

Review

Herbal Arsenal against Skin Ailments: A Review Supported by In Silico Molecular Docking Studies

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Abstract: Maintaining healthy skin is important for a healthy body. At present, skin diseases are numerous, representing a major health problem affecting all ages from neonates to the elderly worldwide. Many people may develop diseases that affect the skin, including cancer, herpes, and cellulitis. Long-term conventional treatment creates complicated disorders in vital organs of the body. It also imposes socioeconomic burdens on patients. Natural treatment is cheap and claimed to be safe. The use of plants is as old as mankind. Many medicinal plants and their parts are frequently used to treat these diseases, and they are also suitable raw materials for the production of new synthetic agents. A review of some plant families, viz., Fabaceae, Asteraceae, Lamiaceae, etc., used in the treatment of skin diseases is provided with their most common compounds and in silico studies that summarize the recent data that have been collected in this area.



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1. Introduction

Molecular docking is an in silico procedure that is able to predict the mechanism of binding of a suggested ligand to its macromolecular target during the formation of a stable complex. Therefore, docking has become of great importance for the illustration of molecular interactions of natural compounds with different receptors [1–3].

The skin, the largest organ of the human body, functions as a physical barrier and an exterior interface of the body with the outer environment. The skin prevents the body from the invasion of external pathogens, as well as mechanical, thermal, and physical injuries from any substance that can be hazardous to humans. Just like any other organ and system of the body, this system is also very complex. The skin, with its derivatives such as nails, sweat glands, oil glands, and hair, makes up the integumentary system [4]. It is an incredible organ that protects the whole body. It consists of three main layers, including the epidermis (outermost layer), which consists of three types of cells, i.e., squamous cells, basal cells, and melanocytes; the second layer of the skin, the dermis, which contains blood and lymph vessels, hair follicles, etc.; and the subcutaneous fat layer. The focus on skin health is because everyone wants clearer, healthier, younger, and fresher skin, as skin-related complications can cause problems related to mental health, as well as low self-esteem [5].

Herbal medicine can be traced back to ancient civilizations. It entails the use of plants for medicinal purposes to cure illnesses and improve overall health [6]. Although herbal plants are low in toxicity and readily available, they play an important role in not only pharmacological research and drug production but also as plant components, being used

specifically as therapeutic agents for drug synthesis [7]. The most widely used plant parts in the preparation of traditional medicines are the leaves (62%), either alone or in combination with other plant parts [6,7].

Skin disease refers to problems with the surface layer of the skin. Skin disorders have a serious impact on well-being and are difficult to manage due to their persistence [8]. Several microorganisms trigger skin ailments, including boils, scratching ringworm, skin diseases, leprosy, injury, skin infections, eczema, skin allergy inflammation, scabies, and psoriasis [9].

Scabies, a parasitic infection, has always been the most prevalent skin disorder, but, in some areas, it is entirely absent [10]. *Sarcoptes scabiei* is the mite that causes scabies. Infection with the scabies worm causes a rash of vesicles, nodules, and papules. The majority of this is due to host hypersensitivity, but the direct impact of worm invasion also plays a significant role [11].

A rash is a red, inflamed patch of skin or a set of discrete spots. Irritation, inflammation and allergies, fundamental conditions, and structural issues may all contribute to these symptoms. Acne, eczema, psoriasis, hives, etc., are causes of rashes [4].

Atopic eczema, a chronic condition that affects people who are genetically organized to overreact towards environmental stimuli, has become an inflammatory disease. It is often seen in people with asthma, allergic rhinitis, and atopy symptoms. Eczema is a common skin problem in children. Severe skin dryness and inflammation, scaly patches, redness, and lichenified plaque with abrasions are the most common dermatitis symptoms [12].

Acne is a contagious disease and one of the most common in humans. Acne leads to seborrhea, papules, comedowns, blackheads, nodules, and scars [13]. Acne is most often found on the face, chest area, and back of people who have a large number of oil glands [14].

Psoriasis is an inflammatory skin problem that causes keratinocytes, excessive proliferation resulting in scaly patches, extreme inflammation, and erythema [15].

The uncontrolled development of cells present in the skin is known as skin cancer. It occurs due to unfixed DNA damage to skin cells, most commonly due to UV from sunlight, causing mutations and even genetic abnormalities. This causes skin cells to grow rapidly, resulting in the formation of malignant tumors [16].

A burn is considered tissue damage due to fire, chemicals, or radiation. Burn wounds are classified as superficial, partial thickness, or full thickness. Swelling, epithelization, wound contraction, and granulation are all part of the healing process after a burn wound [17].

The current review presents the effect of different medicinal plants and FDA-approved formulas on the management of various skin disorders. A molecular docking study was conducted for major components of these medicinal plants on the active sites of granzyme B and human leukocyte elastase (HLE) enzymes, aiming to identify the potential compounds or class of compounds that may be responsible for the ameliorative effects on different skin ailments.

2. Medicinal Plants and Skin Disorders

Medicinal plants reported for the management of skin disorders (Table 1) are classified below according to their uses.

Table 1. Botanical sources and medicinal plants used to treat different skin disorders.

No.	Botanical Source (Latin Name, Common Name, Family)	Uses	References
A	Medicinal Plants Used to Treat Skin infections		
1	<i>Achyranthes aspera</i> Prickly chaff flower Family Amaranthaceae	Used to treat boils and scabies	[18]
2	<i>Aconitum chasmanthum</i> Gaping monkshood Family Ranunculaceae	Used to treat mumps and measles	[19]
3	<i>Butea monosperma</i> Flame of forest Family Fabaceae	Used to treat skin diseases such as inflammation	[20]
4	<i>Boerhavia diffusa</i> Tar vine, wine flower Family Nyctaginaceae	Used to treat abscesses	[21]
5	<i>Curcuma longa</i> Turmeric Family Zingiberaceae	Used to treat skin inflammation	[22]
6	<i>Crocus sativus</i> saffron Family Iridaceae	Used to treat psoriasis	[23]
7	<i>Commelina benghalensis</i> Tropical spiderwort Family Commelinaceae	Used to treat wound infection	[24]
8	<i>Cyperus difformis</i> Family Cyperaceae	Used to treat skin infections	[25]
9	<i>Cassia tora</i> Stinking cassia Family Caesalpiniaceae	Used to treat psoriasis	[26]
10	<i>Capsicum frutescens</i> Chilli Family Solanaceae	Used to treat psoriasis	[27]
11	<i>Dalbergia sissoo</i> North Indian rosewood Family Fabaceae	Used to treat abscesses	[28]
12	<i>Eucalyptus globulus</i> Eucalyptus Family Myrtaceae	Used to treat acne, fungal infections, and heal wounds	[29]
13	<i>Euphorbia wallichii</i> Wallich spurge Family Euphorbiaceae	Used to treat skin infections and warts	[30]
14	<i>Ficus carica</i> Fig Family Moraceae	Used to treat itching, pimples, and scabies	[31]
15	<i>Fagopyrum tataricum</i> Tartary buckwheat Family Polygonaceae	Used to treat erysipelas	[32]
16	<i>Gnaphalium affine</i> Cotton weed Family Asteraceae	Used to treat weeping pruritus of skin	[33]
17	<i>Juniperus excelsa</i> Eastern savin Family Cupressaceae	Used to treat skin infections	[34]

Table 1. Cont.

