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Research Progress on Anti-inflammatory, Antioxidant, and Bone Metabolism Regulating Effects of Punicalagin

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Abstract: *A large body of epidemiological evidence in the scientific community emphasizes that proprietary Chinese patent medicine can reduce the prevalence of common diseases such as diabetes, cardiovascular disease, cancer and stroke. The therapeutic effect of Chinese patent medicine is partly explained by phenolic secondary metabolites or polyphenolic compounds. Therefore, polyphenols are widely found in plants and have antioxidant and anti-inflammatory effects. In addition, polyphenol compounds have natural biocompatibility and safety, and are harmless to human body. Punicalagin makes up half of the pomegranate fruit and has more pronounced antioxidant and anti-inflammatory properties than the rest of the fruit. And the most important active ingredient in pomegranate peel, found only in this plant, is Punicalagin. These polyphenolic compounds in pomegranate peel are known to have the most dramatic therapeutic effects. Several studies have shown that Punicalagin has anti-inflammatory, antioxidant, antibacterial, antiviral and other effects. However, despite extensive research in recent years, a review of the data shows that there is insufficient evidence to support the therapeutic effects of polyphenol compounds in pomegranate peel. In this review, the research progress of antiinflammation, antioxidation and regulation of bone metabolism of angarnet was reviewed.*

Keywords: *Punicalagin, anti-inflammatory, antioxidant, bone metabolism*

1. Introduction

Chinese patent medicines can reduce the prevalence of common diseases such as diabetes, cardiovascular disease, cancer and stroke. The therapeutic effect of Chinese patent medicine is partly explained by phenolic secondary metabolites or polyphenolic compounds. Therefore, polyphenol compounds widely exists in plants, antioxidant and anti-inflammatory effects. In addition, polyphenol compounds have natural biocompatibility and safety, and are harmless to human body.

Punicalagin (PUN)-is a unique phenolic component of pomegranate, especial1y in the pee1. Punicalagin (2,3,hexa-1ight dipheny1-choline D-glucose) has a molecular formula of C48H28030and a molecular weight of 1084.72. There are two isomers,α-punicalagin and P-punicalagin; PUIN is a brownish-yel1ow indeterminate powder with strong polarity and easily soluble in water. In recent years, it has received attention for its various physiological activities, such as anti-inflammatory, antioxidant, antibacterial and antiviral, and is increasingly used in the prevention studies of inflammatory and infectious diseases. This paper reviews the biopharmacologica1 activities of PUN such as anti-inflammatory, antioxidant and bone metabolism regulation, in order to provide a theoretical basis for the clinical application of PUN and a reference for further development and utilization of PUN.

2. Anti-inflammnatory activity of PUN and·its role in related diseases

The anti-inflammatory activity of PUN has been a hot topic of research in recent years, with a wide variety of cells and sites of action. PUN has significant effects in combating neuroinflammation. Research has found [1]that PUN significantly reduces IL-8 and IFN in human foot cell lines induced by

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protease activated receptor 2- γ And TNF- α The increase significantly alleviated renal injury in NZB/WF1 mice. The results suggest that PUN is a potential drug for treating lupus nephritis. Olajide et al. [2] found that prior to LPS stimulation, primary rat microglia were treated with PUN, which could disrupt NF kB signaling and reduce tumor necrosis factor (TNF) levels- α) The content, interleukin-6 (IL-6) gene expression, and levels of prostaglandin E2 (PGE2) can inhibit microglial cell-mediated neuroinflammation. Rojanathammanee et al. [3] reported that PUN inhibited T ce11 activation and microglia NF-kB signaling pathway activation in a mouse model of Alzheimer's disease and reduced amyloidβ (Aβ) induced TNF-α secretion, exerting anti-inflammatory effects and thus delaying the progression of Alzheimer's disease, and this study provides a new strategy for the clinical treatment of Alzheimer's disease. In addition to the above-mentioned inflammatory indicators, PUN can also inhibit mitogen-activated protein kinase (MAPK) phosphorylation, including p38, c-Jun N-terminal kinase and extracellular signal-regulated kinase.

