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The Antioxidant and Anti-inflammatory Properties of Chamomile and Its Constituents

Saeedeh Talebi (MD)[1], Payam Sharifan (MD)[1], Andisheh Norouzian Ostad (MD)[1], Seyedeh Elaheh Shariati (MD)[1], AmirAli Moodi Ghalibaf (MD)[2], Mehdi Barati (MD)[3], Malihe Aghasizadeh (Ph.D)[4], Sahar ghoflchi (MSc)[5], Hamideh Ghazizadeh (Ph.D)[1,4], Niloofar Shabani (MSc)[6], Gordon.A Ferns (Ph.D)[7], Hamid Reza Rahimi (MD)[4,8*], Majid Ghayour Mobarhan (MD)[4*]

[1] *Department of Nutrition, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[2] *Student Research Committee, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran*
[3] *Department of Immunology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[4] *International UNESCO Center for Health-Related Basic Sciences and Human Nutrition, Mashhad University of Medical Sciences, Mashhad, Iran*
[5] *Deparment of clinical biochemistry; faculty of medical; University of Zahedan, Zahedan, Iran*
[6] *Department of Biostatistics, School of Health, Tehran University of Medical Sciences, Tehran, Iran*
[7] *Brighton & Sussex Medical School, Division of Medical Education, Falmer, Brighton, Sussex BN9 1PH, UK*
[8] *Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*

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ABSTRACT

Introduction: An imbalance has been reported in the oxidant-antioxidant system of infants with febrile convulsion. This study aimed to compare serum vitamin C levels between febrile children with or without seizures.

Methods: This multicenter case-control study was conducted on febrile infants and children referred to Mashhad University of Medical Sciences pediatric emergency wards. The subjects were equally divided into two febrile groups of case (with seizures) and control (without seizures). A visible spectrophotometer was used to determine the total vitamin C level.

Results: In total, 100 febrile children were included in the study. Based on the results, there was no statistically significant difference between the two groups in terms of age, gender, and family history of febrile convulsion (FC) ($P>0.05$). The mean vitamin C levels in the case and control groups were 42.73±7.2 and 78.59±11.1 µg/l, respectively. There was a significant difference between the groups regarding the vitamin C level ($P<0.001$). Regression analysis revealed that age ($P=0.74$), gender ($P=0.66$), and family history of febrile convulsion ($P=0.52$) had not any correlation with vitamin C levels. On the other hand, vitamin C levels were associated with FC ($P=0.001$).

Conclusion: The serum levels of vitamin C were lower in children with febrile seizures than in the control group. Thus, reduced vitamin C levels can be considered a predisposing factor for FC.

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Introduction

Many chronic diseases are related to long-term inflammation and oxidative stress (1-3). The latter refers to an imbalance between the generation of reactive oxygen species (ROS) and cellular antioxidant defense capacity (4-6). Excessive ROS is associated with impairment in the function of cellular macromolecules, such as proteins,

***Corresponding author:** Hamid Reza Rahimi & Majid Ghayour-Mobarhan, International UNESCO Center for Health-Related Basic Sciences and Human Nutrition, Mashhad University of Medical Sciences, Mashhad, Iran.*
Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
***E-mail:** RahimiHR@mums.ac.ir, GhayourM@mums.ac.ir*

causing a failure in the regulation of cellular signaling events, and in the long run leading to the development and progressions of inflammatory complications (7). However, inflammation and oxidative stress are frequently a consequence of normal cellular processes, although excessive oxidative stress and prolonged inflammation may lead to chronic diseases, including diabetes, cancer, and obesity, which, in turn, increase the aging process (8-10). As a result, it is of utmost importance that they are adequately regulated to inhibit the development of chronic diseases. At present, the influence of oxidative stress and subsequent events has constituted a critical part of human health (11). Endogenous enzymatic and nonenzymatic antioxidants sometimes cannot control the excessive production of ROS, accordingly culminating in the imbalances of the process, cellular injury (12), and other health concerns (13). The suboptimal content of dietary antioxidant substances may contribute to the progression of degenerative diseases (11), which include cancer, cardiovascular disease(14), Alzheimer's disease, and neurodegenerative disease (15).

Herbal medicines, phytonutrients, and nutraceuticals have gained popular appeal globally so numerous people prefer these new products for overcoming different health issues (16, 17). Of note, herbal medicines have been used as a complementary and/or alternative remedy to cure many inflammatory diseases owing to the report of the adverse side effects associated with anti-inflammatory drugs and synthetic antioxidants (18-20). The literature suggests that flavonoids and phenolic content play a pivotal role in the antioxidant activities of natural products (21). *Matricaria chamomilla* L. (English: Chamomile, Persian: Baabune) is a medicinal plant species with a broad range of applications, described over the centuries in different human cultures. Historically, it has been reported that chamomile can be beneficial for the treatment of many inflammatory conditions, namely eczema, ulcers, gout, neuralgia, rheumatic pains, and Diabate (22-25). Many people have used the dried flowers of chamomile as tea, which is drunk at a daily rate of above a million cups (26). The useful impacts of chamomile are ascribed to several flavonoids, with the core structure being composed of either flavone (e.g.apigenin, luteolin) or flavonol derivatives (e.g. quercetin, patuletin)(27). We aimed to review the anti-oxidant and anti-inflammatory potential of chamomile products.