No.	Botanical Source (Latin Name, Common Name, Family)	Uses	References
18	<i>Lens culinaris</i> Lentil Family Fabaceae	Used to treat skin infections and acne	[35]
19	<i>Marsilea quadrifolia</i> Water clover Family Marsileaceae	Used to treat abscesses	[36]
20	<i>Mahonia aquifolium</i> Oregon grape Family Berberidaceae	Used to treat psoriasis	[37]
21	<i>Pleurospermum brunonis</i> Brown's paper cup flower Family Apiaceae	Used to treat skin infections	[38]
22	<i>Pinus roxburghii</i> Chir pine Family Pinaceae	Used to treat pruritus, inflammation, and other skin diseases	[39]
23	<i>Pinus wallichiana</i> Bhutan pine Family Pinaceae	Used to treat wound infection	[40]
24	<i>Rubia cordifolia</i> Common madder Family Rubiaceae	Used to treat psoriasis	[41]
25	<i>Solanum nigrum</i> Black nightshade Family Solanaceae	Used to treat pimples, pustules, ringworms, eczema, syphilitic ulcers, and leukoderma	[42,43]
26	<i>Simmondsia chinensis</i> Jojoba Family Buxaceae	Used to treat acne and psoriasis	[44]
27	<i>Taxus wallichiana</i> Himalayan yew Family Taxaceae	Used to treat psoriasis and ringworm	[45]
28	<i>Tectona grandis</i> Teak Family Lamiaceae	Used to treat pruritus and heal wounds	[46,47]
29	<i>Thespesia populne</i> Indian tulip tree Family Malvaceae	Used to treat psoriasis	[48]
30	<i>Wrightia tinctoria</i> Sweet indrajao Family Apocynaceae	Used to treat psoriasis	[49]
B	Medicinal Plants Used to Treat Eczema		
31	<i>Abrus precatorious</i> Rosary pea Family Fabaceae	Used to treat eczema	[50]
32	<i>Avena sativa</i> Oat Family Poaceae	Used to treat eczema, wounds, inflammation, itching, burns, and irritation	[51]
33	<i>Arnebia euchroma</i> Pink arnebia Family Boraginaceae	Used to treat burns, eczema, and dermatitis	[52,53]

Table 1. Cont.

No.	Botanical Source (Latin Name, Common Name, Family)	Uses	References
34	<i>Actinidia deliciosa</i> Kiwi fruit Family Actinidiaceae	Used to treat inflammation and eczema	[54]
35	<i>Aristolochia indica</i> Indian birthwort Family Aristolochiaceae	Used to treat eczema and wounds	[55]
36	<i>Betula alba</i> Paper birch Family Betulaceae	Used to treat eczema, psoriasis, and acne	[56]
37	<i>Cannabis sativus</i> Charas, ganja Family Cannabaceae	Used to treat sores, eczema, dermatitis, psoriasis, seborrheic, and lichen planus	[57]
38	<i>Matricaria chamomilla</i> Chamomile Family Asteraceae	Used to treat eczema and skin inflammation	[58,59]
39	<i>Sarco asoca</i> Ashoka Family Caesalpiniaceae	Used to treat skin diseases, inflammation, eczema, and scabies	[60]
40	<i>Saponaria officinalis</i> soapworts Family Caryophyllaceae	Used to treat eczema, acne, boils, and psoriasis	[61,62]
41	<i>Vitex negundo</i> Nirgundi Family Verbenaceae	Used to treat skin diseases such as eczema, acne, pimples, ringworms, etc.	[35]
C	Medicinal Plants Used for Wound healing		
42	<i>Achillea millefolium</i> Common Yarrow Family Asteraceae	Used to treat burn wounds	[63]
43	<i>Albizia lebbek</i> Siris Family Fabaceae	Used for wound healing, leucoderma, itching, and inflammation	[64]
44	<i>Allium sativum</i> Garlic Family Alliaceae	Used to treat psoriasis, scars, and heal wounds	[65]
45	<i>Aloe barbadensis</i> Aloe vera Family Aloeaceae	Used to treat skin injuries	[66]
46	<i>Alternanthera brasiliana</i> Brazilian joyweed Family Amaranthaceae	Used to heal inflammation wounds	[64]
47	<i>Abelmoschus esculentus</i> Okra Family Malvaceae	Used to cure pimples and wounds	[67]
48	<i>Adiantum venustum D</i> Himalayan maidenhair Family Pteridaceae	Used to heal wounds	[68]
49	<i>Argemone Mexicana</i> Mexican poppy Family Papaveraceae	Used to treat wounds	[69]

Table 1. Cont.

No.	Botanical Source (Latin Name, Common Name, Family)	Uses	References
50	<i>Alkanna tinctoria</i> Alkanet Family Boraginaceae	Used to treat itching, skin wounds, and rashes	[70]
51	<i>Brassica oleracea</i> Red cabbage Family Brassicaceae	Used to treat dermatitis and wounds	[71]
52	<i>Berberis lycium</i> Indian lycium Family Berberidaceae	Used to heal wounds	[72]
53	<i>Bergenia ciliata</i> Winter begonia Family Saxifragaceae	Used to heal wounds	[73,74]
54	<i>Bergenia ligulata</i> Asmabhedaka Family Saxifragaceae	Used to heal wounds and treat boils	[75]
55	<i>Bauhinia purpurea</i> Orchid tree Family Fabaceae	Used to heal wounds and treat inflammation	[76]
56	<i>Carissa spinarum</i> Bush plum Family Apocynaceae	Used to heal wounds and treat boils	[77]
57	<i>Cannabis sativa</i> Marijuana, hemp Family Cannabaceae	Used to treat dandruff and heal wounds	[78]
58	<i>Capparis decidua</i> Bare caper Family Capparaceae	Used to heal wounds	[79]
59	<i>Cynodon dactylon</i> Bermuda grass Family Poaceae	Used to heal wounds and skin problems	[80,81]
60	<i>Cocos nucifera</i> Coconut Family Arecaceae	Used to treat skin wounds	[82]
61	<i>Euphorbia helioscopia</i> Sun spurge Family Euphorbiaceae	Used to heal wounds	[83,84]
62	<i>Ferula foetida</i> Asafoetida, Hing Family Apiaceae	Used to heal wounds	[85]
63	<i>Ficus benghalensis</i> Banyan tree Family Moraceae	Used to treat skin injuries	[86]
64	<i>Gerbera gossypina</i> Hairy gerbera daisy Family Asteraceae	Used to heal wounds	[87]
65	<i>Galium aparine</i> Goosegrass Family Rubiaceae	Used to treat wounds as an antiseptic	[88]
66	<i>Hackelia americana</i> Nodding stickseed Family Boraginaceae	Used to treat wounds, tumors, and inflammation	[89]

Table 1. Cont.

No.	Botanical Source (Latin Name, Common Name, Family)	Uses	References
67	<i>Hypericum perforatum</i> Perforatejohn's wort Family Hypericaceae	Used to treat wounds, abrasions, inflammatory skin disease, and burns	[90]
68	<i>Isodon rugosus</i> Wrinkled leaf isodon Family Lamiaceae	Used to heal wounds	[91]
69	<i>Launaea nudicaulis</i> Bhatal Family Asteraceae	Used to heal wounds	[92]
70	<i>Momordica charantia</i> Bitter gourd Family Cucurbitaceae	Used to heal wounds	[93]
71	<i>Micromeria biflora</i> Lemon savory Family Lamiaceae	Used to heal wounds and treat skin infections	[94]
72	<i>Nigella sativa</i> Black cumin Family Ranunculaceae	Used to heal wounds	[95,96]
73	<i>Plantago major</i> Great plantain Family Plantaginaceae	Used to treat wounds	[97]
74	<i>Plantago lanceolata</i> Ribwort plantain Family Plantaginaceae	Used to heal wounds	[98]
75	<i>Rumex dissectus</i> Arrowleaf dock Family Polygonaceae	Used to stop wound bleeding	[99]
76	<i>Salvia moorcroftiana</i> Kashmir salvia Family Lamiaceae	Used to treat skin itching and wound healing	[100]
77	<i>Trigonella foenum-graecum</i> Fenugreek Family Fabaceae	Used to heal wounds	[101,102]
78	<i>Tephrosia purpurea</i> Wild indigo Family Fabaceae	Used to heal wounds	[103]
79	<i>Urtica dioica</i> Stinging nettle Family Urticaceae	Used to heal wounds	[104,105]
80	<i>Verbascum Thapsus</i> Common mullein Family Scrophulariaceae	Used to treat pimples, heal wounds, and treat other skin problems	[106]
D	Medicinal Plants Used to Treat Skin Burns		
81	<i>Astilbe thunbergii</i> Astilbe Family Saxifragaceae	Used to treat burns	[107]
82	<i>Anaphalis margaritacea</i> Pearly everlasting Family Asteraceae	Used to treat sunburn	[108]

Table 1. Cont.

