RESEARCH PAPER

Chamomile Active Constituents,Clinical Uses and Pharmacological Actions

Mohammad Hussein AlRifaie[1], Idrees Bakr Qader[2], Ameera Kamal Khaleel[3]*, Ali Sultan AlRifai[4]

[1]Pharmacy Department, School of Medicine, University of Kurdistan Hewlêr (UKH), Erbil, Kurdistan Region/Iraq
Email id:- mohammad.hussein@ukh.edu.krd
[2]College of Pharmacy, Hawler Medical University , Erbil, Kurdistan Region/Iraq
Email ID:- idrees.qader@hmu.edu.krd
[3]Al-Hussain University College, Department of Dentistry, Karbala/Iraq
Email Id:- amera3kam@gmail.com
[4]Al-Hussain University College, Department of Dentistry, Karbala/Iraq
Email ID:- dr.ali.alrifaee@huciraq.edu.iq
Corresponding Author
Ameera Kamal Khaleel
Al-Hussain University College, Department of Dentistry, Karbala/Iraq
Email Id:- amera3kam@gmail.com

ABSTRACT
Egypt, Germany, Hungary, and Argentina are the world's most dominant agricultural centers for commercial chamomile cultivation which has been employed for thousands of years in herbal remedies. Its multitherapeutic, nutritional, and cosmetic qualities have earned it the title of star of medicinal plants. The two primary species are German Chamomile (Matricaria chamomilla) and Roman Chamomile (Chamaemelum nobile). German chamomile is mainly used in traditional herbalism. It contain organic acids, flavonoids, coumarins, volatile oil, monoterpenes, sesquiterpenes, diterpenes and triterpenes, polysaccharides, ascorbic acid, adenosine, phenyl propionic acids, benzodiazepines, γ-aminobutyric acid, choline, gums, amino acids, and different trace elements.
It have analgesic, antimicrobial, anti-inflammatory, anti-oxidant, wound healing, antihypertensive, antihyperglycemic, hepatoprotective, and nephroprotective activities. It is important for gut health and for treating some nervous disorders and oral mucositis. It shows anti-osteoporosis, anti-allergy,and anticancer activities.
In this review we describe the chamomile pharmacological activities and highlight the recent findings as a therapeutic agent to promote human health.
Keywords: Chamomile, flavonoids, polyphenols, coumarins, volatile oil, human health..
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1.INTRODUCTION

Chamomile is a medicinal plant species from the Asteraceae family often referred to as the star among medicinal species. Its curative effect has been known before many years. Nowadays it is a highly favored and much used medicinal plant in traditional medicine. It has a cosmetic, multi-therapeutic, and nutritional values which have been established through years of scientific uses and research [1].
Chamomile is nowadays found throughout Germany, North America, Europe, and Australia. The commercial product is mainly cultivated in Egypt, Hungary, Argentina, and Slovakia [2].
Matricaria chamomilla (Chamomilla recutita; German chamomile) is mainly used in traditional herbalism. This herb belong to the Asteraceae/Compositae family [1]. The name of this plant is derived from Greek word CHAMOS which means ground, and MELOS which means apple. These refer to slowness of growing and apple odor of the fresh flowers of the chamomile. The Latin name of recutitus refers to the petals, which is the soft, leaf-like parts that form the outer ring of a flower [3].

DESCRIPTION OF THE PLANT

Chamomile is a daisy-like flowering plant that is widely used. It is a charming, ground-hugging herb that releases a very beautiful, apple like scent when crushed. Chamomile is an annual plant with a thin roots which penetrating into the soil. The stem is erect, heavily branched and grows to a height of 10-80 cm, with long and narrow leaves. The flower heads have a diameter of 10 to 30 mm, and they are pedunculated. The golden yellow tubular florets (Figure -1) are 1.5 to 2.5 mm long, ending always in a glandulous tube. The 11 to 27 white plant flowers are 6 to 11 mm long and 3.5 mm wide and arranged concentrically. The receptacle is 6 to 8 mm wide, flat in the beginning, and cone-shaped later [4]. The flower is a common ingredient of herbal teas which is consumed at a rate of more than a million cups per day

*Author for Correspondence: haricholera30@gmail.com



Figure -1: Matricaria chamomilla flowers.

