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REVIEW ARTICLE

A brief review of physiological roles, plant resources, synthesis, purification and oxidative stability of Alpha-linolenic Acid

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ABSTRACT

Alpha-linolenic acid (ALA) is a polyunsaturated fatty acid (PUFA) comprising of 18 carbon atoms and three double bonds. Because the first double bond counted from the methyl terminus, is at position three, ALA belongs to the so-called n-3 group. Derived mainly from natural plants such as *Linum usitatissimum* and *Perilla frutescens*, it is an essential fatty acid for the human body. ALA is essential for the regulation of blood lipid, blood pressure and blood sugar, for the prevention of diseases and for the protection of retina and brain. It is the precursor of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are crucial for human health. This review summarizes the current knowledge on physiological roles, plant resources, and synthesis, purification and oxidative stability of ALA, providing the scientific basis for its sustainable development and utilization towards human health.

Keywords: Alpha-linolenic acid (ALA); Physiological roles; Plant resources; Purification; Oxidative stability

INTRODUCTION

Fatty acids (FAs) are major components of dietary fats and are primarily stored as triglycerides (TAGs). Similar to proteins, amino acids, vitamins, minerals and other bioactive substances, FAs have extensive physiological roles which are vital for human health and growth (Solfrizzi et al., 2005; Acuff et al., 2007; Vannice and Rasmussen, 2014). Based on their chemical structures, FAs can be categorized into saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). Among them, PUFAs have higher bioactivities because there are 18 or more carbons in length with two or more methylenes interrupted double bonds in the cis position (Schuchardt et al., 2010; Yoon et al., 2014). Besides, they are associated with fluidity, flexibility and selective permeability of the cellular membrane in higher eukaryotes (Wallis et al., 2002). Thus, PUFAs play an important role in maintaining human's normal growth and health (Yehuda et al., 2002; Schuchardt et al., 2010; Yoon et al., 2014).

Based on the position of the carbon in the first double bond from the methyl terminus, PUFAs can be divided into series of n-3, n-6, n-7 and n-9. Among which, n-6 and n-3 PUFAs have important biological significance that is closely related to human health (Pischon et al., 2003; Astorg, 2004). The most abundant in the human diets are alpha-linolenic acid (ALA; $18{:}3^{\Delta 9,12,15}$ n-3) and linoleic acid (LA; $18{:}2^{\Delta 9,12}$ n-6) for they could not be synthesized by the body. However, the imbalance of n-6 and n-3 PUFAs could increase the risk of many chronic diseases such as inflammation and allergy (Harris et al., 2006; Orchard et al., 2010). Nevertheless, human's inappropriate dietary habits would result in the increase of content of n-6 PUFAs, which would overcharge the balance between n-3 and n-6 PUFAs and eventually affect the health. To ease the imbalance of n-3 and n-6 PUFAs and reduce the risk of the disease, an appropriate increase of n-3 PUFAs is necessary.

Recent studies show that n-3 PUFAs mainly include ALA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Among these, EPA and DHA have generated much research interest in recent years (Kris-Etherton et al., 2009) because they have a variety of physiological healthy functions (Oliver et al., 2010; Mozaffarian and

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Wu, 2011). ALA, the precursor of EPA and DHA, has three cis-double bonds in positions 9-10, 12-13, and 15-16 counting from the carboxyl end of the FAs (Fig. 1) (Barceló-Coblijn and Murphy 2009; Calder, 2012). Moreover, ALA is referred to as 'essential fatty acids' for human (Das, 2006a, 2006b). Compared to animal oils rich in ALA, the ALA derived from plant oils are more affordable, available globally and without cholesterol (Pan et al., 2012a). Therefore, more and more attentions have been paid to the functional verification and utilization of ALA in recent years. This review aims to summarize current knowledge on the physiological roles, plant resources, biosynthesis and conversion, purification and oxidative stability of ALA.

PHYSIOLOGICAL ROLES OF ALA

ALA is the basic substance of the cell membranes and biological enzymes (Bjerve et al., 1987). ALA and PUFAs are the main component of the cell and mitochondrial membranes. Also, the component of FAs in the biological membranes would directly affect the functions of membranes such as catalyzed reaction, receptor activity, membrane operation and metabolic rate of enzymes. The fluidity and formability of membranes would improve with the increase of n-3 PUFAs contents, which could have an effect on opposing atherosclerosis and restoring the elasticity of blood vessels (Calder, 2012, 2014). Apart from its structure function, as the biological enzyme, ALA may competitively inhibit several enzymes in the n-6 PUFAs pathways and inhibit these enzymes especially *Δ6-desaturase* which were related in FAs and cholesterol biosynthesis (Stroud et al., 2009; Domenichiello et al., 2017). Thus, it has a great range of physiological roles in preventing cardiovascular disease (CVD), cancer, inflammation and allergy, providing neurological protection, enhancing immunity, protecting retinal and brain development (Barceló-Coblijn and Murphy 2009).

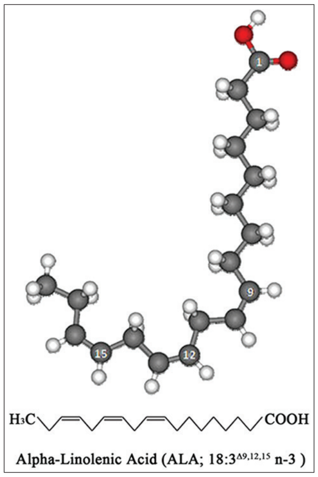

Fig 1. Molecular and chemical structure of alpha-linolenic acid (ALA).

