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Investigation of the medicinal significance of phytic acid as an indispensable anti-nutrient in diseases

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SUMMARY

Background & aims: Inadequate knowledge and intake of a balance diet is a contributing factor of micronutrient deficiencies in developing countries. Phytic acid contributes in inhibiting the bioavailability of some micronutrients. In spite of the anti-nutritional effect of phytic acid, it is known to exhibit some medicinal effects. This study investigated the medicinal significance of phytic acid as an indispensable anti-nutrient in diseases.
Methods: Relevant scientific literatures from the major databases such as Pubmed, Medline and Google Scholar. The keywords searched and reviewed in this study were phytic acid, anti-nutrients, minerals, diseases and plants.
Results: The published peer reviewed literatures searched showed that phytic acid, though an anti-nutrient, plays an indispensable role directly or indirectly in several disease conditions. It exhibits antioxidant function, a property that qualifies it to possess multiple medicinal values like: anti-diabetic, anticancer, anti-inflammatory properties to mention a few. Its chelating property

Abbreviations: AAS, atomic absorption spectrophotometer; Aβ, amyloid-β-peptide; AD, alzheimer's disease; AGEs, advanced glycation end product; AFB_1: aflatoxin B_1, AIDS, acquired immunodeficiency syndrome; ALP, alkaline phosphatise; ALT, alanine amino transferase; ART, antiretroviral therapy; BC, breast cancer; CC, colorectal cancer; DM, diabetes mellitus; DMBA, 7,12-dimethylbenz α-anthracene; GIT, gastrointestinal tract; HIV, human immunodeficiency virus; HMG-CoA reductase: β-Hydroxyl β-methylglutaryl-CoA reductase, ISO; isoproterenol, MI; myocardial infarction, MPP^+: 1-methyl-4-phenylpyridinium. PA; phytic acid, PC; prostate cancer, PD; parkinson's disease, PO_4^{3-}: phosphate; RCT, randomized control trial; RD, Rhabdomyosarcoma; TC, total cholesterol; TSA, total sialic acid; T2DM, type-2-diabetes mellitus; TG, triacylglycerol; UVB, ultraviolet B-rays.

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affects the absorption and toxicities associated with essential and nonessential heavy metals, a scenario that could prevent neurodegenerative diseases such as Alzheimer's, Parkinson diseases and other related diseases.

Conclusion: The medicinal values of phytic acid outweighed its negative impact. Hence, there is critical need for developing countries to improve on the dietary pattern of its people in addition to nutrition education.

Contents

1. Introduction

Nutrients are required by humans for cellular activities, and overall, physiological functions. Though the primary reason for eating food is to quench hunger, the quest to eat good and nutritious food is strongly wished by humans at all times. Food is considered good and nutritious when it is conducive to maintaining health, preventing diseases and providing adequate amount of nutrients in composition. Aside nutrients in food matrix, other metabolite (including secondary metabolites that exhibit anti-nutritional properties) are also present, although the degree varies depending on the type of food and the method of preparation. The presence of the anti-nutrients such as phytic acid in food affects

nutrients absorption and bioavailability. Anti-nutrients are natural or synthetic molecule that interferes with nutrients absorption and bioavailability. Phytic acid (PA) amongst other anti-nutrients exhibits such properties of interfering with nutrients bioavailability. It affects intestinal absorption and bioavailability of some vital minerals like calcium, magnesium, iron and zinc needed for the basic chemistry of life [1–3].

Phytic acid (PA) is a unique natural substance found in plant seeds. It is a major form of phosphorus found in edible plants such as grains, nuts and legumes [4]. It is found only in plant derived food and exist predominantly in its salt form: phosphate ester of inositol or inositol polyphosphate where it accounts for about 60–70% total plant phosphorus [5]. At physiological pH the phosphate is partially ionized. The resulting anions are colourless species that has significant nutritional role as the principal storage form of phosphorus in plant tissues. The composition of PA varies amongst plants and within plant species [6]. The variability of PA composition depends on certain factors like: growing conditions, harvesting and processing techniques and age of the food grains harvested etc [7].

PA was first perceived as a small round particle in the seeds of a number of plants [3]. It was later found that the small particles were free of starch, proteins, and lipids, but contains some elements like: phosphorous, magnesium and calcium. In 1914, the molecular structure of PA was presented as myo-inositol-1,2,3,4,5,6-hexakisphosphate (Fig. 1). PA has received considerable attention since its discovery due to its effects on mineral absorption. It has a very strong binding affinity to some dietary minerals. It impairs the absorption of Iron, Zinc, and calcium and may promote mineral deficiencies, hence it is regarded as anti-nutrient [3].

There has been much emphasis placed on the anti-nutritional attributes of PA, which could be reduced by domestication processes. However, reduction of PA is nutritionally favorable, though it may limit or alter its medicinal importance, as its presence in food(s) plays multifarious role in maintaining and promoting health integrity. To this effect, this review provides an overview of PA in health and diseases. The sources of PA cannot be overemphasized, as almost every plant contains PA (Table 1). Infact every effort being made in reducing the PA in edible plants for nutritional purposes, via biofortification, so as to generate plants low in PA, may pose serious threat and steered conflict of interest for plant growth and development. However, genetic modification of some plant based foods is necessary, especially in frequently consumed foods high in PA, and low in micronutrients. For instance, rice, a common and one of the most frequently consumed staple food especially in developing countries contain high PA, as evident in the work of Norhaizan and Norfaizadatu [8]. They revealed that Malaysian rice (Brand A-F) contained PA ranging from 36.40 to 91.52 mg/100 g, Indian rice (66.40 mg/100 g) etc. while the micronutrients were extremely low.

The estimated intakes of PA in the developing countries are far higher than the intake in the developed countries [31]. For example, Ghana and Nigeria have estimated intake of PA as 1800 and 2100 mg/day respectively as compared to 200 and 750 mg/day reported for UK and USA respectively

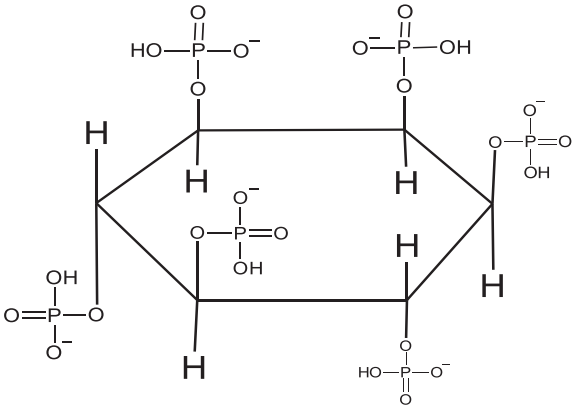

Fig. 1. Structure of phytic acid.

