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REVIEW ARTICLE

A Comprehensive Review on Therapeutic potentials of *Matricaria chamomilla* (chamomile) Against Inflammation-Mediated Chronic Diseases

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Abstract: *Matricaria chamomilla*, commonly known as chamomile, is a widely used medicinal plant renowned for its anti-inflammatory properties. Chronic inflammation plays a pivotal role in the pathogenesis of many disorders including metabolic syndrome, arthritis, inflammatory bowel disease and cancer. This comprehensive review explores the phytochemistry, traditional uses, pharmacological activities and molecular mechanisms of chamomile against inflammation-driven chronic illnesses. Chamomile contains several bioactive constituents such as flavonoids, terpenoids and phenolic compounds that exert anti-inflammatory effects by inhibiting pro-inflammatory cytokines, targeting redox imbalance and modulating critical inflammatory signaling cascades like NF-kB and MAPK pathways. Accumulating experimental and clinical evidence indicate that chamomile extracts and isolated compounds effectively reduce inflammation and ameliorate disease symptoms in various chronic conditions. However, more rigorous human trials are still warranted to validate its therapeutic efficacy and fully harness chamomile's anti-inflammatory potential. This review provides insights into chamomile's anti-inflammatory properties and its role as an adjuvant or alternative therapy for chronic inflammatory disorders.

Keywords: *Matricaria chamomilla*, chamomile, inflammation, chronic disease, anti-inflammatory, phytochemicals

1. Introduction

Chronic inflammation is a persistent biological response to cellular injuries and pathogens that disrupts physiological homeostasis. It plays a fundamental role in the onset and progression of various chronic and degenerative diseases affecting human health globally. Conditions like autoimmune disorders, metabolic syndrome, cancer, cardiovascular diseases, neurodegenerative diseases prominently feature a state of low-grade inflammatory activity at their root [1,2]. While acute inflammation is an essential defense mechanism, chronic inflammation becomes maladaptive over time leading to tissue damage and pathological consequences if left uncontrolled [3]. Currently available anti-inflammatory drugs are accompanied by severe adverse effects with long-term usage, necessitating research on safer and natural therapeutic alternatives [4].

Matricaria chamomilla, commonly known as chamomile, is one such widely used medicinal plant that has been credited with notable anti-inflammatory properties. It belongs to the composite family Asteraceae and the two most commonly utilized species are Matricaria recutita (German chamomilla) and Chamaemelum nobile (Roman chamomilla) [5,6]. Chamomile has a long tradition of use in folk medicine systems as an herbal preparation for various ailments involving inflammation. The Egyptian papyrus dating to 1500 BC and Greek physicians like Hippocrates have documented chamomile's application in reducing fever and soothing skin inflammations [7,8]. Even today, chamomile tea is one of the most consumed herbal teas globally due its relaxing and soothing attributes.

Modern research has substantiated chamomile's traditional uses by revealing a complex profile of anti-inflammatory phytochemicals. Various studies have identified flavonoids (apigenin, quercetin), terpenoids (bisabolol, matricin, chamazulene), coumarins and mucilage polysaccharides as the major anti-inflammatory constituents of chamomile [9,10]. These compounds exert their effects by modulating critical inflammatory pathways, inhibiting pro-inflammatory cytokine production and blocking redox imbalances associated with chronic inflammation [11,12]. Preclinical investigations demonstrate that chamomile attenuates inflammation in diverse chronic disease models like metabolic syndrome, arthritis, colitis and cancer [13-16]. Human trials also

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indicate chamomile's potential to safely reduce clinical symptoms when used adjunctively with conventional therapies for inflammatory bowel disease and rheumatoid arthritis [17,18].

2. History

Chamomile has a long and globally widespread history of medicinal usage that can be dated back to ancient civilizations. The plant was listed in Egyptian papyri dating as far as 1500 BC among other important medicinal herbs where it was prescribed for fever reduction and anti-inflammatory purposes [19]. Ancient Greek physicians Hippocrates and Dioscorides recommended chamomile preparations for wound healing, abdominal pain, fever and inflammation related disorders [7,20]. The Greeks also coined the term "chamomile" which means "ground apple" referring to the plant's low-growing and apple-scented nature. During the Roman Empire, chamomile was extensively cultivated in Italy and Greece for various household, medicinal and cosmetic uses [21]. It later spread across Europe during the Middle Ages where it was popularly used as an herbal tea and folk remedy. In medieval Europe, chamomile was valued as an important medicinal plant to treat diseases associated with inflammation like rheumatism, wounds, ulcers, ear infections and dermatitis [22,23]. The German Commission E has approved the internal use of chamomile tea and extracts for digestive issues and inflammation in the gastrointestinal tract based on its historical use and safety profile [24].

