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Phytanic acid, an inconclusive phytol metabolite: A review

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ABSTRACT

Phytanic acid (PA: 3,7,11,15-tetramethylhexadecanoic acid) is an important biometabolite of the chlorophyll-derived diterpenoid phytol. Its biological sources (occurrence) and ADME (absorption, distribution, metabolism, and elimination) profile are well-discussed in the literature. Cumulative literature suggests that PA has beneficial as well as harmful biological roles in humans and other animals. This study aimed to sketch a brief summary of PA's beneficial and harmful pharmacological effects in test systems on the basis of existing literature reports. Literature findings propose that PA has anti-inflammatory and immunomodulatory, antidiabetic, anti-obesity, anticancer, and oocyte maturation effects. Although a high plasma PA-level mediated SLS remains controversial, it is evident to link it with Refsum's disease and other peroxisomal enzyme deficiency diseases in humans, including RCDP and LD; ZHDA and Alzheimer's disease; progressive ataxia and dysarthria; and an increased risk of some lymphomas such as LBL, FL, and NHL. PA exerts toxic effects on different kinds of cells, including neuronal, cardiac, and renal cells, through diverse pathways such as oxidative stress, mitochondrial disturbance, apoptosis, disruption of Na^+/K^+-ATPase activity, Ca^{2+} homeostasis, alteration of AChE and MAO activities, etc. PA is considered a cardiac biomarker in humans. In conclusion, PA may be one of the most important biometabolites in humans.

Introduction

Phytol ($C_{20}H_{40}O$), a branched-chain fatty alcohol, is derived through the side-chain cleavage of chlorophyll by ruminant bacteria (Fig. 1) (Jansen and Wanders, 2006). To date, several studies suggest that it has many important biological activities (Costa et al., 2014, Islam et al., 2015, Islam et al., 2016b, Islam et al., 2017, Islam et al., 2016, Islam et al., 2018, Islam et al., 2020, Islam et al., 2019, Islam, 2019, Bhuia et al., 2023a, Costa et al., 2019, Rahaman et al., 2020, Alencar et al., 2018, P Costa et al., 2016, de Alencar et al., 2019). However, *in vitro* studies have revealed that both sterol carrier protein-2/sterol carrier protein-x (Scp-2/Scp-x) and liver fatty acid binding protein [Fabp1 (L-FABP)] gene products improve hepatic absorption and metabolism of lipotoxic dietary phytol (Storey et al., 2017). Defects in phytol metabolism result in the accumulation of lipotoxic phytol metabolites, including phytanic acid (PA: 3,7,11,15-tetramethylhexadecanoic acid), which is also abundant in dairy products, lamb, fish, and beef. An average diet having 50–100 mg/day is beneficial for maintaining normal health (Battaglia Parodi et al., 2016, Hellgren, 2010). The body makes PA by first converting dietary phytol into PA in the endoplasmic reticulum, then transporting that PA to the peroxisomal membrane, where it is converted into phytanoyl-CoA and internalized into the peroxisomal

Abbreviations: AchE, *Acetylcholinesterase*; AV nodal, Atrioventricular Node; CAT, Catalase; EGFR, Epidermal Growth Factor Receptor; FL, Follicular lymphoma; GSH, Glutathione; HDAC, H*istone deacetylase*; IDDM, Insulin-dependent diabetes mellitus; IFN-γ, Interferon-gamma; IL-10, Interleukin-10; IL-17A, Interleukin-17A; IL-2, Interleukin-2; LBL, Large B-cell lymphoma; LD, Leber Disease; MAO, *Monoamine oxidase*; MDA, Malondialdehyde; MNU, 1-methyl-1-nitrosourea; NF-κB, Nuclear factor kappa-light chain enhancer of activated B cells; NHL, Non-Hodgkin lymphoma; NO, Nitric oxide; PPAR, Peroxisome proliferator-activated receptor; PPAR-α, Peroxisome proliferator-activated receptor alpha; RCDP, Rhizomelic chondrodysplasia punctata; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; RXR, Retinoid X *receptor*; SLS, Sjogren Larsson syndrome; SOD, Superoxide dismutase; VLCFAs, Very long-chain fatty acids; ZHDA, Zellweger's disease hyperpipecolic academia.

