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ARTICLE

- Phytanic acid, a daily consumed chlorophyll-yielded phytol bio-metabolite:
A comprehensive review** **1025**
Md. Torequul Islam, Eunus S. Ali, Ricardo M. de Carvalho, Márcia F. C. J. Paz,
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Review

Phytanic acid, a daily consumed chlorophyll-yielded phytol bio-metabolite: A comprehensive review

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An important chlorophyll-derived diterpenoid essential oil, phytol (PYT) bio-metabolite, phytanic acid (PA) has a number of pathophysiological contributions. The PA metabolism and its plasma levels associated phenomena are continuously being researched on. This study aims to look at the complete current scenario of PA. The findings suggest that PA has anti-diabetic, cytotoxic, anticancer and anti-teratogenic activities. Although PA-mediated Refsum's Diseases (RD), Sjogren-Larsson Syndrome (SLS) and prostate cancer are still controversial; Zellweger's Disease Hyperpipecolic Academia (ZDHA), Rhizomelic Chondrodysplasia Punctata (RCDP), Leber Disease (LD) and oxidative stress leading to mitochondrial and cardiac complications are also evident. In conclusion, PA may be a good biomarker of some pathophysiological phenomena and can be used for medico-pharmaceutical functions.

Key words: Phytanic acid, phytol bio-metabolite, biomarkers, pathophysiological contributions.

INTRODUCTION

Chemically, 3,7,11,15-tetramethylhexadecanoic acid (phytanic acid) is a phytol (PYT) degraded and saturated branched-chain fatty acid, which is a C20 oxygenated hydrocarbon. It is made up of a C16 backbone and 4 methyl (-CH₃) groups. Phytanic acid (PA) is a good substrate for chemical synthesis and is found in both marine and terrestrial food chains (Islam et al., 2015).

From the earlier evidence, elevated serum PA levels are characterized by a number of childhood complications as well as the most well-known incident, Refsum's

Disease (RD). PA may be associated with the production of formic acid, cardiac complications, Sjogren-Larsson Syndrome (SLS), cytotoxicity, lymphomas (Islam et al., 2015) as well as neurological damages (Nagai, 2015) due to its elevated serum levels. The high plasma PA levels are also evident in Rhizomelic Chondrodysplasia Punctata (RCDP), chronic polyneuropathy, bilateral shortening of the proximal phalanges, ichthyosis, progressive ataxia and disarthria (Islam et al., 2015).

However, PA, due to its specific action on receptors,

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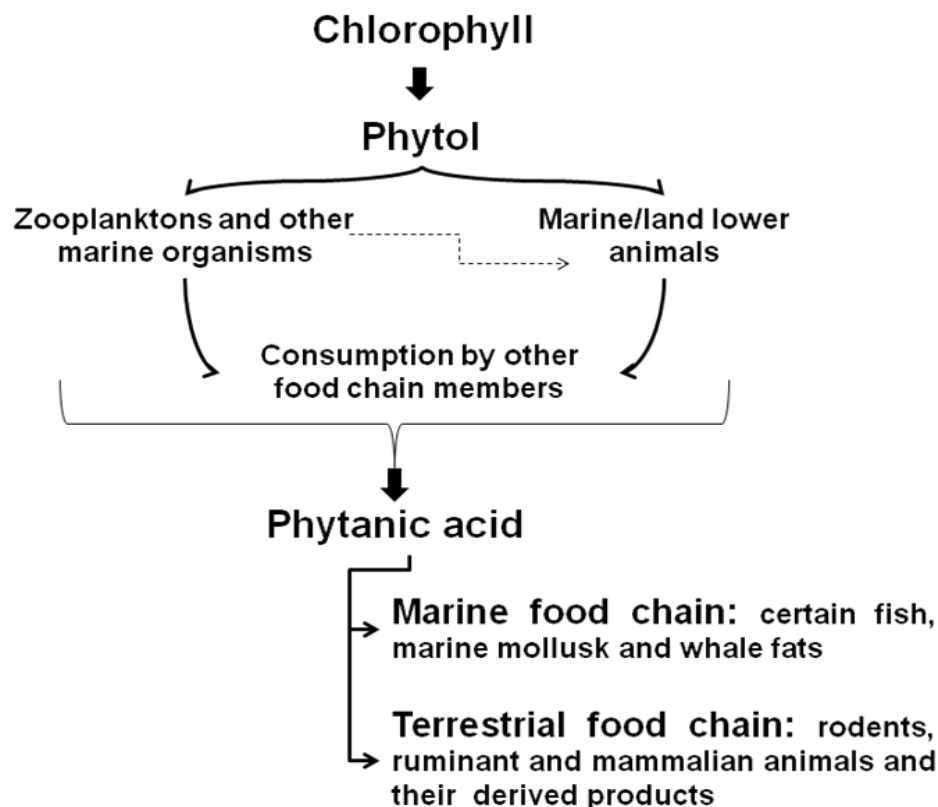