Ala and cardiovascular disease (cvd)

Studies have proved that ALA can prevent CVD by lowering lipid levels (Gebauer et al., 2006), inhibiting platelet aggregation (Kim et al., 2016), thrombosis (Owren et al., 1964), arrhythmia (Abeywardena and Patten, 2011) and preventing the formation and development of atherosclerosis (Sala-Vila et al., 2010, 2011; Lopez-Moreno et al., 2017). Pan et al., (2012a) summarized the systematic review and meta-analysis of dietary and biomarker studies of ALA and CVD, finding that overall ALA exposure was associated with a modestly lower risk of CVD. After several researches, Mozaffarian (2005) recommended that ALA intake be increased to 2−3 g/day to reduce risk of CVD. Bloedon et al. (2008) studied the effects of flaxseed on the markers of cardiovascular risk in hypercholesterolemic adults who were randomized to 40 g/day of products or matching wheat bran products for 10 weeks while following a low fat and cholesterol diet. The result showed that flaxseed has modest but short lived low density lipoprotein cholesterol (LDL-C) lowering effect, yet reduces lipoprotein and improves insulin sensitivity in hyperlipidemic adults. A randomized controlled trial was taken based on 79 volunteers with impaired fasting glucose were dieted with camelina sativa oil, fatty fish and lean fish. The research showed that the camelina sativa oil which is rich in ALA, but not fatty fish and lean fish, significantly decreased total LDL-C concentrations to improve serum lipid profile (Schwab et al., 2018). Fukumitsu et al. (2013) found that ALA suppressed cholesterol and triacylglycerol biosynthesis pathway by suppressing *sterol regulatory element binding protein* (*SREBP*)*-2*, *SREBP-1a* and *-1c* expression. Moreover, there are many evidences that have demonstrated a beneficial role of ALA for the primary and secondary prevention of CVD (Fleming and Kris-Etherton, 2014).

ALA may protect against coronary heart disease (CHD), which has been verified. Epidemiological studies and dietary trials (de Lorgeril and Salen, 2004) found that moderate amounts of ALA can reduce the risk of CHD, although ALA content in blood and tissue was low comparatively. Zatonski et al. (2008) ensured the relationship between national changes in vegetable oil consumption and trends in CHD in eleven Eastern European countries after 1990. Pan et al. (2012a) suggested that human should have each 1 g intake of ALA per day which is closely related with a 10% lower risk of CHD death. After studying an aggregate association between ALA intake and risk of CHD, Wei et al. (2018) found that compared with people without ALA intake, people with ALA intake <1.4 g/d showed reduced risk of composite CHD. And people with 1 g/L increase in ALA intake were associated with a 12 % decrease in fatal CHD risk.

Recent researches have suggested that foods containing ALA is helpful to reduce the risk of sudden cardiac death (SCD) (Albert et al., 2005; Christensen et al., 2005). To investigate whether ALA in human body adipose tissue has correlation with heart rate variability (HRV; a strong predictor of SCD and arrhythmic events), Christensen et al., (2005) studied in subjects who underwent coronary arteriography due to suspected coronary artery disease (CAD). The results demonstrated that ALA and HRV were compactly related. It may suggest that higher content of ALA in human body have enhancive HRV, which leaves them less likely to suffer forming ventricular arrhythmias, and thereby supporting an anti-arrhythmic effect of ALA. In addition, Sala-Vila et al. (2010) evaluated 499 consecutive subjects with primary dyslipidemia and blood phospholipid enrichment with ALA and DHA, which showed that ALA content in serum phosphatidylcholine was inversely related to mean and maximum intima-media thickness (IMT) in the internal carotid artery (ICA). IMT is a well-validated surrogate marker of future ischemic heart disease (IHD) events (Lorenz et al., 2007; Álvarez-Aguilar et al., 2012). In order to investigate the mechanism responsible for the effect that ALA may be cardioprotective during ischemia, Ganguly et al. (2018) extracted and analyzed the cardiomyocyte phospholipids in adult rats. The result showed that ALA protects the cardiomyocyte from apoptotic cell death during simulated ischemia and reperfusion by inhibiting the production of specific pro-apoptotic oxidized phosphatidylcholine species, which represent a viable interventional target to protect the heart during ischemic challenge. Thus ALA is considered to be helpful to the prevention of CVD.

But there are also studies shown that ALA is not correlated with the prevention of CVD, or even cause side effects (Oomen et al., 2001; Djoussé et al., 2005; Wang et al., 2006; Geleijnse et al., 2010; de Goede et al., 2011; Bork et al., 2016). Lemaitre et al. (2009) organized a population-based study which included 265 cases of SCD without previously diagnosed heart disease and 415 individually matched controls, while the study result was inversely correlated with inherent considered benefits of dietary ALA, and even higher levels of ALA in red blood cell (RBC) membranes increased the risk of sudden cardiac arrest (SCA). A study from the Netherlands showed that ALA intake was not associated with incident CHD and a low intake of ALA may be induced incident stroke (de Goede et al., 2011). In Denmark, Bork et al. (2016) suggested that ALA has no appreciable association with risk of incident myocardial infarction which may cause CHD in either men or women. In post-myocardial infarction patients with chronic kidney disease, after long-term supplementation with modest quantities of ALA, the fibroblast growth factor 23 (FGF23) level was not reduced. As FGF23 is an independent risk factor for cardiovascular mortality, ALA was not inversely associated with the cardiovascular risk (de Borst et al., 2017). Thus, further studies will be needed to confirm the association of dietary ALA with CVD such as investigating other populations with no disease history and other improper habits, gene variation in metabolic processes and so on.

Ala and cancer

ALA can reduce the incidence of breast cancer, pancreatic cancer, colon cancer and kidney cancer and inhibit tumor growth. Assuming that ALA may play an effective role in breast cancer risk, a case-control study (Klein et al., 2000) among homogeneous population of 123 patients with non-metastatic invasive breast carcinoma and 59 women with benign breast disease had been conducted. The result indicated the odd ratio for breast cancer among women in the highest quartile of adipose breast tissue ALA level compared with the lowest quartile was 0.36, proving a protective effect of ALA on breast cancer risk. Recent studies have showed that ALA reduces growth of breast cancer cell lines (MCF-7, BT-474, MDA-MB-231 and MDA-MB-468) and demonstrates a dynamic gene expression in treated breast cancer cells (Wiggins et al., 2015; Mason-Ennis et al., 2016). Hirko et al. (2018) reported that there were inverse associations of n-3 PUFA (e.g. ALA) with breast cancer among overweight/obese women (BMI≥25) after examed the relationship between 34 individual fatty acids and cases.