No.	Botanical Source (Latin Name, Common Name, Family)	Uses	References
83	<i>Aquilegia pubiflora</i> Himalayan columbine Family Ranunculaceae	Used to heal wounds and treat skin burns	[109]
84	<i>Amygdalus communis</i> Almonds Family Rosaceae	Used to treat burn wounds	[53]
85	<i>Bergenia stracheyi</i> Himalayan Bergenia Family Saxifragaceae	Used to treat sunstroke and heal wounds	[110]
86	<i>Calendula officinalis</i> Marigold Family Asteraceae	Used to treat burns and bruises	[111]
87	<i>Cucumis melo</i> Muskmelon Family Cucurbitaceae	Used to treat skin burns	[112]
88	<i>Corydalis govaniiana</i> Govan's corydalis Family Papaveraceae	Used to treat skin burns	[113]
89	<i>Carica candamarcensis</i> Mountain papaya Family Caricaceae	Used to treat burn wounds	[114]
90	<i>Clitoria ternatea</i> Butterfly pea Family Fabaceae	Used to treat boils, acne, and skin outbreaks	[115]
91	<i>Datura stramonium</i> Jimsonweed, thornapple Family Solanaceae	Used to treat boils	[116]
92	<i>Dodonaea viscosa</i> Hop bush Family Sapindaceae	Used to treat skin burns and heal wounds, acne, pimples, rashes, itching, and pustules	[117–119]
93	<i>Echinacea angustifolia</i> Purple coneflower Family Asteraceae	Used to treat psoriasis, burns, acne, ulcers, and skin wounds	[120]
94	<i>Ginkgo biloba</i> Maidenhair tree Family Ginkgoaceae	Used to treat skin burns	[121]
95	<i>Hippophae rhamnoides</i> Sea buckthorn Family Elaeagnaceae	Used to treat rashes and skin burns	[122,123]
96	<i>Impatiens edgeworthii</i> Edgeworth Balsam Family Balsaminaceae	Used to treat skin burns	[124]
97	<i>Mangifera indica</i> Mango Family Anacardiaceae	Protect skin from sun damage	[125]
98	<i>Malus pumila</i> Apple Family Rosaceae	Used to treat boils	[126]
99	<i>Malva sylvestris</i> High mallow Family Malvaceae	Used to treat burn wounds	[53]

Table 1. Cont.

No.	Botanical Source (Latin Name, Common Name, Family)	Uses	References
100	<i>Matricaria chamomilla</i> Chamomile Family Asteraceae	Used to treat burn wounds	[127]
101	<i>Onosma hispida</i> Bristly onosma Family Boraginaceae	Used to treat skin burns	[128]
102	<i>Portulaca oleracea</i> Purslane, little hogweed Family Portulacaceae	Used to treat burns, skin eruptions, rashes, skin inflammation, eczema, abscesses, and pruritus	[129–131]
103	<i>Pisum sativum</i> Garden pea Family Fabaceae	Used to treat skin burns	[132]
104	<i>Picrorhiza kurroa</i> Kutki Family Plantaginaceae	Used to treat burning sensation	[133]
105	<i>Rumex dentatus</i> Toothed dock Family Polygonaceae	Used to treat boils	[134]
106	<i>Rubus abchaziensis</i> Akhray Family Rosaceae	Used to treat boils and wounds	[135]
107	<i>Solanum virginianum</i> Thorny nightshade Family Solanaceae	Used to treat swelling of skin	[136]
108	<i>Scrophularia deserti</i> Desert figwort Family Scrophulariaceae	Used to treat burn wounds	[53]
109	<i>Sesamum indicum</i> Sesame Family Pedaliaceae	Used to treat burn wounds	[137]
110	<i>Silybum marianum</i> Blessed thistle Family Asteraceae	Used to treat burn wounds and improve skin health	[138]
111	<i>Tamarix aphylla</i> Athel Family Tamaricaceae	Used to treat skin burns and wounds	[139]
112	<i>Tridax procumbens</i> Coatbuttons, tridax daisy Family Asteraceae	Used to treat burn wounds	[140]
113	<i>Zanthoxylum armatum</i> Winged prickly ash Family Rutaceae	Used to treat skin burns	[141]
E	Medicinal Plants Used to Treat Miscellaneous Disorders		
114	<i>Allium cepa</i> Garden onion Family Alliaceae	Used to treat skin lesions	[142]
115	<i>Azadirachta indica</i> Neem Family Meliaceae	Used to treat acne and protect skin from UV rays	[143]

Table 1. Cont.

No.	Botanical Source (Latin Name, Common Name, Family)	Uses	References
116	<i>Anethum graveolens</i> Dill Family Apiaceae	Used to treat pimples	[144]
117	<i>Androsace rotundifolia lehm.</i> Rock jasmine Family Primulaceae	Used to treat skin problems	[145]
118	<i>Arnica montana</i> Mountain arnica Family Asteraceae	Used as anti-inflammatory to treat boils and acne eruptions	[146,147]
119	<i>Bauhinia variegata</i> Kachnar, orchid tree Family Fabaceae	Used to treat skin disease and skin ulcers	[148]
120	<i>Beta vulgaris</i> Beetroot Family Brassicaceae	Used to treat tumors	[149]
121	<i>Brassica juncea</i> Mustard Family Brassicaceae	Used against skin eruptions and ulcers	[150,151]
122	<i>Berberis aquifolium</i> Oregon grape Family Berberidaceae	Used to treat acne scars	[152]
123	<i>Camellia sinensis</i> Green Tea Family Theaceae	Used to treat skin tumors and cancer	[153]
124	<i>Coriandrum sativum</i> Dhaniya Family Apiaceae	Used to treat pimples	[154,155]
125	<i>Calotropis procera</i> Giant milkweed Family Apocynaceae	Used to treat inflammation	[156]
126	<i>Cerastium fontanum</i> Mouse ear chickweed Family Caryophyllaceae	Used to treat skin diseases; also acts as anti-inflammatory	[157]
127	<i>Citrus medica</i> Citron Family Rutaceae	Used to treat skin irritation	[158,159]
128	<i>Citrus sinensis</i> orange Family Rutaceae	Used to treat pimples	[160]
129	<i>Catharanthus roseus</i> Periwinkle Family Apocynaceae	Used to cure pimples	[161]
130	<i>Carthamus tinctorius</i> safflower Family Asteraceae	Used to treat eruptive skin problems	[162]
131	<i>Clerodendrum viscosum</i> Hill glory bower Family Verbenaceae	Used as antiseptic skin wash	[163]
132	<i>Equisetum arvense</i> Field horsetail Family Equisetaceae	Used to treat skin allergy	[164]

Table 1. Cont.

No.	Botanical Source (Latin Name, Common Name, Family)	Uses	References
133	<i>Lavendula officinalis</i> Lavender Family Labiatae	Used to prevent and heal acne	[165]
134	<i>Lawsonia inermis</i> Henna Family Lythraceae	Used to treat inflammation and tumors	[166]
135	<i>Lycopersicon esculentum</i> Tomato Family Solanaceae	Used to treat acne and sunburn	[167]
136	<i>Ledum groenlandicum oedar</i> Labrador tea Family Ericaceae	Used to treat itching, acne, and redness	[61]
137	<i>Mirabilis jalapa</i> Four o'clock Family Nyctaginaceae	Used to treat allergic skin disorders	[168]
138	<i>Melia azedarach</i> Persian lilac Family Meliaceae	Used to treat pimples and inflammation	[169]
139	<i>Myrsine Africana</i> Cape myrtle Family Myrsinaceae	Used to treat skin disorders	[170]
140	<i>Melaleuca alternifolia</i> Tea tree Family Myrtaceae	Used to treat acne	[171]
141	<i>Olea europaea</i> Olive tree Family Oleaceae	Used as skin cleanser	[172]
142	<i>Ocimum sanctum</i> Tulsi Family Lamiaceae	Used to treat acne and inflammation	[173,174]
143	<i>Plumbago zeylanica</i> Doctor bush Family Plumbaginaceae	Used to treat skin diseases such as sores, acne, and dermatitis	[31]
144	<i>Prunus persica</i> Peach Family Rosaceae	Used to treat skin disorders	[175]
145	<i>Piper nigrum</i> Black pepper Family Piperaceae	Used to treat acne	[176]
146	<i>Pterocarpus santalinus</i> Red sandalwood Family Fabaceae	Used to treat skin inflammation and acne	[177]
147	<i>Rosmarinus officinalis</i> Rosemary Family Lamiaceae	Used to block skin tumor cells	[178]
148	<i>Ricinus communis</i> Castor oil plant Family Euphorbiaceae	Used in children for skin diseases	[179]
149	<i>Rheum officinale</i> Rhubarb Family Polygonaceae	Used to treat acne	[180]

Table 1. Cont.

