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Bioactive constituents and pharmacological importance of *Matricaria chamomilla*: A recent review

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Abstract

Matricaria chamomilla contained oils, sterols, triterpenes, flavonoids, saponins, tannins, alkaloids, sugars, proteins, mucins, sesquiterpenes, coumarins, polyacetylenes, phenyl carboxylic acids, amino acids, phytosterols, choline and mineral substances. The pharmacological studies revealed that *Matricaria chamomilla* possessed dermatological, antioxidant, anticancer, anti-inflammatory, analgesic, antimicrobial, reproductive, antiulcerogenic, antidiarrheal, antispasmodic, antidiabetic, antiparasitic, antiallergic, protective, anxiolytic, sedative, antidepressant, anticonvulsant, hypotensive, hypolipidemic, memory enhancing and many other effects. This review was designed to highlight thechemicalconstituents andpharmacological effects of *Matricaria chamomilla*.

Keywords: *Matricaria chamomilla*; Constituents; Pharmacology; Safety

1. Introduction

Herbal medicine is the oldest form of medicine known to mankind. It was the mainstay of many early civilizations and is still the most widely practiced form of medicine in the world today. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavors, fragrances, colors, biopesticides, and food additives [1-10]. Phytochemical investigation of *Matricaria chamomilla* revealed that the plant contained oils, sterols, triterpenes, flavonoids, saponins, tannins, alkaloids, sugars, proteins, mucins, sesquiterpenes, coumarins, polyacetylenes, phenyl carboxylic acids, amino acids, phytosterols, choline and mineral substances. The previous pharmacological studies showed that *Matricaria chamomilla* possessed dermatological, antioxidant, anticancer, anti-inflammatory, analgesic, antimicrobial, reproductive, antiulcerogenic, antidiarrheal, antispasmodic, antidiabetic, antiparasitic, antiallergic, protective, anxiolytic, sedative,antidepressant, anticonvulsant, hypotensive, hypolipidemic, memory enhancing and many other effects. This review presented a comprehensive overview of the phytochemical and pharmacological profile of *Matricaria chamomilla*, whichis used for therapeutic purposes as traditional medicine across the world by various cultures.

2. The plant profiles

2.1. Synonyms

Chamaemelum suaveolens, Chamaemelum vulgare, Chamomilla chamomilla, Chamomilla courrantiana, Chamomilla officinalis, Chamomilla recutita, Chamomilla recutita subsp. bayeri, Chamomilla vulgaris, Chrysanthemum chamomilla, Chrysanthemum suaveolens, Courrantia chamomilloides, Matricaria bayeri, Matricaria capitellata, Matricaria chamomilla f. kochiana, Matricaria chamomilla subsp. pusilla, Matricaria chamomilla var. recutita, Matricaria chamomilla var.

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recutita, Matricaria chamomilla f. suaveolens, Matricaria courrantiana, Matricaria exigua, Matricaria kochiana, Matricariapusilla, Matricaria recutita, Matricaria recutita var. coronate, Matricaria recutita var. kochiana, Matricaria recutita var. recutita, Matricaria salina and Matricariasuaveolens [11].

Kingdom*: Plantae,* Subkingdom*: Viridiplantae,* Infrakingdom*: Streptophyta, Superdivision: Embryophyta,* Division*: Tracheophyta,* Subdivision*: Spermatophytina,* Class*: Magnoliopsida,* Superorder*: Asteranae,* Order*: Asterales,* Family*: Asteraceae,* Genus*: Matricaria,* Species*: Matricaria chamomilla* [12].

2.2. Common names

Arabic: Baboon, Bebong, babong; **Chinese**: mu ju; **English**: blue chamomile, chamomile, common chamomile, German chamomile, Hungarian chamomile, Matricaria, scented chamomile, scented mayweed, sweet false chamomile, true chamomile, wild chamomile; **French**: camomille allemande, camomillevraie, matricaire; **German**: EchteKamille, Kamille; **Korean**: Kamille; **Portuguese**: camomila; **Spanish**: camomila, manzanilla; **Swedish**: kamomill [13].

2.3. Distribution

It is nativeto **Africa** (Algeria and Morocco), **Asia** (Afghanistan, Cyprus, Iran, Iraq, Palestine, Lebanon, Syria, Turkey, Azerbaijan, Georgia, Russian Federation, Kazakhstan, Kyrgyzstan, Uzbekistan, Mongolia, China, and India), **Europe** (Denmark, Finland, Norway, Sweden, United Kingdom, Austria, Belgium, Czech Republic, Germany, Hungary, Netherlands, Poland, Slovakia, Switzerland, Belarus, Russian Federation-European part, Ukraine, Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Greece, Italy, Montenegro, Romania, Serbia, Slovenia, France, Portugal, and Spain) and it is widely cultivated [13].

2.3.1. Description

Annual or short-lived perennial, glabrous. Stems 10-60 cm tall, erect, striate, and much branched in the upper part. Proximal stem leaves sessile, leaf blade oblong or oblanceolate, 1.5-6 × 0.5-2 cm, 2-pinnatisect; ultimate segments linear, apex mucronulate. The distal stem leaf is similar to the proximal leaf, ovate, or long ovate. Capitula heterogamous, 1-1.5 cm in diameter, apically corymbose, pedunculate, peduncle 3-6 cm. Involucres are cup-shaped; phyllaries are in 2 rows, margin broadly, apex obtuse. Ray florets white, lamina ca. 6 mm. Disk florets are many, yellow, and tubular. Achenesare 0.8-1 mm, with 5 mainly adaxial thin ribs. Corona is absent [14].

2.3.2. Traditional uses

The essential oils of flower heads of *Chamomilla recutita are* characterized by flavoring and coloring properties and for these properties, it was widely used in industry for commercial products like soaps, detergents, perfumes, lotions, ointments, hair products, baked goods, confectioneries, beverages and herbal teas [15].

Matricaria recutita was one of the most popular herbal medicines. The flowers were used for centuries for their anti-inflammatory, analgesic, antimicrobial, antispasmodic, and sedative properties. The infusion of chamomile was used traditionally to calm nerves and reduce anxiety and treat hysteria, nightmares, insomnia, and other sleep problems. The infusion was also used for relieving gastrointestinal disorders, especially in babies and small children, and for the treatment of flu and bronchitis [16-17].

In external use, the camomile was applied in badly healed wounds, as a bath for abscesses, female furuncles, hemorrhoids, and genital diseases, and for babies to soften the skin. It was also used for acne [18].

2.3.3. Parts used medicinally

Flowers and essential oils [15].

2.4. Physicochemical characteristics

Chamomile flower oil exhibited the following physicochemical properties: specific gravity at 15°C: 0.9326 to 0.9459, acid number:18.7 to 31.7, ester number: 1.9 to 12.1, ester number after acetylation: 66.3 to 115.7 and boiling point: 105-180C [19].

2.5. Chemical constituents

Phytochemical investigation of *Matricaria chamomilla* revealed the presence of oils, sterols, triterpenes, flavonoids, saponins, tannins, alkaloids, sugars, proteins, mucins, sesquiterpenes, coumarins, polyacetylenes, phenyl carboxylic acids, amino acids, phytosterols, choline and mineral substances [20-22].

The analysis of flowers of four Polish chamomile cultivars showed that they contained: crude fiber 1.84-2.29% of fresh weight, total ash 1.76-2.23% of fresh weight, total protein 3.60-4.44% of fresh weight, total sugar 1.15-1.85 % of fresh weight, reducing sugar 0.94-1.33 % of fresh weight, saccharose 0.20-0.50 % of fresh weight, essential oil 0.7-2.69 % of dry matter, total polyphenols 308.78-420.35 mg/100g of fresh weight, total flavonoids 0.37-0.50 % of dry matter, L-ascorbic acid 37.92-41.76 mg/100g of fresh weight and total carotenoids 134.76-162.25 mg/kgof fresh weight [22].