A study (Dwivedi et al., 2005) was designed to investigate the efficacy of varying amounts of perilla oil rich in ALA and safflower oil rich in LA on colon carcinogenesis in mice. The result provided that a certain amount of vegetable n-3 PUFA, ALA, added in a total dietary food may exhibit a large beneficial effect for the prevention of colon cancer. Chamberland and Moon (2015) also suggested a down-regulation of malignant potential on colon cancer cells. Apart from breast and colon cancer cells, a reduction on the expression of several genes was in the esophageal and cervical cancer cells (Moon et al., 2014; Deshpande et al., 2016). After validate the effect of ALA on mitochondrial apoptosis, hypoxic microenvironment and de novo fatty acid synthesis, Roy et al. (2017) concluded that ALA mediates mitochondrial apoptosis, curtails hypoxic microenvironment along with inhibition of de novo fatty acid synthesis to impart anticancer effects.

However, researches reporting no correlation between ALA and the prevention of cancer also exist (Brouwer et al., 2004). During the study of ALA and prostate cancer

(Koralek et al., 2006), a randomized of 38,350 men between the ages of 55 and 74 years were enrolled. These men were screened annually in case of newly incident prostate cancer, moreover followed up for subsequent ascertainment of cancer outcomes. The result from this survey was inconsistent with the other protective epidemiologic studies, for the ALA content was not related to the risk of prostate cancer. Based on the relative risk from five prospective and seven case–control studies, Carleton et al. (2013) drew a conclusion that ALA intake is positively but non-significantly associated with prostate cancer risk. Besides, a 24-year prospective study of dietary ALA and lethal prostate cancer reported that higher intake of ALA was associated with an increased risk of lethal prostate cancer in the pre-PSA era (before February, 1994) but not in the PSA era followed from 1986 to 2010 (Wu et al., 2018).

Ala, anti-inflammation and anti-allergy

ALA and its metabolites, EPA and DHA, can reduce the production of leukotriene B4 (LTB4), neutrophils, monocytes and macrophages, as well as the adhesion and aggregation of white blood cells and vascular endothelial cells, which can effectively inhibit the damage of endothelial inflammation and allergy reactions (Wang et al., 2007b). Supplied with ALA would significantly reduced inflammation and some persistent effects could be observed after 2 weeks supplyment (Faintuch et al., 2007). In the research for 12 weeks (Rallidis et al., 2003), subjects were randomly assigned to two groups of oils supplementation, ALA group and LA group. ALA group was provided with 15 ml linseed oil per day containing approximately 8 g ALA, and LA group 15 ml safflower oil per day containing approximately 11 g LA. C-reactive protein (CRP), serum amyloid A (SAA) and interleukin (IL)-6 levels, the biomarkers of inflammation, showed statistically significant decrease after administration of ALA, supporting a higher intake of ALA is associated with a lower relative risk of inflammation.

It was also reported that perilla oil rich in ALA and corn oil rich in LA were selected to feed the mice with allergic bronchoalveolar inflammation (Chang et al., 2008). The result from this study showed that perilla oil administration might alleviate bronchoalveolar inflammation by decreasing the secretion of pro-inflammatory cytokines, IL-1β, IL-6 and tumor necrosis factor (TNF)-alpha (TNF-α), in bronchoalveolar lavage fluid. In rats with 2-4-6-trinitrobenzen sulfonic acid (TNBS)-induced colitis, ALA intake is benefit to the inhibition of inflammation stress by regulating nuclear factor-κB (NF-κB) activation (Hassan et al., 2010). In diabetic rats, dietary ALA group showed a significantly decreased in TNF-α, soluble P-selectin (sP-selectin) and soluble intercellular adhesion molecule-1 (sICAM-1) compared to control which indicate that diet rich in ALA exerted the anti-inflammatory effects in diabetic rats (Zhang et al., 2012). Rich-ALA intake is also benefit to anti-inflammatory in overweight-to-obese patients with metabolic syndrome traits (Egert et al., 2014). In addition, inflammation is a major cellular strain causing increased risk of osteo-degenerative diseases. Song et al. (2017) studied the effect of ALA in mice models. The result shows reductions in levels of IL-1b, IL-2, IL-6, IL-10, TNF-α, monocyte chemoattractant protein 1 (MCP-1), nitric oxide synthases (iNOS) and cytokine-activated cyclooxygenase-2 (COX-2), which suggest that ALA prevents inflammatory bone loss via downregulation of NF-κB-iNOS-COX-2 signaling. But there are experimental researches indicating the intake of ALA has no protective effect to inflammation, and even cause side effects (Bemelmans et al., 2004).

Ala and neurological protection

It was reported ALA was a potent neuroprotective agent against soman-induced neuropathology (Pan et al., 2012b). Subchronic ALA treatment significantly promoted neurogenesis in the adult brain that could have an effect in motor and cognitive functional recovery of neurological disorders (Blondeau et al., 2009). There was another study demonstrating that ALA provided a beneficial effect on the infarct size, neurological score, neuronal survival and mortality rate of ischemic mice in a clinically relevant model of stroke (Heurteaux et al., 2006). Recent review by Blondeau (2016) has presented the capacity of ALA for protecting the brain from stroke by direct neuroprotection, triggering brain artery vasodilatation and neuroplasticity to reduce the stroke damage. And in a mouse model of ischemic stroke, it was found that ALA intake would provide an enteral or parenteral nutritional intervention for sensorimotor and cognitive deficits (Bourourou a et al., 2016). Alzheimer's disease (AD) is characterized by progressive cognitive and memory impairment. Lee et al. (2017) research showed that ALA might be a potential candidate for prevention or treatment of neurodegenerative diseases such as AD by inhibiting the amyloidogenic pathway through the down-regulation of β-site APP-cleaving enzyme and enhancing Aβ degradation enzyme.

Ala and others

As we know, there are some other potential effects of ALA being suggested. The ability of ALA in protecting brain and retina has been investigated (Uauy et al., 2001; Shen et al., 2013). At the same time, ALA is the precursor for converting into DHA, which is beneficial to brain (Singh, 2005).Studies have shown that lack of DHA will seriously affect brain and vision of infants (Birch et al., 2000; Uauy et al., 2000). ALA might be an important value in enhancing immunity. It was reported that about 20g ALA intake per day can restrain cell-mediated immune response

(Kelley et al., 1991). In the experimental animal models of mice, Yao et al. (2007) provided evidence that ALA could promote the carbon clearance and abdominal macrophage phagocytosis of monocyte-macrophages, promote delayed hypersensitivity, improve the activity of natural killer, and consequently the immunity of mice was enhanced. Besides, Wang et al. (2016) reported that dietary ALA-rich flaxseed oil might be a promising approach for prevention of alcoholic fatty liver and Lavado-Garcia et al. (2018) found that there was positive correlation ALA intake with bone mineral density at both the hips and the lumbar spine in normal and osteopenic women.