Figure 1. Phytanic acid in food chain.

retinoid X receptor (RXR) and proliferator-activated receptor- γ (PPAR γ), is now considered to have a number of beneficial physiological effects such as -cellular growth and differentiation, reproduction, embryonic development (Islam et al., 2015), management of type 2 (insulin dependent) diabetes (Che et al., 2013; Elmazar et al., 2013) and cholesterol lowering (Peter et al., 2014), respectively. In addition, there are also talks for PA mediated anti-teratogenic and mitochondrial membrane permeability (Islam et al., 2015) capabilities. Although PA interceded prostate cancer is controversial (Kataria et al., 2015), there is a notion for anti-mammary cancer potentials of some PA derivatives (Liska et al., 2012).

This study aims to make a comprehensive review on the chlorophyll-derived PYT bio-metabolite, PA.

FINDINGS

Sources and synthesis

In rats, about 95% of intact chlorophyll passes through the digestive system, leaving only 5% of the PYT available for conversion to PA. PA is especially abundant in the contents of ruminant animals (cows and sheep)

such as fat, liver, plasma, milk, butter, cheese, meat and rumen; although there is no evidence in poultry meat. However, PA is also present in pigs (non-ruminant). PA amount ranges from 0.01 to 0.3% of the total fatty acid pool, but can exceed the 10% mark in milk from cows fed with silage, the fermented grass that is used as winter-feed for cattle. High amounts were also detected in Antarctic krill (1.4%), plankton, mollusks, fish oil, whale oil and milk. In addition, high levels of PA are present in earthworms up to 3.5%. However, almost no PA is present in vegetables (Islam et al., 2015). PA in the food chain is shown in Figure 1.

PA is degraded by a process called α -oxidation, because a methyl group on its C3 position makes β -oxidation impossible and the hydroxylation of PA at C2 is the first step of α -oxidation. Pristanic acid (PRA) (2,6,10,14-tetramethylpentadecanoic acid) is the C19 α -oxidation product of PA. At first, by the help of phytanoyl-CoA hydroxylase, PYT converts to α -oxidation of phytanoyl-CoA. This results in 2-hydroxyphytanoyl-CoA, followed by shortening of one carbon to aldehyde, pristanal (2,6,10,14-tetramethylpentadecanal) and finally to PRA in liver and fibroblasts in humans (Wanders et al., 2011; Islam et al. 2015).

It is noted that PYT is converted into PA in the microsomes of ER, which is rich in fatty acid oxidation (FAO) enzymes. This is done by the subsequent action of

alcohol and aldehyde dehydrogenase (ADH) enzymes, where acyl-CoA synthetase helps to get phytanoyl-CoA (a bona fide intermediate of PYT), then a reductase enzyme reduces it to phytanoyl-CoA. Phytanoyl-CoA is further broken down via the peroxisomal α -oxidation to PA. However, PA can be obtained after reduction of PYT to dihydro-PYT leading to phytanal. PA occurrence and metabolism pathways are depicted in Figure 2 (Wanders et al., 2011).

Once the α -oxidation product, PRA occurs, it is now converted to pristanoyl-CoA in peroxisomes. However, peroxisomal membrane is semi-permeable with compounds having molecular wt. 300 to 400 Da; thus allowing both of them through the porin PXMP2; whereas larger Mw compounds like phytanoyl-CoA require specific carrier proteins including PMP34 for ATP. Thus, both of them may act as starting materials. 2-hydroxyphytanoyl-CoA is the prime in the α -oxidation pathway followed by pristanal, PRA and pristanoyl-CoA. The latter is ready for subsequent β -oxidation in peroxisomes and mitochondria. It undergoes three cycles of β -oxidation in peroxisomes. In a study, fibroblasts from patients with a deficiency at the level of mitochondrial carnitine/acylcarnitine shows an accumulation of 4,8-dimethylnonanoylcarnitine. Finally, the end-products of pristanoyl-CoA β -oxidation are subsequently shuttled to mitochondria for further degradation following two distinct pathways: 1) carnitine-dependent and 2) carnitine-independent routes. Although the ultimate products in the former case are un-clear, CoA esters (acyl-CoA thioesterases) present in peroxisomes are thought to be responsible for various short and medium chain fatty acids (Wanders et al., 2011) (Figure 2).

