African Journal of Pharmacy and Pharmacology Vol. 6(8), pp. 508-511, 29 February, 2012
Available online at http://www.academicjournals.org/AJPP
DOI: 10.5897/AJPP10.197
ISSN 1996-0816 ©2012 Academic Journals

Review

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

Hamed Ghavimi[1]*, Ali Shayanfar[2], Sanaz Hamedeyazdan[3], Afshin Shiva[4], Afagh Garjani[5]

[1]Drug Applied Research Center, Department of Pharmacology and Toxicology, Faculty of pharmacy Tabriz University of Medical Sciences, Tabriz, Iran.
[2]Liver and Gastrointestinal Diseases Research Center, Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran.
[3]Biotechnology Research Center and Faculty of Pharmacy Tabriz University of Medical Sciences, Tabriz, Iran.
[4]Department of Clinical Pharmacy, Faculty of Pharmacy, Pharmaceutical Sciences Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
[5]Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

Accepted 2 August, 2011

***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 E_2 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 dicolo 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 B_4 in the neutrophilic

*Corresponding author. E-mail: Hamed.ghavimi@gmail.com or Hamed.ghavimi@hotmail.com. Tel: +98-411-3341315; +98 9143066096. Fax: +98-411-3344798.

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 areduction 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 (Avallone 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 (Avallone 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 pharmacolgic 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).

GOUT

Gout is a type of inflammatory arthritis that is triggered by the crystallization of uric acid within the joints and soft tissues (Baker and Ralph Schumacher, 2010). Xanthine oxidase (XO) is an enzyme that catalyzes the oxidation of hypoxanthine to xanthine and can further catalyze the oxidation of xanthine to uric acid. The XO enzyme is critical in gout since inhibition of this enzyme can reduce the production of uric acid and superoxide radicals (Kim et al., 2003; Pauff and Hille, 2009). The acute attack in gout is due to an inflammatory response initiated by a complex interaction between immune cells and monosodium urate crystals (MSU) deposited in the joints or other soft tissues. Increased vascular permeability is a consequence of this process similar to other inflammatory conditions. In the later phases of the attack, macrophages infiltrate and release other inflammatory cytokines and chemokines (Dalbeth and Haskard, 2005). The formation of the vasoactive peptide, bradykinin, may also contribute to the augmentation of the inflammatory response to MSU crystals. The bradykinin, promotes vasodilatation, increases vascular permeability, and enhances arachidonic acid metabolism through endothelial cell activation (Kaplan et al., 2002). In gouty arthritis, urate crystals are phagocytosed by synoviocytes which then release arachidonic acid, prostaglandins, lysosomal enzymes, and interleukin-1. Attracted by these chemotactic mediators, polymorphonuclear leukocytes migrate into the joint space and amplify the ongoing inflammatory process (Dalbeth and Haskard, 2005). Leukotriene B_4 (LTB_4), a metabolite of arachidonic acid is generated by polymorphonuclear leukocytes exposed to MSU. The LTB_4 is an important chemical mediator in an acute gouty attack owning to its role as a potent cytotoxin and phagocyte activator agent (Rae et al., 1982). Elevated concentrations of LTB_4 have been found in secretions of neutrophilic granulocytes in gout (Crooks and Stockley, 1998). The MSU crystal can induce some protein kinases such as mitogen-activated protein kinase (MAPK) which regulates cellular responses during the acute gout attack. Within mononuclear phagocytes, the MAPK pathway plays a particular role in NF-κB activation (Ganzera et al., 2006). The MSU can stimulate inducible NO synthase (iNOS) and nitric oxide (NO) generation in human monocytes via activation of NF-κB pathway and therefore it has a pro-inflammatory role in immune responses (Jaramillo et al., 2004).

