROUND

Phytic acid or inositol hexaphosphate (IP6) is a naturally occurring substance that is present in most legumes, including corn, soy beans, wheat bran and nuts.[1] There are numerous studies in the medical literature that have implied that wheat bran has anti-neoplastic capabilities. This has especially been true in the area of colon cancer.[1–8] Further research has indicated that the potential active ingredient for this effect is IP6, which is also known as phytate or phytic acid.[9–13] In animal studies, phytic acid has been shown to inhibit neoplastic growth in multiple types of cancer including breast,[14] colon,[15] liver,[16] prostate,[17] rhabdomyosarcoma,[18] and skin.[19] The proposed mechanisms of action are an increase in natural killer cell activity,[20] alteration in signal transduction,[21] stimulation of genes toward greater cell differentiation,[22] and anti-oxidant activity.[23] The objective of this study is to review the evidence for anti-cancer properties of phytic acid or IP6.

METHODS

A Medline search from 1966 to first week in April 2002 using the key words phytic acid and cancer revealed 176 articles. A further search using the MeSH heading of phytic acid limited to adverse effects, therapeutic use, and toxicity showed 93 articles. Combining this search with the keyword "cancer" resulted in 28 articles. These formed the major part of our review. Other references were secondary references from these articles or were derived from the larger search and used as background information. There was no restriction on the study selection based on the research methodology. Both authors were actively involved in deciding which articles were to be included in the review.

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Table 1 Mechanisms of action: phytic acid (IP6)

Gene function
Interference with signal transduction by blocking phosphatidyl inositol 3 kinase
Stimulation of p53 suppressor gene
Stimulation of tumor suppressor gene p21 WAF1/Cip1
Decreasing mitosis by arresting proliferation in the G0/G1 phase
Enhanced immunity
Increase NK cell function
Antagonizing fibroblast growth factors
Antioxidant properties
Forms an iron chelate thereby inhibiting iron mediated oxidative reactions

RESULTS

Biologic mechanisms

Multiple mechanisms of action, including gene alteration, cell cycle inhibition, increased natural killer (NK) cell activity, and antioxidant functions, have been proposed for phytic acid's anti-neoplastic abilities. However, the exact mechanism by which it exerts these effects has yet to be elucidated. These are summarized in Table 1.

Gene alteration

Carcinogenesis is now believed to be a multistage process in which numerous genes are likely affected.[19] Phytic acid has been shown to exert influence at the genetic level by affecting signal transduction pathways, cell cycle regulatory genes, and tumor suppressor genes.[24] By acting at this level, phytic acid may cause greater differentiation of malignant cells and complete reversions to normal phenotypes.[17,24] Huang et al. demonstrated that phytic acid significantly blocked phosphatidyl inositol-3 kinase (PI-3 K). This is an enzyme known to influence neoplastic cell transformation activity in a dose-dependent manner.[25] Dong et al. supported this finding suggesting PI-3 K may ultimately serve as a biomarker for the effectiveness of phytic acid in future clinical studies.[21] In addition, several colon studies have supported phytic acid's ability to favorably influence colon morphology by increasing both cell apoptosis and differentiation.[15]

The p53 is a tumor suppressor gene. The loss of this gene results in enhanced resistance of cancer cells to chemotherapeutic agents. Saied and Shamsuddin have shown that phytic acid upregulates the expression of p53, as well as another tumor suppressor gene, p21 WAF1/Cip1.[22]

Phytic acid further affects the cell cycle by decreasing the S phase of mitosis and arresting cells in the G0/G1 phase. This produces an anti-proliferative effect on tumor cells. In human breast and colon cancer cell lines, phytic acid lowered the percentage of cells expressing Ki-67, a proliferative marker.[26] When Shamsuddin et al. injected F344 rats with the carcinogen azoxymethane (AOM) and treated them with phytic acid, there was a significantly lower mitotic rate in the phytic acid group than in those treated with AOM alone.[27]

Enhanced immunity

The conversion of phytic acid to its lower forms IP 1–5 by dephosphorylation contributes to phytic acid's anticancer properties. IP3 plays an integral role in cellular signal transduction and intracellular function. At the cellular level, enhancing the intracellular phosphate pool amplifies NK cell cytotoxicity.[10] This boost to NK cell activity augments the body's immune response to carcinogenic threats.[5] NK cells have been shown to contribute to tumor cell destruction. Baten et al. showed a correlation between enhanced tumor suppression and NK cell activity by treating mice which had been exposed to dimethylhydrazine (DMH, a colon carcinogen which induces depressed NK cell activity) with phytic acid. In vivo treatment with phytic acid reversed the DMH induced depression of NK activity, and it also enhanced the baseline NK cell activity. This resulted in an inverse correlation between phytic acid exposure and tumor incidence.[20]