PUN also has good therapeutic effects on intestinal, bone, and pulmonary inflammation. Shah et al. [4] established a rat model of inflammatory bowel disease and found that the PUN intervention group had TNF- α, IL-18 and IL-1 β The mRNA expression level of significantly decreased. Hollebeeck et al. [5] used Caco-2 cells in vitro to detect IL-1 β, TNF- α At the levels of pro-inflammatory factors such as IFN-V, it was found that pomegranate peel extract rich in PUN exhibited significant anti-inflammatory activity. Jean Gilles et al. [6] found that polyphenolic compounds such as PUN and tannic acid inhibit matrix metalloproteinase-13 (MMP-13) mediated osteoarthritis in a concentration dependent manner in vitro. Another study also showed [7] that punalagin has a protective effect on ankylosing spondylitis by reducing oxidative stress and the production of inflammatory cytokines in Th17 cells and IL-17A/IL-23 axis. In addition, the research results of some scholars also indicate that Punicalagin blocks TNF- α-Simulated NF- κ Activation of the B signaling pathway. Treatment reduces synovitis and bone destruction in the body without damage to liver cells or glomeruli [8].

Besides, PUN the most abundant of these polyphenols, has powerful anti-inflammatory biological activity, Including inhibition of tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), or interleukin 6 (IL-6)production in RAW264.7 macrophages and primary human chondrocytes stimulated by lipopolysaccharide (LPS). Some researchers[9]confirmed that PUN inhibits macrophage inflammation by inhibiting NF-KB,MAPK signaling pathway and Fox03a/autophagy signaling pathway, and the findings suggest that PUN may inhibit LPS-induced macrophage inflammatory, response through Fox03a/autophagy signaling pathway, taken together, these results are of value for the prevention and treatment of inflammatory diseases, as wel1 as for the development of PUN and its application as a novel immunotherapy in the treatment of inflammatory diseases. Also, researchers[10]·found that PUN, the most abundant ellagitannin among these polyphenols, possesses potent anti-inflammatory biological activities, including inhibition of tumor necrosis faction(TNF-α),interleukin1(IL-1) or interleukin6 (IL-6) production inlipopoly saccharide(LPs) stimulated·RAW264.7 macrophages and primary human chondrocytes.

Overall, PUN has significant anti-inflammatory effects on several tissues and organs such as nerve, brain, intestine, and lung through different pathways. Some scholars established LPS inf1ammattion model with abdomina1 macrophages and found that the PUN intervention group could significantly inhibit the mRNA levels of TNF-α, I-1β, IL-6 and MMP-13, and elevate the mRNA levels of arginase 1(Arg-1), IL-10, aromatic hydrocarbon receptor (AhR) and other factors, playing an anti-inflammatory and pro-healing role[11].

3. Antioxidant·activity of PUN and its role in related diseases

In addition to anti-inflammatory effect, the antioxidant effect of PUN is also quite p0werful.As the 1iver is an important metabolic organ of the body, how to reasonably protect the liver is an important issue that needs to be addressed nowadays. Studies have shown that PUN dose-dependently inhibited the elevation of serum alanine aminotransferase, tumor necrosis factor-α, interleukin-18, malondialdehyde and NO levels, as well as the activation of hepatic NF-kB in a cyclophosphamide induced 1iver injury model, and prevented the decrease of total antioxidant capacity of the liver; meanwhile, PUN alleviated the pathologica1-1iver injury in rats by inhibiting oxidative stress, inflammation and apoptosis, decreased hepatic cycloocygenase-2 expression[12].Lin et al.[13-14]also found that PUN and anisidine had antioxidant and hepatoprotective effects on hepatic injury induced by acetaminophen and hepatic injury induced by carbon tetrachloride in rats. However, it should- be noted that this investigator also mentioned that tannins have strong antioxidant activity at very small doses and large doses can cause 1iver damage instead. Furthermore, the study by Zou et al. also showed that PUN may reduce trig1yceride and

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cholesterol levels in HepG2 ce11s by promoting mitochondrial function and eliminating oxidative stress and inflammation, leading to the treatment of obesity-related nonalcoholic fatty·1iver disease (NAFLD).

