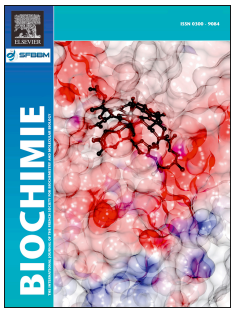

Vegetable lecithins: a review of their compositional diversity, impact on lipid metabolism and potential in cardiometabolic disease prevention

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ABSTRACT

Vegetable lecithins, widely used in the food industry as emulsifiers, are a mixture of naturally occurring lipids containing more than 50% of phospholipids (PL). PL exert numerous important physiological effects. Their amphiphilic nature notably enables them to stabilize endogenous lipid droplets, conferring them an important role in lipoprotein transport, functionality and metabolism. In addition, beneficial effects of dietary lecithin on metabolic disorders have been reported since the 1990s. This review attempts to summarize the effects of various vegetable lecithins on lipid and lipoprotein metabolism, as well as their potential application in the treatment of dyslipidemia associated with metabolic disorders.

Despite controversial data concerning the impact of vegetable lecithins on lipid digestion and intestinal absorption, the beneficial effect of lecithin supplementation on plasma and hepatic lipoprotein and cholesterol levels is unequivocal. This is especially true in hyperlipidemic patients. Furthermore, the immense compositional diversity of vegetable lecithins endows them with a vast range of biochemical and biological properties, which remain to be explored in detail. Data on the effects of vegetable lecithins alternative to soybean, both as supplements and as ingredients, is undoubtedly lacking. Given the exponential demand for vegetable products alternative to those of animal origin, it is of primordial importance that future research is undertaken in order to elucidate the mechanisms by which individual fatty acids and PL from various vegetable lecithins modulate lipid metabolism. The extent to which they may influence parameters associated with metabolic disorders, such as intestinal integrity, low-grade inflammation and gut microbiota must also be assessed.

Keywords: *Lecithin, vegetal phospholipid, food additive, lipoprotein, metabolic diseases*

Vegetable lecithins: a review of their compositional diversity, impact on lipid metabolism and potential in cardiometabolic disease prevention

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Author contribution: C.R. performed the literature review and wrote the original draft. M-C.M., C.V. and L.C. revised the manuscript for important intellectual content. All authors have read and approved the final manuscript.

Highlights

- Vegetable lecithins possess an immense compositional diversity arising from genetic, agronomical and processing factors, which grants them with a wide range of biochemical and physiological properties
- There is an evident lack of data concerning the impact of vegetable lecithins other than soybean on lipid metabolism and metabolic health
- Despite controversial data on lipid absorption specifically, there is substantial evidence that vegetable lecithins are capable of modulating lipoprotein metabolism, decreasing hepatic lipogenesis and blood cholesterol levels, as well as delivering specific fatty acids to target tissues
- Their pleiotropic physiological effects imply that vegetable lecithins may act as potential preventive or therapeutic agents for cardiometabolic diseases

ABSTRACT

Vegetable lecithins, widely used in the food industry as emulsifiers, are a mixture of naturally occurring lipids containing more than 50% of phospholipids (PL). PL exert numerous important physiological effects. Their amphiphilic nature notably enables them to stabilize endogenous lipid droplets, conferring them an important role in lipoprotein transport, functionality and metabolism. In addition, beneficial effects of dietary lecithin on metabolic disorders have been reported since the 1990s. This review attempts to summarize the effects of various vegetable lecithins on lipid and lipoprotein metabolism, as well as their potential application in the treatment of dyslipidemia associated with metabolic disorders.

Despite controversial data concerning the impact of vegetable lecithins on lipid digestion and intestinal absorption, the beneficial effect of lecithin supplementation on plasma and hepatic lipoprotein and cholesterol levels is unequivocal. This is especially true in hyperlipidemic patients. Furthermore, the immense compositional diversity of vegetable lecithins endows them with a vast range of biochemical and biological properties, which remain to be explored in detail. Data on the effects of vegetable lecithins alternative to soybean, both as supplements and as ingredients, is undoubtedly lacking. Given the exponential demand for vegetable products alternative to those of animal origin, it is of primordial importance that future research is undertaken in order to elucidate the mechanisms by which individual fatty acids and PL from various vegetable lecithins modulate lipid metabolism. The extent to which they may influence parameters associated with metabolic disorders, such as intestinal integrity, low-grade inflammation and gut microbiota must also be assessed.

Keywords: *Lecithin, vegetal phospholipid, food additive, lipoprotein, metabolic diseases*

1. Introduction

Food additives represent an increasingly growing market within the food industry, estimated to reach USD 25 billion by 2024 in Europe only [1]. In response to this and due to a rise in consumer awareness regarding health consciousness, food additives are under intense scrutiny and are constantly being assessed and revised for health concerns. Concomitantly, the demand for natural products has increased dramatically. Lecithin, commonly used in the food industry under the number E322 for their emulsifying and stabilizing properties, are a mixture of naturally occurring lipids containing more than 50% of phospholipids (cf. section 2 for official definition). Phospholipids, as major constituents of cell membranes in ubiquitous tissues, components of bile, and active messengers involved in cell signal transduction, exert numerous important physiological effects. They enable the micellar solubilisation of lipids in the lumen and hence facilitate lipid hydrolysis and absorption within the enterocyte. Their amphiphilic nature makes them important components of the coat of lipid droplets and lipoproteins, attributing them an important role in lipid transport and metabolism. In this way, they have been shown to modulate lipoprotein metabolism, decrease cholesterol levels and exert beneficial effects on hepatic function. These pleiotropic beneficial health effects have generated much interest and many studies have investigated the potential role of lecithins in the prevention and/or treatment of metabolic diseases. A growing interest in marine PL has appeared in the last few years, which has yielded promising results regarding the effects of lecithin of marine origin on metabolic health (as reviewed by Lordan et al. [2]). But data is still lacking when it comes to vegetable lecithin. We have found no systematic review that effectively resumes and concludes on the effects of vegetable lecithin on lipid metabolism and their potential role in metabolic disorder prevention. With an expanding need to restrain from animal and marine sourced ingredients, vegetable products are expected to explode on the food market and it is crucial that their nutritional, bioactive properties are known. This mini-review will hence attempt to gather the existing literature and succinctly conclude on the role of lecithin of vegetable origin on fatty acid bioavailability and metabolism.

2. Dietary vegetable lecithins: major sources and composition

The term lecithin must first be clearly defined. Many studies, especially within the field of medicine, have used the terms “lecithin” and “phosphatidylcholine” (PC) interchangeably [3]. In this review, the term lecithin refers to the mixture of lipids composed predominantly of phospholipids (>50%) derived from animal or vegetable origin. This is in agreement with the definition reported in the *Codex Alimentarius* presented by FAO/WHO and by EFSA [4]. Conversely, PC refers to a glycerophospholipid composed of a phosphatidic acid linked to a choline polar head group by a phosphoester bond.

2.1. Dietary lecithin composition and structure

Lipids represent an extremely vast range of molecules with diverse structures and functions. While the majority of dietary lipids are present as triacylglycerols (TAG), PL account for 3-6% of total lipid intake [5]. Indeed, PL are ubiquitous components of biological membranes, and as such, are present in foods of animal, marine and vegetable origin. Commercial lecithin may thus be obtained from a wide range of sources, the most common being eggs, milk, fish or oil-bearing seeds (notably soybean).