Table 1
Phytic Acid composition (g/100 g) of some plants based food.

Plant name		Composition (g/100 g)	Reference
Lupine	*Lupinus polyphyllus*	1.38 g/100 g	[9].
Bambara groundnut	*Vigna subterranean*	0.294 g/100 g, 1.1 g/100 g	[10,11]
Pigeon pea	*Cajanus cajan*	0.220 g/100 g	[10]
Cowpea	*Vigna unguiculata*	0.42 g/100 g	[9]
Lentils	*Lens culinaris*	0.86 g/100 g	[12]
Cherry tomato	*Lycopersicon esculentum*	0.11282 g/100 g	[13]
Citrus fruits juice	*Citrus maxima*	0.086 g/100 g	[14]
African yambean	*Sphenostylis stenocarpa*	0.429 g/100 g	[15]
Pumpkin leaf	*Telfiaria occidentalis*	0.02835–0.02843 g/100 g	[16]
Potatoe	*Solanum tuberosum*	0.111–0.269 g/100 g	[17]
Cocoyam	*Colocasia esculenta*	0.08748 g/100 g	[18]
Sickle pod green leaf	*Cassia obtusifolia*	0.64913 g/100 g	[19]
Maize (8 varieties)	*Zea mays*	0.635–0.947 g/100 g	[20]
Bitter leaf	*Vernomia anydalira*	0.00000811 g/g	[21]
Pearl millet	*Pennisetum glaucum*	0.050 g/100 g	[22]
Pearl millet flour (13 varieties)	*Pennisetum glaucum*	0.577–0.620 g/100 g	[23]
Wheat	*Triticum aestivum*	0.440 g/100 g	[24]
Oats	*Avena sativa*	1.01 g/100 g	[9]
Brown rice (5 varieties)	*Oryza sativa*	1.24–1.71 g/100 g	[25]
Rice (10 varieties)	*Oryza sativa*	0.00405–0.00665 g/g	[26]
Ginger (white and yellow)	*Zingiber officinale*	0.02018 g/100 g, 0.02888 g/100 g	[27]
Cassava flour (2 varieties)	*Manihot esculenta*	0.3395 g/100 g, 0.45130 g/100 g	[28]
Yam tubers (7 cultivers)	*Dioscorea alata*	0.0586–0.198 g/100 g	[29]
White guinea yam	*Dioscorea rotundata*	0.00785 g/100 g	[30]

[31]. Moreso, the PA in foods is expected to increase due to climate change, and may further deplete some essential minerals in rice grain [32]. As such, micronutrient deficiencies are also expected to increase in the developing countries. For this reason, there is need for people from this region (developing countries) to improve on their dietary pattern in addition to nutrition education. This is because micronutrient deficiencies sometimes ensue due to inadequate knowledge of consuming the right food in appropriate proportion.

The practice of enriching soil fertility via chemicals containing phosphorous to improve the growth of plants may contribute in the increased composition of PA in plants. Coulibaly et al. [7], reported that when phosphorous from exogenous source(s) such as fertilizer is applied to soils, plant roots pick it up mainly as phosphate (PO_4^{3-}). The PO_4^{3-} is further esterified through the hydroxyl group to the carbon chain (C–O–P) as a single phosphate ester or attached to another phosphate, by an energy rich pyrophosphate bond [11]. This implies that fertilizer application to soil may further strengthen the plant anti-nutritional traits. So, the use of fertilizer (NPK fertilizer) "amongst other factors" to enrich soil nutrients may in part contributes to micronutrient deficiencies, and subsequently "hidden hunger" a nutritional problem peculiar to underdeveloped and developing countries.

2. Effects of phytic acid on essential mineral elements

PA impairs the absorption of iron, zinc, iron and calcium and may promote mineral deficiencies [33]. It has the ability to bind to two or more mineral at a time. This is due to the presence of six negatively charged phosphate groups in PA that enables it form stable complexes with two or more positively charged metals (Fig. 2), notably minerals (Ca, Zn, and Fe) of nutritional importance [34] (see Fig. 3 and fig. 4).

For PA to elicit mineral deficiency depends on PA mineral molar ratio. The molar ratio between PA and Ca, Fe and Zn may provide a useful tool to estimate the mineral bioavailability [35]. The molar ratio PA:Zn, PA:Ca, PA: Fe can be calculated following Eq (1) below [36]. The calculated PA; Mineral molar ratios are compared to the critical levels (Table 2) [37]. Levels below critical levels suggest no effect on

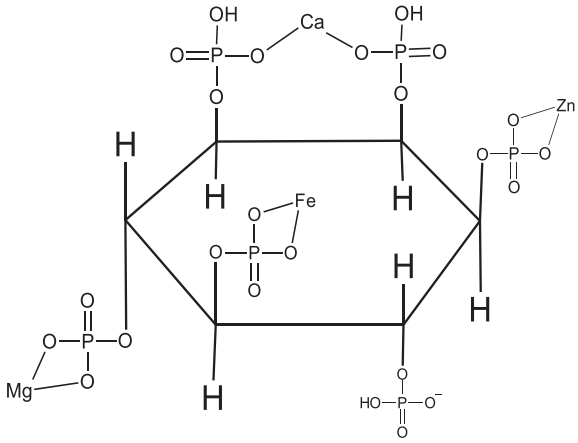

Fig. 2. Structure of phytic acid–metals complex calcium.