PUN has a protective effect not only on liver, but also on kidney, lung, heart muscle, testis and other parts through its anti-oxidative stress effect. Fouad et al. found that PUN improved acute kidney injury induced by endotoxemia in rats through anti-inflammatory, antioxidant/oxidative stress and anti-apoptotic activities. It can not only reduce the levels of LPs-induced inflammatory factors such as IL-18, TNF-β, IL-6 and NO, but also reduce the proportion of Bax/Bcl-2, and the activities of myeloperoxidase, inducable nitric oxide synthase and caspase 3, 8 and 9, so as to reduce the histopathological damage. Yujue Wang.et. The pregnant rats was induced using an oral dose of NG-nitro-L-arginine methyl ester (L-NAME, 50 mg/kg/day) on days 14-19 of pregnancy. Punicalagin (25, 50 or 100 mg/kg) was given orally on days 14-21 of Punicalagin also restored angiogenic balance by increasing the expression of vascular endothelial growth factor and downregulating vascular endothelial growth factor receptor-1/fms-like tyrosine kinase-1. Punicalagin, significantly increased the placental nitric oxide levels as compared to PE group. The increased levels of oxidative stress in rats with PE were markedly decreased by treatment with punicalagin. Punicalagin at the tested doses markedly ($p<0.05$) enhanced the placental antioxidant capacity in L-NAME-treated rats. The raised catalase activity observed following L-NAME induction was significantly ($p<0.05$) and restored to normal activity levels in punicalagin treatment. Further, 100 mg dose of punicalagin exhibited higher protective effects as compared to lower doses of 25 and 50 mg. Yin Shanshan et al. found that when PUN alleviated UC inflammation and oxidative stress injury, SIRT1/PGC-1α/NRF1 pathway was at a higher activation level, and the higher the therapeutic dose of PUN, the protein expression of SIRT1/PGC-1α/NRF1 pathway continued to increase. It is suggested that PUN's effect on intestinal inflammation and oxidative stress injury of UC may be related to exogenous activation of SIRT1/PGC-1α/NRF1 protective pathway. Testis: Rao et al. confirmed that PUN alleviated testicular injury induced by oxidative stress in mice by activating Nrf2, and suggested that PUN may play an important role in the treatment of male infertility caused by oxidative stress. In addition, other studies have shown that a key mechanism of pomegranate influence on type 2 diabetes is to reduce oxidative stress and lipid peroxidation.

In addition, PUN also acts on different cells and exhibits some degree of antioxidant effects.·Pathakoti et al. found that PUN reduced glutamate induced intracellular reactive oxygen species(ROs) and restored mitochondrial membrane depolarization with neuroprotective effects in mouse hippocampal cell line HT22 via antioxidant stress. Some scholars and researchers found that pomegranate glycoside can reduce the weight of diabetes mice and improve the fasting blood glucose level of diabetes mice. At the same time, it can significantly reduce the levels of TC, TG, FFA, LDL-C in the serum of diabetes mice, and significantly increase the level of HDL-C, indicating that pomegranate glycoside can significantly improve the disorder of glucose and lipid metabolism in diabetes mice, and can play a role in regulating lipid metabolism in a short time without being affected by dose. The effect of pomegranate glycoside on lipid metabolism in diabetes mice may be related to its significant antioxidant capacity.

Regarding the study-of antioxidant mechanism, Xu et al..also clearly indicated that PUN exerted antioxidant stress by inducingNrf2/H0-l expression through upregulation of PI3K/AKT pathway and inhibiting LPS induced ROS and NO production in RAW264.7.ce1ls,and increasing the expression of antioxidant enzyme super Oxide dismutase (SOD) mRNA levels.

4. The regulatory role of·PUN·in bone metabolism and its role in related diseases

In recent years, PUN-has received increasing attention in the study of bone tissue. The function of bone is to provide attachment sites for muscle contraction and to protect vital organs such as internal organs. Lee et al. screening of 1400-herbal extracts revealed that amphiregulin in pomegranate pee1 is a potent immunosuppressant, which inhibits activation of NFATc1,an important transcription factor in the differentiation and maturation of osteoblasts ,which is involved- in regulating the expression of a variety of 0steoblast-specific genes. Jean-Glles et a1. found that amphiregulin, e1lagic acid and other polyphenols in pomegranate inhibited the degradation of type II co1lagen by matrix metalloproteinase 13 co1lagenase, preventing the destruction of cartilage in joint sand preventing arthritis from the inhibitory effect of amphiregulin was dose-dependent with its concentration. It has also been found that amphiregulin can promote the proliferation, differentiation and calcified nodule formation of osteoblasts, inhibit the expression of RANKL in osteoblasts, and have a regulatory effect on bone volume and bone remodeling. Some domestic scholars found that amphiregulin could significantly reduce the expression of interleukin-1, matrix metalloproteinase-1and-matrix-metalloproteinase-3 through postmenopausal rat osteoarthritis model. Geng lei Chu et al. investigated the effects of different concentrations of

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amphiregulin on the proliferation and differentiation of osteoclasts through a titanium particle-induced differentiation model of mouse monocyte/macrophage cell line RAW264.7 toward osteoclasts, and concluded that amphiregulin showed a concentration-dependent decrease in the number of mature osteoclasts, the levels of nuclear factor κB inhibitory protein and nuclear factor κBp65phosphorylation, activated T-cel1 nuclear factor cl mRNA, anti-tartrate acid phosphatase mRNA and matrix metalloproteinase 9mRNA expression. Although amphiregulin has a role in the prevention of anti-osteoporosis, arthritis and wear particle-mediated osteolysis and other bone resorption disorders, there may be some negative effects of amphiregulin in humans. Some studies have reported that amphiregulin can cause liver necrosis and kidney virus production in cattle, but these negative effects only occur at high doses of amphiregulin.

