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Phytochemicals of *Punica granatum* L. in inflammatory bowel diseases: an update

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Abstract: *Punica granatum* L., known as pomegranate, is used culturally in folk medicine for its antiinflammatory activity. Its mechanisms are derived from its bioactive compounds, predominantly polyphenols and, according to their structural arrangement, corroborate the prophylaxis of diseases such as Inflammatory Bowel Diseases (IBD). The present study aims to highlight the polyphenols present in *Punica granatum* L., as well as their positive effects in the context of inflammatory bowel diseases. The methodology was based on an analytical reading of materials already elaborated in the years 2009 to 2018, using descriptors such as: pomegranate, anti-inflammatory activity and secondary metabolites. Polyphenolic compounds isolated from fruits of *Punica granatum* L. present several pharmacological activities. Urolithine-A reduced inflammation by inhibiting the synthesis of PGE₂, attenuated oxidative stress, which is a stimulator of ERK1 / 2, also inhibited by Ellagitannins. Cyanidin represses IL-8, iNOS, COX-2 and NF-κB, Gallic Acid inhibited ROS and STAT3. TNF-α targets Punicalagin, Punic Acid and Ellagic Acid, as well as interleukins IL-1b, IL-6, perform the progression of homeostasis in IBD. Ellagic Acid, in an acute model of ulcerative colitis, improved the severity of the disease through the profile of inflammatory mediators (IL-6, TNF-α and IFN-γ). In addition, mediators such as COX-2 and iNOS were repressed and the p38, MAPK, NF-κB and STAT3 signaling pathways were blocked. The mechanisms of action of pomegranate extracts are predominantly due to Ellagic Acid. However, the synergistic action of the constituents of the pomegranate makes it therapeutically beneficial. Inflammation is closely related to oxidative stress and this is the result of the chemical imbalance between antioxidants and pro-oxidants. Functional groups of hydroxyl groups as well as the double bonds of phenolic compounds measured their antioxidant effects by the elimination of free radicals and / or the chelation of metallic ions.

Keywords: Punica granatum L.; Anti-inflammatory activity; Inflammatory Bowel Diseases.

1. Introduction

Punica granatum L., popularly known as pomegranate, is used culturally in popular medicine, because it has anti-inflammatory activity, and this is an effector action evidenced in literature [1]. Its mechanisms as phytotherapies are derived from its bioactive compounds, being predominantly polyphenols, which have been identified 23 different compounds [2]. Polyphenols are secondary metabolites of pomegranate, mainly concentrated in the portion of the fruit peel, such as ellagic acid, which, according to its structural arrangement, corroborates for prophylaxis of diseases [3,4].

2. Results and Discussion

Polyphenolic compounds isolated from fruits of *Punica granatum* L. have several pharmacological activities including anti-inflammatory, hepatoprotective, antigenotoxic and anticoagulant activities [6].

Urolitin-A inhibited the synthesis of prostaglandin E2, reducing inflammation, as well as attenuating the oxidative stress, which is a stimulator of ERK1/2, also inhibited by Ellagitannins, which activates NF- κ B [7,8].

Cyanidin represses the inflammatory stimulus raised by IL-8, iNOS, COX-2 and NF- κ B, as well as Gallic Acid, which inhibits ROS and STAT3 stimuli on NF- κ B activation. TNF- α is the target of compounds such as Punicalagin, Pubic Acid and Ellagic Acid, repressions in mediators such as p-38, histamine, MPO and MCP, as well as interleukins IL-1b, IL-6, perform the progression of homeostasis in IBD [9,10,11,12,13,14,15].

The Ellagic Acid, one of the most predominant components of pomegranate, presented protective and therapeutic effects in the management of Inflammatory Bowel Disease, mediated by negative regulation of cytokines and inflammatory enzymes, increasing antioxidant defense and suppressing inflammatory pathways and their cellular signaling mechanisms [6,16]. Experiments using murine macrophages have shown that the extract of fermented pomegranate residues is able to reduce the proinflammatory expression induced by LPS genes, interleukin IL-1 β , tumor necrosis

factor alpha (TNF- α) and inducible nitric oxide synthase (iNOS) [17].

Among these, we highlight Inflammatory Bowel Diseases (IBD), a conglomeration of diseases characterized by chronic inflammation, mucosal ulceration, gastrointestinal tract (GIT) edema and hemorrhage, its debilitating condition affects about 70,000 people each year and has been described as "a disease without known cure". In addition, its pathophysiology increases the risk of developing colon cancer [5].

Therefore, the present study aims to highlight the polyphenols present in *Punica granatum* L., as well as its positive effects in the context of inflammatory bowel diseases.

Another study reported that in the acute model of ulcerative colitis, Ellagic Acid improved the severity of the disease in a discrete way, both macroscopically and through the profile of inflammatory mediators (IL-6, TNF- α and IFN- γ).

