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Review article

Matricaria chamomilla: an Updated Review on Biological Activities of the Plant and Constituents

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Abstract

Chamomile or camomile (*Matricaria chamomilla* L. syn. *Matricaria recutita* L.) belongs to the family Asteraceae. It is native to Europe and West Asia and has spread to other parts of the world. The plant essential oils and extracts have been frequently used for thousands of years in traditional and folk medicines across the world, due to their valuable medicinal properties. Currently, it is widely applied in different industries such as pharmaceutical, cosmetics, and food industry. Herein, the literature was carefully reviewed via search engines such as Google Scholar, Pub Med, and Scopus using keywords including biological activity, chamomile, flavonoids, pharmacological activity, *Matricaria chamomilla*, and *Matricaria recutita*. Sesquiterpenes such as bisabolol oxide B, bisabolone oxide, and bisabolol oxide A have been identified as the major constituents of chamomile essential oil. Also, various phenolic compounds and flavonoids were mostly reported as active compounds in the plant extracts. Although there are various reports pinpointing the mechanisms of action of chamomile and its constituents, some points have remained ambiguous and further well-designed clinical trials are required. Focusing on the importance of valuable biological properties of chamomile, the present review precisely discussed the characterized chemical constituents of the plant along with their mechanisms of action.

Keywords: biological assays; chamomile; essential oil; *Matricaria chamomilla* phytochemicals

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Introduction

Matricaria chamomilla L. synonym *Matricaria recutita* L. belongs to the family Asteraceae, commonly known as chamomile or camomile. It is an annual branching plant with finely divided leaves that reaches the heights of 30 to 60 cm. The plant is native to Europe and West Asia, while it has spread worldwide to the most temperate zones. It has been counted among the medicinal treasures of various culture groups and used in the pharmaceutical and cosmetic industries with a long history of application in traditional medicine dating back to 7000-9000 BC, referenced by Hippocrates, Galen, and Asclepius [1,2].

Sesquiterpenes are the most dominant compounds identified in the chamomile essential oil. Bisabolol oxide A, bisabolol oxide B, and bisabolone oxide have been frequently reported as the main constituents of the plant essential oil in the literature. However, more than 200

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compounds have been identified in the plant essential oil with different origins. Isolated compounds from the extracts generally include polyphenols, flavonoids like apigenin, luteolin, quercetin, patuletin, isorhamnetin and their derivatives, coumarins, peptides, and polyacetylene [3-5]. It has been well documented that multi-therapeutic properties, cosmetic, and nutritional applications of chamomile both in traditional medicine and current scientific research, are indebted to important classes of volatile and non-volatile active compounds obtained from its essential oils and extracts. Also, different commercial products like tea, infusion, liquid, and capsules have been provided from chamomile [6-8].

According to the studies of both experiments and clinical reports [9], various biological and pharmacological properties including antioxidation, anti-inflammation, antimicrobial, cytoprotection and neuroprotection, wound healing, antiatherogenic and antithrombotic, antidiabetic, gastroprotection, hepatoprotection, antimigraine, and anti-anxiety activities were attributed to the chamomile extracts and essential oils. Moreover, the chamomile extracts and oil market size is noticeable and is expected to grow in the pharmaceutical field as well as perfumery, cosmetics, aromatherapy, and the food industry [10]. In this respect, this review discussed the properties of the plant focused on the identified active constituents and their mechanisms of action to find whether the available data is sufficient.

Methods

The literature was comprehensively searched without time restriction until March 2023 using search engines like Google Scholar, Pub Med, and Scopus by different keywords such as biological activity, chamomile, flavonoids, pharmacological activity, *Matricaria chamomilla*, and *Matricaria recutita*. The search results obtained with the common name of chamomile were refined with the exact mentioned scientific names. All results were extracted and analyzed to construct a correlation between the plant's constituents and biological activity.

Results and Discussion

Constituents

Characterization of chamomile essential oil

Analysis of chamomile essential oil samples has been fully achieved in different countries of the world and more than 200 compounds have been reported by various research groups. The major components include thymol (up to 5.8%), β-farnesene (0.8-29.8%), β-bisabolene (up to 19.6%), α-bisabolol oxide B (1.3-35.6%), (*Z*)-α-santolol (0.1-15.9%), α-bisabolone oxide A (0-63.5%), chamazulene (0.2-19.3%), α-bisabolol oxide A (4.9-75.4%), (*Z*)-ene-yne-dicyclo ether (0.6-10.3%), *cis*-lanceol (0.1-5.1%), (*Z*)-spiroether (5.1%), *cis*-pinocamphone (0-73.5%), (*Z,Z*)-farnesol (1.1-8.3%), and 8-isobutyryloxy isobornyl isobutyrate (11.1-14.0%) [11-17]. The content and composition percent not only depend on the geographical area and climatic conditions of the plant collection site but are also associated with the methods and techniques applied for the preparation of the essential oil, which may include hydro-distillation, supercritical fluid extraction, and headspace analysis.

The study reported by Pirzad et al. [15] showed that the essential oil content and chemical compositions of chamomile were affected by different irrigation regimes (100, 85, 70, and 55% field capacity). It was found that irrigation at 70% field capacity afforded a high amount of essential oil and irrigation at 100% field capacity was not appropriate. Also, the effect of saline irrigation water on the agronomical and phytochemical characteristics of chamomile was investigated by Baghalian et al. It was shown that saline irrigation water had no remarkable effect on oil quantity, both yield, and content of biologically important constituents such as α-bisabolol oxide B, α-bisabolon oxide A, chamazulene, α-bisabolol oxide A, α-bisabolol, and *trans* β-farnesene [18].

Homami et al. used different methods for oil extraction including microwave-assisted hydro-distillation and hydro-distillation laboratory scale which yielded 0.08 and 0.06%, respectively. α-Bisabolol oxide A (42.3%), chamazulene (15.1%), α-bisabolol oxide B (9.6%), and (*Z, Z*)-farnesol (8.1%) were the main constituents by microwave irradiation method. However, using laboratory scale method led to the isolation of *cis*-pinocamphone (73.5%) and α-bisabolol oxide A (7.9%) [17].

Rahmati et al. investigated the effect of nitrogen application (in the form of urea), plant density, and climate conditions on yield and oil constituents of chamomile [19]. The application of urea was found to be very important. The best yields of dry flower and essential oil were related to a plant density of 50 $pl.m^{-2}$ with 20 $g.m^{-2}$ urea

fertilization. The main compounds were α-bisabolol oxide A (53.45%), α-bisabolol oxide B (9.90 %), α-bisabolone oxide A (5.24%), chamazulene (4.29%), (*Z*)-β-farnesene (2.75%), and spathulenol (0.81%). It should be noted that analysis of the plant essential oil revealed presence of di-(2-ethylhexyl)-phthalate which could be associated with contamination of the oil with plasticizers. The contamination with plasticizers can happen through soil, water, or during processing of the plant [20-22].

Characterization of chamomile extracts

Žlabur et al. investigated the effect of different extraction methods and solvents on the composition of bioactive compounds of the chamomile flower extracts. Extraction methods included conventional methods and ultrasound-assisted extraction [5]. It was found that not only the extraction time of bioactive compounds was remarkably decreased by ultrasound-assisted extraction but also the content of polyphenolic compounds following with antioxidant capacity were significantly higher than conventional methods. Also, the ultrasonic treatment afforded an increase in total acid content. However, other properties such as the density, total soluble solids, and pH value did not show considerable changes. In this respect, the extraction of vitamin C from chamomile flowers was directly affected by the extraction conditions. The highest vitamin C content was obtained using the conventional method with EtOH-water (80:20) at room temperature for 35 min. The ultrasound-assisted method reduced the amount of vitamin C which probably caused by degradation during sonolysis.

Bisabolol oxides: Different bisabolol oxide derivatives (Figure 1) have been identified in the methanol extract of flower heads of German chamomile [23]. The compounds 9-hydroxybisabolol oxide A **1**, seco-bisabolol oxide B **2**, (1R)-l-hydroxybisabololoxide B **3**, and bisabolol oxide A glycoside **4** were obtained from *n*-hexane fraction while 15-hydroxybisabolol oxide A β-D-glucoside **5** was isolated from the combination of ethyl acetate and *n*-butanol fractions.

