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New insights on pentadecanoic acid with special focus on its controversial essentiality: A mini-review

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ABSTRACT

Pentadecanoic acid (C15:0, PDA) is an odd and minor fatty acid that has been neglected in the literature until the last decade. Indeed, as a specific fatty acid of dairy fat, PDA was only used as a biomarker of dairy fat consumption. Lately, PDA was first correlated negatively with the incidence of metabolic syndrome disorder, then its physiological effects have been investigated as a protective fatty acid. PDA supplementation has been demonstrated as negatively correlated with elevated levels of leptin, plasminogen activator inhibitor-1 and insulin, and has been shown to exhibit sensitizing insulin effects with activation of AMPK pathway. PDA also reduced the severity of metabolic dysfunction-associated steatohepatitis (MASH), notably through reduced alanine transaminase and pro-inflammatory cytokines levels. The final effect described for PDA is its ability to display anti-inflammatory properties in several pathology models. Hence, considering these multiple effects, the presence of PDA could be associated with a healthier physiological state, this raises the question of whether the presence of PDA in the body, in adequate quantities, is needed to participate to health maintenance. PDA is not synthesized in sufficient quantities endogenously, so it must be provided by the diet, mainly through dairy fat, although other types of food can also contribute to the dietary intake of PDA. Essential fatty acids are described as not being endogenously synthesized in sufficient and required quantities to maintain physiological health. Thus, PDA might gather both conditions to be described as essential, yet further investigations on both criteria are needed to enhance knowledge on this odd chain fatty acid with promising impact as potential protective supplement nutrient.

Contents

Abbreviations: ALT, Alanine transaminase; AST, Aspartate transaminase; AT, Adipose tissue; CAC, Citric acid cycle; CD-HFD, Choline deficient high fat diet; EFA, Essential fatty acid; ELOVL, Elongation of very long-chain fatty acid; FA, fatty acid; FADS, Fatty acid desaturase; HDA, C17:0, Heptadecanoic acid; LPS, Lipopolysaccharides; MASH, Metabolic dysfunction-associated steatohepatitis; MASLD, Metabolic dysfunction-associated liver disease; MCD, Methionine and choline deficient; MRI, Magnetic resonance imaging; MUFA, Monounsaturated fatty acid; OCFA, Odd chain fatty acid; PDA, C15:0, Pentadecanoic acid; T2D, Type 2 diabetes; SCD1, Stearyl CoA desaturase 1; SCFA, Short chain fatty acid.

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1. Introduction

Pentadecanoic acid (PDA, C15:0), an odd chain fatty acid (OCFA), is a minor yet specific saturated fatty acid (FA) of ruminant fat. In bovine milk, PDA is the major OCFA followed by heptadecanoic acid (HDA, C17:0), accounting respectively for approximately 1 % and 0.5 of total milk FAs [1]. Dietary intake of dairy products and more specifically dairy fats has been linked to protective effects of metabolic syndrome linked pathologies like type 2 diabetes (T2D), cardiovascular diseases and metabolic dysfunction-associated liver disease (MASLD) [2–5]. For over 25 years, PDA and HDA have been described as marker of dairy fat intake in the adipose tissue (AT), as these OCFAs were found exclusive of dairy [6]. While their use as specific dairy fat intake plasma biomarker is now recently challenged [7], PDA, and in lesser extent HDA, plasma concentrations are found inversely correlated with T2D [8,9], coronary heart disease [10] and metabolic dysfunction-associated steatohepatitis (MASH) incidents [11]. The associations of PDA plasma concentrations and lower incidences of various pathologies are leading studies to suggest that PDA intakes might have protective effects against them. Although the potential protective role of PDA has only been described through correlations, a causal relationship between PDA intake and reduced incident of metabolic pathologies is not totally demonstrated. More recently, PDA has been investigating as a supplement FA in both *in vitro* and *in vivo* metabolic syndrome disorder studies to better comprehend its role as a protective FA. Henceforth, the literature is beginning to gain arguments in favor of the hypothesis of PDA's protective effects against metabolic syndrome disorder. More recently, some original studies introduced the hypothesis that PDA might have sufficient characteristics and metabolic functions to be considered as essential in human nutrition [12]. Indeed, a fatty acid is described as essential when it meets the following criteria: 1) it is not endogenously sufficiently synthesized by the body, hence it must be supplied by the diet. 2) is required to maintain a healthy physiological state. Therefore, in light of the reported health effects of PDA, notably on metabolic health, and its very low synthesis in human, PDA appears as a potential candidate for a newly described essential fatty acid (EFA). However, this claim by S. Venn-Watson must be cautiously examined to avoid over-interpretation of scientific data [12]. As a minor and very uncommon FA, PDA is not the subject of many literature revues, yet it appears to be an interesting controversial FA regarding its origin and its partially understood physiological effects. Hence, the present mini review aims to discuss about the controversial potential essentiality of PDA, focusing on its (dietary) origin, metabolism and its reported protective health effects against metabolic syndrome disorders.