Digestion and absorption

PA is nearly completely absorbed in the small intestine of ruminants and non-ruminants. Pancreatic lipase and phospholipases A2 and B in the digestive tract release PA from dietary triglycerides or other lipids, which are incorporated into mixed micelles. Micelles then transfer their contents into enterocytes, thus leading to PA incorporation into triglycerides and other lipids. They are exported with chylomicrons, just like other long-chain fatty acids (Wierzbicki et al., 1999).

Transport and cellular uptake

PA is transported with all major lipoproteins and enters cells through receptor-mediated uptake. There is a possibility of reverse transport from tissue deposits via high-density lipoproteins (HDL) (Wierzbicki et al., 1999).

Storage, excretion, and regulation

The triglycerides in adipose tissue are thought to be the

major storage sites of PA and its oxidation product, PRA (Chambrud et al., 1999).

Excretion is still controversial, but it passes through the same means as the fatty acid intermediates occur (Chambrud et al., 1999).

Regulation may involve phytanoyl-CoA dioxygenase through intracellular signaling, since it is the specific target of the immunosuppressant binding protein immunophilin, FKBP52 (Chambrud et al., 1999).

Metabolism profile in human and/or other animals

According to Little et al. (2002), human UDP-glucuronosyl transferases (UGTs) are responsible for PA glucuronidation in the liver, stomach and intestinal microsomes. However, Gloerich et al. (2007) demonstrated that peroxisome proliferator-activated receptor- α (PPAR α) is responsible for PYT metabolism to PA in mice (Watkins et al., 2010).

Ruminants and great captive apes/cohort of humans (e.g. chimpanzees, bonobos, gorillas, and orangutans) after the fermentation of ingested plant materials by gut microbes can liberate PA and accumulate in fats. Otherwise, the members of marine food chain can accumulate PA by ingesting zooplankton and/or krill, which are rich in PYT and chlorophyll-related precursors (Wanders et al., 2011).

PA can be obtained as RBC bound stuff (Watkins et al., 2010), which could serve as a biomarker for evaluating digestive health (Moser et al., 2013) and influence the functions of nervous, cardiovascular, and skeletal systems in human and great apes (Watkins et al., 2010).

PATHO-PHYSIOLOGIC CONTRIBUTIONS

Childhood complications

Infantile PA storage disease (IRD), ZDHA or NALD have been depicted with characteristic facial dysmorphism, sensorineural hearing loss, severe visual impairment, retinitis pigmentosa, hypotonia, hepatomegaly, and shunted growth at an elevated serum PA and PA-oxidase levels (Islam et al., 2015).

PA in Refsum's disease (RD)

RD is termed PA storage disease categorized as Early Refsum's Disease (ERD) and Adult Refsum's Disease (ARD). It is more common phenomenon in elevated PA levels (Mukherji et al., 2002) where PA is accumulated in lipids of liver, kidney, muscle and urine of patients (Klenk and Kahlke 1963). RD (heredopathia atactica polyneuriformis) was first described by Sigvald Refsum (neurologist), in 1946. The symptoms are characterized by retinitis pigmentosa, peripheral neuropathy, cerebellar

