PHYTIC ACID (MYO-INOSITOL HEXAPHOSPHATE)- A PROMISING PHARMACEUTICAL AGENT: A REVIEW

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ABSTRACT

Phytic acid (myo-inositol hexaphosphate) has gained much attention among researchers for its therapeutic value. This review focuses on pharmacological activities of phytic acid, which have been demonstrated by pre-clinical studies. Anticarcinogenic, antioxidant, anti-diabetic, hypolipidemic, anti-angiogenic, and immunomodulation are the most extensively studied pharmacological activities of phytic acid. In addition to these, phytic acid and its derivatives also possess enzyme inhibitory activities against few key enzymes such as 5-alpha reductase, aldose reductase, cyclooxygenase, lipase, matrix metalloproteinase-2 & 9, pepsin, polyphenol oxidase, protease, β-secretase, tyrosinase, and xanthine oxidase were emphasized. The profound pharmacological activities of phytic acid have proven to be a good therapeutic agent and could be employed in preventing as well as treating such diseases.

Keywords: Phytic acid (myo-inositol hexaphosphate), Anticarcinogenic, Hypoallergenic, 5-alpha reductase (type-2), β-Secretase (type-1).

INTRODUCTION

Phytic acid is a unique negatively charged molecule in a wide pH range and having 12 replaceable protons in it [8]. These characteristic chemical natures allow the formation of metal complexes with polyvalent metals and having 12 replaceable protons in it [8]. Phytases are the only enzymes, which capable of hydrolyzing phytic acid into myo-inositol and inositol phosphates [1]. Phytic acid has been well known as an anti-nutrient agent. Sodium phytate (sodium salt of phytic acid) has been reported to inhibit Escherichia coli growth in raw or cooked meats including beef, chicken, and pork [10]. In other study, phytic acid from rice bran has been reported to inhibit the growth of both Salmonella typhimurium and E. coli [11].

Antidiabetic activity of phytic acid

Yoon et al. [12] reported that phytate-enriched diets result in low blood glucose (glycemia) levels in humans. Later two reports shown that phytate regulates insulin secretion through inhibiting the serine/threonine-specific protein phosphatase activity, which, in turn, opens intracellular calcium channels required for insulin release [13,14]. Kuppusamy et al. [15] reported that phytic acid has been shown to inhibit both α-glucosidase and α-amylase inhibition in dose-dependent manner (in vitro) and also shown to possess antidiabetic activity against streptozotocin-nicotinamide induced diabetes (type 2) in rats. In other study, phytic acid extracted from Kenyan local vegetables and grains have been shown to possess both α-glucosidase and α-amylase inhibition [16].

Anti-inflammatory activity of phytic acid

Recent investigations suggest that bioactive natural dietary products play a key role in the alleviation and control of inflammation-related diseases [17,18]. Phytic acid has been reported to exhibit anti-inflammatory activity against carrageenan induced paw edema in experimental rats [19].

Antineoplastic/Anticarcinogenic activity of phytic acid

Phytic acid has been shown to exhibit anticarcinogenic activity on a wide variety of tumors [20,21], which includes Barrett’s adenocarcinoma [22], breast cancer [23,24,25], glioblastoma [26], laryngeal carcinoma [27], oral cavity squamous cell carcinoma [28], pancreatic cancer [29], prostate cancer [30], and skin cancer [31]. Key mechanism actions of phytic acid against tumors have been shown in Fig. 2.
Phytic acid has been reported to inhibit the proliferation of human immunodeficiency virus (HIV) under in vitro condition [38]. In other study, anti-HIV1 activity of both myo-inositol hexaphosphoric acid (IP6) and myo-inositol hexafluorosulfate (IS6) has been reported in detail [39].

Phytic acid has been reported to possess cariostatic activity using in vivo studies [40-42]. Kaufman and Kleinberg [43] reported that the cariostatic action of phytic acid and its derivatives have been attributed mainly, due to its ability to lower solubilizes of calcium, fluoride, and phosphate as they major components of tooth enamel. Phytic acid has been tested in toothpaste as a tool for preventing tooth plaque formation [44].

Phytic acid has been reported to inhibit the enzymes such as cyclooxygenase-2 (COX-2), human neutrophil elastase, lipoxygenase, microsomal prostaglandin E synthase-2, and tyrosinase using in silico approach [55].

Vucenik et al. [36] reported that phytic acid inhibits human platelet aggregation in a dose-dependent manner under in vitro condition. 5 years later, phytic acid has been reported to possess anti-angiogenic activity against both in vitro and in vivo induced angiogenesis [37].