PL are made up of a hydrophobic tail consisting of two fatty acid chains esterified at the *sn*-1 and *sn*-2 positions of a glycerol moiety, to which a phosphate group with a hydrophilic residue is attached at the *sn*-3 position. The *sn*-2 position of PL usually carries an unsaturated fatty acid, such as oleic acid, linoleic acid or alpha-linolenic acid, whereas a saturated fatty acid typically occupies the *sn*-1 position [2]. This is only true however when concentrations of unsaturated fatty acids are high. When these concentrations are low, unsaturated fatty acids are equally distributed between the *sn*-1 and *sn*-2 positions [6]. This non-random regiodistribution of fatty acids in PL is seemingly similar amongst vegetal and animal species, and may result from the intrinsic properties of the enzymes involved in the synthesis pathway for PL in eukaryotes, the so-called “Kennedy pathway”. Indeed, the acyltransferase involved in the esterification of the glycerol backbone at the *sn*-1 position tends to favour saturated fatty acids, whereas that involved in the succeeding esterification at the *sn*-2 position preferentially binds unsaturated fatty acids [7]. The fatty acid moiety at the *sn*-2 position of vegetal PL may further be modified by the Land’s cycle [8]. Enzymes involved in this cycle (notably lysophospholipid acetyltransferases and phospholipases A_2) also tend to favour PUFA as substrates [7]. This then results in the typical PL structure containing a saturated fatty acid at the *sn*-1 position and an unsaturated fatty acid at the *sn*-2 position.

The most common bioactive PL in biological vegetable cells are phosphatidylcholine, phosphatidylethanolamine (PE), phosphatidylinositol (PI) and phosphatidylserine (PS). While animal cells also contain sphingomyelin (SM), a PL containing a choline head and a sphingosine moiety instead of the glycerol backbone, it is absent in vegetable cells. Vegetable lecithin are therefore devoid of SM. Vegetable lecithin may also contain lyso-phospholipids, which consist of PL whose fatty acid chain has been hydrolysed at the *sn*-1 or the *sn*-2 position. Other lipids, such as triacylglycerols, glycolipids and sterols, as well as liposoluble vitamins may be found in negligible quantities in vegetable lecithin.

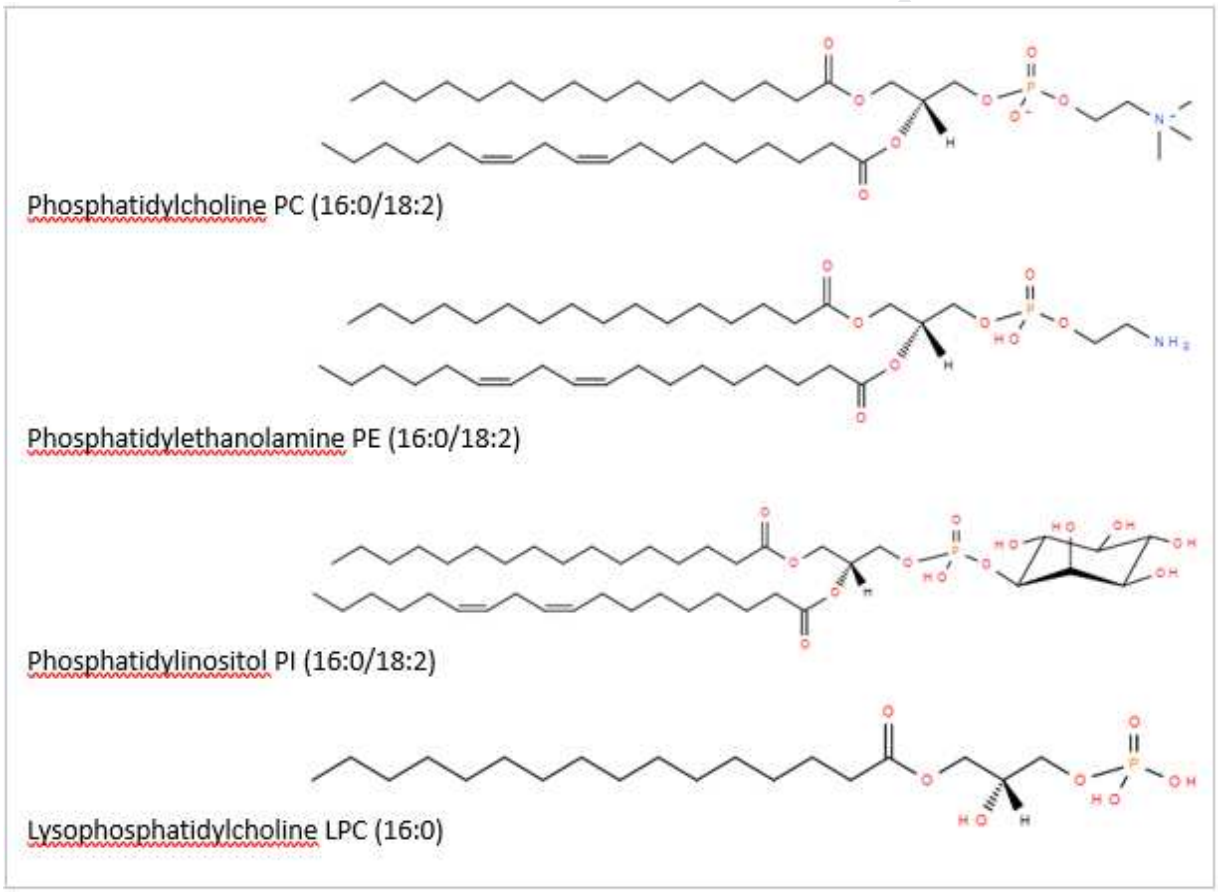

Figure 1. Structures of the major phospholipids found in soybean lecithin. Lipid structures were drawn using LIPID MAPS tools.

2.2. Phospholipids: biological function

PL are essential components of all cellular and sub-cellular membranes, in association with cholesterol, glycolipids and peripheral and integral proteins. The biological importance of PL derives from their amphiphilic properties. They are indeed capable of forming selectively permeable lipid bi-layers, which act as barriers between cells or organelles and their

surroundings. In doing so, they provide a unique, biologically rich environment, suitable for proteins and other bioactive compounds. Along with cholesterol, they are responsible for the formation of lipid rafts, which are involved in cell signalling and apoptosis. The inherent amphiphilic nature of PL additionally allows them to act as important constituents of the coat of lipid droplets and lipoproteins, attributing them an important role in lipid transport and metabolism. This intrinsic property endows PL with potent emulsifying capacities: they are capable of stabilising lipid droplets endogenously, but also within a food matrix, where they contribute to the texture and palatability of foods. Lecithin are consequently extremely widespread food emulsifiers: their market is projected to reach USD 350 million by 2024 [1].

In addition, PL, along with bile salts and cholesterol, enable the micellar solubilisation of lipids in the lumen and hence facilitate lipid hydrolysis and absorption of lipolysis products within the enterocyte. Certain PL also act as lipid mediators of inflammation or as secondary messengers in cell signaling. In this way, PL possess pleiotropic properties, which are, not least of all, dictated by their fatty acid composition. Indeed, the fatty acid composition of PL defines and determines its structural and functional properties [9]. The higher the degree of unsaturation, the less rigid its molecular structure will be and hence the more fluid the membrane. In this way, the ratio of saturated to unsaturated fatty acid in phospholipids has a direct impact on the functionality of the cellular membrane, lipid droplet or lipoprotein coat which they form. Consequently, cellular functions, as well as the activity of membrane bound enzymes, carriers and receptors may be modulated by dietary PL. In addition to their structural roles, as integral components of cell membranes, PL are also involved in cell signalling, as precursors of lipid mediators and are therefore essential for communication and interaction between the body cells.

In this way, PL participate in a variety of metabolic, neurological, and intracellular signalling processes [10] such as cell development, necrosis and apoptosis, transport, DNA replication, neuronal signalling, or secretion [11].

2.4. The compositional diversity of vegetable lecithins

The lipid composition of PL membranes varies amongst tissues and organisms, and as such, the lipid composition of lecithin reflects that of its origin. Generally, the fatty acid composition of vegetable lecithin typically reflects that of the corresponding oil-bearing seed [12]. As a result, rapeseed lecithin, like rapeseed oil, generally possess high concentrations of mono-unsaturated fatty acids (MUFA), notably oleic acid, whereas soy lecithin contain a high proportion of n-6 polyunsaturated fatty acids (PUFA), most of which is represented by

linoleic acid. **Table 1** presents the typical phospholipid and fatty acid composition of soy, sunflower and rapeseed lecithin. An early study has demonstrated that these fatty acids are equally distributed amongst the different classes of PL (such as PC, PE, PI) within lecithin [6].

