Cancer Preventive and Therapeutic Properties of IP6: Efficacy and Mechanisms

Abstract

Recently, IP6 has received much attention for its role in cancer prevention, and control of experimental tumor growth and progression. A striking, 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 NFκB. Enhanced natural killer (NK) cell activity, suppressed tumor angiogenesis and antioxidant properties also contribute to cancer inhibition. Preliminary 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. A prospective, randomized, pilot clinical study showed that IP6 as an adjunctive therapy ameliorates the side effects and preserves quality of life in breast cancer patients receiving chemotherapy.

INTRODUCTION

Number of cancer cases are expected to increase due to growing of aging population. About 10.9 million new cases and 6.7 million cancer deaths occur worldwide every year. 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. In our attempts to reduce the burden of cancer, the practice of cancer prevention (chemoprevention) by use of non-toxic, naturally occurring compounds, as opposed to chemotherapy, is considered a better 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 (1). Extensive research over the past several decades has identified numerous dietary and botanical natural compounds that have chemopreventive potential.

One of the promising dietary phytochemicals with enormous chemopreventive and chemotherapeutic potential is inositol hexaphosphate (IP6 or Ino6P, or phytic acid). In this review, we discuss IP6 as a promising natural anticancer compound, its efficacy, molecular targets, and mechanisms of action, which may help the further design and conduct of preclinical and clinical trials.
IP₆ and myo-inositol, naturally occurring carbohydrates, are widely distributed among plants. IP₆ is found in concentrations from 0.4–6.0% in rice, corn, beans, whole-grain cereals, non-refined cereals derivatives, and all types of nuts (2, 3). IP₆ is also present in mammalian cells and tissues at concentrations that range between 0.01 to 1 mM (4–7). A six-carbon inositol ring represents the basic carbohydrate moiety in IP₆ and its lower phosphate derivatives (IP₁–₅). These various inositol phosphates (IPs) are physiologically interconvertible by complex metabolic cycles of phosphorylation and dephosphorylation by IPs kinases and phosphatases, and regulate vital cellular functions (8, 9).

**Anticancer Efficacy of IP₆**

The epidemiological studies have indicated that only fiber diet with high IP₆ 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 (9–11). This observation triggered and initiated a series of studies to investigate and determine the anticancer efficacy and potential of IP₆.

Numerous studies pioneered by Shamsuddin et al. have demonstrated that IP₆ has chemopreventive as well as therapeutic anticancer activity in a wide variety of tumors types, both in vitro and in vivo (9, 10, 12). In the first in vitro studies, the effectiveness of IP₆ to prevent cancer was evaluated after administration of IP₆ in the drinking water. The exogenous 1% IP₆ in drinking water 1 week before or 2 weeks after administration of azoxymethane inhibited the development of large intestinal cancer in Fisher 344 rats (13). In the same model, administration of 2% IP₆ in the drinking water was effective even when the treatment had begun 5 months after carcinogen initiation. Compared to untreated rats, animals on IP₆ had 27% fewer tumors (14). These findings pointed towards the possible therapeutic use of IP₆. Furthermore, IP₆ decreased the incidence of aberrant crypts often used as an intermediate biomarker for colon cancer (15, 16). 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-methyl-nitrosourea; the effect was seen on tumor incidence, tumor size, and tumor multiplicity (17–21). With regard to the in vivo efficacy of IP₆ against prostate cancer, recent 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 (22). Additionally, chemopreventive efficacy of IP₆ was observed against prostate tumor growth and progression in the Transgenic Adenocarcinoma Mouse Prostate (TRAMP) model (23). Peritumoral, intratumoral or intraperitoneal administration of IP₆ significantly inhibited growth of rhabdomyosarcoma tumor xenografts, regressed liver cancer xenotransplants, and in murine fibrosarcoma FSA-1 model inhibited tumor growth and prevented lung metastases (24–26). 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 (27). Gupta et al. also demonstrated prevention of skin carcinogenesis in a mouse carcinogenesis model where IP₆ caused a reduction in the number of skin tumor formation (28). Most recently, using UVB light known as a complete carcinogen, IP₆ has been shown to prevent UVB-induced tumor formation in mice (29).

