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Review

TRADITIONAL USE OF CHAMOMILE FLOWERS (*MATRICARIAE FLOS*) IN INFLAMMATORY-ASSOCIATED SKIN DISORDERS

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ABSTRACT

Chamomile (*Matricaria chamomilla* L.) is one of the world's oldest, and best-documented Asteraceae family medicinal herbs. It is now a popular and widely used therapeutic plant material in folk and traditional medicine. The plant includes numerous components. More than 120 secondary metabolites were identified in it, including flavonoids, terpenoids, sesquiterpenes, coumarins, essential oils, and organic acids. Due to its rich chemical composition, chamomile has many beneficial properties. These include anti-inflammatory, antibacterial, antiseptic, antispasmodic, sedative, antitumor, antioxidant, hypoglycemic, hypotensive, anti-allergic, antidepressant, antianxiety, analgesic, antipruritic, antidiarrheal, hepatoprotective and neuroprotective effects. Chamomile's effectiveness in treating various skin issues is also attributed to its diverse bioactive components. The research delving into chamomile's therapeutic potential reveals that its historical use for skin conditions is not merely based on folklore, but is substantiated by the intricate interactions among its chemical constituents at the molecular level. The goal of this review is to synthesize existing knowledge about chamomile's traditional uses in the treatment of inflammatory skin disorders, with a focus on the findings reported in contemporary scientific literature by scanning PubMed and Scopus for research.

KEYWORDS: Chamomile flowers, *Matricariae flos*, skin disorders, traditional use.

1. Introduction

In recent years, there has been a growing interest in using natural remedies to treat a variety of health conditions, particularly dermatology. Among these botanical agents, chamomile flowers (*Matricariae flos*) have received attention for their long-standing use in treating inflammatory-related skin disorders. Chamomile, a member of the Asteraceae family, has been used medicinally for centuries in various cultures due to its purported anti-inflammatory and skin-soothing properties. Chamomile has been used in skincare since ancient times when it was valued for its calming and healing properties [1].

Inflammatory skin disorders, such as dermatitis, eczema, and psoriasis, pose significant healthcare challenges, affecting millions of people worldwide. Conventional treatments frequently cause side effects, prompting a search for alternative, natural remedies. Chamomile, with its long history of use and anecdotal evidence, emerges as an appealing candidate for research [2].

The purpose of this review is to synthesize existing knowledge on chamomile's traditional uses in the treatment of inflammatory skin disorders, with a particular emphasis on the results reported in contemporary scientific literature. As we explore the traditional roots and scientific advances surrounding chamomile's role in skincare, we may gain a better understanding, paving the way for novel and effective approaches to the treatment of inflammatory skin conditions.

2. Materials and Methods

Scientific databases, including PubMed and Scopus, were utilized to perform a literature search for pertinent studies. The search involved the use of specific keywords, such as “chamomile”, “matricaria”, “traditional use”, “topical”, “skin”, “phytotherapy”, “dermatology”, and “inflammatory”. Various combinations of these search terms were used, and the studies were evaluated for their relevance by examining their abstracts. Studies in English and Polish languages were used for the review. In conducting the literature search, we focused on studies published between 1950-2023 years to ensure a comprehensive and up-to-date review of relevant

literature. After an exhaustive review of 1079 articles, a total of 130 articles were selected for inclusion in this study based on their relevance to the research question and adherence to the inclusion criteria. Other articles were rejected due to duplicates, full-text articles inaccessibility, and irrelevance. Then 45 articles were cited that were most directly related to key findings.

3. General Description

Chamomile (*Matricaria chamomilla* L., *Chamomilla recutita* L., *Matricaria recutita* L.) is an annual herbaceous plant belonging to the Asteraceae (Compositae) family [3]. It is native to southern and eastern Europe and Asia (India, China, and Afghanistan). It grows wild in Central European countries and is especially abundant in Eastern Europe [4,5]. It has also been discovered in North America [6], South America, Australia [7], New Zealand, and North Africa [6]. It is farmed in Hungary, Germany, France, Brazil [4,6], and Asia (including northern India, Afghanistan, and China) [8,9]. Hungary is a major biomass producer of this plant [4,10]. Due to its low requirements for climatic and soil conditions, it can be found in meadows and among cereals, as well as in wastelands, yards, and roadsides [3,7,9,11]. *M. chamomilla* grows in a temperature range of 7 to 26 °C, but can also survive frosts [4,9]. The term "chamomile" is derived from the Greek language and translates to "ground apple", because of the apple-like fragrance of chamomile. It is known by various colloquial names, including German chamomile, Italian chamomile, Hungarian chamomile, and wild chamomile [12].

Matricaria chamomilla is an annual herbaceous plant reaching 10–80 cm in height [4,5]. It possesses slender, spindle-shaped taproots that extend horizontally into the soil [5]. It has erect, highly branched, smooth stems [4,8]. The compound, tripartite, bipartite, and pinnate leaves are arranged torsionally on the stem. They have long, narrow, thread-like leaf blades [4,5,11,13].

The flowers are gathered in heterogamous inflorescences in the form of a basket with radial symmetry and a diameter of 10–30 mm [5,7]. They are distributed singly at the tips of the stem branching [11]. The base of the flower is yellow, cone-shaped, and hollow [3]. Set on it is yellow tubular, hermaphrodite, five-toothed flowers, 1.5–2.5 mm long, terminating in a glandular tube [4,5,7]. The marginal flowers are white, uvular, female, 11–27 in number [4], three-toothed [7], and measure 6–11 mm in length and 3.5 mm in width. They are arranged in a concentric pattern. The flowers in a basket, from the outside, are surrounded by covering leaves, arranged tile-like in two to three whorls [7]. The flowers do not have the calyx cup characteristic for plants belonging to the Asteraceae family.

The fruit of chamomile is a small, smooth, yellowish achene [4,5] with a cylindrical shape, measuring approximately 0.8–1 mm in length and about 0.5 mm in width [10].

4. Chemical Composition

Many groups of chemical components with biological properties are present in chamomile (Table S1). More than 120 compounds have been identified in it, including 36 flavonoids and 28 terpenoids, of which mainly the latter two groups are responsible for the medicinal properties of this plant [10,14,15]. Chamomile flowers' main constituents are terpenoids, α-bisabolol, chamazulene (1–15%), and apigenin [10].