2. Dietary origin of pentadecanoic acid: ruminal synthesis

PDA's odd carbon length specificity originates from bacterial synthesis. Indeed, rumen bacteria can produce propionate, a short chain fatty acid (SCFA), notably as end products of fiber fermentation [13]. Propionate (C3:0) can be used instead of acetate (C2:0) as starter unit of *de novo* fatty acid synthesis in rumen bacteria [14,15]. The final product of this synthesis is PDA instead of palmitic acid (C16:0) when acetate is used as stater unit. Ruminal PDA produced can be absorbed through enterocytes and distributed in the bloodstream, as chylomicrons, notably in the mammary gland cells [16]. Noteworthy, like a great diversity of saturated FA synthesized *de novo* in the mammary gland cells, PDA was shown to also be produced *de novo* from propionate in cows and goats [15,17]. Nonetheless, to our knowledge such synthesis has not been described in the mammary gland cells in humans, most likely due to lower concentrations of propionate. Noteworthy, propionate levels in Holstein cow milk are found on average at 1.68 mg/L while it was found on average at 0.01 mg/L in human milk [18]. Hence, in ruminants PDA is then excreted in the milk as triglycerides in milk fat droplet (Fig. 1) [16]. The fact that PDA production occurs by ruminal synthesis leads to a higher quantity of PDA in ruminant milk than that in other food products. Yet, another pathway has been described for the synthesis of PDA, the α-oxidation of C16:0. α-oxidation is a process that yields the removal of a single carbon from the carboxyl end of the FA. Using C16:0 as substrate of this reaction, the product formed is PDA. Culture of isolated rumen bacteria species incubated with [1–^{14}C] palmitate confirmed PDA can be produced by α-oxidation in some bacteria *in vitro* [14]. Nonetheless, later studies indicate the occurrence of this phenomenon is minor *in vivo* compared to *de novo* lipogenesis using propionate [19]. Noteworthy, α-oxidation also occurs in eukaryote cells (in peroxisomes), however the importance of C16:0 oxidation

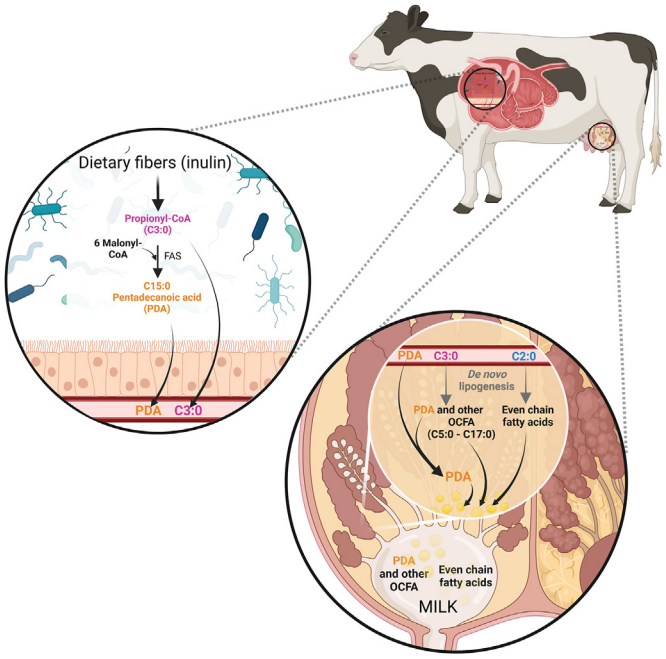

Fig. 1. Ruminal and bacterial synthesis appears the main synthesis pathway of pentadecanoic acid (PDA).
Pentadecanoic acid is synthesized by the microbiota in the rumen, from propionyl-CoA (C3:0) mostly derived from dietary fibers digestion. PDA and C3:0 can be absorbed by enterocytes and distributed in the body in the bloodstream. In the mammary gland, PDA enter the cells and is excreted in the milk. Circulant C3:0 can also be used to synthesize *de novo* PDA and other odd chain fatty acids (OCFA) from C5:0-C17:0, in a similar way as the *de novo* synthesis of even chain fatty acids from acetyl-CoA. Hence, even chain fatty acids, PDA and other OCFAs are extracted in the milk.

into PDA is not yet described. Indeed, this reaction is an intermediary step of the entire process of α-oxidation which ultimately leads to acetyl-CoA formation. Therefore, bacterial *de novo* lipogenesis using propionate appears to be the main pathway of PDA exogenous synthesis.

Recent studies have investigated the possibility of endogenous PDA synthesis from fiber fermentation by the gut microbiota in humans [20]. The fermentation of soluble fiber (e.g. inulin) by the gut microbiota resulted in propionate formation causing a slight, yet significant, increase of PDA and HDA plasma levels after 7 days of high inulin intake in patients (30 g/day). The supplementation of high quantities of propionate in the diet resulted in the same OCFA plasma level elevations. Thus, authors hypothesized a hepatic synthesis of OCFA from gut-derived propionate. To confirm, they incubated HepG2 cells, as an *in vitro* liver cellular model, with acetate and propionate at 500 μM with different ratios of these SCFA. Results showed elevated OCFA % in cells only when concentrations of propionate were higher than acetate. Thus, endogenous hepatic synthesis of PDA from gut-derived propionate seems unlikely as propionate concentration doesn't exceed acetate concentration in liver cells. Besides, studies showed inulin fermentation produces a 74:16:10 ratio of acetate: propionate: butyrate, *i.e.* higher bioavailable concentration of acetate than propionate [21,22].

Finally, another study showed that high soluble fiber intake (40 g/day) for 4 days does not increase PDA plasma levels in human [22]. Therefore, the use of high intake of soluble fiber fermentation for the synthesis of PDA in humans needs to be further characterized, but considering available data it does not appear to be an important pathway leading to OCFA intake.

Thus, considering the proportion of the different possible synthesis pathways of PDA, bacterial synthesis in ruminants appears as the main pathway leading to a significant synthesis and therefore presence of PDA in dairy products. Hence, dietary intake of PDA occurs as the only way to increase substantially its concentration in the body, as opposed to reported low endogenous synthesis.