**Biochemical Mechanisms Responsible for Anticancer Potential of IP₆**

Studies demonstrated the promising chemopreventive and anticancer potential of IP₆ have attracted considerable attention from cancer researchers as well as general public (9, 10). There has been progress in determining not only the anticancer efficacy and properties of IP₆ in various cancer models, but also in uncovering the molecular mechanisms of this action. The biochemistry behind the anticancer property of IP₆ has been extensively studied over past ten years. As illustrated and summarized in Figure 2, after rapid intake and dephosphorylation, IP₆ enters the pool of inositol phosphates and interacts with cellular processes involved with cancer. The chemopreventive and chemotherapeutic potential of IP₆ has been related to its antioxidant functions and the ability to block the activation of various carcinogen and/or to stimulate their detoxification, to immune-enhancing and antiinflammatory activities, suppression of proliferation and its influence on cell cycle and cell differentiation. The induction of apoptosis in various premalignant and cancerous cells can contribute to both cancer preventive and therapeutic potential of IP₆. Suppression of angiogenesis and blockade of metastatic processes of tumor progression, synergism with anticancer drugs and alleviation of chemotherapeutic resistance further indicate the chemotherapeutic potential of IP₆ (Figure 2).

**Antioxidant Capacity, Carcinogen Blocking and Detoxifying Activity**

The antioxidant role of IP₆ is widely recognized. This function of IP₆ occurs by chelation of Fe³⁺ and suppression of -OH formation (45) and by inhibiting xanthine oxidase (46). Thus, IP₆ can reduce carcinogen mediated active oxygen species and cell injury as well as inhibit free radical production in inflammation, radiation, etc. via its antioxidant function. Although IP₆ is known as a strong natural antioxidant, in vivo data of its antioxidant
effect are very limited. Its *in vivo* antioxidant action was recognized in different experimental models of myocardial reperfusion injury (47), pulmonary inflammation (48), and inflammation and ulcer induction (49). A protective role of IP₆ against lipid peroxidation in the colon associated with high level of iron was shown in rats (50), mice (51) and pigs (52) affecting glutathione peroxidase and catalase activity. IP₆ can modulate biochemical events linked to carcinogen blocking activities, modifying enzymes involved in metabolic activation of chemical carcinogens, such as phase I (53) and phase II detoxification enzymes (16, 51). The induction of glutathione S-transferase, the phase II carcinogen detoxifying enzyme, was also shown in azoxymethane-induced colon tumorigenesis (16). Interestingly, not only IP₆, but also inositol, its parent compound, has antioxidative properties by inhibiting xanthine oxidase and scavenging superoxide in *vitro* and *in vivo*, and preventing formation of ADP-iron-oxygen complexes that initiate lipid peroxidation (46, 54). The anticancer action of IP₆ may be further related to mineral binding ability; IP₆ by binding with Zn²⁺ can affect thymidine kinase activity, an enzyme essential for DNA synthesis. Similarly, excess iron, which may augment colorectal cancer formation, can be removed by IP₆ (50, 55).

**Immune Enhancing Activity**

IP₆ and inositol augment natural killer (NK) cell activity *in vitro* and normalize the carcinogen-induced depression of NK cell activity *in vivo* (56, 57). An inverse relationship between NK activity and tumor incidence has been shown in these models of colon carcinogenesis; an increased incidence is correlated with a decreased NK cell activity. The animals on IP₆ and inositol had a lower incidence of cancer and a concomitantly enhanced NK cell activity. But, those animals that received the combination of IP₆ and inositol had the highest NK activity and lowest tumor incidence (56). Neutrophils, which as

