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REVIEW

A Comprehensive Review on Promising Phytopharmacological Applications of Chamomile Flower

PALLISHREE BHUKTA[1], DEEPANKAR RATH[1], GURUDUTTA PATTNAIK[1,*], BISWAKANTH KAR[2,*] and SANTOSH KUMAR RANAJIT[1,*]

[1]Department of Pharmacology, School of Pharmacy and Life Sciences, Centurion University of Technology and Management, P.O. Jatni, Dist. Khurda-752050, India
[2]Department of Pharmacology, School of Pharmaceutical Sciences, Siksha O Anusandhan University, Bhubaneswar-751030, India

*Corresponding authors: E-mail: biswa_kanth2005@yahoo.co.in; sanrancol@gmail.com

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Chamomile (*Matricaria recutita* L., *Chamomilla recutita* L., *Matricaria chamomilla*) is one of the most favoured single ingredient herbs. Chamomile tea is prepared by brewing the dried flower heads which has been used as traditional remedy. It is a crop introduced into India, mainly grown in Assam, Uttar Pradesh, Jammu & Kashmir states of India. The valuable unknown properties of this multipurpose herb should be explored to determine the therapeutic properties of its different parts, extracts, oils, *etc*. The flowers constitute many phenolic compounds like flavonoids, apigenin, patuletin, glucosides, luteolin and quercetin as main components. This herb is used as an antioxidant, antidepressant, antidiarrheal, antimicrobial, anti-inflammatory, antidiabetic, anticarcinogenic and hepatoprotective agents. In addition to that, it is also useful in treatment of gastrointestinal disorders, premenstrual syndrome, knee osteoarthritis andulcerative colitis. *Matricaria Recutita chamomilla* L. is used for both therapeutically and non-therapeutically around the globe that precipitate its remarkable worth. Chamomile contents of essential oils are widely used in aromatherapy and cosmetics. Most popular chamomile preparation is herbal tea which has been developed and consumed by more than one million cups per day across the globe. This review article briefs about the therapeutic efficiency along with phytology and cultivation techniques.

Keywords: Chamomile, Phytochemicals, Essential oil, Medicinal plant, Flavonoids.

INTRODUCTION

The present-day progress of modern therapeutics has picked up the indigenous products throughout the globe for diverse ailments, infirmities and diseases [1]. The other names of chamomile or chamomile are Hungarian chamomile, Italian chamomilla, wild chamomile, German chamomile, *etc*. [2]. Chamomile (*Matricaria chamomilla* L.) is an essential medicinal herb native to southern and eastern Europe. In India, the plant turned into cultivated in Lucknow for approximately 200 years, whether or not delivered in Punjab approximately 300 years in the past at some stage in the Mughal period. It turned into delivered in Jammu in 1957 [3]. The herbal beverage of flower chamomile is used as an anti-inflammatory, a mild sedative and an antiulcer remedy. Chamomile has antioxidant activity and the essential oil extract of the chamomile flowers possess antimicrobial activity [4-6]. Chamomile has been employed in many skin ailments like wounds, eczema and in treatment of inflammations, irritations like ulcers, neuralgia, gout and rheumatic pains and the human cancer cells growth has been suppressed by the extracts of chamomile, which leads to apoptosis [7,8]. The chemical components found in this plant are apigenin-7-O-glucoside, apigenin, luteolin, chlorogenic acid, caffeic acid, luteolin-7-O-glucoside, terpenoid like bisabolol, chamazulene, farnesene, flavonoids like patuletin, apigenin, quercetin, luteolin and coumarin [9-11]. The coumarins esculetin, herniarin and umbelliferone make up about 0.1% of the total ingredients. Apigenin, luteolin and quercetin are the chief active flavonoid constituents, which constitutes 16.8, 1.9 and 9.9%, respectively of total flavonoids. Chamomile is one of the richest reassets of nutritional antioxidants. Some appreciable evidence reported that coumarins and flavonoids suppress oxidative damage to proteins, DNA, skins and membranes by inhibition of free radical scavenging activity and

protecting from chronic diseases such as hypertension and atherosclerosis [12]. The present study directs the elucidation of advantages of chamomile, its major components and clinical identification of its potency in managing several human disorders.