5. Conclusion and outlook

PUN has the above-mentioned activities and pharmacological efficacy, and shows good application prospects in the medical field. However, many studies on- the mechanism of action are not in- depth, and more-extensive and in-depth pharmacological studies are needed to better develop and utilize PUN; on the other hand, there are few studies on the oral aspects of anisidine, and relevant oral studies need to be conducted1ater. Meanwhile, it should be noted that treatment with larger doses of PUN may cause ce11 damage and may have hepatotoxicity at higher doses, so further exploration and improvement are needed in the design of research studies.

References

[1] Rojanathammanee L, Puig KL, Combs CK. Pomegranate polyphenols and -extract inhibit nuclear factor of activated T-cell activity and microglial activation in vitro and in a transgenic mouse model of Alzheimer disease[J]. JNutr, 2013,143(5): 597-605.

[2] Wang Youxin, Peng Luyuan. Protective effect of punicalagin on lipopolysaccharide induced damage to chicken glandular gastricepithelial cells [J]. Chinese Journal of Veterinary Medicine, 2023.3.12, 45(5).

[3] Holle beeck S, Win and JHerent MF, et al. inflammatory effects 'of pomegranate (Punica granatum L.) husk ellagitannins in Caco-2cells, an in vitro model of human intestine [J].Food Funct,2012,3(8)875-885.

[4] Feng X, Yang Q, Wang C, Tong W, Xu W. Punicalagin exerts protective effects against ankylosing spondylitis by regulating NF-kappaB-TH17/JAK2/STAT3 signaling and oxidative stress. Biomed Res Int. 2020; 2020:4918239.

[5] Huang Mingcheng, Wu Keping, Zeng Shan et al. Punicalagin Inhibited Inflammation and Migration of Fibroblast-Like Synoviocytes Through NF-κB Pathway in the Experimental Study of Rheumatoid Arthritis.[J] .J Inflamm Res, 2021, 14: 1901-1913.

[6] Cao Y, Chen J, Ren G. Punicalagin Prevents Inflammation in- LPS--Induced RAW264.7-Macrophages by-Inhibiting FoxO3a/ Autophagy Signaling-Pathway-[J] Nutrients, 2019, 11(2794).

[7] Marques, L.C.; Pinheiro, AJ, Arauj0, J.G.,de Oliveira, RA., Silva, S.NAbreu, IC. de Sousa, E.M, Femnandes, E.S., Luchessi, AD. Silbiger, VN., et al ·Anti- Inflammatory Effects of a Pomegranate Leaf Extract in LPS-Induced Peritonitis. Planta Medica 2016, 82, 1463-1467.

[8] Fouad AA, Qutub HO, A1-Melhim WN. Punicalagin alleviates hepatotoxicity in rats challenged with cyclophosphamide [J]. Environ Toxicol Pharmaco1, 2016, 45:158- 162.

[9] Rao F, Tian H, Li W, et al. Potential role of punicalagin against oxidative stress induced testicular damage]J]. Asian- JAndro 1, 2016,18(4)627-632.

[10] Banihani S, Swedan S, Alguraan Z. Pomegranate and type 2 diabetes [J]. Nutr Res, 2013,33(5):341-348.

[11] Lee SI,Kim BS Kim KS,et al. Immune-suppressive activity of punicalagin via inhibition of NFAT activation. Biochem Biophys Res Commun.2008; 371(4):799-803.

[12] Ramage SC, Urban NH, Jiranek WA, et al. Expression of RANKL in osteolytic membranes. association with fibroblastic-cell markers. JBone Joint Surg Am. .2007 89(4):841-848.

[13] Jean-Gilles DLi L,Vaidyanathan- VG,et al. Inhibitory effects of polyphenol unicalagin on type-Il collagen degradation in vitro and inflammation in vivo. Chem Biol Interact. 2013: 205(2):90-99.

[14] Kim YH, Choi EM. Stimulation of osteoblastic differentiation and inhibition of interleukin-6and nitric-oxide imn MC3T3-E1 cells by pomegranate ethanol extract. Phytother Res. 2009, 23(5):737-739.