The constituents of chamomile flowers are mainly phenolic compounds, namely, flavonoids (up to 6%) [16]. Thirty-six flavonoids have been isolated from chamomile [4]: the flavones apigenin, luteolin, patuletin, and their glucosides (apigenin 7-O-ß-D-glucoside, luteolin 7-O-ß-D-glucoside [8,12], luteolin 4′-ß-glucoside, luteolin 6-hydroxy-7-glucoside) [8]; the flavonol quercetin and its glucosides, including quercetin 3-glucoside and rutin; the flavanone naringenin; and the monoterpenes geraniol, bornanol, citronellol, and men-thol [3,8].

To date, 27 sesquiterpenes have been isolated from chamomile, including α-bisabolol, chamazulene, α-farnesene, ß-bisabolene, spathulenol, α-bisabolol A-oxide, and α-bisabolol B-oxide [8]. Moreover, diterpenes (phytanetriol), triterpenes (oleanolic acid, taraxanol, taraxasterol) [8], sesquiterpene lactones (matricin) [17], and matricarin [18] are present in the plant material. Ten coumarins have been isolated from chamomile: umbelliferone and its methyl ether herniarin, skimmin (umbelliferone glucoside), coumarin, 7-methoxy-coumarin, 3,4-dihydrocoumarin, esculetin, daphnin, daphnetin, scopoletin, and isoscopoletin [8]. A total of 26 organic acids have also been isolated from chamomile (4 of which are primary metabolites: saturated (palmitic acid and stearic acid) and unsaturated (linoleic acid and oleic acid)fatty acids, and 22 are secondary metabolites: caffeic acid, cinnami acid, isochlorogenic acid A, B, C, ferulic acid, galacturonic acid, 4-hydroxybenzoic acid, and chlorogenic acid, among others) [8,12].

Chamomile flowers have an essential oil content ranging from 0.24 to 2.0 percent. The European Pharmacopoeia recommends that the oil content of chamomile should be no less than 4 mL/kg [14]. The essential oil extracted from German chamomile is a dark blue and thick liquid that possesses a strong and distinctive herbal fragrance [4].

The quality of the oil is determined by its color. The dark blue color indicates a high concentration of terpenoids, mainly chamazulene, which is responsible for its color [4]. This compound is formed from a colorless matricin (sesquiterpene lactone) found in chamomile flowers using steam distillation. Deacetylation, dehydration, and decarboxylation then occur [4].

The essential oil is found throughout the plant, but it is most abundant in the flowers [9], and is extracted from fresh or dried flowers through the process of distillation.

Based on the content of the main components, 4 different chemotypes of chamomile can be distinguished within the species. Type A is dominated by bisabolol A oxide, type B is mainly composed of bisabolol B oxide, type C has α-bisabolol as the main ingredient, and type D contains comparable amounts of α-bisabolol, bisabolol A oxide, and bisabolol B oxide [19].

Although many chemical compounds found in chamomile have been identified, their proportions vary among individuals of this species [20]. It is also difficult to give the exact quantitative and qualitative composition of the essential oil extracted from this plant [9].

Table 1. Chemotypes of chamomile based on the content of the main components.

Type A	bisabolol A oxide
Type B	bisabolol B oxide
Type C	α-bisabolol
Type D	α-bisabolol, bisabolol A, and bisabolol B oxide

The main feature that differentiates the composition of *Matricaria* is its geographical origin, i.e., country or region. Flowers from central Europe contain more oil than those from southeastern Europe [11]. The chamazulene content can be more than 15% for chamomile growing in Poland, and less than 2% for that from India or Egypt [9]. Likewise, the α-bisabolol content can vary considerably. The highest is for plants from Malta and Crimea, at 67 and 69% [9]. Variations in chamomile essential oil composition can be attributed to factors like the season, specific harvesting, climatic conditions, soil type, storage of the raw material, and processing, including the time between harvesting and distillation. The method used for extraction can influence the efficiency of extracting essential oils, their chemical composition, and their biological activity. A delay in drying flowers can cause a change in oils color, as well as a decrease in their essential oil content. The phase of growth, the size of the green parts of the plant, and the drying process are also significant [9,20]. The amount of α-bisabolol and α-bisabolol A and B oxides in flowers reaches its highest point during full bloom and then declines [4]. The build-up or concentration of essential oils in the flowers continues during the drying process [4]. The source and age of the raw material also influence the chamazulene content in chamomile. It decreases when the flowers are in storage [4].

The standardization of plant material is crucial for medicinal purposes [9]. Apigenin is one of the main, most active compounds in this plant. It is considered a marker of chamomile's quality, which is why it is often used to standardize extracts. The European Pharmacopoeia recommends that dried chamomile flowers must contain a minimum of 0.25% apigenin 7-glucoside to be considered suitable for use in therapeutic applications [13,17]. The US Pharmacopeia specifies that dried chamomile flowers should have a minimum content of 0.3% apigenin 7-glucoside [10]. In addition, the content of blue essential oil in dried chamomile flowers must be a minimum of 4 mL/kg of raw material [17].

Terpenoids, spiroethers, flavonoids, and coumarins are mainly responsible for chamomile's broad spectrum of actions. The terpene compounds matricin, chamazulene, which additionally has anti-allergic properties (Fig. 1), α-bisabolol, α-bisabolol, and A and B bisabolol oxides have anti-inflammatory and antispasmodic effects [20]. They inhibit the secretion of endogenous histamine, enhance the phagocytic activity of leukocytes, and induce macrophages [3]. The oil, thanks to its content of α-bisabolol and spiroethers, has antimicrobial properties against Gram-positive bacteria and antifungal properties against Candida albicans (Fig. 1) [3]. In its turn, umbelliferone inhibits fungal growth, while chamazulene acts as an antimicrobial agent [4]. In addition, α-bisabolol shows ulcer-protective activity [20]. Thanks to its content of flavonoids, spiroethers, and coumarins, *Matricaria* has antispasmodic and tracheal effects. It is used, therefore, in digestive disorders, including infantile colic [3]. α-Bisabolol is known to decrease the secretion of stomach pepsin, making it a recommended treatment for gastro-intestinal diseases. Additionally, it promotes epithelization and granulation [4]. Aqueous extracts of the raw material have an immunostimulating effect, probably due to its poly-saccharide content [21]. The terpenoid geraniol has a strong apoptosis-inducing effect [15].