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**Figure 1.**

A. IP₆ inhibits colony formation of breast cancer cells. MCF-7 and MDA MB-231 cells were incubated in a humidified atmosphere of 5% CO₂ for 10 days. The growth medium contained various concentrations of IP₆ ranging from 0.1 to 2 mM. As a control, cells of the same density (10² cells/plate) were plated in dishes containing growth medium only. Cells were fixed in 4% formaldehyde for 15 min, stained with 0.5% crystal violet for 5 min and then rinsed with tap water. The ability of cells to form colonies decreased proportionally with increasing concentration of IP₆. B. IP₆ causes G0/G1 cell cycle arrest. MCF-7 cells were grown until 60–70% confluence and later synchronized by serum starvation (0.1% FCS in culture medium) for 48 h. The cells were then stimulated with medium with 10% FCS in the presence and absence of 2 mM or 5 mM IP₆ and collected after 24 h. For cell cycle analysis, cells were stained by propidium iodide using the Cellular DNA Flow Cytometric Analysis Kit by Roche Diagnostics Corp. Indianapolis, IN. As expected, IP₆ (both 2 mM and 5 mM) induced a G0/G1 cell cycle arrest. Based on these results shown in a representative histogram, 5 mM of IP₆ caused G0/G1 arrest in 66% percent of cells, as compared to 47% in controls (p=0.004).
a part of the body’s innate immune system form a first line of defense, are also affected by IP₆. IP₆ functions as a neutrophil priming agent and appears to up-regulate a number of diverse neutrophil functions (58).

Modulation of Cell Cycle Regulatory Machinery

Uncontrolled proliferation is a hallmark of malignant cells, and as discussed before, IP₆ reduces the cell proliferation rate of many different cell lines of different lineage and of both human and rodent origin [24,30–43]. IP₆ induces G₁ phase arrest and a significant decrease of the S phase of human cancer cell lines by modulations of Cyclins and cdks, up-regulation of p27Kip1 and p21WAF1/CIP1 and decrease in retinoblastoma (Rb) protein phosphorylation (33, 34, 59, 60). IP₆ induced up-regulation of p27Kip1 and a decrease in expression levels of hyperphosphorylated Rb (ppRb) in both estrogen receptor-positive (MCF-7) and negative (MDA-MB 231) cells. As a consequence, a markedly increased level of hypophosphorylated pRb form (pRb) was observed (33, 59).

Using specific inhibitors for PKCd (rottenin-R), MAPK (MEK/Erk) (U0126-U), and PI3K/Akt (LY294002-LY) we concluded that the effects of IP₆ on PKCd are responsible for the observed up-regulation of p27Kip1 (59). In leukemia cells, IP₆ appears to cause the accumulation of cells in the G₂M phase of the cell cycle; a cDNA microarray analysis showed up-regulation of p57 mRNA and a down-modulation of multiple genes involved in transcription and cell cycle regulation by IP₆ (42). Recently it was shown that p21 and p27, the Cip/Kip family proteins, are essential molecular targets of IP₆ for its anti-tumor efficacy against prostate cancer and are indispensable in causing growth arrest and apoptotic death of advanced prostate cancer DU145 cells by IP₆, both in vitro and in vivo (61).

Induction of Apoptosis and Cell Survival

Apoptosis is a hallmark of action of many anticancer drugs. It has been reported that IP₆ induces apoptosis in vivo (22, 61, 62) and in vitro in prostate (33, 34, 60), breast (59), cervical cancer (38), pancreas (37), glioblastoma (39), melanoma (40) and KS (Kaposi’s sarcoma) cell lines (63), involving cleavage of caspase 3, caspase 9 and poly ADP-ribose polymerase (PARP), an apoptotic substrate, in a time- and dose-dependent manner. A role of IP₆ in apoptosis is further suggested by findings that inositol hexaphosphate kinase-2 is a physiologic mediator of cell death (64). While IP₆ inhibited late apoptosis and necrosis in BIC-Barrett adenocarcinoma cell line, in SEG-1 cells it caused inhibition of both early and late apoptosis and necrosis (65). In malignant glioblastoma, T98G cells IP₆ down-regulated cell survival factors such as baculovirus inhibitor-of-apoptosis repeat containing-2 (BIRC-2) protein and telomerase, and up-regulated calpain and caspase 3 activity to promote apoptosis (39).

