Review

Chamomile: An ancient pain remedy and a modern gout relief - A hypothesis

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Matricaria chamomilla (MC) is a well-known medicinal plant. In the present paper, the researchers intended to focus on the possible anti-inflammatory pharmacological mechanisms of MC preparations in the treatment of gouty arthritis and the constituents of MC responsible for its effects. The medicinal preparations of MC are composed of several classes of biologically active compounds with an inhibitory effect on inflammation including essential oils and flavonoids. Apigenin, quercetin and luteolin are flavonoids, which exhibit their anti-inflammatory effects via different mechanisms. Apigenin exhibits anti-inflammatory activity via inhibition of proinflammatory cytokines production. Luteolin suppresses production of nitric oxide (NO), prostaglandin E2 and expression of inducible NO synthase (iNOS) and cyclooxygenase-2 – which are all associated with inflammatory responses. In addition, Luteolin along with quercetin, inhibit xanthine oxidase (XO) enzyme. There are also additional components of the MC preparations which play a role in its anti-inflammatory action via other pathways. The mentioned mechanisms are in accordance with the authors’s concept that MC can alleviate inflammation in gouty arthritis.

Key words: Matricaria chamomilla, gout, inflammation, essential oils, flavonoids.

INTRODUCTION

Chamomile has a widespread usage and holds a high reputation among herbal medicines during the history due to its anti-inflammatory, analgesic, antimicrobial, antispasmodic and sedative properties (McKay and Blumberg, 2006; Gardiner, 2007). The chamomile belongs to the family compositae (Asteraceae) and in folk medicine its aqueous infusion and tea preparations are used. Chamomile is widely represented by two known varieties viz. Roman chamomile (Chamaemelum nobile L.) and German chamomile (Matricaria chamomilla). The common variety used for medicinal purposes is Matricaria chamomilla (MC). The flowering parts of chamomile can be used both externally and internally to alleviate, even cure a range of disorders, particularly those involving an inflammatory condition (Gardiner, 2007). 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 oils extracted from chamomile flowers (McKay and Blumberg, 2006). The latter mainly consist of terpenoids and azulenes (including chamazulene and enyne diol ether) (Ganzera et al., 2006). It has been shown that terpenoids, bisabolol and chamazulene possess anti-inflammatory properties (Gardiner, 2007). Chamazulene strongly suppresses the formation of leukotriene B4 in the neutrophilic...
granulocytes (Safayhi et al., 1994). It also inhibits lipid peroxidation, via antioxidant activity (Rekka et al., 1996). Furthermore, chamazulene blocks peroxidation of arachidonic acid causing a reduction in inflammatory mediators that are derived from arachidonic acid. A number of papers have been published on the identification of the phenolic compounds of MC including apigenin, quercetin, and luteolin (Avalone et al., 2000; Svehliková et al., 2004). 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 (Avalone et al., 2000). For instance, luteolin, a member of the flavone (subclass of flavonoids) displays specific anti-inflammatory activities such as activation of antioxidative enzymes, suppression of the nuclear factor KappaB (NF-κB) pathway, inhibition of pro-inflammatory substances, and reduction in the enhanced vascular permeability (Seelinger et al., 2008). 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 cyclooxygenase-2 expression, and is a potential apoptosis inducer (Lee et al., 2007). The pharmacologic 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 (Srivastava and Gupta, 2009).

**HYPOTHESIS**

There are a lot of literatures documenting the role of inflammation in the initiation and development of several pathological disturbances, as discussed above. Steroidal anti-inflammatory drugs (corticosteroids) and non steroidal anti-inflammatory drugs (NSAIDs) have a long and illustrious history in handling acute and chronic inflammations. Nevertheless, they have not been entirely successful in curing inflammatory disorders, as one of the major issues that have restricted the application of these medications in treatment of inflammatory disorders is their undesirable side effects (for example, abdominal pain and peptic ulcer). Consequently, there is a necessity to seek for safer anti-inflammatory compounds (Yoon and Baek, 2005).

In the search for anti-inflammatory agents, alternative strategies such as natural products are becoming more popular and are being practiced extensively by a large number of people. These natural products are increasingly being investigated for their biological activity to confirm their role in the prevention and treatment of inflammatory diseases. In vitro and In vivo studies show that natural products have good anti-inflammatory effects (Sy et al., 2009; Bedi et al., 2010; Mwale and Masica, 2010; Nkomo et al., 2010; Saraiva et al., 2011). As an alternative therapy, extracts of plants have traditionally been a rich source of medicinal compounds for the treatment of a wide range of disorders including acute and chronic inflammation (Robak and Gryglewski, 1996; Russo et al., 2000).

