

Research progress of ellagic acid in systemic and oral diseases

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Abstract: Ellagic acid (EA) is a kind of natural polyphenol dilactone derived from pomegranate, grape, strawberry and other fruits and nuts, which has a high content in pomegranate peel. A large number of research results show that ellagic acid has anti-tumor, antiviral, antioxidant, anti-inflammatory, anti-allergic, anti-fibrosis and other pharmacological activities. In the past ten years, more and more attention has been paid to the study of the physiological effect and mechanism of ellagic acid. Therefore, this paper reviews the relevant literature at home and abroad, and summarizes the role of ellagic acid in systemic and oral diseases in recent years.

Keywords: ellagic acid, Polyphenols, Biological activity

1. Introduction

In recent years, more attention has been paid to the potential health effects of polyphenols, particularly in the prevention of cancer, cardiovascular disease and other conditions. Studies have found that pomegranate peel is rich in polyphenols, mainly including flavonoids (mainly quercetin) and tannins (mainly pomegranate glycosides, angellin and ellagic acid)^[1-4]. In this paper, various biological activities of ellagic acid were summarized, which provided theoretical basis and reference for the follow-up study.

2. Biological activities of ellagic acid

2.1 Anti-inflammatory effects

LPS can significantly increase the content of inflammatory factors in serum, and treatment with ellagic acid can reduce the concentrations of TNF- α , IL-6 and IL-1 β in serum induced by LPS. These results indicated that ellagic acid could inhibit the secretion of inflammatory cytokines and thus inhibit the occurrence^[5] of inflammation. In Lu Guang's study, the effect of ellagic acid on the production of LPS-TLR4-NF- κ B pathway was studied using cultured RAW264.7 macrophages as a model. The results showed that the use of ellagic acid could increase the content of I κ B in a dose-dependent manner, and ellagic acid could reduce the content of P-I κ B and inhibit the expression^[6] of NF- κ B. Dell'Ali et^[7] al. found that the methanol extract from pomegranate peel, ellagic acid and angpomegranate side could inhibit the activity of NF-KB promoter in transfected THP-1 cells and exert anti-inflammatory effects. These studies indicated that its anti-inflammatory effects were achieved by inhibiting the secretion of inflammatory factors, inhibiting the release of pro-inflammatory cytokines and blocking the LPS-TLR4-NF- κ B signaling pathway.

2.2 Antioxidant effects

Oxidative stress damages proteins, lipids, and nucleic acids, causes chronic inflammation, and is an important factor in a variety of diseases. Studies have shown that ellagic acid, as a strong oxidant that can effectively remove free radicals, plays an important regulatory role^[8] in maintaining the body's REDOX homeostasis and repairing oxidative stress damage. Les et^[9] al. showed that ellagic acid has strong antioxidant activity, which can reduce oxidative or inflammatory stress and increase protective signals. The content of MDA can reflect the degree of lipid peroxidation in the body or organs. Yonar et^[10] al. took rainbow trout as the research object and tested the antioxidant activity of ellagic acid at 50, 100 and 150 mg/kg mb respectively. The results showed that ellagic acid at three concentrations could reduce the levels of MDA in liver, kidney and spleen. Ellagic acid has a protective effect on organ injury induced by

various chemicals and drugs under certain conditions.

2.3 Anti-cancer effects

Ellagic acid shows obvious inhibitory effect on carcinogenesis induced by chemical substances and a variety of other carcinogenesis. It has the ability^[11] to inhibit tumor growth and proliferation, induce cell apoptosis, inhibit cell metastasis and angiogenesis. Mouad et^[12] al. found that ellagic acid can promote the apoptosis of human pancreatic cancer PaCa cells by stimulating the DNA fragmentation of apoptotic nucleosome. Further study showed that ellagic acid had a dose-dependent inhibitory effect on the proliferation of MIA PaCa-2 and PANC-1 cells, and the best effect was at 50 μ mol/L. Ellagic acid inhibited tumor^[13] by regulating micrnas. Zhong Chen^[14] found that ellagic acid inhibited Hep G2 liver cancer cells in a dose and time dependent manner. The results showed that ellagic acid could block the cell cycle at G0/G1 and induce DNA damage at the same time. In vitro experiments proved that ellagic acid combined with doxorubicin hydrochloride or cisplatin could effectively inhibit the growth of hepatocellular carcinoma cells and induce apoptosis through the activation of mitochondrial pathway. In a clinical study, daily administration of pomegranate extract before surgery significantly reduced the level^[15] of lipopolysaccharids-binding protein, a marker of endotoxin in the blood of patients. The regulatory effect of pomegranate extract rich in ellagic acid on colon cancer was preliminarily obtained. The specific mechanism of action was further analyzed in the colon cancer cell line model to verify the promoting effect^[16] of ellagic acid on cancer cell apoptosis.