No.	Botanical Source (Latin Name, Common Name, Family)	Uses	References
150	<i>Salix babylonica</i> Weeping willow Family Salicaceae	Used as skin cleanser	[181]
151	<i>Serenoa repens</i> Saw palmetto Family Arecaceae	Used to treat acne and inflammation	[182]
152	<i>Thymus vulgaris</i> Thyme Family a	Used to treat cellulitis	[153]
153	<i>Taraxacum officinale</i> Common dandelion Family Asteraceae	Used to treat pimples	[183]
154	<i>Tussilago farfara</i> coltsfoot Family Asteraceae	Used to treat sores and inflammation of skin	[184]
155	<i>Valeriana jatamansi</i> Jatamansi Family Caprifoliaceae	Used to treat pimples	[185]

3. Some Reported Mechanism of Action

The use of herbal medicine is becoming popular worldwide. Herbal medicines are preferred over synthetic medicines, as they produce fewer side effects [186–189]. Additionally, phytochemicals can treat skin ailments by different mechanisms and by displaying various biological activities such as antioxidant, anti-inflammatory, and antiallergic [190–192]. Each plant has its own bioactivity, which depends upon the chemical nature and potency of the constituents present in it [193,194]. Some components reduce skin inflammation by inhibiting NF- κ B, for example, *Zingiber officinale*. The squeezed extract of this in rats and mice elevates TNF- α in peritoneal cells, and its long-term use can increase the level of serum corticosterone and thus reduce proinflammatory markers [195]. Drugs such as *Rosmarisum officinalis* also help in the improvement of abnormal skin conditions. It constitutes rosmarinic acid, which can disturb the system activation inhibition of the C3b attachment. It also acts on the inhibition and reduction of proinflammatory mediators such as TNF- α and IL-1 [196]. *Oenothera biennis* constitutes β -sitosterol, which modulates NO, TNF- α , IL-1 β , and TXB2, leading to the suppression of COX-2 gene expression, hence causing anti-inflammatory action [197].

4. FDA-Approved Formulas

The Food and Drug Administration (FDA), as well as in vitro and in vivo study results, has approved bacterial cellulose (BC) and plant cellulose (PC) products to be incorporated into the biomedical field and their applications due to their biocompatibility with human cells and potential activity in wound healing and in the therapeutics field [198].

Moreover, honey, a natural product, is rich in several phenolic compounds, sugars, and enzymes that possess antioxidant, anticarcinogenic, anti-inflammatory, and antimicrobial activity. The main role of honey in the development of the wound healing process appeared to be via the acceleration of dermal repair and epithelialization, angiogenesis promotion, immune response promotion, and the reduction in healing-related infections with pathogenic microorganisms. The FDA approved many formulas containing honey as the main ingredient, among which is L-Mesitran[®] (manufactured by Triticum Company—UK) Ointment, which consists of 48% medical-grade honey, lanolin, cod liver oil, sunflower oil, calendula, aloe vera, zinc oxide, and vitamins C and E. Additionally, Revamil Gel[®] (manufactured by Maximed Pharrma—Lebanon) was FDA approved, containing 100%

medical-grade honey, together with Therahoney[®] Gel (manufactured by Medline Industries Inc.—USA), containing 100% Manuka honey [199].

5. Phytoconstituents of Medicinal Plants

Many phytochemical constituents have shown potential bioactivities, to which the biological activities of medicinal plant extracts can be attributed. Table 2 summarizes some of them in the context of treating skin disorders.

Table 2. Selected reported phytoconstituents of herbal plants used to treat skin diseases.

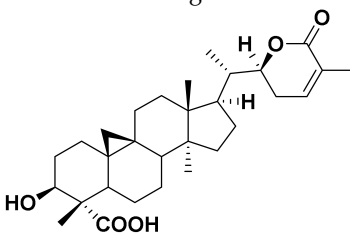
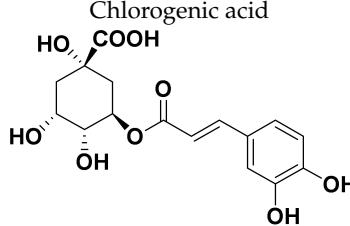
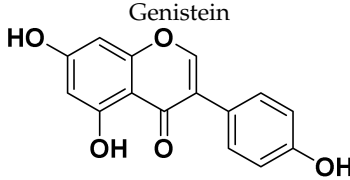
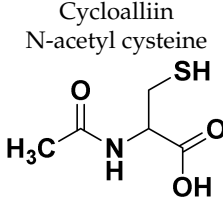
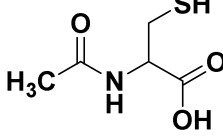
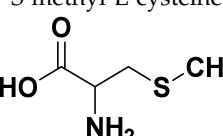
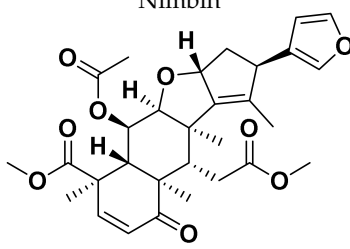
Serial No.	Botanical Name	Some Phytoconstituents and/or Classes of Compounds	Selected Structures	Ref.
1.	<i>Abrus precatorious</i>	Stigmasterol, β -sitosterol, and abrusogenin	<p>Abrusogenin</p> 	[200]
2.	<i>Achillea millefolium</i>	Chlorogenic acid, apigenin-7-glucoside, and luteolin-7-glucoside	<p>Chlorogenic acid</p> 	[201]
3.	<i>Achyranthes aspera</i>	Rutin, chlorogenic acid, and genistein	<p>Genistein</p> 	[202]
4.	<i>Allium cepa</i>	Quercetin, S-methyl-L-cysteine, cycloalliin, N-acetylcysteine, S-propyl-L-cysteine sulfoxide, and dimethyl trisulfide	<p>Cycloalliin</p>  <p>N-acetyl cysteine</p>  <p>S-methyl-L-cysteine</p> 	[203]
5.	<i>Azadirachta indica</i>	Nimbin, nimbanene, ascorbic acid, n-hexacosanol, nimbolide, 17-hydroxy azadiradione, 6-desacetyl nimbinene, and nimbandiol	<p>Nimbin</p> 	[204]

Table 2. Cont.

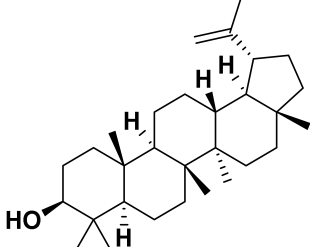
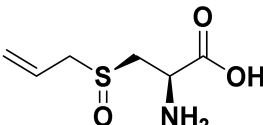
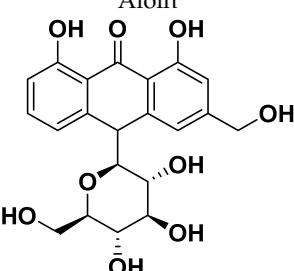
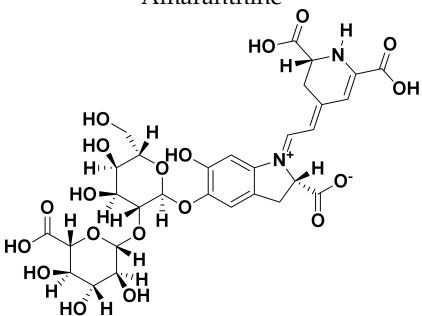
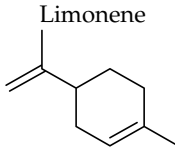
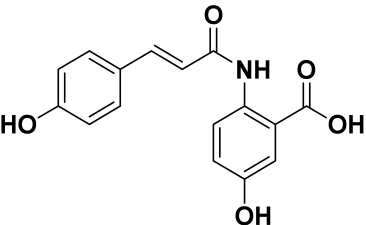
Serial No.	Botanical Name	Some Phytoconstituents and/or Classes of Compounds	Selected Structures	Ref.
6.	<i>Albizia lebbek</i>	Lupeol, lupenone, luteolin, rutin, sapiol, friedelin, stigmasterol, β -sitosterol, stigmasterol-3-glucoside, β -sitosterol-3-glucoside, alkaloids as 3,3-dimethyl-4-(1-aminoethyl)-azetidin-2-one, 2-amino-4-hydroxypteridine-6-carboxylic acid, and 2,4-bis(hydroxylamino)-5-nitropyrimidine	<p>Lupeol</p> 	[205]
7.	<i>Allium sativum</i>	Alliin, allicin, S-allyl cysteine, diallyl sulfide, diallyl trisulfide, diallyl disulfide, and ajoene	<p>Alliin</p> 	[206]
8.	<i>Aloe barbadensis</i>	Aloesin, cinnamic acid, isoaloesin D, caffeic acid, chlorogenic acid, aloin A and B, emodin, isovitexin, and orientin	<p>Aloin</p> 	[207]
9.	<i>Alternanthera brasiliana</i>	Amaranthine, iso amaranthine, betanin, isobetanin, hydroxybenzoic acid, hydroxycinnamic acid, kaempferol glucoside, rhamnoside, and dirhamnosyl-glucoside	<p>Amaranthine</p> 	[208]
10.	<i>Anethum graveolens</i>	Limonene, carvone, α -phellandrene, β -phellandrene, and <i>p</i> -cymene	<p>Limonene</p> 	[209]
11.	<i>Avena sativa</i>	Proteins, lipids, polysaccharides, β -glycan, dietary fibers, avenanthramides, gramine alkaloid, flavonolignans, flavonoids, saponins, and sterols	<p>Avenanthramide A</p> 	[210]