Carboxylic acids and esters: The presence of caffeic acid and chlorogenic acid in the chamomile extract [6,24] was reported by Fonseca et al. [24]; (*Z*)- and (*E*)-2-β-D-glucopyranosyloxy-4-methoxycinnamic acid [25] were also identified in the ethanol extract of chamomile flowers using HPLC/MS and HPLC/NMR techniques as the precursor of biosynthesis of herniarin in the plant [26]. Moreover, 3-caffeoylquinic acid, 4-caffeoylquinic acid, 5-caffeoylquinic acid, quinic acid, ferulic acid-l-*O*-glycoside, ferulic acid-7-*O*-glycoside, dicaffeoylquinic acid derivative, 1,3-dicaffeoylquinic acid, dicaffeoylquinic acid derivative, quinic acid derivative, caffeoylquinic acid derivative [27], neochlorogenic acid, cryptochlorogenic acid, isochlorogenic acid A, isochlorogenic acid B, isochlorogenic acid C [28], and 1-*O*-2'-hydroxy-4'-methoxycinnamoyl-β-D-glucose [29] were reported to be isolated from the chamomile extracts.

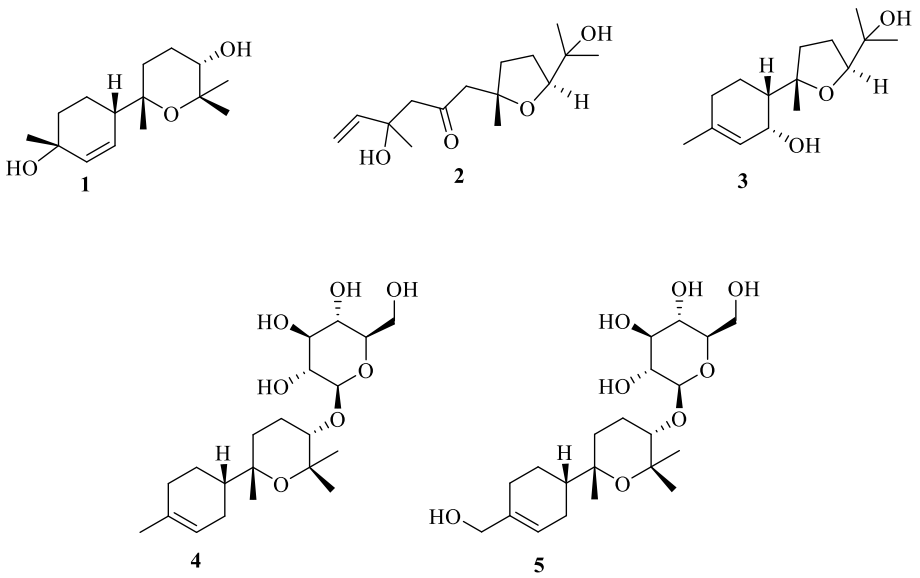


Figure 1. Bisabolol oxide derivatives isolated from *Matricaria chamomilla*

Coumarins: Coumarin (2H-chromen-2-one) [30] and its derivatives (Figure 2) such as herniarin, umbelliferone, aesculetin (cichorigenin), scopoletin and isoscopoletin have been found in the chamomile alcoholic extract. Among them, umbelliferone and herniarin were found to be more abundant [30,31]. Molnar et al. compared different methods such as soxhlet, hydro-distillation, maceration, and supercritical CO_2 extraction, for the isolation of umbelliferone and herniarin in chamomile [32]. The highest yield of umbelliferone and herniarin were obtained using a maceration technique with 50% aqueous ethanol solution. Herniarin and umbelliferone have been identified as stress metabolites. The increased amount of umbelliferone was reported in the leaves of chamomile, 12 h after abiotic stress elicitation by $CuCl_2$ and this amount increased approximately 10 times within 48 h. Also, the content of herniarin increased along with a decrease of its precursor, (*Z*)- and (*E*)-2-β-D-glucopyranosyloxy-4-methoxy cinnamic acid [33]. Skimmin, daphnin, and daphnetin were found in diploid and tetraploid leaves and anthodia of *M. chamomilla* L., reported by Petrul'ová-Poracká et al. for the first time [34].

Flavonoids: Flavonoids and their glycoside derivatives are ubiquitous in the extracts of *M. chamomilla*. According to the Haghi et al. report, the total flavonoid contents of aerial parts of *M. chamomilla* ranged from 0.82-36.75 g quercetin equivalent (QE)/100 g in dry material [35]. Also, the total phenolic contents of aerial parts of *M. chamomilla* ranged from 1.77 to 50.75 gram (g) of gallic acid equivalent (GAE)/100 g.

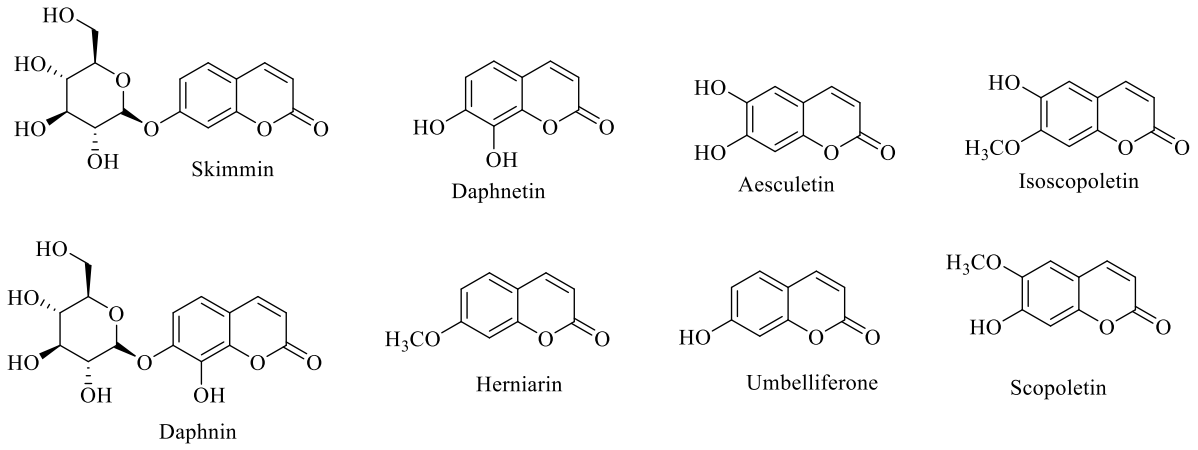
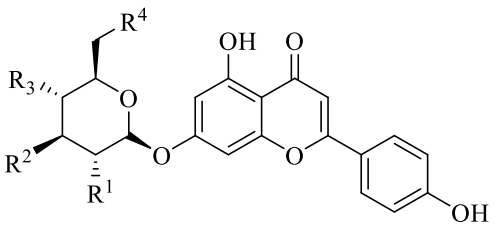


Figure 2. Coumarin derivatives isolated from *Matricaria chamomilla*



R^1 = OH, R^2 = OH, R^3 = OH, R^4 = OH
R^1 = Acetyl, R^2 = OH, R^3 = OH, R^4 = OH
R^1 = OH, R^2 = Acetyl, R^3 = OH, R^4 = OH
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R^1 = OH, R^2 = OH, R^3 = OH, R^4 = Malonyl
R^1 = OH, R^2 = OH, R^3 = OH, R^4 = Caffeoyl
R^1 = OH, R^2 = OH, R^3 = Acetyl, R^4 = Malonyl

Figure 3. Flavonoid derivatives isolated from *Matricaria chamomilla*

The presence of apigenin and its derivatives (apigenin-7-O-β-glucoside, apigenin-7-O-apiosylglucoside, pigenin-7-O-glucosyl-6"-acetatee, apigenin-7-O-glucosyl-2"-acetate, apigenin-7-Oglucosyl-2",3"-diacetate, and apigenin-7-O-glucosyl-3",4"-diacetate), luteolin and its derivatives (luteolin-7-O-β-glucoside, luteolin-4'-O-β-glucoside, luteolin-7-O-β-rutinoside, and 6-hydroxyluteolin-7-glucoside), quercetin and its derivatives (quercetin-7-O-β-glucoside, quercetin-3-Oβ-rutinoside, and quercetin-3-O-β-galactoside), patuletin and its derivative (patuletin-7-O-βglucoside), isorhamnetin and its derivative (isorhamnetin-7-O-β-glucoside), chrysoeriol-7-Oβ-glucoside [36], jaceidin, chrysosplenol, eupatoletin, spinacetin, axillarin, eupalitin, chrysosplenetin, astragalin [37], and naringenin [24] have been reported in the literature. Isorhoifolin (apigenin-7-O-rutinoside) as well as various acylated derivatives of apigenin 7-O-glucoside (Figure 3) have been also isolated from the flower of *C. recutita* [25,38-40].

