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Research progress of plant α-linolenic acid

Yuxin Bai

Chongqing Foreign Language School,Chongqing,400050,China;

Abstract:

α-Linolenic acid is a polyunsaturated fatty acid characterized by three double bonds and is recognized as one of the essential fatty acids for human health. It serves multiple critical functions, including nutritional supplementation, enhancement of brain development, and protection of nerve cells. In recent years, researchers globally have investigated natural plant sources abundant in α-linolenic acid and developed more efficient extraction methods, thereby significantly advancing the study of this fatty acid. This paper reviews the physiological effects and sources of plant-derived α-linolenic acid, summarizes the biosynthetic pathways, and outlines the primary extraction processes to provide the theoretical evidence for ongoing research and innovation in this field.

Keywords: plant α-linolenic acid; Physiological efficacy; Synthesis pathway; Extraction technology.

1. Introduction

Fatty acids are carboxylic acids with an aliphatic chain, which can be saturated, unsaturated, polyunsaturated, etc. The molecular chains of polyunsaturated fatty acids contain at least two double bonds, and those that have important functions in the biological world are usually ω-3 unsaturated fatty acids and ω-6 unsaturated fatty acids. α-linolenic acid, an essential ω-3 unsaturated fatty acid, is an important component of biological tissue biofilm and a precursor to synthesize human unsaturated fatty acids with important physiological functions such as EPA and DHA [1]. Moderate intake of α-linolenic acid has the effects of anti-saccharification, promoting brain development, and enhancing immunity [2]. The human body cannot synthesize α-linolenic acid itself, and it can only be obtained from outside food, especially oil crops. In this paper, the physiological effects, sources, synthetic pathways, and extraction methods of α-linolenic acid are reviewed, which will provide evidence for the subsequent functional research and application development of α-linolenic acid in plants.

2. Chemical properties of α-linolenic acid

α-linolenic acid, an omega-3 polyunsaturated fatty acid (Figure 1, has the formula C18H30O2 (278.43 g/mol), and contains three double bonds, which is full cis-form [3]. A-linolenic acid is colorless to light yellow odorless oily liquid, soluble in ethanol and ether, insoluble in water, usually in the form of glycerides in plants, involved in phospholipid synthesis, metabolism, and transformation.

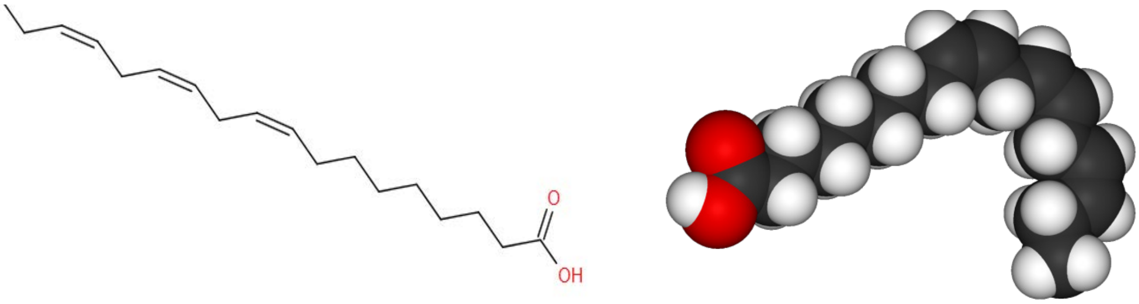

Figure 1 Chemical structure and protein structure of α-linolenic acid

3. Physiological Effects of α-Linolenic Acid

The development and application of the functions of α-linolenic acid are significant areas of ongoing exploration and research by scientists worldwide. α-Linolenic acid was first documented in 1965 and recognized as an essential fatty acid greatly beneficial to human health at the International Conference on Omega-3 Fatty Acids in Washington in 1990 [4]. After years of research and exploration, the physiological effects of α-linolenic acid mainly encompass the following aspects.