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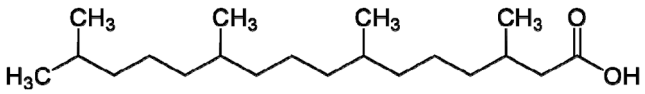

Fig. 1. Chemical structure of phytanic acid.

matrix (Storey et al., 2017, Mukherji et al., 2002). PA is linked to Refsum's disease (a peroxisomal genetic disorder) and other peroxisomal enzyme inadequacy ailments in humans, including Rhizomelic Chondrodysplasia Punctata (RCDP) and Leber Disease (LD) (Wanders et al., 2001, Yamamoto et al., 1995, Mukherji et al., 2002, Schönfeld et al., 2006, Wanders and Komen, 2007, Wanders et al., 2011). An increased plasma PA level has also been linked to developing ataxia and disarthria (Clayton et al., 1996), an enhanced threat of some lymphomas such as follicular lymphoma (FL), large B-cell lymphoma (LBL), and non-Hodgkin lymphoma (NHL) (Ollberding et al., 2013), Zellweger's disease hyperpipecolic academia (ZHDA) (Wanders et al., 2011), and Alzheimer's disease (Ruiz-Roso et al., 2018).

Verhoeven et al. (1998) demonstrated that alpha-oxidation of PA results in formic acid by decarboxylation (Table 1), which is another toxic component for our body cells. Among the other metabolites, PA is quite important due to its debated pharmacological roles in humans and other animals. Therefore, a brief current scenario on its beneficial and toxicological effects might be important to summarize its significance in the medical science study. This study summarizes the pharmacological effects of PA on the basis of literature reports (Verhoeven et al., 1998).

Beneficial effects of phytanic acid

Effects on lipid metabolism

Peroxisomes are recognized as important dynamic organelles in nearly all eukaryotic cells (Gabaldón, 2010). Alpha-oxidation frequently takes place in the peroxisomes and needs PA, an essential origin for the subsequent process of metabolism (Van den Brink et al., 2006). In a study, we found that PA is beneficial for the embryonic development of porcine oocytes. The findings of the study revealed that the administration of PA enhanced both the lipid droplets and fatty acid substances within the oocytes. Furthermore, the treatment of PA led to the activation of mitochondria and an increase in mitochondrial membrane potential, which subsequently resulted in the generation of more ATPs within the oocytes. This elevation in ATPs potentiated the processes of oocyte maturation, peroxisomal lipid oxidation, and mitochondrial activities (Kim et al., 2020).

The retinoid X receptor (RXR, a nuclear receptor) plays an important function in cell signaling through coupling with a host of other receptors. An earlier report suggests that PA specifically dislocated [3H]-9cRA from RXR with Ki values of 4 μM and produced concentration-dependent (4–64 μM) effects on this receptor (Kitareewan et al., 1996). De Keyser (2006) suggests that PA is a true physiological ligand for peroxisome proliferator-activated receptor (PPAR)-α, -δ and -γ subtypes as well as the RXR (Fig. 2) (De Keyser, 2006).

Recently (Fig. 3), it has been investigated that an ablation in the sterol carrier protein-2/sterol carrier protein-x (Scp-2/Scp-x) gene is responsible for a sex-dependent accumulation of phytol and its peroxisomal metabolites, branched-chain fatty acids, (e.g., phytanic acid ≫ pristanic acid and 2,3-pristenic acids) (McIntosh et al., 2017). The role of this gene in female is still unresolved. Thus, the authors reported that the accumulation of phytol and its metabolite PA is larger in male animals than females. Watkins et al. (2010) stated that the levels of PA may be a contributing factor to variations observed in the transcriptomes of humans and great apes, particularly those related to lipid metabolism, and these differences could vary depending on sex and species (Watkins et al., 2010). Moreover, a carrier protein-x-mediated sex-dependent toxic response of PA in mouse liver was reported by Mackie et al. (2009).

Table 1
The beneficial effects of phytanic acid in different test systems.