Phytology: German chamomile or true chamomile, *Matricaria recutita*, belongs to Compositae or Asteraceae family, which is most diverse family of flowering plant that includes dandelions and sunflowers and lettuce. The botanical name for the plant chamomile is *Chamomilla recutita* L. Rauschert, *Matricaria chamomilla*, *Matricaria recutita* belonging to the genus *Chamomilla* and the family Asteraceae [13]. This herb, having identical flowers, produces wider variety and more significant numberof seeds. Chamomile is an annual herb having thin spindle-shaped roots penetrated flatly into the soil. The stem of this shrub is branched, erect, heavily offshoot having long and narrow leaves of bi- to tripinnate and grows upto 10-80 cm of height. The heterogamous and pedunculate flower heads are separately placed, with a 10-30 mm diameter. The golden yellow 1.5-2.5 mm long tubular florets have five teeth that ends in aglandulous tube. This well-known ancient drug, chamomile, has different names, *e.g*. Babuna, Baboonig, Babuna camornile, Babunj, German chamomile, Hungarian chamomile, Flos chamomile, Roman chamomile, chamomilla, single chamomile, pinheads, sweet false chamomile, English chamomile and scented mayweed that suggests its far-reaching use [14,15].

Cultivation: German chamomile grows on any fertile soil, but the crop cannot be developedon rich, heavy and damp soils. It can also hold out against cold weather with lower temperatures *i.e.* 2 to 20 ºC. The harvest has been successfully grown on the loamy sand at the Regional Research Laboratory farm, Jammu, India whether on basic soil of pH of 9 at Banthra farm of the National Botanical Research Institute, Lucknow, India [16]. In north Indian hills it is sown on December second fortnight, whereas in lowlands, in late September or early October as it is a rabi crop. To get better yields, the crop should be transplanted in the first week of December [17]. Flowering starts after two to 3 months of transplanting, depending upon climates. Fully developed flowers are plucked manually at 15-20 days intervals. Three to four harvests of buds are obtained and then taken for shade drying for 3-4 days and then distilled. Shade dried flowers give the highest oil content, *i.e.* 0.44% [18].

Phytochemical constituents: Isolated bioactive constituents of chamomile are commonly used for both medicinal and cosmetics preparations [19]. The volatile oil content of the plant is 0.24-1.9%. When steam distillated, the oil varies from bright blue to dark green when fresh but after storage, it turns into yellowish colour. Although the fat fades, it does not lose its strength. Chamomile flower constitutes more than 120 chemical components as secondary metabolites which includes 36 flavonoids, 28 terpenoids and 52 more compounds having inherent pharmacological activity [20-23]. The oil carriesas much as 20% polyynes. The vital essential oil extracts of the flowers are terpene alcohol (farnesol), chamazulene (2.3-10.9%), (E)-β-farnesene (4.9-8.1%), α-bisabolol oxides A (25.5-28.7%), α-bisabolol oxides B (12.2 30.9%) and α-bisabolol (4.8-11.3%). These are known for their spasmolytic, antiphlogistic, antiseptic and anti-inflammatory properties [24-32]. The very unstable chamazulene and bisabolol should be preserved in an alcoholic tincture which is best for it. The content of chamazulene is less in Roman chamomile. Esters of angelic acid and tiglic acid, α-pinene and farnesene are the components of chamazulene. Both α-bisabolol, bisabolol oxides A and B and chamazulene or azulenesse, farnesene and spiro-ether sesquiterpene lactones, glycosides, coumarins (herniarin and umbelliferone), terpenoids, flavonoids (patuletin, luteolin, apigenin and quercetin) and mucilage are assessed as primary bioactive ingredients [33] (Fig. 1). Several phenolic compounds like flavonoids, quercetin, apigenin, patuletin as glucosides and several acetylated derivatives are the other chief constituents of the flowers. Apigenin, which is the chief active flavonoid content, is present in a little quantity as free apigenin but exists primarily in the form of various glycosides [8,34-36]. There is a remarkable affect in qualitative and quantitative differences of chamomile essential oil are by the growth conditions (*e.g.* fertilizer rate, pesticide application, irrigation). Still, they significantly vary between fertilizing regions, cultivated *versus* wild plant populations and with different conditions of processing [37,38].