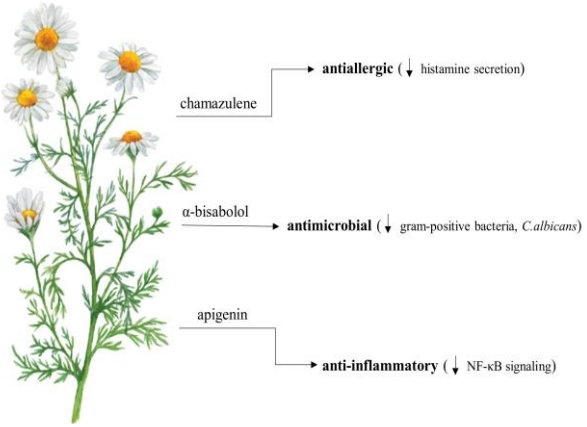


Fig 1. The main topical effects of chamomile with potential mechanism of action.

5. Traditional Uses and Directions of Action

Chamomile is among the oldest, most extensively utilized, and thoroughly documented medicinal plants worldwide [14]. For thousands of years, chamomile has been employed in herbal medicine. It was already known in ancient Egypt, Greece, and Rome [6]. It was also used in traditional Chinese medicine [14]. According to Hippocrates, Galen, and Asklepios, the flowers, roots, and oil were used to treat a wide range of health issues [18]. It is an ancient aromatic medicine with soothing, antiseptic, and anti-inflammatory properties [19]. In ancient Egypt, it was used as a preparation for inflammatory skin conditions. In ancient Rome, it was used as an abortifacient, and in ancient Greece, it was used to treat colds and rinse the eyes, ears, or mouth. The Greeks also used it to urolithiasis and to remove gallstones and in the treatment of gastrointestinal disorders, including peptic ulcers, flatulence, and cramps. The plant was applied externally as an anti-inflammatory agent to treat wounds, insect stings, ulcers, and burns. During the Middle Ages, it was employed for treating various forms of inflammation of the genitals, stomach pains, and skin diseases. In the Arab countries, on the other hand, it was used to accelerate the healing of wounds, as well as to treat fever, swelling, headache, toothache, conjunctivitis, and jaundice [9]. The *Matricaria chamomilla* species is widely used against bacterial infection symptoms in Europe, Latin America, Asia, and Africa [9].

Chamomile is a botanical remedy that is extensively utilized in traditional medicine. It has traditional use status. Currently, this plant has been incorporated into the pharmacopeias of 26 countries worldwide [4,13,20]. Chamomile has many beneficial properties. These include anti-inflammatory, antibacterial, antiseptic, antispasmodic, sedative, anti-tumor, antioxidant, hypoglycemic, hypotensive, anti-allergic, antidepressant, antianxiety, analgesic, antipruritic, antidiarrheal, hepatoprotective,

and neuroprotective effects [4,5]. In addition, it has fungicidal, insecticidal, and antiviral effects, and inhibits the replication of the polio virus. It also prevents osteoporosis and is used to treat oral mucositis and accelerate wound healing [4]. Chamomile is classified as generally recognized as safe (GRAS). Additionally, the United States Food and Drug Administration (USFDA) also recognizes chamomile essential oil, extracts, and distillates as GRAS [9,13,22].

Chamomile can be used in many forms. According to the European Medicines Agency (EMA), this plant substance can be used orally, trans-mucosally, on the skin, as an inhalation, and as a bath additive. The liquid form, i.e. a solution, extract, infusion, or herbal tea, can be used [23]. Chamomile, depending on the form of administration, can be used for other ailments [3].

Infusions and extracts can be administered orally in gastrointestinal disorders, i.e., colitis, gastric and duodenal ulcers, and gastritis. In inflammation of the upper respiratory tract, bronchial asthma, or hay fever, infusions and inhalations are also used. Poultices, on the other hand, are used in diseases and inflammation of the skin, including burns, ulcers, sores, or radiation skin lesions [24]. Irrigations are used for inflammation of the genitourinary tract for vaginitis, vulvitis, hemorrhoids, and anal fissures. Compresses are used in diseases of the eyes, e.g. inflammation of the eyelids and barley [3,9].

Chamomile is recognized as a traditional medicinal remedy [18]. It is primarily employed as an anti-inflammatory and antiseptic as well as an antispasmodic, and is mildly obstructive [4]. Internally, it is used to alleviate the symptoms of minor gastrointestinal issues including pain, slow digestion, diarrhea, and nausea, to relieve cold symptoms, and to treat minor ulcers and mouth and throat inflammation [4,23]. It is also commonly used for the treatment of irritations of the mucous membranes, skin, and anal and genital areas, as well as minor inflammations of the skin, including sunburn and slow-healing wounds [16]. As a whole plant, chamomile is traditionally used to treat bronchitis, indigestion, colic and diarrhea, epilepsy, hypertension, neuralgia, toothache, and pain during menstruation. The flowers are also used as a digestive aid and fever alleviator; meanwhile, the oil was historically used to alleviate the symptoms of conditions such as rheumatism, flatulence, and colic [13]. Chamomile has also found applications in the treatment of anxiety and in addressing mild cases of insomnia related to nervous disorders [23].

Chamomile flowers are commonly employed, either by themselves or in combination with crushed poppies, as a poultice for relieving neuralgia or external swelling [14]. *M. chamomilla*, due to its high safety in use, is used in baby cosmetics, eye and ear washes, and in gum preparations for teething [3]. Tea from chamomile is among the most commonly used herbal teas. It can contain only powdered flowers, as well as be blended with other popular herbs. It is consumed over a million times a day worldwide [9]. It is especially popular in Italy and France. An infusion of chamomile tea is used to rinse the throat and mouth for inflammation [14]. Chamomile tea is used for sleep disorders and is a common component in traditional home remedies for alleviating various bodily discomforts and reducing stress [20,24].

Aromatherapy makes use of chamomile oil. It is believed to reduce tension and depression. In addition, it is used for hair care and is an ingredient in many cosmetics [14]. It is utilized in bath soaps, shampoos, and other hair care products as a medicinal and aromatic element [20,25]. Chamomile is also used to make a lotion and is used externally for toothache, earache, neuralgia, and external swelling [14]. In addition, in the food sector, chamomile is used as a colorant and flavoring for food products [25]. Medicinal constituents are usually extracted from dry chamomile flowers using water, ethanol, or methanol as solvents, resulting in aqueous, ethanol, or methanol extracts [14].

6. Application in Skin Diseases

Medicinal plants have great potential for treating a variety of conditions. Many of them are commonly used to treat skin diseases. Natural medicine based on the use of plants is widespread throughout the world. Due to the presence of many active ingredients in plants, herbal therapies are effective and have few side effects compared to synthetic medicines. Despite the general safety of use, certain plants may induce contact dermatitis or allergy responses in some people who are allergic or sensitive to them [26].