Peptide: A peptide, MCh-AMP1possessing antifungal activity was purified by reverse phase HPLC from flowers of *M. chamomilla* by Seyedjavadi et al. The confirmed sequence was LSVKAFTGLQLRGVCGLEVKARG [4].

Polyacetylenes: Polyacetylene tonghaosu ((*Z*)-Ene-yne-dicyclo ether) was identified in the hexane fraction of methanol extract of chamomile flower heads. This compound is chemically unstable and transforms to spirolactone, 1,6-dioxaspiro[4.4] non-3-en-2-one under a photochemical reaction (Figure 4) [3].

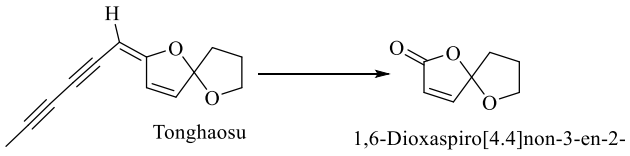

Figure 4. Transformation of tonghaosu to 1, 6 dioxaspiro [4.4] non-3-en-2-one

The mineral elements: Mineral components play an auxiliary role in inducing the biological properties of chamomile. It has been perceived that wild populations contain higher amounts of mineral elements than the cultivated Degumil type. However, the ratios of K/Na and Ca/Mg in the cultivated type are mostly higher than in wild chamomile populations. Mineral content in infusions of chamomile is relatively low in which relatively high concentrations of potassium, calcium, and magnesium were found. The dissolution of mineral elements in tea was reported between 10-26% for most of the elements and the highest value was associated with magnesium (26%) [41].

Chizzola et al. reported the amounts of calcium, potassium, magnesium, zinc, and cadmium as 19-23, 65-73, 47-48, 2324, and 15-21%, respectively, in boiling water extraction of chamomile flower heads within 10-20 min [42]. A longer extraction time led to slightly higher recovery rates for potassium and zinc.

Biological activities of chamomile: in vitro and in vivo and studies

Biological activities of essential oil constituents considering their relevant mechanisms of action are reported in Table 1. Various pharmacological properties of chamomile and its essential oil constituents, in several health conditions related to oxidation, inflammation, microbial infections, and cancer disorders have been fully documented in the literature.

The biological activities of the main constituents of chamomile extracts along with their mechanisms of action are summarized in Table 2.

Antioxidant activity

Numerous chronic pathologies like cancers and cardiovascular diseases are associated with lipid peroxidation which is triggered by free radicals. DPPH, 2.2-Diphenyl-1-picrylhydrazyl, (•) is a stable lipophilic radical that is applied as a model for the evaluation of antioxidant activity in vitro. Methanol extract of chamomile showed higher radical scavenging activity in comparison to other extracts obtained with ethanol, diethyl ether, and hexane which is attributed to the higher phenolic content of the methanol extract including chlorogenic acid, caffeic acid, *p*-coumaric acid, and ferulic acid [43]. The chamomile flower extract obtained by aqueous ethanol 70% contained a total flavonoid content of 157.9±2.22 mg quercetin equivalent (QE)/g and 21.4±0.327 mg gallic acid equivalent (GAE)/g dry extract and inhibited DPPH with EC_{50} value of 26.7 µg/mL [44]. A high positive correlation was observed between total phenolics content, total flavonoids, and condensed tannins in methanol and aqueous extracts of chamomile flowers and scavenging of DPPH and 2,2-azino-bis-(3-ethylbenzthiazoline-6-sulphonic acid)

(ABTS) radicals [45]. Radical scavenging activity of flower decoction of the plant was significantly higher in comparison to vitamin C against DPPH [46]. Full-fat diet significantly increased SOD, CAT, and GPx in the kidney and liver of rats which were restored to their normal levels by administration of chamomile flower decoction. In addition, the plant decoction increased non-enzymatic antioxidant levels in the kidney and liver [47].

Antimicrobial activity

Essential oil and different extracts of *M. chamomilla* obtained by solvents with different polarities including methanol, ethanol, diethyl ether, and hexane were tested against *Escherichia coli* O157, *Salmonella typhi*, *Bacillus cereus*, *Staphylococcus aureus*, *Candida albicans*, and *Aspergillus flavus* (Table 3). Minimum inhibitory concentration (MIC) of essential oil generally were in the lower range of 10-12.5 µg/mL in comparison with the plant extracts which inhibited the microorganisms with MIC values ranging from 10-17.5 µg/mL. The plant EO was rich in α-bisabolol oxide A, α-bisabolol oxide B, and α-bisabolol [43, 48]. α-Bisabolol may inhibit fungal growth through inhibition of ergosterol biosynthesis [49]. Chamomile EO had generally bacteriostatic activity, especially against gram-positive bacteria. Chemical composition and biological activities of chamomile extracts were also studied which affected by different solvents with various polarities and methods of extraction (Table 3) [50]. The composition of the plant EO varies based on the season of harvest and method of extraction which can affect the composition and therefore their antibacterial activity [51-53].

Table 1. Biological activities of essential oil constituents of *Matricaria chamomilla* and their mechanisms of action

Compound	Biological function	Mechanism of action	Ref.
α-Bisabolol	Anti-inflammatory	**In vitro**: suppression of NF-κB, p38 and JNK signaling **In vivo**: increase of the MPO activity and reduction of NO production in systemic infection model in mice; reduction in phosphorylation levels of ERK1/2, p38 and JNK proteins in pulmonary inflammation model; reduction in leukocyte migration, protein extravasations and TNF-α	[129-132]
	Anti-bacterial	**In vitro**: inhibition of NorA and TetK efflux pump in *Staphylococcus aureus*	[133]
	Leishmanicidal activity	**In vitro**: active against *Leishmania amazonensis* and *Leishmania infantum* by promotion of programmed cell death process, externalization of phosphatidylserine and membrane damage, reduction in mitochondrial membrane potential and levels of ATP	[134]
	Anti-genotoxic	**In vitro**: antigenotoxic effect against H_2O_2 by terminating the free radicals	[135]
	Peripheral nervous blocker	**In vitro**: blocking sodium and potassium voltage-gated channels, decreasing nervous excitability	[136]
	Wound healing	**In vivo**: reduction of NF-κB and elevation of cytokeratin expressions	[137]
	Neuroprotection	**In vivo**: increase of the MPO activity, TNF-α immunoreactivity in the temporal cortex, and iNOS in both temporal cortex and striatum	[138]
	Nephroprotection	**In vivo**: nephroprotection in ischemia/reperfusion animal model through antioxidant activity and reduction of tubular damage	[139]
Bisabolol oxide A	Cytoprotective and Cytotoxicity	**In vitro**: inhibition or delaying necrosis and some apoptotic features through the Ca^{2+}-dependent process (1-10 µM) while inducing apoptosis and necrosis by concentrations higher than 30 µM	[140-142]
	Antipruritic action	**In vivo**: inhibition of vanilloid receptor activation suppressing sensory irritation and inflammation	[143]
Matricin	Anti-inflammatory	**In vitro**: inhibition of NF-κB transcriptional activity, decrease in adhesion molecule of ICAM-1 and TNF-α	[123]
	Cytotoxicity	**In vitro**: induction of apoptosis, suppression of cell migration and invasion, caspase activation, and blocking the mTOR/PI3K/AKT signaling pathway	[144]
Chamazulene	Antioxidant	**In vitro**: scavenging free radicals DPPH and ABTS; inhibition of ROS production	[145,146]
	Anti-inflammatory	**In vitro**: reduction of TNF-α and IL-6, suppression of the expressions of COX-2, iNOS, MMP-3, MMP-9, and p65 NF-κB; inhibition of production of leukotriene B4, block chemical peroxidation of arachidonic acid **In vivo**: decrease in the levels of TNF-α and IL-6	[124,125]