Ulcer is a common GI disorder. Ulcers are lesions on the srfuace of skin or a mucous membrane clinically characterized by a superficial loss of tissue. Phytic acid has been reported to possess anti-ulcer activity against ibuprofen, ethanol, and cold stress-induced ulcers in experimental rats [19].

Antioxidant activity of phytic acid
Phytic acid has been reported to inhibit the hydroxyl radical formation [32,33] and lipid peroxidation activities [1,34]. In other study, phytic acid extracted from Kenyan local vegetables and grains have been shown to possess 2,2-diphenylpicrylhydrazyl radical scavenging activity [16]. Furthermore, phytic acid has been reported to exhibit antioxidant activity [35].

Antiplatelet and anti-angiogenic activity of phytic acid
Phytic acid has been reported to inhibit the calcium oxalate crystal formation, which, in turn, prevents approximately 80% of all of these stones. Phytic acid has been shown to possess neuroprotective activity against pathologies of neurodegenerative disorders such as amyotrophic lateral sclerosis, Alzheimer’s disease, and Parkinson’s disease. Phytic acid has been shown to possess anti-angiogenic activity against both in vitro and in vivo induced angiogenesis [37].

Hemolytic activity of phytic acid
Hemolytic activity of any substances or compounds is a measure of general cytotoxicity toward normal healthy cells. Phytic acid has not shown any hemolysis at ≥1 mM concentration level, however significantly increases the percentage of annexin V-binding erythrocytes [45].

Hypoallergenic activity of phytic acid
Peanut allergy is one of the most common food allergies among the schoolchildren in United States of America (USA) and United Kingdom. Phytic acid has been shown to possess hypoallergenic activity against peanut allergens [46].

Immunomodulatory activity of phytic acid
Phytic acid has been reported to inhibit the calcium oxalate crystal formation, which, in turn, prevents renal stone formation [53,54]. Phytic acid has been shown to possess immunomodulatory activity against bacterial lipopolysaccharide-induced human mononuclear cells [50].

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Neuroprotective activity of phytic acid
Alterations in antioxidant status in nervous tissue have been implicated in pathologies of neurodegenerative disorders such as amyotrophic lateral sclerosis, Alzheimer’s disease, and Parkinson’s disease. Phytic acid has been shown to possess neuroprotective activity against Parkinson’s disease [51,52].

Renal stone disease is an ailment affecting human beings for many centuries. A majority of renal stones are calcium stones, which account approximately 80% of all of these stones. Phytic acid has been reported to inhibit the calcium oxalate crystal formation, which, in turn, prevents renal stone formation [53,54].

ENZYME INHIBITORY ACTIVITIES OF PHYTIC ACID AND ITS DERIVATIVES
Few reported enzyme inhibitory activities of phytic acid and its derivatives have been shown in Fig. 3 and discussed below in detail. Recently, phytic acid has been reported to inhibit the enzymes such as cyclooxygenase-2 (COX-2), human neutrophil elastase, lipoxigenase, microsomal prostaglandin E synthase-2, and tyrosinase using in silico approach [55].

Phytic acid as 5-alpha-reductase inhibitor
5-alpha-reductase is an enzyme which catalyzes conversion of testosterone to dihydrotestosterone. In men elevated enzyme activity is associated with benign prostatic hypertrophy and premature baldness.
Phytic acid has been reported to inhibit the 5-alpha-reductase (type 2) activity using in silico study, which could prevent prostate cancer and hair fall [56].

**Phytic acid derivative (PP-56) as aldose reductase inhibitor**

Aldose reductase is the key regulatory enzyme in the polyol pathway, which catalyzes glucose to sorbitol. Elevated enzyme has been implicated in the development of diabetic retinopathy, leading cause of blindness. Phytic acid derivative, namely D-myoinositol 1,2,6-trisphosphate (PP-56) has been reported to modulate the aldose reductase activity against streptozotocin-induced diabetic rats, which could prevent diabetic cataract formation [57].

**Phytic acid as COX-2 inhibitor**

COX is the key regulatory enzyme which catalyzes the conversion of arachidonic acid to prostaglandins, where cyclooxygenase-2 is mainly an inflammatory, inducible enzyme. Phytic acid has been reported to suppress the COX-2 expression in azazyme methane-induced colon cancer cells [59].

**Myo-inositol phosphate ester (hydrolyzed product of phytic acid) as lipase inhibitor**

Lipase is an enzyme which catalyzes the hydrolysis of fats. Elevated enzyme activity is associated with inflammatory or neoplastic disease of the pancreas. Myo-inositol phosphate ester has been reported to inhibit the lipase activity [59].