Table 1. Summarised data on phospholipid composition [4] and fatty acid composition [13] of three liquid vegetable lecithins (soy, sunflower and rapeseed).

	Soy lecithin	**Sunflower lecithin**	**Rapeseed lecithin**
Phospholipid composition (%) [4]			
PC	12.69 – 16.7	14.34 – 17.23	16.74 – 18.18
PI	6.47 – 11.84	12.30 – 14.92	10.45 – 12.30
PE	6.45 – 13.57	4.85 – 6.82	6.46 – 8.03
PA	2.28 – 5.96	1.32 – 3.21	2.44 – 3.59
Fatty acid composition (%) [13]			
16:0	16	11	7
18:0	4	4	1
18:1	17	18	56
18:2	55	63	25
18:3	7	0	6
Others	1	4	5

The phospholipid and fatty acid profiles of lecithin also hugely depend on the agronomical, genetic and environmental parameters of the seed crops they originate from [12]. Agronomical conditions, such as storage and extraction conditions, have been shown to modulate the lipid composition of vegetable lecithin [13]. Vegetable lecithin are by-products of the refining of oil. They may be obtained via diverse extraction methods, such as physical or enzymatic degumming. Canola lecithin obtained from enzymatic degumming demonstrated higher emulsion stability than that derived from water degumming and this was attributed to the phospholipid composition of the lecithin [14]. The crop- or process-induced variability within one vegetable lecithin source may hence be higher than that between lecithin sources [13]. However, Nguyen et al. demonstrated via the use of biplots and principal component analysis that, despite their heterogeneity, vegetable lecithins could be distinguished according to their origin [12]. They found rapeseed lecithin to be the most different amongst soybean,

sunflower and rapeseed lecithin. In comparison to soy and sunflower lecithin, rapeseed lecithin tended to possess the highest relative concentration of PC. Sunflower lecithin displayed the highest and lowest concentration of PI and PE respectively [6,12,15].

This composition data plays an important role, as the phospholipid composition of lecithin determines its emulsifying capacity. PC, which forms a lamellar layer at the lipid/water interface, and lysoPC, which engenders a hexagonal phase, promote oil-in-water emulsion stability, whereas PE (reverse hexagonal phase) facilitates water-in-oil emulsions [16]. The amount of neutral lipids, such as TAG, present in lecithins also modulates emulsifying properties. Lecithins that have undergone a deoiling fractionation process and hence contain reduced neutral lipid concentrations, possess enhanced oil-in-water dispersion functionality [17].

Furthermore, different lecithin from various sources (soy, rapeseed) or with differing PL compositions have been reported to exert varying antioxidant properties [18]. PL may indeed act as antioxidative agents: they are able of chelating pro-oxidative metals, forming anti-oxidative Maillard reaction products, changing the location of primary antioxidants or regenerating primary antioxidants. These mechanisms are clearly summarised by Cui et Decker [19] and may be, in part, attributed to the negatively charged phosphate head group, which can bind pro-oxidative metals, thereby inhibiting lipid oxidation. The basic amino functions and intramolecular hydroxyl groups of the side-chain moieties of PL have also been reported to be implicated in such mechanisms [20]. However, the antioxidative activities of PL depend massively on the conditions and food matrices in which they are contained. In addition, processing conditions may further alter the antioxidant capacity of lecithin. It has been shown *in vitro* that rapeseed lecithin obtained via both chemical or water-degumming displayed higher antioxidant capacities than soy lecithin when associated with fish oil [21]. The presence of phenols, such as sinapic acid and canolol, in rapeseed lecithin appears to increase its antioxidant and ion-chelating capacities, most probably due to the synergism between phenols and phospholipids [22]. This synergistic effect has also been observed between quercetin and lecithin [23]. The role of individual fatty acids inherent to each vegetable lecithin must not be undermined with regards to the antioxidant activity of lecithin. N-3 PUFA such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) possess higher antioxidant properties, for example, than saturated fatty acids. Extraction processing may also affect the oxidative stability of lecithins. The deoiling process of lecithin reduces significantly the content of phenolic compounds in rapeseed lecithin and consequently its antioxidant effect [18].

2.4. Socio-economic and environmental preoccupations concerning soy lecithin

Soybean lecithin dominates over the vegetable lecithin market, representing more than 90% of available lecithin products [24]. With arising concerns about genetically modified organisms (GMOs) and awareness concerning environmental issues, there is an expanding demand/need for the development of alternative sources of vegetable lecithin. In Europe, the market for sunflower and rapeseed lecithin, which are locally produced, is increasing [13]. However, the majority of studies using vegetable lecithin have used soy lecithin and data concerning rapeseed or sunflower lecithin are lacking. The presence of concomitant compounds such as pollutants and phytoestrogens in soy lecithin must also be evaluated and subsequent impact on metabolic and intestinal health must be studied [25,26].

3. Vegetable lecithins influence lipid digestion and intestinal absorption

Vegetable lecithin provide food-derived PL with specific fatty acid profiles that, once incorporated in host membranes, have the potential to modulate membrane-dependant cellular functions. Whereas there is an expanding knowledge regarding the mechanisms by which PL are digested and absorbed, their incorporation into membranes *in vivo* and their ability to exert subsequent beneficial health effects remain to be elucidated.

3.1 Digestion and intestinal absorption of dietary phospholipids

Phospholipids, unlike TAG, are not hydrolysed by gastric lipases. Their digestion begins in the intestinal lumen, where they are readily hydrolysed by phospholipases A_1 (PLA_1s) or phospholipases A_2 (PLA_2s), which catalyze the hydrolysis of the ester bond of the acyl group at the *sn*-1 or the *sn*-2 position of the PL respectively, to produce one lyso-phospholipid (LysoPL) and a free fatty acid [27]. It has been demonstrated that other pancreatic enzymes, such as pancreatic lipase related protein 2 (PRLP2) and cholesterol ester hydrolase (CEL) also possess phospholipase activity of the PLA_1 type [28]. Inhibition of PLA_2 reduces fatty acid absorption in rats, suggesting the importance of this hydrolysis step in maintaining normal lipid absorption [29]. Nearly the entirety of dietary PL are absorbed (>90%) into enterocytes, where they are resynthesized, incorporated into the surface layer of chylomicrons (CM), and to a lesser extent, of intestine-derived very low density lipoproteins (VLDL) and liberated into the lymph to finally reach the systemic circulation [30]. In the bloodstream, CM are catabolised by lipoprotein lipase (LPL) which hydrolyses TAG contained within the core of

CM and liberates free fatty acids, which are then available for uptake by receiving tissues. Once the TAG-rich lipoproteins such as CM are degraded by LPL, a part of the PL located on the CM interface is hydrolysed by the endothelial lipase (EL), whose activity is similar to that of PLA1. The non- hydrolysed PL may be incorporated into high-density lipoprotein (HDL) fractions [31]. Interestingly, certain studies carried out in human intestinal Caco2-cells [32] and rats [33] have demonstrated that a non-negligible amount of PL in the lumen is absorbed passively and preferentially integrated into HDL fractions already present in the intestine [30,34]. In this way, the fatty acid composition of dietary lecithin affects the composition of lipoproteins in the bloodstream, in turn influencing the lipid composition and functionality of the various receiving tissues. The efficiency of PL in delivering specific fatty acids has recently generated much interest, notably for their potential in increasing the bioavailability of fatty acids of nutritional importance. In the current context of the epidemic explosion of obesity and metabolic disorders, limiting the intake of total lipids while increasing that of essential fatty acids such as n-3 PUFAs has become one of the major challenges of nutrition scientists.