2. Active constituents

All biological applications of chamomile are related to its chemical components which are mainly present in the fresh or dried flower. This chemical composition of the plant varies due to differences in the specific environment, the type of soil, and the different genotypic backgrounds[5].The active constituents are Table-1:[6]

26 Organic acids, like palmitic acid, linoleic acid, oleic acid, and stearic acid.

50 Flavonoids, like apigenin, Galangin, Naringenin, and Luteolin.

10 Coumarins, like 3,4-Dihydrocoumarin,Umbelliferone 7-methoxy- coumarin, and esculetin.

19 Sterols and guaiacolides (16 Sterols like Stigmasterol, β-sitosterol and Stigmasterol 3-O-β-D glucoside; and 3 guaiacolides like Guaianolide and Matricin).

102 components are reported in the volatile oil such as 3-Methyl-2-butanone, 3-Methyl-2-butanol, Isoamyl alcohol, and 2-Methyl-1-butanol .

71 Terpenes (39 monoterpenes like Camphene, Citronellol, and Geraniol; 27 sesquiterpenes like α-bisabolol, Chamazulen, and Humulene, 2 diterpenes and 3 triterpenes [6,7].

Other constituent are polysaccharides,L(+)-ascorbic acid, adenosine, phenyl propionic acids, benzodiazepines, γ-aminobutyric acid, choline, gums, amino acids, and trace elements, such as Ca, Fe. Zn,Mg, Mn, and Na [8,9].

Table-1:Active constituents of chamomile [6]

Organic acids	flavonoids	Coumarins	Sterols and guaiacolides
1.Palmitic acid 2.Linoleic acid 3.Oleic acid 4.Stearic acid 5.Isobutyric acid 6.Tiglic acid 7.Isovaleric acid 8.L-2-Methylbutyric acid 9.4-Hydroxybenzoic acid 10.Cinnamic acid 11.Anisic acid 12.Nonanoic acid 13.Vanillic acid 14.Decanoic acid 15.Caffeic acid 16.Quinic acid 17.Ferulic acid 18.Galacturonic acid 19.Syringic acid 20.Chlorogein acid 21.Neochlorogenic acid 22.Cryptochlorogenic acid 23.Isochlorogenic acid 24.Isochlorogenic acid 25. Isochlorogenic acid 26.1,5-Dicaffeoylquinic acid	1.Apigenin 2.Galangin 3. Naringenin 4.Luteolin 5.Kaempferol 6.Hispidulin 7.Hydroxygenkwanin 8.Chrysoeriol 9.Quercetin 10.Ermanin 11.3-O-Methylquercetin 12.3Methylquercetin/Isorhamnetin 13.6-Methoxykaempfero 14.Eupafolin 15.Eupalitin 16.Jaceosidin 17.Patuletin 18.Esculin 19.Eupatoletin 20.Spinacetin 21.Axillarin 22.Scopolin 23.Jaceidin 24.Chrysosplenol 25.4,5-Di-hydroxy-3,3,6,7-tetramethoxy-flavone 26.Chrysosplenetin B 27.Cosmosiin 28.Sophoricoside 29.Luteolin-4-β-glucoside 30.Cynaroside 31.Quercitrin 32.Astragalin 33.Cynaroside 34.Cyanidin-3-O-glucoside 35.Chrysoeriol-β-glucoside	1.Coumarin 2. 3,4-Dihydrocoumarin 3. Umbelliferone 4. 7-Methoxycoumarin 5. Esculetin 6. Daphnetin 7. Scopoletin 8. Isoscopoletin 9. Skimmin 10. Daphnin	1.(22E,24R)-3β-Hydroxyergosta-5,8,22-trien-7-one 2. Stigmasterol 3. β-sitosterol 4.Stigmasteran-22-ene-3,6-dione 5.β-Hydroxystigmaster-4,22-dien-3-one 6. 3β-Hydroxy-6,22-diene-5α,8β-Cyclodioxyergosterol. 7. 7α-Hydroxy-β-stigmasterol 8. 7β-Hydroxy-β-stigmasterol 9. 5α-Stigmasteran-3,6-dione 10. 6-Hydroxystigmaster-4-en-3-one 11.7,22-Diene-3,5,6-trihydroxy-ergosterol 12. 7α-Hydroxy-β-sitosterol 13. 7β-Hydroxy-β-sitosterol 14.3β-Hydroxy-7α-hydroxyethyl-24β-ethyl cholest-5-ene 15.Stigmasterol 3-O-β-D glucoside 16. Daucosterol 17. Matricarin 18. Matricin 19. Guaianolide