Materials and Method

The present comprehensive review study was

the latter possesses high ratios of K/Na and Ca/Mg (41). Whole plants were reported to contain approximately 36 µg/g Mn (42).

A number of flavonoids and phenolics have been recognized in the various parts of the chamomile flower head. Ordering from highest to lowest, these include: apigenin (16.8%), quercetin (9.9%), patuletin (6.5%), luteolin (1.9%), and their glucosides, are known as the main flavonoids found in the flower. Their relative percentages differ depending on the flower parts used for extraction(28, 43, 44). In the study btMulinacci*et al.* (2000), great amounts (39.1%) of the cinnamic acid derivatives and other undetermined phenolic derivatives (25.8% of the total flower) were demonstrated. The coumarins seem to form about 0.1% of the total components (45, 46).

Antioxidant properties

In vitro studies

Recent studies have been carried out to assess the antioxidant activities of chamomile and its component. In one of the in vitro assays performed by Lis-Balchin et al.(1998), many commercially available essential oils extracted from chamomile using an agar plate-based method were studied, in which the essential oil samples were put onto plates containing β-carotene as well as linoleic acid, and subsequently underwent incubation at 45 °C before the background color became bleached. In their study, the antioxidant capacities have been described as the intensity of retained color and diameter of the color retention zone. These findings showed a small disparity between the two Germanoils (diameter: 10.5 vs 13.6; color intensity: very modest vs modest), yet a marked disparity between the German and Roman oils as two similar chamomile oils in commerce but different in chemical nature and biological activity (diameter: 0). However, this measurement method is not an accurate way of evaluating antioxidant activity because of its intra-assay variability (35).

With specific assay organized by Dragland et al. (2003) using the ferric reducing ability of plasma, demonstrated that the antioxidant activity of chamomile was low (below 18 mmol/100 g) as opposed to a collection of medicinal and culinary herbs. The mean value of German chamomile was greater than coriander (17.7 mmol/100 g vs 3.3 mmol/100 g), yet much lower than peppermint (78.5 mmol/100 g) and oregano (137.5 mmol/100 g) (47). Other investigators have addressed the antioxidant properties of the chamomile extracts using other methods. Al-Ismail and Talal (2003) assessed the antioxidant

effects of water and alcohol extracts obtained from the chamomile flowers on long-term storage of anhydrous butterfat. It was found that the two extracts exerted a moderate effect in order to regulate hydrolytic rancidity, with the water extract having a remarkably higher antioxidant activity than the alcohol extract (48).

In the study by Lee and Shibamoto (2002), the activity of a dichloromethane extract of a steam-distilled solution of dried chamomile (20 g/L water) was investigated by applying two different methods in vitro. The results of the aldehyde/carboxylic acid assay indicated that given BHT and α-tocopherol as the standards, the chamomile extract at the highest concentration of 500 µg/mL had an inhibitory effect on hexanaloxidation by 50% for 40 days. The extracts obtained from thyme, basil, rosemary, chamomile, lavender, and cinnamon had dose-dependent antioxidant activity within the range of 10 µg/mL and 500 µg/mL. The inhibition potentials of thyme and basil were higher (100%) than chamomile, lavender, and cinnamon were lower (5–6%), and rosemary was similar (59%). The conjugated diene assay that determines the inhibition of hydroperoxide synthesis from methyl linoleate resulted in similar measures of inhibition close to that of the hexanaloxidation. At the highest concentration (200 µg/mL), chamomile exhibited 31% inhibition of conjugated diene formation (49).

Using a different study design, Duman et al. fabricated copper oxide nanoparticles (CuO NPs) utilizing the flower extract of chamomile. They reported that CuO NPs carried concentration-dependent antioxidant effects and were able to interact with plasmid DNA (pBR322). On the basis of these results, it was assumed that CuO NPs had such capability to cleave and break DNA double helix structure (50). Comparing leaf and flower head extracts from feverfew (*Tanacetum parthenium*), German chamomile, and marigold (*Calendula officinalis*) from the Asteraceae family, Agatonovic-Kustrin et al. demonstrated that extracts from chamomile flower heads and leaves had the most notable antioxidant activity. Furthermore, bisabolol and chamazulene were identified as chamomile extract's most potent antioxidant components (51). More recently, Al-Dabbagh et al. have reported that for ethanolic extract of chamomile, the percentage inhibition of DPPH scavenging activity relied on the dose, being within the range of 94.8% ± 0.03 at 1.50 mg/mL and 84.2% ± 0.86 at 0.15 mg/mL. They found a high content of polyphenols (21.4 ± 0.327 mg GAE/g) and flavonoids (157.9 ± 2.22 mg QE/g) (52). The antioxidant activity of Chamomile in in-vitro studies has been summarized in table 1.