Antimicrobial activity: The extractions of chamomile having essential oil exhibits antimicrobial activity against fungi,viruses and bacteria *in vitro*. Essential oils of German chamomile (*M. chamomilla*) exhibit potent activity against 25 different Gram-negative and Gram-positive bacteria and 20 strains of *Listeria monocytogenes* than Roman chamomile oils (*Chamaemelum nobile*), but not comparatively as Moroccan 'chamomile' (*Ormensis multicaulis*) [39]. In an *in vivo* and *in vitro* study, formation of an inhibitory zone of about 7.6 mm diameter evaluated wound dressings activity of chamomile. The study revealed that the wound healing activity of samples were achieved by formation of mucous tissue but deposition of collagen fibers and presence of necrosis are not responsible [40]. In a study of 14 patients, chamomile produced efficacious wound drying and speeding epithelialization [41]. In the test group, there is a significant decrease in the wound area on 15th day as compared to the controls (61% *versus* 48%). In addition, the weight of the dry and wet granules and the hydroxyproline amount were remarkably higher. In wound management, histological observations support *M. recutita* in increasing the wound contraction rate, hydroxyproline content and breaking strength of wound [42]. Recent studies indicate that chamomile causes wounds to heal faster than corticosteroids [43-45].

Anti-inflammatory activity: The volatile oilcontent of chamomile flowers is 1-2%, which includes α-bisabolol oxides A, α-bisabolol oxides B, α-bisabolol and matricin. The matricingets converted to chamazulene and different flavonoids that express anti-inflammatory effects [46]. Chamomile possesses anti-inflammatory activity as it inhibitsprostaglandin E [2] release induced by LPS and without affecting the constitutive form of COX-1, it causes debilitation of cyclooxygenase (COX-2) enzyme activity [47]. Reductionin production of TNF-α in apigenin-7-glucoside treated mice, followed by lipopolysaccharide treatment confirmed the anti-inflammatory activity [48]. In a study of clinical trial, chamomile proffered improved