Matricaria chamomilla contained 0.4–1.5% oil, characterized byintense blue color owing to its chamazulene content (1–15%) [23-24].

The main constituents identified in the oil of *Matricaria chamomilla* from Bulgaria were: farnesene 27.72, chamazulene 17.64, α-bisabolol oxide B 11.17, α-bisabolol 9.55, α-bisabolol oxide A 8.93, delta-cadinene 5.20, α-muurolene 3.41, (E)-β-ocimene 1.73, ϒ-muurolene 1.31, β-caryophyllene 0.50, α-copaene 0.24, limonene 0.10; 1,8-cineole 0.10, para-cymene 0.05 and α-terpinene 0.01% [25].

The essential oil composition of different commercial samples of *Chamomilla recutita* from Curitiba, Brazil, and their percentage were: .artemisia ketone 0.39, *n*-decanoic acid 1.55, b-farnesene 15.04- 21.85, spathulenol 0.8-3.67, b-eudesmol 1.89-4.50, a-bisabolol oxide B 25.31-32.99, a-bisabolol 10.88- 16.42, chamazulene 0.45- 1.54, a-bisabolol oxide A 11.61-16.57, *cis*-en-in-dicycloether 5.82- - 8.57, *n*-hexadecanoic acid 1.59- 5.63, *n*-hexadecanoic acid ethyl ester < 0.1 andhexatriacontane 0.83-2.88% [17].

Thirty seven compounds were identified in the essential oil of *Matricaria chamomilla* collected from western Iran, these included: α-pinene (22.11%), camphene (10.8%), sabinene (4%), limonene (5.64%),1,8-cineole (6.45%), camphor (4%) and α-bisabolol (6.35%), d-3-carene (0.13%), α-terpinene (1.6%), p-cymene (0.31%), β-phellandrene (0.35%), benzeneacetaldehyde (0.36%), γ-terpinene (1%), Artemisiaketone (0.34%), Z-sabinenehydrate (0.87%), α-linalool (0.22%), α-thujone (0.34%), β-thujone (0.45%), E-sabinol (0.89%), borneol (0.65%), 4-terpineol (0.47%), α-terpineol (0.69%), E-piperitol (0.48%), α-terpinylacetate (0.22%), α-cubebene (0.47%),α-isocomene (0.36%),β-elemene (0.4%),α-funebrene (0.65%), isocaryophyllene (0.65%), β-caryophyllene(0.5%),E-β-farnesene (0.68%), germacrene D (0.9%), bicyclogermacrene (0.85%), E-nerolidol (0.28%), spathulenol (0.76%), caryophyllene oxide (0.63%), bisabolol oxide B(0.45%) and α-bisabolol (6.35%) [26].

The chemical composition of the essential oils of seven *Matricaria chamomilla* samples (dried chamomile flowers and chamomile teabags at a food supermarket in Spain) was analyzed by GC-MS. Two types of chamomile essential oils existed, onewas rich in oxygenated sesquiterpenes (66.85-77.48%) and the other wasrich in sesquiterpene hydrocarbons (58.12%). α-bisabolol oxide B (6.57±1.20 and 23.65±3.27%), α-bisabolol oxide A (7.89±0.36 and 7.01±0.44%), and α-bisabolol oxide A (58.18±1.99% and 27.95±4.32%) were the main oxygenated compounds in the essential oils from both chamomile flowers and teabags at commercial food items respectively, whereas a large amount of the sesquiterpene hydrocarbon *trans*- α -farnesene (38.22%) followed by α-bisabolol oxide A (16.74%) were found in the chamomile essential oil at retail Pharmacies. Chamazulene was presented (1.5-4.44%) in all analyzed essential oils [27].

However, the major constituents in the essential oils from Morocco samples were: chamazulene (25.21 %), cis-beta-farnesene (12.51 %), eucalyptol (9.19 %), coumarin (7.72 %), galaxolide (6.28 %), camphor (4.3 %) and salicylic acid (2.62 %) [28-30].

Analysis of thevolatile constituents of *Matricaria recutita* cultivated in Estonia showed that they contained thirty-seven components. The main components were bisabolol oxide A (20–33%), bisabolol oxide B (8–12%), bisabolol oxide A (7-14%), β-farnesene (4-13%), α-bisabolol (8-14%), chamazulene (5-7%), and en-yn-dicycloether (17-22%). The content of sesquiterpenoid compounds was high, reaching up to 70% of the total oil [31].

Elmastaş *et al*. found that the concentration of total phenolic compounds was 29.4 µg/ kg dry weight in the flower, 22.3 µg/ kg dry weight in the stem, and 32.1 µg/ kg dry weight in the whole *Matricaria chamomilla* herb [32].

While, Haghi*et al* found that the total phenolic and total flavonoid contents in *Matricaria chamomilla* ranged from 1.77 to 50.75-gram gallic acid equivalent/100 g and 0.82 to 36.75 g quercetin equivalent /100 g in a dry material, respectively. There was a considerable difference from 40 to 740 mg/100 g for apigenin and 210 to 1110 mg/100 g for apigenin 7-glucoside in dry material [33].

The phenolic compounds identified in the infusion and decoction of *Matricaria recutita* were included (g/100 g dry weight): 3-*O*-caffeolyquinic acid 0.15 ± 0.01 and 0.12 ± 0.00, protocatechuic acid 0.07 ± 0.01 and 0.05 ± 0.01, 1,5-dicaffeolyquinic acid undetected and trace, 4-*O*-caffeolyquinic acid 0.21 ± 0.00 and 0.13 ± 0.00, *cis* 5-*O*-caffeolyquinic acid 0.17 ± 0.04 and 0.15 ± 0.00, *trans* 5-*O*-Caffeolyquinic acid 0.26 ± 0.04 and 0.22 ± 0.01, *cis* feruloyl hexoside acid 0.32 ± 0.02 and 0.28 ± 0.01, *trans* feruloyl hexoside acid 0.46 ± 0.01 and 0.38 ± 0.01, 5-*O*-feruloylquinic acid 0.03 ± 0.00 and 0.02 ± 0.00, feruloyl hexoside acid dimer 0.59 ± 0.00 and 0.55 ± 0.01, 1,3,5-*O* or 1,4,5-tricaffeolyquinic 0.03 ± 0.00 and 0.02 ± 0.00, luteolin acetylhexosidehexoside 0.02 ± 0.00 and 0.03 ± 0.00, 3,4-*O*-dicaffeolyquinic acid 0.73 ± 0.03 and 0.33 ± 0.01, luteolin-7-*O*-glucoside 0.17 ± 0.01 and 0.09 ± 0.00, 3,5-*O*-dicaffeolyquinic acid 0.26 ± 0.07 and 0.16 ± 0.00, luteolin *O*-acylhexoside 0.09 ± 0.01 and 0.06 ± 0.00, 4,5-*O*-dicaffeoylquinic acid 0.17 ± 0.03 and 0.13 ± 0.01, luteolin *O*-acylhexoside 1.29 ± 0.12 and 0.81 ± 0.04 respectively. The total phenolic in the infusion and decoction were 3.43 ± 0.22 and 2.53 ± 0.02 g/100 g dry weight, and the total flavonoids in the infusion and decoction were1.56 ± 0.12 and 0.98 ± 0.04 g/100 g dry weight respectively [34].

However, Kato *et al*., mentioned that the major flavonoids were apigenine, luteoline and quercetin represented 16.8, 1.9 and 9.9% of total flavonoids, respectively [35].

