DOI 10.26724/2079-8334-2025-3-93-210-219
UDC 615.322:582.998.16

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BIOLOGICAL ACTIVITY AND THERAPEUTIC PROPERTIES OF MATRICARIA CHAMOMILLA L

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Matricaria chamomilla L. is one of the most widely used medicinal plants. The main components of the flowers include phenolic compounds, mainly the flavonoids apigenin, quercetin, patuletin, luteolin and their glucosides; the main components of the essential oil extracted from the flowers are the terpenoids α-bisabolol and its oxides and azulenes, including chamazulene. Components of Matricaria chamomilla L., such as α-bisabolol, β-farnesene, chamazulene, apigenin, geraniol, gerniarin, umbelliferone, luteolin, quercetin, and rutin, are believed to have anti-inflammatory effects. It has been established that α-bisabolol of Matricaria chamomilla gives it antimicrobial properties against both Gram-positive and Gram-negative bacteria. Chamomile (Matricaria chamomilla) has been used since ancient times to treat various skin lesions such as burns and wounds. To date, it has been established that the biologically active substances of Matricaria chamomilla L. have antioxidant, antispasmodic, analgesic, anti-inflammatory, antiseptic, diaphoretic, choleretic effects; reduce allergic reactions, enhance regeneration processes, increase the secretory activity of the digestive glands, stimulate appetite, eliminate intestinal spasms, and reduce fermentation processes. The chemically active components of essential oils, or volatile oils, have been shown to have neuroprotective effects, which may help alleviate symptoms of depression and anxiety. The long-term use of chamomile in clinical medicine has shown the numerous effects of this medicinal plant, which are due to the powerful potential of biologically active substances, a wide spectrum of biological and pharmacological activity and proven efficacy, along with good tolerability.

Key words: phytotherapy, chamomile, Matricaria chamomilla L., chemical composition, biological activity, pharmacological properties.

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БІОЛОГІЧНА АКТИВНІСТЬ І ТЕРАПЕВТИЧНІ ВЛАСТИВОСТІ РОМАШКИ АПТЕЧНОЇ

Matricaria chamomilla L. є однією з найбільш широко використовуваних лікарських рослин. Основні компоненти квіток включають фенольні сполуки, головним чином флавоноїди апігенін, кверцетин, патулетин, лютеолін та їх глюкозиди; тоді як основними компонентами ефірної олії, що видобувається з квіток, є терпеноїди α-бісаболол та його оксиди й азулени, включаючи хамазулен. Вважається, що компоненти Matricaria chamomilla L., такі як α-бісаболол, β-фарнезен, хамазулен, апігенін, гераніол, герніарин, умбеліферон, лютеолін, кверцетин, рутин, мають протизапальну дію. Встановлено, що α-бісаболол Matricaria chamomilla надає їй антимікробні властивості, як проти грампозитивних, так і грамнегативних бактерій. Ромашка лікарська (Matricaria chamomilla) з давніх часів використовується для лікування різних захворювань, таких як опіки та рани. Біологічно активні речовини Matricaria chamomilla L. чинять антиоксидантну, спазмолітичну, болезаспокійливу, протизапальну, антисептичну, потогінну, жовчогінну дію; знижують алергічні реакції, посилюють процеси регенерації, підвищують секреторну діяльність травних залоз, збуджують апетит, усувають спазми кишечнику, зменшують бродильні процеси. Продемонстровано, що хімічно активні компоненти ефірних олій або летких олій мають нейропротекторну дію, що може допомогти полегшити симптоми депресії та тривоги. Тривалий час використання ромашки у клінічній медицині показав численні ефекти цієї лікарської рослини, що обумовлено потужнім потенціалом біологічно-активних речовин, широким спектром біологічної та фармакологічної активності та доведеною ефективністю, поряд хорошою переносимістю.

Ключові слова: фітотерапія, ромашка аптечна, Matricaria chamomilla L., хімічний склад, біологічна активність, фармакологічні властивості.

The work is a fragment of the research project "To determine the features of immunocytokine imbalance in comorbid patients with hypertension and type 2 diabetes and cardiovascular and renal complications", state registration No. 0123U101711.

A feature of today, along with a wide range of synthetic drugs, is the use of alternative treatments for the prevention and treatment of many diseases, including phytotherapy [27]. One of the oldest methods of treatment is the use of medicinal plants. Centuries-old experience of a huge variety of natural raw materials has allowed us to isolate the most commonly used medicinal plants [31]. Among them, a special place is occupied by chamomile (Matricaria chamomilla L., Matrcaria recutita L., Chamomilla recutita L.). The World Health Organization has included chamomile in traditional, complementary and integrative medicine (TCIM) [47]. Particular attention is paid to German chamomile, as the most common variety, which is often defined as a "star among medicinal species" [48].