3.1 α-Linolenic Acid's Physiological Role in Reducing Cholesterol Levels and Regulating Blood Lipids and Blood Pressure

Cholesterol and triglycerides constitute the primary components of blood lipids in serum. Due to long-term smoking, lack of exercise, excessive alcohol consumption, and other unhealthy habits, the incidence of dyslipidemia, hypertension, and related diseases is increasing each year [5]. Djousse et al. found that increasing the dietary intake of α-linolenic acid by 1.09g per day could significantly reduce the risk of systolic blood pressure and hypertension [6]. Tsukamoto I et al. reported that elevated plasma concentrations of α-linolenic acid can effectively decrease the incidence of hypertension [7]. Additionally, α-linolenic acid may reduce blood lipid levels by enhancing cholesterol excretion, inhibiting endogenous cholesterol synthesis, and regulating plasma HDL-C metabolism [8-10].

3.2 α-Linolenic Acid's Role in Regulating Gut Microbiota

The intestinal environment is the largest microecosystem in the human body, and the gut microbiota is closely related to human health. Using an anaerobic culture system of animal feces in vitro, Liu found that α-linolenic acid inhibited the growth of Enterococcus, promoted the growth of Lactobacillus, and increased the production of short-chain fatty acids in the fermentation broth of rat intestinal flora. Furthermore, the adhesion of intestinal probiotics (Lactobacillus acidophilus and Bifidobacterium bifidum) to colon epithelial cells (Caco-2 and NCM460 cells) was enhanced [11]. Through high-throughput sequencing of the 16S rRNA gene V3-V4 region, Gao et al. discovered that α-linolenic acid could significantly ameliorate high-fat diet (HFD)-induced changes in the structure and composition of the intestinal microbial community in mice [12].

3.3 α-Linolenic Acid's Anti-sensitivity and Anti-Inflammatory Effects

The immune response is one of the critical functions of the human defense system; however, if it exceeds a certain threshold, it may produce allergic and inflammatory symptoms that can harm human health. High concentrations of α-linolenic acid can compete with 5-lipoxygenase (5-LOX) through its metabolites EPA, DHA, and arachidonic acid (AA) during their actions in the body, thus achieving the effect of inhibiting inflammatory responses [13-14]. Chang et al. found that after ovalbumin sensitization, mice that ingested perilla seed oil rich in α-linolenic acid exhibited significantly reduced levels of pre-inflammatory cytokines (tumor necrosis factor TNF-α, IL-1β, and IL-6) in tracheoalveolar lavage fluid (BALF), subsequently alleviating inflammation [15]. Ruixin Cai et al. discovered that α-linolenic acid could inhibit the mTOR/NF-κB signaling pathway by increasing the autophagic flux in mouse macrophages stimulated by lipopolysaccharide (LPS), resulting in the activation of autophagy and a reduction in inflammatory responses [16]. Additionally, α-linolenic acid can inhibit airway inflammation and epithelial-interstitial transformation in asthmatic rats, improving lipid metabolism by correcting the imbalance between Th1/Th2 and Treg/Th17 cells and regulating the FGF23-Klotho-FGFR4 signaling pathway [17].

3.4 α-linolenic acid has the effect of protecting nerve tissue and promoting brain development

α-Linolenic acid is an essential fatty acid critical for maintaining brain and nervous system function, contributing to brain development and cognitive enhancement. According to public data from the U.S. Food and Drug Administration (FDA), a deficiency in α-linolenic acid can lead to delays in brain and retinal development in children, attentional deficits, nutritional imbalances, slow absorption rates, and may directly result in mental retardation, impaired vision, obesity, anorexia, and decreased immunity, among other symptoms and conditions [18].

Additionally, α-linolenic acid has been shown to prevent Alzheimer's disease. Gao Hui et al. discovered that long-term supplementation with α-linolenic acid inhibits the PERK/eIF2α signaling pathway involved in the unfolded protein response, thereby alleviating the pathological symptoms associated with Alzheimer's disease [19-20]. Furthermore, a daily intake of foods enriched with α-linolenic acid can improve cognitive function and enhance overall cognitive performance [21]. Consumption of α-linolenic acid-rich foods significantly impacts liver n-3 fatty acid metabolism, potentially mitigating damage to the blood-brain barrier through the remodeling of brain endothelial cell membranes, and enhancing the brain's resilience to Alzheimer's disease [22].