Organic acids identified in the infusion and decoction of *M. recutita* were included (g/100 g dry weight): oxalic acid 8.45 ± 0.32 and 8.60 ± 0.47, quinic acid 0.24 ± 0.00 and 0.88 ± 0.19, malic acid 2.26 ± 0.06 and 1.97 ± 0.03, shikimic acid 0.02 ± 0.00 and 0.02 ± 0.00, citric acid 6.44 ± 0.85 and 6.14 ± 0.14, succinic acid 7.00 ± 0.21 and 5.74 ± 0.13 andfumaric acid 0.01 ± 0.00 and 0.01 ± 0.00 respectively. The total organic acids in the infusion and decoction were 24.42 ± 1.32 and 23.35 ±0.65 g/100 g dry weight, respectively [34].

3. Pharmacological effects

3.1. Dermatological effect

Many experimental and clinical trials showed that formulationsof *C. recutita* [contained aqueous extracts, alcoholic extracts, hydroalcoholic cream, and ointment containing α-bisabolol and chamazulene (Kamillosan)] wereeffective inacute skin reactions due to physical, chemical, andimmunological causes. Chamomile extract 1%, effectivelyreduced the ultraviolet erythema, but 0.1% betamethasone was more effective in reducing erythema after 24 and 48 hrs [36].

The effect of chamomile was compared withcorticosteroids in the treatment ofwounds in rats. Animals treated with chamomile presented significantly faster-wound healing in comparison to those treated with corticosteroids [37].

The efficacy of hydroalcoholic cream chamomile extract of 10% compared to placebo cosmetic cream was evaluated inpityriasis alba and eczema lesions. 36% of the patients were cured and 45.5% were improved [38].

The effects of the aqueous extract of German chamomile application were compared with thetopical corticosteroids in the management of peristomal lesions in patients with colostomy. Healing of the lesions was significantly faster in camomile treated group (8.89 ±4.89 days) than in the hydrocortisone-treated group (14.53 ±7.6 days) (P = 0.001) [39].

The clinical efficacy of two formulations containing extracts enriched with *C. recutita*, (a liposomal and non-liposomal) were studiedin treating contact dermatitis. In the cream samples, 2 mg/cm^2 doses were applied to the affected areas of the skin three times daily over a period of 2 weeks. The liposomal cream was more effective than non-liposomal formulations [40].

The efficacy of a cream containing 2% ethanol extract of chamomile flowers (Kamillosan$^{(R)}$) was studied in comparison with hydrocortisone cream in patients with atopic eczema. The difference between the average scores showed that Kamillosan was superior to hydrocortisone [41].

The effect of Kamillosan was evaluated in patients undergoing radiation therapy presented with radiodermatitis. There was a delay in the onset of the reactionstreated with Kamillosan (which occurred between the 5th and 7th week) [42].

The effect ofchamomile extract (standardized to 3 mg of chamazulene and 50 mg of α-bisabolol) in the healing of injuries from tattoo dermabrasion was studied after 3 applications a day. The reduction of the wound area and the reduction of secretions by chamomile were statistically significant [43].

The efficacy of Kamillosan®, compared with hydrocortisone, fluocortin, and bufexamac in maintenance therapy of eczema was studied in 161 patients with eczema in hands, forearms, and legs. Kamillosan® showed the same efficacy as hydrocortisone at 0.25% (22% vs. 18%) and was superior to fluocortinat 0.75% (25.5% vs. 2.2%) and bufexamac (53, 6% vs. 14.3%) [44].

The hands of healthcare workers were the primary routes of transmission of nosocomial infection to patients, which represented a critical issue in hospital care outcomes, resulting in substantial morbidity and mortality. The antimicrobial activity of the prepared chamomilehand wash was investigated against skin pathogens using the disc diffusion method. Its efficacy was checked and compared with the commercial ones. Results revealed that chamomile soap formulation was more efficient in reducing the number of organisms from hands than the commercial antiseptic soaps thus it can be used as an antiseptic soap with fewer or no side effects [45].

3.2. Antioxidant effect

The antioxidant capacity of different parts of *Matricaria chamomilla*, was studiedusing various antioxidant assays (linoleic acid emulsion, ferric ions reducing antioxidant power, ferrous ions chelating capacity, superoxide radical scavenging activity). All parts (flower, stem, and whole herb) possessedantioxidant activity. The obtained results indicated that the methanol extract of the flower, stem, and whole herb of *Matricaria chamomilla* was the most effective antioxidant [32].

The methanol extract of *Matricaria recutita* and its decoction and infusion were studied for antioxidant activity by free radicals scavenging activity, reducing power, and inhibition of lipid peroxidation. The antioxidant activity (EC_{50} values, µg/ml) of infusion, decoction, and methanol extract were: DPPH scavenging activity (394.97 ± 44.31, 344.02 ± 18.65 and 800.36 ± 49.09), reducing power (316.61 ± 2.46, 318.75 ± 3.01 and 232.49 ± 26.19), β-carotene bleaching inhibition (422.72 ± 92.91, 497.34 ± 107.67 and 661.11 ± 21.93) and TBARS inhibition (511.01 ± 17.28, 508.44 ± 4.43 and 183.48 ± 3.52) respectively. Plant methanol extract presented the highest amounts of phenolic acids (3.99 g/100 g dry weight) and flavonoids (2.59 g/100 g dry weight) [34].

The methanolic and aqueous extracts of *Matricaria recutita* contained more total polyphenols, total flavonoids, and condensed tannins than chloroformic and hexanic extracts. ABTS and DPPH assays showed that methanolic extracts had the highest antioxidant potency (IC_{50} = 1.19 µg/ml and 1.18 µg/ml, respectively). The total phenolic, total flavonoid, and condensed tannin values were correlated with antioxidant activity [46].

The total phenols and flavonoids of *Matricaria recutita* were determined by the Folin-Ciocalteu assay, and antioxidant activity was studiedusing DPPH assay. The percentage inhibition of DPPH scavenging activity was dose-dependent ranging between (94.8% ± 0.03) at 1.50 mg/ml and (84.2% ± 0.86) at 0.15 mg/ml. The antioxidant effects were attributed to high polyphenols (21.4 ± 0.327 mg GAE/g) and flavonoid contents (157.9 ± 2.22 mg QE/g) [47].

The polyphenolic-polysaccharide conjugates isolated from *Matricaria chamomilla* possessed antioxidant properties. Measurements of DPPH and ABTS radical scavenging indicated considerable anti-free radical action of *Matricaria chamomilla*. Pre-incubation of blood plasma with *Matricaria chamomilla* considerably diminished the extent of $ONOO^-$ - induced oxidative modifications such as protein carbonyl groups, SH groups, 3-nitrotyrosine, as well as the formation of lipid hydroperoxides. FRAP assay showed a considerable increase in ferric reducing ability of blood plasma in the presence of *Matricaria chamomilla* [48].

3.3. Anticancer effect

The essential oil of *Matricaria chamomilla* possessed cytotoxic activity against mammalian cells of the promonocytic human cell line U937 (LC_{50} of 30.21µg ml) [49].

The anticancer effect of *Matricaria recutita* flowers methanolic extract was investigated against human melanoma and epidermoid carcinoma cells. *Matricaria recutita* flower's methanolic extract possessed strong anticancer activity. The cytotoxic activity of extract on melanoma cells (IC_{50}: 40.7 µg/ml) was approximately twofold higher than on epidermoid carcinoma cells (IC_{50}: 71.4 µg/ml) [16].