Herbal raw materials may have anti-inflammatory effects that inhibit cytokine and eicosanoid production, stopping the cascade of inflammatory reactions and reducing burning, itching, or peeling of the skin [24].

Chamomile is a constituent of creams, lotions, shampoos, soaps, and specialty bath products due to its emollient and moisturizing effects [27].

A literature review was conducted to determine what topical effects *C. recutita* has in preventing and treating skin damage. It was demonstrated that chamomile is efficient in the treatment of UV-induced erythema, plaque psoriasis (pityriasis alba), eczema-like lesions, perioral lesions, phlebitis, atopic eczema, radiation-induced erythema, radiation-induced acute skin reaction (radiodermatitis), induced contact dermatitis, skin irritation, and eczema. The preparations used in the study were aqueous and alcoholic extracts, an infusion, an aqueous–alcohol cream, and Kamillosan® (an ointment containing α-bisabolol and chamazulene) [28].

6.1. Eczema

Eczema is regarded as a collection of disorders characterized by the inflammation or irritation of the skin. Eczema is among the primary dermatological conditions. The precise origins of eczema remain unclear. It is thought to be linked to an overreactive immune system response to an irritant, whether it originates from within the body or from an external source [29]. The treatment of eczema is complicated. It cannot be completely cured. Treatments involve avoiding irritants and regularly applying moisturizers to the skin. The treatment goal is to alleviate and prevent itching which can result in infection. To keep the skin moist, it is recommended that ointments and creams are used, i.e., 1% hydrocortisone cream or steroid creams and ointments. Additional oral antihistamines can be used to reduce and control pruritus [24].

Chamomile is effective in healing wounds and treating skin inflammation, and is therefore used in atopic

dermatitis and eczema. In addition, it has applications in relieving itching, irritation, inflammation, allergic conditions, bacterial skin diseases, erythema, diaper rash, insect bite wounds, and frostbite [24]. Chamomile helps regenerate skin cells and serves as an antioxidant, combating the skin damage induced by free radicals [30].

It is also thought to possess qualities that reduce allergies, with the capacity to neutralize irritants on the skin. Chamomile cream applied topically in humans has been found to have an effect that is 60% as effective as 0.25% hydrocortisone [31].

Due to the presence of chamazulene, α-bisabolol, and apigenin, *M. chamomilla* is used to treat inflammatory illnesses. Extracts of chamomile are believed to potentially possess properties that promote wound healing and may help in the prevention of eczema [32].

A study was conducted with the primary aim of evaluating the safety and efficacy of a cream with hydro-alcoholic extract of chamomile with a concentration of 10% for treating scabby dandruff and lesions similar to eczema. Twenty-two individuals received treatment with a cream containing chamomile water-alcohol extract, while another group of twenty-two were treated with a placebo cream. Treatment with the chamomile cream produced clear results. The lesions in 8 people were cured, and in 12 people they improved. In addition, no side effects were reported. However, statistical analysis did not reveal any significant differences in the outcomes between both groups. As the authors write, this could probably be due to the low content of the chamomile extract's anti-inflammatory components, namely, α-bisabolol and apigenin. The efficacy of both of the tested creams is likely attributable to the moisturizing characteristics inherent in both formulations, coupled with their consistent application by the patients [32].

Aertgeerts et al. (1985) conducted a clinical trial on 161 eczema patients using chamomile extract cream. It had similar efficacy to a steroid cream and greater efficacy than a non-steroid cream [30].

6.2. Atopic Dermatitis

An imbalance between Th1 and Th2 lymphocytes can cause various immune disorders. Atopic dermatitis arises due to a dominance of T-helper type 2 cells over T-helper type 1 cells. The immune mechanism involved in the pathogenesis of this disease is related to the activation of T lymphocytes and the interaction among keratinocytes, Langerhans cells, endothelial cells, eosinophils, and many cytokines. The hallmarks of AD are the excessive production of IgE that initiates inflammatory reactions, elevated eosinophilia in the blood, and increased levels of histamine, which is released immediately after exposure to an allergen [24,33].

Atopic dermatitis, also known as atopic eczema or AD, is a chronic inflammatory condition that affects individuals who are genetically predisposed to hypersensitivity to environmental triggers. AD is a common skin disorder prevalent among children.

The typical symptoms of atopic dermatitis include severe dryness and itching of the skin, along with redness, scaly patches, thickened areas resembling lichen, and the presence of pimples. Genetic and environmental factors influence the onset of the disease [34].

Atopic dermatitis can be treated with steroids, antihistamines, or immunosuppressants. However, the long-term use of these treatments may lead to unintended effects. GC (German chamomile) oil has long been used traditionally for the treatment of skin disorders including eczema, as it reduces inflammation and histamine secretion because of sesquiterpenes (azulene, α-bisabolol, farnesene). In addition, it relieves dryness and itching of the skin [33].

The effects of German chamomile oil were studied on mice with immune disorders and with skin lesions similar to atopic dermatitis. To induce these changes, the animals were treated with 2,4-dinitrochlorobenzene (DNCB). They were then treated with 3% chamomile oil, jojoba oil, or saline for 4 weeks. The application of DNCB resulted in a significant increase in serum histamine, IgE, IgG1, and IgG2a levels [33].

After two weeks of application of GC oil, the group treated with this oil exhibited a significant histamine reduction in serum, approximately 51% lower, compared to the control group, which was also lower (about 40%) than in the group that had jojoba oil applied. After using chamomile oil for four weeks, there was an observed reduction in IgG1 levels of about 31%, along with a notable two-fold decrease in IgE levels. In addition, the application of GC oil over four weeks led to a roughly 50% reduction in IL-4 production in the supernatants of spleen cell cultures compared to control mice [33].

In addition, a reduced frequency of scratching was observed in mice treated with GC oil. Compared to the control, which was treated with saline, the frequency of scratching after chamomile application was 45% lower, and compared to the group treated with jojoba oil, it was 32% lower. In mice treated with GC oil for four weeks, there was a significant decrease in the count of various immune cells compared to the saline-treated control mice. The reductions were 31% for neutrophils, 33% for lymphocytes, 42% for monocytes, 50% for eosinophils, and 50% for basophils [33].

Chamomile likely demonstrates antihistamine effects through several mechanisms: directly inhibiting the release of histamine from mast cells, reducing IL-4 production by Th2 cells, and subsequently suppressing the overproduction of IgE or IgG1 [33].