3.5 α-linolenic acid has anti-cancer and anti-tumor properties

Omega-3 fatty acids are regarded as potential dietary candidates for cancer prevention [23]. As early as 1990, researchers found that long-term consumption of perilla oil, rich in α-linolenic acid, could inhibit the development of breast, colon, and kidney tumors [24-25]. Mason-Ennis et al. further demonstrated that α-linolenic acid decreases the growth rate of human breast cancer cells (MCF-7) by inhibiting the activity of estrogen receptors [26]. Moreover, α-linolenic acid has been shown to inhibit the proliferation and migration of osteosarcoma cells in a dose-dependent manner by down-regulating fatty acid synthase expression. Additionally, it can regulate the expression of extra-retinal receptors and signaling proteins in osteosarcoma cells, providing a foundation for identifying potential targets for osteosarcoma treatment [27].

3.6 α-linolenic acid has the effect of preventing cardiovascular disease

Given the increasing incidence of cardiovascular diseases, preventative measures are essential for enhancing public health and improving living standards. Studies have indicated that α-linolenic acid intake is linearly associated with a reduced risk of fatal coronary heart disease, with each additional gram of α-linolenic acid consumed daily correlating with a 12% decrease in coronary heart disease risk [28]. Flaxseed oil, which is rich in α-linolenic acid, can ameliorate HFD-induced atherosclerosis in ApoE-/- mice by regulating the "gut microbiota-inflammation-artery" axis. It may be an inexpensive intervention to prevent and treat the disease [29]. α-linolenic acid can prevent the formation and development of atherosclerosis, prevent the occurrence of acute myocardial infarction and reduce death from heart disease, and have cardiovascular protective effects by reducing blood lipid levels, inhibiting thrombosis and anti-arrhythmic effects [30-32]. The administration of α-linolenic acid can reduce the inflammatory response after myocardial infarction and improve cardiac function. It may have a certain preventive effect on the occurrence and development of heart failure after myocardial infarction and can be used as a means of adjuvant treatment of this disease [33].

4. Source of α-linolenic acid

The body cannot synthesize α-linolenic acid on its own and can only obtain it through diet. Plant seeds are the primary organs for oil storage, and α-linolenic acid is widely present in plant seeds mainly in the form of triacylglycerol, which is the primary means for humans to acquire α-linolenic acid [34]. However, the content of α-linolenic acid in commonly consumed edible oils in the daily diet, such as peanut, rapeseed, soybean, palm, olive, corn germ, rice bran, sunflower, oil tea, etc., is mostly lower than 1%, with the highest content in rapeseed being only 7.9%, far below the daily demand for α-linolenic acid by individuals [34]. α-linolenic acid has become a limiting nutrient in the national diet.

Since the first isolation of α-linolenic acid from hemp seed oil in 1887, α-linolenic acid has been found in the oil of an increasing number of plant species, especially Linaceae, Duzonaceae, and Labiaceae, and has become a major source of α-linolenic acid [35]. At present, the top seeds of α-linolenic acid content include patchouli, Chinese Elsholtzia, Perilla, euperia, flax, kiwi, etc. Some seeds contain α-linolenic acid and their general situation are shown in Table 1. Studies have shown that the unsaturated fatty acid content in kiwifruit seed oil accounts for 92.12% of the total, and the α-linolenic acid content is 62%. However, kiwifruit seed is difficult to obtain, and the cost of obtaining oil from its seeds is too high [36]. Patchouli and Chinese elsholtzia are difficult to plant and expensive seeds, so they are not suitable for widespread promotion. At present, Perilla seed oil and flaxseed oil are ideal plant sources of α-linolenic acid.

Today, the use of crops as a source of α-linolenic acid faces many challenges, including but not limited to reduced planting area, limitations in growing areas, and insufficient production and processing technology. Therefore, finding a plant raw material with a high content of α-linolenic acid and not competing with crops for land is an important way to enrich the raw material types of α-linolenic acid and increase the yield of α-linolenic acid [37]. For example, emerging oil plant resources such as chia, Astragalea and oil peony have been developed as ideal materials for α-linolenic acid products [34].