	36.Pratensein-7-O-glucoside 37.7-O-(β-D-glucopyranosyl-galactin 38.6-Hydroxy-luteolin-7-'glucoside 39.Quercetin-3-glucoside 40.Hyperoside 41.Quercimeritrin 42. Isokaempferol-7-O-glucuronide 43.Isorhamnetin-7-O-β-glucoside 44.Patulitrin 45.Dimerized coniferyl isovalerate 46 .Apiin 47 .Rhoifolin 48 .Luteolin-7-O-β-rutinoside 49 .Quercetin-3-O-rutinoside 50. Rutin		

Table-1.Cont

Volatile oil		Terpenes (Monoterpenes,Sesquiterpenes,Diterpenes,Triterpenes
1.3-Methyl-2-butanone 2.3-Methyl-2-butanol 3.Isoamyl alcohol 4.2-Methyl-1-butanol 5.Leaf alcohol 6.3-Methyl-1-pentanol 7. Hexyl alcohol 8.Benzaldehyde 9.1-Octene 10. Methyl tiglate 11.Vinyl butyrate 12.Heptaldehyde 13.Cyclopentane, nitro- 14.Isobutyl acetate 15.Methallyl acetate 16.2-Heptanol 17.Heptylalcohol 18.Methylheptenone 19.Propyl methacrylate 20.Ethyl tiglate 21.Prenyl acetate 22.Naphthalene 23.Ethyl 2-methyl cyclo 23.propanecarboxylate 24. Ethyl 1-methylcyclo propanecarboxylate 25.Octanal 26.Dihydro-3-hydroxy-4, 4-dimet hyl-,(R)-2(3H)-Furanone 27.Ethyl 2-methylbutyrate 28.Ethyl isovalerate / Ethyl3 -methylbutanoat 29. Isopropyl butyrate 30. Isobutyl propionate 31. Isoamyl acetate 32. 2-Methylbutyl acetate 33.1-Octanol ′ 34. 2-Methyl acetophenone 35. 2-Pentylfuran 36. 2-Propenoic acid, 2-methyl-, oxiranylmethyl ester 37.Isobutyl methacrylate 38. Butyl methacrylate 39. Leaf acetate 40. Propyl tiglate 41. 1-Nonanal 42. 2-Furanmethanol, tetrahydro-, acetate	52.Iso-amyl methacrylae 53.Isobutyl tiglate 54.Cis-3-hexexnyl propionate 55.Butyric anhydride 56.Isobutyl 2-methyl butyrate 57.Isobutyl isovalerate 58.Isopentyl isobutyrate 59.2-Methyl-butanoic acid butyl ester 60. Butyl isovalerate 61. Hexyl propionate 62. Amyl butyrate 63. 2-Methylbutyl isobutyrate 64.Phenethyl acetate 65.2-Propenoic acid,2-methyl-,(tetrahydro-2-furanyl) methyl ester 66. Isoamyl 2-methyl butyrate 67 2-Methylbutyl isovalerate 68 2-Methylbutyl 2-methylbutyrate 69 Pentanoic acid, 3-methylbutyl ester 70 3-Methyl-butanoic aci pentyl ester 71 Hexyl isobutyrate 72 Hexyl isobutyrate 73 Butanoic acid, 2-methyl-, 3-methylbutylester 74 Hexanoic acid,2-methylpropyl ester 75 4-Methyl-5-decanol 76 Methyl eugenol 77 Cis-3-Hexenyl tiglate 78 3-Methyl-, 3-hexenyl ester, (Z)-Butanoic acid 79 2-Butenoic acid,3-methyl-, hexyl ester 80 Isobutyl 3-hydroxy-2- methylenebutanoate 81 Propanoic acid, 2-methyl-, heptyl ester 82 Hexyl 2-methylbutyrate 83 Isopentyl hexanoate 84 Decanoic acid, methyl ester 85 Isobutyl phenylacetate 86 Phenethyl butyrate 87 Sabinylacetate 88 (−)-Trans-pinocarvyl acetate 89 Lavandulyl acetate 90 (R)-Dihydrcarvyl acetate 91 Decanoic acid, ethyl ester 92 3-Buten-2-one, 94-(2-hydroxy-2,6,6-trimethyl	1. O-Cymene 2. P-Cymene 3. α-Thujene 4. α-Pinene 5. Camphene 6.3-Cyclohexadiene, 2-methyl-5-(1-methylethyl)-1 7.4(10)-Thujene,(1R,5R) -(+) -(8CI)/d-SabiNee 8. Myrcene 9 (Z)-Ocimene 10.(E)-3,7-Dimethylocta-1,3,6-triene 11. γ-Terpinene 12. Dipentene 13. Pinocarvone 14. Myrtenal 15. (−)-Verbnone 16. Carvone 17. 2(10) -Pinen-3-one 18.3,3,6-Trimethyl-1,5-heptadien-4-one 19.Pinocarveol 20. Isocamphopinone 21.3-Cyclopentene-1-acetaldehyde,2,2,3-trimethyl- 22.Yomogialcohol C10H18O 23 Cineole 24.5-Methyl-2-(1-methylethyl)-,cis-Cyclohexanonene 25.D,L-2-Bornanol 26.4-Carvomenthenol 27. (−)-Trans-Myrtanol 28.1,6-Octadien-3-ol,3,7-dimethyl 29. Camphene hydrate 30.Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-,(1S-end) - 31.Artemisia alcohol 32.Geraniol 33. D-Isomenthol 34. D,L-Menthol 35. Decanal 36. Citronellol 37. Eugenol 38.2-Propenoic acid, 2-methyl-, 2-ethylbutyl ester 39.(1R,2R,3S,5R)-(−)-2,3-Pinanediol 40. Chamazulen 41. β-Elemene 42. (+)-Calarene 43. (−)-α-Gurjunene 44.(+)-Aromadendrene 45.(−)-Allaromadendrene 46. (E)-β-Farnesene 47.Humulene 48. Germacrene 49. α-Selinene 50. α-Zingiberene 51. (+)-Ledene 52.(+)-Bicyclogermacrene

