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Chamomile an Adjunctive Herbal Remedy for Rheumatoid Arthritis Treatment

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Abstract

One of the most frequently consumed herbal remedies available today is the chamomile preparations prepared from Matricaria chamomilla (MC). The medicinal preparations of MC are composed of several classes of biological active compounds with inhibitory effects on inflammation including essential oil and flavonoids. Apigenin, quercetin and luteolin are the major flavonoids of MC which exhibit their anti-inflammatory effects through different mechanisms. Apigenin exhibits anti-inflammatory activity via inhibition of proinflammatory cytokines production, whilst luteolin suppresses production of nitric oxide (NO), prostaglandin E2 and expression of inducible NO synthase and cyclooxygenase-2 all of which are associated with inflammatory responses. However, there are also some additional components of the MC preparations which have a role on the anti-inflammatory actions of the plant through other pathways. The mentioned mechanisms are in reference with the authors' concept that MC would be of value in alleviating inflammation and pain in rheumatoid arthritis.

Keywords: Essential oil; flavonoids; Matricaria chamomilla; polyphenols; rheumatoid arthritis

1. Introduction

Not surprisingly, the wide range of herbal medicines available today has been brought about by one of the most significant ancient heritages, the sophisticated experience of people who have tried over millennia to find useful plants for health improvement, with each generation adding its own experience to this tradition. Following on from scientific advancements, in a time of increased considerations to natural products as a safe herbal remedies, it is as important as ever to gather detailed documentations of the latter in

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every aspect. Compositae family has been holding a place of value for hundreds of years due to the infusions and tinctures of numerous medicinal plants used as components of herbal treatments for a variety of ailments. Considering the endemism and diversity of the species used in traditional and folk medicine in Iran, *Matricaria* a genus of different species of flowering plants in this family has a widespread usage by different cultures and also a high reputation in herbal medicine by several known healing attributes. Chamomile is widely represented by two known varieties viz. Roman chamomile (Chamaemelum nobile) and German chamomile (*Matricaria chamomilla*). The common variety used for medicinal purposes is MC. Chamomile holding a high reputation among herbal medicines during the history due to its anti-inflammatory, analgesic, antimicrobial, antispasmodic and sedative properties (1,2).

The flowering parts of chamomile could be used both externally and internally to alleviate, even cure a range of disorders, particularly those involving an inflammatory condition (2). The merit of the traditional use of MC has been supported by the isolation and identification of several biologically active chemicals including polyphenols (flavonoids) and essential oil extracted from chamomile flowers (1). The latter mainly consist of terpenoids and azulenes (including chamazulene and en-yne dicolo ether) (3). It has been shown that terpenoids, bisabolol and chamazulene possess anti-inflammatory properties (2). Chamazulene strongly suppresses the formation of leukotriene B_4 (LTB_4) in the neutrophilic granulocytes (4). It also inhibits lipid peroxidation, via antioxidant activity (5). Moreover, chamazulene blocks peroxidation of arachidonic acid (AA) causing a reduction in inflammatory mediators that are derived from arachidonic acid. A number of literatures have been published on the identification of the phenolic compounds of MC including apigenin, quercetin, and luteolin (6,7). Some reports suggest that flavonoids play an important role in inflammatory processes and immune functions through inhibition of several enzymes which are activated during certain inflammatory conditions (7,8). For instance, luteolin, a member of the flavone type flavonoids displays specific anti-inflammatory activities such as activation of anti-oxidative enzymes, suppression of the nuclear factor Kappa B (NF-κB) pathway, inhibition of pro-inflammatory substances, and reduction in the enhanced vascular permeability (9). Apigenin, another flavone in the MC, that is non-toxic, non-mutagenic, and a potent antioxidant, effectively blocks intercellular adhesion molecule-1 up-regulation, leukocyte adhesion in response to cytokines, suppress COX-2 expression, and is a potential apoptosis inducer (10). The pharmacolgical properties of MC made it increasingly popular in the form of tea which is consumed at a rate of over one million cups per day in the world (11).

2. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by the accumulation and persistence of an inflammatory infiltrate in the synovial membrane that leads to synovitis (12). In addition, a progressive destruction of the joint architecture resulting in an impaired function is associated with proliferation of the synovial cells and infiltration of activated immune inflammatory cells. Following on from recent advancements, in a time of increased considerations to the inflammatory diseases, it is as important as ever to study different aspects and treatments of autoimmune disorder, RA. As a systemic disease, RA has extra manifestations in systems such as the pulmonary, ocular, vascular, and other organs that may be affected by the inflammatory process. There is an accumulation of inflammatory cells (T and B lymphocytes, neutrophils, and monocytes), tissue edema,

endothelial cell proliferation, and matrix degradation (13,14). Although the etiology of RA is basically unknown, numerous studies have implicated that RA is mostly modified by systemic, genetic, and environmental variables. Factors such as infections and smoking lead to defects in immune regulation and also a host of inflammatory mechanisms involved in joint tissue damage include a role for oxidative stress (15). In general, an imbalance between oxidants and anti-oxidants in support of the oxidants, bring about an interruption of redox signaling and molecular damage which is called oxidative stress (14).

Several sources of reactive oxygen species (ROS), as oxidants, in the synovial joint, include free radicals liberated by activated phagocytic cells at the site of inflammation (16). As follows, free radicals especially ROS have been considered as mediators of accelerated joint damage and osteoclast activation in RA, in combination with proinflammatory cytokines (17-19). Furthermore, ROS degrade synovial fluid and depolymerize hyaluronic acid, leading to a loss of viscosity in the joint, inactivation of anti-proteinases and induction of bone resorption (20).

Other features of oxidative stress in RA synovial fluid lymphocytes is manifested by NF-κB–dependent gene transcription, initiating the up-regulation of tumor necrosis factor α (TNF-α) and interleukin (IL)-1β (16). A number of cytokines, such as TNF-α, IL-1β, IL-6, IL-8, IL-12, IL-17, IL-18, IL-23 and IFN-γ are considered to have a role in the continuance of chronic inflammatory process in the inflated joints. The known inflammatory mediators of TNF-α and IL-1β are the initiators of the NF-κB activation cascade and are under its transcriptional control (14). Additionally, in response to different stimulant factors, TNF-α and IL-1β that are released from the inflammatory cells activate the fibroblast-like synovial cells.

Like other inflammatory cells, fibroblast-like synovial cells stimulate COX-2 expression and PGE_2 production (21). Moreover, the TNF-α and IL-1β, present in synovial fluid of RA patients, have shown to have a role in COX-2 induction and PGE_2 production, as well (22). Likewise, in view of the fact that the lipid mediator PGE_2 is found at a high level in the synovial fluid of RA patients, is thought to be a key prostaglandin species working in RA pathogenesis (21).

Eventually, owing to the fact that RA affects about 0.5 to 1% of adults which is associated with increased morbidity and mortality worldwide, it seems important to have a deeper insight into RA as a result of an imbalance between pro-inflammatory and anti-inflammatory cytokines to develop newer treatment strategies for RA.

3. Hypothesis

A great body of literature has been documenting the role of inflammation in the initiation and development of several pathological disorders, as discussed above. Steroidal anti-inflammatory drugs (corticosteroids) and non steroidal anti-inflammatory drugs (NSAIDs) have a long and illustrious history in managing acute and chronic inflammations. Nevertheless, they have not been entirely successful in the treatment of inflammatory disorders, as one of the major issues that have restricted the application of these medications in this regard, are their undesirable side effects (e.g. osteoporosis and peptic ulcer). Consequently, there is a necessity to seek for safer anti-inflammatory compounds (23).

In the search for anti-inflammatory agents, alternative strategies such as natural products are becoming more popular and being used extensively by a large number of people. Natural products are being ever more investigated for their biological activity to confirm their role in the prevention and treatment of inflammatory diseases. As an alternative therapy, extracts of plants have

traditionally been a rich source of medicinal compounds for the treatment of a wide variety of disorders including acute and chronic inflammatory ones (24,25).