Table 1 Plants rich in α-linolenic acid

Plants	Family	oil(%)	α-linolenic acid(%)	Ref
Actinidia chinensis	Actinidiaceae	35.0	62.0	[38]
Linum usitatissimum	Linaceae	29.6-43.5	42.0-60.0	[39]
Perilla frutescens	Labiatae	34.0-45.0	51.0-63.0	[40]
Eucommia ulmoides	Eucommiaceae	32.3	42.0-62.0	[41]
Paeonia suffruticosa	Paeoniaceae	25.9	39.7	[42]
Zanthoxylum bungeanum	Rutaceae	27.0-35.1	36.2	[43]
Salvia Hispanica	Labiatae	30.0-35.0	66.0	[44]

Camelina sativa	Brassicaceae	36.0-47.0	41.3	[45]
Plukenetia Volubilis	Euphorbiaceae	33.0-54.0	60.59	[46]

5. Research progress of plant α-linolenic acid

5.1 Biosynthetic pathways of α-linolenic acid in plants

The biosynthesis of α-linolenic acid primarily requires the production, dehydrogenation, and assembly of triacylglycerol [47]. Most seeds' carbon source for fatty acid biosynthesis is sucrose produced during plant photosynthesis, which is transported from photosynthetic organs such as leaves and green fruits to seed cells, where hexose is formed via glycolysis and oxidized to acetyl-CoA (acetylCoA) as a raw material for fatty acid biosynthesis [48]. De novo fatty acid synthesis begins with acetyl-CoA and is catalyzed by acetyl CoA carboxylase to create malonyl-ACP-CoA, which is subsequently transferred from CoA to an acyl carrier protein by malonyl-COA-ACP transferase. FAS is a fatty acid multienzyme complex made up of 3-ketoacyl-CoA synthase, 3-ketoacyl-CoA reductase, 3-hydroxyacyl-CoA dehydratase, and enoyl-CoA reductase. These enzymes catalyze enzymatic events such as condensation, reduction, dehydration, and reduction in the expansion of the fatty acid carbon chain, and they extend the fatty acid carbon chain by adding two carbons per cycle to form stearic acid, an 18-carbon saturated fatty acid. Stearic acid dehydrogenated and desaturated to oleic acid under the action of Δ9 stearoyl-ACP desaturase (SAD), oleic acid under the action of some plasmid δ12-fatty acid dehydrogenase (FAD6) or endoplasmic reticulum δ12-fatty acid dehydrogenase (FAD2) to produce linoleic acid, Further dehydrogenation by platinoid δ12-fatty acid dehydrogenase (FAD7/8) or endoplasmic reticulum δ12-fatty acid dehydrogenase (FAD3) leads to the formation of α-linolenic acid [49-52].

5.2 Extraction process of α-linolenic acid from plants

Following the publication of Dyerberg's survey report on the Eskimo diet and cardiovascular disease in 1978, there has been a growing interest in omega-3 fatty acids among the international scientific community. Given that the human body is unable to synthesize α-linolenic acid de novo, the question of how to optimize the extraction of α-linolenic acid from raw materials has become a topic of continuous research. The most commonly employed methods at present are the urea inclusion method, the silver ion complex method, the molecular vacuum distillation method, the supercritical fluid extraction method, the fatty acid metal salt method, the low-temperature crystallization method and the lipase catalytic hydrolysis method.

The urea inclusion method employs a range of urea-fatty acid inclusion compounds of varying complexity to facilitate the separation of high, medium and low unsaturated fatty acids, thereby enabling the isolation of α-linolenic acid. Hao et al. employed flaxseed as the raw material and identified the optimal conditions for extracting α-linolenic acid via the urea inclusion method. These conditions included a urea-ethanol solution with a concentration of 1 mol/L, and a volume ratio of fatty acid to urea solution was 1:45, the inclusion temperature was -15°C, the inclusion time was 24 hours, and the extraction rate of α-linolenic acid was up to 81% [54]. The urea encapsulation method is a commonly used separation method. It has the advantages of simple equipment, simple process operation and low production cost. However, it also has some disadvantages, including low extraction purity, long time consumption, residual organic solvent and easy pollution.