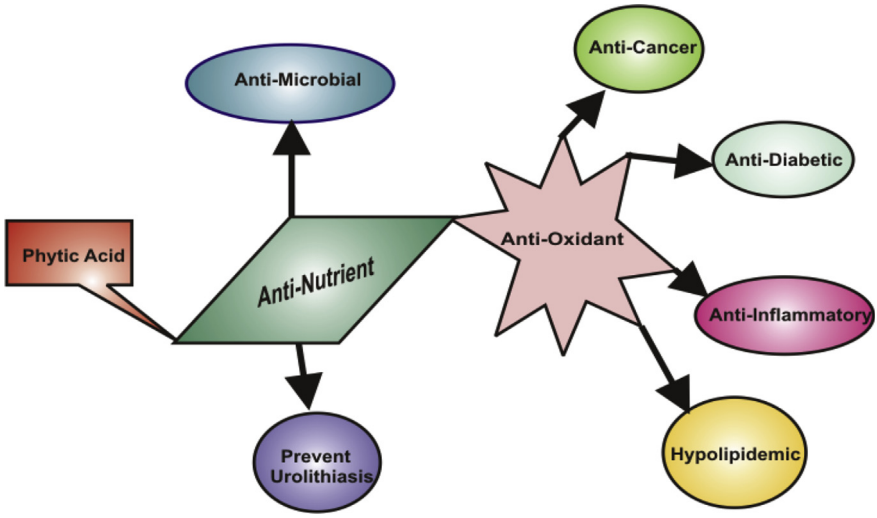

Fig. 3. Schematic representation of some medicinal properties of phytic acid.

mineral absorption and bioavailability, while levels above the critical levels suggest PA may elicit mineral deficiencies.

$$\boldsymbol{PA : Min\ molar\ ratio} = \frac{\boldsymbol{PA/MwPA}}{\boldsymbol{Min/MwMin}} \tag{1}$$

PA: Calculated PA content in the sample.
MwPA: PA molecular weight (600Da).
Min: mineral content in the sample.
MwMin: molecular weight of mineral (Zn – 65, Fe – 56, Ca - 40).

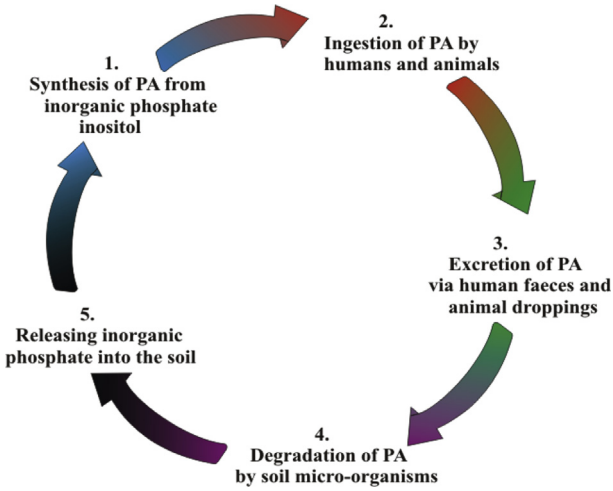

Fig. 4. Schematic representation of phytic acid–phyate cycle.

Table 2
Phytate to mineral molar ratio.

Molar ratio	Critical level
[PA]/[Ca]	0.2
[PA]/[Fe]	0.4
[PA]/[Zn]	10
[Ca][PA]/[Zn]	0.5

2.1. Calcium

Calcium (Ca) is one of the essential nutrients affected by PA. The binding ability of PA to Ca in different food samples using atomic absorption spectrophotometer (AAS) and capillary electrophoresis revealed that it is pH dependent [38]. Moreso, the amount of PA and Ca (PA/Ca ratio) sometimes define their binding feasibility. For instance, foods low in PA may have little or no influence on calcium, especially in a calcium rich food. This was evident in study by Tamim et al. [39], that calcium inclusion in low calcium diet mitigates PA binding efficacy.

The negative influence of PA on Ca may be nutritionally unfavorable, but have some health benefits. It prevents kidney stone formation and subsequently kidney stone disease (urolithiasis) [40]. Most likely, PA has more affinity for Ca than oxalate (an antinutrient), so its presence prevents the crystallization of Ca and oxalate, which has been shown to contribute to kidney stone formation [41]. A study by Israr et al., affirmed that higher ratio of PA to Ca is sufficient enough to prevent Oxalate–Ca complex, and subsequently urolithiasis [42].

2.2. Magnesium

Magnesium (Mg) is an element of biological importance. More than three hundred (>300) metabolic processes depends on Mg as a co-factor, especially processes involving macromolecules (carbohydrate, protein and lipid metabolism etc) [43]. The negative effect of PA on bioavailability of Mg is not in any way exceptional. Inclusion of PA to foods has been shown to decrease Mg absorption in humans [44], and this may affect several of its metabolic functions. Although, the influence of PA on Mg absorption is determined by the quantity of Mg [45]. Study revealed that marginal content of Mg in a diet

is affected by the presence of PA [46]. Suggesting that PA may display antinutritional traits, if the nutrients are not adequate enough.

[37].

2.3. Iron

Iron (Fe): The negative effect of PA on Fe bioavailability has similar characteristics as desferrioxamine. Desferrioxamine is often used to physiologically eliminate Fe beyond physiologic need [47]. Alteration in Fe bioavailability due to PA may contribute to Fe deficiency anemia, "a very serious nutritional challenge globally". It is characterized by a defect in hemoglobin synthesis. Approximately two billion people are suffering from anemia [48,49]. Causes of anemia are multifactorial, but the major contributor is Fe deficiency [50]. Fe from plant sources are poorly absorbed, which maybe complicated further in the presence of antinutirients (including PA) [51]. However, bio-fortification of plant based foods with Fe, and consumption of vitamin C rich foods, enhances the bioavailability of non heme Fe [52]. Chelating of Fe by PA has beneficial prominence, especially in a state of oxidative stress. At physiologic pH, PA complexes with Fe [53] and may counteract Fe induced lipid peroxidation. This was evident in studies by Grases et al. [54], that consumption of food(s) containing 1% PA depletes brain Fe status of albino rats. Depleting brain Fe status would in no doubt protects and maintain the brain integrity.

2.4. Zinc

Zinc (Zn): Amongst the essential minerals chelated by PA, Zn exhibits the most stable complex with PA. Thus, it is probably the most affected mineral, in terms of bioavailability [55]. A study also revealed that one third of the world population is affected by Zn deficiency [56], and PA may in part contributes in Zn deficiency.