3. Plant description

In terms of taxonomy, chamomile is classified under the Asteraceae family and two most commonly utilized species are Matricaria recutita Mill. (German chamomile) and Chamaemelum nobile (L.) All. (Roman chamomile) [25]. M. recutita, native to Europe and western Asia, is an annual herb that grows up to 30 cm tall with feathery leaves. It produces yellow Composite capitula flowers (flower heads) that are surrounded by white ray florets [26,27]. The flower heads contain blue essential oil that turns into a dark yellow waxy material called “chamazulene” after drying [28]. Roman chamomile (C. nobile) is a low-growing aromatic perennial herb native to Europe. It possesses finely dissected, grass-like leaves and daisy-like flowers that are white to pale pink in color [29,30]. Modern cultivation practices for chamomile farming have led it to be commercially grown worldwide today including countries like Hungary, Germany, United Kingdom, Czechoslovakia and USA [31]. The primary plant parts used are the flowers which are harvested just before or during blooming for maximum oil content. Dried chamomile flowers have a subtle apple-like scent and bitter, aromatic taste. They contain a wealth of pharmacologically active compounds concentrated in the essential oil that confers its therapeutic properties [32]. Standardized extracts prepared from the flowers are commonly used in pharmaceutical preparations, food products and cosmetics [33]. Overall, chamomile has truly earned its traditional reputation as a significant herbal medicinal worldwide due to its versatile uses and safety.

4. Chemical composition and bioactive constituents

Chamomile contains a very diverse assortment of phytochemicals that have been linked to its pharmacological activities. The major portions of the flowers comprise essential oils (0.2-1%), flavonoids, terpenoids and coumarins [34,35]. Essential oils are volatile, aromatic compounds concentrated in the flower heads. German chamomile oil is composed of the terpene matricin (up to 0.4%), bisabolol (36-48%), bisabolol oxides A and B, and chamazulene (6-16%) which is derived from matricin during drying [36,37]. Roman chamomile oil containsangelic acid and tiglic acid esters as major components instead [38]. Flavonoids are important anti-inflammatory phenolics present in abundance. Apigenin, luteolin and their glycosides like apigenin-7-glucoside have been frequently reported [39]. Other flavonoids identified include quercetin, patuletin and diverse acylated derivatives [40]. Terpenoids beyond the oil constitute sesquiterpene lactones (matricarin, desacylmatricarin), polyacetylenes (farnesene) and sterols (sitosterol, stigmasterol) [41,42]. Phenolic acids like caffeic acid, p-coumaric acid and polymeric metabolites of flavonoids also contribute [43]. Mucilage polysaccharides constitute 10-15% dry weight which mainly consists of arabinogalactans that confer demulcent properties [44]. Mineral content includes potassium, calcium, iron and manganese.

Table 1. Main bioactive constituents of chamomile and their anti-inflammatory activities

Constituent	Concentration	Activities
Apigenin	0.1-0.5%	Inhibits COX-2, iNOS, TNF-α, IL-1β, IL-6, NF-ϰB
Bisabolol	15-20%	Scavenges free radicals, inhibits cytokines
Chamazulene	6-16%	Strong anti-inflammatory and antioxidant
Quercetin	0.5-1%	Inhibits LOX, COX-2, PGE2, NF-ϰB
Luteolin	1-3%	Inhibits 5-LOX, COX-2 and reduces cytokines

5. Mechanism of action of chamomile

Chamomile exerts anti-inflammatory effects through diverse mechanisms involving inhibition of pro-inflammatory pathways, mediators and modulating the redox balance. Apigenin is recognized as the most pharmacologically active constituent that targets inflammation. It suppresses iNOS and COX-2 expression via inhibiting NF-ϰB and MAPK signaling to reduce inflammatory mediator generation [45,46]. Other flavonoids similarly downregulate cytokines TNF-α, IL-1β, IL-6 and IL-8 production through modulating transcriptional factors including NF-ϰB and AP-1 [47,48]. Terpenoids like bisabolol, chamazulene aid apigenin's effects on reducing lipid peroxidation and scavenging reactive oxygen/nitrogen species linked to chronic inflammation [49,50]. Mucilage functions as an antioxidant and also protects mucosal membranes by decreasing permeability to inflammatory stimuli [51]. Collectively, these multi-targeted actions help chamomile counteract the complex process of chronic inflammation at various levels like mediator generation, redox status and cell signaling pathways crucial to inflammatory disorders.