In vivo studies

These *in vitro* findings were also confirmed using *in vivo.* Sebai et al.aim to indicated that pre-treatment with chamomile decoction extract (CDE) could successfully recover oxidative stress-associated changes after castor oil administration on male Wistar rats. Indeed, CDE appeared to reduce malondialdehyde (MDA) level of intestinal fluid and depletion of antioxidant enzyme activities (i.e.superoxidedismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)) (53). Further investigations showed that CDE was replete with total polyphenols, total flavonoids, and condensed tannins. Using another animal model exposed to ethanol, they found that CDE restoredethanol-induced liver lipoperoxidation, preserved thiol -SH groups, and repressed the depletion of antioxidant enzyme activity of SOD, CAT, and GPx (54). The antioxidant potential of chamomile was also corroborated by Javadi and Emami. Bleomycin is a small peptide with two junction areas, one for interaction with DNA and the other for iron. For bleomycin, iron is accepted as a key factor in the generation of free radicals, and this then causes cytotoxic activity. Bleomycin produces a complex with Fe 2+, oxidizes to Fe3+, and consequently leads to oxygen reduction as well as free radical production. Chamomile, either individually or in combination with anthocyanoside, a structural flavonoid glucoside, was used to evaluate their protective effects against bleomycin-induced pulmonary toxicity in rats. It was observed that following three weeks, MDA in the rats' lungs decreased by 44.27%, 37.80%, and 46.07% in anthocyanoside, chamomile, and combined groups, respectively. Therefore, chamomile and anthocyanoside have the ability to scavenge oxygen free radicals and prevent lipid peroxidation (55).

Another animal model of oxidative stress was developed by Jabri et al. to investigate the effectiveness of CDE against stimulated neutrophils ROS production, as well as ethanol-induced hematological changes and erythrocytes oxidative stress in rats (56). The study showed that CDE prevented the synthesis of neutrophil ROS, and recovered ethanol-induced alterations in hematological parameters and erythrocytes oxidative stress. They concluded that hemato-protection provided by chamomile is more likely to partly arise from its antioxidant properties besides its opposite influences on some intracellular mediators, like H_2O_2, free iron, and calcium (56). The antioxidant activity of Chamomile in in-vivo studies has been summarized in table 1.

Table 1: The antioxidant activity of Chamomile in in-vitro, in-vivo and human studies

Antioxidant activity of Chamomile						
Author	**Study Design**	**Microenvironment/ Animal model/ Study population**	**Dose and Route of administration of the plant or constituents**	**Duration of treatment**	**Outcomes**	**Refrence**
Lis-Balchin et al (1998)	In-vitro	Agar plate-based method containing β-carotene; the antioxidant capacities were described as the intensity of retained color and diameter of the color retention zone	100 µl Chamomile oil were added to the agar.	The plates incubated at 45^{C} until the background color was bleached.	Findings showed a small disparity between the two German oils (diameter: 10.5 vs 13.6; color intensity: very modest vs modest), yet a marked disparity between the German and Roman oils as two similar chamomile oils in commerce but different in chemical nature and biological activity (diameter: 0).	(35)
Dragland et al (2003)	In-vitro	The antioxidant capacities were described as the ferric reducing ability of plasma (FRAP)	1-18 mmol/100g by FRAP	-	The mean value of German chamomile was greater than coriander (17.7 mmol/100 g vs 3.3 mmol/100 g), yet much lower than peppermint(78.5 mmol/100 g) and oregano (137.5 mmol/100 g).	(47)
Al-Ismail and Talal (2003)	In-vitro	The antioxidant capacities were described as the long-term storage of anhydrous butterfat	-	-	The antioxidant effects of water and alcohol extracts obtained from the chamomile flowers exerted a moderate effect in order to regulate hydrolytic rancidity, but the water extract had a remarkably higher antioxidant activity than the alcohol extract.	(48)
Lee and Shibamoto (2002)	In-vitro	The antioxidant capacities were described as the oxidation of the aldehyde to carboxylic acid	20 g of the component (Chamomile) was placed in a 3-L round-bottom flask with 1 L of deionized water. (10 µg/mL - 500 µg/mL) The components were added to 2 mL of a dichloromethane solution of hexanal (3 mg/mL) containing 0.2 mg/ mL of undecane as a gas chromatography internal standard.	10 minutes for 40 days	The chamomile extract at the highest concentration of 500 µg/mL had an inhibitory effect on hexanaloxidation by 50% for 40 days. The antioxidant activities of the extracts decreased in the following order in both of the lipophilic assay systems: thyme > basil > rosemary > chamomile > lavender and cinnamon.	(49)
Duman et al (2016)	In-vitro	The antioxidant activities were measured using the 2, 2-diphenyl-1-picrylhydrazyl (DPPH) assay. Fabricated copper oxide nanoparticles (CuO NPs) utilizing the flower extract of chamomile.	7.5, 15, 30 and 60 ppm mixed with 450 µL of Tris–HCl buffer (pH = 7.4) and 1 mL of methanolic DPPH solution.	30 minutes	CuO NPs carried concentration-dependent antioxidant effects and were able to interact with plasmid DNA (pBR322).	(50)
Agatonovic-Kustrin et al (2015)	In-vitro	The antioxidant activities were measured using the 2, 2-diphenyl-1-picrylhydrazyl (DPPH) assay	-	-	Extracts from chamomile flower heads and leaves had the most notable antioxidant activity. Furthermore, bisabolol and chamazulene were identified as chamomile extract's most potent antioxidant components.	(51)
Al-Dabbagh et al (2019)	In-vitro	The antioxidant activities were measured using the 2, 2-diphenyl-1-picrylhydrazyl (DPPH) assay	0.15 mg/mL- 1.50 mg/ mL of the extract.	24 hours	The percentage inhibition of DPPH scavenging activity relied on ethanolic extract of chamomile dose, being within the range of 94.8% ± 0.03 at 1.50 mg/ mL and 84.2% ± 0.86 at 0.15 mg/mL.	(52)