3. Therapeutic effects of phytic acid

The anti-nutritional property of PA is a "unique one" in that it is responsible for most of its medicinal values. Till date, PA is still perceived as threat to nutrient bioavailability. However, reduction of PA in foods by simple, convenient and inexpensive techniques such as soaking, germination, malting, and fermentation have been shown to enhance nutrient bioavailability [57,58]. Most food sources containing PA are usually not consumed in their raw form. They undergo simple method of domestication (like soaking and cooking) before consumption. So, the PA contents in the unprocessed foods may not in any way reflect the actual contents being consumed. As such, more emphasis should be on the assessment of PA in ready to use foods, rather than its contents in raw foods. Karkle and Beleia [36] examined the effect of soaking and cooking on PA, mineral composition and texture of soybean. Their finding revealed that soaking promotes PA reduction, thereby enhancing nutrients bioavailability in soybean. This implies that soaking of food items containing PA is necessary especially for people with marginal mineral intake. Their findings also revealed that cooking did not promote further reduction in PA. Although, the reason for this remains obscure, however, it has been reported that cooking (solar and pressure cooking) significantly reduces PA content in cowpea cultivars, and that soaking prior to cooking was more effective [59].

Aside domestication processes, inclusion of phytase play vital role in the reduction of PA and enhancement of mineral bioavailability [60]. The phytase (myo-inositol hexakisphosphate phosphohydrolase) also catalyzes hydrolysis of PA. Inclusion of phytase is necessary, especially in phytase deficient animals (monogastric animals). In the case of humans, the vegetarians and vegans, sometimes possess gut-inhabited microbes. These microbes produce phytases [61] capable of detaching phosphorus (one at a time) in PA to its derivatives or catabolites (Ip5, Ip4, Ip3 and so on), and inositol (metabolites of glucose). So, it is difficult for PA to elicit its anti-nutritional role in vegetarians and in vegans. In essence, the composition of the diets sometimes determines the metabolic fate of PA.

4. Antioxidant role of phytic acid

Antioxidants are natural or synthetic molecules that inhibit oxidation, and subsequently prevent damage to membrane structure [62]. Damage to the membrane architecture is mostly caused by bioaccumulation of free radicals, generated especially during impaired oxygen metabolism. Oxygen supply is necessary for living organism, preferentially for the release of energy. However, certain exogenous factors, such as cigarette smoking, exposure to toxic substances. and to a lesser extent, endogenous factors such as respiratory burst, interferes with oxygen metabolism [63]. Such metabolic interruption heightens free radical formation. The free radicals produced have the tendency of progressing in series of chain reaction, a scenario that could lead to membrane degradation [63].

Phytic acid, being a natural plant antioxidant possesses the ability to terminate the series of chain reaction [64]. It inhibits iron catalyzed hydroxyl radical (OH^-) formation [65]. For instance, a study affirmed that PA inhibits linoleic acid auto-oxidation and Fe (II)/ascorbate induced lipid peroxidation in human colonic epithelial cells [66]. It also act as a potent inhibitor of Fe catalyzed free radical formation [67]. PA chelates free Fe and inhibits its co-ordination site. Similarly, Brindha and Rajasekapandiyan [68] examined the role of PA on mitochondria lipid peroxide and antioxidant status of male Wister albino rats, subcutaneously injected with 85 mg/kg isoproterenol (ISO) (a medication used for the treatment of bradycardia (slow heart beat), heart blocks to mention a few). Injection of ISO is capable of generating superoxide and hydroxyl radical. Their findings revealed a decrease in the activities of catalase, glutathione peroxide, and glutathione transferase, which subsequently increases in activities upon treatment with PA (25 and 50 mg/kg). PA also exhibits protective efficacy against methotrexate induced acute liver injury via attenuating oxidative stress [69]. Methotrexate is effectively and extensively used in treating malignancies, but its use is limited because of its dose dependent hepatic injury [70].

Aside protective role of PA against oxidative stress induced by chemical agents, it can also mitigate oxidative stress induced by microbes. This has been reported in a study by Abdelaziz et al. [71]. They investigated the role of PA on aflatoxin B_1 (AFB_1) (30ug/kg) induced reproductive dysfunction in male albino rats. AFB_1 intoxication deleteriously decreases testicular total thiols, glutathione, total peroxidase and superoxide dismutase activities, which subsequently increases upon treatment with PA. Suggesting that, PA may serve as pharmacological agent in abating AFB_1 induced oxidative stress, and subsequent toxicity. Oxidative stress, irrespective of the cause, may progress to life threatening diseases like, 'neurodegenerative diseases (Alzheimer's, Parkinson diseases etc.)' 'Cardiovascular diseases' 'cancer' 'diabetes' etc.

5. Role of phytic acid in diseases

5.1. Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a progressive cognitive decline [72]. Accumulation of amyloid-β-peptide (Aβ) in the brain has been implicated in the pathogenesis of AD [73]. The prevalence of AD is higher in western society. For example, about 5.7 million American people have AD, which is expected to project to 13.8 million in the nearest future [74]. Infact, someone develops AD every 67 s in USA [72]. Whereas in Africa, the rate of AD is lower among Africans living in Africa [73]. Since AD lacks effective cure, thus dietary intervention might play a role in its prevention [72]. In a report by Abe and Taniguchi [75], it was hypothesized that rice grains contain some component like PA capable of preventing Aβ accumulation in the brain. According to the report, Aβ is excised from amyloid-beta precursor protein through sequential cleavage by aspartic protease β-secretase 1(BACE 1) and γ-secretase [75]. Inhibition of the aforementioned enzymes (β-secretase 1and γ-secretase), could be a logical target for the prevention of AD. Study also revealed that rice component (PA) significantly inhibits Aβ production in neurobalstoma cells, with no harm to normal cells, suggesting PA as a potent and safer therapeutic agent in preventing AD [75]. Similarly, Anekonda et al. [76] examined the protective role of PA against Aβ pathology in MC65 cells and Tg2576 mouse model. Their

findings demonstrated that PA (100 μM) has neuroprotective effect in a cell culture (MC65) model, and treatment with the same concentration (100 μM) of PA provided a complete protection against Aβ cytotoxicity by reducing hydrogen peroxide level [76].