Morrison et al. proposed another possible mechanism in a study that showed phytic acid inhibits tumor growth by antagonizing fibroblast growth factors. This adversely affects tumor angiogenesis.[28]

Antioxidant properties

Phytic acid may exert its greatest biologic effect through its antioxidant properties. Phytic acid forms an iron chelate which inhibits iron mediated oxidative reactions and limiting site specific DNA damage.[23,29] By suppressing the formation of damaging hydroxide free radicals and other reactive oxygen species, phytic acid limits tumor growth. Graf and Eaton propose that phytic acid's antioxidative properties help explain the suppression of colon carcinogenesis by diets rich in phytic acid.[3] Tumor progression may also be limited by phytic acid's chelation of other divalent cations such as magnesium and zinc since both are critical for tumor cell proliferation.[10]

PROPHYLACTIC AND THERAPEUTIC USES

The anti-neoplastic activity of phytic acid has been established in multiple varied tumor models, including breast, colon, leukemia, liver, prostate, sarcoma, and skin.

Breast

Many studies have demonstrated an inhibitory effect of phytic acid on the development and progression of mammary tumors in animal models. In a review of these studies entitled 'Mammary Tumor

Inhibition by IP6', Shamsuddin and Vucenik investigated whether dietary fiber which contains high phytic acid exhibits a dose response inhibition of 7,12-dimethylbenz (alpha) anthracene (DMBA) induced rat mammary carcinogenesis.[14] The authors further considered the question of whether isolated phytic acid has stronger anticancer action than phytic acid present in a high fiber diet. The results showed that a high fiber diet produced a small, statistically non-significant inhibitory effect on mammary tumors. On the other hand, treatment with pure phytic acid significantly reduced tumor number, incidence and multiplicity. This led the authors to conclude that phytic acid alone is more effective than a high fiber cereal diet in preventing experimental mammary tumors.[14]

In a similar study by Vucenik et al., rats in which mammary tumors were induced with DMBA were placed on several diets, including 5, 10, 20% Kellogg's All Bran cereal, or 0.4% phytic acid in drinking water. While those rats on all bran diets had statistically non-significant changes, the phytic acid treated group experienced a 33.5% reduction in tumor incidence and had 48.8% fewer tumors.

Further research by Shamsuddin et al. on the anticancer functions of phytic acid revealed phytic acid's growth inhibition of human mammary cancer cell lines is independent of the oestrogen receptor (OR) status.[30] Two human mammary carcinoma cell lines with different OR status exhibited dose dependent growth inhibition after treatment with phytic acid.

Treatment with phytic acid influenced mammary tumor carcinogenesis in a study conducted by Hirose et al. Female Sprague–Dawley rats initiated with DMBA were placed on one of six diets, including a 2.0% phytic acid diet and a basal control diet, for 35 weeks. Those rats that were fed the phytic acid diet had a significantly lower mortality rate than those fed the basal diet alone. Moreover, the average size of palpable mammary tumors was significantly smaller in rats on a phytic acid diet.[31]

A comparable study by Vucenik et al. found that rats initiated with DMBA who were fed diets supplemented with phytic acid, with or without inositol, exhibited a 48% reduction in number of tumors. In addition, there was a 40% reduction in the number of tumors per rat compared to those rats exposed to DMBA only. Only 8% of animals in the treatment groups had five or more tumors compared to 20% in the DMBA only control group. Rats treated with phytate further showed a 19% reduction of tumor incidence and 16% smaller tumors size.[32]

Colon

Multiple studies support an inverse relationship between dietary fiber and colon cancer risk. Compared to oat or corn bran, wheat bran seems to suppress the development of cancerous growths in the colon most reliably.[9] Shamsuddin et al. state that phytic acid is the component of a high fiber diet that is most responsible for cancer prevention.[14] Several other authors have supported this hypothesis that phytate has a primary role as the active ingredient in bran that is responsible for tumor prevention. For example, after treating HT-29, human colon cancer cells, with phytic acid in vitro, Yang and Shamsuddin observed a dose- and time-dependent growth inhibition. There was down regulation of PCNA, a known tumor proliferation marker.[33] Using aberrant crypts as an intermediate biomarker for colon cancer, Pretlow et al. found that in F344 rats exposed to azoxymethane (AOM), those concomitantly treated with supplemental phytate had fewer aberrant crypt foci (ACF).[34] In another study, Reddy found that oral administration of phytic acid inhibited colon carcinogenesis in rodents. Using aberrant crypt foci as a marker for pre-neoplastic lesions in rats, the authors found that dietary phytic acid decreases the incidence of such crypts.[5]