3. Controversial use of PDA as biomarker of dietary intake

Due to its ruminal synthesis origin, PDA is present in higher quantities in ruminant milk fat than in other food in which it is almost exclusively found as traces. HDA, the elongation product of PDA, is also found in higher proportion in dairy fat. Hence, for over 20 years PDA and HDA have been considered as biomarkers of dairy fat consumption with strong associations established between the plasma or the AT PDA and HDA relative content and the intake of milk fat [6,23,24]. These associations between dairy fat consumption and PDA and HDA have been described even though PDA and HDA are present in low concentrations in the AT and plasma in humans with respectively 0.39 and 0.27 % of total FAs in the AT and 0.21 and 0.41 % of total FAs in plasma [8,25].

Yet, recent studies are challenging this assumption of dairy fat exclusivity and therefore their use as biomarker. Indeed, Bethancourt et al. showed that in an intervention trial with dairy fat consumption, PDA or HDA plasma levels and dairy intake were not significantly associated when the linear regression models were adjusted to the liver fat content (determined by magnetic resonance imaging (MRI)) [7]. Hence, they questioned the use of PDA and HDA as valid biomarkers of dairy fat. Nonetheless, a study on the European Food4Me database showed PDA serum levels were strongly associated with high-fat dairy intake yet not with low-fat dairy [26]. HDA associations with dairy fat intake were lower than PDA's ones, thus concluding only PDA should be used as biomarker, not HDA. Furthermore, studies about dairy intake should be viewed cautiously since dairy consumption highly differs between countries or more generally world regions [27]. Also, in these studies dairy products are not considered as a single group, e.g. with low fat dairy products or high fat dairy products, for which consumptions is also highly variable.

Another argument for challenging PDA as biomarker of dairy product is its detection in nondairy food in recent studies. Indeed, PDA have been detected and quantified in several food products [28]. For instance, in beef PDA accounts for 0.45 % of total FAs [29]. Hence, in a dietary meat intervention study, Mitchell et al. showed levels of PDA increase with higher meat consumption for 12 weeks in men [30]. In certain type of fish PDA represents over 1 % of total FAs (e.g. mullet, PDA = 1.56 % of total FAs) [31]. However, to better comprehend PDA's dietary importance, further studies need to investigate the dietary intake of PDA according to the fat content of the food product. Taken together, these elements appear to contribute to the absolute PDA dietary intake.

To conclude on the validity of PDA as a biomarker of dairy fat consumption, there is a need to quantify the nondairy products dietary PDA intakes to compare to the one of dairy fat. Nonetheless, considering the reported good correlations between PDA plasma concentrations and dairy fat intake, PDA appears as a good biomarker of dairy fat.

4. Pentadecanoic acid's metabolism

Only a few studies have investigated PDA's metabolism, i.e. its metabolic conversion into longer chain length saturated or unsaturated FAs, its incorporation into complex lipids such as triglycerides or phospholipids or its metabolic use through mitochondrial β-oxidation. Concerning PDA conversion, Wang et al. showed that the elongation of PDA to HDA is mainly yielded by elongation of very long-chain fatty acid (ELOVL) 6 protein in human cells *in vitro*. ELOVL 7 was also shown to catalyze the elongation of PDA into HDA yet with lower activity than ELOVL 6 [32]. Hence, as expected PDA can be converted into HDA in human. Fatty acid desaturase (FADS) 2 activity towards OCFA has also been studied [33]. In this study FADS2, encoding Δ6 desaturase, was shown to yield the desaturation step of HDA (C17:0) into monounsaturated FA (MUFA) C17:1 n-11. PDA was not found substrate of FADS2 desaturation. Noteworthy both PDA and HDA were not found substrate of the Δ5 desaturase, encoded by FADS1 gene. Finally, authors described only HDA to be substrate of the Δ9 desaturase, encoded by Stearyl CoA desaturase 1 (SCD1) gene, though specific activity of SCD1 was determined for HDA and PDA. Indeed, PDA was found substrate of SCD1, leading to the formation of C15:1 n-6 from Δ9 desaturation of PDA [34]. Finally, PDA mitochondrial β-oxidation can lead to the synthesis of anaplerotic substrates of the citric acid cycle (CAC). Indeed, it can be entirely β-oxidized yielding 6 acetyl-CoA molecules and one of propionyl-CoA. Propionyl-CoA can be converted to methylmalonyl-CoA which can itself be converted in succinyl-CoA, an anaplerotic intermediary substrate entering in the CAC. Hence, in case of mitochondrial dysfunction, like long chain FA oxidation disorder, β-oxidation of PDA (and other OCFA) could provide anaplerotic intermediary substrates of the CAC, through the propionyl-CoA conversion into succinyl-CoA, thus potentially improving mitochondrial metabolism [35].

5. Health benefits: reported protective effects on metabolic syndrome - focus on T2D and MASH

Dairy products intake has been reported to be protective against T2D and MASLD [2,5]. Later, PDA plasma concentration has been negatively correlated with incidence of T2D and MASH [8,9,11]. Hence, PDA presence seems to be associated with protective effects against T2D and MASH incidence. So far, only correlations were described, no causal relationship has been demonstrated. Recently,