**Phytic acid as matrix metalloproteinase-2 & 9 (MMP-2 & 9) inhibitor**

MMP’s are a group of zinc-dependent endopeptidase which capable of degrading extracellular matrix and are involved in remodelling and turnover of dermis [18]. Phytic acid has been reported to modulate the MMP-2 gene expression in colon cancer cells [60]. In other study, phytic acid has been reported to modulate both the MMP-2 and 9 gene expressions against phorbol-12-myristate 13-acetate stimulated colon cancer cells [61].

**Phytic acid as pepsin inhibitor**

Pepsin is a digestive enzyme which capable of degrading food proteins into peptides. Pepsin is one of the main causes of mucosal damage during laryngopharyngeal reflux. Phytic acid has been reported to inhibit the pepsin activity [62].

**Phytic acid as polyphenol oxidase (PPO) inhibitor**

PPO is copper-containing enzyme having both catecholase and cresolase activity. It plays defence role against pathogens and responsible for browning reactions. Phytic acid has been reported to inhibit the PPO activity, which could prevent browning of apple [63].

**Phytic acid as protease inhibitor**

Protease is a digestive enzyme, which hydrolysis protein into shorter fragments. It occurs in all organisms from pmkaryotes to eukaryotes to viruses. Phytic acid has been reported to inhibit the protease activity in fish [64].

**Phytic acid as β-Secretase (BACE-1) inhibitor**

BACE-1 is a rate-limiting enzyme involved in production and deposition of amyloid-β peptide (Aβ). It is now emerging as marker enzyme for the treatment of Alzheimer’s disease. Phytic acid has been reported to inhibit the BACE-1 activity, which could prevent Aβ accumulation [65].

**Phytic acid as tyrosinase inhibitor**

Tyrosinase is the main regulatory enzyme in melanogenesis process particularly in the first two steps such as (i) tyrosine hydroxylation to 3, 4-dihydroxyphenylalanine (DOPA) and (ii) the oxidation of DOPA to dopaquinone. Graf et al. [4] have reported phytic acid, as inhibitor of mushroom tyrosinase. In other study, phytic acid containing formulation (Amelan M) has been shown to reduce pigmentation in melasma patients [66].

Phytic acid as xanthine oxidase (XO) inhibitor

XO is the key regulatory enzyme in purine metabolism. It catalyzes the oxidation of hypoxanthine to xanthine and then to uric acid. Phytic acid has been reported to inhibit the XO activity which could prevent gout [67].

**APPLICATIONS OF PHYTIC ACID**

Phytic acid has been reported for five major applications (Fig. 4) such as adsorption and corrosion inhibition, cosmetic, dental care, industrial, and medical applications [68].

Among these applications, food industry applications of phytic acid have been reported as predominant one, where it has been added to alcoholic beverages, bread, canned seafoods, cheese, fish meal pastes, fruits, juices, meats, miso, noodles, soysauce, and vegetables to prevent colour and as well as to prolong shelf life of products. In 1997, Food and Drug Administration of the USA regarded sodium phytate as generally recognized as safe status for using the same as preservative in baked foodstuffs [1]. Second medical applications of phytic acid have been gaining importance among researchers, due to its potential therapeutic value [68,69].

**CONCLUSION**

Phytic acid has shown a number of pharmacological activities such as antibacterial, anti-diabetic, anti-inflammatory, anticarcinogenic, antioxidant, anti-angiogenic, antiulcer, antiviral, hypoallergenic, hypolipidemic, immunomodulation, and neuroprotection. In addition to these, phytic acid and its derivatives also posses enzyme inhibitory activities against few key enzymes such as 5-alpha-reductase (type-2), aldose reductase, cyclooxygenase (type-2), lipase, MMP-2 and 9, pepsin, PPO, protease, BACE-1 (type-1), tyrosinase, and XO. The profound pharmacological properties have paved way for various applications

![Fig. 3: Represents the enzyme inhibitory activities of phytic acid and its derivatives](image3)

![Fig. 4: Represents various applications of phytic acid](image4)
of phytic acid. Encouraging pre-clinical studies suggest that phytic acid as a promising pharmaceutical agent for prevention and treatment of various diseases; however, more controlled clinical trials are required to demonstrate its novel therapeutic potential.

AUTHORS’ CONTRIBUTIONS
RN (first author), who wrote the manuscript and submitted the same as part of PDF programme. NME (research supervisor), who had added value to it. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST
The authors have declared no conflicts of interest.

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