6. Traditional uses

Chamomile has a wide-ranging history of traditional medicinal uses that can be broadly classified as:

6.1. Gastrointestinal applications

Chamomile tea or extracts have been used as a carminative to relieve abdominal pain, colic, indigestion, diarrhea, vomiting and gut inflammation. The mucilage aids soothe irritated digestive mucosa [52,53].

6.2. Sleep and anxiety

Chamomile tea works as a mild sedative, anxiolytic and relaxing nervine due to apigenin and flavonoid content. This makes it popular herbal tea before bedtime for insomnia, restlessness and irritability relief [54,55].

6.3. Dermatological uses

Topical formulations with chamomile are utilized extensively in cosmetics and for soothing skin inflammations like eczema, psoriasis, wounds and burns due to antiseptic and anti-inflammatory effects [56,57].

6.4. Gynecological and menstrual uses

Traditional medicine systems prescribed chamomile for relieving menstrual discomfort, promoting uterine toning, hormonal balancing and as an abortifacient [58].

6.5. Oral care

Mouthwashes and dental products contain chamomile due to its antifungal, antibacterial, anti-inflammatory and tooth whitening attributes effective against gingivitis, stomatitis and mouth ulcers [59,60].

6.6. Nervous system disorders

Chamomile has been indicated to help alleviate headaches, migraines, neuralgia due to sedative effects on cerebral vasculature and calcium antagonism at neuronal level [61,62].

6.7. Rheumatic diseases

Based on clinical observations, herbalists recommended chamomile for relieving symptoms of arthritis, gout, lumbago and muscle sprains likely due to its anti-inflammatory properties [63]

7. Preparations of chamomile

Proper quality, concentration and formulation considerations ensure chamomile preparations retain maximum therapeutic potency and safety for integrating as alternative or adjunct therapies. More research can optimize these utilization aspects. Main preparations where chamomile's therapeutic benefits can be derived include:

- Tea: Dried flowers infused in hot water makes a soothing aromatic tea consumed for its calming effects.
- Capsules/tablets: Enteric coated tablets offer convenience and accuracy for internal use as supplements.

- Tinctures: Hydro-alcoholic extracts preserve volatile constituents in liquid form for oral intake.
- Topical preparations: Creams, gels, lotions containing extracts are applied to skin for various purposes.
- Aromatherapy: Essential oil is used as inhalant/massage aid for relaxation and cosmetic fragrances.
- flower powders: Finely ground material is useful for poultices and compresses externally or mixed with foods.
- Standardized extracts: Concentrated preparations containing quantified marker compounds ensure product consistency.

8. Contraindications and safety profile

Chamomile is generally recognized as safe for oral and topical use in recommended doses due to its long history of traditional consumption. Overall, chamomile self-medication seems relatively safe for majority of people if occasional use and traditional preparations are adhered to. However, more targeted clinical research may help objectively ascertain optimal therapeutic doses devoid of risks, especially for vulnerable groups. Close medical supervision is advised when substituting or combining chamomile with prescribed medications. However, there are some precautions to take:

Allergy: People hypersensitive or allergic to plants in the Asteraceae/Compositae family may develop contact dermatitis or other allergic reactions to chamomile due to cross-reactivity [64].

Pregnancy: Despite traditional use as an emmenagogue, there are no clear human studies supporting chamomile's safety during pregnancy. It may act as a uterine stimulant at high doses so caution is advised [65].

Surgery: Chamomile's herb-drug interactions through inhibition of P-glycoprotein efflux transporters and CYP enzymes warrant dose modification or avoidance before surgery due to bleeding risks [66].

Autoimmune disorders: Chamomile might provoke disease flares in conditions like rheumatoid arthritis, multiple sclerosis or autoimmune hepatitis through unknown immunological mechanisms. Careful dosage is needed [67].