Matricaria chamomilla L. has been used in traditional medicine for thousands of years in Egypt, Greece, and Rome. This medicinal plant has been used for a variety of ailments, but most commonly for the treatment of infections, neuropsychiatric disorders, respiratory disorders, gastrointestinal disorders, and liver disorders. A Uyghur medical work written in the 10th century notes that chamomile nourishes the nerves and stomach, improves appetite, and relieves painful swelling and sweating, and is often used for chronic headaches, constipation, amenorrhea, joint swelling, and urinary disorders [11]. Other pharmacological properties include anti-inflammatory, antiseptic, carminative, wound healing, sedative, and antispasmodic activities [14]. Chamomile is included in the pharmacopoeias of 26 countries around the world.

The purpose of the study was to summarize the literature on the phytochemistry of the main molecular mechanisms of action and pharmacological properties of Matricaria chamomilla L, as well as the results of experimental and clinical studies of its use in clinical medicine.

Chemical composition

The chemical composition of Matricaria chamomilla L. with established properties is given in Table 1.

Table 1

Chemical components of Matricaria chamomilla L. and their properties [41]

Chemical components	Properties
1. Essential oil	Anti-inflammatory, bactericidal, anti-inflammatory, fungicidal, anti-spasmodic, analgesic, antiseptic, anti-pyretic, antianaphylactic, antispasmodic, carminative
a) Hamazulen	Antioxidant, sedative
b) Bisabolol	Anti-corrosion, anti-inflammatory, antimicrobial
2. Polyphenolic compounds a) Luteolin	Anti-inflammatory, hypotensive
b) Apigenin	Antitumor
c) Quercetin	Antitumor, antiarthritic
d) Limonen	Antitumor
3. Spiroether	Antispasmodic, anxiolytic, sedative
4. Choline	Liver disease
5. Bodegold	Sedative, anxiolytic, antispasmodic
6. Apple pectin	Antidiarrheal for children

Matricaria chamomilla L. has been found to contain flavonoids, coumarins, essential oils, terpenes, sterols, organic acids, polysaccharides, and other compounds [25]. Analysis of the photochemical composition of essential oils and extracts of Matricaria chamomilla L. has allowed the identification of over 120 components [12]. 26 organic acids have been isolated from chamomile, of which four acids (palmitic, linoleic, oleic, stearic) are primary metabolites, and the rest are secondary metabolites [26, 50]. Fifty flavonoids have been identified as the main active components of chamomile (apigenin, quercetin, patuletin, luteolin, rutin, etc.). It is believed that apigenin is not only the main biologically active compound in chamomile, but also a key quality indicator [17]. Thus, for therapeutic use, dried chamomile flowers, according to the European Pharmacopoeia, must contain at least 0.25 % apigenin-7-glucoside, and according to the United States Pharmacopoeia, at least 0.3 % of this compound and at least 0.15 % of bisabolane derivatives [44].

Quantitative analysis of multicomponent compounds of Matricaria chamomilla L. showed the presence of 10 coumarins (coumarin, 7-methoxycoumarin, esculetin, skimine, daphnine, daphnetin, umbelliferone, scopoletin, isoscopoletin and 3,4-dihydrocoumarin) [35]. A large number of terpenes were also found: 39 monoterpenes (O-cymene α-pinene myrtenal cineole, etc.), 27 sesquiterpenes, among them α-bisabolol, E-β-farnesene, etc., di- and triterpenes [35].

It has been shown that the concentration of bioactive compounds varies in different parts of the flower, for example, apigenin is found in high concentrations in white ligulate flowers, while luteolin and quercetin are found in lower concentrations in ligulate flowers, but in higher quantities in tubular flowers and in the flower head [26]. Essential oils are usually composed of terpenoids, such as α-bisabolol and its oxides A and B, bisabolol oxide A, chamazulene. β-farnesene, etc. [7, 32, 39]. Chamazulene, bisabolol and cis-farnesene are hydrophobic in nature. Chamazulene is not present in natural raw materials, but proazulene and matricin, which are present in chamomile flowers, are known to decompose into chamazulene during steam distillation processes [11].

Chromatographic analysis of the chemical composition of Matricaria chamomilla L. extracts revealed the presence of phenolic compounds, including phenolic acids (ellagic, chlorogenic, catechol, etc.), flavonoids, coumarins, and amino acids (proline, alanine, etc.) [24]. In addition, the extracts contain sterols, triterpenes, saponins, tannins, and alkaloids.

Matricaria chamomilla L. also contains polysaccharides (1.29–3.25 %), L(+)-ascorbic acid, adenosine, phenylpropionic acids, benzodiazepines, γ-aminobutyric acid (GABA), choline, bitter substances, mucus, gums, as well as trace elements such as calcium, zinc, iron, magnesium, manganese, sodium, etc. [44].

Biological activity. Anti-inflammatory effects.

Chamomile has long been used in folk medicine to treat inflammatory diseases. Components of Matricaria chamomilla L., such as α-bisabolol, β-farnesene, chamazulene, apigenin, geraniol, gerniarin, umbelliferone, luteolin, quercetin, and rutin, are believed to have anti-inflammatory effects [2, 44].