Sebai et al (2014)	In-vivo	Adult male Wistar rats & adult male Swiss Albino mice (Chamomile flowers were cultivated from the region of Beja (North-West of Tunisia))	12.5, 25, 50,100, 200, 400, 800, 1600 and 3200 mg/kg was orally administered to different groups of mice.	24 hours	CDE could successfully recover oxidative stress-associated changes after castor oil administration on male Wistar rats. CDE appeared to reduce the MDA level of intestinal fluid and depletion of antioxidant enzyme activities.	(53)
Javadi and Emami (2015)	In-vivo	Male Wistar rats	50mg/kg of Chamomile (0.5 CC) injection.	7 days	It was observed that following three weeks, MDA in the rats' lungs decreased by 44.27%, 37.80%, and 46.07% in anthocyanoside, chamomile, and combined groups, respectively. Therefore, chamomile and anthocyanoside have the ability to scavenge oxygen free radicals and prevent lipid peroxidation.	(55)
Jabri et al (2016)	In-vivo	Adult male Wistar rats (Chamomile flowers were collected from the region of Beja (North-West of Tunisia))	25, 50, 100 and 250 mg/kg, b.w. p.o.	10 days	CDE prevented the synthesis of neutrophil ROS and recovered ethanol-induced alterations in hematological parameters and erythrocytes oxidative stress.	(56)
Zemestani et al (2016)	RCT	64 participants with type II diabetes mellitus	Consumption of chamomile tea 3g/150mL hot water)	3 times a day immediately after meals for 8 weeks	Chamomile tea lowered the concentration of serum MDA as compared to the control. Total antioxidant capacity, SOD, GPx, and CAT activities were significantly increased by 6.81%, 26.16 %, 36.71 %, and 45.06% respectively in reference to the control group.	(57)

conducted by searching electronic databases including Scopus, Web of Sciences, Embase, and PubMed, using relevant keywords such as "Chamomile", "antioxidant", "anti-inflammatory", and other related MeSH terms from 1984 to 2020. All in-vitro, in-vivo and human studies were included in the review process. Duplicate studies and unrelated articles were excluded.

Results

Chemical constituents

Camomile flowers contain over 120 components (28). Ganzera et al. reported various forms of flavonoids such as glyco- mono- and di-glycosides and/or acyl-derivatives in chamomile. Other chief constituents are terpenoids, α-bisabolol and its oxides, sesquiterpene lactones(e.g.chalmuzene), and acetylene derivatives, all known as essential oils(27). Amino acids, polysaccharides along fatty acids are found in the mucilage, constituting around 10% of the flowerhead. Chamomile extracts contain volatile or essential oil obtained from the lower ranges between 0.4% and 2.0%. The resultant oil principally contains terpenoids (≤ 78%)and azulenes (1–15%) (29-33). Chamazulene (7-ethyl-1,4-dimethylaniline), synthetically transformed from matricine, under high-temperature conditions and/or abstraction of acetic acid and water from matricin (prochamazulene), is abundant in fresh flower heads. Using aCO_2 extraction method can reduce the content of chamazulene in the chamomile extract (34). The presence of farnesene (12–28%), spathulenol, and spiroethers, like the *cis*/*trans*-en-yn-dicycloethers (8–20%), have been identified in the volatile oil, as well (35-37). Teas made from chamomile appear to be rich in the essential oil detected in the flower. It has been shown that there are no substantial qualitative and quantitative differences in the essential oil content of chamomile from different growing regions of cultivated or wild plants, and that processing conditions, growth conditions, including fertilizer rate, irrigation, pesticide application do not alter its composition(38-40). However, the wild and cultivated populations of chamomile do have a different mineral content; the former has a wide variety of minerals whereas

