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Oleanolic acid: Biological activities and therapeutic potential in chronic diseases

Zilong Wang[1], Lu Li[2], Yushan Jiang[1], Ying Liu[3], Hui Liang[1*]

[1]School of Public Health, Qingdao University, Qingdao, 266021 China

[2]Psychiatric Ward Ⅷ, Qingdao, Mental Health Center, Qingdao, 266034 China

[3]College of Basic Medicine, Qingdao University, Qingdao, 266021 China

Abstract: **Oleanolic acid is a pentacyclic triterpenoid compound with a wide spread occurrence throughout the plant kingdom. In nature, the compound exists either as a free acid or as an aglycone precursor for triterpenoid saponins, in which it can be linked to one or more sugar chains. This review consolidates and expands on recent reports on the biological effects of oleanolic acid and their mechanisms of action in vitro and in vivo study models. Oleanolic acids are important candidates in the search for alternative therapy in the treatment and management of chronic diseases.**

Keywords: Oleanolic acid; Biological activity; Chronic diseases

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*Corresponding Author: Hui Liang

1. Introduction

In recent years, the rapid development of chemical extraction and preparation technology has continuously promoted the advancement of the modern pharmaceutical industry, which has led to the deepening of research on oleanolic acid, which has received extensive attention due to its various biological activities. At present, a large number of studies have shown that they have been seen to exert a wide range of pharmacological effects, such as anti-oxidant, anti-tumor, anti-viral, anti-allergic, anti-inflammatory, and anti-viral effects[1, 2, 3, 4]. In addition, studies have shown that oleanolic acid has also hypoglycaemic, hypolipidaemic and hepatoprotective effect [5].

2. Oleanolic acid and chronic diseases

2.1. Diabetes mellitus

OA exerts antidiabetic effects through multiple mechanisms which include alpha glucosidase inhibition, insulinomimetic activity,insulin sensitization and acceleration of glucose metabolism. It was found that oleanolic acid could decrease the blood sugar concentration and increase the hepatic glycogen concentration in rats with hyperglycemia induced by intraperitoneal injection of alloxan, and the distribution of glycogen granules in rat hepatic lobules increased[6]. Observing human hepatocellular carcinoma cells (HepG2), we found that oleanolic acid can only slightly increase the consumption of sugar and inhibit the secretion of insulin[7], which proves that oleanolic acid may have other mechanisms of hypoglycemic effect. In addition, oleanolic acid was found to reduce the blood sugar level of normal mice and inhibit the increase of blood sugar induced by adrenaline or glucose. Meanwhile, the levels of hepatic glycogen and serum insulin were significantly increased during the hypoglycemic process of oleanolic acid[8]. Its mechanism may be that oleanolic acid can block the transport of sugar from stomach to small intestine and from small intestine villi, thereby lowering blood sugar[9]. In addition, oleanolic acid can also inhibit the absorption of carbohydrates in the intestine and regulate the secretion of insulin, thus affecting the level of sugar metabolism function[10, 11].

2.2. Hypertension

According to epidemiological data, "China's Guidelines for the Management of Geriatric Hypertension in 2019" pointed out that over half of Chinese elderly people have hypertension, and for those aged 80 years or over, the prevalence is 90%. Hypertension is the leading risk factor of stroke, myocardial infarction and cardiovascular mortality. During the past years, hypertension management in China has been improved significantly, with the control rate of hypertension in elderly patients increased from 7.6% in the year of 2002 to 18.2% in 2015[12]. Ahn YM et al. [13]found that oleanolic acid has a good antihypertensive effect on renal hypertensive rats. Studies have shown that oleanolic acid can inhibit rat renin-angiotensin-aldosterone system and blood vessels. The activity of the angiotensin II receptor reduces the level of plasma central natriuretic peptide, increases the glomerular filtration rate, and excretes sodium, thereby lowering blood pressure. The renin-angiotensin-aldosterone

system plays an extremely important role in complex systems that maintain blood pressure in the body. Renin is a hydrolyzed protease synthesized by the liver that can be stored in the liver or released into the bloodstream by the liver. Renin can directly interact with angiotensinogen to produce angiotensin. Angiotensin regulates blood pressure by promoting vasoconstriction. Aldosterone is an important hormone in the body, which can maintain the body by regulating the reabsorption of sodium by the kidney. The water is balanced to achieve the purpose of regulating the blood volume of the body. In addition, atrial natriuretic peptide plays an important role in cardiovascular homeostasis. Oleanolic acid may inhibit plasma atrial natriuretic peptide by regulating plasma renin-angiotensin, thereby reducing blood volume and blood pressure.