The methanol extract of *Matricaria recutita* and its decoction and infusionwere studied for antitumor potential against many human tumor cell lines (breast, lung, colon, cervical, and hepatocellular carcinomas) and for hepatotoxicity using a porcine liver primary cell culture (non-tumor cells). Decoction had no antitumor activity (GI_{50}: >400 µg/ml). Both methanol extract and infusion showed inhibitory activity of the growth of HCT-15 (GI_{50}: 250.24 and 298.23 µg/ml, respectively) and HeLa (GI_{50}: 259.36 and 277.67 µg/ml, respectively), without hepatotoxicity (GI_{50}: >400 µg/ml) [34].

The anticancer properties of aqueous and methanolic extracts of chamomile were studied against various human cancer cell lines[androgen-responsive LNCaP (obtained from metastatic prostate cancer in a supraclavicular lymph node), androgen-refractory PC-3 (obtained from metastatic prostate cancer in bone), DU145 (obtained from metastatic prostate cancer in the brain), and virally transformed PZ-HPV-7 cells]. Chamomile extracts caused a significant decrease in cell viability in various human cancer cell lines, whereas they caused minimal growth inhibitory responses in normal cells. Chamomile exposure caused apoptosis in cancer cells but not in normal cells. Apigenin glucosides which are identified in chamomile extracts inhibited cancer cell growth but to a lesser extent than the parent aglycone, apigenin [50].

The anticancer and anticancer mechanisms of hydroalcoholic extract of *Matricaria chamomilla* (50-1300 µg/ml, for 24, 48, and 72 h) were studied againsthuman breast cancer MCF-7 and MDA-MB-468 cell lines. Apoptosis and necrosis, cell proliferation and clone formation, cellular migration, invasion, and attachment were investigated. The results showed that the extract possessed time- and dose-dependent anti-invasive, anti-migration and anti-proliferative effects [51].

The anti-proliferative activity of ethanolic extract of *Matricaria recutita* was investigated against the human hepatoma (HepG2) cancer cell line. A dose-dependent reduction in cell viability was recorded in cells treated with the extract. The IC_{50} was ~ 300 µg/ml. It significantly inhibited the level of important prerequisite angiogenesis markers both in HepG2 cells and *ex vivo* [47].

3.4. Antiinflammatory and analgesic effects

Matricaria chamomilla (intraperitoneal injection of 1/10 LD_{50} doses of 80% ethanol extracts) significantly suppressed the carrageenan-induced paw edema in rats [52].

The anti-inflammatory potential of the aqueous extract of *Matricaria chamomilla* (300 and 500 mg/kg) was studied using carrageenan and experimental trauma-induced hind paw edema in mice. The aqueous extract of *Matricaria chamomilla* showed significant anti-inflammatory activity comparable to the control in both models [53].

The anti-inflammatory and analgesic effects of the hydroalcoholic extract (500, 1000, and 1500 mg/kg, bw) of capitols of *Matricaria chamomilla* were tested using xylene-induced inflammations and acetic acid-induced inflammatory pain modelsin rats. The extract at a dose of 1500 mg/kg BW significantly reduced the xylene-induced inflammation in the rats ($P<0.01$). Furthermore, the extract at the doses of 500, 1000, and 1500 mg/kg BW, significantly reduced the acetic acid-induced inflammatory pain ($P<0.001$) [54].

The ethanolic chamomile solution and the raw ethanolic chamomile extract were formulated and evaluated topically for anti-inflammatory activity. Concentrations of 3.0% and 5.0% of extracts were used in gel formulations of 1.0% carbopol 940. Sodium lauryl sulfate was used as the permeation enhancer in gelling formulations. The formulations were applied to the skin of the rats with paw edema induced by carrageenan. These types of preparation showed no anti-inflammatory action even with the use ofthe permeation enhancer [55].

The effect of (-)-α-bisabolol on the inflammatory response and survival rate was testedin a systemic infection model and *in vitro* neutrophils phagocytic activity. (-)-α-bisabolol at a dose of 100 mg/kg reduced the leukocyte recruitment in the peritoneal cavity. The bacteria CFU number was reduced in mice blood in the (-)-α-bisabolol treatment, at doses of 100 and 200 mg/kg. The (-)-α-bisabolol treatment at doses of 50 and 100 mg/kg increased the myeloperoxidase activity and reduced NO production in the lung tissue of mice in the cecal ligation and puncture model. At a dose of 100 mg/kg, the (-) -α-bisabolol treatment reduced the mortality rate of mice submitted to cecal ligation puncture-induced sepsis. Furthermore, (-)-α-bisabolol at a concentration of 3, 10, 30, and 90 µg/ml did not present *in vitro* cytotoxicity in the MTT assay, and at concentrations of 1 and 3 µg/ml, it increased *in vitro* phagocytic neutrophil activity [56].

Apigenin, quercetin, and luteolin were the major flavonoids of *Matricaria chamomilla*, they exerted their anti-inflammatory and anti-gout effects through different mechanisms. Apigenin exhibited anti-inflammatory activity via inhibition of proinflammatory cytokines production, whilst luteolin suppressed the production of nitric oxide (NO), prostaglandin E2 and expression of inducible NO synthase and cyclooxygenase-2. Chamazulene inhibited LTB4

formation, inhibited peroxidation of arachidonic acid, and subsequently reduced the inflammatory mediators and possessed antioxidant activity. Accordingly, *Matricaria chamomilla* can alleviate inflammation and pain in rheumatoid arthritis [57-58].

The peripheral analgesic activity of the essential oil and aqueous extracts of aerial parts of *Matricaria chamomilla* was investigated using the acetic acid-induced writhing reflex test in mice, and acute central analgesic activity was investigated by tail immersion method in rats. The essential oil of *Matricaria chamomilla* (100, 200, and 300 mg/kg, orally) and aqueous extract (200, 400, and 600 mg/kg, orally) exhibited analgesic activity in both tested models. In the acetic acid-induced writhing model, both extracts showed an analgesic effect characterized by a reduction in the number of writhes when compared to the control and reference drugs. In the tail immersion method, essential oil exhibited significant analgesic activity at a low dose (200 mg/kg) comparable to the aqueous extract at a high dose (600 mg/kg) [28].

The analgesic activity of ethyl acetate and n-butanol extracts of *Matricaria chamomilla* was studied using a writhing reflex test in mice in comparison with diclofenac sodium. Diclofenac sodium and *n*-butanol extract of chamomile produced significantly less (1.7 ± 0.8) writhe than the ethyl acetate extract (9.2 ± 5.9) [59].

The analgesic effect of *Matricaria recutita* extract (10, 30, and 50 mg/kg, ip) in acute pain was investigated in mice in the presence and absence of sex hormones. *Matricaria recutita* extract increased analgesia time both in intact and gonadectomized male and female mice but had no effect in the presence of pharmacological doses of testosterone (2 mg/kg, sc) in male mice, and estradiol benzoate (0.1 mg/kg, sc) and progesterone (0.5 mg/kg, sc) in female mice [60].

The antinociceptive effect of *Matricaria chamomilla* hydroalcoholic extract and morphine was studied in vincristine-induced peripheral neuropathy in mice. Administration of *Matricaria chamomilla* extract before formalin injection showed a significant ($P<0.05$) decrease in pain responses in both phases. Administration of vincristine produced a significant ($P<0.05$) increase in pain response in the second phase of the formalin test, while, injection of the extract and vincristine together, the extract decreased the vincristine-induced pain significantly ($P<0.05$). Morphine possessed analgesic effects in the first phase and the extract exerted anti-inflammatory effects in the second phase of the formalin test significantly ($P<0.05$) [61].