The silver ion complex method is employed for the separation of fatty acids based on the difference in the number of C=C double bonds. In their study, Li Peihong selected Zanthoxylum seed oil as the raw material and treated it with the silver nitrate method, resulting in an increase in the α-linolenic acid content from 36.8% to 86.41% [56]. This extraction method has minimal equipment requirements and a high enrichment rate; however, it results in the presence of elevated levels of heavy metal residues, and the process is complex, with the highest cost. Consequently, it is not suitable for application in the food and drug industries [57].

The molecular vacuum distillation method employs the differential in molecular weight between fatty acids for separation. This is achieved by utilizing the disparity in the mean free path of molecular motion exhibited by different fatty acids, thereby facilitating the separation of distinct fatty acids. This process can be conducted at temperatures exceeding the boiling point, without compromising the integrity of the substance, and addresses challenges such as thermal decomposition that remain unresolved by conventional distillation techniques. Molecular distillation technology is particularly well-suited to the separation of low-volatility, high-molecular-weight, high-boiling-point, high-viscosity, heat-sensitive, and biologically active natural substances and materials with high added value. The study conducted by Hao Wenlai demonstrated that the optimal distillation temperature and pressure should be within a specific range. The highest separation efficacy of α-linolenic acid was observed when the distillation temperature was set between 100 and 120 degrees Celsius, and the distillation pressure was maintained at 0.5 Pascal. It can be observed that an increase in the feed rate results in a reduction in the residence time of α-linolenic acid, which in turn leads to an unfavorable separation outcome. The optimal feed rate is therefore considered to be within the range of 70 to 90 mL/h. Similarly, an increase in the feed temperature has been shown to result in a higher loss rate of α-linolenic acid. The best separation effect has been observed at a scraping film speed of 150 r/min, with the optimal feed temperature being within the range of 70 to 80°C. Molecular distillation is a pure physical separation technology with a relatively straightforward operational principle.

The supercritical fluid carbon dioxide (CO_2) extraction method is based on the separation and purification of each component of a mixture of fatty acids on the basis of their different solubility in supercritical CO_2 fluid, under the condition of modifying the pressure and temperature of the system. Hao Wenlai conducted a simulation of the industrial production process for extracting flaxseed oil and determined that the optimal extraction rate was 64.53% and the α-linolenic acid content was 57.72% when the supercritical extraction time was 2 hours, the temperature was 40 degrees Celsius, the pressure was 3 MPa, and the CO2 flow rate was 25 kg/h. As no organic solvent is employed throughout the process, supercritical fluid CO2 can be recycled during production. Furthermore, the operating temperature is close to room temperature, conferring the additional advantages of non-toxicity, non-burning, non-polluting, non-reactivity to most substances, and cost-effectiveness. Nevertheless, this technology necessitates the utilization of high-pressure apparatus, which entails considerable initial investment and maintenance costs. Furthermore, the separation of fatty acids with analogous molecular weights remains a challenging endeavor.

6. Conclusion

The phenomenon of population aging represents a fundamental demographic characteristic of our nation. As time progresses, the proportion of the elderly population inevitably increases. α-Linolenic acid has been demonstrated to prevent cardiovascular diseases, regulate blood lipids and blood pressure, and provide an effective means for society to cope with population aging. Furthermore, recent data suggest that the prevalence of Alzheimer's disease will double in Europe and triple worldwide by 2050. This estimate is three times higher than previously estimated based on the biological definition of Alzheimer's disease. [60] α-Linolenic acid is a high-value unsaturated fatty acid that has been demonstrated to protect nerve tissue and strengthen the body's immune system. It may be employed as an auxiliary treatment for neurological diseases. α-Linolenic acid was initially identified in deep-sea fish oil, however, the production of fish oil products is constrained by limitations in availability and significant variability, compounded by concerns related to marine pollution and other factors. The production of deep-sea fish oil rich in α-linolenic acid is declining annually. α-Linolenic acid is a prominent component of plant sources, offering high nutritional value and health benefits, with a diverse range of applications and a more flexible extraction method. Consequently, the development of plant α-linolenic acid has become a prominent area of research in recent years, with a series of related studies on the cultivation of transgenic Perilla [61-62] and elderberry seed oil [63] facilitating the application of α-linolenic acid. The future focus of research on α-linolenic acid will be the exploration of new natural resources, the cultivation of high-yield germplasm of existing resources, and the development of new and efficient extraction technology.

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