


DOI 10.36074/grail-of-science.12.05.2023.109

BIOLOGICAL ACTIVE SUBSTANCES OF NATURAL ORIGIN AND RHEUMATOID ARTHRITIS, PREVENTION OR TREATMENT?

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According to population-based studies, the global prevalence of RA between 1980 and 2019 was 460 per 100,000 population. Trend analysis showed that RA was observed more in developed countries than developing countries (Almutairi, 2020, pp. 863-877). Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the symptomatic treatment options for RA. However, these medications are known to have multiple adverse effects including nephrotoxicity, gastrointestinal bleeding and ulceration, increasing blood pressure and the risk of first hospitalization due to congestive heart failure. Conventional disease modifying anti-rheumatic drugs (DMARDs) are usually the first choice to diminish disability and improve long-term outcomes for people with RA. Biologics are much more costly than other subsets of DMARDs, they are commonly used as partial responders to traditional DMARDs. Although the combination of biologics and traditional DMARDs has demonstrated improved efficacy, the potential benefits and harms (such as cancer and infections) are still controversial. However, in spite of applying aggressive pharmacologic treatment regimens early in disease onset, complete clinical remission is not achieved (Guo et al., 2018, p.15). Although biological medications seem to effectively target molecular pathways involved in the inflammatory process of RA, there is a lack of long-term safety data regarding their use. Various investigations have demonstrated an increased prevalence in the use of herbal medicine in developing countries. Interestingly, a rise in the prevalence of herbs used as complementary and alternative medicine among chronic disease patients has been reported in recent years. The anti-inflammatory properties of some herbal products are well-known and they have fewer unwanted effects than existing anti-inflammatory medications. As such, herbs and their derivatives constitute a promising arena in novel medical therapies. Furthermore, the cost-effectiveness of natural products has been explored and summarized by high quality studies. Certain phytochemicals are

considered to inhibit the release of inflammatory molecules to suppress inflammatory responses (Gandhi et al., 2022, pp.1-15). is the precursor of ellagitannin and has been reported to be the most active polyphenol obtained from different parts of the pomegranate tree (*Punica granatum* Linn.). Methanolic (and ethanolic) pomegranate peels extract contains a high amount of bioactive compounds including punicalagin (10-50 mg/g) (Xu et al., 2021, pp.1-12). Historically, seeds and juices are believed to have been taken as supplements to reduce the clinical symptoms of RA (Singh, Singh, & Mahajan, 2020, pp. 1306-1327). Marques and coauthors (2016) have already revealed that Punicalagin diminished TNF α and interleukin (IL) 6 secretion in macrophages and primary human chondrocytes with lipopolysaccharide (LPS)-induced inflamed RAW264.7. (Marques et al., 2016, pp- 463-1467). Anthocyanins have been shown to represent potent anti-inflammatory, anti-oxidant, anti-cancer, anti-obesity and immunomodulatory activity. (Salehi et al., 2020, pp.1-20). Min and coauthors (2015) reported inhibitory effect of ACNs on osteoclasts via the downregulation of cytokines including IL-1, IL-6, IL-17, and TNF- α in vitro. the study showed EA reduced cartilage destruction, synovial hyperplasia and bone erosion generated by Freund's adjuvant. Significant suppression of caspase-3 expression in models treated with EA testifies to the anti-apoptotic property of this biologic compound (Fikry, Gad, & Eid, 2019, pp. 878–886).

The established origin of many modern medications in ethnobotanical remedies testifies to the important role of phyto-compounds not only in traditional but conventional medicine. Increasingly, studies are investigating the role of herbal medicine in treating autoimmune disorders (e.g., multiple sclerosis, Crohn's disease, ulcerative colitis, atopic dermatitis, and RA). Preliminary results from many recent studies have shown the effect of immunomodulatory plants on the immune system as immunostimulants and/or immunosuppressors. However, regarding the immunomodulatory power of some bioactive compounds, the result of clinical studies differs from those in experimental models. Thus, the lack of reliable data in clinical studies is the main limitation for supporting experimental evidence. The incompatible anti-inflammatory or proinflammatory properties of these bioactive constituents in different autoimmune disorders further necessitates more supportive clinical trials (Di Sotto, Vitalone & Di Giacomo 2020, p.468).

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