43. Isobutyl isobutyrate 44. Propyl 2-methyl butanoate 45. Butyl isobutyrate 46.Isoamyl propionate 47. Hexyl acetate 48.1-Nonanol 49.Benzyl acetate 50.Benzaldehyde dimethyl acetal 51.Cyclobutanecarboxyli cacid, cyclobutyl ester	cycohexyl) 93.1-Pentadecanamine,N-dimethyl 94. Pentadecanoic acid, methyl ester 95. Perhydrofarnesyl acetone 96.3,4,5-Trimethoxy-trans-stilbene 97. Hexadecanoic acid, methyl ester 98. Hexadecanoic acid, ethyl ester 99.9,12,15-Octadecatrienoic acid, methyl ester, 100. 9,12-Octadecadienoic acid (Z,Z)-, methyl ester 101. 5-Pentadecylresorcine 102. Monopalmitin 2.3.7. Diterpenes and Triterpenes	53. β-Bisabolene 54. (+)-δ-Cadnene 55. α-Farnesene C15H24 56. D-Longifolene 57. Longifolenaldehyde 58. Cayophyllene oxide 59. Spathulenol 60. Nerolidol 61. Himbaccol 62 α-Bisabolol 63 Epiglobulol 64 Atractylenolide 65 α-Bisabolol oxide 66 α-Bisabolol oxide Diterpenes 67 Plant alcohol 68 Phytanetriol 69 Taraxerol 70 Taraxasterol 71 Oleanolic Acid

3. CLINICAL USES AND PHARMACOLOGICAL ACTIONS

3.1. Analgesic Activity

Chamomile is a medicinal herb traditionally used for its analgesic properties. In animals study, using a 30 mg/kg dose compared to the control with 10 ml/kg of saline solution, the chamomile demonstrated analgesic property [10].The meta-analysis done by Kiani et al [11] also provides evidence supporting the analgesic efficacy of chamomile. Chamomile was shown to be effective in reducing postoperative pain, including post cesarean, coronary artery bypass graft surgery, tonsillectomy, and surgery of impacted lower third molar. In addition it decrease the need for a large quantities of analgesics [12].

3.2. Anti-microbial activities

3.2.1. Anti-bacterial action: The constituents of chamomile thought to have antimicrobial properties include luteolin, alpha-bisabolol, quercetin, and apigenin. Chamomile extract demonstrates anti-bacterial activity against Staphylococcus aureus, Escherichia coli, Salmonella species, and Psedomonas aeruginosa. The leaf extract showed 24 mm inhibition zone and the flower extract showed 15 mm. The minimum bactericidal concentration at low extract concentration of 100 mg/ml[13].

Whole plant chamomile extract at 10 mg/ml demonstrates a similar effect, completely inhibiting growth of Streptococcus in vitro. In addition, chamomile extracts blocks aggregation of Helicobacter pylori and various strains of Escherichia coli. Its esters and lactones demonstrate activity against Mycobacterium tuberculosis [14]. It was also found that it can be considered as a good antimicrobial material and used for endodontic irrigation [15].