Test system(s)	Mechanism of action	Dose/ concentration/ IC_{50}	References
	Effect on cells		
Monkey COS-1 cells and human HepG2 cells	Interactions with PPAR-α at physiological concentrations	3 μM, *in vitro*	(Zomer et al., 2000)
CV-1 and C3H10T1/2 cells	Role of management of insulin resistance	30–100 μM, *in vitro*	(Heim et al., 2002)
Mouse splenocytes, purified T-cells, B-cells, and J774.1 cells	Anti-inflammatory activity: Decreased IFN-γ, interleukin (IL)-2, IL-10 and IL-17A expressions in splenocytes, interferon gamma (IFN-γ) and IL-17A levels in T-cells, and inhibited antibody release by B-cells and NO formation by J774.1	–	(Nakanishi et al., 2023)
	Effects on IDDM and other metabolic disorders		
Hepatocytes	Stimulates the transcriptional activity of PPARs/RXR heterodimers, resulting for 2-deoxy-D-glucose uptake and metabolism	650–950 mg/g	(Lopez, 2015)
AGN19420 and BRL49653 cellular lines	Acts as a natural origin retinoid in adipose cells, suggesting a potential utilization in the management of IDDM and obesity	10 μM, *in vitro*	(SCHLüTER et al., 2002a)
Primary porcine myotubes	Stimulates glucose uptake	10 μM, *in vitro*	(Che et al., 2013)
Adult male Wistar albino rats	Modulation of biochemical alterations and shows antidiabetic activity	5 mg/kg, *in vivo*	(Elmazar et al., 2013)
	Anti-cancer effect		
Rat mammary tumour model	Co-treated with a vitamin D analogue exerts an anti-mammary cancer effect	500 mg/kg, *in vivo*	(Liska et al., 2012)
	Effect of oocytes		
Porcine oocyte	Potentiate peroxisomal lipid oxidation, maturation processes, and mitochondria activities	40 μM, *in vitro*	(Kim et al., 2020)

A difference in PA metabolism may impact the activities of the cardiovascular, nervous, and skeletal systems in humans and great apes (Mackie et al., 2009).

Anti-inflammatory and immunomodulatory effects

Autoimmune diseases are capable of affecting a variety of tissues and nearly every organ in the body, and they are responsible for a number of diseases, such as rheumatoid arthritis, insulin-dependent diabetes mellitus, scleroderma, thyroiditis, systemic lupus erythematosus, and multiple sclerosis (Smith and Germolec, 1999; Pisetsky, 2023; Islam et al., 2023).

PA is well known for its health benefits for the immune system. For example, 3**RS**, 7**R**, 11**R**-isomer, a naturally derived derivative available in the human body and foods, has been seen to ameliorate T-cell-mediated autoimmune diseases (Nakanishi et al., 2018). In this study, the findings stated that PA (Fig. 2) can downregulate the nuclear factor