3. 2. PL vs TAG as vectors of fatty acids of nutritional importance

Growing evidence indicates beneficial biological activities of PL compared to that of dietary TAG [2,35]. Notably, there is a current explosion in the number of studies concerning marine PL as preferential vectors of the long chain n-3 PUFA (LC n-3PUFA), EPA and DHA. Burri et al concluded in his review on marine PL that research so far tended to indicate a higher bioavailability of n-3 PUFAs when they were incorporated into PL comparatively to TAG [34]. A systematic review by Ulven also compared EPA and DHA bioavailability in PL-rich krill oil vs. TAG-rich fish oil in 14 studies [36]. They concluded that krill oil, rich in PL, presented a potential beneficial role compared to fish oil, but that more studies were required to certify this claim and to affirm positive effects on lipid metabolism. A study by [37] focused on lysophospholipids and demonstrated no differences in EPA and DHA bioavailability between TAG-bound or LysoPL-bound EPA and DHA in male Wistar rats. Although the effect of marine PL on lipid absorption are so far inconclusive, the efficiency with which these PL deliver specific fatty acids in receiving tissues is now recognised. For instance, studies have shown PL to be preferential carriers of DHA in the brain [38–40] and other tissues, such as liver, white adipose tissue and muscle [34] (cf. section 4.1 for further information and mechanisms).

Marine PL are not the subject of this review and readers curious to learn more may refer to the various reviews and studies listed above. Nonetheless, it could be extrapolated based on the plethora of evidence concerning marine PL that the bioavailability of FA present in vegetable lecithin would be increased comparatively to vegetable oil (TAG). But data concerning the optimal vectorization of typical vegetable fatty acids as either PL or TAG is lacking and more research must be undertaken to study these differences. This is all the more necessary as vegetable lecithin, although devoid of LC n-3 PUFA, contain other fatty acids of nutritional importance. Rapeseed and, to a lesser extent, soybean lecithin, contain alpha-linolenic acid (ALA), an essential fatty acid and precursor of the LC n-3 PUFA, EPA and DHA. The intake of ALA is particularly important, as it may not be synthesised endogenously in humans. Its presence in human cells relies on its uptake from the diet. Oleic acid, another major fatty acid in vegetable lecithin, is one of the staple components of the Mediterranean diet, which is proven to be one of the most beneficial diets in terms of cardio-metabolic health. It is important to determine whether PL have the potential to increase the bioavailability of these fatty acids, comparatively to TAG.

Nonetheless, dietary lecithins have been shown to impact lipid metabolism in other ways than merely by delivering specific fatty acids. They have been reported to exert beneficial anti-dyslipidaemia effects by modulating postprandial lipid absorption and metabolism.

3. 3. Impact on gastro-intestinal (GI) lipid digestion

Lipid metabolism is a complex process that involves a number of succeeding steps. Phospholipids play an important role in lipid metabolism since its early stages: the micellar solubilisation of lipids in the lumen. Lipids are hydrophobic by definition and their transport across the intestinal lumen towards enterocytes relies on the addition of biliary lipids. Bile salts secreted into the small intestine form lipid micelles with dietary lipids capable of withstanding the hydrophilic conditions of the intestinal lumen. Bile salts are hence essential for lipid micellisation and digestion, and their absence has been shown to result in severe intestinal fat malabsorption [41]. Bile is naturally rich in PL and more specifically in PC, which represents more than 95% of biliary PL. In fact, the contribution of endogenous PC to bile is much higher (10-15 g/day) than that of dietary, exogenous PC (1-2 g/day) [42]. The intrinsic amphiphilic structure of biliary phospholipids enables them to stabilise lipid micelles in the lumen and their presence hence facilitates micellar lipid solubilisation, increasing the surface of lipid droplets required for hydrolysis by digestive enzymes and ultimately leading to a higher bioavailability of fatty acids for uptake by the enterocyte. This increase in lipid

droplet dispersion has been suggested as a limiting step in lipolysis [43]. In this way, it is now widely acknowledged that the pre-emulsification process of an oil enhances the digestion of the fatty acids it contains [44–47]. According to *in vitro* and human studies, fine emulsions made up of small lipid droplets (~0,5µm) are more efficiently hydrolysed than those comprised of larger particles (>1.5µm) [48,49]. Lipid hydrolysis kinetics are not only affected by the size of lipid droplets, but also largely depend on the nature of the surfactant molecule used to stabilise the lipid emulsion. Couëdelo et al. reported that soy lecithin-stabilised emulsions displayed higher lipolysis rates in an *in vitro* digestion model than those stabilised by either sodium caseinate or Tween 80 [50]. This is in accordance with a previous study by Vors et al. comparing sodium caseinate-stabilised and soy lecithin-stabilised emulsions [51]. A study by Lecomte et al. however demonstrated an increase in lipid hydrolysis with milk PL comparatively to soy PL [50]. This could be attributed to the presence of SM, a characteristic dairy phospholipid absent in vegetable lecithin. The impact of emulsifier type on subsequent lipolysis kinetics are mainly due to physicochemical parameters. Different emulsifiers interact differently with bile salts, generating varying molecular assemblies at the interface of lipid micelles, which affect the ability of bile salts to remove fatty acids from lipid droplets [52]. Moreover, the nature of the emulsifier determines its ability to modulate the activity of lipolytic enzymes [53]. Early *in vitro* studies have demonstrated that bile PL exert a regulatory effect on the binding of lipases onto the surface of lipid droplets [54]. LysoPC exerts an inhibitory effect on pancreatic lipase-mediated hydrolysis, by reducing both substrate affinity and lipase activity, effect which is counterbalanced however by the presence of bile salts [55]. Gargouri et al. reported that vegetable lecithin, naturally rich in PC, is capable of increasing the activity of gastric lipase and, as such, may enhance lipolysis efficiency [56]. PL contained in vegetable lecithin differently modulate gastric lipase activity: lipid droplets coated with PC, PI or PS induce a higher activity of gastric lipase, compared to PE or SM [57]. Nonetheless, the mere presence of soy phospholipids without any emulsification process has also been shown to increase lipolysis rates. Lin et al. demonstrated via an *in vitro* digestion model that emulsification of algal oil with soy lecithin increased the initial lipolysis rate and DHA accessibility compared to that of bulk oil and to a non-emulsified mixture of similar composition containing soy lecithin [58]. However, the extent of lipolysis was similar between the bulk oil, the emulsified and the non-emulsified mixtures.

In this way, research so far demonstrated the efficiency by which soy lecithin impacts one of the initial steps of lipid metabolism: their solubilisation and hydrolysis in the lumen. Future research must be undertaken to study other sources of vegetable lecithin on such parameters.

3. 4. Impact on intestinal lipid absorption

Lipids released from lipid micelles at the unstirred layers of the brush-border membrane (pH gradient) are then absorbed by the intestinal microvilli of enterocytes via passive or active pathways. The hydrolysis products are then resynthesized into TAG and PL within enterocytes, and liberated into the lymph via CM and, to a lesser extent, VLDL particles.

Early research investigating the biological activities of lecithin on intestinal lipid absorption was carried out in the 1970s up to the end of the 1990s and focused mainly on the role of endogenous phosphatidylcholine. Studies undertaken in bile-diverted rats showed that endogenous PC is required for and enhances the intestinal absorption of lipids and their lymphatic transport [59,60]. Indeed, by providing the surface coats of CM, promoting apolipoprotein B48 (ApoB48) synthesis and maintaining adequate enterocyte membrane composition, biliary PL facilitate the transport of dietary lipids from the lumen into lymph [61]. Importantly, small lipid droplets present a greater surface/core ratio than large lipid droplets and consequently require larger amounts of surface compounds such as PL. Consistently, it has been demonstrated that impaired biliary PL secretion in genetically modified rodents leads to delayed intestinal lipid absorption and engenders the secretion of significantly larger lipoproteins in lymph [61–63]. On the contrary, rodents with excess biliary PL secretion synthesize small CM particles [61]. This effect on lipoprotein size has major biological impacts. In effect, lipoprotein size and composition play an important role in the postprandial lipoprotein metabolism and TAG appearance in plasma [64]. At similar lipid load, smaller CM possess a lower affinity for LPL and their plasma clearance is considerably slower than that of larger lipoproteins [65].