5.2. Parkinson's disease

Parkinson's disease (PD) is characterized by a selective degradation of dopaminergic neuron in the substantial nigra [77]. It is the second neurodegenerative disorder after AD [78]. Causes of PD may be multifactorial, however, excess Fe accumulation in the brain is associated with PD [79–81]. Studies have implicated accumulation of excess Fe in the brain of PD patients [78,82]. So, reducing the brain Fe load could be a logical remedy for PD [84]. The protective effects of PA on 1-methyl-4-phenylpyridinium (MPP^+) induced neurodegeneration in a cell culture medium of PD has been investigated [83]. In the investigation, MPP^+ was used to induce oxidative stress and apoptosis in the culture medium. The results revealed a significant protection with 30 μM PA against MPP^+ induced neurotoxicity. By implication higher dose of PA may be needed to offer complete protection against MPP^+ induced cell apoptosis in excess Fe condition. Furthermore, Xu et al. [77] examined the protective effects of PA against 6-hydroxydopamine (6-OHDA) induced apoptosis in a normal and excess iron condition of a cell culture model. Their findings revealed that PA offers protection against 6-OHDA induced cell apoptosis in excess Fe condition. Till date, it is not clear whether Fe accumulation in the brain is the "cause or an effect" in the pathogenesis of PD. Though the use of Fe chelators in the treatment of PD slows down the progression of the disease [77].

5.3. Diabetes mellitus

Diabetes mellitus (DM) is a disorder of carbohydrate metabolism characterized by the presence of hyperglycemia, either as a result of defective insulin secretion, defective insulin action or both [85,86]. It is a serious complicated metabolic disorder, that affects every ethnicity irrespective of age, gender and/or social economic status [87,88]. Although a complicated disorder, but effective blood glucose control by PA plays a vital role in the management of diabetes [86]. Food types (e.g. wheat) that are used by the traditionally medical practitioners in the management of type 2 diabetes has reasonable percentage (0.72–1.05 g/100 g) of PA [9,89,90]. These food types may be responsible for health improvement in persons with diabetes.

Consumption of foods rich in PA slows down the rate of carbohydrate digestion, which may in turn delay the onset of diabetes and hyperlipidemia [91]. Phytic acid possesses binding efficacy to transition metals, and could be used in the prevention, management or treatment of metal catalyzed protein glycation, which contributes in diabetic related diseases [92]. For instance, randomized trial conducted to investigate the impact of PA on protein glycation in patient with type-2-diabetes mellitus (T2DM) showed that daily consumption of PA inhibits protein glycation in patients with T2DM [92]. An advanced glycation end product (AGEs) seems to be a pathologic event that may trigger cross linking of collagen molecules to each other, and leads to plaque formation [93]. Plaque formation begins in artery walls and slowly blocks blood flows in the arteries thereby causing heart attack and stroke.

5.4. Hypolipidemic

Hypolipidemia is a decrease in plasma lipoprotein usually defined as a total cholesterol (TC) less than 120 mg/dL or low density lipoprotein cholesterol (LDLC) less than 50 mg/dL [94]. PA exhibits hypolipidemic properties of unregulating intestinal lipase activity, increasing faecal cholesterol output, and lowering cholesterol level [91]. This may in turn reduce the chances of developing cardiovascular diseases and other related diseases. Report has shown that 1% and 1.5% PA supplementation in diabetic mice reduces serum and liver lipid profile [95]. In a related study, Onomi et al. [96] investigated the efficacy of PA (0.02–10%) on hepatic and serum lipid profile of albino rats fed a high sucrose diet. Their findings revealed that supplementation with as low as 0.02% PA lowered the hepatic total cholesterol (TC), triacylglycerol (TG), while hepatic phospholipid was not affected. This could possibly mean that

the amount of PA needed to lower hepatic lipid level may be 10 fold lower than the amount capable of reducing mineral absorption and bioavailability [97].

Preventive role of PA on ISO induced myocardial infarction (MI) has also been investigated in albino rats [98]. The rats were pretreated with PA (25 and 50 mg/kg b.w.) orally for a period of 56 days, prior to subcutaneous administration of ISO (85 mg/kg b.w), at intervals of 24 h for two days. The pretreatment decreases the level of free cholesterol, TG, and free fatty acid in the heart and serum of the experimental rats. Its ability to lower lipid level, and prevents health issues associated with hyperlipidemia may be multifarious. However, inhibition of β-Hydroxyl β-methylglutaryl-CoA reductase (HMG-CoA reductase) could be the probable mechanism. Also, increasing fecal lipid output by PA may partially explain its cholesterol lowering efficacy [97]. Cholesterol is the precursor for bile acid synthesis, a metabolic event that involves series of enzyme catalyzed reaction. Perhaps, the presence of PA may over expressed 7-α hydroxylase "rate limiting enzyme in the bile acid synthesis.

5.5. Anticancer

Anticancer: Cancer is a major public health problem worldwide [99] Unhealthy diets strongly contributes in cancer development [100], and this could be the reason why some cancers "especially colorectal cancer" are sensitive to dietary intervention [101]. Till date, it is difficult to provide absolute cure for cancer. So, the simplest approach maybe preventive measures using dietary agent such as PA, a constituent of natural diet [102,103]. The advantage of PA over cancer drugs is that, it exhibits specific target for cancer cells, leaving normal cells unaffected [104]. For example, de–Lima et al. [104] examined cytotoxic effects of PA–Nickel complex on human acute leukemia Jurkat T cells and observed that PA remarkably decreases the viability of Jurkat cells, leaving normal lymphocytes unaffected. Also, the PA–Nickel complex of much lower concentrations (0.05 mM and 0.30 mM) significantly potentiates cytotoxic effects on cancer cells. Suggesting PA–Nickel complex could be a potential adjuvant in the treatment of cancer. Unlike PA, most cancer drugs do not exhibit specific target for cancer cells, as they could possibly affect both cancer cells and normal cells, and this makes PA a better therapeutic option in preventing cancer initiation and progression. Since most cancer drugs are synthetic, study suggests that natural products such as PA may be more suitable for chemoprevention of carcinogens than the former, as their actions are milder [105].

