

Research Progress of Functional Nano Drug Carrier Puerarin in The Treatment of Skin Diseases

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Abstract: Functional nanofibers have good porosity to exchange oxygen and appropriate surface hydrophilicity to promote cell adhesion and proliferation, which has attracted extensive attention in the medical research field in the treatment of skin repair diseases. Puerarin is a kind of isoflavones extracted from the roots of the leguminous plant *pueraria lobata* or kudzu vine. Because of its strong antioxidant, free radical scavenging and anti-tumor effects, puerarin has made some preliminary exploration in the research field of skin diseases in recent years. This paper summarizes the research progress of skin wound repair, puerarin treatment of skin diseases and nanotechnology in skin wound repair, with a view to providing new therapeutic ideas for the research and development of puerarin skin wound repair.

1 INTRODUCTION

Skin repair is an extremely complex, dynamic and difficult process. These processes mainly include inflammation, proliferation and remodeling. During this period, improper treatment will induce different complications, such as bleeding, infection and excessive inflammation, which will have a negative impact on the results of wound healing. Traditional gauze wound dressings are mostly made of cotton and have no biological characteristics. At present, excellent wound dressings including hydrogels, sponges, nanofibers and other biological materials have been used to accelerate wound healing. Among these therapeutic strategies, nanofibers have attracted extensive attention from the medical research community. Functional nanofibers have good porosity to exchange oxygen and appropriate surface hydrophilicity to promote cell adhesion and proliferation.

Puerarin is one of the main effective components of *Pueraria lobata*, which is a isoflavone compound extracted from the root of *Pueraria lobata*. Puerarin has many functions such as anti inflammation, anti-oxidation, promoting cell proliferation and differentiation, scavenging oxygen free radicals, anti oxidative damage, expanding cardio cerebral vessels and reducing myocardial oxygen consumption. Puerarin is now widely used clinically, not only in the treatment of cardiovascular and cerebrovascular diseases, but also in the treatment of various skin diseases. Recent studies have shown that Puerarin is playing a role in the treatment of severe contusion of skin and soft tissues in special parts of orthopedics. After treatment, it can reduce the degree of necrosis, reduce the area of skin necrosis, and have a certain role in the repair of skin trauma. In recent years, the ability of puerarin to promote wound repair has been proved. The hydrogel containing puerarin can improve the

activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx), reduce oxidative stress, and accelerate skin regeneration. Therefore, this article reviews the skin treatment of puerarin monomer, which can replace the common drug puerarin, in order to provide a basis for the further development of puerarin.

2 APPLICATION OF PUERARIN IN SKIN DISEASES

2.1. Delay Skin Aging

Pueraria and puerarin can reduce the oxidative damage of skin tissue in mice, and slow down the aging process of skin tissue. The mechanism is related to that *Pueraria* and puerarin can eliminate free radicals in body tissues, improve the total antioxidant capacity (T-AOC) of skin tissue, and increase the inhibition rate of hydroxyl free radicals ($\cdot\text{OH}$) (Zheng, 2013). Studies have shown that a certain dose of *pueraria* and puerarin can reduce the deletion and mutation of mitochondrial DNA in the skin tissue of aged mice, inhibit the damage of mitochondrial respiratory chain and oxidative phosphorylation function, ensure the energy supply required for all physiological and biochemical activities of cells, inhibit the decline of tissue and organ functions, and delay the natural aging of skin (Wu, 2011).

2.2. Skin Cancer

Pueraria is a widely used traditional Chinese medicine in clinical practice. Its active ingredient puerarin has been proved to have anti-tumor effect. Research by Li Bing in China has confirmed that puerarin has an inhibitory effect on the proliferation and invasion of esophageal cancer

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cells. Inhibition of PI3K/AKT pathway is a related molecular mechanism (Li, 2020). Cutaneous Squamous cell carcinoma is one of the common skin malignant tumors, which originates from epidermal keratinocytes. The incidence rate is increasing year by year. CSCC is characterized by high malignancy and rapid growth. Its pathogenesis is affected by many factors, involving abnormal activation of complex biological signal networks (Zheng, 2020; Guo, 2020). Phosphatidylinositol-3 kinase (PI3K)/Protein kinase B, (PKB/AKT) is an important signal pathway that regulates biological behaviors such as cell proliferation and invasion. The abnormal activation of this pathway is closely related to the occurrence of esophageal squamous cell carcinoma and cervical squamous cell carcinoma (Xu, 2021; Li, 2020). The cell experiment of CSCC confirmed that the PI3K/AKT pathway inhibitor LY294002 has an inhibitory effect on the proliferation and invasion of CSCC cells (Ren, 2020), suggesting that the PI3K/AKT pathway is a potential therapeutic target of CSCC. Duan Qiang et al. confirmed that puerarin has anti CSCC effect through cell experiment and animal experiment. At the cell level, puerarin significantly inhibits the proliferation and invasion of CSCC cells, and at the animal level, puerarin significantly inhibits the growth of CSCC transplanted tumors; At the same time, puerarin significantly inhibited the activation of PI3K/AKT pathway in CSCC cells and transplanted tumors, which is one of the molecular mechanisms of puerarin's anti CSCC effect.