Kobayashi et al. showed that the oral administration of GC extract in conjunction with histamine receptor antagonists proved to be more effective in reducing scratching behavior in mice compared to the use of histamine receptor antagonists alone. GC oil can impede the binding of histamine to its receptors, thereby controlling histamine-induced effects like itching [35].

6.3. Wound Healing

Drugs with anti-inflammatory, antibacterial, or antioxidant properties are good candidates for wound treatment. Chamomile contains active ingredients such as chamazulene, apigenin, and bisabolol, which have such properties. Free radicals, produced at the site of an injury, can hinder the healing process by causing damage to cell membranes, proteins, and lipids. Therefore, antioxidants, that counteract these free radicals, hold potential for use in wound treatment. Chamomile flowers contain a high concentration of flavonoids, potent antioxidants known for

their ability to scavenge free radicals [36]. The effect of *Matricaria chamomilla* extract on wound healing in rats has been investigated. To achieve this objective, a linear incision was made on the back skin of the animals. The animals were then divided into three experimental groups: a control group, a group treated with olive oil, and a group treated with *M. chamomilla* extract dissolved in olive oil. In the group treated with *M. chamomilla*, a faster healing rate was observed (especially on days 5, 8, and 11 of the experiment). In addition, there was a marked drying of the wound edges, tissue regeneration, and reduction in the wound area compared to the control. The authors suggested that, due to the components of chamomile, there was an increase in epithelial cell migration, so improved wound healing was observed. The study demonstrated that chamomile extract, when used as a rubbing oil, has the potential to promote the healing of surgical skin wounds [36].

In a study conducted with patients undergoing tattoo removal, the application of a standardized chamomile extract (containing 50 mg of α-bisabolol and 3 mg of chamazulene per 100 mg) notably lessened exudation and enhanced drying in the wound area. This was in comparison to the placebo group, which used a hydrophilic gel. Wound healing was also faster by about 4 days [37].

α-(-)-Bisabolol is a natural monocyclic sesquiterpene found in *M. chamomilla* essential oil. The therapeutic efficacy of chamomile against skin inflammation has been investigated. This involved assessing its impact on the production of pro-inflammatory cytokines in macrophage cells that were stimulated with lipopolysaccharide and 12-O-tetradecanoylphorbol-13-acetate in an in vitro setting. The production of pro-inflammatory cytokines in cells treated with α-(-)-bisabolol, in both LPS-induced (lipopolysaccharide) and TPA-induced (12-O-tetradecanoylphorbol-13-acetate) inflammation, was significantly reduced in a dose-dependent manner. Moreover, no toxic effect was observed. In an in vivo study, ear swelling was reduced in mice treated with sesquiterpene. In addition, MDA (malondialdehyde), which is a marker of lipid peroxidation, was at lower levels in these mice. A study conducted on rabbits verified that this sesquiterpene is safe for topical application to the skin. Additionally, an in silico analysis demonstrated the high binding affinity (indicated by low docking energy) of α-(-)-bisabolol with receptors of pro-inflammatory cytokines. As is well known, the better the binding to the target protein, the better the therapeutic efficacy [38]. In the above study, based on in vitro, in vivo, and in silico studies, α-(-)-bisabolol was found to reduce the release of TNF-α and IL-6 (pro-inflammatory cytokines) and relieve skin inflammation [38].

6.4. Peristomal Wounds

A study compared the effectiveness of German chamomile solution and hydrocortisone ointment in treating perianal skin lesions in colostomy patients. Patients were treated with 1% hydrocortisone ointment once a day or a chamomile compress twice a day. The results showed that chamomile was more effective in relieving symptoms of pain and itching and in facilitating the healing of skin lesions. In the group treated with chamomile, the healing of lesions occurred significantly faster compared to the group treated with hydrocortisone. The average duration for wound healing in the chamomile group was 9 days, compared to 15 days in the hydrocortisone group. By day 15, complete wound healing was observed in 100% of the chamomile group, whereas only 76% of the hydrocortisone group showed complete healing by day 21. In addition, the plant compress was devoid of the side effects that occur with long-term corticosteroid use. This suggests that chamomile may be recommended as an alternative to long-term corticosteroid treatment [39].

German chamomile is recognized for its anti-inflammatory properties, attributed to the presence of chamazulene. Additionally, it exhibits bacteriostatic and antibacterial capabilities and aids in the formation of granulation tissue and the epithelialization of ulcers [39].

Another clinical study found comparable results when comparing the use of chamomile extract and 0.25% hydrocortisone cream in patients with inflammatory dermatoses [30].

6.5. Burn Wounds

Burn wounds are among the most severe types of injuries, leading to disability, significant hospitalization and treatment expenses, and, in some cases, death. Such accidents can result in lasting mental and physical alterations in the victim [29]. Burn injuries can lead to several complications, such as pain, inflammation, scarring, deformity, and impaired organ function [40]. The primary objective of burn therapy is to expedite the wound-healing process, which can help minimize the risk of developing complications such as infections [41].

Burns affect all aspects of life. Although synthetic drugs are effective in treatment, they are increasingly being abandoned due to the side effects of therapy. In contrast, the trend toward using drugs of natural origin is increasing.

The anti-inflammatory, antimicrobial, and wound-healing properties of certain plants are beneficial for treating infectious and burn wounds. Burns are often accompanied by elevated oxidative stress, characterized by an increase in free radicals. Plants contain numerous antioxidants, which help protect cells from peroxidative damage [29].

Ghorbani Ranjbary writes that a plant's active components may stimulate collagen production and speed wound closure, improve angiogenesis and vasodilation, and reduce inflammation, hemorrhage, and edema [42].

The effect of chamomile water-alcohol extract on second-degree burn healing in rats has been investigated. Topically, the animals in the test group were given olive oil or chamomile water-alcohol extract dissolved in olive oil. The control group received no treatment. The treatment was repeated twice a day until the wound was completely healed. When chamomile extract was used instead of olive oil, wound healing was observed to be faster and more effective. This study showed that chamomile aqueous-alcohol extract has a healing effect on burn wound healing in an animal model [43]. Such effects could be observed due to the anti-inflammatory, antibacterial, antioxidant, moisturizing, and soothing effects of chamomile.

6.6. Radiation-induced Skin Reactions

Acute radiation-induced skin reactions, such as erythema and moist peeling, are common side effects of radiation therapy. However, there is no effective method

to prevent this. Chamomile has long been used in skin diseases, so there is a chance that it will also be effective in treating this ailment [44].