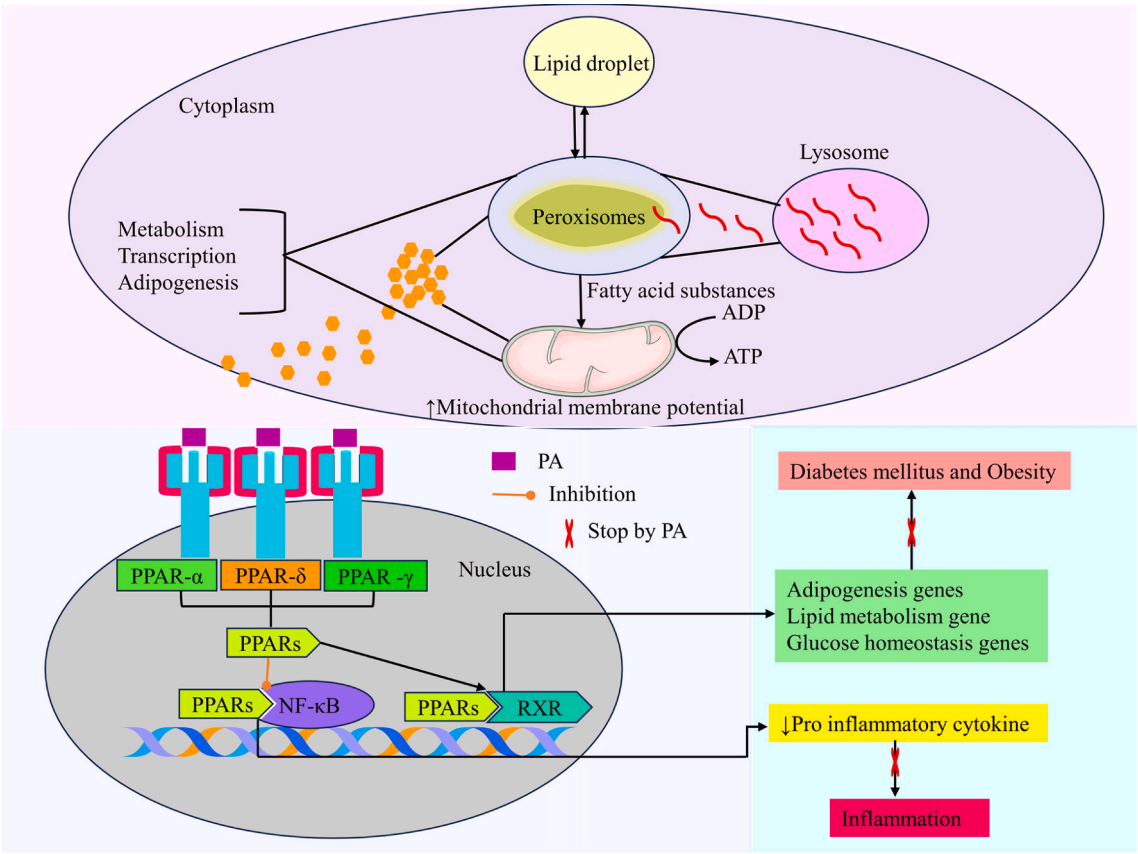

Fig. 2. Possible mechanism of action of phytanic acid on different peroxisome proliferator-activated receptors. [↑: increase/upregulated; ↓: Decrease/downregulated; PA: Phytanic acid; RXR: Retinoid X receptor; NF-κB: Nuclear factor kappa B]. (Decara et al., 2020).

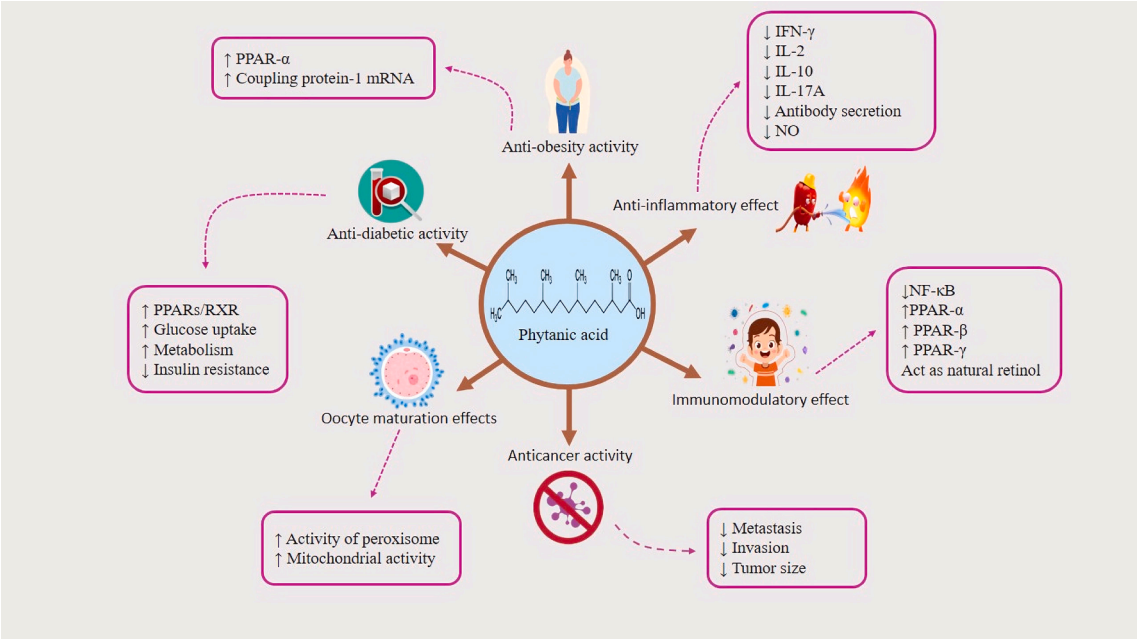

Fig. 3. Overall beneficial effects of phytanic acid. (↑: increase/upregulated; ↓: Decrease/downregulated).

kappa-light chain enhancer of activated B cells (NF-κB) pathway, thereby activating PPAR-α thus exerting its potential immunomodulatory effects. A recent study suggested that PA exerts anti-inflammatory effects on mouse splenocytes, purified T-cells, B-cells, and J774.1 cells (Nakanishi et al., 2023).