The dephosphorylated metabolites (IP4 and IP5) of PA also have anticancer efficacy, and are more potent at inducing apoptosis than PA [106]. Ferry et al. [106] in their investigative research, treated HeLa cells with IP4 and IP5, and found out that the lower metabolites of PA are more active at inducing apoptosis.

5.6. Colorectal cancer

Colorectal Cancer *(CC):* is one of the most common cancer diagnosed in both male and female, especially in the developed countries including USA [107,108]. Prevalence of CC is lower in developing countries (including Nigeria), compared to the developed countries [109–111]. Although, in the developed countries, the incidences of CC and mortality has been steadily declining (especially among adult older than 50 years for the past few years [112]. The lower incidence of CC in the developing countries maybe as a result of the consumption of unrefined foods in many parts of the developing countries. The unrefined foods may contain more phytochemicals, especially in West African countries. Fibers and phytochemicals mitigate cancer occurrence [113], however, intake of total dietary fiber within the range of a typical American diet is unlikely to substantially reduce CC risk [114].

PA rich foods are known to be a major player mitigating CC initiation and progression [115–117]. PA has been recognized as an important component of fiber associated with reducing cancer risk and incidences of CC mortality [118]. Study revealed that it is only fiber with a high PA contents that correlates negatively with CC prevention and development. This implies that, it could be "PA and not fiber" that suppresses CC [119]. There are few fiber rich diets, traditionally used in the management of CC. An example is wheat bran (WB), which has been shown to exhibit protection against CC occurrence, due to its high fiber content [120,121]. Such effects are analogous to the role of PA, a major fiber associated component of WB. Likewise, Jenab and Thompson [122] opined that it is only fiber foods rich in PA that

exhibits CC protection, and not fiber foods low in PA. Although PA is a good remedy in the preventing or mitigating cancer initiation and progression, It is however, unfortunate that thepotency of PA in the prevention and mitigation of CC is limited by its low solubility and short half-life. The best way to overcome this limitation is via nanotechnology application [123]. Recent report, revealed that treatment of human colorectal cancer (HT-29) cell line with phytic acid-chitosan-iron oxide nanocomposite (Phy-Cs-MNP) triggered apoptosis, as well as G0/G1 cell cycle arrest [124].

5.7. Prostate cancer

Prostate Cancer *(PC):* Is one of the most common invasive malignancy, and the fifth leading cause of death from cancer in men [124]. Just like the industrialized nations, the increasing rate of PC in developing countries is also overwhelming, especially among Nigeria men [125], and this calls for concerted research activities in Nigeria [126]. Although most African countries have incidence and mortality rates of PC that are far below cases reported in the developed countries [124]. The ill health nature of PC has matured to public health concern, but yet to significantly attract government attention in the developing and underdeveloped countries.

Just like CC, PC is also not spared from the anti-proliferative effect of PA. PA inhibits progression of PC at prostatic intraepithelial neoplasia stage. Appreciable adenocarcinoma reduction, and 3–5 fold, increase in apoptotic cells [127]. Raina et al. [127], opined oral PA supplementation has potential clinical value on PC prevention and progression. Similarly, feeding PA to DU145 (a classical cell line of PC), resulted in suppression of hormone refractory human prostate tumor growth, while increased apoptotic cell was noticed. Suggesting PA might possibly have significant control of PC growth [128]. Sometimes, PA polices the affairs of the cell cycle. It has shown to inhibit androgen dependent human prostate carcinoma cell growth, possibly through G1 arrest in cycle. Since apoptosis frequently occur in cells at G1 phase, so arrest in G1 phase or S phase of the cell cycle could potentiate apoptosis. Repressing of telomerase activity, an enzyme that catalyzes the synthesis and extension of telomeric DNA [129] could also be a logical target in apoptotic events. For instance, Jagadeesh and Banerjee [130] examined the efficacy of PA in the regulation of telomerase activity in prostate cancer cells. Their findings revealed that PA represses telomerase activity in mouse and human prostate cancer cells in a dose dependent manner. The repression of telomerase activity by PA strengthens its role as a potential chemotherapeutic agent for prevention of prostate cancer [130].

5.8. Hepatocarcinoma

Hepatocarcinoma: is the third cause of cancer related death worldwide [131,132]. The relationship between hepatocarcinoma and PA has also been studied, as its role in the prevention of hepatocellular carcinogenesis has been exploited. Al-Fatlawi et al. [133] investigated the anticancer activity of PA against hepatocellular carcinoma cells $HepG_2$. In their study, apoptotic activity was evaluated by expression analysis of apoptosis regulatory genes. Their findings revealed that PA inhibited the growth of $HepG_2$. Likewise, Norazina et al. [134] examined inhibitory effect of PA extracted from rice bran on $HepG_2$, cell cycle modulation and apoptosis induction. It was revealed that PA induced growth inhibition and differentiation in a dose and time dependent manner. Indicating it (PA) could be a potent candidate for hepatocellular progression and prevention.

5.9. Rhabdomyosarcoma

Rhabdomyosarcoma (RD) is an aggressive form of cancer that developed especially in skeletal muscle cells that are not fully differentiated. It affects mostly children, thus considered as one of the most common soft tissue sarcoma in children [135]. Notwithstanding, RD also account for less than three percent (<3%) of adult soft tissue sarcoma [136].

Therapeutic efficacy of PA on soft tissue sarcoma has been demonstrated in different experimental studies. For instance, Vucenik et al. [137] performed an *in-vitro* and *in-vivo* studies to investigate the effect of PA on human RD cells growth. Findings from the *in-vitro* study revealed that PA inhibited the growth of RD cells in a dose dependent manner. Remarkably, concentration of less than 1 mM PA

resulted in a 50% inhibition while concentration of 1 mM induced a higher inhibition in a culture media. Upon removal of PA from the culture medium, the culture cells regained their growth. Implying that, PA of a lower concentration (<1 mM and 1 mM) is only cytostatic. So, a higher concentration (10 mM) of PA is needed to achieve a cytotoxic effect. Findings from the *in-vivo* study also showed that PA suppresses the tumor cell growth [34,137].