3.5. Antimicrobial effects

Thehydroalcoholic extract of Matricaria chamomilla inhibited the growth of Staphylococcus aureus, Streptococcus mutans, Streptococcus salivarius, group B Streptococcus, Bacillus megatherium, and Leptospira icterohaemorrhagiae [62].

Essential oil of chamomile was evaluated for its antibacterial activities against three Gram-positive and four Gram-negative pathogenic bacteria: Staphylococcus aureus, Bacillus cereus, Bacillus subtilis, Proteus sp., Pseudomonas aeruginosa, Shigella sonnei, and Shigella Shiga. The result revealedthat Gram-positiveStaphylococcus aureus was the most sensitive to the oil of Matricaria chamomillawith the largest inhibition zone (35 mm). The oil also exhibited high antimicrobial activity against Bacillus cereus and Bacillus subtilis (30 and 28 inhibition zone, respectively). Regarding Gram-negative bacteria, maximum activity was observed against Shigella Shigaand Shigella sonneiwith an inhibition zone of 20 mm, and lower antimicrobial activity was recordedagainst Pseudomonas aeruginosa and Proteus sp [26].

The antibacterial activity of the petroleum ether, ethyl acetate, methanol, and ethanol extracts of Matricaria chamomilla was investigated against two Gram positives (Staphylococcus aureus ATCC 25923and Bacillus subtilis NCTC 8236) and two Gram-negatives (Escherichia coli ATCC 25922 andPseudomonas aeruginosa ATCC 27853). The results showed that ethanol, methanol, and petroleum ether extracts of Matricaria chamomillapossessed different degrees of antibacterial activities against the tested bacteria, whereas, the ethyl acetate extract did not show antibacterial activities [20].

The methanolic extract of Matricaria chamomilla showed significant antibacterial activity against Staphylococcus aureuswhen compared with Escherichia coli. In comparison, ethanolic extracts of Matricaria chamomilla have shown a more significant antibacterial effect against Staphylococcus aureusthan Escherichia coli ($P \leq 0.05$). However, it possessed no antibacterial activity against Salmonella typhi [63].

The antibacterial activity of the alcoholic extract of Matricaria chamomilla was investigated against five bacterial strains (Pseudomonas aeruginosa, Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, and Klebsiella pneumonia). The alcoholic extract showed higher action against Klebsiella pneumonia (35±1.57 mm), followed by Staphylococcus aureus (23±0.83 mm) and Pseudomonas aeruginosa (16±0.07 mm) [64].

The antimicrobial activity of different concentrations of Matricaria chamomilla and chlorhexidine gel was studiedagainst Candida albicans and Enterococcus faecalis.

Vancomycin was used as a positive control for E. faecalis and fluconazole for C. albicans. 2% chlorhexidine showed the maximum inhibitory zone for C. albicans (33.26 mm) and E. faecalis (24.54 mm). 25% Matricaria chamomilla showed zones of growth inhibition of 24.16 mm and 20.62 mm against C. albicans and E. faecalis, respectively [65].

The antifungal activity of compounds isolated fromchamomile oil, crude chamomile oil, aqueous flower extracts, and toilet soap impregnated with various concentrations of crude chamomile oil and bisabolol oxides were studiedagainst Trichophyton mentagrophytes. Crude chamomile oil, farnesene, (-) -α-bisabolol, and bisabolol oxides were active antifungal constituents. Chamazulene and aqueousflower extracts wereinactive. After three days, farnesene, (-) - α - bisabolol, bisabolol oxides, and crude chamomile oil possessed antifungal activity with an inhibitory zone of 18.50 mm, 29.50 mm, 40.00 mm, and 36.50 mm, respectively.After two months, the inhibition zone was 10.00 mm, 16.00 mm, 25.50 mm, and 17.50 mm, respectively [66].

Camomile essential oils were screened forantiviral effects against herpes simplex virus type 2 (HSV-2) in vitro on RC-37 cells using a plaque reduction assay. A clearly dose-dependent virucidal activity against HSV-2 was demonstrated for camomile essential oils. The inhibitory concentrations (IC_{50}) were determined at 0.003%. In order to determine the mode of the inhibitory effect, essential oils were added at different stages during the viral infection cycle. They affected HSV-2 mainly before adsorption probably by interacting with the viral envelope. Camomile oil exhibited a high selectivity index and seemed to be a promising candidate for topical therapeutic application as a virucidal agent for the treatment of herpes genitalis [67].

Hydroalcoholic extract of Matricaria chamomilla added during the early stage of poliovirus development induced partially reversible inhibition of cellular and viral RNA synthesis [68].

3.6. Reproductive effect

Theeffects of *Matricaria recutita* extract (100 and 150 mg/kg/day for 56 consecutive days) on spermatogenesis and camp-responsive element modulator (CREM) expression at mRNA level (as a key factor in the regulation of the expression of a number of post-meiotic genes during spermatogenesis) were investigated in rats. The extract caused a significant decrease in the epididymal sperm counts and sperm motility of experimental groups compared to the control group. Reverse transcription polymerase chain reaction (RT-PCR) showed a decrease in the expression of CREM in the testes of experimental groups. Accordingly, the authorsconcluded that *Matricaria recutita* exerted anti-spermatogenic effects [69].

The protective effect of hydroethanolic extractof *Matricaria chamomilla* (200 and 500 mg/kg, bw, ip, for 30 days) was studied against formaldehyde toxicity of the reproductive system of male rats. The results revealed that testosterone and LH levels were significantly increased, and sperm count, motility, and viability were significantlyenhanced when *Matricaria chamomilla* extract was used alone or with formaldehyde [70].

The effect of *Matricaria chamomilla* extract on histological damage and oxidative stress induced by torsion/detorsion was investigated in adult rat ovaries.The levels of estrogen, glutathione peroxidase, and superoxide dismutase significantly decreased in the untreated group and increased in the 200mg/kg extract-treated groups (71).

The effects of a hydroalcoholic extract of *Matricaria chamomilla* flowers (20, and 40 mg/kg of the extract for 14 days) on the pituitary-gonadal axis and on the ovaries were studied in female rats. No significant changes in body weight were detected for the extract doses, except that thegroup that received 40mg/kg BW, showed decreased body weight. Chamomilla extract possessedno effect on the LH and FSH levels. In the experimental group receiving 10 mg/kg chamomilla extract, the serum concentration of estrogen was significantly decreased, while the progesterone level was meaningfully increased.A significant decline was observed in the mean number of primary and graafian follicles in the experimental group treated with 20 and 40 mg/kg hydroalcoholic extract of the chamomilla flower [72].

The efficiency of chamomile (*Matricaria chamomilla*) extract on the eduction of dysmenorrhea and premenstrual syndrome (PMS) was evaluated clinically, women with PMS symptoms were studied for two monthly menstrual cycles, the first cycle without chamomile extract and the second cycle with the administration of the chamomile extract before menstruation. Chamomile extract was effective in reducing PMS symptoms. The most prominent effect of chamomile extract was the reduction of the severity of anxiety and retention symptoms [73].

The effects of *Matricaria chamomilla* extract and mefenamic acid on the severity of premenstrual syndrome symptoms were carried out ina randomized double-blind clinical trial. Participants received one 100 mg capsule of *Matricaria chamomilla* or 250 mg mefenamic acid three times daily from day 21 of the menstrual cycle till the beginning of the menstruation. The reduction of symptoms was significantly greater among *Matricaria chamomilla* extract users (25±13.8 and 28±14.5%) than that among mefenamic acid users (14.8±18.5 and 16.2±18.2%) after the first and second cycles (P<0.05). The decreasing of the severity of emotional symptoms was significantly higher among *Matricaria chamomilla* extract users (30.1±26.6 and 33.4±25.3%) than that among mefenamic acid users (11.6±25.7 and 10.7±26.8%) after the two cycles intervention (P>0.05). The reduction of physical symptoms was not significantly different between the two groups [74].