ataxia and elevated protein concentrations in the cerebrospinal fluid in the absence of an increased number of cells. In addition, anosmia was found in nearly all RD patients; while deafness, ichthyosis shortened metacarpals or metatarsals, and cardiac arrhythmias were also regularly present (Wierzbicki, 2007). RD is mainly characterized by defective α -oxidation (Wierzbicki, 2007) but normal Ω -oxidation at β -end of PA to 3-methyladipic acid (3-MAA), thus an increase in the clearance of PA (Wanders and Komen, 2007). This ω -oxidation pathway is NADPH (reduced nicotinamide adenine dinucleotide phosphate); it is dependent and can be inhibited by imidazole derivatives (Komen et al., 2005) such as ketoconazole, clotrimazole, bifonazole, miconazole and CO (carbon monoxide) but these are the powerful inhibitors of cytochrome P-450 (CYP450); thus CYP450 may be involved in PA metabolism (Matsunaga et al., 1998). CYP4 (Xu et al., 2006) CYP4F3A, CYP4F3B, CYP4F2, and CYP4A11 are the important clearance mediator enzymes (Komen and Wanders, 2006). There is a methyl group at the β -position of PA, which hinders its α -oxidation. However, the urine of RD patients revealed the presence of 3-methyladipic acid and 3,6-dimethyl octanedioic acid, which are presumed intermediates due to PA ω -oxidation. This has increased the interest in the research of its ω -oxidation route. In a study done on mouse model, there was a possible pathway for ω -oxidation of PA where the gene encoding phytanoyl-CoA 2-hydroxylase was disrupted. Briefly, ω -oxidation of PA yields phytane-1,16-dioic acid upon activation which may be degraded by β -oxidation from the ω -end to produce the different acyl-CoA esters and corresponding free fatty acids after thioesterase-mediated cleavage of the CoA esters (Wanders et al., 2011) (Figure 2). Ultimate result is the corresponding short and medium chain fatty acids, which after further mitochondrial oxidation may produce water and carbon-dioxide.

PA in cytotoxic and oxidative stress

A cytotoxic effect in astroglia cells was addressed to a combined action on Ca^{2+} regulation, mitochondrial depolarization, and increased reactive oxygen species (ROS) generation in the brain (Kahlert et al., 2005), where there is a decline of Ca^{2+} loading and severe release of CYPc (Schönfeld et al., 2006). Thus by apoptosis in mitochondrial route, it initiates cell death (Reiser et al., 2006). PA stimulates ROS generation by inactivating aconitase and oxidation of the mitochondrial glutathione pool, thus resulting in oxidative damage (Schönfeld and Reiser, 2006), the eventual characterization of the impairment of mitochondrial respiration and homeostasis (Busanello et al., 2013). According to Busanello et al. (2010), PA disrupts Na^+K^+ -ATPase activity and the electron flow through the respiratory chain in the brain cortex of the PA disordered

patients, resulting in neurological damage and raised body PA levels. Moreover, both the PA and PRA mediated Ca^{2+} deregulation can stimulate the free fatty acid receptor GPR40 (G-protein-coupled receptor), which is the signaling cascade of the toxicity of these two acids (Kruska and Reiser, 2011). Conversely, Nagai (2015) claimed that PA induces mitochondrial abnormality and cell death by the activation of Hdac2, 3 in Neuro2a cells, thus the neuronal damage in RD with associated peroxisomal disorders and the accumulation of PA in tissues and body fluids. However, the PA (>1 mM) in RD can perturb normal lipid homeostasis through PPAR α gene leading to lipid degradation, which might explain the loss of adipose tissue in this category of patients (Gloerich et al., 2005).

PA in other phenomena

Along with RCDP, other well-known peroxisomal disorder, Leber Disease (LD) also has been reported with elevated PA levels in tissues and body fluids (Schönfeld, 2004). Later an elevated serum PA concentration was reported in an older patient (age 47 yrs) with poor nearsighted vision characterized by chronic polyneuropathy, bilateral shortening of the proximal phalanges, and ichthyosis (Yamamoto et al., 1995). A lofty plasma PA and PRA levels was also demonstrated in the progressive ataxia and disarthria (Clayton et al., 1996). Patients suffering from RD have the deficiency of PA α -hydroxylase namely phytanoyl-CoA hydroxylase (Zomer et al., 2000a) and more specifically phytanoyl-CoA2 hydroxylase (Wanders et al., 2011) in peroxisomes; on the other hand, the RCDP patients experience α -hydroxylation of PA as well as decarboxylation of α -hydroxy-PA deficiency (Pahan et al., 1996). Now, it is evident that transport and biochemical pathways of PA are mediated by phytanoyl-CoA 2-hydroxylase (PAHX) and 2-hydroxyphytanoyl-CoA lyase in peroxisomes (Wierzbicki et al., 2002). Thus, not only α -hydroxylation of PA but also decarboxylation of α -hydroxy-PA complications may raise plasma PA levels. According to Verhoeven et al. (1998), the toxic substance, formic acid is a decarboxylation product by the α -oxidation of PA.

