Anticancer Properties of Inositol Hexaphosphate and Inositol: An Overview

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Summary Inositol hexaphosphate (IP₆) and its parent compound myo-inositol (Ins) are active compounds from rice and other grains, with a broad spectrum of biological activities important in health and diseases. However, the most striking is the anticancer effect of IP₆ and Ins that has been actively investigated during the last decades. A consistent and reproducible anticancer action of IP₆ has been demonstrated in various experimental models. IP₆ reduces cell proliferation, induces apoptosis and differentiation of malignant cells via PI3K, MAPK, PKC, AP-1 and NF-kappaB. Very few clinical studies in humans and case reports have indicated that IP₆ is able to enhance the anticancer effect of conventional chemotherapy, control cancer metastases, and improve quality of life. Reduced burden of chemotherapy side-effects in patients receiving IP₆ alone or in combination with Ins has been reported. Because of the highly promising preclinical and emerging clinical data, large clinical trials and further mechanistic studies are warranted.

Key Words phytate, inositol, inositol hexaphosphate, IP₆, cancer, prevention, treatment

Cancer incidence and mortality are rapidly growing worldwide, mostly reflecting both aging and growth of the population, but also changes in the prevalence and distribution of the main risk factors for cancer, several of which are associated with economic development. There will be 18.1 million new cases of cancer and 9.6 million people will die with the disease this year worldwide, a report predicts (1). According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI), American Cancer Society (ACS) and World Health Organization (WHO), this toll is projected to grow to 24 million cases and over million deaths annually by 2050. Therefore, despite the enormous efforts to search for cure, cancer still remains a challenge for global public health.

To reduce the burden of cancer, cancer prevention by the use of non-toxic, naturally occurring compounds is a good strategy for the management of cancer. It has been shown that simply by modification of diet by increasing vegetable and fruit intake, maintenance of optimum body weight, and regular physical activity, 30% to 40% of all instances of cancer could be prevented (2, 3). Extensive research over the past several decades has identified numerous dietary and botanical natural compounds that have cancer-preventive potential. The protective role of diet with high fiber content has been observed not only against cancer, but also against development of many metabolic diseases. The epidemiological studies have indicated that only fiber diet with high IP₆ (myo-inositol hexaphosphate, InsP₆, phytic acid) content, such as cereals and legumes, show negative correlation with colon cancer, suggesting that it could be IP₆ and not fiber that suppressed colon cancer (4–6). And, indeed, it has been shown that IP₆ is one of the biologically active components of fiber, responsible for its anticancer effect. This observation initiated studies on anticancer activity of IP₆.

Structure, Importance and Mode of Action

IP₆ is a very stable and the most abundant polyphosphate in nature. It is a component of cereal diets and legumes, found in rice, wheat, peas, beans, oats, barley, in concentrations ranging from 0.4–6.4%, where it is referred as phytic acid (7, 8). The presence of phosphate group in positions 1, 2, 3 (axial, equatorial, axial) is giving unique properties to this molecules, such as antioxidant and specific chelating capacity of potentially toxic elements (4, 5) (Fig. 1A). Its parent compound myo-inositol (Ins) is a cyclitol naturally present in animal and plant cells (Fig. 1B). There are nine possible stereoisomers of inositol: cis-, epi-, allo-, myo-, musco-, neo-, (+)-chiro, (−)-chiro-, and scyllo-inositols, formed through epimerization of its six hydroxyl groups. Five of them, myo-, scyllo-, musco-, neo- and D-chiro-inositol occur naturally, while the other four possible isomers (L-chiro-, allo-, epi-, and cis-inositol) are derived from Ins (9–11). Although originally thought that only 63 isomers were possible (12), today we know that the number of inositol phosphates of those nine isomers (excluding pyrophosphates) is 357 (9, 10). Introduction of Agranoff’s turtle analogy helped to visualize Ins in the form of turtle, in which the axial hydroxyl was its head, and the five equatorial hydroxyls serve as forelimbs, hind limbs, and the tail as illustrated in the Fig. 1D (12, 13). This structural mnemonic, the turtle configuration, was actually suggested by the International Union of Biochemistry Nomenclature Committee to aid biochemists, and eased the confusion in numbering when depicting

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the Haworth projection (Fig. 1C) (12).