The effectiveness of camillosan (chamomile) cream was compared with almond ointment in the treatment of radiation-induced skin lesions caused by radiation therapy. While the skin reactions in areas treated with camillosan cream and almond ointment were not significantly different, these reactions manifested later and in fewer patients in the group using the chamomile cream. The incidence of itching and pain was also very rare in both groups. Skin reactions decreased in almost all cases two weeks after radiotherapy and completely disappeared in all patients three months later. Camillosan cream was preferred by patients due to its ease of application, quick absorption, and non-staining properties [44].

6.7. Ulcers

Corticosteroids are most commonly used to treat ulcers and inflammatory lesions. Although they are effective in therapy, prolonged use can lead to several side effects. This is dangerous, especially when corticosteroids pass into the general circulation, as this can cause systemic side effects, i.e., adrenal suppression, hypertension, skin thinning, immunosuppression, hyperglycemia, or decreased bone density [38]. Therefore, safer but equally effective substances are being sought to replace corticosteroids in wound treatment. Of plant substances, such properties are attributed to tannins, saponins, flavonoids, triterpenes, and alkaloids [45].

Manoela Domingues Martins et al. conducted in vitro and in vivo studies to compare the effects of chamomile and corticosteroids in the treatment of ulcers. In vitro, they observed that chamomile-treated cultures showed the lowest ulcer cell viability. In vivo, the complete healing of lesions in rats occurred after 5 days, which was 9 days earlier than for the other substances tested. The wounds of chamomile-treated animals healed significantly faster than those of the corticosteroid-treated animals [45].

Chamomile, due to its composition, has antibacterial, anti-inflammatory, and antifungal properties, giving it even greater therapeutic potential than corticosteroids, which lack these properties. Compared to corticosteroids, chamomile not only stimulates the healing process but also significantly accelerates it [45]. In addition, obtaining preparations from this plant is easy and inexpensive [39].

7. Limitations

Many studies on chamomile may be based on traditional uses and anecdotal evidence rather than rigorous clinical trials. The scarcity of well-designed clinical trials may limit the ability to draw definitive conclusions about the efficacy of chamomile for specific skin disorders. Moreover, the variability in chamomile species and preparations might introduce inconsistencies in the reported effects. Standardization of chamomile products used in studies is lacking. The exact mechanisms by which chamomile works on inflammatory skin disorders may not be fully understood. A lack of mechanistic insights may limit the scope of the review and the ability to explain observed results. It's important to distinguish between bioactive compounds that were purified and structurally characterized versus those identified solely through GC-MS or LC-MS analysis of crude extracts or fractions, as is common in natural product-based research.

The review may be influenced by publication bias, as studies that report positive outcomes are more likely to be published than those with neutral or negative results. This bias may influence the overall perception of chamomile's efficacy.

8. Conclusions and perspectives

The longstanding traditional use of chamomile for the treatment of various skin disorders finds robust support in a wealth of anecdotal evidence and contemporary scientific research. Chamomile, derived from the *Matricaria chamomilla*, has garnered attention for its multifaceted therapeutic properties, particularly in addressing conditions such as eczema, dermatitis, wounds, and ulcers.

Central to chamomile's efficacy are its notable anti-inflammatory, antioxidant, and antimicrobial attributes. These qualities add to its promise as a natural cure for a variety of skin-related ailments. Chamomile has a complex chemical composition that underpins its varied spectrum of functions, according to scientific research. Among the key constituents are flavonoids, terpenoids, sesquiterpenes, coumarins, essential oils, and organic acids.

Chamomile's anti-inflammatory properties, owed mostly to its flavonoid content, make it an appealing option for alleviating inflammatory skin conditions. These substances work synergistically to reduce the inflammatory response, providing relief to people who are suffering from skin problems. Simultaneously, the antioxidant properties of chamomile contribute to the neutralization of damaging free radicals, potentially aiding in the prevention of oxidative damage to the skin. Furthermore, chamomile's antimicrobial characteristics, particularly associated with its essential oils, position it as a possible treatment for infections that may exacerbate skin diseases. Its traditional use in wound healing and ulcer treatment is consistent with these antibacterial properties, implying a multifaceted approach to treating both acute and chronic skin problems. While the efficacy of chamomile is promising, it is important to proceed with caution when including it in skincare routines, keeping in mind that individual responses can differ. Before using chamomile, consultations with a healthcare practitioner are needed, especially if allergies or sensitivities take place. This provides a safe and knowledgeable approach to reaping the plant's benefits.

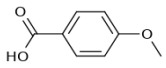
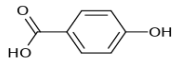
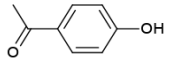
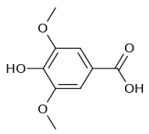
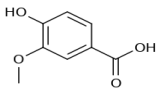
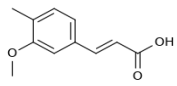
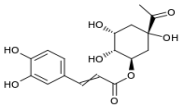
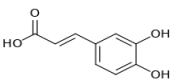
Chamomile's lasting popularity as a skin-soothing herb attests to its time-honored reputation in the world of skincare, where trends come and go. Chamomile's varied array of bioactive components not only explains its usefulness in treating numerous skin problems but also emphasizes the need to know its actions at the molecular level. As scientific research explores deeper into chamomile's therapeutic potential, it becomes clear that its historic use as a skin cure is supported not only by folklore but also by the complicated interplay of its chemical constituents. Nevertheless, studies are needed to offer definite scientific proof and validate chamomile's medicinal properties. Hence the development and implementation of standardized chamomile preparations are needed. As the mechanism of action is not fully

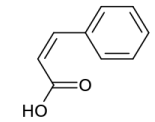
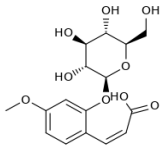
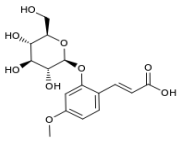
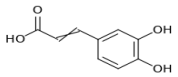
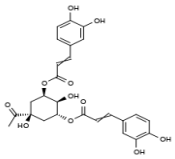
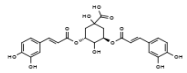
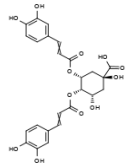
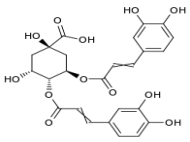
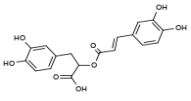
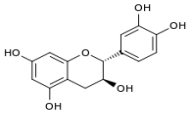
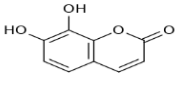
explained, mechanistic studies are necessary to elucidate the specific pathways through which chamomile exerts anti-inflammatory effects on the skin. Understanding the underlying mechanisms will enhance the credibility of chamomile's therapeutic potential and guide the development of targeted interventions. Collaboration with dermatologists will help to close the gap between traditional herbal remedies and modern dermatological practices.