2.4 Detoxification effect

Studies have proved that ellagic acid can relieve the lesions caused by nitrite, which is used in vascular dilators, bronchial dilators and to relieve cyanide poisoning, etc. However, long-term low dose intake of nitrite will cause health damage, such as respiratory diseases, nervous system damage, birth defects, etc. Long-term high dose intake may lead to cancer risk^[17]. Studies by Amira et^[18] al. showed that ellagic acid has a alleviating effect on the lesions caused by ingestion of nitrite. After continuous ingestion of 2 g/L aqueous solution of ellagic chitosan granules for 8 weeks, some rats suffered death, hemiparalysis and abdominal tumors, and the level of hemoglobin in the blood decreased significantly. However, when taking ellagic acid in combination with ingestion of nitrite, the hemoglobin content was close to normal level.

2.5 Anti-diabetic effect

Insulin resistance is one of the key links in the pathogenesis of type 2 diabetes. The study of Gu Lihaxia et^[19] al. proved that ellagic acid can significantly improve dyslipidemia in diabetic mice and correct insulin signal transduction dysfunction in adipose tissue of diabetic mice. Streptozotocin can cause the destruction of islet beta cells, and then affect the production of insulin, resulting in insulin-dependent diabetes. Ellagic acid (25, 50, 100 mg/kg) was administered to streptozotocin diabetic rats 60 min before oral glucose tolerance test. Ellagic acid reduced blood glucose in a dose-dependent manner while increasing insulin levels^[20-21]. Diabetic ocular tissue disease is one of the most common chronic microvascular and neurological complications of diabetes. Studies have shown that ellagic acid can protect the ocular histopathology of diabetic mice from damage, reduce ocular tissue edema and inhibit retinal neovascularization. Meanwhile, the protective effect may be related^[22] to activation of autophagy and improvement of autophagy flow disorders.

2.6 Other Functions

The study of Mingyue Xue et^[23] al. showed that type I allergy mediated by Ig E antibodies caused passive skin allergy. After establishing a passive skin allergy mouse model, ellagic acid treatment significantly reduced the light density of the blue patch on the skin of the mice and inhibited the delayed skin allergic reaction caused by dinitrochlorobenzene, indicating that ellagic acid has a significant anti-allergic effect. Zhong Lili et^[24] al. exercised the memory of mice by using water maze, and gavage transgenic mice with pomegranate juice rich in ellagic acid. The experimental results showed that the spatial learning and memory of mice given gavage were higher than those in the blank group, and the accumulation of amyloid beta in the brain of mice was reduced. For the cause of Alzheimer's disease, the more recognized pathogenesis is amyloid beta accumulation. Therefore, it can be shown that ellagic acid has a alleviating effect on Alzheimer's disease. A number of studies have shown that ellagic acid has an inhibitory^[25] effect on intestinal flora, including *Helicobacter pylori*, *Vibrio cholerae*, *Shigella dysentery* and *Campylobacter*. The extract from male flower sequence of chestnut has a better^[26] inhibitory effect on *Escherichia coli* and *Staphylococcus aureus*.

3. The role of ellagic acid in oral diseases

Oral candidiasis often occurs in immunocompromised patients, of which 42% to 66% cases are caused by *Candida albicans*. Alin da et al.^[27] established a mouse experimental model of oral candidiasis by using 2-transpropyl β -cyclodextrin (HP-B-CD) as the carrier of ellagic acid. It was found that ellagic acid could improve the water solubility of ellagic acid and inhibit *Candida albicans* at the same time. Therefore, it was suggested that ellagic acid could be used as a potential local antibacterial agent for oral candidiasis.