3.7. Anti-ulcerogenic activity

The anti-ulcerogenic and antioxidant activities of the hydroalcoholic extract of *Matricaria chamomilla* were evaluated in ethanol-induced gastric mucosal injuryinrats. Pre-treatment with the extract significantly reduced gastric lesions. It also significantlyreduced the MDA and increased GSH levels in gastric tissue and serum beta-carotene and retinol levels [75].

Ethanoladministration in rats caused marked macroscopic and histologic changes in gastric mucosa, induced lipoperoxidation (486.99%), decreased thiol groups (40.98%), depleted antioxidant enzyme activity such as superoxide dismutase (49.05%), catalase (46.80%) and glutathione peroxidase (38.20%), increased tissue and plasmatic hydrogen peroxide, calcium, and free iron levels. *Matricaria recutita* decoction extract also reversed all macroscopic, histologic, and biochemical changes induced by ethanol administration [76].

The antiulcerogenic effect of *Matricaria chamomilla* was also investigated in the treatment of ibuprofen-induced gastric ulcers in rats. The mean number and surface area of gastric ulcers in the group receiving 500mg/kg of *Matricaria chamomilla* were significantly decreased in (P<0.01) [77].

3.8. Antidiarrheal and antispasmodic effect

The antidiarrheal effect of apple pectin and chamomile extract was studied in children (6 months to 5.5 years of age) with acute, non-complicated diarrhea, in a prospective, double-blind, randomized, multicentre, parallel-group study. Children received either a preparation containing apple pectin and chamomile extract or a placebo in addition to the usual rehydration and re-alimentation diet. At the end of three days of treatment, the preparation reduced the duration of diarrhea significantly (P< 0.05) [78].

Oral administration of crude aqueous-methanolic extract of *Matricaria chamomilla* to mice at 150 and 300 mg/kg showed marked antidiarrhoeal and antisecretory effects against castor oil-induced diarrhea and intestinal fluid accumulation. These effects of the extract were attenuated in animals pretreated with K^+ channel antagonist, glibenclamide, or 4-aminopyridine. Crude aqueous-methanolic extract of *Matricaria chamomilla* caused a dose-dependent (0.3-3 mg/ml) relaxation of spontaneous and low K^+ (25 mM)-induced contractions of theisolated rabbit jejunum, while it exhibited a weak inhibitory effect on high K^+ (80 mM). The inhibitory effect of the extract on low K^+-induced contractions was partially inhibited in the presence of glibenclamide, while completely blocked by 4-aminopyridine. The extract at high concentrations caused a rightward shift in the Ca^{++}concentration-response curves with suppression of the maximum response, similar to the effect of verapamil [79].

The inhibitory effect of chamomile on cAMP- and cGMP-phosphodiesterases (PDE) was investigated to know the mechanism of the spasmolytic activity of chamomile. Chamomile inhibited cAMP-PDE activity (IC_{50} = 17.9-40.5 Mcg/ml), while cGMP-PDE5 was less affected (-15% at 50 Mcg/ml). Among the individual compounds tested, only flavonoids showed an inhibitory effect (IC_{50} = 1.3-14.9 microM), contributing to around 39% of the infusion inhibition [80].

3.9. Antidiabetic effect

The hypoglycemic and antioxidative effects of *Matricaria chamomilla* leaf extract were evaluated in streptozotocin-induced diabetic rats. The aqueousleave extract of *Matricaria chamomilla* (100 mg/kg BW/day for 21 days, orally) reverted backthe blood glucose to near the normal limit after treatment. It also elevatedserum insulin and C-peptide to near normal levels after treatment and possessed antioxidant effects as determined bythiobarbituric acid reactive substance (TBARS) [81].

The hypoglycemic effect of *Matricaria chamomilla* and *Origanum vulgare* (at a dose level of either 150 or 300 mg/kg BW by stomach tube for 6 weeks) was studied inalloxan-induced diabetic rats. Treatment with the higher dose of the

extracts (300 mg/kg) as an individual, or as a mixture of low doses (150 mg/kg of both extracts) had a significant mass gain, hypoglycemic effect ($P \leq 0.05$) with increased serum blood insulin levels and decreased amylase activity. Restoration of the renal profile, and lipid profile with an increase in HDL ($P \leq 0.05$) along with the reversal of pro-apoptotic Bax and anti-apoptotic Bcl-2 were observed with 300 mg/kg mixture, showing synergistic activity of the extracts compared with an individual low dose of 150 mg/kg [82].

The hypolipidemicand antioxidative effects of the ethanolic extractof the aerial partsof Matricaria *chamomilla* (20, 50, and 100 mg/kg BW) were investigated in streptozotocin-induced diabetic rats. Treatment with different doses of ethanol extract significantly reduced postprandial hyperglycemia and oxidative stress and augmented the antioxidant system. Histologically, treatment with extract protected the majority of the pancreatic islet cells [83].

The effects of chamomile tea consumption (3 g/150 ml hot water, three times per day immediately after meals for 8 weeks) on glycemic control and serumlipidprofilewere studied inpatients with type 2 diabetes mellitus (T2DM) in a single-blind randomized controlled clinical trial. Chamomile tea significantly decreased the concentration of HbA1C ($P = 0.03$), serum insulin levels ($P< 0.001$), insulin resistance ($P< 0.001$), total cholesterol ($P = 0.001$), triglyceride ($P< 0.001$), and low-density lipoprotein cholesterol ($P = 0.05$) compared with the control group, while, itcausednosignificant changes in serum HDL levels [84].

3.10. Antiparasitic effect

*In vitro,*the anthelmintic activityof *Matricaria recutita* was investigated on egg-hatching inhibition and loss of motility of adult worms of *Haemonchus contortus* from sheep. The results showed that both methanolic (IC_{50} = 1.559 mg/ml) and aqueous (IC_{50} = 2.559 mg/ml) extracts had the greatest effect on egg hatching and motility of worms (100% after 8 h post-exposure at 8 mg/ml). Furthermore, methanolic and aqueous extracts contained more total polyphenols, total flavonoids, and condensed tannins than chloroformic and hexanoic extracts. ABTS and DPPH assays showed that methanolic extracts had the highest anti-oxidant potency (IC_{50} = 1.19 µg/ml and 1.18 µg/ml, respectively). The total phenolic, total flavonoid, and condensed tannin values were correlated with the inhibition of egg hatching [46].

The activity of *Matricaria chamomilla* essential oil was evaluated *in vitro* against axenic amastigotes of Leishmania*braziliensis*at concentrations lower than or equal to 250µg/ml. The essential oil of *Matricaria chamomilla* also showed activity against intracellular amastigotes of *L. panamensis*and *L. braziliensis* (EC_{50} of 2.87 and 10.30µg/ml, respectively [49].

Chamomile essential oil possessed larvicidal, ovicidal, and repellant activity against lice and flies infesting water buffaloes. LC_{50} values were 22.79% [85].

3.11. Antiallergic and immunological effects

The effect of the anti-allergic activity of methanol extract of *Matricaria recutita* was studiedon mast cell-mediated allergic models. The methanol extract of *Matricaria recutita* possessed an inhibitory effect on anaphylaxis induced by compound 48/80.Itcausedsignificant dose-dependent anti-pruritis properties mediated by mast cellmembrane stabilization and inhibition ofmast cell degranulation. The extract also caused a dose-dependent reduction in the histamine release, with decreased release of serum, rat peritoneal, and bronchoalveolar fluid nitric oxide levels [86].