Animal and plant cells contain Ins either in its free form, as inositol-containing phospholipids (phosphoinositides) or as phytic acid (IP$_6$), a principal storage form of phosphorus in plants, particular in bran and seeds (14). Because Ins can be synthesized from D-glucose, it is not any more considered as a part of vitamin B family. Not only all plant cells, but almost all mammalian cells contain high concentrations of IP$_6$. Ins and other inositol phosphates, wherein they play important role in regulating vital cellular functions, such as signal transduction, regulation of cell proliferation and differentiation, RNA export, mRNA transcription, DNA repair, energy transduction and ATP generation (10), and de-regulation of their metabolism has been recognized in several illnesses, including neurological disorders (10), polycystic ovary syndrome (15), metabolic diseases (14, 16, 17) and cancer (4, 5).

Although Ins and IP$_6$ are prevalent natural forms and have been much studied over the last 30 y, some “other” cyclitols and inositols might also be medically relevant, and their roles and applications have been recently considered (9, 10, 18). For example, the role of scyllo-inositol in neurodegenerative diseases (11) and the importance of D-chiro-inositol have been reported (9, 10, 18).

However, cancer preventive and therapeutic properties of IP$_6$ have received most attention and its broad-spectrum of anticancer activities has been shown in multiple preclinical experimental studies and in humans, alone or in combination with Ins (4, 5, 19, 20). After rapid intake and dephosphorylation, IP$_6$ enters the pool of inositol phosphates and interacts with cellular processes involved in cancer prevention, progression and treatment. Just a note, that the uptake of exogenous IP$_6$ has been a subject of some debates and controversy (21). The anticancer properties of IP$_6$ and Ins are related to the intracellular inositol phosphate pool, affecting multiple targets and signaling pathways, in particular inhibiting the phosphorylation-based activation of key molecular targets that interfere with specific biological functions (19, 20). The preventive and therapeutic potential of IP$_6$ has been related to its antioxidant functions, ability to block the activation of various carcinogens and/or to stimulate their detoxification, to the immune-enhancing, anti-inflammatory activities, and to the suppression of cell cycle and proliferation. The induction of differentiation and apoptosis in various premalignant and cancerous cells can also contribute to both cancer preventive and therapeutic potential of IP$_6$. Moreover, suppression of angiogenesis (22), inhibition of metastatic processes and tumor progression, synergism with anticancer drugs and alleviation of chemotherapy resistance further indicate its chemotherapeutic potential (4, 5, 19, 20). Just to name few critical molecular targets, IP$_6$ interferes at the receptor level, down-regulates p27, inhibits pRB phosphorylation and cell cycle (23), reduces PI3K and consequently counteracts the activation of PKC/RAS/ERK pathway (23), downregulates Akt and ERK, leading to reduction of NF-kappaB and inhibition of inflammation. Extensive reviews of IP$_6$ and Ins key molecular targets, complex network and modulation of critical pathways associated with biological functions and microenvironment involved in carcinogenesis and cancer progression, have been published (19, 20).

**Anticancer Effects in Experimental Models**

Numerous studies have demonstrated cancer preventive and therapeutic properties of IP$_6$ in a wide variety of tumor types, both in vitro and in vivo (4, 5). In the first studies, pioneered by Prof. Shamsuddin, the effectiveness of IP$_6$ to prevent cancer was evaluated in vivo after administration of IP$_6$ in the drinking water. The exogenous 1% IP$_6$ in drinking water 1 wk before or 2 wk after administration of azoxymethane inhibited the development of large intestinal cancer in Fisher 344 rats (24). In the same model, administration of 2% IP$_6$ in the drinking water was effective even when the treatment had begun 5 mo after carcinogen initiation. Compared to untreated rats, animals on IP$_6$ had 27% fewer tumors (25). A consistent, reproducible, and significant inhibition of mammary cancer by IP$_6$ was shown in experimental models chemically induced by either 7,12-dimethylbenz[a]anthracene or N-methylnitrosourea; the effect was seen on tumor incidence, tumor size, and tumor multiplicity (4, 5, 26). IP$_6$ was effective against prostate cancer as well. Studies demonstrated that continuous administration of 2% IP$_6$ in the drinking water, beginning 24 h after implantation of DU-145 prostate cancer cells, resulted in a 64% decrease in tumor burden (4, 5, 19). Additionally, chemopreventive efficacy of IP$_6$ was observed against prostate tumor growth and progression in the Transgenic Adenocarcinoma Mouse Prostate (TRAMP) model (4, 5, 19). Peritumoral, intratumoral or intraperitoneal administration of IP$_6$ significantly inhibited growth of rhabdomyosarcoma tumor xenografts (27), regressed liver cancer xenotransplants (28), and in murine fibro-
IP6 and Ins in Clinical Studies