studies have investigated its protective effect against MASH incident *in vivo* using PDA supplemented diets. Yoo et al. have correlated negatively PDA plasma concentration to MASH activity and hepatocyte ballooning scores in a 106 patients cohort with MASLD [11]. Noteworthy, in this study PDA was also negatively correlated with fasting glucose levels and aspartate transaminase (AST). To follow up, authors have evaluated the effect of a supplementation of PDA on MASH parameters *in vivo* on mice treated with methionine and choline deficient (MCD) diet, as MASH model. In MCD mice, PDA dietary supplementation reduced AST levels and the number of liver ceroid-laden macrophages. Thus, PDA contributed to improve liver inflammation, acting as a modulator of liver injury parameters. To corroborate, another study assessed the preventive effect of PDA in choline deficient high fat diet (CD-HFD) induced mice [36]. The authors described that PDA reduced AST and alanine transaminase (ALT) levels as well as pro-inflammatory cytokines (TNF-α and IL-6) thus concluding on PDA's hepatoprotective effects. Authors investigated PDA's effect on dysbiosis-driven gut barrier dysfunction as acting parameter contributing to MASH development. In mice, CD-HFD increased portal vein serum lipopolysaccharides (LPS) levels (used as indicator of gut barrier function). PDA supplementation reduced portal vein serum LPS levels thus restoring gut barrier function, notably through higher tight junction protein expression, e.g. E-cadherin. Therefore, PDA seems to have a direct effect on MASH incident by limiting the liver inflammation in mice, hence it remains to be studied in humans. Yet, an *in vivo* study on another model, MASH induced New-Zealand white rabbits, showed daily oral PDA induces less severe liver fibrosis [12]. Thus, the protective effect of PDA on MASH seems to be similar between species. Linked with PDA effect on reduction of inflammatory state, the same authors showed PDA supplementation reduces some metabolic syndrome parameters (e.g. reduction of proinflammatory cytokines, lower weight and cholesterol levels) in high fat diet fed mice.

Noteworthy, it seems to exist some differences between PDA and HDA physiological effects. Indeed, while PDA appears to exhibit protective effect against MASH, a recent study indicates HDA does not [37]. HDA supplementation on high fat diet fed mice does not reduce hepatic fibrosis. However, further investigations are needed to conclude on the differential effects of PDA and HDA. In fact, this study does not compare PDA effect to HDA's one on this HFD fed model, which is a different diet than CD-HFD mentioned in the studies above. Nevertheless Bishop et al. showed PDA, but not HDA, increased insulin-mediated phosphorylation of AKT in primary cultured mice hepatocytes *in vitro*. Another study corroborates the insulin-sensitizing effect of PDA, with the promotion of glucose uptake through AMPK pathway in myotubes [38]. Finally, a 567 participants cohort study aimed to correlate saturated FA levels in serum phospholipids with adipokines levels [39]. Authors showed PDA and HDA serum concentrations were associated with favorable serum adipokine profile (e.g. associated with lower levels of leptin and plasminogen activator inhibitor-1 (PAI-1)) compared to even chain saturated FAs. Another study corroborates these negative correlations in another cohort [4]. Leptin is a hormone involved in feeding behavior regulation and has been shown to contribute to chronic inflammation in obesity [40]. PAI-1 regulates coagulation and has been shown to participate in endothelial dysfunction, both are involved in glucose metabolism [39]. For both adipokines, high concentrations were found associated with an increased risk of T2D incidence in humans [41,42]. Hence, PDA's negative associations with leptin and PAI-1 levels reinforce the hypothesis of PDA's protective effect against T2D incidence.

Thus, all these studies resumed in Table 1 provide arguments and potential underlying mechanisms for the protective effects of PDA against MASH, T2D incidences and more generally metabolic syndrome disorders.

6. Pentadecanoic acid: regular or essential fatty acid in human nutrition?

Considering the reported protective effects of PDA described in the literature, henceforth some studies are now considering PDA has a potential EFA. Indeed, Venn-Watson et al. investigated PDA's reported effect *in vitro* and *in vivo* in models of diet-induced obesity and MASH disorder [12]. Briefly, authors showed PDA supplementation reduces several metabolic linked disorders such as the reduction of pro-inflammatory state in diet-induced obese mice or some MASH parameters. In this study, authors claimed PDA checked the criteria of an EFA with 1) the absence of endogenous synthesis of PDA, 2) PDA is a bioactive fatty acid with activities associated with health benefits in human and lower PDA intake or plasma concentration are associated with poorer physiological state. Therefore, stating PDA should be considered as a potential EFA. Later, same authors investigated PDA's broad range of activities *in vitro* [46,47]. Briefly, these *in vitro* studies concluded on PDA's abilities to decrease several quantitative parameters (e.g. reduction of pro-inflammatory cytokines and markers (TNF-α, IL-8) reduction of fibrosis markers) linked to T2D, MASLD, cancer and heart disease, supporting their hypothesis of essentiality of PDA. While impressive, these results need to be confirmed as they have been described in only one research team and on the same multicellular, high throughput assessment model described. Nonetheless, a molecular support of some PDA effects could have been discovered. Indeed, pentadecanoylcarnitine, a bioactive metabolite derived from PDA has been found in dolphin fed with PDA in the diet [45]. This metabolite has been found anti-inflammatory *in vitro*. Further, it was determined as an activator of cannabinoid receptors 1 and 2, hence having potent pro-cannabinoid activity. Further investigations on this newly discovered PDA metabolite are needed to better understand its physiological effect, potentially linked to the reported effects of PDA described in human and *in vivo* in rodent models. Finally, another molecular support of PDA essentiality could be attributed to its conversion into unsaturated FA. Indeed, demonstrated EFAs like linoleic acid (C18:2 n-6) or linolenic acid (C18:3 n-3) are polyunsaturated fatty acids with the specificity of having methyl end double bond position at position n-6 or n-3. As a matter of fact, PDA can be converted into monounsaturated ω6, with the catalysis of the Δ9 desaturase yielding the synthesis of C15:1 n-6 [34]. Furthermore, in absence of dietary EFA, rats have been shown to convert PDA into ω8 polyunsaturated, an original and previously undescribed FA family, with C19:3 n-8, C21:3 n-8 and C21:4 n-8 [48]. As very recently newly discovered FAs, these molecules still need to be studied to characterize their potential effects as odd chain polyunsaturated FAs. As mentioned above, a few studies investigated PDA metabolism, further investigations are needed to better understand PDA's conversion into other saturated, monounsaturated and polyunsaturated OCFAs.