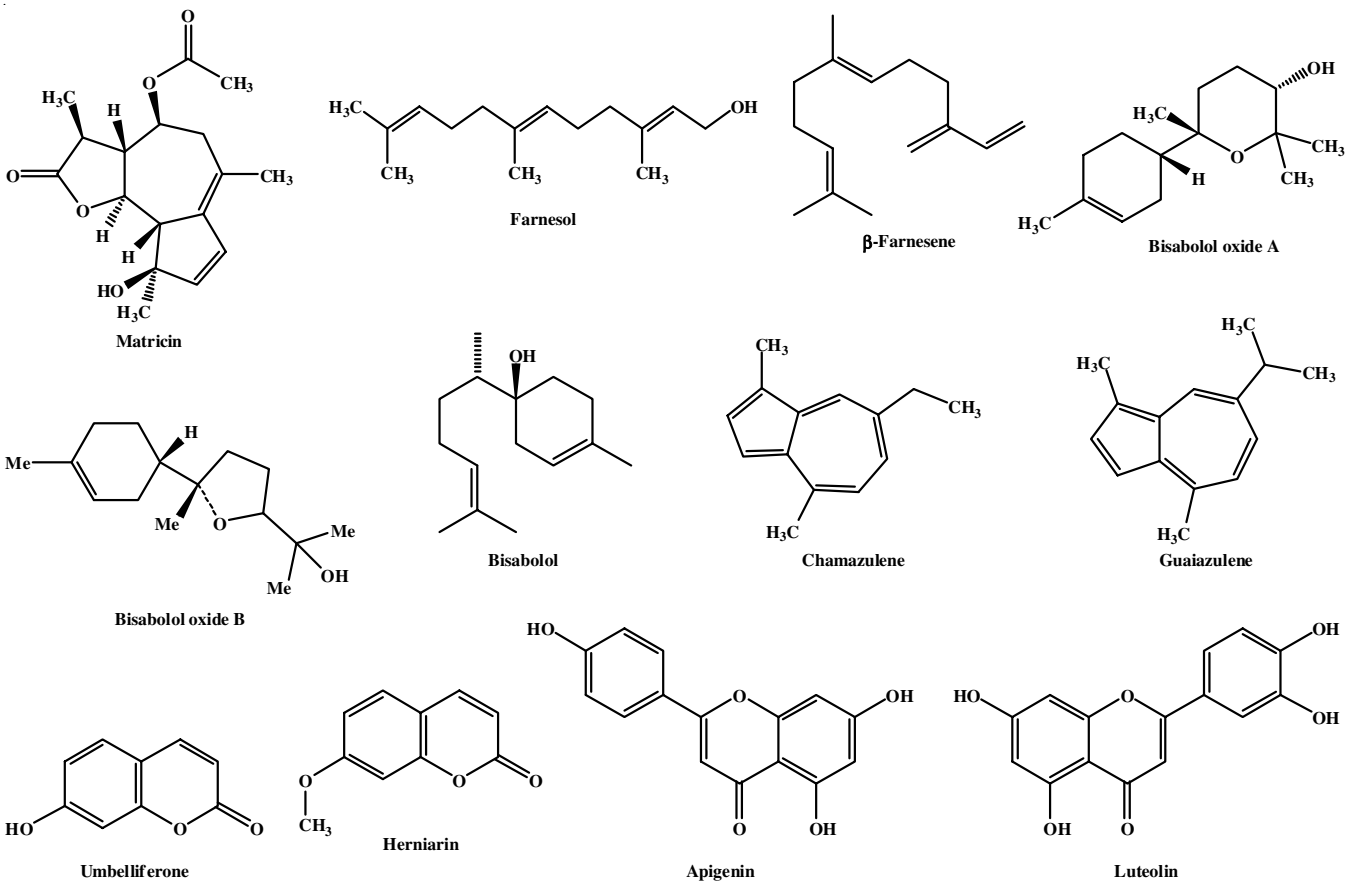

Fig. 1. Phytochemical constituents of *M. chamomilla*

mechanical function of joints and reduced the knee and lowered back pain by effecting systemic inflammation. Still, there were no significant anti-inflammatory effects [49].

Anticancer activity: Apigenin is present in highest amount in chamomile as compared to other substances (840 mg/100 g in contrast to 9 mg/100 g present in peppermint). This flavonoid extract, prepared from the ligules is used commercially. Apigenin influences many cellular activities that includes continuation of cell cycle [50,51], enzymes, pathways involved in cell-signalling and gene expression [52,53], the regulation of cell membrane transport [35,54,55], intracellular transmission through gap junction [56], production of cytokine and the inflammatory response [57]. Rationalizing the evidence of potential mechanisms, chamomile is involved in chemoprevention by acting as an inhibitor of oncogene expression and cell proliferation, anti-inflammatory agent and neuronal activity. Studies involved with apigenin, bioactive constituent of chamomile reported that chamomile inhibits most evaluations of tumor growth. Chamomile showed growth suppression in different studies of preclinical skin cancer, breast, prostate and ovary [58-61]. A test result of the novel agent of seven plant extracts mixture *i.e.* TBS-101 which includes chamomile, confirmed its safety profile with remarkable anticancer effect against androgen-refractory human prostate cancer PC-3 cells, both *in vitro* and *in vivo* [62]. Different studies revealed that apigenin has tyrosine kinases inhibition activity [63]. In prostate cancer cells, it reduces hyperphosphorylation [64], downregulates AR protein expression, NF-kappa B/p65 and decreases prostate-specific antigen in both intracellular and secreted forms [65].

Antidiabetic activity: Chamomile is suggested to have antidiabetic activity by increasing glycogen storage in the liver, suppressing blood sugar levels and hindering sorbitol in human erythrocytes [66]. The therapeutic effect of chamomile is not dependent on insulin secretion [67] and further studies reported the protective activity of chamomile on pancreatic β-cells in reducing oxidative stress associated with hyperglycemia [68]. The antihyperglycemic effects of chamomile tea was evaluated in an animal study by using rats. That investigation indicated the glucose-lowering effect of chamomile tea in diabetic rats, which suggests that daily intake of it, could lower postprandial glucose levels [69].

Gastrointestinal activity: Three trials have examined that chamomile produces gastrointestinal effects in combination with other components but no effects of the individual. A licensed herbal mixture of chamomile, coffee charcoal and myrrh extracts was examined for their clinical efficacy, tolerability and safety in patients suffering from acute diarrhea. A mixture of chamomile, coffee charcoal and myrrh extract has been observed to be efficacious, well tolerable and safe for the patients suffering from acute diarrhea. They have comparative effects with typical routine care treatments [70]. Traditionally used chamomile produces effects in different gastrointestinal disorders which includes spasm, digestive disorders, flatulence, upset stomach,

gastrointestinal irritation and ulcers [71]. A trading preparation (STW5, Iberogast) contains the extracts of lemon balm leaf, bitter candytuft, caraway fruit, milk thistle fruit, chamomile flower, peppermint leaf, Angelica root, liquorice root and greater celandine herb, has been previously reported having protective effect against the occurrence of gastric ulcers. A dose-dependent anti-ulcerogenic effect was produced by STW5 extracts, which is associated with decreased acid formation, increased secretion of mucin, release of prostaglandin E [2] and decreased leukotrienes. It resulted that STW5 was as efficacious in lowering gastric acidity and inhibiting secondary hyperacidity [72].