Table 2. Cont.

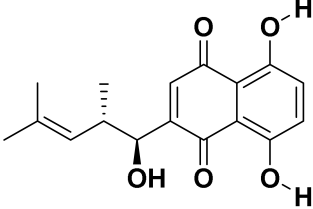
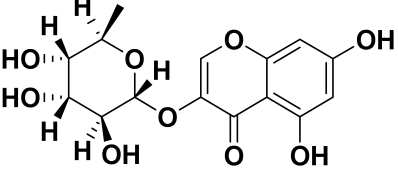
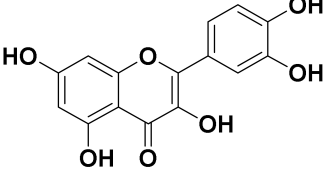
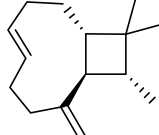
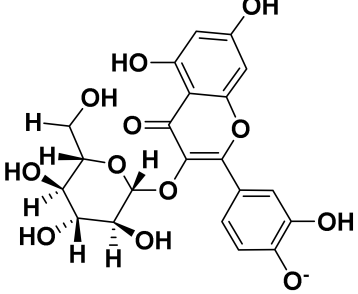
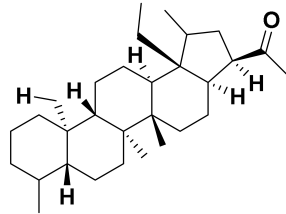
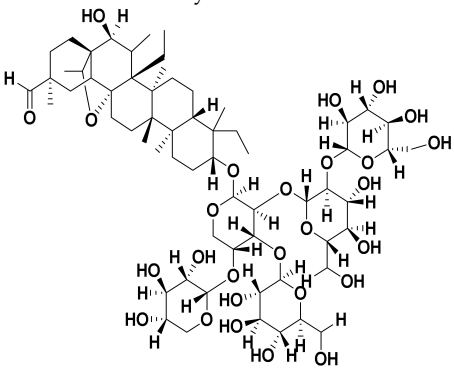
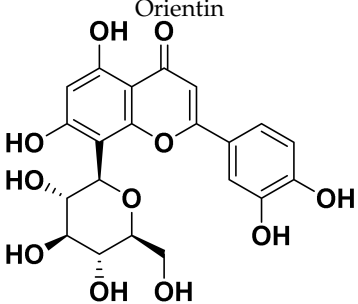
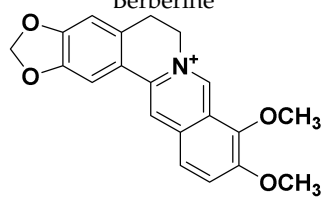
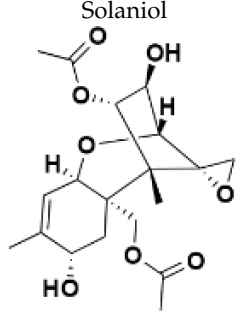
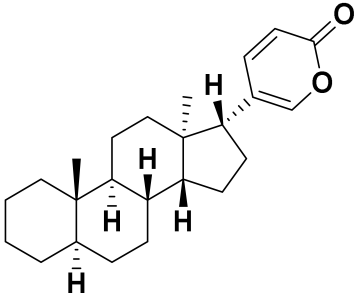
Serial No.	Botanical Name	Some Phytoconstituents and/or Classes of Compounds	Selected Structures	Ref.
12.	<i>Arnebia euchroma</i>	Shikonin, methylasiodiplodin, euchroquinols A-C, and 9,17-epoxy arnebinol	<p>Shikonin,</p> 	[211]
13.	<i>Astilbe thunbergii</i>	Eucryphin, astilbin, and berginin	<p>Eucryphin</p> 	[107]
14.	<i>Actinidia deliciosa</i>	Rutin, quercitrin, quercetin, chrysin, and syringic acid	<p>Quercetin</p> 	[212]
15.	<i>Anaphalis margaritacea</i>	Volatile oil contains E-caryophyllene, and its oxide, δ -cadinene, γ -cadinene, cubenol, ledol, and α -pinene	<p>E-caryophyllene</p> 	[213]
16.	<i>Abelmoschus esculentus</i>	Quercetin-3-glucoside, diglucoside, catechins, and hydroxyl cinnamic acid derivatives	<p>Quercetin-3-glucoside</p> 	[214]
17.	<i>Adiantum venustum</i> Don	Norlupane, noroleanane, lupane triterpenoids, adiantone, and 21-hydroxyadiantone (Norhopane)triterpenes	<p>Adiantone</p> 	[215]

Table 2. Cont.

Serial No.	Botanical Name	Some Phytoconstituents and/or Classes of Compounds	Selected Structures	Ref.
18.	<i>Saponaria officinalis</i>	Saponins	<p>Cyclamin</p> 	[62]
19.	<i>Aquilegia pubiflora</i>	Orientin, coumaric acid, sinapic acid, chlorogenic acid, ferulic acid, vitexin, isoorientin, and isovitexin	<p>Orientin</p> 	[216]
20.	<i>Argemone mexicana</i>	Berberine, oxyberberine, arginine, higenamine, pancorine, sanguinarine, β -amyrin, trans-phytol, luteolin, quercetin, quercitrin, and rutin	<p>Berberine</p> 	[69]
21.	<i>Arnica montana</i>	Sesquiterpene lactones, phenolic acids, flavonoids, helenalin, acetyl helenalin, metacryl helenalin, chlorogenic acid, 3,5-dicaffeoylquinic acid, 4,5-dicaffeoylquinic acid, quercetin-3-glucoside, quercetin-3-glucuronide, kaempferol-3-glucoside, and kaempferol-3-glucuronide	<p>Solaniol</p> 	[217]
22.	<i>Alkannatinctoria</i>	Alkaloid, bufadienolides, carbohydrate, flavonoids, saponins, and tannins	<p>Bufadienolide</p> 	[218]

6. Computational Studies

6.1. Methodology of Molecular Docking Studies

Based on the aforementioned, human granzyme B in complex with 2-acetamido-2-deoxy-beta-D-glucopyranose [219] was downloaded from PDB (Code: 1IAU), while the crystal structure of highly glycosylated human leukocyte elastase in complex with a thiazolidinedione inhibitor (5-[[4-[[[(2~{S})-4-methyl-1-oxidanylidene-1-[(2-propylphenyl)amino]pentan-2-yl]carbamoyl]phenyl]methyl]-2-oxidanylidene-1,3-thiazol-1-ium-4-olate) [220] was also downloaded from PDB (Code: 6F5M). Both enzymes were cleaned for missing amino acids or gaps in their sequences. Hydrogens were added, water molecules were removed if present, and simulation for forcefield CHARMM and partial charge MMFF was applied. A heavy atom was built, and fixation of atom constraints was applied before enzyme minimization. The receptor was identified, and the binding site was highlighted from the complexed ligand, which was later cut off for the comparative docking study. The structures of the selected active constituents were downloaded from PubChem with the .svd extension and opened in the program. A simulation for all selected 23 active constituents was applied with the CHARMM forcefield and partial charge MMFF, and ligand preparation was carried out. The 23 resulting compounds, together with the reference ligand, were allowed to dock against both enzymes using the C-docker protocol.