PLANT RESOURCES OF ALA

In recent years, the source investigation of ALA has become a hotspot among scientists because of its health benefits on preterm and neonates, cardiovascular diseases and neuroprotective properties (Barceló-Coblijn and Murphy, 2009). It is found that plants are abundant in ALA (as phospholipids in leaves and as TAG in seed oils) after long-term study (Imbusch and Mueller, 2000; Sinclair et al., 2002; Barceló-Coblijn and Murphy, 2009). Nowadays, people take ALA through the diet of soybean oil, rapeseed oil, corn oil, nuts and some other plants oil. However, the ALA amount in these plants is far to reach the need of human health (Kris-Etherton et al., 2000; Sanders, 2000). Since 1887 when ALA was first isolated from hempseed oil (Deuel et al., 1951), a wide range of plants from *Linaceae, Eucommiaceae* and *Labiatae* were found as the main plant resources of ALA which has high oil content (Xu et al., 2004). Among these, they found a wide variety of plants with oil content higher than 25% and ALA content higher than 60% as well, such as *Linum usitatissimum, Perilla frutescens, Salvia hispanica* (živković et al., 2017), *Eucommia ulmoides* (Zhang et al., 2018), *Agastache rugosa* and *Elsholtzia ciliata* (Table 1) (Xu et al., 2004; Li et al., 2010a). Besides, some new sources such as *Camptotheca acuminata* (Yin et al., 2002), *Zanthoxylum bungeanum Maxim*, *Paeonia suffruticosa* (Li et al., 2010a), *Sambucus williamsii* (Zhang and Liu, 2000), *Hovenia acerba* (Zhao et al., 2010) and *Descurainia sophia* (Li, 2013). Their relatively high content of ALA (≥30%) has been used for human diet.

Linum usitatissimum

Linum usitatissimum (flaxseed) is an annual herb, which is relatively known as an old crop with a history of about 5000 years used as the food and drug. It mainly planted in Canada, Argentina, America, China and India (Wang et al., 2007a). Flaxseed contains 35%-45% oil (Zhao et al., 2006) of which 50% is ALA (Wanasundara and Shahidi, 1994; Bloedon and Szapary, 2004). Flaxseed oil is usually used as a dietary source of n-3 PUFAs in experimental research (Holman et al., 1982; Visentainer et al., 2005). In an animal model study, it was demonstrated that flaxseed oil can reduce serum cholesterol by increasing the content of ALA, and at the same time increase n-3 very long chain PUFAs in the serum and erythrocyte lipid (Wiesenfeld et al., 2003). In hemodialysis (HD) patients, it was reported that a daily consumption of 6.0 g flaxseed oil reduced serum hepcidin and improved hematologic factors (Tabibi et al., 2016).

Table 1: Plants rich in alpha-linolenic acid (ALA)

Plant	Family	Oil content (%)	ALA (%)
Linum usitatissimum	Linaceae	29.6-43.5	42.0-60.0
Perilla frutescens	Labiatae	34.0-45.0	51.0-63.0
Eucommia ulmoides	Eucommiaceae	32.3	42.0-62.0
Agastache rugosa	Labiatae	33.6	60.0-62.0
Actinidiaceae chinensis	Actinidiaceae	35.0	62.0
Actinidiaceae actinidia	Actinidiaceae	27.9	66.0
Lasiococca comberi	Euphorbiaceae	59.3	65.0
Elsholtzia ciliata	Labiatae	33.4	57.0-65.0
Paeonia suffruticosa	Paeoniaceae	25.9	39.7
Zanthoxylum bungeanum	Rutaceae	27.0-35.1	36.2

Perilla frutescens

Perilla frutescens (perilla) is an annual self-pollination herbaceous plant, and widely grown in China, India, Japan, South Korea, Thailand and the other eastern Asian countries (Longvah and Deosthale, 1991). Perilla seed oil, which constitutes approximately 47.8% of the seed weight (Shin and Kim, 1994), is mainly composed of palmitic acid (C16:0), stearic acid (C18:0), oleic acid (OA; $C18:1^{\Delta 9}$ n-9), LA ($C18:2^{\Delta 9,12}$ n-6) and ALA ($C18:3^{\Delta 9,12,15}$ n-3), which ALA account for 55-65% of the total fatty acids (Stuchlík and Zak, 2002). So far, it is the plant of the richest ALA in seed oil (Longvah and Deosthale, 1991; Kurowska et al., 2003). Its production has been discussed in the physiological and pharmacological action of ALA (Ichihara and Suda, 2003). As researches on the functional verification of health care, perilla seed oil is beneficial in improving immune (Shoda et al., 1995) and mental function (Yamamoto et al., 1987), decreasing the circulating levels of serum cholesterol and triglyceride (Longvah et al., 2000), inhibiting the risk factors platelet aggregation and thrombus formation in cardiovascular disease (Calder 2004; Jang et al., 2014; Kim et al., 2016).

Eucommia ulmoides

Eucommia ulmoides is a kind of deciduous tree. It is well known that its gum has important industrial applications (Yan, 1996). *Eucommia ulmoides* seed oil is mainly composed of myristic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), OA (C18:1$^{\Delta 9}$ n-9), LA (C18:2$^{\Delta 9,12}$ n-6), ALA (C18:3$^{\Delta 9,12,15}$ n-3). Also the polyunsaturated fatty acids, monounsaturated fatty acid and saturated fatty acids account for 69.4%, 17.4% and 13.2%, respectively (Zhang et al., 2010). The content of ALA in the seed oil is approximately 61.4% (Zhang et al., 2018), which is equivalent to that of perilla seed oil. It is proved effective to improve immune function, increase energy expenditure and keep slender figure in modern medicine (Ma et al., 2005).