Several studies have looked at the effect of phytic acid on large intestinal cancers (LIC) in F344 rats.[35–37] Ullah and Shamsuddin fed F344 rats Na-IP6 in drinking water and later injected them with AOM. Sacrificing and autopsying the animals 30 weeks after the last injection, the authors found reductions in tumor size, prevalence, and frequency.[35]

Shamsuddin et al. showed phytic acid in combination with inositol, significantly reduced the prevalence of LIC induced by 1,2-dimethylhydrazine (DMH) in CD-1 mice.[38] The authors further observed a protective effect of phytic acid even 5 months after carcinogenic induction with AOM in F344 rats.[36] In another study, F344 rats started on 1% Na-IP6 in drinking water 1-week prior to injection with AOM had similar reductions in LIC compared to controls.[27]

Leukemia

In an erythroleukemic cell line K-562, Shamsuddin et al. observed treatment of these cells with phytic acid reduced the abnormal cell population by 19–36%. There was also increased cell differentiation.[39]

Liver

Hepatocellular carcinoma (HCC) is currently a deadly malignancy with limited treatment options and associated poor prognosis. Phytic acid has been studied as a possible adjuvant in the arsenal against HCC. Using a multiorgan carcinogenesis model, Hirose et al. investigated the effect of phytic acid on promotion of rat carcinoma. Male F344 rats were initiated over the first three study weeks with 2,2-dihydroxy-di-*n*-propylnitrosamine (DHPN), *N*-ethyl-*N*-hydroxyethylnitrosamine (EHEN), and 3,2-dimethyl-4-aminobiphenyl (DMAB), and then subsequently placed on either a basal diet or a diet supplemented with phytic acid. The appearance of hepatic tumors was suppressed in those rats receiving phytic acid in their diet.[40]

In two elegant studies, Vucenik et al. studied the potential role of phytic acid in the treatment of liver cancer. In the first study, a human liver cancer cell line HepG2, was treated in vitro with phytic acid. Treatment with phytic acid resulted in a dose dependent growth inhibition of HepG2 cells, and it also reduced the cells' ability to form colonies. There was also a marked decrease in the cells' production of alpha-fetoprotein (AFP), a tumor marker of HCC. Phytic acid encouraged differentiation of malignant cells, contributing to conversion of the cancer cells to less aggressive phenotypes. Furthermore, HepG2 cells treated with phytic acid exhibited decreased expression of mutant p53 protein and increased expression of p21WAF1 protein suggesting enhancement of tumor suppressor gene activity.[16,41]

In their follow-up study, Vucenik et al. investigated phytic acid's ability to suppress and regress the growth of HepG2 cells in a transplanted nude mouse model. HepG2 cells were treated with a single dose of phytic acid in vitro and inoculated subcutaneously into mice 48 h later. In those mice that received HepG2 cells pretreated with phytic acid, no tumor was observed, while 71% of mice inoculated with the same number of untreated cells developed solid tumors at the site of transplantation. After injecting those tumors 8–10 mm in size with phytic acid, the authors sacrificed and autopsied the animals discovering tumor weights 86–180% less than those of untreated control mice. Such ability of phytic acid to inhibit tumorigenesis and regress pre-existing human hepatocellular carcinoma xenografts suggests a potential role in the prevention and management of HCC.[41]

Prostate

Phytic acid has also been shown to exert a positive influence on human prostate cancer cells in vitro. Zi et al. using a human prostate carcinoma cell line DU 145, found epidermal growth factor receptor (EGF-R or erbB1) endocytosis and associated mitogenic signaling to occur in human prostate cancer cells suggesting a possible role of endocytosis in cancer cell growth. The authors observed phytic acid to impair essential components of ligand induced erbB1 endocytosis concluding that this inhibition by phytic acid may ultimately prove useful in the treatment of prostate cancer.[42]

A beneficial effect of phytic acid on prostate cancer cells in vitro was also observed by Shamsuddin and Yang. Human prostate cancer cells treated with phytic acid in vitro showed a significant dose dependent growth inhibition, and also a dose dependent suppression of DNA synthesis. Prostate acid phosphatase, a marker of prostatic cell differentiation, was also significantly increased.[17]