PA in retinoid cells and type 2 diabetes (IDDM)

Now, it is evident that PA is a true physiological ligand for PPAR α , PPAR δ and PPAR γ subtypes as well as the retinoid nuclear receptor, RXR (retinoid X receptor) (De Keyser, 2006). The oxidative metabolites of retinoic acid (RA) and all *trans*-forms of it are essential for cellular growth and differentiation, reproduction, and embryonic development (Arnhold et al., 2002). PA being the RXR-agonist stimulates the intestinal CYP26 gene (P450RAI) expression and metabolism of all-*trans*-RA in intestinal

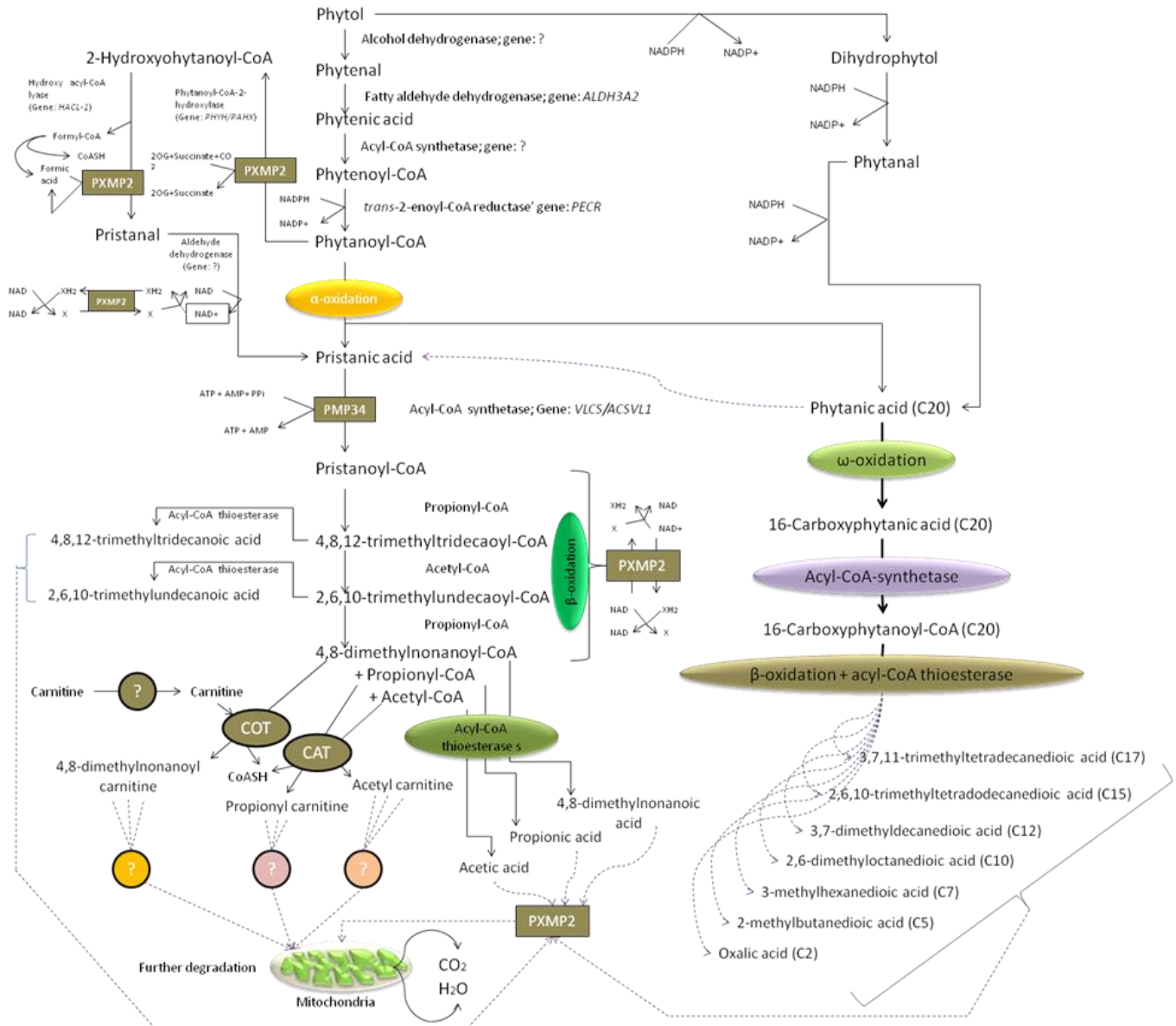


Figure 2. Occurrence and metabolism of phytanic acid (Wanders et al., 2011). NAD⁺, oxidized nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; NADP⁺, oxidized nicotinamide adenine dinucleotide phosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate; ATP, adenosine tri-phosphate; AMP, adenosine mono-phosphate; CoA-SH, co-enzyme-A-thiol; PPI, inorganic phosphate; PHYH, phytanoyl-CoA α -hydroxylase; HAC1, 2-hydroxyacyl-CoA lyase; PHYH/PAHX, phytanoyl-CoA 2-hydroxylase; PXMP2, peroxisomal membrane protein-2; PMP34, peroxisomal membrane protein-34; VLCS, ACSVL1: membrane-bound enzyme at the ER.