Whereas endogenous PC enhances lipid intestinal absorption, the impact of dietary PC is much more controversial. Nakano et al. reported that oral administration of soybean lecithin and its hydrolysates promoted lymphatic TAG output in rats [66]. On the contrary, Davidson et al. reported that endogenous PC increased ApoB48 expression, but excess dietary PC did not enhance its expression any further [67]. A study by Sadouki and Bouchoucha demonstrated no difference in intestinal lipid absorption nor in fecal fatty acid excretion when 30% of lipids (4.5% of total diet) were replaced by lecithin compared to the control group in rats [68]. Likewise, Sugasini et al. observed no statistical difference in lymphatic TAG or PL concentrations in rats fed linseed oil in its non-emulsified form or when it was emulsified by phospholipids or whey protein [69]. In this way, the addition of dietary PL at low PL/TAG ratios (1/16 – 1/7) in several studies did not generate an increase in lipid lymphatic output

[70,71]. However, Nishimikuai et al. demonstrated in two follow-up studies that supplementation with a high dose of soybean PC (PC/TAG with a 1/3 ratio) was capable of enhancing TAG absorption and output in lymph, as well as plasma TAG concentrations in rats [71]. The authors concluded that, based on their previous findings, this increase of TAG absorption by soybean PC must be due to an increase in CM secretion. Consistently, Couëdelo et al. observed an increase in the mRNA expression of proteins involved in chylomicron secretion and exocytosis (Mttp, ApoB and Sar1b) in the duodenum of rats fed linseed oil emulsified with soy lecithin compared to control rats (not gavaged), while rats fed linseed oil devoid of lecithin showed no difference in gene expression vs control rats [50]. Of note, although the expression of these genes were the highest in the soy lecithin group, there was no statistically significant difference between the oil and the oil+lecithin group. However, ApoB48 concentrations in the lymph were doubled in presence of soybean lecithin. Since each CM can only contain one Apob48 molecule, Apob48 concentrations are recognised as accurate measures of CM quantity [50]. Hence, it may be concluded that soy lecithin increases the number of CM particles, leading to an increase in interfacial lipoprotein surface.

Altogether, studies concerning the effect of vegetable lecithin have yielded contradicting results and remain rather inconclusive. In addition, there is a debate on whether the effect of lecithin arises from PC or from its hydrolysed products. Nakano et al. demonstrated that LysoPC and not PC enhanced TAG lymphatic output [66]. This highlights the need for further research on the impact of vegetable lecithin and the role of their individual PL on lipid absorption. In addition, CM coats composed of PUFA-rich PL have been shown to be more effectively cleared from plasma than those composed of saturated fatty acids [63]. Vegetable lecithin, with their high content of PUFA, may therefore exert beneficial effects on lipid intestinal absorption, which may be of use in the prevention of metabolic disorders.

To specifically study lipid intestinal absorption and uptake into enterocytes, *in vitro* models using intestinal cells such as Caco-2 cells or lymph-cannulated animal models are required. The data thus obtained in lymph or in the culture media is a reflection of the absorption of dietary lipids, since these have not yet been subjected to hepatic metabolism and been diluted within the endogenous plasma pool.

However, unlike lymphatic lipids, the lipid profile of plasma is not merely defined by the lipids absorbed at the intestinal level, but is a reflection of whole body homeostasis resulting from the lipid metabolism of individual tissues. Determining the impact of vegetable lecithin on plasma lipemia is therefore crucial in order to grasp a complete understanding of the effect of vegetable lecithin on lipid metabolism and homeostasis.

4. Vegetable lecithins impact lipid homeostasis

4. 1. Lecithins in the regulation of blood lipid profile

The impact of vegetable lecithin on blood lipid profile has been demonstrated in several manners.

Firstly, the pre-emulsification of an oil with vegetable lecithin has been shown to increase the systemic bioavailability of certain fatty acids, without increasing total plasma lipid concentrations. In this way, Sugasini et al. observed no statistical difference in lymphatic TAG or PL concentrations in rats fed non-emulsified or PL-emulsified linseed oil, but reported higher plasma alpha-linolenic acid (ALA) concentrations in the PL-emulsified group [69]. Similar observations using flaxseed oil emulsions stabilised by soy lecithin were related by Couëdelo et al. [50]. Studies exploring the effect of vegetable lecithin supplementation on fatty acid bioavailability without pre-emulsification have generally led to the same conclusions. Geurden et al. demonstrated in carps that the combination of dietary PC and TAG enhanced postprandial plasma TAG concentrations, compared to TAG alone [72]. In rats, combined long-term supplementation of DHA-rich oils and deoiled soy lecithin promoted higher DHA and n-3 PUFA concentrations in erythrocytes and plasma than either DHA or lecithin supplementation alone [73]. The authors suggest that the observations result from a synergistic effect of n-3 PUFA and crude lecithin. The mechanisms behind this specific improvement of fatty acid bioavailability are not well understood and require further research, but synergistic effects between PUFA and PL seem plausible [2]. This may be explained by the impact that lecithins may on specific genes, such as FADS2 and PPARγ and fatty acid binding proteins, notably CD36 and FATP4 [42]. In addition, this may stem from the fact that fatty acids bound to PL are less prone to beta-oxidation, than when they are present as TAG, hence the n-3 and n-6 PUFA largely present in soybean, sunflower and rapeseed lecithin are more shielded from beta-oxidation than those contained in the respective vegetable oils.

Aside from their impact on systemic fatty acid bioavailability, vegetable lecithins have been shown to influence the plasmatic concentrations of other major lipid classes. Notably, PL exert hypocholesterolemic effects and supplementation with soybean PL in patients with primary hyperlipidemia has been reported to significantly reduce blood cholesterol levels [30]. In a study conducted in hypercholesterolemic rabbits, both purified soybean PC and non-purified soybean lecithin (containing 23% PC) significantly decreased plasma total and esterified cholesterol concentrations [74]. Wilson et al. also reported that soybean PC

supplementation in hypercholesterolemic monkeys and hamsters enhances the cholesterol-lowering effects of a lipid-lowering diet, while maintaining plasmatic HDL levels [75]. In this way, dietary PC not only reduces blood cholesterol levels, but it also increases HDL cholesterol, subsequently reducing serum LDL/HDL ratio, a marker of metabolic syndrome [76]. In diabetic patients, it was observed that a 2-month supplementation of polyenylphosphatidylcholine (PPC) purified from soybean lecithin generated elevated HDL cholesterol and Apolipoprotein A-I levels in plasma [77]. The increase in HDL following vegetable PL supplementation may be explained by the fact that PL are preferentially incorporated into HDL particles. Moreover, PL are substrates for lecithin-cholesterol acyl-transferase (LCAT), an enzyme which catalyzes the esterification of cholesterol, enabling the maturation of plasma HDL and consequently promoting cholesterol uptake from peripheral tissues by HDL particles [78]. Increase in Apo A-I also stimulates reverse cholesterol transport [79]. It has also been speculated that PL exert their hypocholesterolemic effect by reducing microsomal HMG-CoA reductase activity and increasing biliary cholesterol excretion [80]. In addition to their impact on enzyme activity and lipoprotein metabolism, vegetable PL promote fatty acid oxidation and impair the uptake of cholesterol by enterocytes [70]. PL are indeed capable of interacting with the membranes of enterocytes, thereby reducing their cholesterol binding capacity [81]. Some authors have reported that the degree of saturation and the length of fatty acids bound to PL control the quantity of cholesterol absorbed in the intestine. The higher the degree of saturation and the longer the chain length of the FA, the less cholesterol is absorbed [70,82,83]. One possible explanation for this finding is the fact that PL carrying saturated fatty acids are poor substrates for $pPLA_2$, therefore hindering the enzyme from accessing the micellar lipids (formed mainly of cholesterol, mono- and diglycerides, and coated with saturated PL) and in consequence impairing the cholesterol uptake [70].