3.2.2. Anti-viral action: Antiviral effects of chamomile were also studied in acyclovir resistant and acyclovir sensitive Herpes simplex virus strains. Chamomile essential oil showed strong antiviral activity against both strains [16]. Common cold is a mild viral infectious disease of the upper respiratory system. Studies indicate that inhaling the steam with chamomile extract has been helpful in common cold symptoms [17]. Chamomile can be also considered as a valuable resource recommended for preventing SARS-CoV-2 invasion into the human body [18,19].

3.2.3. Fungicidal action: The constituents of chamomile thought to have some fungicidal activity against Candida albicans. In a study investigated the antifungal potential of methanolic extracts and essential oils obtained from Matricaria chamomilla against Candida albicans collected from the patients with denture stomatitis. The antifungal susceptibility was assessed using broth microdilution, with agar diffusion assays. Nystatin was included as a control. The result showed that this medicinal plants can act against clinical Candida albicans isolates derived from denture stomatitis patients[20].

Other results demonstrate a dose-dependent antifungal effect of chamomile essential oil against both Candida albicans and Aspergillus fumigatus. Increasing the concentration of chamomile oil from 0.1 to 1.0 g/100 g led to a statistically significant enlargement of the inhibition zone, reaching 15.7 ± 0.6 mm at the highest concentration ($P < 0.001$). This may contribute to the development of more effective and targeted antimicrobial agents for combating the fungal infections and improving the patient health [21].

3.3. Anti-inflammatory and anti-oxidant activities

Chamomile has the potential to act as a natural anti-inflammatory agent [22]. One of chamomile's anti-inflammatory activities involve regulating pro-inflammatory mediators and suppressing key signaling pathways such as COX-1, COX-2, and NF-kB[23], or suppression of tumor necrosis factor-alpha-induced neutrophil adherence responses [24.]

It was found that a higher reduction in lung inflammation, oxidative damage, and apoptosis in rats lungs were prominently observed following administration of chamomile tea(400 mg/kg b.wt) in comparison to the thinner group which inhaled thinner at a dosage of 4500 ppm [25].

Other study reported that it can do selective inhibition of COX-2, suppression of NO production, prevention of IL-1β, IL-6 and TNF-α, reduction of iNOS mRNA and protein

expression, impediment of leukocyte adhesion, and blockage of IL-1α which induce prostaglandin production, and TNF-α-induced IL-6 and IL-8 release [26].
Due to its anti-oxidant effects, chamomile can help to combat the oxidative stress by neutralizing free radicals, which can contribute to premature skin aging and could be used as a natural raw material in cosmetic formulations [27].

3.4. Wound healing
The efficacy of topical use of chamomile to enhance wound healing was efficacious in promote wound healing through fibroblast stimulation, collagen deposition, maintaining skin homeostasis, and antimicrobial activity. In chronic inflammatory dermatoses, including atopic dermatitis and psoriasis, chamomile down regulate pro-inflammatory cytokines, thereby restoring the immune balance [28].
In a study, 5mm wound was inflicted on the tongue of 36 rats. The study group animals were treated topically with 0.04 ml/day of chamomile ointment, whereas control group animals were not treated. Animals were sacrificed after 3, 7 or 10 days. The result showed that animals treated with chamomile showed the best results regarding epithelialization and percentage of collagen fibers after 10 days [29].
Two circular full thickness wounds were made on the dorsum region of male rats with a sterile biopsy punch. Local Matricaria chamomilla essential oil application was done on wounds of the left side as experimental group, whereas the right side was left to heal spontaneously as control. The healing process was followed for the periods (3, 5 and 7 days). Histological examination showed that local application of Matricaria chamomilla was effective in promoting the process of wound healing [30].

3.5. Anti-hypertensive effect
It was found that chamomile can improves hypertension and cardiac hypertrophy through modulating NADPH oxidase-dependent ROS generation and cytokines in hypothalamic paraventricular nucleus [31]. When the chamomile extract was fed orally to normal rats, and was found that it significantly reduced systolic and diastolic blood pressure as well as heart rate, and when administered to a high salt-sucrose diet induced hypertensive rats and again showed significant reduction in blood pressure and heart rate. This was due to reduced angiotensin converting enzyme activities. Furthermore, the results were compared with a standard anti-hypertensive agent, captopril, and chamomile was found to be superior [32].
Other study proved that apigenin acts as an anti-hypertensive agent through the modulation of nicotinamide adenine dinucleotide phosphate hydrogen(NADPH), oxidase-dependent ROS generation, and inflammatory mechanisms [5]. Chamomile extract was also seen it exhibits a significant vasorelaxant and antihypertensive effects, mediated through modulation of calcium channels and bioactive polyphenolsm, so can be used as a therapeutic agent for hypertension and hypoxia-related cardiovascular disorders [33].