Sarcomas

Vucenik et al. have studied the potential value of phytic acid in the treatment of rhabdomyosarcoma. Phytic acid was observed to both suppress growth of the rhabdomyosarcoma (RD) cell line. Greater cell differentiation was also demonstrated. Once phytic acid was removed from the media, the RD cells were able to recover their logarithmic growth. In a xenografted nude mouse model, mice treated with phytic acid showed 25-fold smaller tumors after 2 weeks, and a 49-fold reduction after 5 weeks of treatment.[16]

Phytic acid may eventually have a role in the treatment of fibrosarcomas as well. Vucenik et al. found that intraperitoneal injections of phytic acid in mice reduced the growth of subcutaneous transplanted murine fibrosarcomas. This prolonged the survival of tumor bearing mice, and also reduced the number of pulmonary metastasis.[43]

Skin

Whether treatment with phytic acid has an effect on skin cancer was investigated by Ishikawa et al. using a two-stage mouse skin carcinogenesis model. ICR female mice were divided into six groups and initiated with an application of the carcinogen DMBA. Three weeks after initiation, they were then exposed to the tumor promoter TPA. Over the study period, some mice were given 2% phytic acid in drinking water the entire time, while others received phytic acid during initiation, the first 3 weeks, or during promotion, the last 19 weeks only. The authors found that those animals ingesting phytic acid during the initiation stage had a 50% reduction in the mean number of skin papillomas and number of tumor bearing mice. Such inhibition was not observed in those mice given phytic acid during the promotion period.[44]

Side effects

While multiple studies have investigated the efficacy of phytic acid on tumorigenesis in animal models, there is uncertainty regarding its safety in humans. There is conflicting evidence regarding possible nutritional implications. Due to phytic acid's ability to chelate multivalent metal ions, such as zinc, magnesium, calcium and iron, protein complexes are formed, reducing the solubility of the metals.[10] Such binding produces highly insoluble salts which are not readily absorbed from the gastrointestinal tract, thereby reducing the bioavailability of these minerals.[45] On the other hand, Ullah and Shamsuddin found no significant differences in serum magnesium, calcium, iron and zinc levels between control F344 rats and those fed 1% phytic acid in their drinking water. They concluded that long-term administration of phytic acid has no demonstrable toxic effect with regard to its ability to chelate multivalent cations.[35]

Some studies have also suggested a positive correlation between ingestion of phytic acid and incidence of urinary bladder papillomas. Hirose et al.

initiated rats with multiple carcinogens including DHPN, EHEN and DMAB. One week after the last injections were given, only the rats with the diet containing phytate supplementation showed increased tumor incidence.[46] In a similar study by Hirose et al., the authors again found that sodium phytate salt acts as a promoter of bladder carcinogenesis.[40] Takaba et al. also established a promoting activity of the sodium salt of phytic acid, Na-PA on urinary bladder carcinogenesis. In a 2-stage urinary bladder carcinogenesis model, male F344 rats were initiated with nitrosamine in drinking water for 4 weeks and then fed with basal diet containing 2% phytic acid, Na-PA salt, K-PA salt, Mg-PA salt or no added chemicals. After 32 weeks, Na-PA, but not the potassium or the magnesium phytic acid, was shown to significantly encourage development of pre-neoplastic and neoplastic lesions of the urinary bladder.[47]

In addition to an undesirable effect of phytic acid on the urinary bladder in animal models, it appears that phytic acid as a food additive may also induce renal papillae changes including necrosis and calcification. Such changes in the renal papilla seemed to correlate with development of renal papillomas. When Hiasa et al. studied male and female F344 rats adding PA to drinking water, at levels of 1.25 or 2.5% for 100–108 weeks, they found PA treated rats developed such papillae changes while controls did not.[48]

Present evidence on phytic acid's toxicity is limited to only a few studies. It is therefore difficult to state with confidence phytic acid's ultimate safety at therapeutic doses. Human trials are needed to answer these basic questions of safety, efficacy, and proper dosage of phytic acid.

CONCLUSIONS

Phytic acid has shown significant anti-cancer effects in both a wide range of cancers and in a variety of animal models. Potential mechanisms of action include gene alteration, enhanced immune effects, and antioxidant properties. There is clearly enough animal evidence of the safety and effectiveness of phytic acid to justify Phase I and Phase II clinical trials in humans.

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