COX-2: cyclooxygenase; GGT: gamma glutamyl transferase; GSH: glutathione; iNOS; inducible nitric oxide synthase; IFN: interferon; IL: interleukin; JNK; c-Jun N-terminal kinase; MAPK: mitogen activated protein kinase; MMP-9: matrix metalloproteinase-9; MPO: myeloperoxidase; NO: nitric oxide; NF-κB: nuclear factor kappa B; ROS: reactive oxygen specious; SOD: superoxide dismutase; TNF: tumor necrosing factor

Table 2. Biological activities of constituents of *Matricaria chamomilla* extracts and their mechanisms of action

Compound	Biological function	Mechanism of action	Ref.
Apigenin	Anti-inflammatory	**In vitro**: inhibition of enzymes COX-2 and iNOS, suppression of production of NO, inhibition of pro-inflammatory cytokines like IL-1β, IL-8, and TNF-α secretion, TNF-induced NF-*κ*B transcriptional activation **In vivo**: down-regulation of P2X7/NF-*κ*B pathway, inhibition of IL1b, MMP3,1,13 ADAMTS-5 in arthritis rheumatoid; decrease in inflammatory cell infiltration to synovial	[120-122, 126,147-151]
	Antioxidant	**In vitro**: DNA protection against free radicals	[152]
	Anti-mutagenic	**In vitro, In vivo, Ames test**: prevention or inhibition of genotoxicity	[153-155]
	Anti-bacterial	**In vitro**: reduction of α-hemolysin of S. aureus, enhancement of antibiotic activity by inhibition of peptidoglycan synthesis, *β*-lactamase enzymes, and alteration in permeabilization of outer membrane and cytoplasmic membrane, reduction of *Helicobacter pylori* colonization and monocyte and neutrophil infiltrations with atrophic gastritis, inhibition of water-insoluble glucans synthesis by *Streptococcus mutans*, targeting DNA gyrase, d-alanine ligase and the type II fatty acid synthetic pathway **In vivo**: decrease in cytokines in a mouse model of *Staphylococcus aureus* pneumonia	[156-162]
	Anti-viral	**In vitro**: inhibition of cytopathogenic effect and replication, interference with viral IRES activity and inhibition of virus induced JNK activation critical for virus replication EV71, replication inhibition of HCV, interference with the translational activity of FMDV by internal ribosome entry site, prevention of cytopathic effect and inhibition of ASFV-specific protein synthesis	[163-166]
	Antifungal	**In vitro**: cell shrinkage induction in *Candida albicans* resulting in alteration of the cell membrane potential and causing leakage of intracellular components	[167]
	Antiparasitic	**In vitro**: antiproliferation activity against *Leishmania amazonesis* via rupturing of the trans-Golgi network, swelling in parasite mitochondria, alteration in mitochondrial membrane potential, and cytoplasmic vacuolization	[168-170]
	Antidiabetic	**In vivo**: reduction of NO, MDA, ICAM, and glucose, increase of GSH, SOD and insulin	[171]
	Effect in autoimmune diseases	**In vivo**: in lupus inhibition of APCs and autoantigen presentation, apoptosis of the hyperactive cells, prevention of the production of autoantibodies against nuclear antigens; in MS, reduction of T cells proliferation, restrain phagocytosis, producing IFN-ɣ, ROS, regulation of miR-155 in inflammation; in myocarditis suppression of the infiltration of inflammatory cells, modulation of the Th1/Th2 cytokine balance; in ulcerative colitis suppression of the infiltration of inflammatory cells and cytokine production, reduction of MPO, MDA, COX and iNOS	[157,172-180]
	Cytotoxicity	**In vitro**: induction of apoptosis; modulation of glycolytic and mitochondrial pathways of ATP production, blocking IL-6 and IL-10 secretion and up regulation of mRNA expression of TNF-α, caspase 3 and 8; decrease in cancer cell growth, glucose utilization, invasion into matrix, reduction in angiogenesis and endothelial attachment; inhibition of ornithine decarboxylase; down regulation of MMP-2, -9 and slug and snail, down regulation of NF-κB p105/p50, PI3K, and Akt and its phosphorylation; activation of proteasomal degradation apparatus	[135,181-184]
	Suppression of cancer	**In vivo**: suppression of metastasis in animal models; delay in tumor growth; suppression of IL-6-linked downstream signaling pathway resulting in anti-invasive effect	[182,185-189]
	Neuroprotection	**In vivo**: providing anti-ischemic effect through increase in activity of HO-1 and Nrf2	[190]
Luteolin	Anti-inflammatory	**In vitro**: inhibition of TNF-α secretion	[120]
	Antiatherogenic property	**In vitro**: augmentation of the homeostatic potential of HO-1 through modulation of the Nrf2/MAPK signaling pathway; inhibition of Ang II-mediated oxidative stress and apoptosis in macrophages; antagonize p38 MAPK apoptotic signal **In vivo**: inhibition of proatherogenic mediators like IL-1, TNF-α, and MMP-9, ICAM-1, VCAM-1, and E-selectin in LPS-challenged mice; suppression of serum TG, total cholesterol, LDL, creatine kinase, lactate dehydrogenase, and CTGF in male rats; attenuation of oxidative stress and dysfunction of eNOS in diabetic rats with ischemia and reperfusion injury	[191-197]
	Antithrombotic property	**In vitro**: reduction in fibrin clot mass through suppression of fibrin polymers, inhibition of enzymatic activities of thrombin and FXa **In vivo**: inhibition of the development of oxidative stress which induced thrombosis	[198,199]
	Anti-diabetic	**In vitro**: epigenetic changes in monocytes resulting in inhibition of	[200]

Table 2. Continued

		hyperglycemia-induced cytokine production through NF-κB suppression	
	Anti-inflammatory	**In vitro**: inhibition of TNF-α secretion	[120]
Quercetin	Antiatherogenic	**In vitro**: inhibition of thrombin, ADP-induced aggregation of platelets, and 12-HETE, reduction of oxidation and aggregation of LDL **In vivo**: elevation of cytochrome P450 content in the liver of experimental animals, attenuation of lipid peroxidation and hyperlipidemia in the aorta of high cholesterol-fed white rabbit, reduction of LDL oxidation in LDL receptor–deficient mice	[201-207]
	Suppression of cancer	**In vivo**: suppression of metastasis in animal models, delay in tumor growth and raising survival rate	[185,187]
Umbelliferone	Antioxidant	**In vitro**: scavenging DPPH free radical, suppression of membrane reactive free hydroxyl radical, chelating ferrous ion, inhibition of lipid peroxidation, suppression of ROS production	[208]
	Anti-inflammatory effect	**In vitro**: dual inhibition against COX-2 and 5-LOX enzymes **In vivo**: reduction in lung inflammation and mucus production in an inflammation model induced by ovalbumin administration in mice	[127,209]
	Anti-genotoxic	**In vitro**: inhibition against oxidative DNA damage	[210]
	Antinociceptive	**In vivo**: antinociceptive property involved in NO system not opioid pathway, inhibition of both peripheral and centrally acting pain mediators	[211,212]
	Effect on hyperpigmentation	**In vitro**: weak inhibition of tyrosinase compared to kojic acid	[213]
	Anti-diabetic effect	**In vitro**: inhibition of aldose reductase and α-glucosidase; activation of PPARγ and PPARβ **In vivo**: improvement of glucose tolerance, modulation of hepatic lipid metabolism and antioxidant defense system with increase in levels of adiponectin; protective effect in liver cells by reduction of GGT, AST, and ALT	[214-217]
	Anti-cancer activity	**In vitro**: reduction in cell viability and cell migration; induction of cell cycle arrest, apoptosis, and DNA fragmentation	[218-220]
Herniarin	Anti-genotoxic	**In vitro**: inhibition against oxidative DNA damage **In vivo**: decrease in the apoptotic and necrotic cells and the ROS level in bone marrow cells	[210,221]
	Cytotoxicity	**In vitro**: increase in chromatin condensation	[222]