In the chronic UC model, it significantly inhibited the progression of the disease, reducing inflammation. In addition, mediators such as COX-2 and iNOS were repressed and the p38, MAPK, NF- κ B and STAT3 signaling pathways were blocked [18-19]. A histopathological analysis revealed that the lesions of the small intestine of mice were attenuated when treated with the ethyl acetate fraction, composed of Ellagic Acid and other phenolics. It had significant antidiarrheal activity [20].

Ellagic Acid acts by modifying, negatively, the gene expression related to inflammation. Inflammatory bowel diseases are characterized by autoimmune and inflammatory complications of the large intestine (ulcerative colitis) and other parts of the digestive tract (Crohn's disease) [21]. Ellagic Acid has shown a beneficial effect against intestinal inflammation by reducing the expression of inflammatory mediators and by blocking / inhibiting signaling pathways.

In addition, polyphenol contains antioxidant action, responsible for many of its pharmacological activities, which reduces

oxidative stress, lipid profile and metabolism [22].

The mechanisms of action of pomegranate extracts in inflammatory diseases

3. Materials and Methods

From an analytical reading of materials already elaborated within the years of 2009 to 2018. Using descriptors such as, pomegranate,

4. Conclusions

Experimental investigations have concluded that phenolic radicals can be stabilized by establishing intramolecular hydrogen bonds and delocalization and prolonged conjugation, with the structure-activity relationship of these compounds being exploited in aqueous media [23]. Inflammation is closely related to oxidative

are applicable to inflammatory bowel diseases, predominantly due to ellagic acid. However, the synergistic action of the constituents of the pomegranate makes it therapeutically beneficial.

anti-inflammatory activity and polyphenols, searched the PubMed and Google Scholar database, totalizing 25 articles.

stress and this is the result of the chemical imbalance between antioxidants and pro-oxidants [24]. Functional groups such as hydroxyls, as well as double bonds of phenolic compounds mediated their antioxidant effects by the elimination of free radicals and / or the chelation of metallic ions [25].

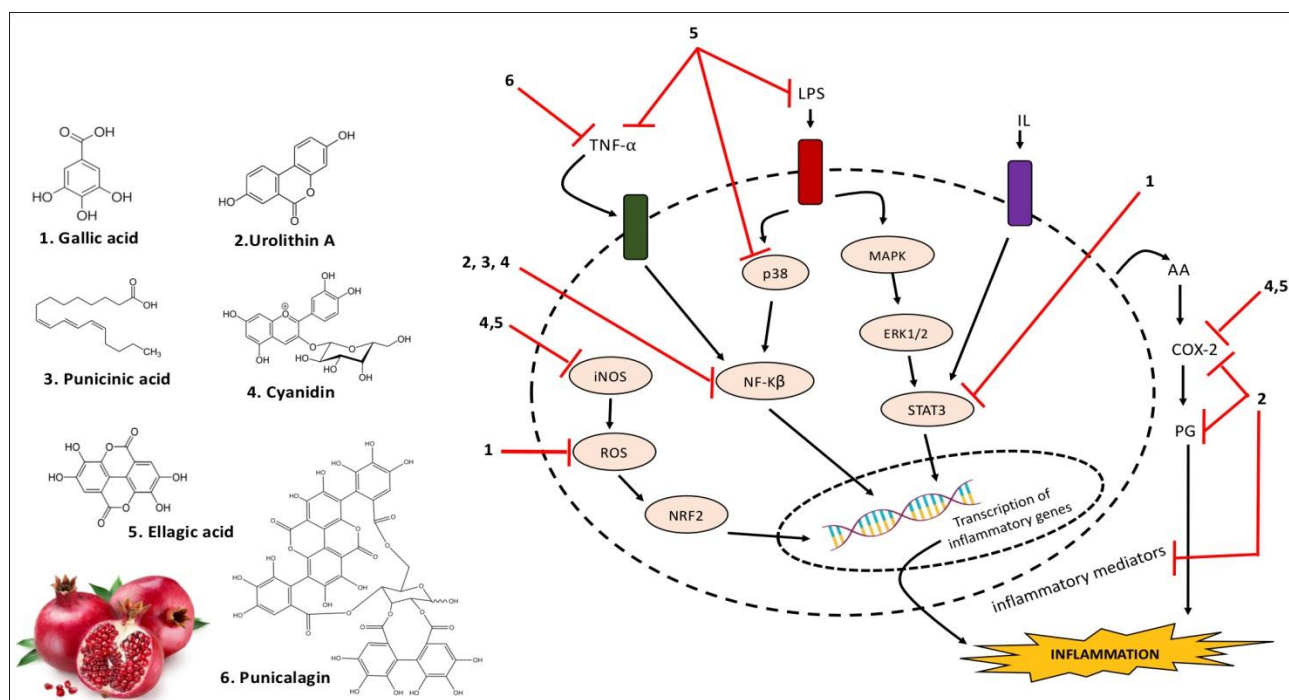


Figure 1. Mechanisms of activity of the phytochemicals of *Punica granatum* L.

Conflicts of Interest

The authors declare no conflict of interest.

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