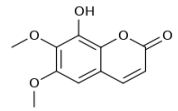
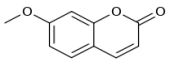
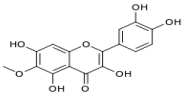
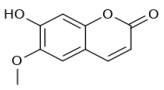
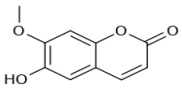
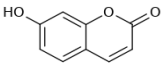
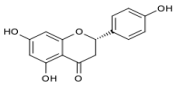
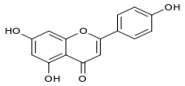
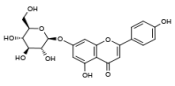
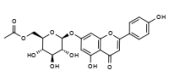
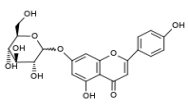
As research advances, we can expect a deeper understanding of chamomile's processes and potential applications in skin care, solidifying its place in the ever-expanding range of natural remedies for skin problems. More study is needed to offer definite scientific proof and validate its medicinal properties.

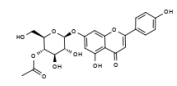
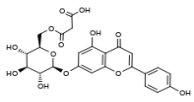
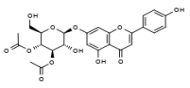
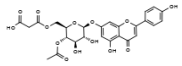
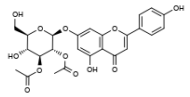
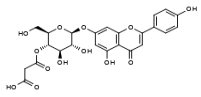
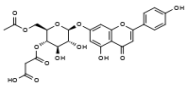
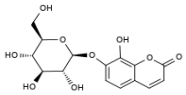
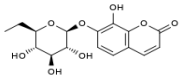
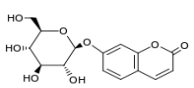
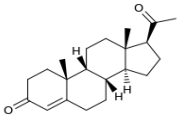
Appendix

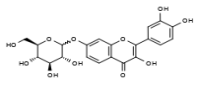
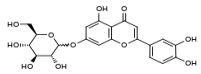
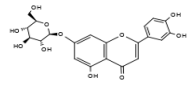
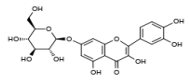
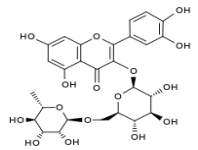
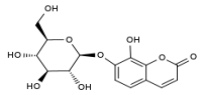
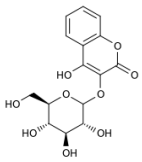
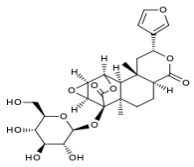
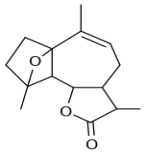
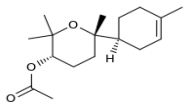
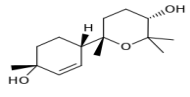
Table S1. The main constituents of *Matricaria chamomilla*

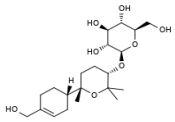
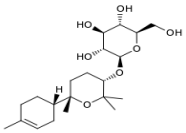
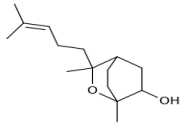
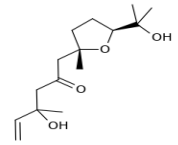
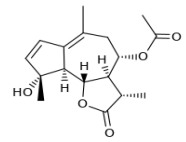
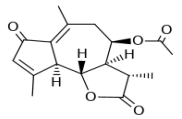
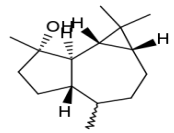
№	Structure	CAS Registry Number	Chemical Name	Linear Structure Formula	Molecular Weight	Links to Reaxys
1		100-09-4	anisic acid	C8H8O3	152.15	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D508910&database=RX&origin=ReaxysOutput&ln=
2		99-96-7	4-hydroxy-benzoic acid	C7H6O3	138.123	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D970950&database=RX&origin=ReaxysOutput&ln=
3		99-93-4	4-hydroxyacetophenone	C8H8O2	136.15	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D774355&database=RX&origin=ReaxysOutput&ln=
4		530-57-4	syringic acid	C9H10O5	198.175	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D2115262&database=RX&origin=ReaxysOutput&ln=
5		121-34-6	vanillic acid	C8H8O4	168.149	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D2208364&database=RX&origin=ReaxysOutput&ln=
6		132980-20-2	ferulic acid	C11H12O3	192.214	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D4310406&database=RX&origin=ReaxysOutput&ln=
7		-	chlorogenic acid	C17H20O8	352.341	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D27722423&database=RX&origin=ReaxysOutput&ln=
8		331-39-5	caffeic acid	C9H8O4	180.16	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D1954563&database=RX&origin=ReaxysOutput&ln=

9		-	(Z)-cinnamic acid	C9H8O2	148.161	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D2040579&database=RX&origin=ReaxysOutput&ln=
10		-	(Z)-2-β-D-glucopyranosyloxy-4-methoxycinnamic acid	C16H20O9	356.329	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D27505953&database=RX&origin=ReaxysOutput&ln=
11		-	(E)-2-β-D-glucopyranosyloxy-4-methoxycinnamic acid	C16H20O9	356.329	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D10595610&database=RX&origin=ReaxysOutput&ln=
12		331-39-5	caffeic acid	C9H8O4	180.16	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D2210883&database=RX&origin=ReaxysOutput&ln=
13		-	3,5-di-O-caffeoylquinic acid	C26H26O11	514.486	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D32453436&database=RX&origin=ReaxysOutput&ln=
14		-	isochlorogenic acid A	C25H24O12	516.458	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D23267260&database=RX&origin=ReaxysOutput&ln=
15		-	isochlorogenic acid B	C25H24O12	516.458	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D33781785&database=RX&origin=ReaxysOutput&ln=
16		-	isochlorogenic acid C	C25H24O12	516.458	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D28178839&database=RX&origin=ReaxysOutput&ln=
17		179462-74-9	rosmarinic acid	C18H16O8	360.32	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D2227586&database=RX&origin=ReaxysOutput&ln=
18		154-23-4	catechin	C15H14O6	290.273	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D92761&database=RX&origin=ReaxysOutput&ln=
19		486-35-1	daphnetin	C9H6O4	178.144	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D9372&database=RX&origin=ReaxysOutput&ln=