ASFV: African swine fever virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; COX-2: cyclooxygenase-2; eNOS: endothelial nitric oxide synthase; EV71: enterovirus 71; FMDV; foot-and-mouth disease virus; GGT: gamma glutamyl transferase; GSH: glutathione; HO-1: heme oxygenase-1; HCV: hepatitis C virus; 12-HETE: 12-hydroxyeicosatetraenoate; ICAM: intracellular cell adhesion molecule; iNOS: inducible nitric oxide synthase; IFN: interferon; IL: interleukin; JNK: c-Jun N-terminal kinase; LDL: low density lipoprotein; MAPK: mitogen activated protein kinase; MMP-9: matrix metalloproteinase-9; HO-1: heme oxygenase-1; 5-LOX: 5-lipoxygenase; CTGF: myocardial connective tissue growth factor; MS: multiple sclerosis; MPO: myeloperoxidase; NO: nitric oxide; NF-κB: nuclear factor kappa B; PPAR: peroxisome proliferated activated receptor; Nrf2: E2-related factor 2; ROS: reactive oxygen specious; SOD: superoxide dismutase; TG: triglyceride; TNF: tumor necrosing factor; VCAM: vascular cell adhesion molecule

No growth inhibition was observed by the essential oil of chamomile flower against *Salmonella paratyphi*, *Salmonella typhimurium*, *Shigella* spp., *P. aeruginosa*, *S. aureus*, and *E. coli* which can be explained by the low concentration of α-bisabolol (4%) that known as a responsible component for antibacterial activity [54].The plant essential oilwas examined against 12 strains of *P. aeruginosa* and 8 strains of *S. aureus* which were isolated from patients diagnosed with external otitis. No inhibition was observed against *P. aeruginosa*, while the plant oil showed inhibition activity against growth of three *S. aureus* with inhibition zone diameter of 10 mm [55]. While, in another study the methanol extract of chamomile providing inhibition activity against *P. aeruginosa* with MIC value of 78 µg/mL. The presence of terpenoids, phenols, tannins, and flavonoids were proven in the extract which may responsible for the observed antibacterial activity [56].

The result of a study showed that hydroethanolic extract of chamomile exhibited small antiadhesive activity in human colon carcinoma cells affected by *Campylobacter jejuni* [57]. Alternatively, the hydroethanolic extract of the plant was tested against two other responsible bacteria for gastrointestinal diseases, *Helicobacter pylori* and *C. jejuni*, showing very satisfactory results against *C. jejuni* in that with a concentration of 20 mg/mL the growth of bacteria 100% inhibited [58]. The 50% hydroalcoholic extracts of chamomile flowers and leaves were fractioned and tested against *Bacilus subtilis* and *Pseudomonas syringae*. Both flowers and leaves suppressed the growth of *Pseudomonas syringae* and some of the fractions

showed antibacterial activity which was ascribable to *cis*-, *trans*-spiroethers, and the coumarins like herniarin and umbelliferone [59]. The 70% ethanol extract of the flowering part of *M. chamomilla* was tested against *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *S. epidermidis*, *P. syringae* pv. *maculicola*, *Xanthomonas vesicatoria*, *Aliivibrio fischeri*, and *Bacillus subtilis*.

The chamomile extract suppressed the growth of *Staphylococcus epidermidis*, MRSA, and *S. aureus* with an inhibition zone diameter ranging 6-7 mm, while vancomycin only inhibited the growth of MRSA with a zone diameter of 7 mm. Two active compounds, apigenin and α-linolenic acid, were detected in the tested extract [60].

Antiparasitic activity

Amoebae of *Acanthamoeba castellani* was sensitive to α-bisabolol, the main sesquiterpene in the chamomile essential oil, in a dose-dependent base with respective IC_{50} and IC_{90} values of 20.83 and 46.60 µg/mL. The compound caused apoptosis by externalization of phosphatidylserine, cellular membrane damage, decrease in the mitochondrial membrane potential, and reduction of ATP level [61]. With concentrations of 1000 and 500 µg/mL α-bisabolol, caused 100% inhibition against *Leishmania infantum* promastigote [62]. Solid lipid nanoparticles containing α-bisabolol with diminazene aceturate in *Trypanosoma evansi* infected mice improved the therapeutic effectiveness of diminazene aceturate [63].

Table 3. Antimicrobial activity of *Matricaria chamomilla* extracts and essential oil against different microorganisms

Plant extract/EO	Microorganisms	MIC (µg/mL)	Ref.
Methanol extract	*Escherichia coli*	15	[43]
	Salmonella typhi	15	
	Bacillus cereus	12.5	
	Staphylococcus aureus	12.5	
	Aspergillus flavus	12.5	
	Candida albicans	10	
Ethanol extract	*Escherichia coli*	15	
	Salmonella typhi	15	
	Bacillus cereus	12.5	
	Staphylococcus aureus	12.5	
	Aspergillus flavus	15	
	Candida albicans	12.5	
Diethyl ether extract	*Escherichia coli*	17.5	
	Salmonella typhi	15	
	Bacillus cereus	15	
	Staphylococcus aureus	15	
	Aspergillus flavus	17.5	
	Candida albicans	15	
Hexane extract	*Escherichia coli*	15	
	Salmonella typhi	15	
	Bacillus cereus	12.5	
	Staphylococcus aureus	10	
	Aspergillus flavus	12.5	
	Candida albicans	10	
Essential oil	*Escherichia coli*	12.5	
	Salmonella typhi	12.5	
	Bacillus cereus	10	
	Staphylococcus aureus	10	
	Aspergillus flavus	12.5	
	Candida albicans	10	
Essential oil	*Staphylococcus aureus*	0.01	[48]
	Bacillus cereus	0.02	
	Bacillus subtilis	0.03	
	Shigella shiga	0.14	
	Shigella sonnei	0.2	
	Pseudomonas aeruginosa	4	
	Proteus sp.	0.15	
Ethanol extract	*Pseudomonas aeruginosa*	10^6	[223]

MIC: minimum inhibitory concentration; EO: essential oil

The ethyl acetate fraction of chamomile showed the highest antioxidant activity with stronger amoebicidal activity against *Acanthamoeba castellanii* in comparison with other fractions of extract including hexane, chloroform, and aqueous fractions. The analysis of the ethyl acetate fraction indicated the presence of a mix of coumarin derivatives in it [64].

Food preservation

The application of chamomile as a food preservative was evaluated in some studies. Decoction of chamomile improved the antioxidant potential of cottage cheese by lowering lipid peroxidation and the higher free radical scavenging activity that prolonged the shelf life of the cheese. This bioactivity may be related to the release of phenolic compounds possessing antioxidant and antimicrobial activities [65]. The microencapsulation of the extract also prolonged antioxidant activity in the cheese after seven days, but had similar color parameters and nutritional as well as fatty acid profiles [66]. Decoction of chamomile as an antioxidant agent was used in wheat biscuits, and samples were analyzed for 60 days of storage monitoring nutritional profile, sugars, fatty acids, and antioxidant capacity. The incorporation of natural or synthetic antioxidants did not significantly change the color or nutritional values of the biscuits. Similar antioxidant capacity was achieved by both antioxidants; therefore, the extract of the plant is a good replacer for synthetic additives [67]. *Matricaria chamomilla* essential oil was applied in casein-based film to increase its barrier properties and antibacterial activity. The film showed an inhibitory effect against *Listeria monocytogenes*, *S. aureus*, and *E. coli* in vitro which was evaluated by the disk-diffusion method. α-Bisabolol and other components in the oil were responsible for the antibacterial activity of refined casein-based film [68]. The majority of essential oils are classified as generally recognized as safe (GRAS) including *M. chamomila*. While their application may be limited due to the flavor consideration because doses of the antimicrobial amount of oil may exceed organoleptically acceptable levels [69].