The singleoral dose of *Matricaria recutita* ethyl acetate extract or essential oil (2 h before pruritus) in mice caused remarkableantipruriticeffects in the compound 48/80-induced itch-scratching test without affecting spontaneous motor activity. The antipruritic effects of H1 antagonists (oxatomide,10 mg/kg and fexofenadine,10 mg/kg) were remarkably enhanced by thecombinedadministration oftheethyl acetate extract of *Matricaria recutita* (300 mg/kg) [87].

The antipruritic effects of the diets containing German chamomile on the compound 48/80-induced scratchingwere examined in mice. In the mice fed the diet containing 1.2 w/w % of the ethyl acetate extract of dried flower of *Matricaria recutita* for 11 days, the extract significantly and dose-dependently suppressed 48/80-induced scratching behavior. The antipruritic effect of the German chamomile extracts was comparable to oxatomide (10 mg/kg, PO). The ethyl acetate fraction of the ethanol extract and the ethanol extract of hot water extraction residue of German chamomile flower also showed strong inhibition on the compound 48/80-induced scratching [88].

Intragastric and parenteral administration of heteropolysaccharides of *Matricaria chamomilla* normalized the development of the immune response upon air cooling and enhance the immune response upon immersion cooling. The immunomodulating effect of the heteropolysaccharides upon cooling was attributed to the initiation of

immunostimulating properties of heavy erythrocytes (macrocytes), activation of immunoregulation cells of peripheral blood, and increased sensitivity of effector cells to helper signals [89].

3.12. Protective effects

The protective effect of oral *Matricaria chamomilla* flowers hot liquid extract on hepatotoxicity induced by methomyl 90% was investigated in mice. Methomyl 90% led to toxic effects that appeared as a decrease inbody weight and noticeable changes in liver tissue accompanied by increasing in its weight, with a significant increase in the level of liver enzymes (ASAT, ALAT). Two doses of hot aqueous extract of chamomile 5 and 7mg/kg BW, possessedmarked improvement in the symptoms of pesticide poisoning compared with the positive control group. Histopathological examination of liver sections of mice administered *Matricaria chamomilla* hot aqueous extract demonstrated a reduction of damaged liver tissue induced by methomyl 90% [90].

The hepatoprotective activity of aqueous ethanolic extract of *Chamomile recutita* capitula was investigated against paracetamol-induced hepatic damage in albino rats. The effect of aqueous ethanolic extract of *Chamomile recutita* capitula on blood and liver glutathione, Na^+ K^+- ATPase activity, serum marker enzymes, serum bilirubin, glycogen, and thiobarbituric acid reactive substances were studied. The extract of chamomile reversed all the elevated parameters in paracetamol hepatotoxicity [91].

The protective effect of *Matricaria chamomilla* extract (50mg/kg BW) against hepatic-renal toxicity of ceftriaxone (180 mg/kg BW for two and one weeks) was investigated in rats. *Matricaria chamomilla* extract significantly declined ALP, ALT, AST, urea, and creatinine levels elevated by ceftriaxone [92].

The protective effects of ethanolic extract of *Matricaria chamomilla* were investigated against hippocampal neuron damage in rats exposed to formaldehyde, which caused hippocampal cell death and memory impairment. Shuttle box assay was used for the evaluation of passive avoidance learning. The apoptosis rate of hippocampal tissue, malondialdehyde (MDA) free radicals, and total antioxidant capacity were evaluated. The ethanolic extract of *Matricaria chamomilla* reduced cell death, time spent in a dark room, and MDA free radicals in the hippocampus, leading to increased total antioxidant capacity [93].

Administration of cisplatin produced a significant ($P< 0.05$) increase in pain response in both phases of the formalin test. Injection of *Matricaria chamomilla* hydroalcoholic extract and cisplatin together showed that the extract wasable to decrease the second phase of cisplatin-induced pain significantly ($P< 0.05$) [94].

The neuroprotective effect of ethyl alcohol extract of *Matricaria chamomilla* extract (50, 100, and 200 mg/kg, bw) on cerebral ischemia-induced motor dysfunctions was studied in rats. The extract of *Matricaria chamomilla* significantly improved ischemia/ reperfusion-induced motor dysfunction. It was also significantly reduced serum MDA level which elevated by ischemia/reperfusion. However, it possessed no significant effects on the total antioxidant capacity of the brain (hippocampus and cortex) and serum, and serum NO level [95].

The protective effects of a commercial eye drop (Dacriovis™) containing *Matricaria chamomilla* and *Euphrasia officinalis*extract in corneal epithelial cells damage (HCEC-12) caused by oxidative stress and inflammation induced by UVB radiation were studied in humans. HCEC-12 cells were exposed to UVB radiation and treated with eye drops at various concentrations. Cell viability, wound healing, reactive oxygen species (ROS) levels, protein, and lipid oxidative damage, and COX-2, IL-1β, iNOS, SOD-2, HO-1, and GSS gene expression, were investigated. Eye drops protected corneal epithelial cells from UVB-induced cell death and ameliorated wound healing, they possessed a strong antioxidant activity, decreasing ROS levels and protein and lipid oxidative damage. It also possessed anti-inflammatory activities by decreasing COX-2, IL-1β, and iNOS expression counteracted UVB-induced GSS and SOD-2 expression and restored HO-1 expression to control levels [96].

4. Anxiolytic sedative and antidepressant effects

The inhaling of chamomile oil leads to a reductionin stress-induced plasma ACTH inovariectomized rats [97].

CNS activities of oral uses of seven vegetable extracts and their combinationswere tested in mice.The results revealed that Matricaria *chamomilla* possessed sedative andanxiolytic effects [98].

As aroma therapy, the essential oilof *Matricaria chamomilla* was recommended for emotional frustration, anger, irritability, agitation, sudden fits of rage, mood swings, and anxiety. The essential oil of *Matricaria chamomilla* calmed the mind and promoted relaxation [99].

The sedative properties of *Matricaria recutita* were investigated in the presence and absence of flumazenil as a benzodiazepine receptor antagonist in rats. After 7 doses of morphine, naloxone was injected for induction of morphine withdrawal syndrome which is characterized bysigns of climbing, jumping, and face washing. *M. recutita* decreased significantly the number of climbing in comparison to the control group ($P<0.001$), but it had no significant effect on other signs. Flumazenil increased significantly the signs of jumping ($P<0.01$), and face washing ($P<0.05$) in comparison to the control group. *M. recutita* in the presence of flumazenil had no sedative effect and the climbing behavior increased significantly ($P<0.05$) [100].

The behavioral and hematological effects of the treatment of chamomillawere investigated in mice subjected to experimental stress. Mice who cohabitated with a sick cage mate showed a decrease in their general activity, but those treated with chamomilla were less severely affected ($P=0.0426$). No hematological changes were observed. In the forced swimming, mice pre-treated with chamomilla scored intermediate between water control and ethanol or amitriptyline treatment. Furthermore, a decrease in the leukocyte count was observed in the chamomilla-treated groups ($P=0.039$). Accordingly, chamomilla enhanced recovery of basal behavioral conditions in mice subjected to stressful conditions [101].

The long-term *Matricaria chamomilla* use was evaluated for prevention of generalized anxiety disorder relapse by the clinical study included two-phase, during Phase 1, eligible participants received 12 weeks of open-label therapy with chamomile pharmaceutical grade extract 1500mg (500 mg capsule 3 times daily), while, during Phase 2, treatment responders were randomized to either 26 weeks of continuation chamomile therapy or placebo in a double-blinded, placebo-substitution design. The primary outcome was time to relapse during continuation therapy andthe secondary outcomes included the proportion who relapsed treatment-emergent adverse events and vital sign changes. Long-term chamomile was safe and significantly reduced moderate-to-severe generalized anxiety disorder, but did not significantly reduce the rate of relapse [102].