cells (Zomer et al., 2002b). In addition, PA by its stimulatory and influencing actions on nuclear receptors and gene expression can mediate cell differentiation especially adipocyte (both brown and white) in which high expression of phytanoyl-CoA hydroxylase occurs (Schluter et al., 2002). On the other hand, PA like thiazolidinedione drugs apparently stimulates the transcriptional activity of PPARs/RXR heterodimers, which is responsible for 2-deoxy-D-glucose uptake in hepatocytes in liver and metabolism. This suggests its potential role in the management of IDDM (Manuel,

2012). It may occur at no or inadequate insulin concentrations (Che et al., 2013); thus there is an indication for insulin resistance pathways by activation of nuclear receptors and heterodimerization of RXR with PPAR γ (Elmazar et al., 2013).

PA as anti-teratogenic agent

Retinoids and their receptors are involved both in normal and abnormal embryonic development (Chambon, 1993).

It is evident that all *trans*-RA and its natural precursor, retinol are teratogenic in a wider range of species (Lammer and Scott 1994). A research done on albino mice (mated female) demonstrated that PA greatly reduced the oxidative metabolism and teratogenic effects of retinol. As the ligand selective retinoid receptors, RAR (retinoic acid receptor) and RXR are required for efficient DNA binding and transactivation of target genes responsible for teratogenic effects, PA is evident for its action in this pathway (Arnhold et al., 2002). Tang et al. (2007). demonstrated that PA could increase the levels of retinyl esters (REs) in retinal cells and thus the inhibition of cell proliferation. However, a teratogenic potential was demonstrated by co-administration of a natural RXR ligand with a synthetic RAR agonist (Am580), thus this activity of PA is still contentious (Elmazar and Nau, 2004).

Hypo-/hyper-PA and their ultimate role in physiology

A low plasma PA (hypo-PA) level was claimed due to the deficiency of the enzyme, α -methylacyl-CoA racemase (Wierzbicki et al., 2002). Hypo-PA levels cause hypersensitization of mitochondria thus results in rapid permeability transition, which eventually increases membrane H^+ conductance and disturbs the protein-linked functions in energy coupling; and finally a reduction of ATP supply is the consequence of de-energized mitochondria. In this short term PA toxicity, a depolarization occurs by the stimulation of non-phosphorylating oxygen uptake and inhibition of the reduction of tetrazolium dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (Schönfeld et al., 2004). Moreover, the nonesterified PA in the high (hyper-PA) tissue levels increases the mitochondrial inner membrane permeability by opening the permeability transition pore, and initiating the release of endogenous Mg^{++} along with increasing H^+ conductance (protonophoric action); however it slightly stimulates the conductance of the inner membrane to K^+ and Cl^- (Komen et al., 2007).

PA in prostate and mammary cancers

Prostate cancer is substantiated in linking risk with polymorphisms in the α -methylacyl-CoA racemase (AMACR) gene and branched-chain fatty acids. PA may be one of them (Wright et al., 2012) but there is no causal link between circulating PA levels and the prostate cancer (Kataria et al. 2015). On the other hand, PA precursor (PYT) co-treatment with vitamin D analogue has been pointed out for anti-mammary cancer potential (Liska et al., 2012).

PA in cardiac complications

PA can be readily incorporated in phospholipid fraction of

retinal cells in human (Young et al., 2011) and myocardial membranes in mice. The latter one is responsible for bradycardia and impaired AV nodal as well as intraventricular impulse conduction, which may lead to a sudden cardiac death (Monnig et al., 2004).

PA in other diseases

Patients suffering from SLS are characterized by ichthyosis, mental retardation and spastic diplegia or tetraplegia thought to be accumulation of long-chain aliphatic alcohols; it is evident that there is a deficiency in microsomal enzyme, FALDH that is the ultimate result of elevated PA levels in SLS patients. However, it is still controversial whether PA contributes to produce this disease or not (Willemsen et al., 2004).