It must be noted however that these effects are mainly described under dyslipidemic conditions [30]. Whereas the cholesterol-lowering effects of lecithin are widely validated under dyslipidemic conditions and in hypercholesterolemic patients, they remain more controversial in normal lipidemic conditions [30,84]. In a scientific opinion report, the EFSA concluded that there was insufficient evidence to establish a cause and effect relationship between the consumption of soy PC and the maintenance of normal cholesterol levels in humans [85]. Nonetheless, this concerns PC specifically and data have revealed a promising role of PE and PI as a lipid-lowering agents [86–88].

The same conclusion may be made concerning the effect of lecithin on triglyceride metabolism. Whereas certain studies affirm a hypotriglyceridemic effect of lecithin in plasma, this causal relationship is far from unequivocal. The lack of convergence of existing data may be explained by the diversity and specificity of the lipid metabolism of each tissue. Of these, the liver and adipose tissue are central organs in the regulation and maintenance of whole body lipid homeostasis; hence alterations of their lipid profile by dietary factors may have major impacts on lipid metabolism as a whole.

4. 2. Impact on lipid metabolism in liver and adipose tissue

The liver plays a central role in lipid metabolism, hence investigating the impact of lecithin on this organ is crucial. The partial replacement of dietary TAG by vegetable, and more specifically soybean, lecithin has been associated with an amelioration of the lipid profiles in the liver and most importantly, a reduction of hepatic TAG levels [89–91]. Buang et al. reported that the replacement of 20% of TAG by PC with similar fatty acid composition in a rat model diminished hepatic TAG accumulation by two thirds through a simultaneous downregulation of *de novo* fatty acid synthesis (PAP and FAS mRNA expression) and upregulation of mitochondrial beta-oxidation in the liver [92]. Similarly, Rouyer et al. demonstrated in fasted re-fed rats that diets containing 4% of soybean or safflower phospholipids markedly decreased hepatic fatty acid synthase and malic enzyme activity and mRNA expression in comparison to diets containing soybean oil [93]. Hence, the beneficial physiological effects of vegetable lecithin seem to result, in part, from an inhibitory effect on the activity and gene expression of enzymes involved in fatty acid synthesis. In addition, soy lecithin is associated with reduced hepatic and VLDL cholesterol levels, similar to those previously described in plasma [81,89].

Furthermore, PL metabolism in the liver plays an important role in hepatocyte lipid metabolism, as illustrated by the important role of LCAT and phospholipid transfer protein (PLTP) in hepatic lipid metabolism [94]. These enzymes are indeed modulated in NAFLD, leading to dyslipidaemia [95]. It may be extrapolated that PL imported via the intake of dietary lecithin modulate the activity of these enzymes, subsequently modulating hepatic lipid metabolism. This hypothesis deserve to be tested.

Moreover, the phospholipid composition of hepatocytes and, more specifically, their PC/PE ratio has been reported to be crucial in insulin signalling [96]. A stable PC/PE ratio in the liver is required for proper glucose and energy metabolism [97] and its alteration is associated with liver disease [98]. PE is essential for health and mice lacking either of the two major PE-

producing pathways are not viable [99]. A considerable proportion of PE is converted to PC in the liver, via a reaction catalysed by PE methyltransferase (PEMT) [100]. The subsequent PC/PE ratio may hence be a result of both the activity of this enzyme and the amount of these phospholipids delivered from endogenous and exogenous pools. Vegetable lecithin, predominantly composed of PC and PE, may hence contribute to balance this PL ratio, which may partially explain its beneficial effect on hepatic lipid metabolism.

Several studies have also described the impact of marine or vegetable lecithin on adipocytes. Awada et al. reported that DHA-rich marine PL in a high fat diet induce lower adipose tissue mass with smaller adipocytes that, DHA-rich TAG in mice [101]. Soy PC supplementation was also associated with smaller adipocytes in high fat fed mice [102]. Nonetheless, data concerning the impact of vegetable lecithin, and notably of lecithin sources other than soy, on adipose tissue and its lipid profile remains scarce. Considering the crucial role of adipocyte lipid profile and metabolism in metabolic disorders, it is of primordial importance that further research be carried out on the impact of such commonly used emulsifiers on adipose tissue.

Despite this lack of evidence, the data obtained so far concerning vegetable lecithin tends towards a beneficial impact on lipid profile (cf **figure 2**), which represents a non-negligible potential within the current upsurge of dyslipidaemia and associated metabolic disorders.

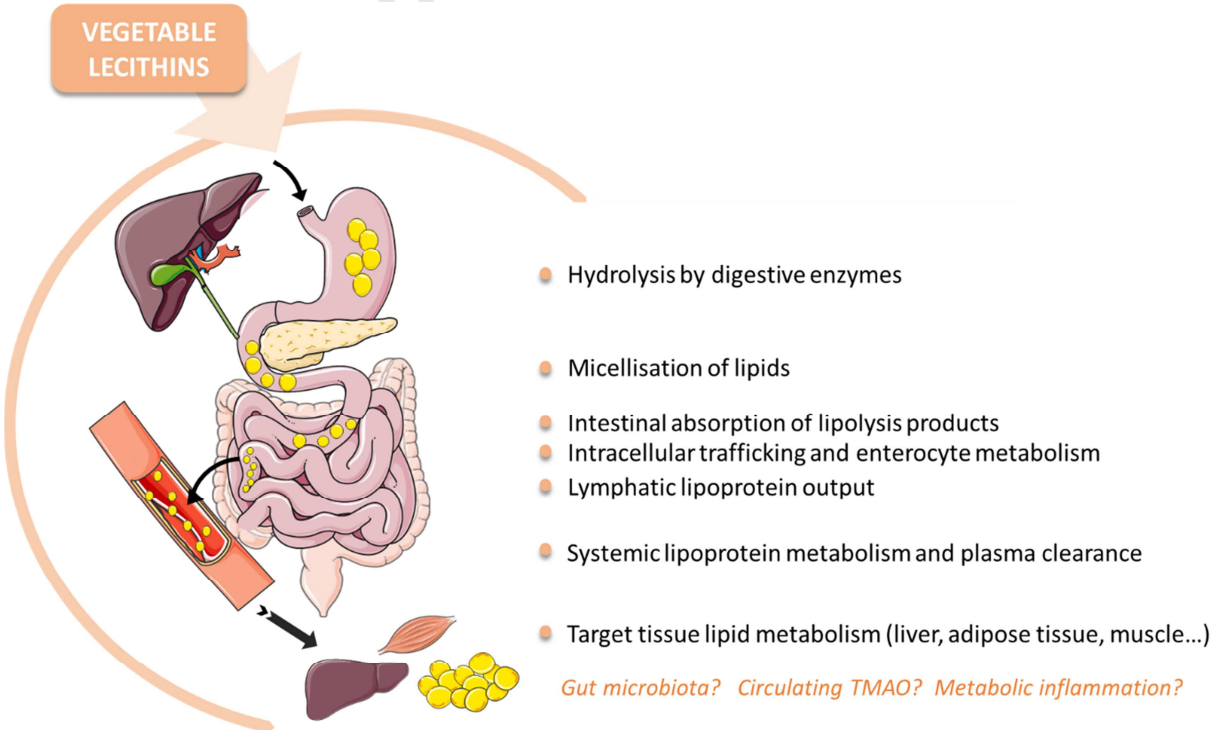

Figure 2. Plausible impacts of vegetable lecithins on lipid and lipoprotein metabolism.