Periodontitis is a chronic infectious disease caused by plaque microorganisms, which is manifested as gingival soft tissue inflammation and progressive loss of alveolar bone, damage and destruction of periodontal tissue. The balance of oral flora is broken, resulting in immune disorder and destruction of periodontal tissue. Non-surgical treatment is the key to periodontitis treatment, except mechanical scraping. Adjuvant local or systemic use of antibiotics is indispensable, in order to overcome the resistance of traditional antibacterial drugs and other adverse reactions, natural drugs because of its small side effects, no resistance and other characteristics have returned to the researchers' attention.

Yan Li et al. found that ellagic acid can inhibit the growth of *Streptococcus mutans* and the formation of biofilms. The mechanism may be through inhibiting the production of extracellular polysaccharide, reducing bacterial adhesion and destroying bacterial cell membrane, thus reducing bacterial activity. In a study conducted by Sastravaha et al. pomegranate extract was made into a gel. After subgingival curettage and root surface flattening, ellagic acid was placed in the periodontal pocket to observe the periodontal indexes. The experimental results showed that the probe depth, adhesion level and other clinical indexes in the experimental group were significantly improved compared with the baseline. Therefore, ellagic acid, as a tannin compound of pomegranate peel polyphenols, has anti-inflammatory and antibacterial properties, which can be used to treat gingivitis and periodontitis.

4. Summary and Prospect

Ellagic acid, as a natural polyphenol dilactone, is widely distributed in nature. At present, medical research focuses on the application of ellagic acid's anti-inflammatory and anticancer functions in systemic diseases, while there are few studies on the treatment and prevention of periodontitis, which is an independent risk factor for systemic diseases such as hypertension, diabetes and Alzheimer's disease. Therefore, it can be assumed that whether ellagic acid, which has various biological activities such as antioxidant, anti-inflammatory and anti-diabetes, can be used as an adjuvant drug after periodontal basic treatment, can also have better effects on periodontal tissues. Therefore, the biological activities of ellagic acid were systematically sorted out in this paper, providing part of the theoretical basis for the application and development of ellagic acid in periodontitis in the later stage.

References

- [1] Wu Jianhua, Wu Zhikui, Pei Jianguo, Liu Jing, Sun Yanchao, WU Guofang, Peng Shuimei, Fu Xiaomei. *Research progress of polyphenols [J]. Chinese Journal of Modern Chinese Materia Medica*, 2015, 17(06):630-636.
- [2] Ding Nan, GAO Xiaoli. *Determination of ellagic acid in pomegranate peel extract by HPLC [J]. Journal of Xinjiang Medical University*, 2012, 35(06):770-772.
- [3] Gao XP, Zhang Lihua. *Research progress of ellagic acid extraction from pomegranate peel [J]. Modern Agricultural Science and Technology*, 2020(14):218-220.
- [4] Carmen Vanessa Ortiz-Ruiz et al. *Action of ellagic acid on the melanin biosynthesis pathway [J]. Journal of Dermatological Science*, 2016, 82(2): 115-122.
- [5] Baradaran Rahimi Vafa et al. *Antiinflammatory and anti-cancer activities of pomegranate and its constituent, ellagic acid: Evidence from cellular, animal, and clinical studies. [J]. Phytotherapy research : PTR*, 2020, 34(4) : 685-720.
- [6] Lv G. *Study on the inhibitory effect of ellagic acid on lipopolysaccharide-induced inflammation and its mechanism [D]. Jilin University*, 2016.
- [7] Dell'agli M, Galli GV. *Ellagitannins of the fruit rind of pomegranate antagonize in vitro the host inflammatory response mechanisms involved in the onset of malaria. Malar J*. 2010 Jul 19; 8 ruler.
- [8] Espin Juan Carlos et al. *Biological significance of urolithins, the gut microbial ellagic Acid-derived metabolites: the evidence so far. [J]. Evidence-based complementary and alternative medicine : eCAM*, 2013, 2013 : 270418.
- [9] Les F, Arbones-Mainar JM, Valero MS, Lopez V. *Pomegranate polyphenols and urolithin A inhibit alpha-glucosidase, dipeptidyl peptidase-4, lipase, triglyceride accumulation and adipogenesis related genes in 3T3-L1 adipocyte-like cells. J Ethnopharmacol*. 2018 Jun 28; 220:67-74.