For almost twenty years, IP6 and Ins have been available for the optimal efficacy. Although IP6 and Ins exist naturally in plants and prevented lung metastases (29). Anticancer potential of IP6 was demonstrated in several models of skin cancer. The effect of IP6 on skin cancer was investigated in a 2-stage mouse skin carcinogenesis model; a reduction in skin papillomas was found when IP6 was given during the initiation stage but not when given during the promotion stage (4, 5, 19). Prevention of skin carcinogenesis was also shown in a mouse carcinogenesis model where IP6 caused a reduction in the number of skin tumor formation (4, 5, 19). Using ultraviolet B (UVB) light known as a complete carcinogen, topical application of IP6, also significantly decreased UVB-induced tumor incidence and multiplicity in SKH1 hairless mice (30).

In vitro studies have shown that IP6 inhibits growth and induces differentiation and apoptosis of human breast cancer cells (both estrogen-receptor-positive and estrogen-receptor-negative), colon, prostate, liver, pancreatic and cervical cancer cell lines, as well as of rhabdomyosarcoma, glioblastoma, melanoma and human leukemia cells (4, 5, 19). Additionally, IP6 was able to inhibit cell transformation in mouse epidermal JB6 cells and to reverse the transformed phenotype of HepG2 liver cancer cells (4, 5).

Its parent compound, Ins itself was also shown to have modest anticancer activity. It inhibited colon, mammary, soft tissue and lung tumor formation (4, 5). More importantly, it was shown that Ins potentiates both the antiproliferative and antineoplastic effects of IP6 in vivo (4, 5, 25) and in vitro (19). Synergistic cancer inhibition by IP6 when combined with inositol was observed in colon and mammary cancer studies (4, 5, 19). Similar results were seen in the metastatic lung cancer model (29). IP6 and Ins inhibited the development and metastatic progression of colorectal cancer to the liver in BALB/c mice, and the effect of their combined application was significantly greater than the effect of either compound alone (31). Not only the combination of IP6 and Ins was significantly better in different cancers than was either one alone, but it also consistently reduced all tumor growth parameters (Table 1) (26). Therefore, for clinical studies, the combination of IP6 and inositol has been considered for the optimal efficacy.

Table 1. Effects of IP6 and Ins on DMBA-induced rat mammary carcinoma.

|                  | Tumor incidence (%) | Total number of tumors | Number of tumors/tumor bearing rat | Rat with 5 or more tumors (%) |
|------------------|---------------------|------------------------|-----------------------------------|-----------------------------|
| Control          | 92.5                | 113                    | 3.1 ± 0.4                         | 17.5                        |
| IP6              | 71.5                | 69                     | 2.5 ± 0.2                         | 5.3                         |
| Ins              | 75.0                | 64                     | 2.1 ± 0.2*                        | 2.5*                        |
| IP6 + Ins        | 76.3                | 51                     | 1.8 ± 0.1*                        | 0.0*                        |

*p < 0.05.