5. Vegetable lecithins: towards a preventive role in dyslipidaemia associated with metabolic disorders

5.1. Potential of vegetable lecithin on obesity and associated metabolic disorders

The prevalence of obesity is rising at unprecedented rates in developed countries, so that it now represents one of the main public health issues in the world [103]. Obesity is associated with a number of cardio-metabolic chronic diseases, such as type II diabetes mellitus, non-alcoholic fatty acid liver disease (NAFLD) and cardiovascular diseases (CVD). All of these disorders are characterised by hyperlipidaemia, that is to say abnormally elevated plasma triglyceride and cholesterol levels [104]. Based on the plethora of evidence concerning the crucial role of endogenous biliary PL on lipid metabolism, as well as the aforementioned lipid-lowering capacities of lecithin, it is not surprising that several studies have recently attempted to investigate the potential of lecithin on the prevention and amelioration of obesity-related metabolic disorders [89,92,102].

The findings obtained so far, mostly in preclinical models, conveys rather encouraging information concerning the ameliorative effects of lecithin on obesity-related dyslipidaemia. Amongst many reasons, this is in part due to the aforementioned physiological effects of PL on lipid gastro-intestinal metabolism. Long-term soybean-derived PC supplementation in mice fed a high-fat (HF) diet has been shown to alleviate obesity-related complications and normalize plasma lipid profiles, notably by reducing plasma triglycerides, cholesterol and leptin levels and diminishing the LDL/HDL ratio [102]. PC supplementation also attenuates HF-induced ApoE expression in the aorta in these mice [102]. In another study conducted in rats, diets supplemented with soybean lecithin presented decreased gastric emptying and food intake, most probably due to the increase in the secretion of gut hormone cholecystokinin (CCK) [105]. These effects observed in preclinical studies show the potential of soybean lecithin in the prevention of obesity and metabolic disorders, as food intake and satiety are important contributing factors of obesity. The possible impact of lecithin in different foods or supplements on satiety and food intake must be confirmed in humans. An additional study performed on obese Otsuka Long-Evans Tokushima Fatty (OLETF) rats, an animal model for obesity- and metabolic syndrome- related complications, reported that omega 3-PC (i.e. EPA and DHA) and not egg PC alleviated obesity-related dyslipidaemia, via reduction of hepatic

fatty acid synthesis and increase in beta-oxidation and serum adiponectin levels [106]. Unlike egg PC, omega-3 PC acted by suppressing the gene expression of SREPB1 and PPARδ, two nuclear receptors involved in the regulation of lipid and energy homeostasis [107]. This clearly demonstrates that the origin of PL and its fatty acid composition determine and modulate their subsequent physiological effects. Such preclinical observations highlight the need for further research investigating the difference between PL from different vegetable sources. To our knowledge, only one review has attempted to gather and compare the effects of individual PL compounds on long-term cardiometabolic health parameters [88]. The review explores the effects of PC, PE and PI on dyslipidaemia, in both animal models and humans, and concludes on the high potential of the use of these PL, especially PI, as alternative or adjunctive therapy for dyslipidaemia in the context of metabolic disorders.

More widely reported are the effects of lecithin supplementation on obesity-related liver diseases, such as NAFLD and steatosis [92]. Indeed, historically, PL have been widely prescribed in the treatment of alcohol-induced liver damage and viral hepatitis. The beneficial impact of plant PL on such hepatic disorders are described in depth in two recent reviews [30,108]. The hepatic lipid-lowering properties of vegetable lecithin endows them with beneficial effects on liver metabolism with potential application in the treatment of hepatic diseases such as NAFLD [88].

Lecithins have also been reported to possess potent anti-inflammatory properties [30,109]. This is of particular interest, since metabolic disorders are highly associated with chronic low-grade inflammation in plasma and adipose tissue [110]. As reviewed in [30,109], beneficial anti-inflammatory properties of vegetable lecithin as a supplement have been reported in a number of inflammatory diseases, including arthritis and ulcerative colitis. However in a dietary context, regarding HF-induced metabolic low-grade inflammation in mice, soy PL (1.2 wt% in a HF diet) have recently been associated with higher markers of adipose tissue inflammation than milk PL [111]. Additionally, the addition of soy PL to a HF diet rich in flaxseed oil also induced higher markers of adipose tissue inflammation in mice than the HF diet enriched with flaxseed oil devoid of lecithin [112]. As outlined in a recent EFSA report, this supports the need for further research investigating the mechanisms and the effects of vegetable lecithin on metabolic inflammation [4] and warrants research in humans.

In addition, a study by Karantonis et al. reported that the polar lipid compartment (which constitutes vegetable lecithin) and not the neutral lipids of seed oils generated biologically active, antithrombotic and anti-atherogenic properties [113]. Vegetable lecithin may then play a promising role in the prevention of atherosclerosis. Interestingly, the study demonstrated the

superiority of lecithin derived from olive oil compared to that of other seed oils (sunflower, corn or soybean) as a platelet aggregation factor (PAF) antagonist. This highlights once again the need for more research concerning individual phospholipids and different lecithin sources. More research must also to be undertaken, which takes into consideration the other minor components of dietary vegetable lecithin. Notably, phyto-oestrogens may be present in non-negligible amounts. Phytosterols, such as those found in rapeseed lecithin, may equally play a synergistic role [18]. The presence of lipid soluble vitamins, such as vitamin E, may further explain certain observed effects of lecithin on lipid metabolism and homeostasis [22].

5. 2. Impact on gut microbiota

A plethora of recent research has demonstrated the importance of gut microbiota on lipid metabolism and homeostasis [114,115]. As such, microbiota affects lipid absorption and, vice versa, ingested lipids influence the number, diversity and health status of the gut microbiota. It has recently been demonstrated that intestinal microbiota converts dietary phosphatidylcholine to trimethylamine (TMA), which is then further metabolised by flavin monooxygenase 3 (FMO3) and other FMO proteins in the liver into pro-atherogenic trimethylamine N-oxide (TMAO) [116]. High TMAO concentrations in plasma are associated with increased cardio-metabolic disease and atherosclerosis risk [116,117]; hence, it is thought that excess dietary PC increases the levels of TMAO resulting in a pro-inflammatory and pro-thrombotic state leading to insulin resistance, type II diabetes, and cardiovascular disease [116,118]. However, recent research indicates that the conversion of choline to the TMAO precursor, TMA, results from the presence of specific gut bacteria, rather than from excess dietary choline [2]. The authors of these studies specify that the need for further research is required in order to clearly understand the relationship between dietary PL and the microbiota-dependent production of TMAO.

The present knowledge regarding the importance of gut microbiota on lipid metabolism and metabolic health renders obligatory that further research on the effect of vegetable lecithin on TMAO production and gut microbiota in general be explored. This is all the more important as the market of vegetable lecithins is expanding at unprecedented rates.

6. Conclusion and future prospects

Vegetable lecithins provide food-derived PL that, similarly to endogenous PL, have the potential to modulate numerous membrane-dependent cellular functions, as well as exert lipid-regulating, anti-inflammatory and antioxidant effects [2]. Despite the lack of converging evidence concerning their effects on lipid digestion and intestinal absorption, it is clear that dietary vegetable lecithin exert an overall beneficial effect on lipid and lipoprotein metabolism. In this way, they have been proposed as novel therapeutic agents for the treatment of hyperlipidaemia associated with metabolic and cardiovascular diseases [89]. Supporting this idea is the fact that PL are capable of forming unique lipid droplets, referred to as liposomes, which have been investigated as drug carriers for decades and which have been associated with ameliorated blood and hepatic lipid profiles [119].

Importantly, this review highlights the evident lack of existing data concerning vegetable lecithin from sources other than soybean, and their effects on lipid metabolism and metabolic health. The immense compositional diversity of vegetable lecithins, arising from both agronomical and genetic factors, grants them with a vast range of biochemical and biological properties, which remain to be explored. Faced with the current epidemical outburst of obesity and the staggering growth rates of the lecithin market, future research must be undertaken in order to determine the health effects of vegetable lecithins, both as supplements and as ingredients in different foods. More specifically, it is of primordial importance that researchers attempt to elucidate the various mechanism by which individual fatty acids and PL from various vegetable lecithin modulate lipid metabolism and the extent to which they may influence parameters associated with metabolic disorders, such as intestinal integrity, low-grade inflammation and gut microbiota.