3.6. Anti-hyperglycemic effect
Studies suggest that chamomile ameliorates hyperglycemia and diabetic complications by suppressing blood sugar levels, and increasing liver glycogen storage. Chamomile ethanolic extract treatment protected the majority of the pancreatic islet cells, exhibited significant anti-hyperglycemic effect and protected beta-cells in diabetic rats in a dose-dependent manner, and diminished the hyperglycemia-related oxidative stress, with respect to the control group [34]. Akhgarjand et al study [35] found that chamomile tea can also help to lower the blood sugar levels, inhibiting certain carbohydrate digesting enzyme, improve glycemic control by reducing inflammation, and increasing insulin sensitivity.

3.7. Hepatoprotective property
Gupta and Misra [36] found that chamomile extract has hepatoprotective activity in paracetamol intoxicated albino rats. The treatment with aqueous chamomile extracts reduced levels of AST and ALT by 33–37% in rats administered by 1,2-dimethylhydrazine to induce toxicity to liver . They also found that pretreatment with chamomile before inducing toxicity also had also a protective effect. Chamomile acted by modulating COX-2 and iNOS pro-inflammatory enzymes [37] and by its antioxidant properties through the modulation of SOD and glutathione peroxidase [38].

3.8. Nephroprotective property
It was demonstrated that Matricaria chamomilla extract protects against nephrotoxicity and tissue damage induced by lipopolysaccharide and D-galactosamine in rats. Furthermore it can downregulated inflammatory gene expression (IL-4, IL-6, IL-10, and TNF-α), reduced the lipid peroxidation (MDA), and enhanced the antioxidant defenses, like glutathione and catalase activity. Histopathological results confirmed that chamomile extract can effectively attenuated LPS+D-galactosamine induced renal damage[39]. Hence, it will be a promising nephroprotective agents.
Nephroprotective effects were also studied by Sampaio et al [40], they found that bisabalool attenuated the cell damage caused during kidney injuries, and the antioxidant property might be responsible for nephroprotective effects.

3.9. Gastrointestinal curative property
Chamomile is used traditionally for numerous gastrointestinal conditions, including digestive disorders, colic, upset stomach, flatulence, ulcers, and gastrointestinal irritation [41]. The chamomile extract also plays roles for oral and digestive healths. Extract can be used orally to treat stomach discomfort and pain from functional digestive problems [42]. The use of a chamomile preparation in children with acute, noncomplicated diarrhea reduced the duration of the diarrheal episode compared with placebo and reduced stool frequency [43].
A work was designated to clear out the effect of aqueous extracts of chamomile (400 mg/kg b.wt., for seven days)

on healing of aspirin induced gastric ulcer (200mg/kg b.wt) in rats. The length of gastric ulcer, volume of gastric juice, total acidity and histopathological changes were examined. The results concluded that oral administration with all doses of aqueous extracts of chamomile reduced the length of gastric ulcer, total acidity, volume of gastric juice and histopathological changes [44].

It also decreases inflammation which is associated with many gastrointestinal disorders complaints, such as esophageal reflux, diverticular disease, and aphthous ulceration of the oral cavity.Using chamomile drops as a preventive drug seems to be effective in reducing the incidence of postoperative flatulence [45]. Chamomile has been shown to be comparable to chlorhexidine in terms of reducing gingivitis by decreasing clinical periodontal parameters (PI, GI, and BOP) and inflammatory chemical markers values such as C-reactive protein, alkaline phosphatase and total protein [46].

3.10. Neuroprotective property

A systematic review for chamomile [47] showed it can improved sleep, the number of awakenings after sleep, or staying asleep; but it did not lead to an improvement in the duration of sleep. Another study investigated the behavioral, neurobiological, and protective effects of the ethanolic extract of Matricaria chamomilla in rats previously exposed to harmine and subjected to a forced swimming stress protocol. The chamomile extract ameliorated depression-like behavior by counteracting harmine-induced reductions in locomotor activity, lowered circulating adrenocorticotropic hormone levels and restored antioxidant enzyme activity, reflected by reductions in brain oxidative-stress markers[48].