2.3. Skin Inflammation

Puerarin has rich resources, simple extraction, obvious pharmacological effect and low price, and has been widely used in the treatment of cardiovascular and cerebrovascular diseases (Liu, 2016; Gao, 2015). There is increasing evidence that puerarin is associated with many inflammatory diseases. Puerarin can inhibit the secretion of inflammatory cytokines and chemokines in atopic dermatitis. In vivo and in vitro experiments show that it has a protective effect on atopic dermatitis (Lee, 2018). The molecular mechanism may be that puerarin regulates superoxide dismutase (SOD), endothelial nitric oxide synthase (eNOS), malondialdehyde (MDA), PI3K/AKT, MAPK and NF- κ B signal pathway to inhibit oxidative stress and apoptosis process (Wei, 2014). Langerhans cells are important antigen presenting cells in the immune process and play a key role in immune inflammatory diseases. Wang Wenhong found in the study that although the number of Langerhans cells after the action of puerarin did not change, their expression levels of CD80 and CD86 decreased significantly, indicating that puerarin has the ability to down regulate the excessive immune response, which may play a negative role in regulating the immune state of the body in immune inflammatory diseases. The immature dendritic cells generated in bone marrow gradually mature after phagocytosis and uptake of antigen, and then migrate to the skin to become Langerhans cells. The ability of mature Langerhans cells to ingest and phagocytosis antigens decreases, while the expression

levels of MCH and costimulatory molecules CD80 and CD86 increase, which play a key role in immune response. The results show that puerarin can enhance the antigen phagocytosis of Langerhans cells and inhibit the expression of costimulatory molecules CD80 and CD86. The above results further indicate that puerarin can negatively regulate the immune activity of Langerhans cells and participate in the process of inflammatory diseases. Puerarin can affect the secretion of inflammatory factors and improve inflammatory response (Chen, 2010). Puerarin can inhibit the expression of 3T3-L1 cellular inflammatory factors induced by palmitic acid (PA) in mature adipocytes, thus preventing inflammation in patients and protecting their bodies (Wang, 2018). Puerarin can significantly reduce the proinflammatory factor TNF- α And IL-6, up regulate the expression of anti-inflammatory factor IL-10, thereby inhibiting the occurrence of inflammatory response (Yuan, 2011; Sun, 2008). One of the skin wound repair is anti-inflammatory, and a large number of data prove that puerarin plays an important role in anti-inflammatory protection. In conclusion, the study further clarified the protective mechanism of puerarin in inflammatory diseases, enriched its theoretical basis in the treatment of inflammatory related diseases, not only provided a certain theoretical basis for the clinical application of puerarin in the treatment of skin inflammation and other immune related diseases, but also proposed a direction for the comprehensive application of puerarin in clinical.

2.4. Abnormal Sweating Of Diabetes Skin

Abnormal skin sweating in diabetes is an autonomic neuropathy in diabetes. Its incidence increases with age, mostly in the elderly, but rarely in children. The longer the course of diabetes, the higher its prevalence. Smoking and drinking increase its incidence rate. The pathological mechanism is neurointimal microvascular disease caused by hyperglycemia. Hyperglycemia will lead to activation of sorbitol pathway, increase of protein enzymolysis glycosylation, which will lead to hyperplasia and hypertrophy of neurointima microvascular endothelial cells, thickening of basement membrane, increase of dispersion distance and short circuit of adventitia arteriovenous. In addition, due to the hyperfunction of platelets, rigidity of red blood cells, increased adhesiveness, and increased blood viscosity, the blood flow of neurotrophic vessels decreased, resulting in ischemia and hypoxia of the nerve intima, resulting in abnormal neural metabolism and structural damage and a series of clinical manifestations (Ye, 2000). The main component of puerarin, puerarin flavone, can reduce the blood viscosity, inhibit platelet aggregation, reduce the level of thromboxane A2 (TXA2), reduce the significantly increased plasma endothelin, angiotensin II, and renin activity, thus expanding the microarteries, improving microcirculation, increasing the blood flow of neurotrophic vessels, and improving the ischemic and hypoxic state of the neurointima (Lin, 2000).