Other plants

In addition to the above mentioned plants, there are some other plants which are abundant in ALA. *Portulaca oleracea* is richest in ALA among all the green leafy vegetables (Xiang et al., 2005; Lim and Quah, 2007), and it is one of the few sources of EPA. The oil content of *Actinidia chinensis* seed is approximately 32.0−35.0% and the unsaturated fatty acid is 92.12% of the seed oil, which is extremely high. It is also one of few nature seed oils rich in ALA, containing 61.8% ALA (Li et al., 2007). *Agastache rugosa* and *Elsholtzia ciliata* are aromatic herbs from the same branch of *Labiatae*. The seed oil content of *Agastache rugosa* and *Elsholtzia ciliata* is 35.2% and 42.4%, with ALA accounting for 60.6% and 58.1% of the total fatty acids, separately (Mei et al., 2004a, 2004b). But unfortunately, their seeds are too expensive for mass production (Xu et al., 2004). Besides, the oil content of *Paeonia suffruticosa* seed is 27%, and it is rich in OA, LA and ALA, altogether accounting for 83.1% of the total fatty acids (Zhou et al., 2009). *Lasiococca comberi,* the same family member of *Ricinus communis* and *Jatropha curcas*, is abundant in ALA as well (Guo et al., 2009). *Dracocephalum moldavica* (Labiatae) is particularly used for its content of essential oil in all above ground parts, the seeds with about 15.0% of vegetable oil containing more than 60.0% of ALA (Stuchlík and Zak, 2002).

BIOSYNTHESIS AND CONVERSION OF ALA

The biosynthesis of ALA in plants mainly includes FAs synthesis and ALA synthesis. The precursor of ALA biosynthesis in plants is acetyl-CoA (Davis et al., 2000). It is catalyzed into ALA in turn by *acetyl coenzyme A* (*ACCase*), *fatty acid synthase* (*FAS*), *stearoyl-ACP desaturase* (*SAD*), *⊿ 12-desaturase* and *⊿ 15-desaturase* (Thelen and Ohlrogge, 2002). Subsequently, ALA is converted into n-3 long-chain PUFA such as EPA and DHA in both plants (Truksa et al., 2006; Zhou et al., 2007; Petrie et al., 2010a) and mammals (Barceló-Coblijn and Murphy, 2009; Domenichiello et al., 2015) (Fig. 2).

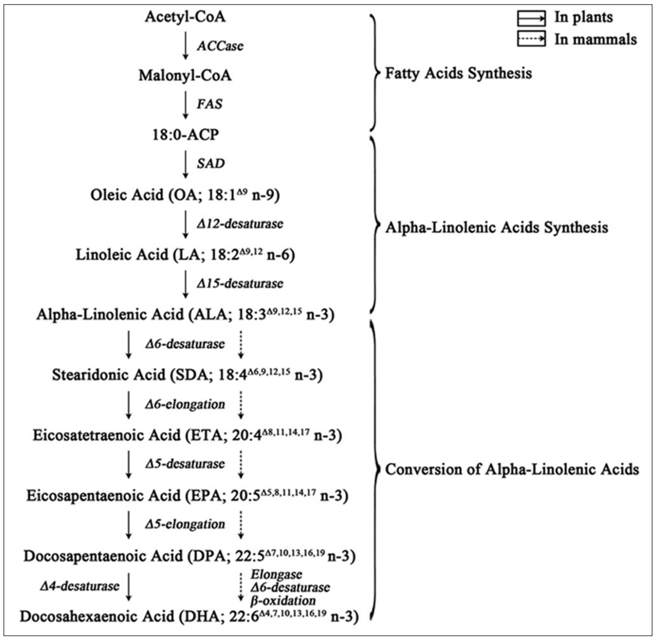

Fig 2. The biosynthesis and conversion of alpha-linolenic acid (ALA). The solid arrows represent for the biosynthesis and conversion of ALA in plants; the dashed arrows represent for the conversion of ALA in mammals.

Fas synthesis in plants

The reactions for FAs synthesis are located in the plastids (Browse and Somerville, 1991).The first dedicated step is the conversion of acetyl-CoA (the precursor of fatty acids synthesis) into malonyl-CoA catalyzed by *ACCase* (Davis et al., 2000; Sasaki and Nagano, 2004). Second, a multi-subunit *FAS* converts malonyl-CoA into a fatty acid product bound to an acyl carrier protein (ACP). Then FAs are characterized by a single ACP for each cycle of chain elongation and its termination is catalyzed by acyl-ACP thioesterases, which hydrolyze acyl chains from ACP. The final products of this enzymatic complex are 16:0- and 18:0-ACP, which are produced in the endoplasmic reticulum (ER) (Ohlrogge and Jaworski, 1997; Thelen and Ohlrogge, 2002; Uemura, 2012). Besides, the flux of acyl chains in the endoplasmic reticulum (ER) eventually leads to the cytosolic acyl-CoA pool to form TAG from sn-glycerol-3-phosphate (G3P) in developing seeds of oleaginous plants (Thelen and Ohlrogge, 2002; Lung and Weselake, 2006).

Ala synthesis in plants

In the ALA synthesis pathway, most of the 18:0-ACP is desaturated by a soluble *SAD*, yielding OA (18:1$^{\Delta 9}$ n-9) (Thelen and Ohlrogge, 2002). In general, the PUFAs synthesis pathway is initiated by *⊿12-desaturase* in the thylakoid of ER (*FAD2*) and plastids (*FAD6*), producing LA (C18:2$^{\Delta 9,12}$ n-6). Subsequently, LA has two directions of chain elongation and desaturation and act as the precursor of n-6 and n-3 PUFAs. In the n-3 PUFAs pathway, LA may be further desaturated by a *⊿15-desaturase* in the thylakoid of ER (*FAD3*) and plastids (*FAD7* and *FAD8*) to generate ALA (C 18:3$^{\Delta9,12,15}$ n-3) (Ohlrogge and Jaworski, 1997). It indicates that most of the higher plants can synthesize the C$_{18}$ PUFAs such as LA and ALA which humans and animals are not capable of producing, yet a small number of plant species do have the faculty to produce very long chain PUFAs (Napier and Graham, 2010). But there are more and more researches about reconstitution of pathways leading to producing such fatty acids in plants.