Bhaskaran N. et al. [11] studied the mechanism of action of dried chamomile flower extract on inflammatory diseases. Macrophages were stimulated by lipopolysaccharide administration, and nitric oxide (NO) production was assessed both in the absence and presence of aqueous chamomile extract. In the absence of chamomile extract, nitric oxide (NO) production significantly increased by 30-fold, while after treatment with chamomile at doses of 5–40 μg/ml, the level decreased by 53–83 %. In another in vivo experimental study using inflammation models, a significant dose-dependent increase in anti-inflammatory responses was demonstrated.

In an experimental study by De Cicco P. et al. [8], the pharmacological mechanisms of the anti-inflammatory action of essential oils of Matricaria chamomilla L. were studied. Chemical analysis of the samples revealed the presence of a high content of oxygenated sesquiterpenes, which constitute more than half of the entire oil. A significant anti-inflammatory effect was demonstrated, due to the inhibition of the production of nitric oxide (NO), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Antioxidant activity was also found, due to the modulation of the immune response of macrophages. Thus, essential oils are able to reduce the activation of CD4 + T-cells, which are also involved in inflammatory processes [8].

In a study by Asadi Z et al. [3], the quantitative content of apigenin and total phenolic content in both aqueous and alcoholic extracts of Matricaria chamomilla were studied. In addition, the authors investigated the effects of aqueous and ethanolic extracts of Matricaria chamomilla on the viability of macrophages and lymphocyte cells separated from BALB/c, and the production of nitric oxide by macrophages, secretion of interferon-γ and interleukin-10 in lymphocytes. The amount of apigenin was found to be 0.078 and 0.25 mg/g of dry weight in the aqueous and alcoholic extracts, respectively. The total phenolic content was shown to be 2.99 % in the aqueous and 3.95 % in the alcoholic extracts.

The viability of BALB/c-separated macrophages significantly increased when treated with an aqueous extract of Matricaria chamomilla and decreased when treated with an alcoholic extract. A significant decrease in the production of nitric oxide by macrophages and the viability of cells of separated BALB/c lymphocytes was found when treated with aqueous and alcoholic extracts. A decrease in the level of interleukin-10 was found in lymphocytes treated with an aqueous extract of Matricaria chamomilla and an increase in the content of interferon-γ, which may indicate Th1 polarization. When treated with an alcoholic extract of Matricaria chamomilla, no significant change in the level of interferon-γ in lymphocytes was observed, but the level of interleukin-10 increased in these cells. It was demonstrated that the anti-inflammatory effect of the alcoholic extract of Matricaria chamomilla was higher than that of the aqueous extract.

In a study on volunteers, it was found that flavonoids and essential oils of chamomile are not only adsorbed on the surface of the skin, but also penetrate into its deeper layers. This makes it possible to use them as local anti-inflammatory agents. One of the mechanisms of anti-inflammatory activity of chamomile is the inhibition of lipopolysaccharide-induced release of prostaglandin E2 and the attenuation of the activity of the enzyme cyclooxygenase-2 (COX-2), without affecting the expression of COX-1.

Antimicrobial activity.

It has been established that α-bisabolol of Matricaria chamomilla gives it antimicrobial properties against both Gram-positive and Gram-negative bacteria [5, 29]. In an experiment on a wound infection model with strains of Pseudomonas aeruginosa, 5 % chamomile ointment was applied and the healing time was compared with tetracycline ointment. It was found that the group receiving chamomile showed a shorter wound healing time (5.3 days) compared to the group receiving the antibiotic (6.3 days) [20].

Matricaria chamomilla has the ability to disrupt microbial biofilms. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of Matricaria chamomilla were found to be 12.5–50 mg/mL and 25 mg/L, respectively. Biofilm inhibition assays were also performed, and chamomile extracts in the concentration range of 1.6–100 mg/mL showed biofilm inhibition [19]. In synergy with synthetic drugs, plant components are also able to enhance the antimicrobial properties of the latter.

At the same time, a recent systematic review by Valmy J. et al. [43] included 11 randomized clinical trials. According to the meta-analysis, no significant antimicrobial effect of Matricaria

chamomilla was found, despite the fact that most of the literature confirms its effectiveness using different approaches [40].

Chamomile essential oil has been found to demonstrate strong antiviral activity against strains of herpes simplex virus (HSV-1) sensitive and resistant to acyclovir. On the other hand, Matricaria chamomilla L can also be used to treat a number of oral diseases. This has been confirmed in a number of studies. It has been found that as a mouthwash, Matricaria chamomilla L. in gingivitis can reduce biofilm accumulation and bleeding gums, and has an anti-caries effect [4]. Chamomile extract has been shown to relieve pain in patients with minor aphthous stomatitis of the oral mucosa.