A vast intake of dairy fat can modify the plasma PA levels (Werner et al., 2011) and according to Ollberding et al. (2013), much consumption of beef milk rich in phytol is associated with increased risk of some lymphoma such as - large B-cell lymphoma (LBL), follicular lymphoma (FL) and non-Hodgkin lymphoma (NHL).

Miscellaneous

PA is evident for a synthetic aid of penicillin and cephalosporin derivatives mainly glutaryl-7-aminocephalo PA (Xu, 2004) and some fatty acids (Rudolf, 2012). In addition, it has topical applicability (Vollhardt, 2010) and is used as a recovering agent for the byproduct methyl chloride of glyphosate acid in chemical industry (Ji, 2003), demonstrating PA as a versatile organic bio-metabolite and use thereof.

DEMONSTRATIVE CONJUNCTURES

Although there is no evidence that the PA content of normal diets affects human health, its elevated levels in body tissue fluids are coined for its contribution to RD, NHL, cardiac death, neurological damages, and few childhood complications. Still, PA contribution to the SLS patients is controversial. Moreover, hypo-PA level in body is evident for de-energization and eventually loss of mitochondrial homeostasis. The anti-teratogenic effects of PA are still controversial but there are evidences for its management of type 2 diabetes (Wanders et al., 2011; Islam et al., 2015).

As the methyl group at C3 position makes PA unable to β -oxidation difficulty, the α - and ω -oxidations are well known (Figure 3). Patients' patho-physiology such as deficiency of metabolic enzymes or mutation in the genes of the enzymes are responsible for high plasma-PA levels of patients suffering from RD, SLS, RCDP and ZHDA (Wanders et al., 2011; Islam et al., 2015).