The MC is one of the most popular single ingredient herbal teas, or tisanes (1). Traditionally, flowering parts of MC have been used both internally and externally to alleviate and even to cure several disorders, particularly those related to inflammatory processes (2). The authors would like to postulate a role for MC as a pain reliever in RA which could be attributed to its flavonoids and essential oil. Apigein, lutelin, and quercetin are the main flavonoids in the MC extract. Nicholas et al. have shown that apigeinin produces anti-inflammatory effects by inactivation of NF-κB pathway through suppression of p65 phosphorylation which in turn blocks the expression of pro-inflammatory cytokines, like interleukin IL 1β, 6 and TNF-α in human monocytes (26). This effect regulates prostaglandin and NO production and suppresses inflammation (13). In rheumatoid arthritis, synovial T cells are highly differentiated and express a phenotype susceptible to apoptosis (27). Fortunately, apigenin is an apoptosis inducer in human leukemic cells and human hepatoblastoma derived cell line Hep G2 (28,29). Besides, luteolin, as a natural antioxidant, displays excellent free radical scavenging activity and cytoprotective properties. Also luteolin produces anti-inflammatory effects by activation of antioxidative enzymes, suppression of the NF-κB pathway and inhibition of pro-inflammatory substances. Furthermore, luteolin is effective in diminution of inflammation through reduction of enhanced vascular permeability (9,30). Luteolin and quercetin also suppress production of NO and PGE_2 as well as the expression of iNOS, COX-2, TNF-α and IL-6 via blocking NF-κB activation pathway (29,31). In addition, it has been reported that quercetin is a potent inhibitor of human 5-Lipoxygenase (5-LPO) (29). Free radical reactions are implicated in numerous pathophysiological conditions like RA. Chamazulene, the active substance of chamomile, inhibits lipid peroxidation via its antioxidant activity and blocks chemical peroxidation of AA and consequent inflammation. Additionally, chamazulene inhibits the formation of LTB_4 in neutrophilic granulocytes (4,5). Another constituent of the MC essential oil, En-yne dicycloether, could inhibit degranulation of mast cells to prevent histamine release and vasodilation (32).

Based on the previous studies and our proposed hypotheses, principle anti-inflammatory mechanisms of MC have been summarized in Table 1. Accordingly, two foremost mechanisms could be described for the efficacy of MC compounds in RA pain relief. The first mechanism is the prevention of NF-κB activation and suppression of iNOS and COX-2 gene expression via apigenin and luteolin. The next one is the antioxidant activity of apigenin, luteolin and chamazulene which prevent lipid peroxidation of AA and subsequent production of inflammatory substances. Moreover, inhibition of vasodilatation and induction of apoptosis might be important mechanisms in anti-inflammatory effects of MC in RA.

In view of these aspects, natural products, particularly higher plant species, continue to be important sources of medicinal and supplementary health products which represent a challenge to science due to their various properties including chemical diversity, synergism to biological activity, and variable compositions. Correspondingly, the mechanisms mentioned above interfere with major inflammation pathways of RA and support our hypothesis that herbal preparations of MC would be of beneficial in alleviating rheumatic pains. Concisely, this issue furnishes background for the experiments on the associated basic studies for the *Matricaria chamomilla* to confirm the therapeutic

potential of this plant in RA.

Conflicts of interest

The authors declare that they have no conflict of interest.

Compound	Mechanism	Reference
Apigenin	Modulation of NF-κB, IL-6 level reduction, antioxidant activity, iNOS and COX-2 gene expression suppression, apoptosis induction, 5-LPO inhibition	10,26,28,33,34
Luteolin	Modulation of NF-κB, vasodilation inhibitor, antioxidant activity, iNOS and COX-2 gene expression suppression, apoptosis induction, 5-LPO inhibition	9,31,34
En-yne dicycloether	Vasodilation inhibitor	32
Chamazulene	Inhibition of LTB_4 formation, antioxidant activity	4,5
Quercetin	Modulation of NF-κB, iNOS and COX-2 gene expression suppression, apoptosis induction, 5-LPO inhibition, IL-6 level reduction	29,33,34

Table 1: Main anti-inflammatory mechanisms of Matricaria chamomilla

NF-κB, nuclear factor Kappa B; IL, interleukin; iNOS, inducible nitric oxide synthase; COX-2, cyclooxigenase-2; 5-LPO, 5-Lipoxygenase; LTB_4, leukotriene B_4

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