Effects on diabetes mellitus and obesity

Obesity is associated with numerous medical, psychological, and social conditions, with type 2 diabetes mellitus (T2DM) possibly being the most debilitating. 171 million persons were estimated to have T2DM

at the turn of the century, and this number is predicted to grow to 360 million by 2030 (McKeigue et al., 1991, Leitner et al., 2017). However, insulin resistance is correlated with both T2DM and obesity (Al-Goblan et al., 2014). Several studies confirmed the beneficial effect of PA in diabetes mellitus and the compound's ability to prevent insulin resistance (Heim et al., 2002). PA mediated the adipocyte differentiation of 3T3-L1 cells in culture, as evaluated by the deposition of lipid droplets and the induction of the aP2 mRNA marker. A synthetic activator of RXR mimicked this activity, whereas a PPAR-α agonist did not induce the identical effect. The findings of this investigation stated that PA has the ability to act as a natural retinoid in adipose cells and propose its efficacious utilization in the management of obesity and human T2DM (SCHLüTER et al., 2002a, Schlüter et al., 2002b). Another study stated that the insulin sensitizing/anti-diabetic activity of phytol is induced partly by the promptness of nuclear receptors and heterodimerization of RXR with PPAR-γ by PA (Elmazar et al., 2013). PA also promotes the transcriptional effect of PPARs/RXR heterodimers, resulting in 2-deoxy-D-glucose uptake and metabolism (Fig. 2) (Lopez, 2015, Che et al., 2013).

Cumulative evidence suggests that promoting beige adipogenesis and the browning of white adipose tissue via nutritional and different pharmacological interventions could be one of the potential approaches to hindering and managing obesity-linked dysfunctions (Villarroya and Vidal-Puig, 2013). PA promotes beige adipogenic differentiation through activating PPAR-α in 3T3-L1 preadipocytes (Wang et al., 2019). Previously, Schlüter and his co-workers (2002b) also reported that PA caused brown adipocyte differentiation through increasing uncoupling protein-1 mRNA expression (SCHLüTER et al., 2002a).

Effects on cancer

The results of a combination therapy demonstrated that administering PA alone did not prevent the advancement of 1-methyl-1-nitrosourea (MNU)-induced breast tumors in rats, but it significantly reduced the size and amount of tumors compared to rats treated uniquely with MNU. When PA was combined with the vitamin D analogue Seocalcitol, it led to a further reduction in tumor size and amount, although it did not have an impact on the aggressiveness or invasiveness of the carcinomas (Liska et al., 2012). The beneficial effects of PA on immunomodulation, inflammation, beige adipogenesis, diabetes, tumors growth and oocyte maturation and the related molecular factors are graphically presented in Fig. 2. And Table 1 shows the beneficial effects of PA in different test systems.

Toxicological effects of phytanic acid

Cumulative reports suggest that phytol and its metabolites have many important biological activities (Islam et al., 2016a, Roca-Saavedra et al., 2017), but, a narrow range of efficacy can be obtained in most cases. Studies reported that the supra-physiological concentrations of the compound may cause cytotoxicity in non-cancerous cells in a laboratory setting and can lead to sickness and death in animal experiments. Therefore, their role in the available human studies on cancer prevention is currently inconclusive and offers limited evidence (Bobe et al., 2020, Bhuia et al., 2023c).

PA exerted toxic effects on different types of cells through inducing oxidative stress (Leipnitz et al., 2010), especially by activating PPAR and NO-dependent cascades (Idel et al., 2002, Dhaunsi et al., 2016); protonophoric action (Komen et al., 2007); inhibition of cell proliferation (Tang et al., 2007, Renner et al., 2013); and so on. Recent evidence suggested that PA has bad impacts on the adipose tissue and liver (Nakanishi et al., 2020b, Nakanishi et al., 2020a).