In human prostate carcinoma PC-3 cells, IP₆ has been shown to downregulate both constitutive and ligand-induced mitogenic and cell survival signaling, causing caspase-mediated apoptotic death (66). The induction of apoptosis by IP₆ was also shown in vivo. IP₆ feeding resulted in suppression of hormone-refractory human prostate tumor growth. Tumor xenografts of DU145 cells from IP₆-fed mice showed significantly (P < 0.001) decreased proliferating cell nuclear antigen (PCNA)-positive cells but increased apoptotic cells (22). Extending this work, Agarwal and his group generated DU145 cell variants with knockdown levels of cyclin-dependent ki-
nase inhibitors p21/Cip1 and p27/Kip1 proteins and provided evidence of the critical role of p21 and p27 in mediating the antiproliferative and proapoptotic effects of IP$_6$ in these p53-lacking human prostate cancer cells both in vitro and in vivo (61). Constitutive activation of phosphoinositide 3-kinase (PI3K)-Akt pathway transmits growth-regulatory signals that play a central role in promoting survival and proliferation. Targeting PI3K-Akt pathway, IP$_6$ was effective against invasive human prostate cancer PC-3 and C4-2B cells in culture and nude mouse xenografts (67). Increased cell apoptosis was also shown by IP$_6$ in wheat bran in azoxymethane-treated male Fischer 344 rats, a widely accepted model of colon carcinogenesis (62).

However, in conditions where apoptosis is harmful and damaging, IP$_6$ is able to prevent apoptosis in order to protect cells and tissues. Neuroprotective effect of IP$_6$ was shown in a cell culture model of Parkinson disease, preventing iron-induced apoptosis in immortalized rat mesencephalic/dopaminergic cells (68). A dual effect and ability of IP$_6$ to induce or prevent apoptosis in order to protect the cells and prevent disease was further shown against UVB-induced massive and excessive apoptosis in HaCaT cells and skin carcinogenesis in SKH1 hairless mice (69). Furthermore, in a TRAMP mouse model and in DU-145 human prostate cancers cells IP$_6$ inhibited telomerase activity, crucial for cells to gain immortality and cell survival (70).

**Inhibition of Angiogenesis**

Tumors depend on the formation of new blood vessels to support their growth and metastasis. Studies initiated by Judah Folkman have revealed the molecular mechanisms of tumor angiogenesis, and angiogenic signaling cascades seems to be a target of various anticancer drugs. Many tumors produce large amounts of vascular endothelial growth factor (VEGF), a cytokine that signals many tumors produce large amounts of vascular endothelial growth factor (VEGF), a cytokine that signals. Increased cell apoptosis was also shown by IP$_6$ in wheat bran in azoxymethane-treated male Fischer 344 rats, a widely accepted model of colon carcinogenesis (62).

**Anti-invasive and Anti-metastatic Effects**

The ability of tumor cells to invade through tumor-associated stroma, infiltrate normal tissue and metastasize are the central events in tumor progression. A significant reduction in the number of lung metastatic colonies by IP$_6$ was observed in a mouse metastatic tumor model using FSA-1 cells (26). Using highly invasive MDA-MB 231 human breast cancer cells, we have demonstrated that IP$_6$ inhibits metastasis in vitro through effects on cancer cell adhesion, migration and invasion (73, 74). Tumor cells emit substances known as matrix metalloproteinases (MMPs) that allow metastatic cells to breakdown the barriers in vessel wall and enter into blood circulation; IP$_6$ significantly inhibits secretion of matrix metalloproteinase-9 (MMP-9) from MDA-MB 231 cells (73). The inhibitory effect of MMPs was functionally confirmed, since it significantly reduced the invasion and invasive properties of cancer cell in vitro (73).