6.2. Results and Discussion of Computational Studies

Molecular docking is of great importance for illustrating the molecular interactions of natural compounds with different receptors [221]. Although each docking program operates slightly differently, they share common features that involve ligand and receptor, sampling, and scoring. Thus, a molecular docking study was performed using the selected software Discovery Studio 4.1 [222–224]. Twenty-three interesting phytoconstituents of the previously detailed plants were selected for *in silico* docking trials to explore their activity and possible mechanism of binding against two essential enzymes human granzyme B and human leukocyte elastase, where the inhibition of either or both of those enzymes could aid in the treatment of various skin diseases.

The 2D interaction energy of the 23 active constituents compared to the reference ligand 2-acetamido-2-deoxy-beta-D-glucopyranose, together with their C-docker interaction energy, is displayed in Table 3. The ligand displayed -27.55 Kcal/mol, saponin showed -28.10 Kcal/mol, and the rest of the constituents showed -21.42 to -1.05 Kcal/mol. Both S-methyl-L-cysteine and N-acetyl cysteine were unsuccessful in the inhibition of granzyme B. The reference ligand performed its inhibitory action via four H-bonds with essential amino acids in the granzyme B sequence (Ala 93, Asn 98, Tyr 175, and Asp 176) and via van der Waals forces with six other amino acids (Asn 95, Ser 100, Asn 101, Ser 177, Thr 178, and Ile 179). Saponin was the only constituent better than the inhibitor, displaying better interaction energy and binding mode comparable to the ligand, as shown in Figure 1. Cyclamin saponin bounded by two H-bonds with Ser 100 and three H-bonds with Asn 101, Asp 176, and Thr178, while it displayed van der Waals force attractions with Asn 93, Asn 95, Asn 98, and Ile 179.

The results of the docking study against human leukocyte elastase are presented in Table 4. It is shown that the reference complexed thiazolidinedione inhibitor displayed C-docker interaction energy equivalent to -33.57 Kcal/mol, while both constituents saponin and amaranthine displayed -48.50 and -47.62 Kcal/mol, respectively. The rest of the compounds displayed in the range of -28.97 – 10.60 Kcal/mol. The thiazolidinedione ligand inhibited the elastase via four essential H-bonds (Val 59, Asn 61, Asn 62A, and Val 62) and Pi-Pi bonding with Leu 35, Val 62B, and Ala 64. The van der Waals interaction was with Arg 36, Ala 60, and Ile 88. Comparably, saponin was able to inhibit elastase in the same mode, as shown in Figure 2, with better interaction energy. Cyclamin (saponin) bounded to the strategic binding site via two H-bonds with Ala 60 and two H-bonds with Asn 61 and Arg 63, Pi–Pi–bonds with Leu 35, and van der Waals interaction with Arg 36, Gly 39, His 40, Val 59, Val 62, Asn 62 Chain A, Val 62 Chain B, Ile 88, and Glu 90. On the other hand,

amaranthine bounded to the binding site via three H-bonds with Ala 60, Asn 61, and Val 62, attractive charge with Arg 36, and van der Waals forces with Leu 35, Val 59, Asn 62 Chain A, and Val 62 Chain B.

Table 3. Results of molecular modeling study of 24 active constituents against human granzyme B (IIAU) compared to reference complexed ligand.

Serial No.	Compound	(C-Docker Interaction Energy)	2D Interaction Diagram *	Type of Binding
1	Ligand (reference)	−27.55		H-bond: Ala 93, Asn 98, Asp 176, Tyr 175 Van der Waals: Asn 95, Ser 100, Asn 101, Ser 177, Thr 178, Ile 179
2	Cyclamin (saponin)	−28.10		H-bond: Ser 100 (×2), Asn 101, Asp 176, Thr 178 Van der Waals: Asn 93, Asn 95, Asn 98, Ile 179
3	Amaranthine	−21.42		H-bond: Asn 95, Asn 98, His 173 (×2) Pi-Pi: Tyr 174 Van der Waals: Lys 97
4	Alliin	−18.53		H-bond: Ser 100 (×2) Pi-Pi: Asp 176 Van der Waals: Asn 95, Asn 98, Asn 101, Ile 179 Unfavorable: Asp 176

Table 3. Cont.

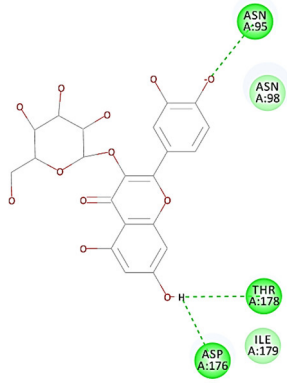
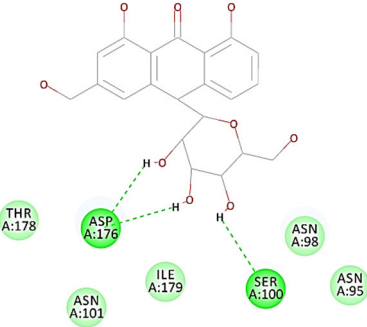
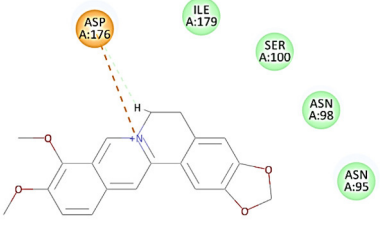
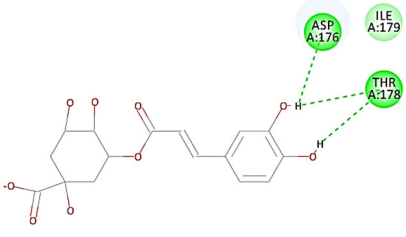
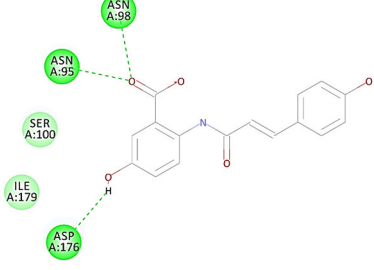
Serial No.	Compound	(C-Docker Interaction Energy)	2D Interaction Diagram *	Type of Binding
5	Quercetin-3-glucoside	−17.59		H-bond: Asn 95, Asp 176, Thr 178 Van der Waals: Asn 98, Ile 179
6	Aloin	−17.35		H-bond: Ser 100, Asp 176 (×2) Van der Waals: Asn 95, Asn 98, Asn 101, Thr 178, Ile 179
7	Berberine	−15.12		Pi-Pi: Asp 176 Van der Waals: Asn 95, Asn 98, Ser 100, Ile 179
8	Chlorogenic acid	−14.09		H-bond: Asp 176, Thr 178 (×2) Van der Waals: Ile 179
9	Avenanthramide A	−14.03		H-bond: Asn 95, Asn 98, Asp 176 Van der Waals: Ser 100, Ile 179

Table 3. Cont.

Serial No.	Compound	(C-Docker Interaction Energy)	2D Interaction Diagram *	Type of Binding
10	Adiantone	−12.76		H-bond: Asn 101 Pi-Alkyl: Ile 179 Van der Waals: Ala 93, Asn 95, Asn 98, Ser 100, Asp 176
11	Orientin	−11.89		H-bond: Asn 98, Ser 100, Asp 176 Van der Waals: Asn 95, Ile 179
12	Eucryphin	−11.34		H-bond: Ala 93, Ser 100 Van der Waals: Tyr 94, Asn 95, Asn 98, Ser 100, Asn 101
13	Lupeol	−11.15		Van der Waals: Ala 93, Asn 95, Asn 98, Ser 100, Asn 101, Asp 176, Ile 179
14	Quercetin	−11.02		H-bond: Asn 98, Ser 100, Asp 176 Van der Waals: Ile 179

Table 3. Cont.