PA is considered one of the potential biomarkers for cardiac diseases (Ahmed et al., 2017). It is evident that it results in bradycardia and hampered AV nodal and intraventricular impulse conduction in the mouse cardiac system (Mönnig et al., 2004). PA disturbed cellular energy and redox homeostasis in rat heart mitochondria (Grings et al., 2012). Another study suggests that PA disrupted mitochondrial bioenergetic and Ca^{2+} homeostasis processes and thereby resulted in cardiomyopathy in cardiac cells (H9C2) (Zemniaçak et al., 2023). It was also found to increase acyl-CoA oxidase 2 expression in the kidneys of SHRs and WKY rats (Okamura et al., 2021). The authors also observed that PA altered gut microbiota through oxidation in the kidney and caused hypertension in the experimental animals.

In the rat cerebellum, PA increased malondialdehyde (MDA) and nitric oxide (NO) formation and diminished reduced glutathione (GSH) levels (Borges et al., 2015). Several studies have stated that PA can mediate oxidative stress via dysregulation of physiological antioxidant systems (e.g., catalase (CAT), GSH, and superoxide dismutase (SOD)) and an elevation in reactive oxygen species (ROS), reactive nitrogen species (RNS), and MDA products in the brains of animals (Kahlert et al., 2005, Schönfeld et al., 2006, Borges et al., 2015, Chaudhary et al., 2017a, Chaudhary et al., 2017b, Bhuia et al., 2023b). It is also evident that it disrupts Na^+/K^+-ATPase function (Busanello et al., 2010, Chaudhary et al., 2017b), alters Ca^{2+} homeostasis (Kahlert et al., 2005, Schönfeld et al., 2006, Kruska and Reiser, 2011), impairs mitochondrial functions (Kahlert et al., 2005, Reiser et al., 2006, Schönfeld et al., 2006, Nagai and Teratology, 2015, Busanello et al., 2013), and induces NO^-dependent apoptosis (Reiser et al., 2006, Chaudhary et al., 2017b) in brain cells. Chaudhary and Parvez (2017) reported that PA can alter acetylcholinesterase (AChE) and monoamine oxidase (MAO) levels in the rat brain (Chaudhary et al., 2017a), while Selkälä et al. (2015) suggested that PA can cause seizures, sensorimotor neuropathy, and relapsing encephalopathy in mice (Selkälä et al., 2015).

In humans, large accumulations of PA commonly develop retinitis pigmentosa, peripheral polyneuropathy, and cerebellar ataxia along with some other important medical situations (Watkins et al., 2010). It may be due to PA's ability to activate the PPAR-α transcription factor, which thereby upregulates the lipid metabolism genes (Idel et al., 2002). A population-based control study done on men and women (age between 20 and 75 years) suggests that PA-containing foods (151 food items) have been linked with an elevated risk of NHL among the participants in the 66 counties of eastern Nebraska (Ollberding et al., 2013).

In general, PA targets mitochondria more severely than very long-chain fatty acids (VLCFAs). The VLCFAs distort the inner membrane constituents along with their functional interactions, while PA is evident for its specific protonophoric activity. It induces ROS generation, and reduces ATP generation. This phytol lipotixic metabolite inhibits Na^+/K^+-ATPase activity. Besides instantaneous effects, PA at low micromolar concentrations (e.g., 5–20 μM) results in neuronal damage in Refsum's disease. It is due to an alteration in epigenetic transcriptional regulation by chronic PA exposure to the brain cells (Schönfeld et al., 2004b, Schönfeld and Reiser, 2016).

Infantile Refsum's disease, one of the less severe of the Zellweger spectrum disorders, results from a generalized peroxisomal function impairment (Poll-The et al., 2004). Increased plasma levels of PA and VLCFAs are the biomarkers of this disease. A 3-year-old child in a case study has been diagnosed with elevated levels of plasma VLCFAs, as well as PA and pristanic acid. The child has also been found to have deficient dihydroxyacetone phosphate acyltransferase activity in their fibroblasts, and a homozygous pathogenic mutation (c.2528G>A, p.Gly843Asp) has been identified in their PEX1 gene. As a result, the child has been given nutritional advice and will be monitored to reduce their intake of foods that are high in PA (Sá et al., 2016). Table 2 shows the toxic effects of PA in different test systems.