- [10] Yan L, ZHOU X Y. Study on the bacteriostatic effect of ellagic acid on *Streptococcus mutans* in vitro and its mechanism [J]. *Chinese Pharmacy*, 2019,31(05):607-611.
- [11] Min Zhao et al. Ellagic acid inhibits human pancreatic cancer growth in Balb c nude mice[J]. *Cancer Letters*, 2013, 337(2) : 210-217.
- [12] Edderkaoui Mouad et al. Ellagic acid induces apoptosis through inhibition of nuclear factor κ B in pancreatic cancer cells[J]. *World Journal of Gastroenterology : WJG*, 2008, 14(23) : 3672-3680.
- [13] Radha Munagala et al. MicroRNA 'signature' during estrogen-mediated mammary carcinogenesis and its reversal by ellagic acid intervention[J]. *Cancer Letters*, 2013, 339(2): 175-184.
- [14] Zhong C. Molecular mechanism of ellagic acid inhibiting hepatocarcinoma and its synergistic effect with two chemotherapeutic agents [D]. *Northeast Forestry University*,2019.
- [15] Gonzalez-Sarrias A et al. Consumption of pomegranate decreases plasma lipopolysaccharide-binding protein levels, a marker of metabolic endotoxemia, in patients with newly diagnosed colorectal cancer: a randomized controlled clinical trial. [J]. *Food & function*, 2018, 9(5): 2617-2622.
- [16] Baradaran Rahimi Vafa et al. Antiinflammatory and anti-cancer activities of pomegranate and its constituent, ellagic acid: Evidence from cellular, animal, and clinical studies.[J]. *Phytotherapy research : PTR*, 2020, 34(4) : 685-720.
- [17] Hiroshi Ohshima et al. Antioxidant and pro-oxidant actions of flavonoids: effects on DNA damage induced by nitric oxide, peroxynitrite and nitroxyl anion[J]. *Free Radical Biology and Medicine*, 1998, 25(9): 1057-1065.
- [18] Amira Ragab EL Barky and Tarek Mostafa Mohamed and Ehab Mostafa Mohamed Ali. Detoxifying and antioxidant effect of ellagic acid nano particles in rats intoxicated with sodium nitrites[J]. *Applied Biological Chemistry*, 2020, 63(1) : 322-332.
- [19] Ziemska J, Szynal T, Maza productive ska M, Solecka J. Natural medicinal resources and their therapeutic applications. *Rocz Panstw Zakl Hig*. 2019; 70 (4) : 407-413.
- [20] Fatima Noor et al. Ellagic acid in *Emblica officinalis* exerts anti-diabetic activity through the action on beta cells of mice pancreas.[J]. *European journal of nutrition*, 2017, 56(2) : 591-601.
- [21] Manna K et al. Amelioration of diabetic nephropathy using pomegranate peel extract-stabilized gold nanoparticles: assessment of NF- κ B and Nrf2 signaling system[J]. *International Journal of Nanomedicine*, 2019, Volume 14:1753-1777.
- [22] N. Babay and F. Alshehri and R. Al Rowis. Majors highlights of the new 2017 classification of periodontal and peri-implant diseases and conditions[J]. *The Saudi Dental Journal*, 2019, 31(3) : 303-305
- [23] Xue Mingyue, Luo Xingye, Zhan Zhihua, Chen Quanbin. Experimental study on anti-allergenic effect of ellagic acid in sweet tea [J]. *Food Research and Development*, 2012, 33(11):208-211.
- [24] Zhong Lili, Yu Ying, Yi Yajing, Ni Xueyan, Liu Siying, Liu Xu, Liu Hong. Effect of ellagic acid on learning and memory ability in mice with Alzheimer's disease and its molecular mechanism [J]. *Shandong Medicine*, 2019,60(35):38-41.
- [25] Espin Juan Carlos et al. Iberian pig as a model to clarify obscure points in the bioavailability and metabolism of ellagitannins in humans.[J]. *Journal of agricultural and food chemistry*, 2007, 55(25): 10476-10485.
- [26] Bo Hongwei, Cheng Jun, Yang Liu, Jiang Yichen, Cao Qingqin, Zhang Qing, Qin Ling. Antioxidant and bacteriostatic effects of male flower sequence extract of chestnut [J]. *Scientia Silvae Sinicae*, 2015, 51(05):145-152.
- [27] Sampaio ADG, Gontijo AVL, Lima GMG, de Oliveira MAC, Lapesqueur LSS, Koga-Ito CY. Ellagic Acid-Cyclodextrin Complexes for the Treatment of Oral Candidiasis. *Molecules*. 2021 Jan 19; 26 (2) : 505.