In vitro study [16] investigated the efficacy of ethyl acetate extract of Matricaria chamomilla L. against Enterococcus faecalis and compared it with standard root canal irrigation solutions. The antibacterial effect of ethyl acetate extract of Matricaria chamomilla was evaluated without or with the addition of dentin powder using the agar diffusion method. Zones of inhibition induced by the EthOAc extract were observed after 5 minutes, 60 minutes and 24 hours and compared with standard irrigation solutions (2 % chlorhexidine and 2 % sodium hypochlorite) without or after mixing with dentin powder. It was found that when Matricaria chamomilla extract was used alone in samples without dentin powder, the zone of inhibition after 24 hours was 9.7 mm, but after the addition of dentin powder this zone decreased (7.7 mm). It was shown that the combination of Matricaria chamomilla extract with chlorhexidine showed that the zone of inhibition in samples with dentin powder was 25.3 mm, but decreased after the addition of dentin powder (21.7 mm). This allowed the authors to conclude that ethyl acetate extract of Matricaria chamomilla L., as an alternative root canal irrigant, could be a useful natural agent with antibacterial activity against Enterococcus faecalis. Furthermore, it showed promising results in endodontic therapy after combination with chlorhexidine in the eradication of Enterococcus faecalis.

In a study conducted by Braga AS. et al. [4], the antibiofilm and anticaries effects of an experimental mouthwash containing an aqueous extract of Matricaria chamomilla L. were evaluated. M. chamomilla L. was found to have a lower antibiofilm effect but the same anticaries effect as that found for chlorhexidine in this model. Another clinical study demonstrated the effectiveness of a saliva substitute using chamomile flowers and flax seeds in alleviating symptoms of primary burning mouth syndrome [1].

Wound healing properties.

Chamomile (Matricaria chamomilla) has been used since ancient times to treat various skin lesions such as burns and wounds. Khashan A. et al. [21] conducted a study to determine the effectiveness of different combinations of chamomile preparations against the growth of Staphylococcus aureus compared to gentamicin using the agar diffusion method. It was found that in the group of experimental animals that received Matricaria chamomilla ointment at a concentration of (60 mg/ml), complete healing was observed after 14 days of treatment and hair regrowth in the wound area, compared to the control group. In the group that received Gentamicin ointment, complete recovery took 21 days. Therefore, Matricaria chamomilla has high antibacterial efficacy against bacterial infections that infect wounds.

The aim of the study by Sadat S. et al. [36] was to determine the antibacterial activity of ethanolic extracts of Matricaria chamomilla, Malva sylvestris and Capsella bursa-pastoris against methicillin-resistant Staphylococcus aureus (MRSA) isolated from clinical specimens. Agar diffusion and broth microdilution methods were used for antibacterial assays. No inhibitory effect of ethanolic extracts of M. sylvestris and C. bursa-pastoris against MRSA isolates was detected in both antibacterial assays. Chamomile flower extract was found to have antibacterial activity against 20 MRSA isolates at concentrations of 50 and 25 mg/mL. Chamomile leaf extract demonstrated inhibitory effects on 7 MRSA isolates. Chamomile flower extracts demonstrated minimum inhibitory concentration (MIC) and minimum major strain concentration (MBC) of 6.25 and 12.5 mg/mL for most MRSA isolates, while chamomile leaf extracts showed 12.5 and 25 mg/mL for several MRSA isolates, respectively. Thus, the ethanolic extract of chamomile flowers demonstrated significant antibacterial activity against MRSA isolates. Hence, this extract may be an alternative to antibiotic therapy and a good option for controlling infections caused by MRSA and pathogenic bacteria.

Another study [33] investigated the antibacterial activity of ethanolic extracts of Matricaria chamomilla, Malva cylvestris and Capsella bursa-pastoris against Pseudomonas aeruginosa strains. It was found that ethanolic extracts of M. sylvestris and Capsella bursa-pastoris did not show any antibacterial activity against MDR isolates of P. aeruginosa in both antibacterial assays. The inhibitory effect of ethanolic extract of chamomile against isolates of P. aeruginosa was also not observed by the agar diffusion method. By the broth microdilution method, chamomile leaf extract demonstrated inhibitory effect, and the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were 12.5 and 25 mg/ml, respectively. The authors concluded that ethanolic extract of chamomile leaf demonstrated

antibacterial activity against MDR isolates of P. aeruginosa. Thus, it can be used in the production of antibacterial agents and is a good option for protection against pathogenic microorganisms, as well as against P. aeruginosa.

In a study [13], the MIC of essential oil and extracts of Matricaria chamomilla in hexane, diethyl ether, dichloromethane against Staphylococcus aureus, Escherichia coli, and Candida albicans was determined. The effect was compared with antibiotics such as ampicillin, cefuroxime, tetracycline, fluconazole, and nystatin. The individual MICs shown by the extracts were comparatively higher than standard antibiotics; however, when used in combination, they showed a synergistic/additive effect. The effect was most pronounced with tetracycline, and a fraction inhibitory concentration index of 0.26–0.37 and a fourfold decrease in MIC against Gram-positive and Gram-negative bacteria were observed. The data obtained demonstrate the synergistic effect of Matricaria chamomilla with synthetic drugs to enhance their antimicrobial properties.