Controversies on phytanic acid

In a study, PA exerted an anti-teratogenic effect on albino mice (matted females), where it significantly reduced the oxidative metabolism and teratogenic consequences of retinol (Arnhold et al., 2002). In contrast, the teratogenic potential of PA was revealed by combination

Table 2
The toxic effects of phytanic acid in different test systems.

Test system(s)	Mechanism of action	Dose/ concentration/ IC_{50}	References
	Effects on cells/ tissues		
Vascular smooth muscle cells of Wistar rats	Activates PPAR and mediates NO-dependent programmed cellular death	100 μM, *in vitro*	(Idel et al., 2002)
Human skin fibroblastcultures	Shows toxic effect mainly due to protonophoric action,	30—100 μM	(Komen et al., 2007)
Retinal cells	Increases the levels of retinyl esters, thereby, inhibition of cell proliferation	50 μM, *in vitro*	(Tang et al., 2007)
Wistar male rats	Induces oxidative stress	1–500 μM, *in vitro*	(Leipnitz et al., 2010)
Bovine bloodmononuclear cells	Inhibition of cell proliferation	20 and 148 μM, *in vitro*	(Renner et al., 2013)
Rat aortic smooth muscle cells	Increased NOX-1, p47phox, and the total and phosphorylated EGFR levels	2.5–10 μg/ml, *in vitro*	(Dhaunsi et al., 2016)
Mice	0.05% dietary PA exerted biological effects on the adipose tissue and liver	0.05%, *in vivo*	(Nakanishi et al., 2020b)
Mice	1.0% dietary phytol exerted biological effects on the adipose tissue and liver	–	(Nakanishi et al., 2020a)
	Neurotoxic effect		
Neuro2a cells	Disturbs normal lipid homeostasis via *PPAR-α* gene causing to lipid deterioration		(Gloerich et al., 2005)
Astroglia cells	Ca^{2+} regulation, mitochondrial depolarization, and elevation of ROS formation in the brain	100 μM, *in vitro*	(Kahlert et al., 2005)
Astroglia cells	Apoptosis in mitochondrial route	100 μM, *in vitro*	(Reiser et al., 2006)
Astroglia cells	Activates the production of ROS by inactivating aconitase and oxidizing the mitochondrial glutathione pool leading to oxidative damage	50 μM, *in vitro*	(Schönfeld et al., 2006)
Astroglia cells	Decline of Ca^{2+} loading and severe secretion of CYPc	50 μM, *in vitro*	(Schönfeld et al., 2006)
Hippocampal cell cultures from Wistar rat pups	Initiate astrocyte cell death	50 μM	(Schönfeld et al., 2006)
Hippocampal cell cultures from Wistar rat pups	Exerts various toxic effects	1–10 μM, *in vitro*	(Rönicke et al., 2009)
PA disordered patients	Disrupts Na^{+}/K^{+}-ATPase function and the electron flow by the respiratory chain in the brain cortex, resulting in neurological damage	200 μM, *in vitro*	(Busanello et al., 2010)
PA disordered patients	Ca^{2+} deregulation, thereby, stimulates the free fatty acid receptor GPR40 (G-protein-coupled receptor)	50 μM, *in vitro*	(Kruska and Reiser, 2011)
Astroglia cells	Disrupts the normal functioning and balance of mitochondrial respiration, leading to impairment	20–100 μM, *in vitro*	(Busanello et al., 2013)
Rats	Enhanced MDA and NO formation and diminished the levels of GSH in rat cerebellum	80 nmol	(Borges et al., 2015)
Neuro2a cells	Initiates mitochondrial abnormality and cellular death by the activation of histone deacetylase (HDAC)-2 and −3	10 μM, *in vitro*	(Nagai and Teratology, 2015)
AMACR deficient mice (Amacr−/−) were formated in a C57BL/6 background	Causes seizures, sensorimotor neuropathy, and relapsing encephalopathy	0.5%	(Selkälä et al., 2015)
Rats	Altered the levels of GSH, CAT, SOD, AChE, Na^{+}/K^{+}-ATPase and MAO levels in rat brain	50 μM, *in vitro* and *in vivo*	(Chaudhary et al., 2017a)
SH-SY5Y cells	Induced NO-dependent apoptosis	100 μM, *in vitro*	(Chaudhary et al., 2017b)
	Cardiotoxic effect		
Mice	Readily incorporated in phospolipid fraction of myocardial membranes, resulting bradycardia and hampered AV nodal and intraventricular impulse conduction	5 mg/g, *in vivo*	(Mönnig et al., 2004)
Rats	Disturbed cellular energy and redox homeostasis in heart mitochondria	1 to 500 μM, *in vitro*	(Grings et al., 2012)
Cardiac cells (H9C2)	Disrupted mitochondrial bioenergetic and Ca^{2+} homeostasis processes, results cardiomyopathy	50–100 μM, *in vitro*	(Zemniaçak A et al., 2023)
	Renotoxic effects		
SHRs and WKY rats	Increased acyl-CoA oxidase 2 expression in the kidney, and altered gut microbiota through oxidation in the kidney and the pathogenesis of hypertension	–	(Okamura et al., 2021)