Central nervous system activity: Significant anticonvulsant activity was not found in apigenin treated mice with up to 80 mg/kg doses, after challenge with 50-80 mg/kg of the seizure-inducing pentylenetetrazole. However, apigenin increased the onset of action of convulsions at respective doses of 20, 40 and 80 mg/kg by two times compared with mice treated with pentylenetetrazole alone [73]. Chamomile extract was reported to have moderate anxiolytic activity from a controlled clinical trial of mild to moderate anxiety disorder patients [74]. Apigenin showed reduction not only latency in the outset of convulsions induced by picrotoxin but also in the locomotor activity but not demonstrated any myorelaxant, anticonvulsant, or anxiolytic activities [75]. Chamomile tea and aromatherapy of its essential oil have been traditionally used to induce sedation and treat insomnia. Chamomile is considered as a sleep-inducer and mild tranquilizer. Its flavonoid apigenin has the ability to bind with benzodiazepine receptors which perhaps the reason behind sedative effect of chamomile [76]. CNS depressant and anticonvulsant effects have shown in preclinical model studies. Clinical trials are marked for their absence, although after consuming chamomile tea, deep and immediate sleep was observed in ten cardiac patients for 90 min [77]. The extracts of chamomile produce hypnotic activity like benzodiazepines [78].

Antioxidant activity: The microencapsulated extracts of this chamomile plant show prominent antioxidant activity after the first week, resulting from the degree of bioactivity of aqueous extracts of this plant [79]. In an investigation, the chamomile, milk thistle and halophilic bacteria were reported to possess antioxidant properties at different concentrations by inhibiting the upregulation of H_2O_2-induced free radicals in human skin fibroblasts *in vitro* [80]. An animal study revealed that chamomile extracts produces protective effects against reactive oxygen species by inhibiting its production and provide protection against hematological agents. Their antioxidant properties either may be due to altered properties or their inconsistent effect on some intracellular intermediaries [81,82].

Topical activity: Chamomile shows moderateeffect in the treatment of atopic eczema when topically applied [83]. The effect of chamomile containing cream *versus* either 5% bufexamac (a nonsteroidal anti-inflammatory) or 0.75% fluocortin butyl ester, 0.25% hydrocortisone, was investigated in 161 number of patients suffering from eczema on their lower legs, hands and forearms who were 0.1% difluocortolone treated initially. During the maintenance period of 3-4 weeks, the chamomile cream was reported to have worthwhile results as 0.25% hydrocortisone and more efficacious than both non-steroidal anti-inflammatory agents and the glucocorticoids [84]. Wound healing properties of chamomile was determined on 14 patients in a double-blind trial who underwent dermabrasion of tattoos. Chamomile was judged to have statistically effective rapid epithelialization and wound drying activity [42]. Recent studies indicate rapid wound healing effect of chamomile as compare to corticosteroids [44].

Osteoporosis and osteoarthritis activity: Osteoporosis is a metabolic ailment characterized by loss of bone density and the bones become week and brittle because of excessive bone resorption due to deficiency of calcium or vitamin D. People with fractured bones have relatively minor injuries. Agents, that are used to prevent bone loss includes selective estrogen receptor modulators, calcitonin, bisphosphonates. Bone loss takes place with increasing age. Bone loss is averted with the aid of the extracts of chamomile through stimulating the mineralization and differentiation of osteoblasts. Chamomile extract was proven to promote osteoblastic cellular differentiation and produced an anti-estrogenic impact, suggesting a mechanism associated with estrogen receptor [85]. The safety and efficacy protocol of topically used chamomile oil in sufferers with knee osteoarthritis had been evaluated. It turned into discovered that chamomile oil precipitated an elevation in analgesic pastime in knee osteoarthritis sufferers. There is a further improvement in their physical features through the topical utility of chamomile oil [86].