A randomized double-blind placebo-controlled trialwas carried out to investigate the antidepressant effect of *Matricaria chamomilla* extract (1500 mg daily for 8 weeks) in subjects with generalized anxiety disorder with and without comorbid depression. *Matricaria chamomilla* produced clinically meaningful antidepressant effects in addition to its anxiolytic activity in subjects with generalized anxiety disorderand comorbid depression [103].

A randomized, double-blind, placebo-controlled efficacy and tolerability trial were carried out to determine the effect of *Matricaria recutita* extract therapy in mild to moderate generalized anxiety disorder using Hamilton anxiety rating scores. Chamomile possessedmodest anxiolytic activity, and a significantly greater reduction in mean total Hamilton anxiety rating scores during chamomile versus placebo therapy ($P = 0.047$) was recorded [104].

4.1. In the treatment of morphine withdrawal syndrome

The effects of *Matricaria chamomilla* extract on both morphine withdrawal syndrome and self-administration of morphine were investigated in rats. The development of morphine dependence was achieved by subcutaneous injection of rats with morphine sulfate twice daily for 7 days. An acute *Matricaria chamomilla* extract administration (10, 25, and 50 mg/kg, IP, 30 min before the naloxone injection) greatly attenuated the withdrawal signs including rearing, jumping, climbing, ptosis, teeth chattering, and wet dog shaking in morphine-dependent rats, at day 7, in a dose-dependent manner. Furthermore, an acute central injection of the extract (10, 25, and 50 µg/µl, 5 min before the naloxone injection) also greatly attenuated the withdrawal signs in morphine-addicted rats in a U shape manner, at day 7. When rats were allowed to self-administer morphine (1 mg/infusion) for 10 consecutive days for 2h/session, intraperitoneal injection of the extract (50 mg/kg, IP, 30 min before morphine self-administration) for 10 days, produced a significant decrease in the initiation of morphine self-administration during all sessions [105].

4.2. Anticonvulsant effects

The antiepilepticeffect of hydro-methanolic percolated extract of *Matricaria recutita* (100, 200, and 300 mg/kg) in seizures induced by picrotoxin was studied in mice. The latency of the beginning time of seizure was increased in mice pretreated with different doses of the extract. The most effective dose was 200 mg/kg ($P< 0.05$). The same dose delayed the time of death in mice ($P< 0.01$). The extract showed no effect on the death rate [106].

The anticonvulsant effects of the hydro-alcoholic extract of *Matricaria chamomilla* on PTZ-induced seizure were studiedinrats. Different doses of extract delayed the initiation time of tonic-clonic seizuresin comparison with the control group. The delay was significant at 600 mg/kg (P< 0. 05), 800, and 1000 mg/kg (P< 0. 001). The extract also significantly decreased the 24 h deathat 800 and 1000 mg/kg (P<0. 01) and 600 mg/kg (P< 0. 05) [107].

The protective effect of ethyl acetate fraction of *Matricaria recutita* (25mg /kg, bw) against strychnine-induced seizure was studiedin mice in comparison with diazepam 0.5 mg/kg. Both treatments were given intraperitoneally 60 minutes before the administration of strychnine. Both, the ethyl acetate fraction of *Matricaria recutita* and the standard drug showed a significant increase in the onset time to seizure and the survival time with an obvious decrease in the severity of the attack compared to the control [108].

4.3. Effect on memory

The effect of the hydroalcoholic extract of *Matricaria chamomilla* on memory was studiedin scopolamine-induced amnesia in rats. The extract reversed the scopolamine-induceddecrease of the spontaneous alternation in the Y-maze test and the scopolamine-induced increase of the working and reference memory errors in the radial arm maze test. Furthermore, the scopolamine-induced alteration of the acetylcholinesterase activity and the oxidant-antioxidant balance in the rat hippocampus was recovered by the treatment with the extract. The extract also restored the scopolamine-decreased BDNF expression and increased IL1β expression in the rat hippocampus [109].

4.4. Hypotensive effects

A single oral administrationof (total alcohol extract, oil extract, and water lifted after oil extraction) of *Matricaria chamomilla* (100 and 200 mg/kg) decreased both systolic and diastolic blood pressure of normotensive rats and decreased heart rate after 1, 1.5, and 2 hr. The water lifted after the oil extract showed the most antihypertensive activity. Serum biochemical parameters and lipid profile levels of treated groups were improved in comparison with induced-hypertensive untreated rats. The investigated extracts also restored the reduced glutathione in tissues and increased theactivity of the significantly depleted SOD activity [110].

The oral administration of *Matricaria chamomilla* beverages causeda significant dose-dependent decrease in systolic blood pressure, diastolic blood pressure, and heart rate compared with their basal values in both normotensive and hypertensive human volunteers [110].

4.5. Hypolipidemic effects

The hypolipidemiceffects of *Camiellasinesis*, *Matricaria chamomilla,* and their blend teas (10, 30, and 50 mg/kg BW orally, once dailyfor 30 days.) were studied in rats. Rats showed a significant decrease in triglycerides, total cholesterol, and LDL anda slight increase in HDL levels [111].

4.5.1. For the treatment of enuresis

The efficacy of the topical use of *Matricaria recutita* oil in the treatment of enuresis was studied in children. Eighty patients diagnosed as monosymptomatic nocturnal or daytime enuresis received *Matricaria recutita* oil or placebo topically for 6 weeks in a double-blind randomized placebo-controlled trial. Patients were evaluated prior to and following 8 weeks of the intervention in terms of frequency of enuresis and any observed adverse effects. The mean frequency of enuresis at the first, second, and third 2 weeks was lower in the *Matricaria recutita* oil-treated group compared with the placebo group (P< .001, P=0.03, and P< .001, respectively). There was no report of any adverse effects in the study groups [112].

4.5.2. For the treatment of oral stomatitis

A case of methotrexate-induced oral mucositis in a patient with rheumatoid arthritis wassuccessfully treated with wild chamomile mouthwashes [113].

Chamomilemouthwashwas also used after 5-FU-based chemotherapy to protect from stomatitis asmajor dose-limiting toxicity from bolus 5-fluorouracil-based (5-FU) chemotherapy regimens. However, the clinical trial did not support the hypothesis that chamomile could decrease 5-FU-induced stomatitis [114].

4.5.3. Side effects and toxicity

The LD_{50} of aqueous Matricaria *chamomilla* extract was found to be more than 2g/kg and did not produce mortality or changes in the general behavior of the test animals [53].

The plant wasgenerally safe for consumption, however, individuals with hypersensitivity to ragweed and other members of the Compositae family should use *Matricaria chamomilla* with caution. Allergic reactions to chamomile were rare and no toxic compounds have been reported in the plant [115].

The primary screening tests upon leukocytes measured with all tested concentrations of *Chamomilla recutita* extracts did not show any signs of cytotoxicity to the human leukocytes, their viability was higher than 95%, before and after the experiments [17].

Many cases of contact dermatitis and anaphylactic reactions to camomile were recorded, these cases were associated with generalized urticaria, angioedema, and severe dyspnoea, with elevatedtotal serum IgE against chamomile [116-119].

5. Conclusion

Plants generally produce many secondary metabolites which constitute an important source of many pharmaceutical drugs.Many previous reviews revealed the wide range of pharmacological and therapeutic effects of medicinal plants**.** This review discusses the chemical constituent, and pharmacological and therapeutic effects of *Matricaria chamomilla* as a promising herbal drug because of its safety and effectiveness.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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