20		525-21-3	fraxidin	C11H10O5	222.197	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D202697&database=RX&origin=ReaxysOutput&ln=
21		531-59-9	herniarin	C10H8O3	176.172	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D141728&database=RX&origin=ReaxysOutput&ln=
22		519-96-0	patuletin	C16H12O8	332.266	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D335897&database=RX&origin=ReaxysOutput&ln=
23		92-61-5	scopoletin	C10H8O4	192.171	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D156296&database=RX&origin=ReaxysOutput&ln=
24		776-86-3	isoscopoletin	C10H8O4	192.171	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D157280&database=RX&origin=ReaxysOutput&ln=
25		93-35-6	umbelliferone	C9H5O2OH	162.145	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D127683&database=RX&origin=ReaxysOutput&ln=
26		480-41-1	naringenin	C15H12O5	272.257	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D90699&database=RX&origin=ReaxysOutput&ln=
27		520-36-5	apigenin	C15H10O5	270.241	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D262620&database=RX&origin=ReaxysOutput&ln=
28		578-74-5	apigenin 7-O-glucoside	C21H20O10	432.384	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D65669&database=RX&origin=ReaxysOutput&ln=
29		72741-92-5	apigenin 7-O-6"-acetyl-glucoside	C23H22O11	474.421	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D5674577&database=RX&origin=ReaxysOutput&ln=
30		495417-72-6	apigenin 7-O-D-glucoside	C21H20O10	432.384	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D1302802&database=RX&origin=ReaxysOutput&ln=

31		-	apigenin-7-O-(β-D-glucopyranoside-4'-acetate)	C23H22O11	474.421	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D9968900&database=RX&origin=ReaxysOutput&ln=
32		-	apigenin 7-O-glucoside malonate	C24H22O13	518.431	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D6553392&database=RX&origin=ReaxysOutput&ln=
33		-	apigenin 7-O-β-glucoside 3",4"-diacetate	C25H24O12	516.458	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D6760734&database=RX&origin=ReaxysOutput&ln=
34		-	apigenin-7-O-(4"-acetyl-6"-malonyl)-β-D-glucopyranoside	C26H24O14	560.468	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D9975847&database=RX&origin=ReaxysOutput&ln=
35		-	apigenin 7-O-β-glucoside 2",3"-diacetate	C25H24O12	516.458	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D6760570&database=RX&origin=ReaxysOutput&ln=
36		-	apigenin-7-O-(4"-malonyl-6"-acetyl)-β-D-glucopyranoside	C26H24O14	560.468	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D32453443&database=RX&origin=ReaxysOutput&ln=
37		-	apigenin-7-O-(4"-malonyl-6"-acetyl)-β-D-glucopyranoside	C26H24O14	560.468	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D32453443&database=RX&origin=ReaxysOutput&ln=
38		486-55-5	daphnin	C15H16O9	340.287	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D49440&database=RX&origin=ReaxysOutput&ln=
39		-	daphnetin-7-O-β-D-glucopyranoside	C16H18O8	338.314	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D32453439&database=RX&origin=ReaxysOutput&ln=
40		93-39-0	skimmin	C15H16O8	324.287	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D44529&database=RX&origin=ReaxysOutput&ln=
41		-	luteolin	C21H30O2	314.468	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D33297793&database=RX&origin=ReaxysOutput&ln=

42		-	luteolin-7-glucoside	C21H20O11	448.383	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D1275321&database=RX&origin=ReaxysOutput&ln=
43		183506-63-0	cynaroside	C21H20O11	448.383	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D1303148&database=RX&origin=ReaxysOutput&ln=
44		-	luteolin 7-O-glucoside	C21H20O11	448.383	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D66982&database=RX&origin=ReaxysOutput&ln=
45		-	quercetin 7-O-β-D-glucopyranoside	C21H20O12	464.383	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D70125&database=RX&origin=ReaxysOutput&ln=
46		153-18-4	rutin	C27H30O16	610.526	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D75455&database=RX&origin=ReaxysOutput&ln=
47		486-55-5	daphnin	C15H16O9	340.287	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D49440&database=RX&origin=ReaxysOutput&ln=
48		-	dihydroxycoumarin hexoside	C15H16O9	340.287	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D37326099&database=RX&origin=ReaxysOutput&ln=
49		-	palmatoside A	C26H32O12	536.533	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D22005200&database=RX&origin=ReaxysOutput&ln=
50		472-16-2	arborescin	C15H20O3	248.322	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D1318332&database=RX&origin=ReaxysOutput&ln=
51		-	α-bisabolol oxide A acetate	C17H28O3	280.408	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D6726380&database=RX&origin=ReaxysOutput&ln=
52		-	9-hydroxybisabolol oxide A	C15H26O3	254.37	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D24623519&database=RX&origin=ReaxysOutput&ln=

53		-	15-hydroxybisabolol oxide A ß-D-glucoside	C21H36O8	416.512	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D24623521&database=RX&origin=ReaxysOutput&ln=
54		-	bisabolol oxide A ß-D-glucoside	C21H36O7	400.513	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D24623522&database=RX&origin=ReaxysOutput&ln=
55		59861-08-4	bisabololoxid C	C15H26O2	238.37	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D1372352&database=RX&origin=ReaxysOutput&ln=
56		-	seco-bisabolol oxide B	C15H26O4	270.369	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D24623520&database=RX&origin=ReaxysOutput&ln=
57		-	matricin	C17H22O5	306.359	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D6427681&database=RX&origin=ReaxysOutput&ln=
58		-	(11S)-8ß-acetoxy-6α-hydroxy-2-oxo-guaia-1(10),3-dien-12-oic acid-lactone	C17H20O5	304.343	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D41209&database=RX&origin=ReaxysOutput&ln=
59		947604-08-2	spathulanol	C15H26O	222.371	https://www.reaxys.com/reaxys/secured/hopinto.do?context=S&query=IDE.XRN%3D1933967&database=RX&origin=ReaxysOutput&ln=

Author Contributions: Conceptualization, S.G., N.M.; data writing—original draft preparation, A.N., N.M.; writing—review and editing, N.M., A.N., and S.G.; supervision, S.G., J.P.P. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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