HYPOTHESIS

There are 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.*

Mechanism	Compound	Reference
Modulation of NF-κB	Apigenin	Nicholas et al. (2007)
	Luteolin	Chen et al. (2007)
XO inhibitor	Luteolin	Pauff and Hille, (2009)
Vascular dilation inhibitor	Luteolin	Seelinger et al. (2008)
	En-yne dicycloether	Miller et al. (1996)
LTB_4 blocker	Chamazulene	Safayhi et al. (1994)
Antioxidant activity	Apigenin	Lee et al. (2007)
	Luteolin	Seelinger et al. (2008)
	Chamazulene	Rekka et al. (1996)
Suppresses gene expression of iNOS and COX-2	Apigenin	Nicholas et al. (2007)
	Luteolin	Chen et al. (2007)
Apoptosis inducer	Apigenin	Chen et al. (2005)

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. Apigein, lutelin, and quercetin are the main flavonoids in the *MC* extract. Nicholas et al. (2007) 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 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 (PGE_2) 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 B_4 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 XO, 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.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Nasrin Maliki-Dizaji,Prof. Abolghasem Jouyban and Dr. Mohammad Amin Abolghassemi Fakhree for their useful comments on this work.

REFERENCES

Avallone R, Zanoli P, Puia G, Kleinschnitz M, Schreier P, Baraldi M (2000). Pharmacological profile of apigenin, a flavonoid isolated from Matricaria chamomilla. Biochem. Pharmacol., 59: 1387-1394.

Baker JF, Ralph Schumacher H (2010). Update on gout and hyperuricemia. Int. J. Clin. Pract., 64: 371-377.

Bedi G, Tonzibo ZF, Oussou KR, Choppard C, Mahy JP, N'Guessan TY (2010). Effect of essential oil of chromoleana odorata (asteraceae) from ivory coast, on cyclooxygenase function of prostagladin-H synthase activity. Afr. J. Pharm. Pharmacol., 4: 535-538.

Chen CY, Peng WH, Tsai KD, Hsu SL (2007). Luteolin suppresses inflammation-associated gene expression by blocking NF- κB and AP-1 activation pathway in mouse alveolar macrophages. Life Sci., 81: 1602-1614.

Chen D, Daniel KG, Chen MS, Kuhn DJ, Landis-Piwowar KR, Dou QP (2005). Dietary flavonoids as proteasome inhibitors and apoptosis inducers in human leukemia cells. Biochem. Pharmacol., 69: 1421-1432.

Crooks SW, Stockley RA (1998). Leukotriene B4. Int. J. Biochem. Cell Biol., 30: 173-178.

Dalbeth N, Haskard DO (2005). Mechanisms of inflammation in gout. Rheumatology, 44: 1090-1096.

Ganzera M, Schneider P, Stuppner H (2006). Inhibitory effects of the essential oil of chamomile (*Matricaria recutita* L.) and its major constituents on human cytochrome p.450 enzymes. Life Sci., 78: 856-861.

Gardiner P (2007). Complementary, holistic, and integrative medicine: Chamomile. Pediatr. Rev., 28: e16-e18.

Ha SK, Lee P, Park JA, Oh HR, Lee SY, Park JH, Lee EH, Ryu JH, Lee KR, Kim SY (2008). Apigenin inhibits the production of NO and PGE2 in microglia and inhibits neuronal cell death in a middle cerebral artery occlusion-induced focal ischemia mice model. Neurochem. Int., 52: 878-886.

Jaramillo M, Naccache PH, Olivier M (2004). Monosodium Urate Crystals Synergize with IFN-³ζ to Generate Macrophage Nitric Oxide: Involvement of Extracellular Signal-Regulated Kinase 1/2 and NF-κB. J. Immunol., 172: 5734-5742.

Kaplan AP, Joseph K, Silverberg M (2002). Pathways for bradykinin formation and inflammatory disease. J. Allergy Clin. Immunol., 109: 195-209.

Kim KY, Schumacher HR, Hunsche E, Wertheimer AI, Kong SX (2003). A literature review of the epidemiology and treatment of acute gout. Clin. Ther., 25: 1593-1617.

Lee JH, Zhou HY, Cho SY, Kim YS, Lee YS, Jeong CS (2007). Anti-inflammatory mechanisms of apigenin: Inhibition of cyclooxygenase-2 expression, adhesion of monocytes to human umbilical vein endothelial cells, and expression of cellular adhesion molecules. Arch. Pharm. Res., 30: 1319-1327.

McKay DL, Blumberg JB (2006). A review of the bioactivity and potential health benefits of chamomile tea (*Matricaria recutita* L.). Phytother Res 20: 519-530.