7. Conclusion

In conclusion, pentadecanoic acid, an odd and minor fatty acid is currently raising questions about its protective health effects and henceforth its potential essential characteristics (Fig. 2). Dietary PDA intake appear to be the only way to ensure its presence in the body, as its endogenous synthesis from α-oxidation or *de novo* from propionyl-CoA are described respectively as minor phenomenons or needing specific criteria to occur. Moreover, an increasing number of studies has been deciphering the physiological effects of PDA against metabolic syndrome disorder. According to the recent literature, PDA supplementation reduces MASH severity, notably

Table 1
Resumed associations and effects of pentadecanoic acid.

Reference	Year	Model	Dose and exposition time of PDA	Main findings
T2D				
[8]	2014	Human – case cohort study	–	PDA inversely correlated to T2D incidence
[9]	2018	Human - pooled analysis of prospective cohort studies	–	Higher PDA concentration associated with lower incidence of T2D
[4]	2004	Human - prospective case-control study	–	PDA serum concentrations negatively correlated to leptin, PAI-1 and insulin levels
[38]	2021	Mice - C2C12 myotubes	40 μM for 48 h in 2 % serum medium	PDA stimulates glucose uptake via AMPK pathway, exhibiting insulin sensitizing effects
[12]	2020	Mice - high-fat diet obesity and T2D mouse model	Daily gastric gavage of 5 mg/kg of PDA for 12 weeks with a high fat diet	PDA reduces glucose and cholesterol levels and weight gain
[39]	2017	Human - cross-sectional study	–	Inverse associations of PDA levels and leptin and PAI-1.
[37]	2023	Mice - cultured isolated primary hepatocytes	125 μM of PDA for 24 h or 48 h SVF free medium	PDA enhances insulin stimulated phosphorylation of AKT.
MASH				
[11]	2017	Human - MASLD patient cohort	–	PDA negatively correlated to MASH activity and hepatocytes ballooning scores, high fasting glucose and AST level
[11]		Mice - methionine and choline-deficient diet MASH mouse model	5 % (w/w) of PDA (i.e. 50 g/kg of diet) for 4 weeks	PDA supplementation reduces AST levels and macrophage infiltration
[12]	2020	White New Zealand rabbit	35 mg/kg of PDA daily oral dosing with a high fat, high cholesterol diet	PDA reduces MASH severity, cholesterol, triglycerides, globulins and platelets levels.
[36]	2023	Mice - choline deficient high-fat diet MASH mouse model	0,4 % (w/w) of PDA (i.e. 4 g/kg of diet) for 16 weeks	PDA reduces NASH severity through the restoration of the gut barrier function, with the reduction of LPS levels and pro-inflammatory cytokines expression
[37]	2023	Mice - cultured isolated primary hepatocytes	125 μM of PDA for 24 h or 48 h in serum free medium	PDA suppresses JAK2/STAT3 signaling
[43]	2024	Human - TANGO randomized controlled trial	Daily 300 mg PDA supplement in low calorie diet (1000–1500 kcal/day)	PDA supplementation lowers LDL-cholesterol levels and alters gut microbiota abundance (increase of *Bifidobacteria*)
Inflammation				
[44]	2017	Human - Cross sectionnal and prospective cohort study	–	PDA negatively associated with PAI-1, TNF-α and IL-18
[36]	2023	Mice - choline deficient high-fat diet MASH mouse model	0,4 % (w/w) of PDA (i.e. 4 g/kg of diet) for 16 weeks	PDA supplementation reduces LPS and pro-inflammatory cytokines (TNF-α and IL-6) levels
[12]	2020	Mice - high-fat diet obesity and T2D mouse model	Daily gastric gavage of 5 mg/kg of PDA for 12 weeks with a high fat diet	PDA reduces proinflammatory chemokine monocyte chemoattractant protein 1 (MCP-1) and interleukin 6 (IL-6) levels
[45]	2022	Human - 12 primary cells (BioMAP cell system)	Range of 1.9–50 μM assays	PDA lowers a broad range of pro-inflammatory cytokines that were tested, e.g. TNF-α, MCP-1
[37]	2023	Mice - cultured isolated primary hepatocytes	125 μM of PDA for 24 h or 48 h in serum free medium	PDA reduces TNF-α levels

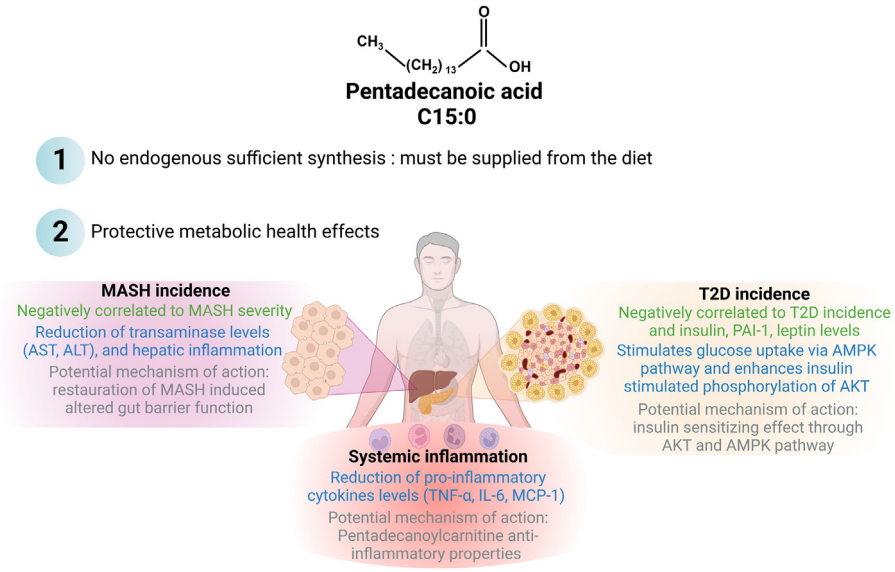

Fig. 2. Hypothesis of essentiality of pentadecanoic acid (PDA).
In green are represented determined associations or correlations of PDA with pathology incidence. In blue are represented determined PDA effect *in vivo* or *in vitro*. In gray are represented potential mechanism of action, described in the literature yet which still need to be confirmed. MASH: metabolic dysfunction-associated steatohepatitis; AST: aspartate transaminase; ALT: alanine transaminase; T2D: Type 2 diabetes.

