

New Developments in the Mechanism of Action of Pomegranate Peel Polyphenols

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Abstract: Pomegranate Peel Polyphenols are a kind of polyphenolic hydroxyl compounds mainly found in pomegranate peel, whose components include nine compounds including amphiregulin, gallic acid, ellagic acid, epicatechin, kaempferol, caffeic acid and quercetin. The results of numerous studies show that pomegranate peel polyphenols have various biological functions such as antioxidant, antibacterial, anti-inflammatory and anti-tumor. And in recent years, the application of pomegranate peel polyphenols in oral cavity, especially in the treatment of periodontitis, has become a research hotspot. Therefore, this paper reviews the research on the function and application value of pomegranate peel polyphenols in the treatment of systemic and periodontitis by domestic and foreign scholars in recent years, which provides some reference value for the further development and utilization of pomegranate peel polyphenols.

Keywords: Pomegranate peel polyphenols; Antioxidant; Anti-inflammatory; Antibacterial; Periodontitis

1. Introduction

Pomegranate (*Punica granatum* L.) belongs to the genus *Punica* (*Punica* L.), a deciduous shrub or small tree of the family Punicaceae, native to Iran, Afghanistan, and other Central Asian regions, is highly adaptable and widely cultivated in tropical and subtropical regions [1]. Pomegranate is a medicinal and edible plant, mostly fresh, which is not only nutritious but also an important herbal medicine in the pharmacopoeia of the ages, and modern scientific studies have also confirmed that pomegranate fruits have potent effects in antioxidant, anti-inflammatory and antibacterial properties. These effects may come from the polyphenols in the fruit [2-3]. All parts of the pomegranate fruit, including the peel, pulp, and seeds, contain some amount of polyphenols, with the peel being the most abundant [4-5]. However, pomegranate peel is often wasted because it is inedible and accounts for 40% of pomegranates [6]. Some studies have reported that pomegranate peel has special medicinal and nutritional value, and 48 phenolic compounds are known to be identified in pomegranate peel [7-8]. Therefore, the study of the bioactivity of pomegranate peel polyphenols in the treatment of systemic and periodontitis is of theoretical importance and practical application for the exploitation of this biological resource.

2. Mechanism of action of Pomegranate Peel Polyphenols

2.1 Antioxidant properties of Pomegranate Peel Polyphenols

Oxidative stress is a state in which there is an imbalance between oxidative and antioxidant effects in the body, tending towards oxidation, leading to inflammatory infiltration of neutrophils, increased secretion of proteases and production of large amounts of oxidative intermediates. Oxidative stress is a negative effect of free radicals in the body and is considered to be an important factor contributing to aging and disease [9]. And several clinical studies and epidemiological data show that oxidative stress is an important determinant in the development of chronic inflammation and many diseases [9-10], while epidemiological studies show that antioxidants play an important role in protecting the body from oxidative damage, and therefore fruits and vegetables are recommended for their high content of antioxidants [11]. Because these effects are derived from a variety of compounds in them, such as

phenolics. Therefore, the extraction of these active ingredients from medicinal plants has received great attention in recent years, and the high content of polyphenols in pomegranate peel extracts has become a hot topic of research.

Several studies have shown that pomegranate peel extract contains a variety of compounds with strong antioxidant capacity. Among them, tannins, flavonoids and phenolic acids contribute the most to its antioxidant capacity. These compounds exhibit their antioxidant activity through scavenging or neutralizing free radicals, metal chelation, affecting cell signaling pathways and regulating gene expression in various ways [12-14]. Moreover, the polyphenol content and antioxidant properties among pomegranate peels are more potent compared to its fruit and juice [15]. Les et al. showed that ellagic acid found in pomegranate peel polyphenols, among others, has potent antioxidant activity, decreases oxidative or inflammatory stress, increases protective signaling, and inhibits lipase, α -glucosidase, and dipeptidyl peptidase-4 in a dose-dependent manner [16].