Various studies has shown that three desaturases, *SAD*, *⊿12-desaturase* (*FAD2* and *FAD6*) and *⊿15-desaturase* (*FAD3*, *FAD7* and *FAD8*) propel the PUFAs synthesis pathway. Rajwade et al. (2014) found that *FAD2-2*, *FAD3A* and *FAD3B* had significant contribution for the differential ALA accumulation in high and low ALA groups of linseed. Meng et al. (2017) reported that *FAD2-1*, *FAD2-2*, *FAD3-2*, *FAD6* and *FAD7* expressed higher in *Paeonia lactiflora* cultivar with high ALA content than in that with low ALA content. Among these desaturases, *⊿15-desaturase* is the key enzyme in the ALA synthesis and genes encoding *⊿15-desaturase* are respectively cloned from *Arabidopsis thaliana* (Arondel et al., 1992; Gibson et al., 1994), *Ricinus communis* (van de Loo and Somerville 1994), *Glycine max* (Anai et al., 2005), *Linum usitatissimum* (Vrinten et al., 2005; Bielecka et al., 2014), *Camelina sativa* (Rodríguez-Rodríguez et al., 2016), *Paeonia lactiflora* (Meng et al., 2017) and other plants.

In respect of the functional verification, Damude et al. (2006) cloned dehydrogenase genes encoding *⊿12-* and *⊿15-desaturase* from several fungi, and used genetically modified technology to insert it into soybean. The result showed that ALA content of the transgenic soybean accounted for 70.9% of the total fatty acid, rather than the original ALA content only accounting for 10.9%. Another study (Eckert et al., 2006) introduced gene encoding *⊿15-desaturase* from arabidopsis into soybean, and the n-3 fatty acid content of transgenic soybean increased to 60% in total fatty acids. Urla et al. (2017) introduced a fatty acid desaturase 3-coding sequence (*Lufad3*) of flax into rice. It showed that the *Lufad3* expression level of the homozygous transgenic rice was 1.64- to 5.75-fold higher compared to untransformed control (UC). And the content of ALA was observed in the *Lufad3*-expressing transgenic rice with 0.67 mol % in 4–9T$_3$, 0.68 mol % in 3–13T$_3$, 1.05 mol % in 2–5T^3 confirming functionality of flax desaturase 3. Besides, in *Camelina sativ*a, homozygous knockout the fatty acid elongase1 (*FAE1*) mutants were successfully created. The ALA content increased from 39% in the wild type to 50% in the best Cas9 transgenic seed (Ozseyhan et al., 2017). Genetic engineering of plant especially oilseed crops will be an effective mean for the larger scale production of ALA.

Conversion of ala

In plants, the first step in the reconstitution of n-3 long chain PUFA synthetic pathways is ALA desaturated by the *⊿6-desaturase*, generating stearidonic acid (SDA; 18:4$^{\Delta6,9,12,15}$ n-3), followed by *⊿6-elongation*, yielding eicosatetraenoic acid (ETA; 20:4$^{\Delta8,11,14,17}$ n-3). EPA (20:5$^{\Delta5,8,11,14,17}$ n-3) is desaturated by a *⊿5-desaturase* from ETA and then elongates to docosapentaenoic acid (DPA; 22:5$^{\Delta7,10,13,16,19}$ n-3). Finally, DPA was catalysed by the *⊿4-desaturase* for the conversion to DHA (22:6$^{\Delta4,7,10,13,16,19}$ n-3) in transgenic plants at present (Truksa et al., 2006; Zhou et al., 2007; Petrie et al., 2010a; Kinney et al., 2011). Qiu (2003) expressed a *⊿4-desaturase* gene from *Thraustochytrium* sp. in *Brassica juncea* that can introduce a 4 double bond into DPA, resulting in generating DHA in the vegetative tissues. In transgenic Arabidopsis, Petrie et al. (2010b) used acyl-CoA *⊿6-desaturase* from the marine microalga *Micromonas pusilla* in *Nicotiana benthamiana* that culminated with the accumulation of 26% EPA in TAG and have confirmed strong n-3 preference. These all provide a basis on the n-3 long chain PUFA biosynthesis in plants through the related genes transgenically expressed.

However, the synthesis of n-3 long chain PUFAs has been described in mammals such as human body clearly, which occurs primarily in the liver or some other tissues (Goyens et al., 2005; Barceló-Coblijn and Murphy, 2009; Domenichiello et al., 2015). The conversion of EPA into DHA in mammals is different from the *⊿4-desaturase* pathway and occurs through the Sprecher pathway which: elongation and desaturation steps act on DPA to produce the 24 carbon intermediates 24:5 n-5 and 24:6 n-3 and limited *peroxisomal (β)-oxidation* to DHA (Burdge, 2006; Fleming and Kris-Etherton, 2014). Indeed, only a small portion of ALA is converted to n-3 long chain PUFAs, most of ALA is β-oxidized to provide energy (Burdge and Calder, 2005). Partitioning of ALA towards β-oxidation was accounted for 33% of administered dose in man and 22% of administered dose in women (Burdge et al., 2002; Burdge and Wootton, 2002).

SEPARATION AND PURIFICATION OF ALA

Nowadays, the content of ALA in the vegetable oil is mostly lower than 60%, makes it difficult to achieve the criterion for medical and health care, so carrying on the separation and purification of ALA will be more conducive to give full play to its health benefits, subsequently with business value increasing. The main separation and purification methods of ALA currently include urea inclusion, silver ion complexation, molecular distillation, supercritical fluid extraction, low-temperature crystallization and column chromatography, respectively (Yan et al., 2014; Ni, 2017).

Urea inclusion

Urea inclusion depends on urea molecules in the crystallization process combining with SFAs or MUFAs to form a relatively stable crystalline clathrate after precipitation. Due to the certain space configuration with multiple double bonds and bending carbon chain, PUFAs are difficult to form inclusion (Gu et al., 2009). It is featured by simple equipment and process, low temperature and better maintaining the nutrients and active of the extraction, which is suitable for mass production. But the FAs with different carbon chain lengths which were same or similar saturation cannot be separate easily (Sajilata et al., 2008). Gu et al., (2009) optimized conditions of concentrating ALA from crude perilla oil by gradient cooling urea inclusion. The maximum amount of ALA (91.50%) was obtained at urea to fatty acid ratio of 3, solvent to fatty acids ratio of 7, reaction temperature of 348 K, and crystallization time of 690 min. Lee (2016) reported that 81.75 % of ALA was obtained from *Perilla frutescens* var. japonica oil under 2.0 g urea treatment with cooling at 10°C for 24h. Tartaric acid can assist the inclusion of fatty acids with urea in inclusion process. Under the optimum conditions of tartaric acid-to-urea ratio of 1:3 (n/n), urea-to-mixed fatty acids (MFAs) ratio of 2.5:1 (m/m), methanol-to-MFAs ratio of 10:1 (V/m), crystallization temperature of -8 °C and crystallization time of 8 h, the purity and yield of ALA in the enriched product were 78.6% and 60.9%, respectively (Chen et al., 2017).