ALT and/or AST levels. PDA helps reducing inflammation in several pathology models, notably through diminished pro-inflammatory cytokines, e.g. TNF-α. Concerning T2D disorder, PDA is negatively correlated to elevation of leptin, PAI-1 and insulin levels and appears to exhibit insulin sensitizing effect, through the stimulation of glucose uptake via AMPK pathway. While these reported effects appear promising, defined action mechanisms are still lacking to determine with accuracy the action of PDA in prevention of those pathologies. Nevertheless, recent arguments concerning its essentiality are rising to better comprehend PDA's potential, especially concerning PDA's bioactive metabolites. Thus, considering these elements, PDA is currently meeting the described criteria of an EFA. Nutritional studies of PDA deficiency are yet needed to better assess and decrypt its essentiality.

CRediT authorship contribution statement

Vincent Ciesielski: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Philippe Legrand:** Writing – review & editing, Conceptualization. **Sophie Blat:** Writing – review & editing, Supervision, Conceptualization. **Vincent Rioux:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

References

[1] H. Lindmark Månsson, Fatty acids in bovine milk fat, Food Nutr. Res. 52 (2008) 1821, https://doi.org/10.3402/fnr.v52i0.1821.

[2] D. Aune, T. Norat, P. Romundstad, L.J. Vatten, Dairy products and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies, Am. J. Clin. Nutr. 98 (2013) 1066–1083, https://doi.org/10.3945/ajcn.113.059030.

[3] R.J. de Souza, A. Mente, A. Maroleanu, A.I. Cozma, V. Ha, T. Kishibe, et al., Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies, BMJ 351 (2015) h3978, https://doi.org/10.1136/bmj.h3978.

[4] E. Warensjö, J.-H. Jansson, L. Berglund, K. Boman, B. Ahrén, L. Weinehall, et al., Estimated intake of milk fat is negatively associated with cardiovascular risk factors and does not increase the risk of a first acute myocardial infarction. A prospective case–control study, Br. J. Nutr. 91 (2004) 635–642, https://doi.org/10.1079/BJN20041080.

[5] E. Yuzbashian, D.N. Fernando, M. Pakseresht, D.T. Eurich, C.B. Chan, Dairy product consumption and risk of non-alcoholic fatty liver disease: a systematic review and meta-analysis of observational studies, Nutr. Metabol. Cardiovasc. Dis. 33 (2023) 1461–1471, https://doi.org/10.1016/j.numecd.2023.04.018.

[6] A. Wolk, B. Vessby, H. Ljung, P. Barrefors, Evaluation of a biological marker of dairy fat intake, Am. J. Clin. Nutr. 68 (1998) 291–295, https://doi.org/10.1093/ajcn/68.2.291.

[7] H.J. Bethancourt, K.A. Schmidt, G. Cromer, M.S. Burhans, J.N. Kuzma, D.K. Hagman, et al., Assessing the validity of plasma phospholipid fatty acids as biomarkers of dairy fat intake using data from a randomized controlled intervention trial, Am. J. Clin. Nutr. 115 (2022) 1577–1588, https://doi.org/10.1093/ajcn/nqac029.

[8] N.G. Forouhi, A. Koulman, S.J. Sharp, F. Imamura, J. Kröger, M.B. Schulze, et al., Differences in the prospective association between individual plasma phospholipid saturated fatty acids and incident type 2 diabetes: the EPIC-InterAct case-cohort study, Lancet Diabetes Endocrinol. 2 (2014) 810–818, https://doi.org/10.1016/S2213-8587(14)70146-9.

[9] F. Imamura, A. Fretts, M. Marklund, A.V. Ardisson Korat, W.-S. Yang, M. Lankinen, et al., Fatty acid biomarkers of dairy fat consumption and incidence of type 2 diabetes: a pooled analysis of prospective cohort studies, PLoS Med. 15 (2018) e1002670, https://doi.org/10.1371/journal.pmed.1002670.

[10] K.-T. Khaw, M.D. Friesen, E. Riboli, R. Luben, N. Wareham, Plasma phospholipid fatty acid concentration and incident coronary heart disease in men and women: the EPIC-norfolk prospective study, PLoS Med. 9 (2012) e1001255, https://doi.org/10.1371/journal.pmed.1001255.

[11] W. Yoo, D. Gjuka, H.L. Stevenson, X. Song, H. Shen, S.Y. Yoo, et al., Fatty acids in non-alcoholic steatohepatitis: focus on pentadecanoic acid, PLoS One 12 (2017) e0189965, https://doi.org/10.1371/journal.pone.0189965.

[12] S. Venn-Watson, R. Lumpkin, E.A. Dennis, Efficacy of dietary odd-chain saturated fatty acid pentadecanoic acid parallels broad associated health benefits in humans: could it be essential? Sci. Rep. 10 (2020) 8161, https://doi.org/10.1038/s41598-020-64960-y.