Cardiovascular activity: Regular consumption of flavonoids containing food may minimize the threat of death in elderly people from coronary heart disease [87]. Flavonoid intake was inversely associated with not only coronary heart disease mortality, but also the incidence of myocardial infarction. It was evaluated from a study of 65 to 84 years aged 805 men by their intake of flavonoid. In spontaneous multiplication of the atria of isolated mice had a positive chronotropic effect when exposed to apigenin. Consumption of 0.01 to 30 μM of apigenin leads to elevated atrial rate, which is dose-dependent and decreased absorption rate of radioactive noradrenaline [88].

Pharyngitis activity: A randomized, double-blind study determined that chamomile produced remarkable effect after lubricating the endotracheal tube cuff earlier than intubation on post operative hoarseness and sore throat. About 161 patients with elective surgical, gynecological, orthopedic or urological surgeries were categorized into two groups. Ten puffs of chamomile extract (370 mg of chamomile extract) produces lubrication of the endotracheal tube in study group. The control group was not given with any lubrication before intubations but to the standard group general anesthesia was given along with tracheal intubations in both groups. In the post-anesthesia care unit of 41 out of 81 patients no postoperative sore throat were reported in the chamomile treated group in comparison to 45 out of 80 patients in the control group. No significant difference of sore throat and hoarseness was observed in the post-anesthesia care unit and 24 h of post-operation. Post-operative sore throat and hoarseness cannot be prevented by lubricating the endotracheal tube with chamomile extract prior to intubations [89].

Antiplatelet activity: From the three herbs *i.e.* chamomile, nettle and alfalfa, chamomile was reported to have remarkable antiplatelet activity *in vitro*. Platelet aggregation induced by not only by ADP (60%) but also by collagen (84%), as well as collagen-induced whole blood pooling (30%) was inhibited by the chamomile treated as compared to controls ($p < 0.05$). Arachidonic acid or thrombin-induced platelet aggregation could not inhibited by any of the above mentioned herb except chamomile, which produces significant synthesis of thromboxane B2 inhibition induced by either ADP or collagen [90].

Hepatic activity: The potency of chamomile decoction extract was identified against ethanol-mediated oxidative stress in rats, which states that the extract possess a potent hepatoprotective activity against ethanol-mediated oxidative stress in rats, by negatively regulating Fenton reaction constituents like H_2O_2 and free iron, which causes cytotoxicity due to the deregulation of intracellular calcium ion [91]. It has been proved from previous studies that a preparation of chamomile flavonoids such as apigenin, apigenin-7-glucosideluteolin-7-glucoside, isorhamnetin, luteolin and quercetin causes active reduction in ceramide levels in the liver of older rats. Ceramide is being accumulated in other cells and tissues during the aging process that leads to regulation of biochemical and genetic episodes that occurs with time. Continuous intake of chamomile flavonoids for 7 days at a dose of 160 mg/kg/day leads to reduction in the liver ceramide contentand decreased effect of sphingomyelinase in 27-28 months old rats in comparison to the adult rats of 24 months [34].

Contraindications with chamomile: Chamomile does not develop allergic reactions yet relatively poor number of people are sensitive to it [92]. A constituent of Chamomile, coumarin has potential effect on warfarin therapy by acting against vitamin K and influencing the blood coagulation processes [93]. When used with aspirin, other non-steroidal anti-inflammatory drugs and/or acetaminophen, coumarin can provide blood thinning and increase antiplatelet or low prothrombin effects [94]. In combination with various sedative drugs such as benzodiazepines, opioid analgesics or alcohol, chamomile potentially increases the CNS depressant effects because of its mild sedative effect. Therefore, contraindications have been proposed in combination with these drugs [95]. Another study reported that washing eyes with chamomile tea of hay fever sufferers having conjunctivitis aggravates inflammation in eye. In contrast, when chamomile tea was orally administered, eye inflammation did not worsen [96].

Conclusion

The pharmacological effects of chamomile were detailed in this review. This study interpreted that this plant is well known for its anti-depression, anti-inflammatory, antioxidant, antimicrobial, angiogenesis, antidiabetic, hepatoprotective, antidiarrheal and anti-carcinogenic activity. In addition to that it is advantageous for gastrointestinal disorders, knee osteoarthritis and ulcerative colitis. Antimicrobial activities such as antibacterial, antiparasitic, antiviral properties also found. More number of research and scientific evidences are needed to evaluatethe therapeutic effects of chamomilein patients. More efforts are required to focus on preclinical studies of chamomile involving different animal screening models for many other ailments. Consequently, this may leads to validation of chamomile in clinical trials as an encouraging therapeutic agent.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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