The efficacy of topical chamomile in accelerating wound healing was evaluated in a double-blind study of 14 patients undergoing tattoo dermabrasion. Chamomile was found to be statistically effective in promoting wound drying and accelerating epithelialization. This effect was confirmed by a recent meta-analysis [44], which showed a statistically significant effect of chamomile in minimizing tissue damage to the oral mucosa.

An experimental study investigated the wound healing and antimicrobial properties of Matricaria recutita L. extract against various microorganisms in rats. The main group of rats was given an aqueous extract of the plant (120 mg/kg/day) mixed with their drinking water. It was found that adding the plant extract to drinking water for 15 days resulted in a significant reduction in wound area compared to the control group (61 % vs. 48 %), faster epithelialization and significantly higher wound tensile strength ($p<0.002$). In addition, the wet and dry granulation tissue mass and hydroxyproline content were significantly higher. A Brazilian study on rats showed that chamomile caused complete wound healing faster than corticosteroids, but further research is needed in this area.

Antioxidant effect.

α-Bisabolol has been shown to strongly inhibit the generation of reactive oxygen species (ROS) and stimulate antioxidant systems [34]. However, the antioxidant mechanisms of bisabolol require further investigation. Apigenin also has the potential to enhance cellular antioxidant defenses by increasing the activities of glutathione, catalase, and superoxide dismutase (SOD) [42].

Experimentally, in vivo and in vitro studies have proven the antioxidant properties of Matricaria chamomilla extract. In an experiment on mice, it was shown that ethanol extract of Matricaria recutita L. increases the activity of superoxide dismutase and glutathione peroxidase and reduces the content of malondialdehyde. It was found that the antioxidant effect of chamomile extract is dose-dependent [11].

The effect of an aqueous extract of chamomile on procyclidine-induced oxidative stress in rats was studied in an experiment by Nasser Hussein M. et al. [28]. The authors demonstrated the importance of using chamomile extract as an antioxidant against oxidative stress and its potential in preventing cancer induced by excessive doses of procyclidine ($p\leq0.005$).

Wang W and Spaw [45] studied the antioxidant potential and anti-inflammatory activity of apigenin-7-O-glucoside and compared it with that of trolox. It was shown that apigenin-7-O-glucoside, like trolox, inhibited H_2O_2-induced ROS formation in RAW264.7 cells. However, apigenin-7-O-glucoside exerted a stronger inhibition of free radical-induced oxidative damage to erythrocytes than trolox. At the same time, compared with trolox, apigenin-7-O-glucoside also had a stronger inhibitory effect on LPS-induced NF-κB/NLRP3/caspase-1 signaling in RAW246.7 cells. Based on the data obtained, the authors confirmed the potential of apigenin-7-O-glucoside as a pharmaceutical drug for antioxidant and anti-inflammatory effects, and the addition of trolox contributed to the enhancement of such efficacy.

In the study of Sah A et al. [37], the antioxidant and antiproliferative activities of ethanolic extract of Matricaria recutita L were determined. Antioxidant activity was measured using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. It was shown that the percentage of inhibition of DPPH scavenging activity was dose-dependent in the range from 94.8 %±0.03 at 1.50 mg/ml to 84.2 %±0.86 at 0.15 mg/ml. The same authors, in an experiment on a human hepatoma cancer cell line (HepG2) treated with chamomile extract, recorded a dose-dependent decrease in cell viability. The IC50 was ~ 300 μg/ml. The authors concluded that Matricaria recutita L extract significantly suppressed the level of important markers of angiogenesis both in HepG2 cells and ex vivo.

Currently, studies are also being conducted to study the anticarcinogenic properties of Matricaria recutita L. To date, it has been established that the biologically active substances of Matricaria chamomilla L. have antispasmodic, analgesic, anti-inflammatory, antiseptic, diaphoretic, choleretic effects; reduce

allergic reactions, enhance regeneration processes, increase the secretory activity of the digestive glands, stimulate appetite, eliminate intestinal spasms, and reduce fermentation processes.