Miller T, Wittstock U, Lindequist U, Teuscher E (1996). Effects of some components of the essential oil of chamomile, Chamomilla recutita, on histamine release from rat mast cells. Planta Med., 62: 60-61.

Mwale M, Masika PJ (2010). Analgesic and anti-inflammatory activities of aloe ferox Mill. aqueous extract. Afr. J. Pharm. Pharmacol., 4: 291-297.

Nicholas C, Batra S, Vargo MA, Voss OH, Gavrilin MA, Wewers MD, Guttridge DC, Grotewold E, Doseff AI. (2007). Apigenin blocks lipopolysaccharide-induced lethality in vivo and proinflammatory cytokines expression by inactivating NF-κB through the suppression of p.65 phosphorylation. J. Immunol., 179: 7121-7127.

Nkomo M, Nkeh-Chungag BN, Kambizi L, Ndebia EJ, Iputo JE (2010). Antinociceptive and anti-inflammatory properties of gunnera perpensa (gunneraceae). Afr. J. Pharm. Pharmacol., 4: 263-269.

Pauff JM, Hille R (2009). Inhibition studies of bovine xanthine oxidase by luteolin, silibinin, quercetin, and curcumin. J. Nat. Prod., 72: 725-731.

Rae SA, Davidson EM, Smith MJH (1982). Leukotriene B_4, an inflammatory mediator in gout. Lancet, 2: 1122-1124.

Rekka EA, Kourounakis AP, Kourounakis PN (1996). Investigation of the effect of Chamazulene on lipid peroxidation and free radical processes. Res. Commun. Mol. Pathol. Pharmacol., 92: 361-364.

Robak J, Gryglewski RJ (1996). Bioactivity of flavonoids. Pol. J. Pharmacol., 48: 555-564.

Russo A, Acquaviva R, Campisi A, Sorrenti V, Di Giacomo C, Virgata G, Barcellona ML, Vanella A (2000). Bioflavonoids as antiradicals, antioxidants and DNA cleavage protectors. Cell Biol. Toxicol., 16: 91-98.

Safayhi H, Sabieraj J, Sailer ER, Ammon HPT (1994). Chamazulene: An antioxidant-type inhibitor of leukotriene B4 formation. Planta Med., 60: 410-413.

Salmon M, Scheel-Toellner D, Huissoon AP, Pilling D, Shamsadeen N, Hyde H, D'Angeac AD, Bacon PA, Emery P and Akbar AN (1997). Inhibition of T cell apoptosis in the rheumatoid synovium. J. Clin. Invest., 99: 439-446.

Saraiva RA, Araruna MKA, Oliveira RC, Menezes KDP, Leite GO, Kerntopf MR, Costa JGM, Rocha JBT, Tomé AR, Campos AR, Menezes IRA (2011). Topical anti-inflammatory effect of Caryocar coriaceum Wittm. (Caryocaraceae) fruit pulp fixed oil on mice ear edema induced by different irritant agents. J. Ethnopharmacol., 136: 504-510.

Seelinger G, Merfort I, Schempp CM (2008). Antioxidant, anti-inflammatory and antiallergic activities of luteolin. Planta Med., 74: 1667-1677.

Srivastava JK, Gupta S (2009). Extraction, characterization, stability and biological activity of flavonoids isolated from chamomile flowers. Mol. Cell Pharmacol., 1: 138-147.

Svehliková V, Bennett RN, Mellon FA, Needs PW, Piacente S, Kroon PA, Bao Y (2004). Isolation, identification and stability of acylated derivatives of apigenin 7-O-glucoside from chamomile (Chamomilla recutita [L.] Rauschert). Phytochemistry, 65: 2323-2332.

Sy GY, Fall AD, Diatta W, Gueye M, Badji K, Bassène E, Faye B (2009). Analgesic and anti-inflammatory activity of aqueous root extract of Cassia sieberiana D. C. (Caesalpiniaceae). Afr. J. Pharm. Pharmacol., 3: 651-653.

Yoon JH, Baek SJ (2005). Molecular targets of dietary polyphenols with anti-inflammatory properties. Yonsei. Med. J., 46: 585-596.