

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 can-

cer (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*-, *muco*-, *neo*-, (+)-*chiro*-, (–)-*chiro*-, and *scyllo*-inositols, formed through epimerization of its six hydroxyl groups. Five of them, *myo*-, *scyllo*-, *muco*-, *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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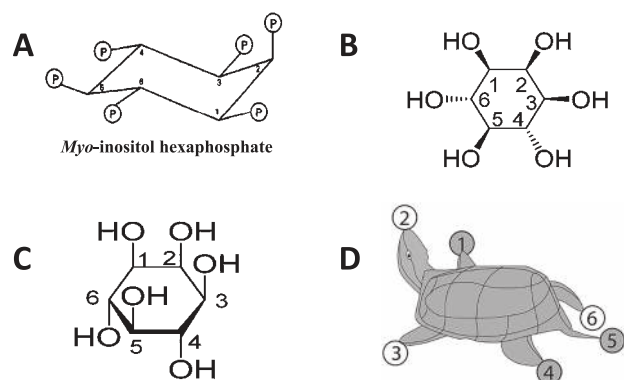


Fig. 1. Structures of IP₆ and *myo*-inositol. (A) Chair conformation of *myo*-inositol hexaphosphate (IP₆, phytic acid) with the unique configuration of phosphate groups in positions 1, 2 and 3 (axial-equatorial-axial). *myo*-Inositol is represented as a wedge-dash notation (B), Haworth projection (C) and schematically as a turtle (D).

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 (IP₆), 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 IP₆, 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 IP₆ 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 IP₆ 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, IP₆ 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 IP₆ has been a subject of some debates and controversy (21). The anticancer properties of IP₆ 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 IP₆ 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 IP₆. 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. IP₆ 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 IP₆ 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 IP₆ 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 IP₆ to prevent cancer was evaluated in vivo after administration of IP₆ in the drinking water. The exogenous 1% IP₆ 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% IP₆ in the drinking water was effective even when the treatment had begun 5 mo after carcinogen initiation. Compared to untreated rats, animals on IP₆ had 27% fewer tumors (25). A consistent, reproducible, and significant inhibition of mammary cancer by IP₆ 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). IP₆ was effective against prostate cancer as well. Studies demonstrated that continuous administration of 2% IP₆ 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 IP₆ 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 IP₆ significantly inhibited growth of rhabdomyosarcoma tumor xenografts (27), regressed liver cancer xenotransplants (28), and in murine fibro-

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
IP ₆	71.5	69	2.5±0.2	5.3
Ins	75.0	64	2.1±0.2*	2.5*
IP ₆ +Ins	76.3	51	1.8±0.1*	0.0*

**p*<0.05.

sarcoma FSA-1 model inhibited tumor growth 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.

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.

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 KS 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-

radiotherapy was reported (36). In a phase I 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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