[13] J. Tan, C. McKenzie, M. Potamitis, A.N. Thorburn, C.R. Mackay, L. Macia, Chapter three - the role of short-chain fatty acids in health and disease, in: F.W. Alt (Ed.), Advances in Immunology, vol. 121, Academic Press, 2014, pp. 91–119, https://doi.org/10.1016/B978-0-12-800100-4.00003-9.

[14] B. Emmanuel, The relative contribution of propionate, and long-chain even-numbered fatty acids to the production of long-chain odd-numbered fatty acids in rumen bacteria, Biochim. Biophys. Acta Lipids Lipid. Metabol. 528 (1978) 239–246, https://doi.org/10.1016/0005-2760(78)90198-4.

[15] A.T. James, The metabolism of propionic acid, Biochem. J. 64 (1956), https://doi.org/10.1042/2Fbj0640726.

[16] P. Gómez-Cortés, M.Á. De La Fuente, Origen metabólico y propiedades bioactivas de ácidos grasos ramificados e impares en leche de rumiantes. Revisión, Rev. Mex. Cienc Pecu 11 (2020) 1174–1191, https://doi.org/10.22319/rmcp.v11i4.5171.

[17] A.M. Massart-Leën, E. Roets, G. Peeters, R. Verbeke, Propionate for fatty acid synthesis by the mammary gland of the lactating goat, J. Dairy Sci. 66 (1983) 1445–1454, https://doi.org/10.3168/jds.S0022-0302(83)81958-4.

[18] X. Wu, M. Chen, F. Wang, B. Si, J. Pan, J. Yang, et al., A new isopropyl esterification method for quantitative profiling of short-chain fatty acids in human and cow milk by gas chromatograph-mass spectrometer, J. Dairy Sci. 107 (2024) 5366–5375, https://doi.org/10.3168/jds.2023-24320.

[19] D. Bauchart, F. Legay- Carmier, M. Doreau, B. Gaillard, Lipid metabolism of liquid-associated and solid-adherent bacteria gin rumen contents of dairy cows offered lipid-supplemented diets, Br. J. Nutr. 63 (1990) 563–578, https://doi.org/10.1079/BJN19900143.

[20] K. Weitkunat, S. Schumann, D. Nickel, S. Hornemann, K.J. Petzke, M.B. Schulze, et al., Odd-chain fatty acids as a biomarker for dietary fiber intake: a novel pathway for endogenous production from propionate, Am. J. Clin. Nutr. 105 (2017) 1544–1551, https://doi.org/10.3945/ajcn.117.152702.

[21] E. Boets, L. Deroover, E. Houben, K. Vermeulen, S. Gomand, J. Delcour, et al., Quantification of in vivo colonic short chain fatty acid production from inulin, Nutrients 7 (2015) 8916–8929, https://doi.org/10.3390/nu7115440.

[22] Y. Wu, J.M. Posma, E. Holmes, G. Frost, E.S. Chambers, I. Garcia-Perez, Odd chain fatty acids are not robust biomarkers for dietary intake of fiber, Mol. Nutr. Food Res. 65 (2021) 2100316, https://doi.org/10.1002/mnfr.202100316.

[23] A. Brevik, M.B. Veierød, C.A. Drevon, L.F. Andersen, Evaluation of the odd fatty acids 15:0 and 17:0 in serum and adipose tissue as markers of intake of milk and dairy fat, Eur. J. Clin. Nutr. 59 (2005) 1417–1422, https://doi.org/10.1038/sj.ejcn.1602256.

[24] A.E. Smedman, I.-B. Gustafsson, L.G. Berglund, B.O. Vessby, Pentadecanoic acid in serum as a marker for intake of milk fat: relations between intake of milk fat and metabolic risk factors, Am. J. Clin. Nutr. 69 (1999) 22–29, https://doi.org/10.1093/ajcn/69.1.22.

[25] Biong A. Sofie, P. Berstad, J.I. Pedersen, Biomarkers for intake of dairy fat and dairy products, Eur. J. Lipid Sci. Technol. 108 (2006) 827–834, https://doi.org/10.1002/ejlt.200600044.

[26] V. Albani, C. Celis-Morales, C.B. O'Donovan, M.C. Walsh, C. Woolhead, H. Forster, et al., Within-person reproducibility and sensitivity to dietary change of C15:0 and C17:0 levels in dried blood spots: data from the European Food4Me Study, Mol. Nutr. Food Res. 61 (2017), https://doi.org/10.1002/mnfr.201700142.

[27] M. Dehghan, A. Mente, S. Rangarajan, P. Sheridan, V. Mohan, R. Iqbal, et al., Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study, Lancet 392 (2018) 2288–2297, https://doi.org/10.1016/S0140-6736(18)31812-9.

[28] G. Dąbrowski, I. Konopka, Update on food sources and biological activity of odd-chain, branched and cyclic fatty acids –– A review, Trends Food Sci. Technol. 119 (2022) 514–529, https://doi.org/10.1016/j.tifs.2021.12.019.

[29] M. Momot, Z. Nogalski, P. Pogorzelska-Przybyłek, M. Sobczuk-Szul, Influence of genotype and Slaughter Age on the content of selected minerals and fatty acids in the Longissimus Thoracis muscle of crossbred bulls, Animals (Basel) 10 (2020) 2004, https://doi.org/10.3390/ani10112004.

[30] C.M. Mitchell, L.E. Oxtoby, P.A. Shaw, S.M. Budge, M.J. Wooller, De Baca T. Cabeza, et al., Carbon isotope ratios of plasma and RBC fatty acids identify meat consumers in a 12-week inpatient feeding study of 32 men, J. Nutr. 152 (2022) 2847–2855, https://doi.org/10.1093/jn/nxac213.

