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Research progress on pharmacological properties of punicalagin and its application in oral diseases

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Abstract: *Punicalagin is a kind of natural plant bioactive ingredient, rich in pomegranate peel, which is a kind of polyphenol compounds. Because it is rich in polyphenols, it has various medicinal values such as anti-inflammatory, antibacterial, anticancer and antibacterial. In recent years, more and more studies have been conducted on the therapeutic effects of pinicalagin. This article reviews the pharmacological effects of punicalagin and its application in oral diseases in order to provide reference for its clinical pharmacological research.*

Keywords: *Punicalagin, Oral disease, Anti-inflammatory, antibacterial, antioxidant, anti-cancer*

1. Introduction

In recent years, due to the emergence of adverse reactions and drug resistance of traditional antibiotics and other drugs, traditional medicinal plants have gradually returned to people's vision because of their huge medicinal value and minimal adverse reactions. Pomegranate is a traditional medicinal fruit, and its peel, fruit and juice all have bioactive components beneficial to health. Among them, punicalagin, which is rich in pomegranate peel, has become a research hotspot due to its powerful antioxidant, anti-inflammatory, antibacterial and anticancer effects [1]. In addition, these pharmacological effects of punicalagin have also been applied in the treatment of oral diseases, such as dental diseases and oral mucosal diseases, and have shown good curative effect.

2. Physicochemical properties of punicalagin

Molecular formula of Punicalagin (PUN): C48H28O30, molecular weight: 1084.72. It is a brown-yellow unformed powder, one of the bioactive components of pomegranate, belonging to hydrolyzed tannins in pomegranate peel polyphenols, accounting for about 10% of pomegranate peel content [2].Man G et al. [3] isolated 64 phenolic compounds from 9 different varieties of pomegranate and conducted quantitative analysis, among which the content of punicalagin was the highest (28.03 ~ 104.14 mg/g). Punicalagin is chemically unstable, strongly polar, soluble in water and soluble in a variety of organic solvents. Under the condition of pH2 ~ 6, the stability of punicalagin is good. With the increase of pH,punicalagin will decompose into ionic state, and the temperature is relatively stable at about 40℃ [4]. Under inappropriate conditions, the stability of punicalagin will be destroyed and decomposed into ellagic acid and punicalin, etc. [5]. α-punicalagin and β-punicalagin are isomers of punicalagin, and these isomers can be converted to each other under certain conditions [6].

3. Pharmacological effects of punicalagin

3.1 Anti-inflammatory

Inflammation is a common pathological reaction in diseases, many diseases will show the corresponding inflammatory response. In recent years, compared with traditional anti-inflammatory drugs, domestic and foreign scholars are particularly interested in plant-derived anti-inflammatory drugs. With the exploration of pharmacological action of punicalagin, many studies have shown that punicalagin has strong anti-inflammatory effect. Chondrocytes play an important role in cartilage injury in osteoarthritis, and their inflammatory response can be activated by a variety of inflammatory factors

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(interleukin-1β, tumor necrosis factor-α, lipopolysaccharide (LPS), etc.). In a rat model of osteoarthritis, punicalagin promotes autophagy by activating Foxo1/Prg4/HIF3α axis, thereby alleviating LPs-induced chondrocyte injury [7]. Autophagy is a cell-free process of self-digestion, in which punicalagin attenuates LPS-induced expression of NO, TNF-α and IL-6 in a concentration-dependent manner, thus achieving the effect of inhibiting inflammatory response [8]. In mouse models of rheumatoid arthritis, punicalagin alleviates the progression of rheumatoid arthritis by regulating the NF-κB pathway to reduce the expression of serum TNF-α and IL-6, thus alleviating the severity of arthritis and the degree of bone destruction in mice [9]. In diabetic mice induced by high fat diet (HFD)/ streptozotocin (STZ), blood urea nitrogen (BUN), serum creatinine (CREA), and urinary albumin/creatinine ratio (UACR) were significantly decreased in diabetic mice after 8 weeks of punicalagin administration, and symptoms of glomerular interstitial hyperplasia and glomerular hypertrophy were relieved. At the same time, the expression of mice pyrodeath related proteins such as interleukin-1 (IL-1β) and aspartic cysteine-specific protease-1 (caspase-1) was significantly inhibited, thus alleviating diabetic nephropathy. Moreover, it was found that argarin could regulate 24 potential biomarkers and their related metabolic pathways [10, 11]. Punicalagin promotes osteogenic activity of MC3T3-E1 cells in periodontal inflammatory conditions and inhibits osteoclast formation of bone marrow-derived macrophages (BMMs) by rankl. At the same time, the ratio of RANKL to OPG can be affected by angarnet in vivo or in vitro, suggesting that punicalagin can also indirectly inhibit osteoclast formation [12]. In conclusion, punicalagin can promote the formation of osteoblasts and reduce the formation of osteoclasts, so as to maintain the balance between the two. Therefore, for alveolar bone defects caused by periodontitis, punicalagin can promote the repair of bone defects, and is a potential and safe drug candidate.