Anthelmintic activity

Methanol and aqueous extracts of flowers of *M. chamomilla* which were rich in phenolic compounds, flavonoids, and condensed tannins showed high inhibitory effects on egg hatching. The methanol extract at a concentration of 4 mg/mL inhibited 100% of egg hatching with an IC_{50} value of 1.52 mg/mL. A high correlation was found between the inhibition of egg hatching and the phytochemical contents of the extracts. After 8 h, the methanol extract (8 mg/mL) induced 91.77% mortality against adult worm *Haemonchus contortus*, while aqueous extract with the same concentration caused 75.05% mortality. Albendazole as a reference, caused 82.26% mortality [45].

Anti-inflammatory activity

Results of a study showed that hydrophilic Carbopol gel containing ethanol extract of flowers of chamomile was not active in the carrageenan paw edema model in rats. Sodium lauryl sulfate (SLS) was applied as the permeation enhancer in gelling formulations. The presence of apigenin was assessed in the plant extract using the HPLC method [70]. Previous studies revealed that luteolin, apigenin, and chamazulene were individually efficacious in inhibition of COX-2, iNOS, and leukotriene expression in cell culture [71].

Anti-platelet activity

Polysaccharide-polyphenolic conjugates isolated from *M. chamomilla* resulted in a dose-dependent decrease of platelet aggregation induced with Adenosindiphosphat (ADP), collagen, and arachidonic acid. The extract showed no toxicity against human blood platelets, mouse fibroblast L-929, and human lung cells A-549. Therefore, compounds obtained from chamomile have the potential for the development of new anti-platelet agents [72].

Cytotoxicity

The chamomile flower extract, obtained by aqueous ethanol 70%, rich in phenolics, and flavonoids showed cytotoxicity against human hepatoma cancer cells (HepG-2) in a dose-dependent manner with an IC_{50} value of 300 µg/mL [44]. Extract of flowering aerial parts of the plant inhibited nitric oxide (NO) production in colorectal cancer cell line HT-29 and exhibited cytotoxicity against the cancer cell line with IC_{50} values of 1881 and 1669 µg/mL after 24 and 48 h, respectively [73].

Antiangiogenic activity

Vascular endothelial growth factor (VEGF) stimulates the process of blood vessel formation; expression of VEGF was inhibited by flower extract of *M. chamomilla*. Additionally, the extract of chamomile flower down-regulated matrix metalloproteinase (MMP-9) substantiating the activity that is responsible for the regulation of tumor angiogenesis [44].

Gastroprotective effect

Decoction of chamomile flowers protected gastric mucosal damage caused by ethanol in rats significantly and dose-dependently. Pre-treatment with the flower decoction with a dose of 100 mg/kg reduced gastric lesions by 90.95%, while famotidine or ascorbic acid decreased lesions by 81.13% and 73.12%, respectively. Considering the mechanism of action of the plant, the decoction might partly reverse the depletion of antioxidant enzymes and sulfhydryls induced by ethanol in a dose-dependent manner. Levels of intracellular mediators including H_2O_2, iron, and calcium were also decreased by chamomile decoction, significantly. The presence of phytochemicals like polyphenols, flavonoids, and condensed tannins with high concentrations has been shown to be responsible for the antioxidant activity of the plant [74].

Anti-diarrheal activity

Decoctions of *M. chamomilla* flower with the doses of 25, 50, and 100 mg/kg were administered in an animal model of diarrhea induced by castor oil significantly reduced the number of defecations. Loperamide with the dose of 20 mg/kg produced a more marked antidiarrheal effect but less than the highest dose of the flower decoction. Intestinal lipoperoxidation with H_2O_2 and labile iron induced by castor oil were reduced with a decoction of chamomile flower in a dose-dependent manner. Castor oil depleted mucosa antioxidant enzymes, the effect which decreased with pre-treatment of chamomile decoction [75].

Hepatoprotective activity

The decoction of *M. chamomilla* flower protected liver injury and histological changes dose-dependently induced with acute alcohol intoxication in rats. Pretreatment with extract significantly reversed lipoperoxidation, antioxidant enzyme depletion, and attenuated liver-SH group level. Alcohol treatment increased calcium, free iron, and H_2O_2 levels in plasma and liver, while pretreatment with a decoction of chamomile flower showed protection against ethanol-induced intracellular mediator disturbances in a dose-dependent manner [46]. High-fat diet in rats increases activities of ALT and AST which is attenuated with the administration of chamomile flower decoction [47].

Spasmolytic activity

The anti-spasmodic and spasmolytic effects of flavonoid components of *M. chamomilla* were evaluated on isolated jejunum of rabbits. The plant showed spasmolytic effect on K^+-induced spontaneous contractions, suggesting that calcium channels are involved in its spasmolytic actions. The results of the study revealed that the spasmolytic effect of the plant was mediated through NO-activated cholinergic and histaminergic receptors [76]. Several other studies indicated the indirect Ca^{2+} channel-blocking activity of chamomile and its flavonoid fraction [77-79]. However, verapamil could not prevent the antispasmodic activity of the plant. The extract of the plant in low doses could augment the effect of verapamil which was irrespective of indirect reaction with Ca^{2+} channels. In addition, the spasmolytic effect of chamomile could be blocked by atropine and cetirizine which possibly indicated that muscle relaxation by chamomile was partly mediated through acetylcholine (Ach) and histidine (His) receptors [80]. Results of a study showed that the spasmolytic effect of *M. chamomilla* and its flavonoid fraction was mediated by the inhibition of cAMP activity and cAMP phosphodiesterase [81,82]. A growing body of evidence suggests that a wide range of signaling cascades are activated by apigenin and quercetin causing smooth muscle relaxation [83,84]. Apigenin has also been attributed to the inhibition of Ca^{2+} release or induction of eNOS and NO production in mouse gastric tissue. An increase in intracellular calcium concentration by apigenin and quercetin resulted in significant NO production. Thus, smooth muscle relaxation is mediated by the blockade of calcium release and NO production by the flavonoid fraction of chamomile [76,79].

Fibrinolytic activity

In a model of alveolar bone resorption (ABR) in

rats, ethanol extract of *M. chamomilla* significantly reduced ABR and furcation lesions besides preservation of trabecular alveolar bone and cementum. Leukocyte infiltration of periodontium and MPO activity were also reduced by the plant extract. Levels of TNF-α and IL-1β with immunostaining for RANKL and TRAP were decreased in the animals treated with the extract. Thus, inflammation and ABR in animals were restricted by reducing neutrophils, TNF-α and IL-1β, and osteoclastogenesis-related molecules (RANKL/TRAP) or increasing molecules that inhibit the RANK-RANKL interaction (OPG), without interfering with bone anabolism [85].

Antidiabetic activity

Aqueous extract of chamomile enhanced insulin levels and reduced amylase activity and HbA1c in alloxan-induced diabetic rats after six weeks. The plant extract with the doses of 150 and 300 mg/kg reduced fasting plasma glucose by 20% and 57%, respectively [86]. Chamomile extract (200 mg/kg) with physical exercise increased insulin levels and decreased fasting plasma glucose in type 1 diabetic rats for 8 weeks [87]. However, results of another study suggested that extract of chamomile flower (500 mg/kg) showed considerable reduction in serum level of glucose up to 64% without an effect on insulin level in streptozotocin (STZ) diabetic rats model after four weeks [88]. Level of insulin and insulin sensitivity increased in STZ-nicotinamide-induced diabetic male rats by administration of 200 mg/kg/day of chamomile extract for 24 weeks. A significant reduction in fasting plasma glucose and serum GPLD1 levels was also observed in the treatment group in comparison to the control group, while serum levels of glypican-4 remained unchanged [89]. Decoction of chamomile (500 mg/kg) in STZ-induced diabetic rats inhibited hepatic glycogen phosphorylase leading to a significant reduction in plasma glucose after 21 days [90]. Administration of aerial parts of the ethanol extract of chamomile to STZ-induced diabetic rats caused an increase in insulin-positive β-cells of pancreatic islets and decreased glucose levels in the serum of animals dose-dependently [91]. Oral administration of both single dose and a daily oral dose of aqueous extract of chamomile leaf and flower (20 mg/kg) significantly attenuated postprandial blood glucose (61%) in STZ-induced rats; however, difference in plasma insulin level was not significant [92]. Levels of HbA1c with fasting and post-prandial blood glucose versus baseline reduced in alloxan-induced diabetic rats by administration of chamomile flower tea for 8 weeks [93]. The addition of chamomile decoction to the mucosal reservoir significantly and dose-dependently inhibited intestinal glucose absorption [47].