Judging IP6 and Ins as anticancer agents, here are few important facts: a) being natural, they are safe; b) they do not affect normal cells; c) they act synergistically with chemotherapy, and d) affect all principal pathways of malignancy. No adverse side effect in animals or human have been noticed and/or reported, even when given at very high doses. They are selective and do discriminate between normal and tumor cells, affecting malignant cells, while sparing normal cells and tissues. When the fresh CD34+ cells from bone marrow were treated with IP6, an inhibition of the clonogenic growth was observed with leukemic progenitor cells, but not with normal bone marrow progenitor cells under the same conditions (32). While IP6 inhibited the colony formation of Kaposi Sarcoma cell lines, KS Y-1 (AIDS-related K5 cell line) and KS SLK (Iatrogenic KS) and CCRF-CEM (human adult T lymphoma) cells in a dose-dependent manner, the ability of normal cells (peripheral blood mononuclear cells and T cell colony-forming cells) to form colonies in a semisolid methylcellulose medium was not affected (19). We have demonstrated that IP6 acts synergistically with tamoxifen and doxorubicin, being particularly effective against estrogen receptor-negative and doxorubicin-resistant tumor cell lines, and both of these conditions are challenges for treatment (19). And, as already discussed, both IP6 and Ins affect all principal pathways of malignancy, known as “hallmarks of cancer” (33).

And indeed, many anecdotal evidence, several clinical case reports and few small clinical studies, have demonstrated an enhanced antitumor activity with improved quality of life by IP6 + Ins. In a pilot clinical trial involving 22 patients with advanced colorectal cancer (Dukes C and D) with multiple liver and lung metastases, IP6 + Ins was given as an adjuvant to chemotherapy according to Mayo protocol. One patient with liver metastasis refused chemotherapy after the first treatment, and she was given only IP6 + Ins; her control ultrasound and abdominal computed tomography scan 14 mo after surgery showed a significantly reduced growth rate (34). A reduced tumor growth rate was noticed overall and in some case a regression of lesions was noted. Additionally, when IP6 + Ins was given in combination with chemotherapy, side effects of chemotherapy, such as drop in leukocyte and platelet counts, nausea, vomiting, alopecia, were diminished and patients were able to perform their daily activities (34, 35). Long-term survival of a patient with advanced non-small cell lung cancer treated with IP6 + Ins treatment combined with chemo-

**IP6 and Ins in Clinical Studies**

Although IP6 and Ins exist naturally in plants and human cells, and their deficiency is evident (16), for the full health benefit and function their supplementation is necessary. And, as common constituents of our diet, both IP6 and Ins met specifications of FDA and have been given GRAS (Generally Recognized As Safe) status. For almost twenty years, IP6 and Ins have been available as food supplements, and despite substantial progress in the understanding of the molecular basis and molecular targets of their anti-carcinogenic activity and potential, there have been very few clinical studies with IP6 and Ins.

**Table 1.** Effects of IP6 and Ins on DMBA-induced rat mammary carcinoma.
radiotherapy was reported (36). In a phase 1 clinical study, inositol was shown to be safe and well tolerated (37). The combination of beta-(1,3)/(1,6) D-glucan and IP6 had beneficial effect on hematopoiesis in the treatment of patients with advanced malignancies receiving chemotherapy (38). In a small prospective, randomized, pilot clinical study, IP6 in combination with Ins ameliorated the side effects of chemotherapy and preserved quality of life in breast cancer patients (39). Topical IP6 treatment was effective and safe in preventing and/or mitigating chemotherapy-induced side effects as well as the preserving quality of life in women with ductal breast cancer in a double-blind, randomized controlled trial (RCT) (40). In a recent review article, a literature search was conducted to identify clinical evidence of the effectiveness of IP6 and Ins on quality of life in cancer patient and demonstrated that that IP6 and Ins are effective in improving quality of life of patients undergoing chemotherapy due to breast cancer (41).

And, most recently, an amazing case report by Khurana et al. (42) on a patient with metastatic melanoma who declined traditional therapy and opted to try the IP6 Ins supplement and who received a complete remission and remained in remission 3 y later. This opens a new avenue for IP6 clinical research, an immunotherapy and a potential for immune stimulating effects of IP6 and Ins in patients with metastatic melanoma.

Because currently available preclinical and encouraging initial clinical data suggest that IP6 and Ins are promising in cancer prevention and adjuvant therapy, more controlled clinical trials are expected.

Disclosure of State of COI

No conflicts of interest to be declared.

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