3.2 Antibacterial

The use of antibiotics has been the main means of bacteriostatic therapy for a long time. However, in recent years, due to the occurrence of more and more reports on the adverse reactions and drug resistance of antibiotics, domestic and foreign scholars have gradually increased their enthusiasm for the research of plant-derived bacteriostatic drugs. Punicalagin is a kind of plant - derived bacteriostatic drug with little toxicity and few adverse reactions. It has certain inhibitory effect on many common bacteria. AGAR diffusion method was used to inhibit Pseudomonas aeruginosa and Staphylococcus epidermidis in vitro. Experimental results showed that punicalagin could effectively inhibit Pseudomonas aeruginosa and Staphylococcus epidermidis [13]. Lakhani M et al. [14] found that punicalagin completely or almost completely inhibits Escherichia coli ATP synthase through in vitro experiments, which can be used as an effective inhibitor of Escherichia coli ATP synthase and is considered as a useful method to combat antimicrobial drug resistance. The occurrence and development of bacterial drug resistance is a headache for medical workers in recent years. Through the study of punicalagin, it is found that traditional antibiotics combined with punicalagin have better bacteriostatic effect, and can reduce the amount of antibiotics, so as to reduce the occurrence of bacterial drug resistance. Methicillin-resistant Staphylococcus aureus (MRSA) is an important human pathogen and one of the multi-drug resistant bacteria that cause hospital and community acquired infections worldwide. In vitro experimental results of phenacillin combined with punicalagin showed that punicalagin not only showed antibacterial activity, but also enhanced the effect of phenacillin on MRSA and increased the sensitivity of MRSA to xacillin by reducing the transcription of methicillin-resistant gene markers [15]. In vivo studies of mice infected with MRSA-induced pneumonia, it was found that punicalagin combined with cefotaxime had more effective efficacy and showed great potential in combating MRSA infection [16]. In addition to the above common pathogens, punicalagin also has a certain antibacterial effect on fungi. Candida albicans and Cryptococcus are common fungi, and angaradin is effectively inhibited by causing severe ultrastructural changes in Candida albicans and cryptococcus, such as disturbance of cytoplasmic contents and/or cell wall thickening [17]. Candida albicans infection is also a common fungal infection in oral mucosal disease . da Silva RA et al. [18] found through in vitro tests that the antifungal effect of punicalagin combined with the traditional antifungal drug nystatin could be improved, and nystatin could reverse eliminate the cytotoxicity of punicalagin on keratinocytes, showing complementary therapeutic effects.Punicalagin also shows an inhibitory effect on Streptococcus mutans and Streptococcus sanguis, which are common caries causing bacteria, and is considered as a potential therapeutic drug for the treatment of oral caries [19].

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3.3 Antioxidation

Natural antioxidant products are widely found in food and medicinal plants. These natural antioxidants, especially polyphenols, exhibit a wide range of antioxidant biological activities. As one of hydrolyzed tannins rich in polyphenols, punicalagin has strong antioxidant activity. LDL oxidation is considered a hallmark of early atherosclerosis. Punicalagin can significantly inhibit oxidative damage of LDL by reducing free radicals produced during oxidative metabolism, preserving endogenous antioxidants in LDL, and regulating the oxidative state of arterial cell walls. These properties inhibit cell-mediated LDL oxidation, increase serum para-phosphonase (PON1) activity, and resist oxidative stress [20]. Pre-eclampsia (PE) is a pregnancy disorder characterized by severe hypertension, and oxidative stress plays an important role in the development of hypertension. Currently, treatment for PE is limited to antihypertensive drugs. Wang Y et al. [21] studied the effects of punicalagin on angiogenesis and oxidative stress in pregnancy-induced hypertension rats. The results showed that punicalagin could significantly reduce diastolic blood pressure, systolic blood pressure and mean arterial blood pressure in infected rats. Meanwhile, by increasing the expression of vascular endothelial growth factor, down-regulating vascular endothelial growth factor receptor-1 / FMS-like tyrosine kinase-1 can restore angiogenic balance. Moreover, the elevated level of oxidative stress in PE rats was significantly reduced after treatment with punicalagin. The alteration of REDOX balance is related to the pathogenesis of depression. Depressed patients have relatively poor antioxidant defense ability, and their brains are susceptible to oxidative stress and lipid peroxidation (LPX). Therefore, REDOX balance is considered to be an important factor in the etiology of depression. In vivo experiments in rats have found that punicalagin plays a role in reducing oxidative damage and preventing brain cell dysfunction, and has anti-depression and anti-oxidation effects [22].