Aqueous extract of chamomile leaves (300 mg/kg) restored levels of urea, uric acid, creatinine, and total protein to normal levels in diabetic rats. The plant extract also maintained the weight gain and reduced apoptosis in the renal cells by reversing lower level of anti-apoptotic Bcl-2 protein and higher levels of pro-apoptotic Bax in the kidney with doses of 150 and 300 mg/kg in combination with oregano [94]. Remarkable decrease in hepatic enzymes including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) with a parallel decrease in urea and creatinine were reported in diabetic rats treated with ethanol extract of chamomile flowers (500 mg/kg) [88]. Weight reduction was improved in alloxan-induced diabetic rats by administration of chamomile tea (1 g in 150 mL boiling water) for 8 weeks [93].

Extract of *M. chamomilla* and its compounds provided potent inhibitory activity against rat lens aldose reductase, advanced glycation end products, and DPPH radical. Additionally, isolated compounds including apigenin-7-O-β-D-glucoside, luteolin-7-O-*β*-D-glucoside, apigenin-7-O-*β*-D-glucuronide, luteolin-7-O-*β*-D-glucuronide, 3, 5-O-di-caffeoylquinic acid, apigenin, and luteolin suppressed sorbitol accumulation in rat lens in high glucose condition in vivo. These results indicated the beneficial effect of chamomile and its constituents in the prevention or treatment of diabetic complications [95].

Anti-obesity activity

Subchronic administration of decoction of chamomile flowers caused protection against high-fat diet obesity and an increase in hepatic, abdominal, and kidney fat weights in rats. The high-fat diet also caused an increase in the serum contents of TG, TC, and LDL and a decrease in HDL level which was significantly corrected by the administration of chamomile decoction [47].

Prevention of post-surgical adhesions

Postsurgical adhesion is a significant clinical problem after surgeries. Chamomile extracts reduced adhesion, fibrosis, inflammation, and post-surgical vascularization after surgery in female rats suggesting anti-inflammatory effects of the plant. The anti-inflammatory activity of chamomile resulted in the prevention of postsurgical adhesion [96].

Clinical Trials

Generalized anxiety disorder (GAD)

Participants with moderate to severe GAD were treated with pharmaceutical-grade chamomile extract (500 mg capsules 3 times a day) for 12 weeks. The responders were then randomized to either continuation of chamomile for an extra 26 weeks or a placebo. A greater number of placebo (25.5%) participants relapsed during follow-up versus chamomile (15.2%). Relapse means time for chamomile (11.4 weeks) was lower than relapse for placebo (6.3 weeks), and during follow-up, chamomile participants maintained significantly lower GAD symptoms than placebo with a significant reduction in body weight and arterial blood pressure [97]. Clinically meaningful and statistically significant improvement in GAD-7 score, anxiety, and well-being occurred in 11.7% of patients treated with chamomile extract (1500 mg per day for 8 weeks) [97]. In another study, patients with mild to moderate GAD were administered pharmaceutical grade German chamomile extract standardized to a content of 1.2% apigenin for 8 weeks and total Hamilton Anxiety Rating (HAM-A) scores reduced significantly versus placebo therapy. Positive changes in secondary outcomes included changes in the Beck Anxiety Inventory score, Psychological Well Being score, Clinical Global Impression Severity score, and the proportion of patients with ≥50% reduction in baseline HAM-A score were also reported which suggests that chamomile has modest anxiolytic activity in patients with mild to moderate GAD [98]. In patients who had anxiety with depression, clinically meaningful changes over time in Hamilton Depression Rating (HAM-D) rating were observed indicating possible antidepressant activity of chamomile [99]. Further comparative studies of higher quality are needed to compare chamomile extract with conventional GAD therapies.

Efficacy in migraine

Traditional preparation containing 2% *M. chamomilla* essential oil rich in bisabolone oxide A (57.37%) and bisabolol oxide A (14.29%) was examined in patients suffering from migraine without aura. Pain based on visual analog scale (VAS) in the treatment group significantly decreased (beta= -0.38, p= 0.001). The nausea or vomiting decreased after 2 h of cutaneous application of the drug or placebo to 86.7% and 17.8%, respectively. Both photophobia- and phonophobia-associated attacks were decreased by chamomile preparation in patients [100].

Efficacy in attention-deficit disorder (ADHD)

The effect of *M. chamomilla* preparation containing 100 mg aqueous ethanol extract of the plant with 0.19 g levomenol (α-(−)-bisabolol) administered to the 3 patients suffering from ADHD was investigated for 4 weeks. Patients' mean scores for Conners' hyperactivity, inattention, and immaturity factors improved suggesting that chamomile may slightly be effective in ADHD [101].

Efficacy in oral health

One of the most common and disturbing side effects in high-dose chemotherapy is oral mucositis which causes erythema, edema, pain, and ulcers. A mouthwash containing *M. chamomilla* extract (1% w/v) with *Mentha piperita* oil (1% v/v) was administered to the patient undergoing chemotherapy and receiving a bone marrow transplant. The results showed that pain, dryness of the oral cavity, dysphagia, need for analgesics or total parental nutrition (TPN), duration of TPN, duration of oral mucositis, and maximum grade of oral mucositis significantly reduced in the intervention group in comparison with placebo [102]. In another study, chamomile mouthwash in patients who received 5-flourouracil had no beneficial effect on the incidence, severity, and duration of oral mucositis [103]. A systematic review considered 11 clinical trials in which patients were treated with chamomile mouthwash when they underwent radiography and chemotherapy. Most of them showed a positive effect of *M. chamomilla* mouthwash in oral mucositis that may be caused through inhibition of nitric oxide and nitric oxide synthase, inhibition of COX-2 and MMP-9 with blocking the transcription factor NF-kβ which reduce discomfort and

severity of oral mucositis [104].
The gingiva bleeding index was reduced by the administration of chamomile mouthwash in both gingivitis and chronic periodontitis [105]. In addition, plaque accumulation and gingival inflammation were lowered in patients who applied chamomile mouthwash [106]. In another work, mouthwash based on chamomile hydroalcoholic extract with chlorhexidine as control, both reduced bacterial plaque significantly, and chamomile had more plaque reduction effect which was not significantly different compared to the control [107]. More high-quality clinical trials to evaluate the positive effects of the mouthwash containing chamomile extract are warranted to indicate the duration of therapy to establish and maintain oral health.

Antidiabetic properties
Human studies reported changes in the levels of lipid profiles by administration of chamomile. Chamomile tea (3 g/150 mL hot water) three times per day for 8 weeks decreased the concentration of HbA1c, total cholesterol, triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) compared with the control group. In both groups, no significant changes were observed in serum high-density lipoprotein cholesterol (HDL-C) levels [108]. In contrast, no changes were observed in another study in total cholesterol, TG, HDL-C, and LDL-C by administration of three cups of chamomile tea to the patients who suffer from depression with type 2 diabetes. The level of HbA1c significantly reduced after the intervention [109].
Chamomile tea (3g/150 mL hot water) reduced malondialdehyde (MDA) levels and increased total antioxidant capacity, superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) activities in patients who suffered from type 2 diabetes [110]. High-fat diet in rats increased renal and hepatic levels of MDA which was corrected by the administration of chamomile flower decoction [47]. The plant provided anti-inflammatory activity in patients with diabetes by lowering tumor necrosis factor-α (TNF-α) and high sensitive-C reactive protein (hs-CRP) [111]. The decrease in serum creatinine was observed by intake of chamomile tea (10 g/100 mL boiling water) twice daily for 4 weeks in diabetic patients [112]. Results of a systematic review of 15 clinical studies showed novel functions of chamomile in the improvement of glycemic and lipid profiles and oxidative stress indicators in diabetes mellitus and related complications [113].