therapy of a natural RXR ligand with a synthetic RAR agonist (Am580) (Elmazar and Nau, 2004). Similarly, its effect on prostate cancer is still controversial (Walsh, 2005; Price et al., 2010; Wright et al., 2012; Wright et al., 2014).

It has been revealed that high levels of saturated fatty acids and dairy fat intake enhance the risk factors of cardiovascular diseases and T2DM (IDDM: insulin-dependent diabetes mellitus) in humans (Steyn et al., 2004, Warensjö et al., 2004, Shahid et al., 2023). However, recent *meta*-analyses using prospective cohort study data suggest an inverse association among them (Elwood et al., 2010). Interestingly, there was no significant enhance in the threat of high-fat dairy contents in comparison to low-fat dairy contents (Soedamah-Muthu et al., 2011). In porcine satellite cells, PA significantly stimulates glucose uptake at low or insufficient insulin concentrations (Che et al., 2013).

Two separate studies conducted by Schönfeld et al. (2004) and Komen et al. (2007) suggest that both hypo- and hyper-PA levels disturb mitochondrial homeostasis through abnormal hypersensitization of mitochondria by modulating permeability transition and membrane H^+ conductance, disturbing protein-associated effects in energy coupling, and thereby reducing ATP supply in the cells. This also significantly modulates the release of endogenous Mg^{2+}, K^+ and Cl^-. These reports suggest that a moderate level of cytosolic PA might be necessary for proper mitochondrial functioning (Schönfeld et al., 2004a, Komen et al., 2007). Studies report that the plasma PA concentration of healthy subjects varies from 0.04 to 11.5 μM (Al-Dirbashi et al., 2008, Nakanishi et al., 2016), while in Refsum disease its level has been seen between 240 and 1400 μM (Nagai and Teratology, 2015). Furthermore, PA-mediated Sjogren-Larsson syndrome (SLS) disease remains unresolved (Willemsen et al., 2004).

Conclusion

PA, known as a phytol-lipotoxic metabolite at high concentrations, may be linked to Refsum's disease and other peroxisomal enzyme deficiency diseases in humans, including RCDP and LD. Hyper-PA is also found to be associated with progressive ataxia and dysarthria and an increased risk of some lymphomas, such as LBL, FL, and NHL. Moreover, ZHDA and Alzheimer's disease have also been associated with a high plasma level of PA. However, hyper-PA-mediated SLS is still controversial. Through the decarboxylation mechanism, alpha-oxidation of PA results in formic acid, which is a toxic component in our body. The accumulation of PA and its effects in humans and other animals are assumed to be sex-dependent, and it is considered a cardiac biomarker. PA is evidently involved in interactions with PPAR-α, -δ and -γ subtypes as well as the RXR for many important biological functions in humans and other animals. PA has anti-inflammatory and immunomodulatory effects and can be used to prevent and treat obesity-linked dysfunctions, metabolic syndrome, or T2DM. The teratogenic potential and effects of PA on prostate cancer remain controversial. A moderate plasma PA level might be necessary to maintain normal mitochondrial functions in humans. The cytotoxic effects of PA through diverse mechanisms might be an indication of its use in cancer chemotherapy, especially in brain and breast cancer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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