[31] Y. Özogul, F. Özogul, E. Çiçek, A. Polat, E. Kuley, Fat content and fatty acid compositions of 34 marine water fish species from the Mediterranean Sea, Int. J. Food Sci. Nutr. 60 (2009) 464–475, https://doi.org/10.1080/09637480701838175.

[32] Z. Wang, D.H. Wang, Y. Goykhman, Y. Yan, P. Lawrence, K.S.D. Kothapalli, et al., The elongation of very long-chain fatty acid 6 gene product catalyses elongation of *n* -13 : 0 and *n* -15 : 0 odd-chain SFA in human cells, Br. J. Nutr. 121 (2019) 241–248, https://doi.org/10.1017/S0007114518003185.

[33] Z. Wang, H.G. Park, D.H. Wang, R. Kitano, K.S.D. Kothapalli, J.T. Brenna, Fatty acid desaturase 2 (FADS2) but not FADS1 desaturates branched chain and odd chain saturated fatty acids, Biochim. Biophys. Acta Mol. Cell Biol. Lipids 1865 (2020) 158572, https://doi.org/10.1016/j.bbalip.2019.158572.

[34] V. Ciesielski, D. Catheline, P. Legrand, V. Rioux, Metabolism of odd chain fatty acids in vivo in mice and in vitro in Fao rat hepatoma cells, in: Personnal Communication, 2023, https://doi.org/10.13140/RG.2.2.21691.22562.

[35] M. Pfeuffer, A. Jaudszus, Pentadecanoic and heptadecanoic acids: multifaceted odd-chain fatty acids, Adv. Nutr. 7 (2016) 730–734, https://doi.org/10.3945/an.115.011387.

[36] W. Wei, C.C. Wong, Z. Jia, W. Liu, C. Liu, F. Ji, et al., Parabacteroides distasonis uses dietary inulin to suppress NASH via its metabolite pentadecanoic acid, Nat. Microbiol. 8 (2023) 1534–1548, https://doi.org/10.1038/s41564-023-

01418-7.
[37] C.A. Bishop, T. Machate, J. Henkel, M.B. Schulze, S. Klaus, K. Piepelow, Heptadecanoic acid is not a key mediator in the prevention of diet-induced hepatic steatosis and insulin resistance in mice, Nutrients 15 (2023) 2052, https://doi.org/10.3390/nu15092052.
[38] W.-C. Fu, H.-Y. Li, T.-T. Li, K. Yang, J.-X. Chen, S.-J. Wang, et al., Pentadecanoic acid promotes basal and insulin-stimulated glucose uptake in C2C12 myotubes, Food Nutr. Res. 65 (2021), https://doi.org/10.29219/fnr.v65.4527.
[39] K. Kurotani, M. Sato, K. Yasuda, K. Kashima, S. Tanaka, T. Hayashi, et al., Even- and odd-chain saturated fatty acids in serum phospholipids are differentially associated with adipokines, PLoS One 12 (2017) e0178192, https://doi.org/10.1371/journal.pone.0178192.
[40] A. Pérez-Pérez, F. Sánchez-Jiménez, T. Vilariño-García, V. Sánchez-Margalet, Role of leptin in inflammation and Vice Versa, IJMS 21 (2020) 5887, https://doi.org/10.3390/ijms21165887.
[41] A. Festa, R. D'Agostino, R.P. Tracy, S.M. Haffner, Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes, Diabetes 51 (2002) 1131–1137, https://doi.org/10.2337/diabetes.51.4.1131.
[42] G.-C. Chen, L.-Q. Qin, J.-K. Ye, Leptin levels and risk of type 2 diabetes: gender-specific meta-analysis, Obes. Rev. 15 (2014) 134–142, https://doi.org/10.1111/obr.12088.
[43] Y.C. Chooi, Q.A. Zhang, F. Magkos, M. Ng, N. Michael, X. Wu, et al., Effect of an Asian-adapted Mediterranean diet and pentadecanoic acid on fatty liver disease: the TANGO randomized controlled trial, Am. J. Clin. Nutr. 119 (2024) 788–799, https://doi.org/10.1016/j.ajcnut.2023.11.013.
[44] I.D. Santaren, S.M. Watkins, A.D. Liese, L.E. Wagenknecht, M.J. Rewers, S.M. Haffner, et al., Individual serum saturated fatty acids and markers of chronic subclinical inflammation: the Insulin Resistance Atherosclerosis Study, JLR (J. Lipid Res.) 58 (2017) 2171–2179, https://doi.org/10.1194/jlr.P076836.
[45] S. Venn-Watson, J. Reiner, E.D. Jensen, Pentadecanoylcarnitine is a newly discovered endocannabinoid with pleiotropic activities relevant to supporting physical and mental health, Sci. Rep. 12 (2022) 13717, https://doi.org/10.1038/s41598-022-18266-w.
[46] S.K. Venn-Watson, C.N. Butterworth, Broader and safer clinically-relevant activities of pentadecanoic acid compared to omega-3: evaluation of an emerging essential fatty acid across twelve primary human cell-based disease systems, PLoS One 17 (2022) e0268778, https://doi.org/10.1371/journal.pone.0268778.
[47] S. Venn-Watson, N.J. Schork, Pentadecanoic acid (C15:0), an essential fatty acid, shares clinically relevant cell-based activities with leading longevity-enhancing compounds, Nutrients 15 (2023) 4607, https://doi.org/10.3390/nu15214607.
[48] V. Ciesielski, T. Guerbette, D. Catheline, P. Legrand, V. Rioux, Dietary pentadecanoic acid (C15:0) increases early growth rate and induces synthesis of omega 8 odd chain polyunsaturated fatty acids in EFA deficient rats, Personnal Commun. (2024), https://doi.org/10.13140/RG.2.2.17654.20803.