5.10. Skin cancer

Skin Cancer: There may be many factors responsible for skin cancer, but solar UV radiation has been demonstrated to be the most important factor responsible for skin cancer [138]. The tendency for ultraviolet B-rays (UVB) to elicit skin tumors depends on a dose and duration of the radiation [139]. Since relationship exist between UV radiation and skin cancer incidences, treatment with conventional therapeutics have not been absolutely effective. Hence, failure of conventional therapeutics against malignant melanoma warrants seeking for a new and a more effective therapeutics. The tumor prevention and tumor progression property, exhibited by PA revealed in numerous experimental studies allured the attention of Wawszczyk et al. [140] to investigate the antiproliferative and cytotoxic potential of PA on human melanoma cell line. Findings from the study revealed that exposure to PA decreases the proliferation of melanoma cells in a time and dose dependent manner. However, concentration up to 0.5 mM did not have any inhibitory effect after 24 h [140]. Study also investigated the protective role of PA in drinking water on UVB induced skin cancer in mouse model [138]. In the study, two groups (treated and control group) each containing 15 mice were investigated and conclusively revealed that PA in drinking water decreases tumor incidence and tumor multiplicity [138].

5.11. Breast cancer

Breast cancer (BC) is one of the leading causes of cancer related death among women [141]. It is worrisome that the incidence of BC has increased by more than 20% with mortality rate of about 14% [133]. Surprisingly, the incidence of BC is higher in developed countries, whereas the mortality rate is higher in the developing countries [142]. This maybe as a result of poor awareness, late diagnosis and poor medical intervention and so on. Many therapeutics available for the treatment of BC have mild to chronic side effects [142], in-spite of available modern medical and technological advancement. As such, a shift to the use of natural therapeutic in treating BC has become necessary. Proietti et al. [142] conducted a double blind randomized control trial (RCT) with twenty patients, divided into two sections (treated and control group). The treated group consisted of ten women undergoing polychemotherapy, treated with 5 g of 4% PA, as sodium salt. Treatment (topical application) with PA after lumpectomy resulted in mitigating chemotherapy inducing side effects, thereby improving quality of life in the treated patients [142].

Hussein et al. [143] tested the potency of PA during mammary tumorigenesis. In their study, a carcinogenic substance 7,12-dimethylbenz α-anthracene (DMBA) was used to induced proliferative changes in the mammary gland. Serum total sialic acid (TSA) and nitric oxide were used to assay for the tumorigenicity and oxidative stress respectively. Administration of DMBA steered an increase in the TSA and NO, and a decrease in apoptotic activity. However, treatment with PA decreased the level of TSA and NO, and an increased in the apoptotic activity [143].

As earlier stated that the vegetarians and the vegans possess phytase capable of interrupting the antinutritional efficacy of PA. As such, it will be difficult for PA to elicit micronutrient deficiencies. However, this may also impair the therapeutic integrity of PA, in terms of cancer (especially colon cancer) prevention, amelioration, cure or absolute management of the menace (cancer). So, for PA to exert its anticancer properties, it is necessary that the integrity of PA is preserved (especially in the colon) [139]. It is obvious also, that the anticancer efficacies of PA are beyond obvious theory. This necessitates the need to enlighten people as to why consumption of PA rich food (high fiber diet) is vital to preventing the menace that is striking hard to become number one killer disease.

5.12. Antimicrobial

Antimicrobial: The emergence of antibiotic resistance in bacteria is considered to be a substantial threat to public health and requires some concrete effort to tackle [144]. Infrequent use of broad-spectrum antibiotics for the treatment of bacterial infections has led to the emergence of antibiotic resistance among bacteria [145]. Moreso, frequent use of synthetic antimicrobial drugs may have many side effects as compared to those from organic sources. This has necessitated the need for exploration of active ingredients from natural sources that is safer, capable of inhibiting and obliterating the growth of life threatening microorganism.

The antimicrobial efficacy of PA has been studied as evident in some studies. For instance [146], evaluated the antibacterial effect of PA on *Enterococcus faecalis* and recorded a zone of inhibition of 39 mm using the agar disc diffusion method and attributed the antibacterial activity of PA solution to the release of hydrogen ion. This could inhibit bacterial metabolism [146]. Puvvada et al. [147] compared the antimicrobial efficacy of PA alone and in combination with other irrigants and discovered that the zone of inhibition of PA alone was 31.33 mm, which was significantly ($p < 0.05$) higher than the other irrigants. However, the antimicrobial efficacy of PA with other irrigants like NaOCl, CHX, and EDTA gave a significantly higher zone of inhibition when compared to individual irrigants [146].

Kim and Rhee [148] developed an antimicrobial composition using PA capable of effectively disinfecting and controlling bacteria such as the acid resistant Entero-hemorrhagic *Escherichia coli*. Their findings showed that PA exhibited significantly, stronger bactericidal effects against acid-resistant *E. coli,* compared to other organic acids of equivalent working concentrations. Also, PA plus NaCl had marked synergistic antibacterial effects. For instance, Yadav et al. [145] examined the inhibitory potency of PA in combination with methanol seed extract of *Syzygium cumini* and sodium chloride over *Bacillus subtilis.* From their findings, the combination of PA with methanol seed extract of *S. cumini* with sodium chloride had a significantly ($p < 0.05$) higher zone of inhibition. Suggesting their suitability for designing potent antibacterial therapeutics.

Generally, the mechanism by which organic acids exert their antimicrobial activity is explained by the weak acid theory. That is, only un-dissociated forms of the acid can enter the cytoplasm, where they inactivate bacteria by gradually dissociating into charged ions that disrupt cytoplasmic pH homeostasis [149]. Unlike other organic acid, the mechanism underlying the antimicrobial properties of PA maybe quite different. Reason being that PA has a unique structure (12 replaceable protons on six reactive phosphate groups bonded to a cyclic six-carbon ring ($C_6H_{18}O_{24}P_{6)}$ and a wide acidity range [150]. Though, neither its bactericidal activity nor its mode of action has been examined in detail [148].

From the forgoing, it is obvious that PA has not been widely studied as a natural antimicrobial agent. Moreso, despite the potential of PA as a natural antimicrobial agent, there have been almost no advanced development cases on antimicrobial agents having PA as an active ingredient or part of the active ingredients.