Human studies

To the best of our knowledge, there has been a single clinical study on the antioxidant effects of chamomile. Zemestani et al. (2016) examined the influence of chamomile tea consumption on glycemic control and antioxidant status using a single-blind randomized controlled clinical trial that included 64 subjects with type 2 diabetes mellitus. The study showed that chamomile tea (3 g/150 mL hot water, 3 times a day immediately after meals for 8 weeks) lowered the concentration of glycosylated hemoglobin, serum insulin levels, homeostatic model assessment for insulin resistance, and serum MDA as compared to the control. Additionally, total antioxidant capacity, SOD, GPx, and CAT activities were significantly increased by 6.81%, 26.16 %, 36.71 %, and 45.06% respectively in reference to the control group. Short-term intake of chamomile tea has beneficial effects on glycemic control and antioxidant status in patients with T2 DM. A larger sample population and a longer intervention period may be required to show significant clinical improvements (57). The antioxidant activity of Chamomile in human studies has been summarized in table 1.

Anti-inflammation activities

In vitro studies

Emerging data reveal that having inflammation for a long time plays an important role in the progression of various diseases, such as cancer (58). Inflammation and disease are correlated with inflammatory mediators production by macrophages and neutrophils. Cyclooxygenase-2 (COX-2), is one of the enzymes involved in the inflammatory mechanism and generates inflammatory mediators such as prostaglandin E2 (PGE2). COX-2 is not able to detect in normal tissues but is increased by growth factors, tumor progression and has been an effect on the various inflammatory disorders including lupus, multiple sclerosis, arthritis (59). Traditionally, chamomile has been applied as an anti-inflammatory drug. Several chamomile constituents, such as apigenin7-O-glucoside, terpene compounds, and chamazulene have been identified due to their anti-inflammatory activities and they are extensively used in the prevention and therapeutic approach. In a previous report, Srivastava et al. (2009) have shown that chamomile isa selectiveCOX-2 inhibitor with anti-inflammatory effects (60).

The other enzyme is nitric oxide synthase (NOS) which is responsible for the production of nitric oxide (NO). The NOS gene expression is regulated via several transcription factors NF-κB/Rel which play an essential role in the regulation of inflammatory responses. Bhaskaran et al. (2010) tested the inhibitory effects of chamomile on NO release and inducible iNOS expression, and its potential anti-inflammatory mechanisms using RAW 264.7 macrophages. The results indicated that chamomile suppressed lipopolysaccharide (LPS)-induced NO production and remarkably prevented IL-1β, IL-6, and TNFα-induced NO levels in RAW 264.7 macrophages. Chamomile decreased the expression of LPS-induced iNOS mRNA and protein. In RAW 264.7 macrophages, LPS-induced DNA binding activity of RelA/p65 was notably repressed by chamomile via inhibiting IKKβ (the upstream kinase regulating nuclear factor-κB/Rel activity) and degrading inhibitory factor-κB (61). The therapeutic efficacy of apigenin was shown *in vitro* with its ability to impede leukocyte adhesion and adhesion protein up-regulation in human endothelial cells (62). Moreover, it carried inhibitory effects on the production of interleukin-1 (IL-1) α-induced prostaglandin, the release of tumor necrosis factor (TNF)-α-induced IL-6 and IL-8, and adhesion of leukocytes to cytokine-treated endothelial cells. In murine macrophage cells, apigenin at the concentrations of 3.7 and 37 μM principally intervened in the synthesis of LPS-induced IL-6 in a dose-dependent fashion, but not TNF-α(63). Figure 1 schematically shows chamomile suppression effects on the pro-inflammatory activity of LPS on macrophages.

Some studies have applied apigenin in cell models and reported that it blocks the expression of adhesion molecules(64, 65), as well as the generation of PGE2, COX-2, and NO (66). Safayhi et al. (1994) documented that chamazulene could inhibit the inflammatory reactions *in vitro* (67). Chamazulene at 15 μM led to the inhibition of the leukotriene B4 production in stimulated rat peritoneal-nucleophilic granulocytes by 50%. Besides, 2 μM chamazulene caused the blockage of the chemical peroxidation of arachidonic acid in a cell-free system. The probable anti-allergenic features of chamomile have been studied in several investigations. It has been presented *in vitro* using human basophils that of the 22 naturally occurring flavonoids, quercetin and apigenin acted as the most effective suppressors of the antigen-induced histamine release. As many as, 50 μM quercetin generated the inhibition of the histamine release by 95.8%, and apigenin did by 89.4%; comparatively, the inhibition potential demonstrated by catechin was only 5.7% (68). The anti inflammatory activity of Chamomile in in-vitor studies has been summarized in table 2.