**Chemotherapy: Selectivity, Chemosensitization and Prevention of Drug Resistance**

A good anticancer agent needs to be selective and to discriminate between normal and tumor cells. IP$_6$ was shown to affect malignant cells only while sparing normal cells and tissues. When the fresh CD34$^+$ cells from bone marrow were treated with IP$_6$, an inhibition of the clonogenic growth was observed with leukemic progenitor cells, but not with normal bone marrow progenitor cells under the same conditions (42). In another type of experiment, IP$_6$ 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, but did not affect the ability of normal cells (peripheral blood mononuclear cells and T cell colony-forming cells) to form colonies in a semisolid methylcellulose medium (63).

Current cancer treatment recognizes the power of combination therapy aiming to increase efficacy, while alleviating unavoidable adverse effects associated with chemotherapy. The cancer chemopreventive phytochemicals used as adjuvants to standard chemotherapy has been shown to sensitize cancer cells to apoptosis or growth arrest while minimizing side effect. Another important aspect of cancer treatment is overcoming acquired drug resistance, what is currently a growing challenge in our attempts to reduce cancer and cancer-related deaths.

We have demonstrated that IP$_6$ acts synergistically with tamoxifen and doxorubicin, being particularly effective against estrogen receptor-negative and doxorubicin-resistant tumor cell lines, both conditions that are challenging to treat (75). These data are particularly important because tamoxifen is usually given as a chemopreventive agent in the post-treatment period and doxorubicin has enormous cardiotoxicity and its use is associated with doxorubicin resistance. Although tamoxifen has been extensively used for the prevention and therapy of breast cancer, almost all initial responders eventually develop resistance. Although the mechanisms by which tamoxifen resistance occurs remain unclear, it includes changes in the cellular signal transduction pathways (76). It seems that agents shown to up-regulate p27$^{kip1}$ (77) and inhibit extracellular signal regulated kinases (ERKs) and Akt (78) pathways are capable, at least in part, of preventing tamoxifen resistance in breast cancer cells. And indeed, our recent data show that IP$_6$ restores sensitivity to tamoxifen in MCF-7 cells expressing a constitutively active Akt, cells that are resistant to tamoxifen (not published).

**Modulation of Upstream Kinases and Transcription Factors**

Additional molecular targets for IP$_6$ are upstream kinases and transcription factors. Extensive preclinical studies conducted in cultured cells and experimental animals...
indicate that IP_6 could modulate abnormal turning on or switching off various upstream kinases and transcription factors.

Many plasma membrane-bond or cytosolic protein kinases, such as proline-directed serine/threonine kinases, tyrosine kinases and different isoforms protein kinase C (PKC), serve as important components of various intracellular signaling pathways and translate extracellular signals into biological responses. The family of mitogen-activated protein (MAP) kinase include several different sets of serine/threonine-specific protein kinases that regulate various cellular activities, such as proliferation, differentiation, gene expression and apoptosis. Representative members of this family are ERK, p38 MAP kinase and C-jun-N-terminal kinase (JNK). IP_6-induced downregulation of phosphorylation of MAP kinases has been associated with its antitumor promoting activity, inhibition of proliferation and induction of apoptosis (35, 59, 79). IP_6 also exerts effect on PKC-mediated signaling. It has been shown that PKC-epsilon is involved in the IP_6-induced exocytosis in pancreatic beta-cells (80). Our data indicate that the effects of IP_6 on PKC are responsible for the up-regulation of p27Kip1 and cell cycle arrest (59). Repression of telomerase activity and translocation of TERT from the nucleus in mouse and human prostate cancer cells via the deactivation of Akt and PKCα was shown by IP_6 (70). Phosphatidylinositol-3,4,5-triphosphate (PIP_3). Binding of PIP_3 to pleckstrin homology domain of Akt results in its recruitment to plasma membrane and activation. It was shown that the phosphorylation of Akt is abrogated with IP_6 in different cells and model systems (38, 43, 44, 59, 67, 70, 79).