Skin aging is closely related to oxidation reaction. Uv radiation causes skin cells to be exposed to reactive oxygen species (ROS), which alters the balance between antioxidants and free radicals, speeding up or slowing down skin aging. And antioxidants can neutralize the harmful effects of reactive oxygen species. Punicalagin can reduce the growth arrest of HFB4 cells, activate the production of col1a1 and Timp3 genes, maintain collagen levels, and reduce MMP3[23]. It's a natural antioxidant that slows down skin aging.A study showed that punicalagin combined with Zn (II) can accelerate the response of fibroblasts and the healing of oral wounds caused by periodontal surgery and trauma through its antioxidant effect, as well as promote the anti-inflammatory response [24].

3.4 Anti-cancer

The increasing incidence of cancer is a major public health challenge. At present, cancer is mainly treated by chemotherapy and radiotherapy. However, the poor efficacy of commonly used chemotherapy drugs, the occurrence of adverse reactions and the occurrence and development of drug resistance eventually lead to the recurrence or deterioration of cancer. Research on natural medicines over the past few years has shown that they have anti-cancer phytochemical properties. Many studies have shown that punicalagin can achieve anti-invasion, anti-proliferation and other anti-cancer effects by down-regulating the expression of various signaling pathways and genes related to cancer development. The study results of Zhang L et al. [25] showed that punicalagin inhibited the vitality of cervical cancer cells in a dose-dependent mode by stimulating mitochondria-mediated apoptosis, and inhibited the proliferation of cervical cancer cells and stimulated cell apoptosis by down-regulating the NF-kB signaling pathway. Through the establishment of subcutaneous tumor xenotransplantation model, it was found that punicalagin treatment significantly reduced the proliferation of osteosarcoma cells and increased cell apoptosis. In addition, the invasive potential of cancer cells was significantly inhibited. Angaratine can not only induce the degradation of iκbα, but also induce nuclear translocation of p65, suggesting that the NF-κB signaling pathway is weakened after treatment [26]. STAT-3 overexpression regulates apoptosis, proliferation, and angiogenesis in lung cancer A549 cells [27]. Punicalagin inhibits the transmutation of STAT-3, thereby inducing apoptosis by inhibiting the expression of Bcl-2 and enhancing the expression of Bax, cytochrome -c, caspase-9, and caspase-3. It is suggested that punicalagin is a possible treatment for non - small cell lung malignancies. Punicalagincan also promote the autophagy degradation of human papillomavirus E6 and E7 proteins in cervical cancer through the ROS-JNK-BCL2 pathway, significantly reduce the levels of major HPV cancer proteins E6 and E7 in cervical cancer cells, and inhibit the occurrence of cervical cancer [28]. In acute leukemia cells [29], argynoside changes Bax and Bcl-2 by activating caspase cascades, and regulates autophagy through mTOR/ULK1 signaling pathway, thus inhibiting cell proliferation and promoting apoptosis and autophagy.

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4. Future Outlook

More and more researchers pay attention to the potential therapeutic value of natural medicine, which has advantages of less side effects and toxicity, and has become a research hotspot in various fields. This article reviews the pharmacological action of punicalagin and its application in oral diseases. At present, pharmacological effects of punicalagin are mainly studied in vitro cell, bacterial and animal experiments, and studies on oral diseases mainly focus on the inhibition of punicalagin on common oral bacteria and its potential osteogenic effect, which provides a theoretical basis for clinical application. However, the current understanding of the specific therapeutic mechanism of punicalagin is still superficial, and whether punicalagin has more pharmacological properties in the treatment of oral diseases is worthy of further study, in order to better use in clinical practice in the future for the benefit of mankind.

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