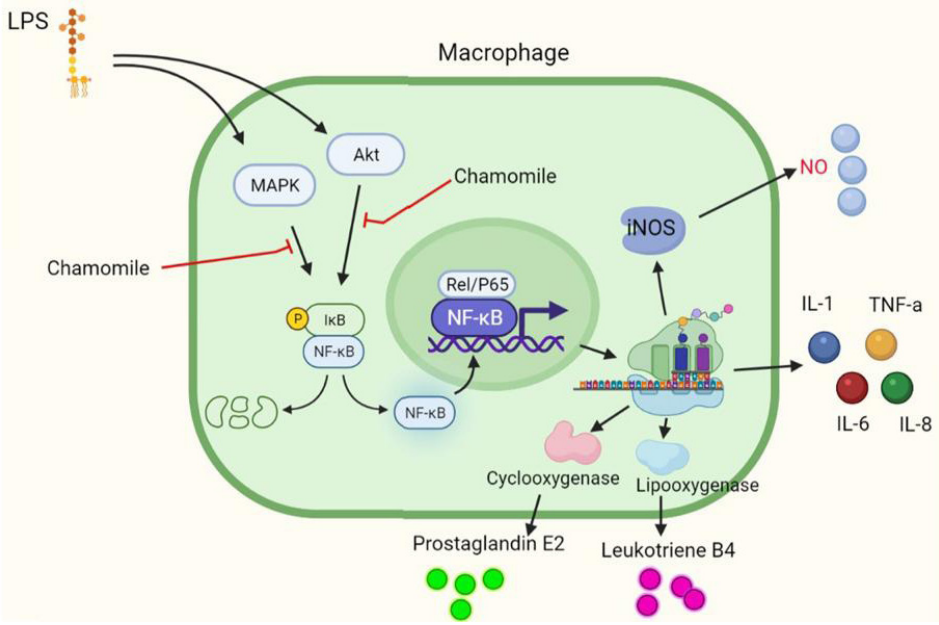

Figure 1: Chamomile suppresses macrophages induced inflammatory responses through inactivation of NF-kb gene transcription of cyclooxygenase, iNOS, and different inflammatory cytokines such as IL-1, IL-6, IL-8, TNF-α. iNOS; Inducible nitric oxide synthase, NO; Nitric Oxide, MAPK; mitogen-activated protein kinase, AKT; Protein kinase B, LPS; Lipopolysaccharides, NF-KB, Nuclear factor-kappa B, TNF-α; Tumour Necrosis Factor-alpha, IL-1,6,8: Interleukine 1,6,8

In vivo studies

Shipochliev et al. exhibited that the extract can afford to repress both the inflammatory activities and leukocyte infiltration associated

Table 2: The anti-inflammatory t activity of Chamomile in in-votro, in-vivo and human studies

Anti-Inflammatory Activity of Chamomile						
Author	**Study Design**	**Microenvironment/ Animal model/ Study population**	**Dose and Route of administration of the plant or constituents**	**Duration of treatment**	**Outcomes**	**Refrence**
Srivastava et al (2009)	In-vitro	LPS-activated RAW 264.7 macrophages	5–40 µg/mL doses of chamof mile dried material from the aqueous extract were weighed and dissolved in culture medium	24 hours	Chamomile is a selective COX-2 inhibitor with anti-inflammatory effects. Chamomile causes a reduction in LPS-induced COX-2 mRNA and protein expression, without affecting COX-1 expression.	(60)
Bhaskaran et al (2010)	In-vitro	LPS, mouse rTNF-α, mouse rIL-6, and mouse rIL-1β activated RAW 264.7 macrophages	10–40 µg/mL doses of chamomile dried material from the aqueous extract were weighed and dissolved in culture medium	12-24 hours	Chamomile suppressed LPS-induced NO production and remarkably prevented IL-1β, IL-6, and TNFα-induced NO levels in RAW 264.7 macrophages. Chamomile decreased the expression of LPS-induced iNOS mRNA and protein in RAW 264.7 macrophages.	(61)
Safayhi et al. (1994)	In-vitro	12-lipoxygenase catalyzed 12- HETE and cyclo-oxygenase catalyzed 12- HHT formation from endogenous arachidonic acid was measured in washed human platelets.	-	-	Chamazulene, but not matricine, may contribute to the anti-inflammatory activity of chamomile extracts by inhibiting the leukotriene synthesis and additional antioxidative effects.	(67)
Panes et al (1996)	In-vivo	Male Sprague-Dawley rats	apigenin (50 mg/kg, p.o.)	5 hours	TNF-induced ICAM-1 upregulation *in vivo* effectively is blocked by apigenin through a mechanism that is unrelated to free radical scavengering or leukocyte function.	(64)