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Table 1. Summarised data on phospholipid composition [4] and fatty acid composition [13] of three liquid vegetable lecithins (soy, sunflower and rapeseed).

	Soy lecithin	**Sunflower lecithin**	**Rapeseed lecithin**
Phospholipid composition (%) [4]			
PC	12.69 – 16.7	14.34 – 17.23	16.74 – 18.18
PI	6.47 – 11.84	12.30 – 14.92	10.45 – 12.30
PE	6.45 – 13.57	4.85 – 6.82	6.46 – 8.03
PA	2.28 – 5.96	1.32 – 3.21	2.44 – 3.59
Fatty acid composition (%) [13]			
16:0	16	11	7
18:0	4	4	1
18:1	17	18	56
18:2	55	63	25
18:3	7	0	6
Others	1	4	5

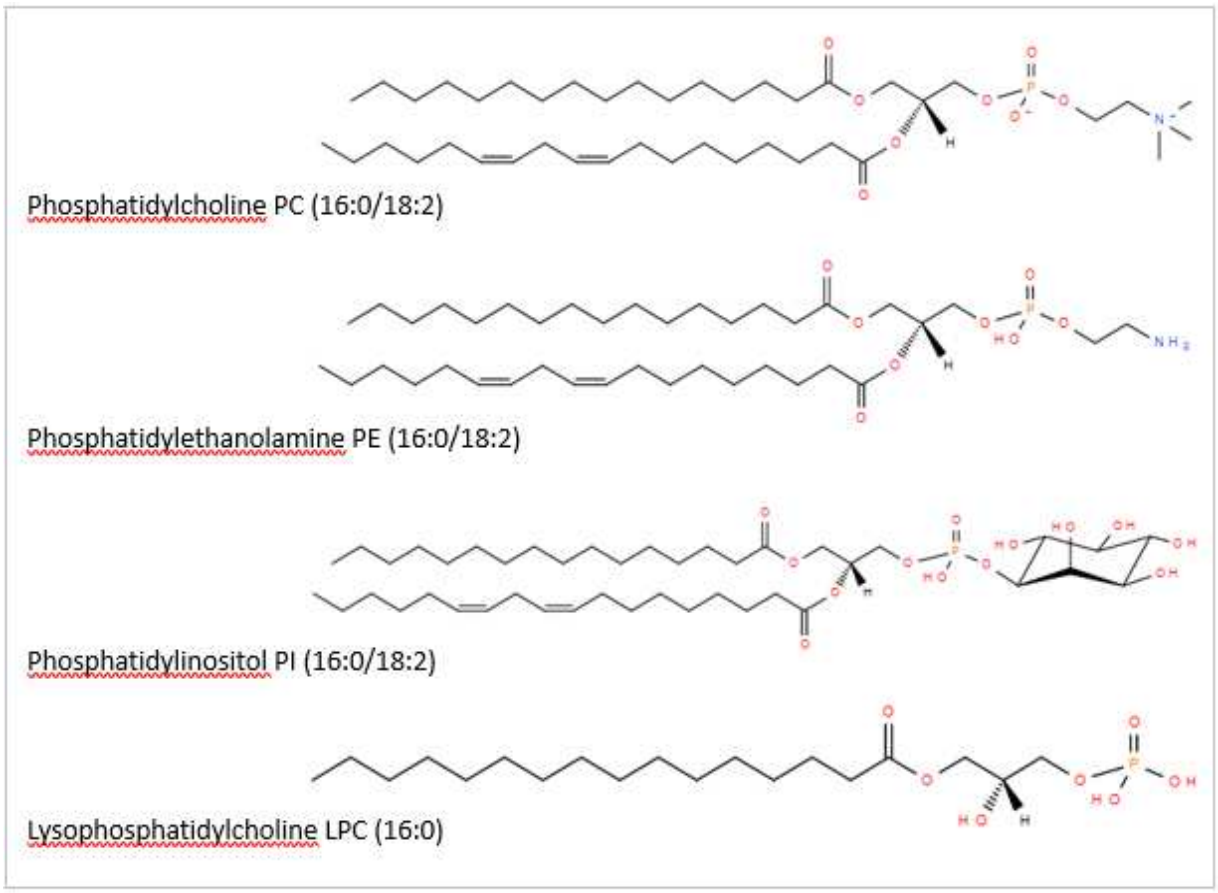

Figure 1. Structures of the major phospholipids found in soybean lecithin. Lipid structures were drawn using LIPID MAPS tools.

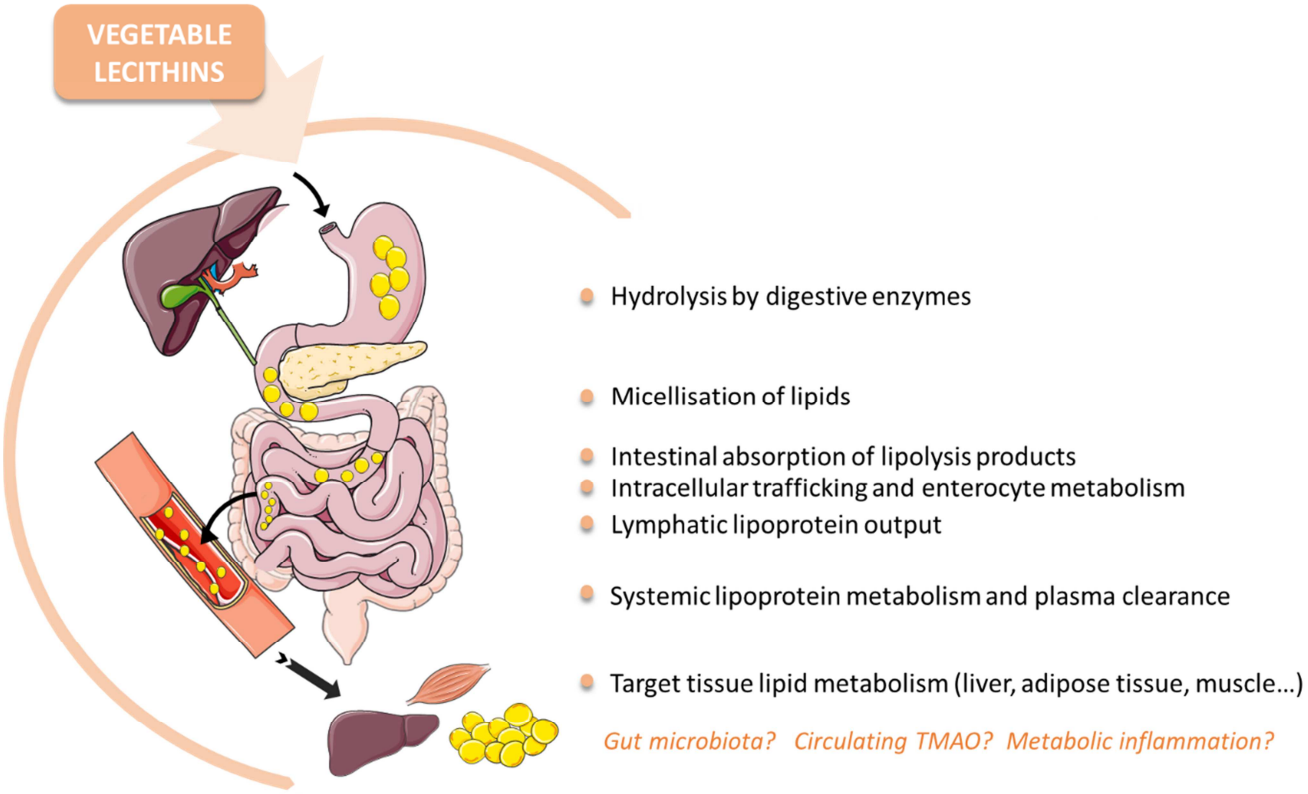

Figure 2. Plausible impacts of vegetable lecithins on lipid and lipoprotein metabolism.