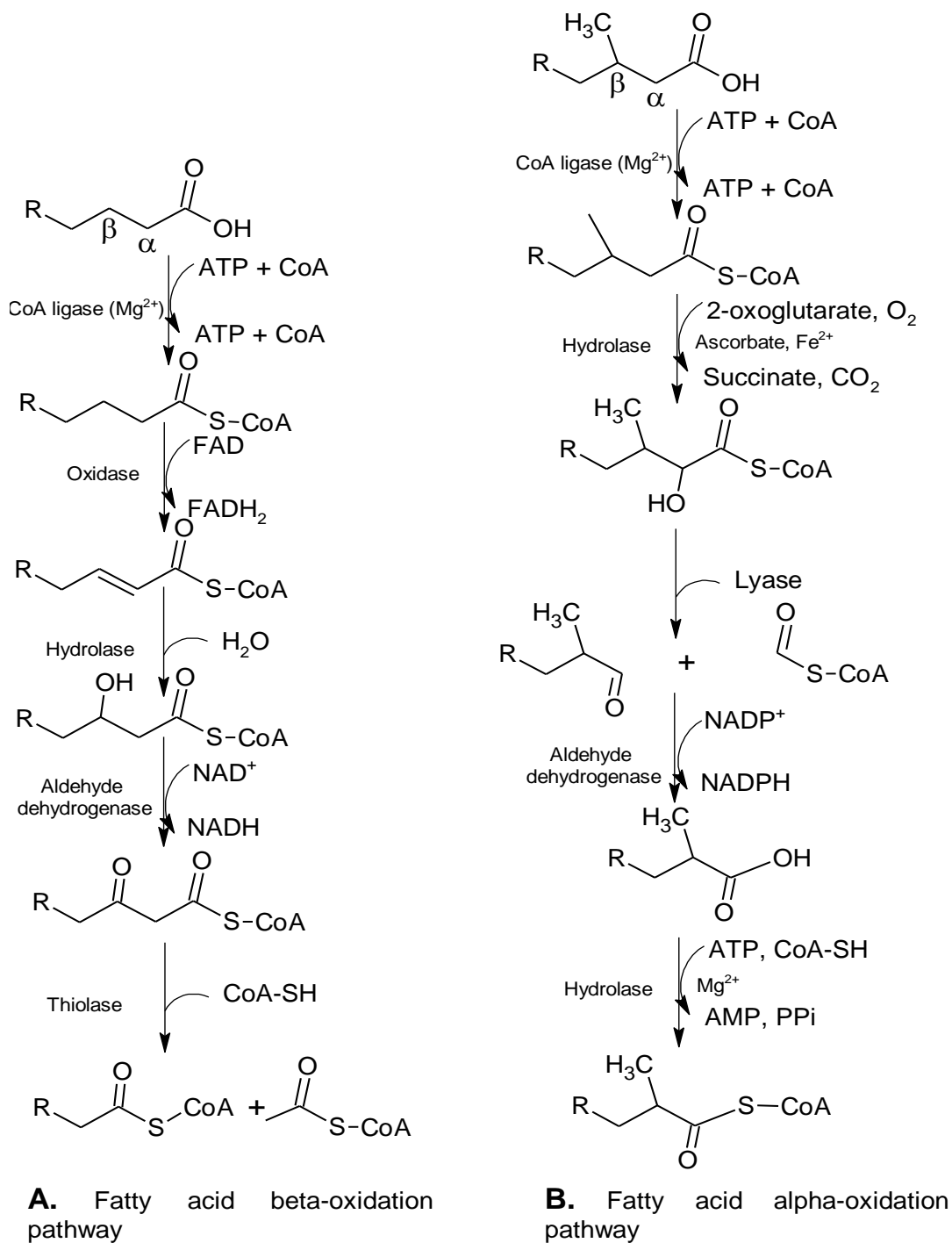


Figure 3. Fatty acid oxidation pathways.

Thus, toxicity due to PA in body elevation may be a controversial and an advance research topic. It has been depicted that PA levels in body fluids may be considered as a biomarker for the patients' benchmarking as PA complications including the digestive anomalies. Thus, phytanic acid may be an interesting bio-metabolite with medical and pharmaceutical considerations.

Conclusion

Phytanic acid may be considered as an important biomarker for some diseases such as RD, SLS, RCDP and ZDHA. However, having anti-diabetic, cytotoxic and anti-cancer, anti-teratogenic and cosmetic like activities makes it an interesting topic from medico-pharmaceutical

view-point.

Conflict of Interests

The authors have not declared any conflict of interests.

Abbreviations: **ACSVL1/VLCS**, Membrane-bound enzyme at the ER; **AMACR**, α -methylacyl-CoA racemase; **ARD**, adult Refsum's disease; **ERD**, early Refsum's disease; **FAO**, fatty acid oxidase; **HDL**, high density lipoproteins; **IDDM**, insulin dependent diabetes mellitus; **IRD**, infantile Refsum's disease; **LD**, Leber disease; **NALD**, neonatal adrenoleucodystrophy; **PA**, phytanic acid; **PPAR**, proliferator-activated receptor; **PYT**, phytol; **PAHX**, phytanoyl-CoA 2-hydroxylase; **RBC**, red blood corpuscles; **RCDP**, rhizomelic chondrodysplasia punctata; **ROS**, reactive oxygen species; **RXR**, retinoid X receptor; **SLS**, Sjogren Larsson syndrome; **ZDHA**, Zellweger's disease hyperperipolc acidemia; **3-MAA**, 3-methyl-adipic acid; **ADH**, aldehyde dehydrogenase; **AMP**, adenosine mono-phosphate; **ATP**, adenosine tri-phosphate; **AV**, arterio-ventricular; **CoA-SH**, co-enzyme-A-thiol; CYP450, - cytochrome P-450; CVS, cardio vascular system; DNA, deoxy ribonucleic acid; ER, endoplasmic reticulum; **FAD**, flavin adenine dinucleotide; **FADH**, reduced flavin adenine di-nucleotide; **FALDH**, fatty aldehyde dehydrogenase; **FL**, follicular lymphoma; **GRP40**, G-protein-coupled receptor-40; **HACL1**, 2-hydroxyphytanoyl-CoA lyase; **LBL**, large B-cell lymphoma; **NAD**, nicotinamide adenine dinucleotide; **NAD⁺**, oxidized nicotinamide adenine dinucleotide; **NADH**, reduced nicotinamide adenine dinucleotide; **NADP**, reduced nicotinamide adenine di-nucleotide phosphate; **NADP⁺**, oxidized nicotinamide adenine dinucleotide phosphate; **NADPH**, reduced nicotinamide adenine dinucleotide phosphate; **NHL**, non-Hodgkin lymphoma; **PDH**, pristanal dehydrogenase; **PHYH**, phytanoyl-CoA α -hydroxylase; **PHYH/PAHX**, phytanoyl-CoA 2-hydrolase; **PMP34**, peroxisomal membrane protein-34; **PXMP2**, peroxisomal membrane protein-2; **RAR**, retinoic acid receptor; **Res**, retinyl esters; **SCPx**, sterol carrier protein; **UDP**, uridine di-phosphate.

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