Al-Hindawi et al (1989)	In-vivo	Albino Wistar rats	Subcutaneus injection of 1.6 g fresh plant/kg body weight.	-	The concentration of 1.6 g fresh lyophilized ethanol extract of dried chamomile / kg body weight ended up inhibiting paw edema by 41.1% when compared with control rats exposed to only carrageenan	(71)
Smolinski et al (2003)	In-vitro	Murine macrophage cell line, RAW 264.7 stimulated by LPS	3.7 and 37 μM of Apigenin	12, 24 and 48 hours incubations	No direct induction of proinflammatory cytokines was observed in the vehicle or apigenin-only treated cells. Co-treatment with the two highest doses, 1 and 10 mg/ml (3.7 and 37 mM, respectively), of apigenin significantly, and dose-dependently, impaired LPS-induced IL6. Significant inhibition of LPS-induced TNF-a was not observed.	(63)
Smolinski et al (2003)	In-vivo	Female B6C3F1 mice	Injection of 50 mg/kg apigenin.	Injection for 1 hour	Apigenin caused a significant reduction in LPSinduced proinflammatory cytokine production. LPS-induced IL-6 was significantly reduced (35%), while TNF-a was significantly reduced (33%) compared to animals treated with LPS alone.	(63)
Tubaro et al (1984)	In-vivo	Male albino-Swiss mic	An ethanol extract obtained from chamomile was composed of 0.05 mg/mL α-bisabolol, 0.45 mg/mL bisabolol oxides, 0.4 mg/mL apigenin and its glucosides, 0.8 mg/mL in dicycloethers, and 0.02 mg/mL azulenes. This extract was administered to animals at the specific concentrations of 0.75, 0.25, and 0.08 mg of dried flowers per animal.	-	The extract of Chamomilla Recutita induced a reduction of the croton oil oedema similar to that obtained with the non-steroidal anti-inflammatory agent.	(72)
Della Loggia et al (1990)	In-vivo	Mouse (croton oil-induced dermatitis in the mouse ear as an experimental model of topical inflammation)	Direct administration of the fresh chamomile extract having 51.8 mg/100 g bisabolol, 29.6 mg/100 g matricine, and 5.3 mg/100 g apigenin at a distinct concentration of 750 μg.	-	Fresh chamomile extract can impede inflammation in mice undergoing croton oil-induced edema, which seemed to be comparable to 0.60 mg benzydamine used. Chamomile essential oil without the presence of matricine or apigenin at a certain concentration of 30 μg essential oil failed to culminate in desired effects (6.6% inhibition)	(73)
Miguel et al (2015)	In-vivo	C57BL/6 mice	225 mg of dried chamomile was weighed and added with 20 mL of sodium hydroxide (1.6%).	7 days	The inhibition of TNF-α production by Apigenin was assessed in LPS stimulated bone marrow macrophages from mice. The results showed a dose-dependent inhibition of TNF-α production (30 and 300 μg/mL) after the stimulation with LPS.	(74)

Drummond et al (2014)	RCT	20 healthy adults	Consumtion of the chamomile beverage in 250 ml portions.	consume once daily in the morning, half an hour before breakfast for 4 weeks.	No significant anti-inflammatory effects were seen for Chamomile, despite improvement of the mechanical joint function and reduction of the knee and low back pain	(76)
Batista et al (2014)	RCT	55 patients with periodental disease	100 g of herbal powder of chamomile added to 900 g of ethanol 96%, used as the mouthwash	two daily, 1 min long, mouthwashes with 10 ml of the chamomile solution, 30 min after morning and night brushing, and for a 15 days period.	Chamomile extracts as mouth rinse had positive contributions due to their anti-microbial and anti-inflammatory characteristics similar to that of chlorhexidine 0.12%	(77)

with simultaneous exposure to carrageenan and prostaglandin E1 (69). In a different design, mice were fed a diet possessing 1.2% w/w ethyl acetate extract obtained from dried *M. Recutita* flowers for 11 days. Scratching behavior caused by the compound 48/80 was inhibited in a concentration-dependent way (70). Furthermore, both the ethyl acetate fraction of an ethanol extract and ethanol extract of a hot water infusion from the German chamomile flower remarkably prevented 48/80-induced scratching. The suppressive influences of these chamomile extracts were akin to those of 10 mg/kg oxatomide, known as an anti-allergenic agent.

Further study by these authors emphasized that the antipruritic activities of the ethyl acetate extract and chamomile essential oil relied on concentrations tested. The ethyl acetate extract at the dose of 300 mg/kg could effectively improve the effects of anti-histamine agents (i.e.oxatomide or fexofenadine at 10 mg/kg) upon combined administration. Panes et al. conducted tests on rats pretreated with apigenin (50 mg/kg, p.o.) and determined that the elevation of TNFα-induced intercellular adhesion molecule-1 (ICAM-1) was successfully counteracted 5 hours following treatment with rTNF(64). The mechanism behind this blocking effect was found out to be irrelevant to free radical scavenging or leukocyte function. Moreover, pro-inflammatory cytokine production was down-regulated in mice pretreated with 50 mg/kg apigenin for 1 hour and then injected with stimulant LPS (63). More analyses of the serum collected 1.5 hours later were indicative of the lower LPS-induced IL-6 (65%) and TNF-α (76%) in apigenin-treated animals as opposed to those treated with an individual LPS (n = 6).