In an experiment [50] on models of diarrhea and intestinal fluid accumulation induced by castor oil, per os administration of Matricaria chamomilla L. extract to mice demonstrated antidiarrheal and antisecretory activity at doses of 150 and 300 mg/kg, similar to the effects of cromakalim and loperamide [41], which are known for their antispasmodic, antidiarrheal and antisecretory activities. It was found that the antidiarrheal and antisecretory effects of Matricaria chamomilla L. are partly mediated by the involvement of potassium channel activation, as evidenced by the partial attenuation of these effects when reproduced in mice previously administered glibenclamide, an ATP-dependent K+ channel blocker, or 4-aminopyridine, a voltage-dependent K+ channel blocker [37]. The inhibitory effect of Matricaria chamomilla L. was strongly suppressed in the presence of 4-aminopyridine compared to glibenclamide. This indicated that the activity of the plant extract mainly involved voltage-gated K+ channels, as well as ATP-sensitive K+ channels, which are widely represented in intestinal smooth muscle and are also known for their inhibitory effect on hypermobile intestine. It was also experimentally established that the effect of the plant extract on the "concentration-response of Ca2+" indicator provided data confirming the antispasmodic properties of Matricaria chamomilla L., due to an action similar to calcium channel blockers, but significantly weaker compared to verapamil [36].

Gastroprotective properties.

Oxidative stress and antioxidant depletion have been shown to play a crucial role in ethanol-induced gastric mucosal injury. Jabri MA, et al. studied the effect of Matricaria recutita L. decoction extract on alcoholic gastric mucosal injury in rats. It was demonstrated that the decoction extract of the plant protects against ethanol-induced gastric mucosal injury, which may be partly due to its antioxidant properties, as well as various mechanisms of gastric mucosal protection, including protection of sulfhydryl groups of gastric cells and opposing effects on some intracellular mediators such as free iron, hydrogen peroxide and calcium [11].

Wind-generating properties.

In a randomized controlled trial [15], patients undergoing laparoscopic cholecystectomy were given chamomile extract. Patients were randomly assigned to one group (n = 32) to receive the extract and the other to receive placebo (n = 32). The drug was administered 1 h before surgery. The severity and frequency of flatulence were recorded using a visual analogue scale in both groups at three times: preoperatively, postoperatively during the recovery period, and 2 h after surgery. Matricaria recutita L. was found to significantly reduce the severity of flatulence after surgery compared with the placebo group. Data analysis showed that the severity of flatulence increased significantly over time in both groups, but the degree of increase in the intervention group was significantly lower than in the control group.

Irritable bowel syndrome.

In a randomized clinical trial involving 45 patients with irritable bowel syndrome (ROOM III criteria) who did not have organic diseases, it was proposed to take Chamomile extract 20 drops daily for four weeks. To assess the effect of the plant extract, a questionnaire of symptoms associated with irritable bowel syndrome was used, which included the intensity of abdominal pain, bloating, nausea, stool consistency and changes in bowel habits. It was found that the symptoms of irritable bowel syndrome significantly decreased in the second and fourth weeks after the start of herbal therapy ($p<0.001$). The relief of symptoms lasted up to 2 weeks after the end of treatment [7].

In a study by Masoumi A.Y. et al. evaluated the effect of aqueous extract of Matricaria recutita L. on an acute experimental colitis model in rats. The highest dose of the plant extract (30 mg/kg) was effective in reducing the severity and extent of inflammation. Histopathological studies of colon sections showed that the therapeutic effect of the extract at 10, 20 and 30 mg/kg was mild, moderate and complete, respectively. Therefore, aqueous extract of Matricaria recutita L. significantly reduced the inflammatory and wound indices of ulcerative colitis in rats.

A study by Weber L. et al. [46] was devoted to the analysis of the effect of myrrh (Commiphora molmol Engl.), coffee charcoal (Coffea arabica L.) and chamomile flower extract (Matricaria chamomilla L.) on the inflammatory relationship between immune and intestinal epithelial cells, as well as on the resulting disruption of the intestinal barrier. In an experimental cell co-culture model consisting of monolayers of intestinal epithelial cells (CECs) (Caco-2, HT29-MTX-E12) and macrophages (THP-1), activation of macrophages with lipopolysaccharide (LPS) led to the release of pro-inflammatory mediators and, thus, to inflammatory stimulation of CECs with the release of chemokines and a decrease in barrier function. The authors showed the effect of individual plant extracts and the triple combination on the release of inflammatory mediators interleukin-6 (IL-6), tumor necrosis factor-α (TNFα), interleukin-8 (IL-8),

monocyte chemoattractant protein-1 (MCP-1), prostaglandin E2 (PGE2). To assess the effect on barrier function, the transepithelial electrical resistance (TEER) of IEC monolayers was measured. It was found that all plant extracts exhibited anti-inflammatory properties by inhibiting the release of inflammatory mediators (IL-6, TNF, IL-8, MCP-1, PGE2) to varying degrees. The intestinal barrier stabilizing effect was observed for myrrh and coffee charcoal. Myrrh had the most pronounced pharmacological activity. In the triple combination, dose reduction and synergistic interaction were observed. The authors concluded that the results provide a mechanistic basis for the use of a herbal combination of myrrh, coffee charcoal, and chamomile flower extract in the treatment of inflammatory bowel disease. It has been experimentally established (in vivo on mice and rats) [38] that extracts of Matricaria chamomilla L. demonstrated analgesic activity and improved sleep. The highest sedative and analgesic effects in rodents were found in the dry extract obtained using 70 % aqueous ethanol for extraction at a dose of 50 mg/kg.