2.2 Antibacterial activity of Pomegranate Peel Polyphenols

Diseases caused by pathogenic infections continue to be a major problem worldwide, so it is necessary to find new ways to control the growth of pathogenic microorganisms and fight infections through different strategies, including the use of new antimicrobial sources, such as plant extracts, which are also an effective way to combine modern medicine with traditional treatments [17]. Among the studies by Gullon [18] et al, pomegranate peel polyphenols had a *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Salmonella* with better antibacterial effect. In another study by Rosas-Burgos et al. showed strong antibacterial activity of pomegranate peel polyphenols against *Salmonella enterica*, *Shigella*, *E. coli* and *E. coli* [19]. Rummun et al. confirmed that the polyphenols in pomegranate peel showed higher antibacterial activity against *Salmonella* and *Staphylococcus* than the flower, leaf and stem extracts [20]. In addition to this Elbatany et al. found that different extraction methods of pomegranate peel polyphenols had different minimum inhibitory concentrations against bacteria such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* [21]. This study from the perspective of extraction methods also provides us with different research ideas.

2.3 Anti-inflammatory activity of Pomegranate Peel Polyphenols

An in vitro study showed that pomegranate peel polyphenols inhibited both cyclooxygenase and lipoxygenase. Cyclooxygenase, also known as prostaglandin endooxygenase reductase, is a key enzyme in the conversion of arachidonic acid to prostaglandins, which in turn are important mediators of inflammation. Lipoxygenase catalyzes the conversion of arachidonic acid to leukotrienes, which is also a key mediator of inflammation [22]. In another study in patients with osteoarthritis, pomegranate peel polyphenols had a significant and widespread inhibitory effect on matrix metalloproteinases, which show high levels of expression in arthritic joints and are involved in and convert the degradation and catabolism of extracellular joint matrix. In pretreated human femoral OA chondrocytes, pomegranate peel polyphenols inhibited interleukin-1 β (IL-1 β)-induced proteoglycan destruction, matrix metalloproteinase expression at the cellular level, and phosphorylation and activation of mitogen-activated protein kinase, a signal transduction molecule involved in matrix metalloproteinase expression [23].

2.4 Anti-cancer mechanism of Pomegranate Peel Polyphenols

It has been shown that pomegranate peel polyphenols are effective against breast cancer through various pathways such as inhibition of cell migration, upregulation of intercellular adhesion molecule-1 expression, downregulation of vascular endothelial growth factor expression levels, and matrix metalloproteinase-9 [24]. In addition, pomegranate peel polyphenols have been shown to block the propagation of prostate cancer cells DU-145, stimulate apoptosis and inhibit PC-3 cell invasion under in vitro conditions [25]. In a study by Bagheri et al. it was shown that in triple negative breast cancer, different concentrations of pomegranate peel polyphenols achieved inhibition of cell migration and invasion by inducing apoptosis and reducing waveform proteins [26].

2.5 Effect of Pomegranate Peel Polyphenols on diabetes mellitus

The treatment and prevention of diabetes continues to be a hot topic of medical research, and in recent years whether natural drugs can play a role in the prevention and treatment of diabetes has gradually attracted the interest of researchers. Scholars at home and abroad have found through cell culture and

animal studies as well as clinical human studies. A key mechanism by which pomegranate peel polyphenols affect type 2 diabetes is the reduction of oxidative stress and lipid peroxidation. This reduction may be achieved by directly neutralizing generated reactive oxygen species, increasing the activity of certain antioxidant enzymes, inducing metal chelating activity, reducing the formation of resistin, and inhibiting or activating certain transcription factors. Pomegranate peel polyphenols may also significantly reduce fasting blood glucose levels. The known compounds in them, such as pomegranate glucosinolates, ellagic acid, and gallic acid, have been identified to have antidiabetic effects [27]. A study in male rats showed that administration of pomegranate peel polyphenols reduced serum glucose concentrations as well as lipid peroxide concentrations in heart, liver, and kidney tissues [28]. Pomegranate peel polyphenols treated with tetraoxypyrimidine-induced diabetic rats for 10 days reduced fasting blood glucose, increased insulin levels, and anti-lipid peroxidation [29].

2.6 Pomegranate Peel Polyphenols in Alzheimer's disease

It has been shown that the neuroprotective properties of pomegranate peel polyphenols were evaluated in an animal model of Alzheimer's disease. Transgenic mice with Alzheimer's disease-like lesions treated with pomegranate peel polyphenols showed a 50% reduction in soluble β -amyloid accumulation and a reduction in hippocampal amyloid deposition compared to mice consuming sugar water, suggesting that pomegranate peel polyphenols may have neuroprotective effects. The animals also showed improvements in learning the water maze task and swam faster than control animals [30].