Efficacy in menstrual problems
Chamomile capsules (100 mg) reduced the intensity of emotional symptoms more significantly than mefenamic acid after two cycle intervention in premenstrual syndrome (PMS). While intensity reduction of physical symptoms in both groups, chamomile and mefenamic acid, were not significantly different. The results of this study suggested that chamomile seems to be more effective than mefenamic acid in control of PMS-associated psychological pain [114]. Both chamomile and yarrow capsules reduced the severity of primary dysmenorrhea, while yarrow caused more reduction in pain severity [115].
The efficacy of chamomile in cyclic breast pain (mastalgia) was assessed for eight weeks. Chamomile preparation reduced mastalgia much more than placebo and was well tolerated and safe in the treatment of moderate mastalgia [116].

Efficacy in idiopathic hyperprolactinemia
In a randomized controlled clinical trial, women with idiopathic hyperprolactinemia was administered chamomile syrup (5 mL twice daily) or cabergoline tablet with a dose of 0.25 mg twice daily for 4 weeks. Results of the study indicated that cabergoline reduced mean prolactin levels significantly greater than that of chamomile [117].

Efficacy in enuresis
Chamomile has been used as a treatment of enuresis in traditional Persian medicine [118]. Aqueous extract of chamomile flowers was traditionally mixed with olive oil and boiled to evaporate the water portion. Chamomile oil which was prepared traditionally was applied on the perineal and suprapubic area of children at night. The mean frequency of enuresis was significantly reduced in the first, second, and third 2 weeks when compared with the base scores. No adverse effect was reported but some parents complained about the greasy nature of the herbal preparation [119]. The spasmolytic and anticholinergic activity of chamomile active constituents may be associated with the observed effect of traditional oil of the plant in children. Chamomile also showed spasmolytic activity in muscle tissues. Flavonoids can inhibit cAMP and cGMP phosphodiesterases which are considered

as the mechanism of spasmolytic activity [77,82].

Conclusion

Matricaria chamomilla has been used since ancient times to treat different diseases. A wide range of secondary metabolites have been isolated and identified in the plant extracts and essential oil. Besides geographical features, the method of preparation of the essential oilinfluenced the composition and amount of the compounds [15,17,19]. Although the constituents of the plant oil were different in the previous studies, bisabolol oxide B, bisabolone oxide, and bisalolol oxide A, α-bisabolol oxide B, β-farnesene, and chamazulene were the main components of the chamomile essential oil. Coumarins (like herniarin and umbelliferone), flavonoids (like quercetin and apigenin with their derivatives), polyacetylenes, and low concentrations of minerals such as calcium, potassium, magnesium, zinc, and cadmium were previously reported in chamomile aerial parts. Anti-inflammatory activity is one of the known properties of chamomile and its contributed mechanism was evaluated in vitro and in vivo. The anti-inflammatory activity of flavonoids, coumarins of the plant, and its volatile terpenoids like matricin and α-bisabolol mostly related to the reduction of TNF-α, IL-6, pro-inflammatory cytokines like IL-1β, IL-8, suppressing the expression of COX-2, iNOS, 5-LOX, MMP-3, MMP-9, and p65 NF-κB with inhibiting the production of leukotriene B4 in vitro [120-125]. In animal models, these compounds reduced levels of TNF-α, NO, and IL-6, increased the MPO activity, reduced phosphorylation levels of ERK1/2, p38, and JNK, leukocyte migration, protein extravasations and TNF-α [122,124,126,127]. Chamomile preparation decreased oral mucositis, gingival inflammation, and increased antioxidant capacity with reduction of stress oxidative in type 2 diabetes in clinical studies [104,106,111,112]. Distinctive characteristic of chamomile, mechanisms of its biological activities and the constituents were evaluated and summarized in Tables 1-3 and discussed in the experimental for GAD, migraine, enuresis, menstrual problems, diabetes, mucositis, and ADHD. In vitro and experimental studies indicated antioxidant, anti-inflammation, anti-microbial, anti-diarrheal, gastroprotective, hepatoprotective, anti-obesity, spasmolytic, antiangiogenic, cytotoxic, anti-platelet, prevention of post-surgical adhesions, and antidiabetic activity of the plant and its constituents. Although in vitro and in vivo studies deepen our knowledge of the mechanism of action of bioactive compounds, in vitro studies because of the lack of biokinetics in these systems and in vivo studies due to the differences in biokinetics parameters in lab animals, provide some drawbacks to extrapolating the obtained results to human [20,128]. The question is whether available data are enough to support the efficacy of the *M. chamomilla* preparations in clinical research. As mentioned, other studies rather than clinical trials can contribute to evaluating the mechanism of action of *M. chamomilla* extracts and its active components, while the final answer to the question about efficacy of the plant preparations in the humans' bodies as it was depicted in pre-clinical studies can only be clarified through well-designed clinical trials.

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Author contributions

Azadeh Manayi and Mina Saeedi contributed to literature data collection and wrote the manuscript. Kasra Shahsavari contributed to drafting the manuscript. Mahnaz Khanavi supervised the study. All authors have read the final manuscript and approved the submission.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

ABTS: 2,2-azino-bis-(3-ethylbenzthiazoline-6-sulphonic acid); ABR: alveolar bone resorption; Ach: acetylcholine; ADP: adenosindiphosphat; ASFV: African swine fever virus; ALT: alanine

aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; COX-2: cyclooxygenase-2; CTGF: myocardial connective tissue growth factor; DPPH: 2,2-Diphenyl-1-picrylhydrazyl; eNOS: endothelial nitric oxide synthase; EV71: enterovirus 71; FMDV: foot-and-mouth disease virus; GAD: generalized anxiety disorder; GGT: gamma glutamyl transferase; GAE: gallic acid equivalent; GRAS: generally recognized as safe; GPx: glutathione peroxidase; GSH: glutathione; HAM-D: Hamilton depression rating; HCV: hepatitis C virus; HDL-CL: high-density lipoprotein cholesterol; 12-HETE: 12-hydroxyeicosatetraenoate; HepG-2: human hepatoma cancer cells; His: histidine; HO-1: heme oxygenase-1; HPLC/NMR: high-performance liquid chromatography-nuclear magnetic resonance; HPLC-MS: high-performance liquid chromatography-mass spectrometry; hs-CRP: high sensitive-C reactive protein; ICAM: intracellular cell adhesion molecule; iNOS: inducible nitric oxide synthase; IFN: interferon; IL: interleukin; JNK: c-Jun N-terminal kinase; LDL: low density lipoprotein; 5-LOX: 5-lipoxygenase; MAPK: mitogen activated protein kinase; MIC: minimum inhibitory concentration; MMP-9: matrix metalloproteinase-9; MRSA: methicillin-resistant *S. aureus*; MDA: malondialdehyde; MS: multiple sclerosis; MPO: myeloperoxidase; NO: nitric oxide; NF-κB: nuclear factor kappa B; Nrf2: E2-related factor 2; PMS: premenstrual syndrome; PPAR: peroxisome proliferated activated receptor; QE: quercetin equivalent; RANKL/TRAP: receptor-activator of nuclear factor kappa beta/translocon associated protein; ROS: reactive oxygen specious; SLS: sodium lauryl sulfate; SOD: superoxide dismutase; STZ: streptozotocin; TG: triglyceride; TNF: tumor necrosing factor; TPN: total parental nutrition; VAS: visual analog scale; VCAM: vascular cell adhesion molecule; VEGF: Vascular endothelial growth factor