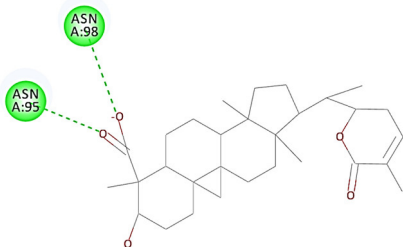
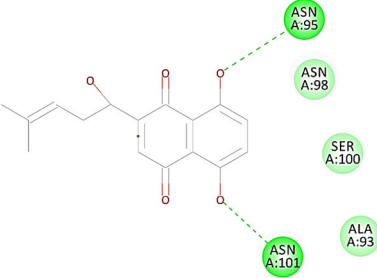
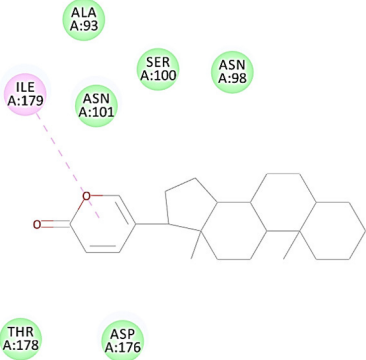
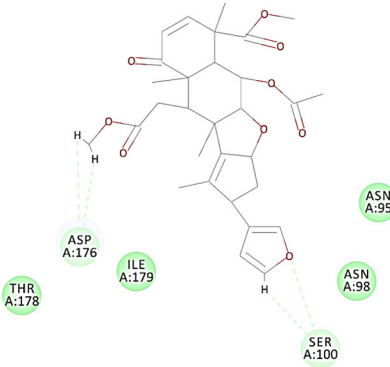
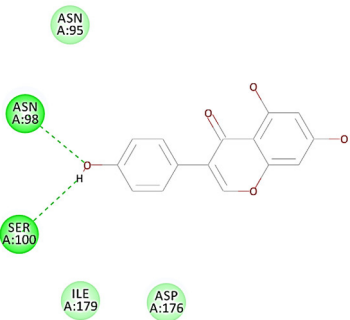
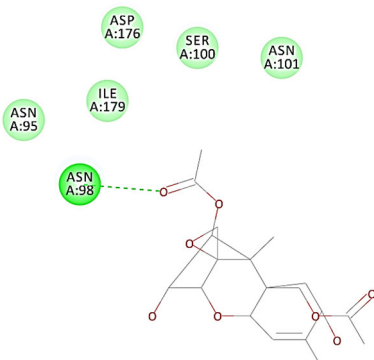
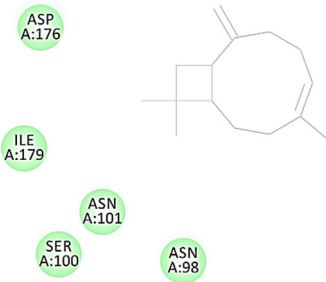
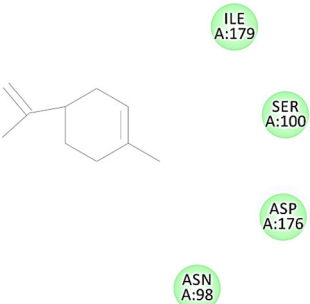
Serial No.	Compound	(C-Docker Interaction Energy)	2D Interaction Diagram *	Type of Binding
15	Abrusogenin	−10.47		H-bond: Asn 95, Asn 98
16	Shikonin	−10.25		H-bond: Asn 95, Asn 101 Van der Waals: Ala 93, Asn 98, Ser 100
17	Bufadienolide	−10.05		Pi-Alkyl: Ile 179 Van der Waals: Ala 93, Asn 98, Ser 100, Asn 101, Asp 176, Thr 178
18	Nimbin	−8.77		H-bond: Ser 100 (×2), Asp 176 (×2) Van der Waals: Asn 95, Asn 98, Thr 178, Ile 179

Table 3. Cont.

Serial No.	Compound	(C-Docker Interaction Energy)	2D Interaction Diagram *	Type of Binding
19	Genistein	-7.64		H-bond: Asn 98, Ser 100 Van der Waals: Asn 95, Asp 176, Ile 179
20	Solaniol	-7.28		H-bond: Asn 98 Van der Waals: Asn 95, Ser 100, Asn 101, Asp 176, Ile 179
21	<i>E</i> -caryophyllene	-3.25		Van der Waals: Asn 98, Ser 100, Asn 101, Asp 176, Ile 179
22	Limonene	-2.48		Van der Waals: Asn 98, Ser 100, Asp 176, Ile 179
23	S-methyl-L-cysteine	-1.79	No interaction	
24	N-acetyl cysteine	-1.05	No interaction	

* Color reference: green dotted line indicates H-bond; faint green dotted line indicates van der Waals interaction; orange dotted line indicates Pi-Pi bond; red dotted line indicates unfavorable interaction; purple dotted line indicates Pi-alkyl bond.

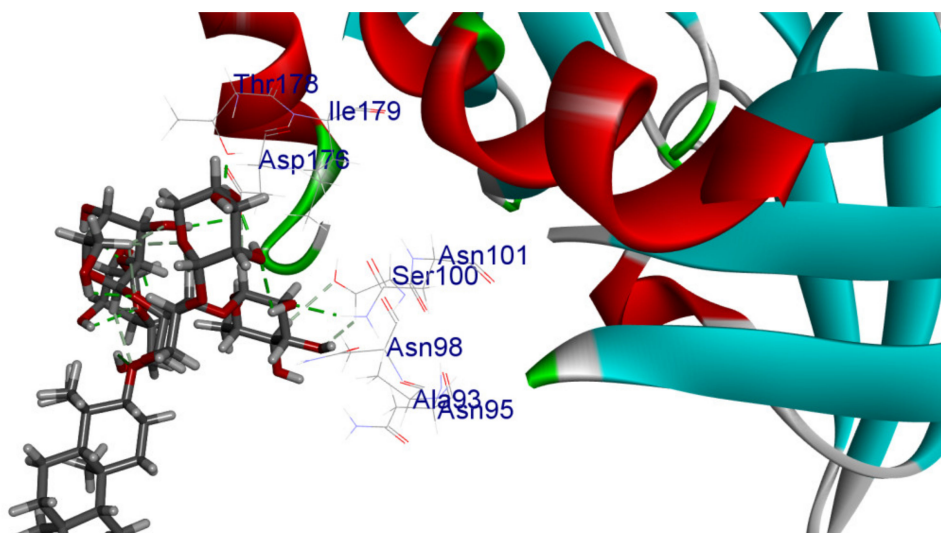


Figure 1. Three-dimensional (3D) interaction diagram of cyclamin (saponin) against human granzyme B (1IAU).

Table 4. Results of molecular modeling study of 23 active constituents against human leukocyte elastase (6F5M) compared to reference complexed ligand.

Serial No.	Compound	(C-Docker Interaction Energy)	2D Interaction Diagram *	Type of Binding
1	Ligand (reference)	−33.57		H-bond: Val 59, Asn 61, Asn 62A, Val 62 Pi-Pi bond: Leu 35, Val 62B, Ala 64 Van der Waals: Arg 36, Ala 60, Ile 88
2	Cyclamin (Saponin)	−48.50		H-bond: Ala 60(×2), Asn 61, Arg 63 Pi-Pi bond: Leu 35 Van der Waals: Arg 36, Gly 39, His 40, Val 59, Val 62, Asn 62A, Val 62B, Ile 88, Glu 90

Table 4. Cont.

Serial No.	Compound	(C-Docker Interaction Energy)	2D Interaction Diagram *	Type of Binding
3	Amaranthine	−47.62		H-bond: Ala 60, Asn 61, Val 62 Attractive charge: Arg 36(×2) Van der Waals: Leu 35, Val 59, Asn 62A, Val 62B
4	Chlorogenic acid	−28.97		H-bond: Asn 61, Asn 62A, Glu 90 Pi-sigma: Ala 60 Van der Waals: Val 59, Val 62, Val 62B, Ile 88, Tyr 94
5	Quercetin-3-glucoside	−27.94		H-bond: Asn 61, Asn 62A Pi-lone pair: Asn 61 Pi-Pi: Val 62 Van der Waals: Leu 35, Val 62B
6	Orientin	−26.43		H-bond: Val 59, Asn 61(×2), Asn 62A, Val 62 Pi-Pi: Val 62 Pi-alkyl: Val 62B Van der Waals: Leu 35, Ala 60

Table 4. Cont.