Effects on the nervous system.

Essential oils used in aromatherapy have been extracted from aromatic plants and herbs for centuries to treat various ailments. [6]. Due to their specific pharmacological functions, essential oils can be used in a variety of ways to stimulate certain physiological responses to alleviate symptoms. [22] The chemically active components of essential oils, or volatile oils, have been shown to have neuroprotective effects, which may help alleviate symptoms of depression and anxiety. Roman chamomile essential oil is often used as a mild sedative to calm nerves, reduce anxiety, and treat nightmares, insomnia, and other sleep problems.

Aromatherapy is a common complementary and alternative medicine practice used by people with insomnia. The effect of inhalation of Matricaria chamomilla L. oil on sleep quality in young people with insomnia was studied in a randomized controlled trial [9] that included 80 participants aged 18–35 years with insomnia. Patients were assigned to an aromatherapy group (n = 40) or a control group (n = 40). The aromatherapy group inhaled Matricaria chamomilla L. oil for 10 minutes per day for 15 days, while the control group continued their usual daily routine. Assessment was performed using the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI). After treatment, between-group analysis demonstrated a significant reduction in PSQI and ISI scores in the aromatherapy group ($P < 0.001$ for both) compared with the control group. Thus, fifteen days of inhalation of Matricaria chamomilla L. oil before bedtime reduced the severity of insomnia and improved sleep quality in young adults suffering from insomnia.

Jia Y et al. [16] conducted a study based on network pharmacology and database analysis. It was shown that the active components of Roman chamomile are involved in the interaction of neuroactive ligands with receptors, the release of 5-HT in the synapse, the cyclic adenosine monophosphate signaling pathway and the neurotransmitter binding pathway, and that LRRK2 may be an important gene of Roman chamomile for the treatment of anxiety disorders.

A meta-analysis [15] of 12 randomized clinical trials examined the efficacy and safety of an aqueous extract of Matricaria chamomilla L for the treatment of anxiety, generalized anxiety disorder, sleep quality, and insomnia in humans. No difference was found in the effect on anxiety (standardized mean difference =-0.15, 95 % CI [-0.46, 0.16], P=0.4214). Using the HAM-A scale, significant improvements were found in generalized anxiety disorder after 2 and 4 weeks of treatment (mean difference =-1.43, 95 % CI [-2.47, -0.39], P=0.007), (MD=-1.79, 95 % CI [-3.14, -0.43], P=0.0097), respectively. A significant improvement in sleep quality was also found after the use of an aqueous extract of Matricaria chamomilla L (standardized mean difference =-0.73, 95 % CI [-1.23, -0.23], P<0.005). The authors concluded that Matricaria chamomilla L is effective and safe for improving sleep quality and eliminating generalized anxiety disorders.

A randomized, double-blind, placebo-controlled trial [23] examined the potential antidepressant effect of Matricaria chamomilla L. extract (1500 mg daily for 8 weeks) in subjects with generalized anxiety disorder with or without comorbid depression. Similar anxiolytic effects were observed over time in both diagnostic subgroups. However, patients with comorbid depression had a greater reduction in HRSD core symptom scores ($p < 0.023$) and a trend toward lower Hamilton Depression Rating Scale ($p = 0.14$) and Beck Depression Inventory (BDI) scores ($p = 0.060$). The results obtained allowed the study authors to conclude that M. chamomilla L. may have clinically significant antidepressant effects in addition to its anxiolytic activity in patients with generalized anxiety disorders and comorbid depression.

Kazemi A. and sang [18] conducted a systematic review that included ten studies (772 participants) to assess the Pittsburgh Sleep Quality Index (PSQI) and sleep duration. under the influence of Matricaria chamomilla L. A significant decrease in PSQI score was found (WMD: -1.88, 95 CI: -3.46, -0.31, I2: 88.4, n=5). An improvement in the ease of falling asleep was noted in three of the four studies. Sleep efficiency

was found to be unchanged in two studies and worsened in one, and the number of awakenings after sleep or sleep continuation improved in two of the three studies. The authors concluded that Matricaria chamomilla L. improved sleep, especially the number of awakenings after sleep or sleep continuation; however, it did not lead to improvements in sleep duration, percentage of sleep efficiency, and daytime functioning.

A randomized controlled trial [49] examined the effect of Matricaria chamomilla L. extract on sleep quality in elderly people. The mean ages in the control and treatment groups were 70.73±6.44 and 69.36±4.99, respectively. The treatment group received chamomile extract capsules (200 mg) twice daily for 28 consecutive days, while the control group received wheat flour capsules (200 mg) in the same manner. Sleep quality was assessed using the Pittsburgh Index. It was demonstrated that after the course of therapy, the sleep quality in the treatment group was significantly better than that in the control group ($P<0.05$). Therefore, the authors concluded that the use of chamomile extract can significantly improve sleep quality in elderly people.