3. Application of Pomegranate Peel Polyphenols in the treatment of periodontitis

As a chronic infectious disease, periodontitis has been plaguing the work and life of patients, non-surgical treatment is the key to periodontitis treatment, excluding mechanical scraping, medication is also an important adjunct to treatment. The most common type of medication is antibacterial drugs, but in recent years, the prolonged use of large doses of antibacterial drugs can lead to dysbiosis, drug resistance and other adverse reactions, affecting the effectiveness of drug therapy. Therefore, the research of natural drugs has become a hot topic again, among which pomegranate peel polyphenols have been favored by researchers for their significant antioxidant, antibacterial and anti-inflammatory activities.

Bhadbhade et al. in a study showed that mouthwash made from pomegranate peel polyphenols inhibited the growth of periodontal pathogens such as *Actinobacillus aggregates*, *Prevotella intermedia*, and *Porphyromonas gingivalis*. This study also showed that mouthwash made from pomegranate peel polyphenols was more effective in reducing gingival and bleeding scores compared to chlorhexidine mouthwash [31]. In a study by Kote et al. reported that mouthwash made from pomegranate peel polyphenols inhibited plaque forming bacteria by 84% compared to chlorhexidine mouthwash. Thus, pomegranate peel polyphenols may be an alternative to antibacterial drugs to prevent plaque formation on dental surfaces. In addition to its properties in antibacterial activity, pomegranate peel polyphenols can also be useful in the treatment as well as prevention of periodontitis through its antiviral activity. Pomegranate peel polyphenols have been shown to be effective against herpes viruses [32]. Since herpes viruses may stimulate the release of cytokines from host cells, compromise host defense mechanisms and lead to increased virulence of resident periodontal bacteria, they may trigger and accelerate the progression of periodontitis [33]. Thus, the antiviral properties of pomegranate may also treat periodontitis. A study by El Sherbini et al. concluded that pomegranate peel polyphenols have a significant effect on *Trichoderma reesei* and may be used to treat acute ulcerative gingivitis [34]. Through its anti-inflammatory properties, pomegranate peel polyphenols can significantly inhibit matrix metalloproteinase expression, prostaglandin E2 production and interleukin-1 (IL-1B) induction, thus achieving the prevention and control of periodontal tissue destruction [35]. In their study, Pereira et al. showed a significant reduction in gingival bleeding after the use of gels made from pomegranate peel polyphenols and also demonstrated in their study that pomegranate peel polyphenols inhibit gingival bleeding by In the study, it was also demonstrated that pomegranate peel polyphenols inhibited IL-6 and IL-8 expression by regulating NF- κ B activation and DNA binding activity. Therefore, the good anti-inflammatory properties of pomegranate peel polyphenols can be used to treat gingivitis and periodontitis. In a study in Thailand, researchers placed pomegranate peel polyphenols to make gels into the pockets of 20 patients with periodontitis with periodontal pockets of 5-8 mm for observation, and clinical indicators such as probe depth, attachment level, and percentage of bleeding from the probe were significantly improved at three and six months compared to baseline, and inflammatory markers IL-1 β and IL-6 were measured in 15 of these patients, again and compared to baseline examination, IL-1 β and IL-6 were significantly decreased at three and six months compared to baseline [36-37].

4. Conclusions

Pomegranate Peel Polyphenols, as polyphenols extracted from pomegranate peel, have been widely studied for their advantages of wide source and easy extraction. It has also been observed and studied in the treatment of systemic diseases with antioxidant, anti-inflammatory and antibacterial properties, but less in the treatment and prevention of periodontitis in comparison. The few existing studies are also mainly clinical studies, lacking more in vitro bacterial and cellular experiments to reveal the mechanism in the treatment of periodontitis. The association of periodontitis with systemic diseases such as cardiovascular diseases, diabetes, rheumatoid arthritis, respiratory and digestive diseases has been the focus of research. Periodontitis has been identified as the sixth major complication of diabetes and both show a bidirectional effect. At the same time, pomegranate peel polyphenols have so many biological properties that it makes us wonder if pomegranate peel polyphenols could be better in patients with systemic diseases associated with periodontitis. This may be a direction for further research on pomegranate peel polyphenols in the future.

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