Diabetes: By possibly lowering blood sugar, chamomile may intensify hypoglycemic effects of antidiabetic drugs if taken together without monitoring levels [68].

Individual case reports have documented isolated allergic reactions, contact dermatitis and oral mucosal ulcerations from topical or oral chamomile intake in hypersensitive patients [69,70]. No toxic or mutagenic effects have been reported from recommended use.

Chamomile oil or concentrates have shown estrogenic and anticoagulant activities in vitro due to apigenin's structure, but the significance at normal intake levels is unclear [71,72]. Studies in animals have found no abnormal fetal development related to chamomile usage [73].

9. *In vitro* studies

Several in vitro studies demonstrate chamomile's potent anti-inflammatory effects on various cell lines:

- Chamomile extracts inhibit NF-kB activation and expression of inflammatory mediators like TNF-α, IL-1β, IL-6, PGE2 in LPS-stimulated macrophages in a dose-dependent manner [74,75].
- Apigenin suppresses COX-2 and iNOS expression in macrophages by blocking phosphorylation and degradation of IkB-α, thus preventing nuclear translocation of NF-kB [76,77].
- On human synoviocytes from rheumatoid arthritis patients, chamomile decreases MMP-3 secretion, a collagenase involved in joint destruction [78].
- In intestinal epithelial cells, chamomile upregulates anti-inflammatory signaling through PPAR-γ activation and reduces cytokine levels [79].
- Bisabolol oxide-A decreases TLR-4 expression and inflammatory cytokines release from adipocytes, implying anti-obesity effects [80].

- Chamomile inhibits neutrophil elastase release and function to control tissue injury during inflammation [81].
- Apigenin inhibits VEGF-dependent neovascularization in vitro, suggesting anti-cancer properties [82].
- Antioxidant assays show chamomile extracts scavenge DPPH, ABTS, superoxide and hydroxyl radicals more potently than synthetic antioxidants [83,84].

10. *In vivo* studies

Animal experimentation lends strong support to traditional uses and in vitro evidence:

- Oral chamomile reduces edema, leukocyte infiltration and TNF-α in multiple models of acute inflammation in rats/mice [85,86].

- It relieves cytokine levels and arthritis scores comparable to indomethacin in rat adjuvant arthritis via downregulating COX-2 and iNOS [87].

- Chamomile attenuates colitis severity by inhibiting MPO activity and restoring antioxidant status in TNBS-induced colitis in mice [88].

- Diet containing chamomile extract improves metabolic parameters, adiposity and liver inflammation in obesity-prone rats [89].

- Apigenin curtails skin inflammation, edema and hyperplasia during phorbol ester-induced mouse model of inflammatory dermatitis [90].

- Chamomile or bisabolol oxide A avert neuroinflammation in rodent models of arthritis, Parkinson's and cerebral ischemia [91,92].

- These observations reflect chamomile's therapeutic potential against various chronic inflammatory pathologies by modulating complex biological networks

Table 2. Summary of in vivo studies showing chamomile's effects on chronic inflammatory conditions

Disease model	Observations	References
Adjuvant arthritis	Reduces paw edema, cytokines, COX-2, iNOS	[87]
Colon colitis	Decreases disease score, MPO, restores antioxidants	[88]
Obesity-induced inflammation	Improves metabolic parameters, adipose inflammation	[89]
Dermal inflammation	Reduces edema, cell infiltration, hyperplasia	[90]
Parkinson's disease	Ameliorates neuroinflammation, motor deficits	[91]
Ischemic brain injury	Prevents infarct size, edema, cognitive impairment	[92]

11. Conclusion

In conclusion, this comprehensive review provides scientific evidence validating chamomile's traditional uses as an anti-inflammatory agent through its diverse phytochemistry and multi-target mechanisms. Accumulating in vitro and in vivo research substantiates chamomile's ability to modulate critical inflammatory pathways and mediators. Clinical investigations also indicate its therapeutic efficacy and safety in managing inflammation-driven chronic diseases when utilized as an adjuvant. However, further rigorous human clinical trials are still required to establish chamomile's full potential. With no severe adverse effects and numerous downstream anti-inflammatory actions, chamomile holds promise as a promising natural complementary therapy or diet supplement for chronic inflammatory conditions.

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