2.3. Dyslipidemia

Dyslipidemia affects the integrity of vascular endothelial structure and function, and brings hidden dangers to multiple organs throughout the body. In recent years, the effect of oleanolic acid on cardiovascular protection has become a hot spot for nutrition experts. Dyslipidemia refers to abnormal lipoprotein metabolism in the body, including elevated plasma triglycerides, total cholesterol, and low-density lipoprotein cholesterol, accompanied by a decrease in high-density lipoprotein cholesterol[14]. The liver plays a key role in maintaining normal lipid metabolism in the body. Once the liver is transported and synthesized, it can cause cardiovascular diseases such as atherosclerosis[15].

Sterol regulatory element binding proteins (SREBPs) are a family of transcription factors that regulate lipid homeostasis by controlling the expression of a range of enzymes required for endogenous cholesterol, fatty acid (FA), triacylglycerol and phospholipid synthesis. The three SREBP isoforms, SREBP-1a, SREBP-1c and SREBP-2, have different roles in lipid synthesis. In vivo studies using transgenic and knockout mice suggest that SREBP-1c is involved in FA synthesis and insulin induced glucose metabolism (particularly in lipogenesis), whereas SREBP-2 is relatively specific to cholesterol synthesis. In addition, PGC-1β coactivates the SREBP transcription factor family and stimulates lipogenic gene expression. However, unlike SREBP, PGC-1β itself reduces liver fat accumulation, while circulating triglycerides and cholesterol in very low density lipoprotein particles are significantly increased. Therefore, inhibition of liver PGC-1β may provide a treatment for the treatment of hyperlipidemia[15].. In 2017, Chen [16] found that both acute and chronic oleanolic treatment reduced serum triglyceride, total cholesterol, and low-density lipoprotein cholesterol levels, and decreased peroxisome proliferator-activated receptors. Liver expression levels of gamma coactivator-1β (PGC-1β). Studies have shown that oleanolic acid can improve hyperlipidemia by regulating the mir-98-5p/pgc-1β axis.

2.4. Obesity

According to epidemiological statistics, obesity has become an increasingly seriously public health problem, which has brought a heavy economic burden to patients and society. The rising prevalence in children and adolescents is of particular concern because of the implications for negative effects on their morbidity and mortality in young adulthood[17]. The following three aspects of the disease are most worthy of attention. First, the proportion of adolescents in obese and overweight patients is constantly increasing. Second, for overweight and obese people, the risk of chronic diseases such as hypertension, diabetes, and hyperlipidemia is higher. Third, patients with abdominal obesity are at higher risk of metabolic abnormalities. From the perspective of modern medicine, the pathogenesis of obesity involves genetic, dietary, exercise, psychological, metabolic disorders, endocrine dysfunction and other factors. Djeziri FZ et al. [18] found that oleanolic acid has a good intervention effect on high fat diet induced mouse obesity model. Oleanolic acid can significantly reduce the body weight of obese mice and the weight of liver and visceral adipose tissue. while reducing triglyceride and total cholesterol levels, further improving insulin sensitivity. Oleanolic acid can alleviate the damage of small intestine villi, epithelial cells tight junctions and mitochondria by improving the levels of inflammatory factors such as lipopolysaccharide. In addition, oleanolic acid improves the taste receptors of obese mice with high fat preference by decreasing the expression level of CD36. Oleanolic acid can be used as a potential therapeutic for controlling and reducing body weight.

Ghrelin is an endogenous peptide found by Japanese scientists in the stomach cells and hypothalamus of animals. Ghrelin is involved in the regulation of nutrient intake and energy metabolism in the body, and in the digestive system and heart. Ghrelin is involved in control of appetite and energy balance, regulation of carbohydrate and lipid metabolism, cell proliferation and apoptosis, as well as modulation of functioning of gastrointestinal, cardiovascular, pulmonary and immune systems[19]. Studies have reported that in the obese mouse model induced by ghrelin combined with high-fat diet, insulin and cholesterol levels in the model group were significantly higher than normal controls, suggesting that ghrelin can cause lipid metabolism disorder and insulin resistance leading to obesity[20]. Nakajima K et al. [21] found that oleanolic acid can reduce the level of ghrelin in vivo and in vitro,

suggesting that it has an inhibitory effect on ghrelin production. This also can be used as a potential anti-obesity agent.

3. Conclusions

Oleanolic acid derived from plants and fruits as well as has been shown to exhibit different biological activities in various models of diseases through diverse mechanisms of action. This review has highlighted evidences from in vitro and in vivo studies of the ability of OA. There is a clear indication that, OA have the potential of providing an alternative and cheaper therapy for various chronic diseases.

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