2.5. Skin Wound Healing

In modern clinical applications, wound healing is still a considerable challenge. Wound healing is an extremely complex, dynamic and difficult process. It mainly includes inflammation, proliferation and remodeling. During this period, improper treatment will induce different complications, such as bleeding, infection and excessive inflammation, which will have a negative impact on the results of wound healing (Hou, 2019). As one of the most popular alternative medicines, traditional Chinese herbal medicine plays an important role in trauma treatment (Wang, 2020). Puerarin is a kind of flavonoids extracted from *Pueraria lobata*, which has strong antioxidant (Zhou, 2019), anti-inflammatory (Deok, 2020) and other pharmacological activities. Several studies have shown that isoflavones have beneficial effects on the wound healing process (Aslam, 2018; Ergene, 2018). A plant extracted from the flower of *Pueraria lobata* contains isoflavones and essential oil components. It has the potential to promote skin regeneration by stimulating the migration, proliferation and collagen synthesis of epidermal keratinocytes (Kim, 2015). Previous studies have reported that puerarin orally can promote wound healing in diabetes rats by enhancing the formation of connective tissue and new blood vessels. In the current study, the external use of puerarin for 14 days also promoted the wound healing process of dexamethasone treated mice. In recent years, the ability of *Pueraria lobata* to promote wound repair has been proved. Recent research reports that hydrogels containing PUE can reduce oxidative stress and accelerate skin regeneration by improving the activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx) (Zhang, 2019). Some scholars also prepared three natural antioxidant loaded hydrogels as wound dressings by combining puerarin with ferulic acid, and proved that drug loaded hydrogels repair tissues by reducing oxidative damage in cells (Ou, 2021). Puerarin has obvious anti atherosclerosis (Jiang, 2021), protection of vascular endothelial cells and myocardial cells (Wang, 2010), resistance to lead induced kidney damage (Huang, 2016), influence on bone proliferation and differentiation (Hwang, 2011), and promotion of pancreas β the role of cell survival (Yang, 2014). Wang Yu et al. found that puerarin can improve the sensory and motor function of the affected upper limb caused by BPRAI modeling through mouse tests on the injury of brachial plexus nerve root avulsion caused by puerarin, which mostly occurred in traffic accidents, childbirth injuries, falls, etc. α - The protective effect of MNs death may be related to puerarin's ability to inhibit iNOS expression and promote CGRP expression, and PI3K/Akt signaling pathway is involved in its regulation (Wang, 2019). In wound repair, the trigger of puerarin protective effect is closely related to PI3K/Akt/e NOS signal pathway.

2.6. Others

Puerarin is widely used in the treatment of cardiovascular and cerebrovascular diseases. Puerarin is also effective in the treatment of skin and soft tissue contusion and

vascular diseases in orthopedics. In the cases of traffic accidents, machine accidents and heavy object injuries, clinically common fractures with severe skin contusion are sometimes located in the hand, foot, front and inside of the lower leg and other parts with less soft tissues. After skin necrosis, the bone and (or) muscle healthy ends are exposed, which is prone to infection, causing bone marrow inflammation, muscle membrane repair failure, and wound failure to heal. The application of blood activating and fatigue removing drugs can greatly reduce the pain and economic burden of patients if skin can survive or necrosis is very little and bone and (or) muscle bonds are not exposed. Puerarin relieves the spasm of injured blood vessels, reduces the resistance of blood vessels and increases blood supply through receptor capture blocking; It can inhibit platelet aggregation induced by adenosine diphosphate (ADP) and play an anticoagulant role. Puerarin is also a reducing agent, which can eliminate free radicals and promote the smooth recovery of injured tissues.

3 CONCLUSION

With the development of modern pharmacological research, the pharmacological effect and clinical efficacy of puerarin have been clearly confirmed. This article reviews the mechanism and treatment of skin wound repair and the research progress of puerarin in treating skin diseases. With the in-depth study of skin wound repair and treatment, the mechanism of skin wound repair is gradually clear, which also provides many new hopes for clinical treatment of skin trauma. At present, many treatment methods are mainly carried out around the skin wound healing mechanism. In different periods of skin trauma, treatment plans are formulated according to the body's own repair mechanism. Therefore, a large number of skin drugs and treatments are mostly started from the repair mechanism, such as the regulation of cytokines, gene therapy, etc., and have achieved good clinical efficacy. However, the repair mechanism of skin wound is not completely clear at present, and the skin wound is still unable to heal without scar. Therefore, there is still a lot of research work to continue in the field of clinical treatment of skin trauma repair.

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