Apigenin came up with delayed-type hypersensitivity in mice (62) and strong anti-inflammatory activity in carrageenan-induced rat paw edema, as well (62, 71). A lyophilized ethanol extract of dried chamomile was prepared and subsequently administered to Wistar rats. It was figured out that a concentration of 1.6 g fresh plant/kg body weight (the same as 1% of the estimated lethal dose) ended up inhibited paw edema by 41.1% when compared with control rats exposed to only carrageenan (71). Comparatively, the inhibition of edema in rats treated with 100 mg/kg acetylsalicylic acid was achieved by 32.4%. In another study on Swiss mice, the inner surface of the ear was directly treated with chamomile extract. The findings showed the reduction of edema induced by a 2.5% emulsion of croton oil (72). In this study, an ethanol extract obtained from chamomile was composed of 0.05 mg/mL α-bisabolol, 0.45 mg/mL bisabolol oxides, 0.4 mg/mL apigenin and its glucosides, 0.8 mg/mL en in dicycloethers, and 0.02 mg/mL azulenes. This extract was administered to test animals at the specific concentrations of 0.75, 0.25, and 0.08 mg of dried flowers per animal. Considering control animals, those mice exposed to 0.25 mg of chamomile extract were found with an 8.5% decline in edema and those receiving 0.75 mg appeared with a 23.4% decrease. Almost no marked alterations were detected in mice treated with 0.08 mg. The highest concentration of the chamomile extract led to a decrease the same as that occurring in the case of 0.45 mg benzydamine (26.6%), known as a nonsteroidal anti-inflammatory agent employed as a reference; nevertheless, none of the treatments showed that level of decline reached with 0.15 mg hydrocortisone (56.4%). Della Loggia et al.(1990) indicated that the direct administration of the fresh chamomile extract having 51.8 mg/100 g bisabolol, 29.6 mg/100 g matricine, and 5.3 mg/100 g apigenin at a distinct concentration of 750 µg of the dry product was able to impede inflammation in mice undergoing croton oil-induced edema, which seemed to be comparable to 0.60 mg benzydamine used as the reference drug. If compared with the control group, the

benzydamine, fresh chamomile extract, and dried chamomile extract (composed of 54.6 mg/100 g bisabolol, 16.4 mg/100 g matricine, and 6.3 mg/100 g apigenin) resulted in the prevention of the inflammatory response by 31.6%, 31.6%, and 23.7%, respectively; but, chamomile essential oil containing 55.6 mg/100 g bisabolol and 4.7 mg/100 g chamazulene without the presence of matricine or apigenin at a certain concentration of 30 µg essential oil failed to culminate in desired effects (6.6% inhibition) (73). Recently, Miguel et al. (2015) put light on the anti-inflammatory activity of apigenin-7-glucoside. They observed a diminished synthesis of TNF-α in mice subjected to apigenin-7-glucoside after LPS treatment (74). The anti inflammatory activity of Chamomile in in-vivo studies has been summarized in table 2.

Human studies

There have been some clinical evidence in favor of the anti-inflammatory potential of chamomile. For instance, a study on nine healthy, female volunteers documented that the chamomile flavonoids and essential oils had an ability to penetrate below the skin surface into the deeper skin layers. This feature plays a key role in their topical application as antiphlogistic agents (75). Thereafter, a clinical trial study including 20 healthy adults was performed to assess the effects of chamomile on systemic inflammation. Intriguingly, despite the improvement of the mechanical joint function and reduction of the knee and low back pain, no considerable anti-inflammatory effects were found (76). Differently, Batista et al. (2014) carried out another randomized controlled clinical trial and elucidated the efficacy of chamomile extracts as a mouth rinse. It was indicated that the herbal mouth rinses had positive contributions due to their anti-microbial and anti-inflammatory characteristics similar to that of chlorhexidine 0.12% (77). The anti inflammatory activity of Chamomile in human studies has been summarized in table 2.

Conclusion

Chamomile has been applied in traditional medicine and at present, its popularity has grown globally. Many research efforts have been made on its bioactivity and phytochemicals and supported its therapeutic effects on a wide variety of medical conditions. In both in vitro and in vivo observation the positive effects of chamomile on the antioxidant enzyme activity were demonstrated. However, the mechanisms involved in the action of chamomile against the production of ROS remain still unknown. When it comes to its anti-inflammatory properties, a number of *in vitro*, *in vivo*, and clinical investigations have been reported that link this potential to the selective inhibition of COX-2, suppression of NO production, prevention of IL-1β, IL-6, and TNFα-induced NO levels, reduction of iNOS mRNA and protein expression, impediment of leukocyte adhesion and adhesion protein up-regulation in human endothelial cells, and blockage of IL-1 α-induced prostaglandin production, TNF-α-induced IL-6, and IL-8 release. Elucidating whether or not patients can benefit from such pharmaceutical effects of chamomile will need rigorous research.

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