Silver ion complexation

Silver ion complexation is according to the number of carbon double bond in different FAs used to form complex polarity with silver ions, which means that more double bonds make the complexation stronger. In addition with acting force, it will achieve the purpose of separation and purification (Jiang et al., 2008; Sun et al., 2011). Ryu et al., (1997) reported that use silver ions complexation to purify ALA in perilla oil which was used to contain 10 g silver nitrate per 100 g silica gel, 2 to 3 g UFAs per 100 g stationary phase. Afterwards, adopting the method of gradient elution by 2%, 5%, 7% acetone hexane solution of each 200 ml, and the result succeeded in the purity of ALA being greater than 90%. Recently, Ge et al., (2017) had succeeded to obtain high purity and yield ALA which were 93.3% and 73.4% though purifying ALA from *Phyllanthus emblica* seed oil by silver iron complexation. The optimal conditions were complexation temperature of 0°C , silver nitrate concentration of 2.29 mol/L, methanol volume fraction of 38.0%, and complexation time of 1.93 h. Moreover, the recovery of silver nitrate was 93.8% and the recovery of Ag^+ still had good complexation effect.

Molecular distillation

Molecular distillation is a new kind of liquid-liquid extraction technology, based on the different molecular weight and mean free path of fatty acids to separate the liquid at the temperature far below the boiling point (Martins et al., 2006). It is characterized by simple operation and high separation efficiency (Lutišan et al., 2002), whereas the equipment demanding is too high to apply in mass industrialized production. Chen et al., (2013) used molecular distillation technology to achieve the ALA content reached to 80.27% of seed oil. After optimizing the design experiment, Huang et al., (2016) further purified ALA and the final ALA mass fraction increased to 86.04%. The optimal conditions were distillation temperature of 90°C , wiper speed 235 r/min, preheating temperature of 70°C and feeding intensity of 0.9 mL/min.

Supercritical fluid extraction

Supercritical fluid extraction is a new separation technology in recent years, which is also a research hotspot. Its basic principle is adjusting the temperature and pressure to make raw material components solubility in the supercritical fluid change greatly to achieve the purpose of separation. Generally, in the purification processes CO_2 is considered as the extraction fluid since it is environmentally benign, non-toxic, non-flammable, non-polluting and economical and compatible. It is simple, fast, efficient and avoids consumption of large amounts of organic solvents (Gouveia et al., 2007; Nisha et al., 2012), whereas it is difficult to separate ALA from the UFAs with the same or similar carbon number to ALA (Teramoto et al., 1994). Li and Jia (2004) used supercritical CO_2 fluid extraction to separate ALA from pine nutlet and the optimum conditions were: extraction pressure of 35 MPa, extraction temperature of 40°C , column temperature of 34°C , and extraction time of 90 min. The result of gas chromatography analysis showed that the recovery rate of ALA was 34.9%. Pan et al. (2012c) found that oak silkworm pupal oil extracted by supercritical CO_2 fluid is rich in unsaturated fatty acids and a-linolenic acid (ALA), accounting for 77.29% and 34.27% in the total oil respectively. The optimal extraction condition was at 28.03 MPa, 1.83 h, 35.31°C and 20.26 L/h as flow rate of CO_2.

Low-temperature crystallization

The method of low-temperature crystallization is mixing FAs dissolved in acetone or ethanol under low temperature, with the decreasing temperature of the solution, we can separate LC-PUFAs from short chain FAs and unsaturated fatty acids (UFAs) from SFAs, achieving purification and concentration of ALA (Ma et al., 2008). It is characterized by simple operation and low energy cost, but the purity of ALA is too low (Gu et al., 2009). In the purification (Hu et al., 2005), the optimal conditions: 95.82% acetone as extraction agent to fatty acid ratio of 6.56, pH of 12.35, temperature of 45°C and crystallization time of 4.74 h, made the concentration of ALA increase from 46.0% to 80.3%.

Yong et al. (2014) used the mixed fatty acid, acetonitrile and acetone (1:6:8, v/v/v), freezing crystallization time for 10 h, solid-liquid separation methods for -18°C , 7000 r/min refrigerated centrifuge 3 min as the best condition. The relative content of α-linolenic acid from rubber seed oil increased from 16.32% to 31.52% and the content of total unsaturated fatty acid also reached to 98.28%.

Column chromatography

Column chromatography is based on the different polarities of PUFAs (Liu et al., 2014). Chromatography on silver (Ag) nitrate-silica gel is a complex column chromatography and is widely used for the separation of fatty acids methyl esters (FAME). The advantages of the method were the performed conditions were mild (no extreme temperatures or pressures are needed) and the purification of FAME was very high (Guil-Guerrero et al., 2003). By means of column chromatography with silver–silica gel as stationary phase, the purity of ALA fractionated from pepper seed oil was reached to 97% (Zhang et al., 2005).

In conclusion, the extraction and purification methods of ALA mainly includes: urea inclusion and silver ion complexation, based on the properties of FAs unsaturated double bond; molecular distillation, based on FAs molecular weight; low-temperature crystallization, based on the FAs solidifying point; supercritical fluid extraction, based on FAs solubility; column chromatography, based on the FAs polarity and so on. The methods mentioned above have both advantages and disadvantages respectively, so that it is inefficient to get high concentration and purity of ALA by single one of them. Chen et al. (2012) found that ALA separated and purified from perilla seed oil through combining urea inclusion and silver nitrate solution complexation extraction method. The purity of ALA is 99.1% and the optimal conditions were under the urea mixed with fatty acids and 95 % ethanol (1: 1.5: 4.8, v/v/v), the temperature is -18C, the inclusion time is 12 h, the concentration of silver nitrate is 4 mol/L. Guo et al. (2013) was fractionated ALA from FAME using Ag nitrate-silica gel column chromatography based on the FAME was concentrated from the flaxseed oil by molecular distillation. The recovery in the combined process was 79%, and the final purity of ALA was 94.7%. Considering comprehensively, a new integrated technology of these methods shows a great potential in large-scale separation and purification of ALA (Yang et al., 2006; Yan et al., 2014).