5.13. Phytic acid and human immunodeficiency virus

Phytic acid and human immunodeficiency virus *(HIV):* Although HIV remains incurable to date, the advent of antiretroviral therapy (ART) in 1997 has led to the control of HIV/acquired immunodeficiency syndrome (AIDS) [151]. In 2015, approximately 36.7 million people were said to have been living with HIV and 1.1 million people died of AIDS [152]. Most anti-HIV drugs work by blocking key steps of the viral replication cycle, making them effective against actively-replicating viruses, but have little effect on latent HIV-1 in that it remains in cellular reservoirs throughout the body [153]. Generally, HIV identifies and enters into CD4+ T lymphocytes. The virus multiplies inside the infected cells to release a vast number of offspring virion that, in turn, spreads to other CD4+ T lymphocytes [153]. Reducing the release of new virions would help manage the virus population and reduce the problem of removing the virus from the body. Therefore, synthesizing a small molecule that would hinder the budding of offspring virus, with the idea of turning an HIV-infected cell into a “prison cell” from which the invaded virus cannot escape could control the virus. The host cell will eventually die without releasing the ‘prisoner’ virus. Consequently, if all reservoir viruses are locked in the host cell prison, and these cells apoptosed, the death of all such infected host cells would mark the eradication of HIV in the body [153].

Otake et al. [154], investigated the *in vitro* antiviral effect of PA on HIV. They reported that in MT-4 cells, PA completely inhibited the cytopathic effect of HIV and the HIV-specific antigen expression at a concentration of 1.67 mg/ml. Also, PA inhibited the replication of HIV-1 in a T cell line, as well as that of a freshly isolated strain in peripheral blood mononuclear cells [155]. The viral protein, Pr55Gag mediates HIV-1 virion budding. It is one of the products produced by the host cells taken over by the virus. Ordinarily, Pr55Gag migrates from the cytoplasm to the plasma membrane and binds to a specific inositol phospholipid (PIP2) in the membrane [156]. Tateishi et al., [153] discovered that PA had a 70 fold binding affinity to the N-terminal matrix antigen domain of Pr55Gag when compared with less phosphorylated PIP2 derivative [151]. This activity was considered sufficient to antagonise PIP2 to suppress the membrane localization of Pr55Gag and subsequent release of the virus induces apoptosis of the host cell. Although the mechanisms of IP6 action remain unclear, it can be speculated that it acts on HIV-1 at an early replicative stage. Studies on this anti-HIV agent might likely provide a basis for subsequent production of more effective drugs for the treatment of AIDS [58].

This was proposed probably for the first time that phytic acid, unlike other anti-nutrient can be degraded yielding an inorganic phosphate product that can in turn, be used to resynthesize PA. From the schematic illustration, the point labelled 1, describes the movement of PA through the biosphere and lithosphere, that is, through plant-animal-soil-plant. In plants PA is synthesized to a larger extent, depending on the plants, and accumulates especially in plant seeds, where it serves as the principal storage form as phosphorus. In plants, PA plays some important roles including plants seedling. At the position labelled 2, animals, including human feed on the plants, thereby ingesting PA. The metabolic fate of PA ingested depends on the kind of animal (monogastric or ruminant). In ruminant animals, ingestion of PA can be efficiently utilized, due to the presence of an enzyme phytase in them. The phytase breaks inositol-phosphate bond, thereby releasing inorganic phosphate from the organic phytic acid (PA). So, in ruminants, ingestion of PA provides bulk of the phosphorus needed for their healthy growth. The monogastric animals (including humans) on the other hand, which lack the digestive enzyme, phytase required to hydrolyze PA. So, bulk of the PA ingested are not absorbed, but bound to some essential minerals like: zinc, calcium, magnesium, iron just to mention a few, to form phytates. The point labelled 3, shows that the unabsorbed phytates pass through the gastrointestinal tract (GIT), and are excreted. Human and animal wastes are usually or ultimately deposited in the soil. The position labelled 4 shows how organic phosphorus in the waste excreted cannot be used by the plants. However, some soil microorganisms possess phytases (myo-inositol hexakis phosphohydrolases), capable of catalyzing the hydrolysis of the indigestible phytates, to release inorganic phosphorus. There are several species (sp) of microorganisms that possesses phytase, but *Bacillus* sp and *Aspergillus* sp are highly specific for PA hydrolysis. The point labelled 5 indicates that inorganic phosphorus is well utilized by plants. So plants pick up the released inorganic Phospate in the soil for the synthesis of PA, a molecule necessary for plants growth and development [157].

6. Toxicity

Information on the toxicities associated with PA is scarce. As such, PA maybe safe and devoid of toxic effect. A study affirmed no gross behavioral, neurologic and autonomic effects were observed in mice intraperitonealy administered PA up to 200 mg/kg [158]. On the contrary, Omoruyi et al. [4], observed increase in serum alkaline phosphatase (ALP) and alanine amino transferase (ALT) activities in streptozotocin induced diabetic rats. However, the increase was attributed to the co-supplementation of PA with streptozotocin, and may not be PA alone.

7. Conclusion

Phytic acid is an important molecule present in nearly all plants. Humans and animals largely depend on plant based foods for their metabolic needs. However, its presence in food may disrupt mineral bioavailability, although the disruption depends on a key factor, that is, PA/mineral ratio. The disruption of mineral bioavailability should be a major concern for those (humans) that consume repeatedly, a particular kind of food high in PA and low in micronutrients. For a mutually supplemented diet practice, it will be challenging for PA to exert its anti-nutritional attributes. Considering its effect

on iron absorption, “dephytinization” has been recommended as a major strategy to improve iron nutrition during the weaning period. So far, no study has implicated dietary PA in nutrients deficiency, except from exogenous supplement. Even if one consumes food devoid of PA for the fear of mineral deficiency, it endogenous synthesis (to a lesser extent) cannot be evaded, as almost all cells contain PA, where it performs cellular function such as regulation of cell function, cell growth and differentiation.

Interestingly, the anti-nutritional role of PA is also responsible for some health benefits. So the fear of consuming PA may provoke health integrity, and may also impair cellular function.

Author contributions

This study was conducted in collaboration between all the authors. All authors critically revised the manuscript for important intellectual content and gave a final approval of the revised version to be published.

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Conflicts of interest

The authors declare no conflict of interest.

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