In other study, convulsions were induced by the administration of kainic acid. Apigenin was then administered orally at 50 mg/kg for six days. This treatment was significantly reduced the onset and severity of the seizures. By immunohistochemical study, the result showed that apigenin can reduced neurodegeneration by increasing the number of living neurons in the hippocampus, and apigenin can restores memory deficits in epilepsy [49].

Chronic oxidative stress is the reason for the stimulation of neurodegeneration. Chamomile, being a natural antioxidant, possesses the ability to scavenge free radicals and, thus, can be effective for the management of neurological disorders such as Alzheimer's disease, Parkinson's disease, and cerebral ischemia [50].

3.11. Anti-osteoporotic activity

Osteoporosis is a metabolic bone disease resulting from low bone mass due to excessive bone resorption, that occurs with increasing age. Chamomile extract showed its ability to stimulate the differentiation and mineralization of osteoblastic cells and to exhibit an anti-estrogenic effect and considered as anti-osteoporosis drug in treatment of post menopausal and senile steoporosis [51]

The anti-osteoporotic activity of ethanol extract from the Matricaria chamomilla flower was also evaluated using steroid-induced osteoporosis in a rat model. The study found that 400 mg/kg body weight dose of the flower extract increased bone strength and thickness. Histopathological examination revealed that the extract caused a significant increase in trabecular thickness, and restored the architecture of the cortical and trabecular structure with well-organized bone matrix. This study concluded that this plant extract showed potential therapeutic benefits for osteoporosis [52].

3.12. Anti-allergic activity

Allergic diseases include asthma, rhinitis, atopic eczema and dermatitis syndrome. Its prevalence has been increasing world wide. Mast cells are present in most organs and tissues, and its activation can triggers the release of histamine and inflammatory mediators such as leukotrienes, proteases; prostaglandins, and proinflammatory cytokines. In a study, allergy was induced in rats by treatments with a mast cell stimulator. These rats were treated with standard drug (disodium chromoglycate) as a control group, and a methanolic chamomile extract as a study group. Chamomile extracts in concentrations of 300 mg/kg showed the inhibition of mast cell degranulation by 73.3% compared to 67.75% by disodium chromoglycate. The histamine levels were also significantly reduced in treated groups in comparison with the control group [53].

Other study found that after treatment of mice with eczema using the positive drugs and different doses of German chamomile volatile oil, the exudate, redness, and swelling in the back of animals were reduced. In the positive drug and high-dose German chamomile volatile oil groups, eczema was reduced [54].

In a randomized double-blind clinical trial involving 52 infants under≤ 12 months with atopic dermatitis. The test group (26 child)were given 60 cc of chamomile oil, while those in the control group (26 child) received 60 cc of Oserin ointment for the treatment. Results showed qualitative and quantitative aspects of atopic dermatitis treatment in the test group were statistically significant ($p<0.001$), and this study highlighted significant and definite benefits of this treatment, including alleviation of skin itching, hydration of dry skin, and overall skin restoration [55].

3.13. Treatment of oral mucositis

A prospective study included 72 patients initiating chemotherapy. Participants were divided to two groups: one using a chamomile mouthwash three times daily and the control group with no mouthwash. Oral mucositis severity was assessed on day 21. The incidence of oral mucositis was significantly lower in the chamomile group (5.4%) compared to controls (26.5%, $p = 0.016$), and no severe cases (grade ≥3) occurred in the chamomile group. These findings support its potential role in supportive cancer care [56].

According to WHO mucositis scale, patients with oral mucositis in chamomile-oral cryotherapy treatment group had never developed grade 2 or higher mucositis with a statistically significant difference found between this group

and oral mucositis oral cryotherapy group at day 15 (80% grade 2 in control group versus 0% in chamomile group)[57]. Chamomile can protect the tongue mucosa of rats from fluorouracil-induced tongue mucositis by significant increase in Ki-67 and Bcl-2 immunoexpression. It attenuate the associated injury if it taken for short duration, but the reverse was occurred if it taken for longer period [58].