A randomized, parallel-controlled trial [10] examined the effects of inhaled aromatherapy using lavender and chamomile essential oils on depression, anxiety, and stress in community-dwelling older adults. The study included 183 participants. They were randomized into three groups: lavender, chamomile, and control. Participants in the experimental groups inhaled three drops of 1.5 % lavender and chamomile essential oils for 30 nights. Participants in the control group inhaled distilled water only. The Depression, Anxiety, and Stress Scale (DASS) was used to assess the effects. Compared with the control group, the lavender and chamomile groups showed statistically significant improvements in depression, anxiety, and stress levels immediately and 1 month after the intervention ($p <0.01$). The study showed that inhaled aromatherapy with chamomile essential oils and lavender extract reduced depression, anxiety, and stress levels in community-dwelling older adults.

The overall therapeutic uses of Matricaria chamomilla L. are presented in Fig. 1.

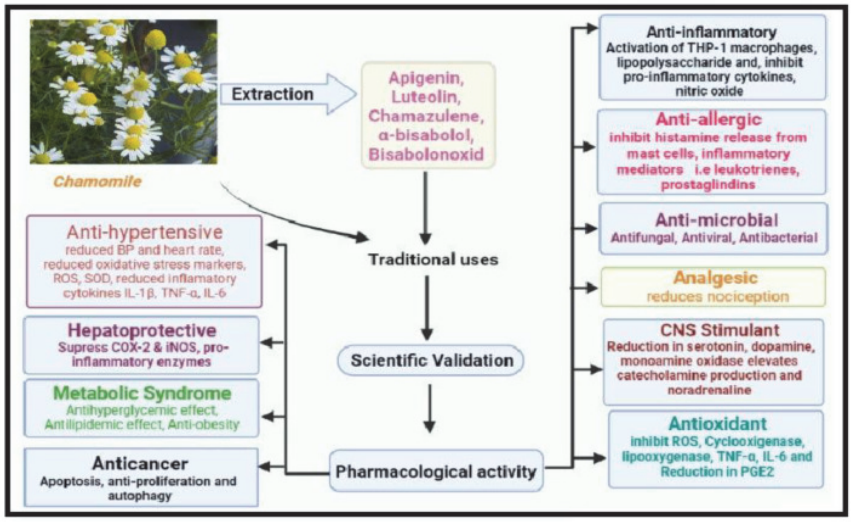

Fig. 1. Therapeutic uses of Matricaria chamomilla L. and the corresponding mechanism of action [37].

A systematic review by Ostovar M et al [30] of adverse events associated with chamomile reported in human studies was conducted. The review included 72 studies and 11 case reports. In these studies, 2896 patients were treated with chamomile, and 65 adverse events were reported in 10 studies. The most common adverse events were gastrointestinal complications and drowsiness, which were self-limiting and non-serious.

No allergic side effects were reported in clinical trials. However, among the 11 case reports, six reported side effects related to allergic reactions to chamomile, ranging from anaphylactic reactions (in three patients) to short-term acute rhinitis. The data obtained allowed the review authors to conclude that Matricaria chamomilla L. is generally safe when used in controlled doses with self-limiting minor side effects. However, clinical cases indicate that allergic reactions should be considered. In addition, there is insufficient data on the safety of Matricaria chamomilla L. during pregnancy and lactation.

Conclusions

1. Matricaria chamomilla L. is one of the most widely used medicinal plants. The main components of the flowers include phenolic compounds, mainly the flavonoids apigenin, quercetin, patuletin, luteolin and their glucosides; the main components of the essential oil extracted from the flowers are the terpenoids α-bisabolol and its oxides and azulenes, including chamazulene.

2. Components of Matricaria chamomilla L., such as α-bisabolol, β-farnesene, chamazulene, apigenin, geraniol, gerniarin, umbelliferone, luteolin, quercetin, and rutin, are believed to have anti-inflammatory effects. It has been established that α-bisabolol of Matricaria chamomilla gives it

antimicrobial properties against both Gram-positive and Gram-negative bacteria. Chamomile (Matricaria chamomilla) has been used since ancient times to treat various skin lesions such as burns and wounds. To date, it has been established that the biologically active substances of Matricaria chamomilla L. have antioxidant, antispasmodic, analgesic, anti-inflammatory, antiseptic, diaphoretic, choleretic effects; reduce allergic reactions, enhance regeneration processes, increase the secretory activity of the digestive glands, stimulate appetite, eliminate intestinal spasms, and reduce fermentation processes. The chemically active components of essential oils, or volatile oils, have been shown to have neuroprotective effects, which may help alleviate symptoms of depression and anxiety.

3. The long-term use of chamomile in clinical medicine has shown the numerous effects of this medicinal plant, which are due to the powerful potential of biologically active substances, a wide spectrum of biological and pharmacological activity and proven efficacy, along with good tolerability.

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Стаття надійшла 19.08.2024 р.