OXIDATIVE STABILITY OF ALA

Inherent with three double bonds, ALA is vulnerable to be oxidation and denaturation by oxygen (O_2), light, heat, microorganism and metal during purification and storage, resulting in loss of physiological activity and becoming harmful to human health. Therefore, a wide spread attention has paid on how to control its oxidation effectively by science and technology workers (Li et al., 2010b). At present, commonly such as polyphenol compounds, VE and VC are natural antioxidants in ALA to maintain its stability (Lampi et al., 1999; Wang et al., 2007c; Schwartz et al., 2008; de Santana et al., 2015).

It is worth mentioning that the combination of ALA and phytosterol to enhance its antioxidant capacity has received much concern of scientists (Schwartz et al., 2008). Phytosterol has potential biological effects of lowering blood lipids, assimilating cholesterol and preventing cardiovascular disease as that of ALA (Acuff et al., 2007; Demonty et al., 2009). The combination of each other solves the low oxidative stability of ALA and weak fat-soluble problem of phytosterol, so this method has been applied in the food and medicine industry gradually (Guderian et al., 2007). Besides, the synthesis of ALA and phytosterol mainly includes chemical and enzymatic methods.

The benefits of chemical method is simple and easy to operate with industrialize production potential, but the reaction temperature is higher, reaction time is longer with a lot of catalyst adopted in the study. Also, it is easy to produce phytosterol oxidative products, trans-fatty acids and fatty acids polymers (Choo et al., 2007). Zhang (2009) adopted solvent-free direct esterification method to synthesize ALA and then used silica gel column chromatography to separate and purify of the product. Under the condition of high temperature ALA sterol ester showed good oxidative stability and under the condition of the same concentration, it is superior to phytosterol in oxidative stability. Enzymatic method is known to have mild reaction condition and fewer side-effects. Its product is of good-quality and easy to separate and purify. But there are some shortcomings: high cost on enzyme and organic solvent with high requirement for reaction conditions (Johnsson and Dutta, 2006). In the study of ALA sterol ester catalyzed by lipase synthesis, Li et al. (2008) selected Novozyme 435 and isooctane as catalyst and solvent with the amount of 5% and 1:1.6 (solvent volume to quality of the substrate). Under the appropriate conditions: the ratio of ALA to sterol of 3, reaction temperature of 55°C, reaction time of 24 h, the esterification rate reached 40.65%. After refining the products, ALA sterol ester presented golden brown oily with the purity of 85% or higher.

In order to further determine the ALA sterol ester whether can be used as a functional food additive for the development and utilization, its physical and chemical properties, such as fat-soluble, crystallization properties and oxidation stability in vegetable oil are needed to be measured or analyzed. Deng et al. (2012) found that ALA sterol ester had excellent physical and chemical properties, for its fat-soluble compared with plant sterols enhances about 20 to 30 times; crystallization temperature range was between 25.9°C and 29.6°C. But its oxidative stability decreased with the increase of concentration. Also, Deng et al. (2016) reported that α-linolenic acid rich phytosterol esters (ALA-PE) dose-dependently lowered plasma total cholesterol (TC), triglyceride (TG) and LDL-C concentrations with a maximal decrease of 42 %, 59 % and 73 %, respectively.

Recently, microencapsulated seed oil by spray drying using antioxidants could also enhance ALA oxidative stability (Sharif et al., 2017; Sanchez-Reinoso and Gutiérrez, 2017). Bibwe et al. (2017) found that microencapsulation of flaxseed oil using spray drying with jack fruit seed starch (JSS)-soya protein isolate (SPI) coating combination would enhance ALA antioxidant capacity. The optimum conditions were the JSS: SPI ratio of 3.24: 1, 23.8% oil loading and 175 degrees C drying air temperature. Microcapsules of octenyl succinic anhydride modified starches (OSA-MS) co ntaining flaxseed oil, BC and EU exhibited the maximum retention of BC (71%), EU (84%) and a-linolenic acid (92%). This indicated a positive role of EU as antioxidant and low *Mw* OSA-starch as wall material for the development of functional foods (Sharif et al., 2017).

CONCLUSION

ALA is considered to be one of the essential fatty acids for human body, belonging to n-3 PUFAs. ALA has extensive physiological functions and plays an important role in human health. On the contrary, there are also studies shown that ALA is not obvious in disease prevention, and even more counter-productive effect. Thereby, long-term prospective studies including precise dietary ALA measurement and especially intervention studies are of interest will be needed to demonstrate the function and regulatory mechanism of ALA. Generally, the ALA derived from vegetables oils would be healthier. However, traditional vegetables oils, such as soybean oil and rapeseed oil, have dominated consumption market despite there are a wide variety of vegetables oils which are more rich in ALA that have not been used efficiently yet. Plants with high oil content and rich in ALA such as *Agastache rugosa*, *Elsholtzia ciliata* and *Lasiococca comberi* lack of extensive scientific knowledge in development and utilization. Therefore, the constraints of ALA content, resources and development cannot satisfy the demand of the society, so further exploration and utilization of natural resources rich in ALA need to be carried on soon. Recent studies demonstrated that it is sensible to use transgenic technology to make gene encoding Δ-15 dehydrogenase enzymes into plants to increase the rate of synthesis of ALA. It is useful to plant cultivations of higher oil yield and ALA content, providing more space for ALA developing. At the same time, future study is needed to improve its concentration, enhance its oxidative stability during the purification and storage so as to keep health care.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Yuhan Tang and Yao Jiang participated in the planning, execution and analysis of this study and wrote the review. Jiasong Meng planned, modified and monitored the progress of the study. Jun Tao is the corresponding author who submitted and revised the manuscript as recommended by the reviewers of EJFA.

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