3.14. Anticancer activity

With minimal effect on normal cells, chamomile exhibited anti-proliferative and apoptotic activity in various human cancer cells. Most evaluations of tumor growth inhibition by chamomile involve studies with apigenin which is one of the bioactive constituents of chamomile. Studies on preclinical models of prostate, breast, skin, and ovarian cancer have shown a growth inhibitory effects [59]. Chamomile extracts revealed a promising antitumor properties provided by their phytochemical composition [60]. A total sample size of 1099 patients with cancer were involved in a study. Various forms of chamomile were used such as mouthwash, topical material, tea, capsule,and syrup. Chamomile effectively reduced depression, skin complications, vomiting. and improved the appetite and the quality of life among cancer patients Therefore, it can be incorporated into routine care along with other therapeutic measures to reduce patients' suffering related to cancer [61]. Figure-2 summarize the clinical uses and pharmacological actions of chamomile

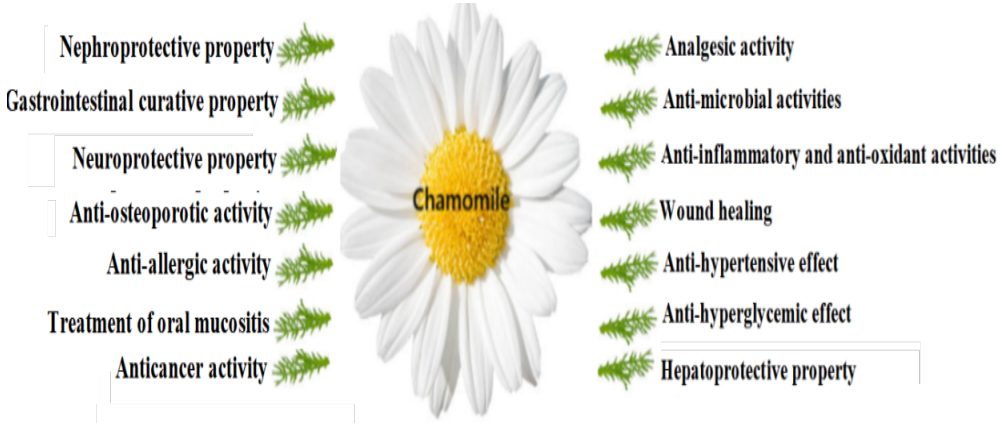


Figure-2:The clinical uses and pharmacological actions of chamomile

4. TOXICITY AND ADVERSE EFFECTS

The US Food and Drug Administration have regarded the oil and extract of both German and Roman chamomile as a safe substance. In an acute toxicity study by a doses of German chamomile flower oil extract of 10, 100, 1000, 1600, 2900, 4300, and 5600 mg/kg which were orally administered to mice, none of the animals was died [62]. Rats were also fed a doses of 1, 2, 4, and 8 g/kg body weight of German chamomile flower aqueous extract for two weeks, and all of the animals remained the physical active [63].

The effect of repeated doses of chamomile tea on the activity of hepatic metabolizing enzymes in rats was studied. Five rats had free access to chamomile tea solution (2% w/v in water), whereas the control group had access to water. After four weeks of treatment, the animals were killed. Result showed no signs of gross pathology of internal organs, and the liver weight/body weight ratios of treated rats were not significantly different from control values [64].

Although this plant has anti-allergic activity, a few studies have reported allergic reactions such as contact dermatitis and hypersensitivity, especially in people who are allergic to pollen or compositae. A case of a man who developed an episode of severe anaphylaxis with generalized urticaria, angioedema and severe dyspnoea nearly one hour after taking camomile tea. Laboratory examination demonstrated a high serum IgE. Skin prick test and labial provocation test with chamomile showed a strong positive reaction [65].

The manifestations of allergy are dependent on ingestion route. Asthma, diarrhea, bowel cramps, and vomiting related to oral intake have been reported; but the inhalation of the chamomile oil predominantly manifests as asthma [66].

Ostovar et al review found that the most common adverse events were gastrointestinal complications and drowsiness,and only three cases showed allergic reactions ranging from anaphylactic reactions to short-lasting acute rhinitis [67].

Chamomile use during pregnancy should be avoided. Abortifacient effects, menstrual cycle irregularities, uterine stimulation with excessive use have been reported [51]. Other study found its possibility to reduce follicular function and development, leading to premature birth in pregnant women when using chamomile [68].

5. INTERACTION WITH DRUGS

Only one report of a possible chamomile-drug interaction has been documented. A 70 year old woman on warfarin was admitted to the hospital with multiple internal hemorrhages after using chamomile products, as a tea and body lotion, to alleviate upper respiratory tract symptoms [69].

Also consumption of chamomile with sedatives, and iron supplementation causes drug interactions, so the use of chamomile with these chemicals should be used with caution to prevent drug interactions and side effects [70].

Chamomile extract shows anti-H. pylori activity and can enhance the effectiveness of standard antibiotics, indicating its potential as a complementary treatment to combat antibiotic-resistant H. pylori infections [71].

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