Enhanced activation of major transcription factors such as nuclear factor κB (NFκB) and activator protein-1 (AP-1) contributes to tumorigenesis either by transactivating proinflammatory, antiapoptotic, and cell cycle regulatory genes or by transcriptional repression of apoptosis-inducing genes. IP_6 inhibits NFκB in different models, such as in UVB-induced skin carcinogenesis (29), in prostate carcinoma, where constitutive activation of mitogen-activated protein (MAP) kinase include several different sets of serine/threonine-specific protein kinases that regulate various cellular activities, such as proliferation, differentiation, gene expression and apoptosis. Representative members of this family are ERK, p38 MAP kinase and C-jun-N-terminal kinase (JNK). IP_6-induced downregulation of phosphorylation of MAP kinases has been associated with its antitumor promoting activity, inhibition of proliferation and induction of apoptosis (35, 59, 79). IP_6 also exerts effect on PKC-mediated signaling. It has been shown that PKC-epsilon is involved in the IP_6-induced exocytosis in pancreatic beta-cells (80). Our data indicate that the effects of IP_6 on PKC are responsible for the up-regulation of p27Kip1 and cell cycle arrest (59). Repression of telomerase activity and translocation of TERT from the nucleus in mouse and human prostate cancer cells via the deactivation of Akt and PKCα was shown by IP_6 (70). Phosphatidylinositol-3,4,5-triphosphate (PIP_3). Binding of PIP_3 to pleckstrin homology domain of Akt results in its recruitment to plasma membrane and activation. It was shown that the phosphorylation of Akt is abrogated with IP_6 in different cells and model systems (38, 43, 44, 59, 67, 70, 79).

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**IP_6, Inositol and Lower Inositol Phosphates**

It seems that the anticancer activity of IP_6 depends primarily on its rapid dephosphorylation and that it is mediated via lower phosphorylated forms. Thus, the conversion of IP_6 to lower inositol phosphates is essential for its anticancer activity, as proposed nearly 20 years ago (9, 10).

Its parent compound, myo-inositol itself was also shown to have modest anticancer activity. It inhibited colon, mammary, soft tissue and lung tumor formation (9, 10). More importantly, it was demonstrated that inositol potentiates both the antiproliferative and antineoplastic effects of IP_6 in vivo (9, 10) and in vitro (83). Synergistic cancer inhibition by IP_6 when combined with inositol was observed in colon cancer (84) and mammary cancer studies (18). Similar results were seen in the metastatic lung cancer model (26). IP_6 and inositol had a lower incidence of cancer and a concomitantly enhanced NK cell activity. Not only the combination of IP_6 and inositol was significantly better in different cancers than was either one alone, but it also consistently reduced all tumor growth parameters. Additionally, as discussed before, animals that received the combination of IP_6 and inositol had not only the lowest tumor incidence, but highest NK activity (56). Thus, it was obvious, that for clinical trials, the combination of IP_6 and inositol should be considered for optimal efficacy. And indeed, inositol and IP_6 in combination as an adjunctive therapy in breast cancer patients receiving chemotherapy, ameliorated the side effects of chemotherapy and preserved quality of life (85).

However, despite substantial progress in the understanding of the molecular basis and molecular targets of its anticarcinogenic activity, there have been very few clinical studies with IP_6. Because currently available preclinical, mechanistic data and encouraging pilot data with humans suggest that IP_6 might be a promising candidate for the molecular target-based cancer prevention and adjuvant therapy, more controlled clinical trials are expected.

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Anticancer Effect of IP₆

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