The MC is one of the most popular single ingredient herbal teas, or tisanes (McKay and Blumberg, 2006). Traditionally, flowering parts of MC are used both...
Table 1. Main anti-inflammatory mechanisms of MC.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Compound</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Modulation of NF-κB</td>
<td>Apigenin</td>
<td>Nicholas et al. (2007)</td>
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<td></td>
<td>Luteolin</td>
<td>Chen et al. (2007)</td>
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<tr>
<td>XO inhibitor</td>
<td>Luteolin</td>
<td>Seelinger et al. (2008)</td>
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<tr>
<td>Vascular dilation inhibitor</td>
<td>Luteolin</td>
<td>Miller et al. (1996)</td>
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<td></td>
<td>En-yne dicycloether</td>
<td>Safayhi et al. (1994)</td>
</tr>
<tr>
<td>LTB4 blocker</td>
<td>Chamazulene</td>
<td>Marian K et al. (1996)</td>
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<tr>
<td>Antioxidant activity</td>
<td>Apigenin</td>
<td>Rekka et al. (1996)</td>
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<td></td>
<td>Luteolin</td>
<td>Marian K et al. (1996)</td>
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<tr>
<td></td>
<td>Chamazulene</td>
<td>Marian K et al. (1996)</td>
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<tr>
<td>Suppresses gene expression of iNOS and COX-2</td>
<td>Apigenin</td>
<td>Nicholas et al. (2007)</td>
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<tr>
<td></td>
<td>Luteolin</td>
<td>Chen et al. (2007)</td>
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<tr>
<td>Apoptosis inducer</td>
<td>Apigenin</td>
<td>Marian K et al. (1996)</td>
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</tbody>
</table>

internally and externally to alleviate and even to cure a vast list of disturbances, particularly those related to inflammatory disorders (Gardiner, 2007). The authors would like to postulate a role for MC as a pain reliever in acute gouty arthritis which could be attributed to its flavonoids and essential oils. Apigenin, luteolin, and quercetin are the main flavonoids in the MC extract. Nicholas et al. (2007) have shown that apigenin produces anti-inflammatory effects by inactivation of NF-κB pathway through suppression of p65 phosphorylation which in turn blocks the expression of proinflammatory cytokines, like interleukin 1 and 6 (IL-1, 6) and tumor necrosis factor-alpha (TNF-α) in human monocytes (Nicholas et al., 2007).

This effect regulates prostaglandin (PG) and NO production and suppresses inflammation (Ha et al., 2008). Synovial T cells in rheumatoid arthritis are highly differentiated and express a phenotype suggesting susceptibility to apoptosis (Salmon et al., 1997). Moreover, apigenin is an apoptosis inducer in human leukemic cells (Chen et al., 2005). Luteolin is a natural antioxidant and displays excellent free radical scavenging and cytoprotective properties. Luteolin has anti-inflammatory effects including activation of antioxidative enzymes, suppression of the NF-κB pathway, and inhibition of pro-inflammatory substances. Luteolin, is effective in diminution of inflammation through reduction of enhanced vascular permeability (Seelinger et al., 2008). It also suppresses production of NO and Prostaglandins 2 (PGE2) as well as the expression of iNOS, cyclooxygenase-2 (COX-2), TNF-α and IL-6 via blocking NF-κB activation pathway (Chen et al., 2007). Moreover, luteolin and quercetin are mixed-type inhibitors of the XO and decrease the production of superoxide radicals and uric acid (Pauff and Hille, 2009). Free radical reactions are implicated in numerous pathophysiological conditions like gouty inflammation. Chamazulene, the active substance of chamomile, inhibits lipid peroxidation via antioxidant activity and blocks chemical peroxidation of arachidonic acid and leading to anti inflammatory effects. Also chamazulene blocks the formation of leukotriene B4 in neutrophilic granulocytes (Safayhi et al., 1994; Rekka et al., 1996). Another essential oil of the MC, En-yne dicycloether, can inhibit degranulation of mast cells to prevent histamine release and therefore blocks vascular dilation (Miller et al., 1996).

Based on previous studies and our proposed hypotheses, the main anti-inflammatory mechanism of MC is summarized in Table 1. Two main mechanisms can be described for the role of MC compounds in gouty arthritis for pain relief. The first mechanism is prevention of NF-κB activation and suppression of iNOS and COX-2 gene expression via apigenin and luteolin. The next mechanism is the antioxidant activity and prevention of lipid peroxidation of arachidonic acid, which block production of inflammatory substances via apigenin, luteolin, and chamazulene. Moreover, mechanisms such as inhibition of NO, vasodilatation inhibitory, and induction of apoptosis might also be important in the expression of anti-inflammatory effect of MC in gouty arthritis.

The above discussed mechanisms can be presumed to interrupt main inflammation pathways in gouty arthritis and support the hypothesis that a cup of M. chamomilla, tea or pharmaceutical formulations could prevent pain in gouty arthritis or at least make it tolerable.
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REFERENCES


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