Serial No.	Compound	(C-Docker Interaction Energy)	2D Interaction Diagram *	Type of Binding
7	Abrusogenin	-26.39		H-bond: Asn 62A, Val 62B Pi-alkyl: Val 62B Van der waal: Leu 35, Arg 36, Ala 60, Asn 61
8	Alloin	-24.93		H-bond: Asn 61, Val 62, Asn 62A(×2) Pi-amide: Val 62 Van der Waals: Leu 35, Val 59, Ala 60, Val 62B
9	Avenanthramide A	-24.18		H-bond: Val 62B Van der Waals: Val 59, Ala 60, Asn 61, Val 62, Asn 62A, Arg 63, Ile 88
10	Nimbin	-22.68		H-bond: Val 62, Asn 62A(×2), Val 62B Pi-Alkyl: Val 62B Van der Waals: Val 59, Ala 60, Asn 61, Arg 63

Table 4. Cont.

Serial No.	Compound	(C-Docker Interaction Energy)	2D Interaction Diagram *	Type of Binding
11	Eucryphin	−22.47		H-bond: Ala 60, Asn 62A Pi-lone pair: Asn 61 Pi-alkyl: Val 62 Van der Waals: Leu 35, Val 62B
12	Quercetin	−20.25		H-bond: Ala 60, Asn 61, Asn 62A Pi-amide: Val 62 Van der Waals: Val 62B, Ile 88
13	Shikonin	−19.80		H-bond: Val 59, Asn 61, Val 62B Pi-sigma: Asn 62A Pi-amide: Val 62 Van der Waals: Ala 60, Ile 88
14	Bufadienolide	−18.71		H-bond: Arg 36 Pi-alkyl: Leu 35(×2), Val 62 Van der Waals: Asn 61, Asn 62A

Table 4. Cont.

Serial No.	Compound	(C-Docker Interaction Energy)	2D Interaction Diagram *	Type of Binding
15	Genistein	−18.31		H-bond: Asn 62A Pi-lone pair: Asn 61 Pi-amide: Val 62 Pi-alkyl: Val 62B Van der Waals: Val 59, Ala 60
16	Lupeol	−18.19		H-bond: Ala 60 Van der waal: Leu 35, Asn 61, Val 62, Asn 62A, Val 62B
17	Adiantone	−17.99		H-bond: Arg 36 Pi-alkyl: Ala 64 Van der Waals: Leu 35, Asn 61, Val 62, Asn 62A
18	Solaniol	−17.44		H-bond: Asn 61, Asn 62A, Val 62 Van der Waals: Ala 60, Val 62B

Table 4. Cont.

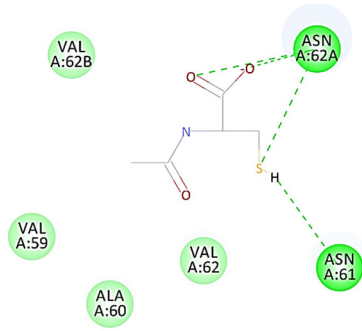
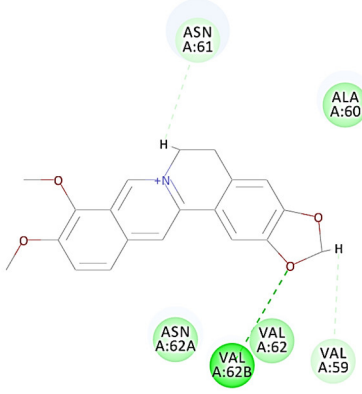
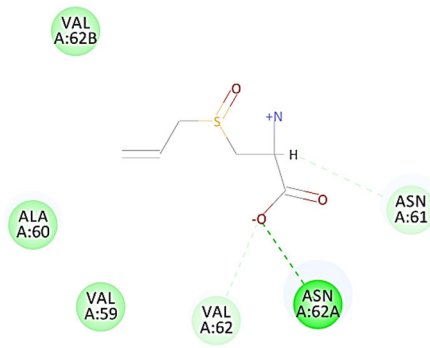
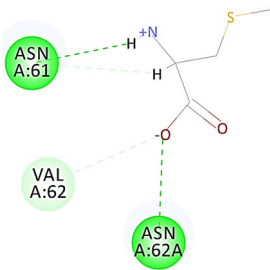
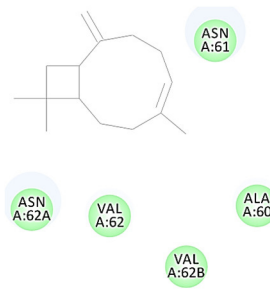
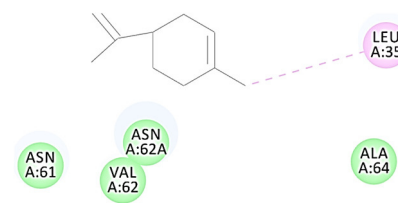
Serial No.	Compound	(C-Docker Interaction Energy)	2D Interaction Diagram *	Type of Binding
19	N-acetyl cysteine	−17.25		H-bond: Asn 61, Asn 62A (×3) Van der Waals: Val 59, Ala 60, Val 62, Val 62B
20	Berberine	−16.59		H-bond: Val 59, Asn 61, Val 62B Van der Waals: Ala 60, Val 62, Asn 62A
21	Alliin	−15.63		H-bond: Asn 61, Val 62, Asn 62A Van der Waals: Val 59, Ala 60, Val 62B
22	S-methyl-L-cysteine	−14.29		H-bond: Asn 61, Asn 62A, Val 62

Table 4. Cont.

Serial No.	Compound	(C-Docker Interaction Energy)	2D Interaction Diagram *	Type of Binding
23	E-caryophyllene	−11.78		Van der Waals: Val 59, Ala 60, Asn 61, Val 62, Asn 62A, Val 62B
24	Limonene	−10.60		Pi-alkyl: Leu 35 Van der Waals: Asn 61, Val 62, Asn 62A, Ala 64

* Color reference: green dotted line indicates H-bond; faint green dotted line; indicates van der Waals interaction; lemon green dotted line indicates Pi-lone interaction; orange dotted line indicates attractive charge; dark purple dotted line indicates Pi-sigma bond; medium purple dotted line indicates Pi-amide bond; light purple dotted line indicates Pi-alkyl bond; pink dotted line indicates Pi-Pi bond.

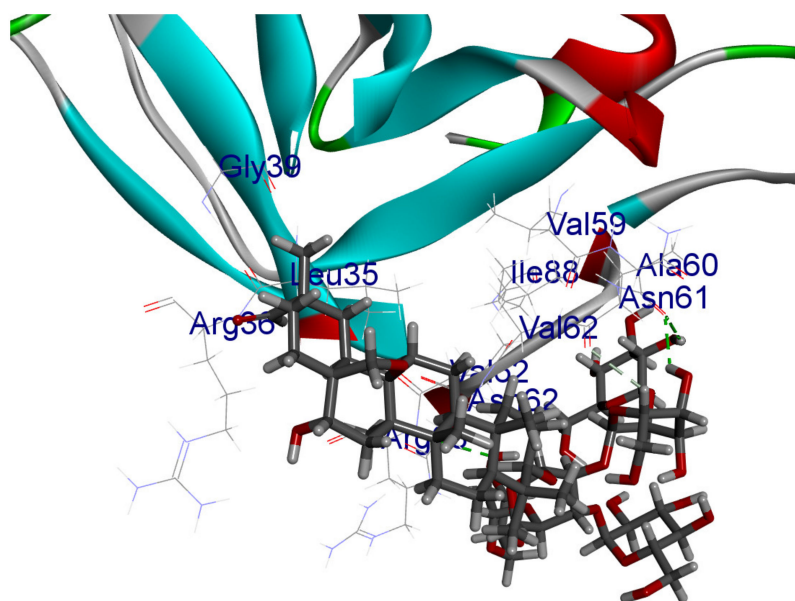


Figure 2. Three-dimensional (3D) interaction diagram of cyclamin (saponin) against human leukocyte elastase (6F5M).

Granzyme B is a serine protease found in the granules of natural killer (NK) cells and cytotoxic T cells. It is involved in inducing inflammation by cytokine release stimulation and also involved in remodeling of the extracellular matrix. Elevated levels of granzyme B are also implicated in various autoimmune diseases, several skin diseases, and type 1 diabetes [225].

On the other hand, human leukocyte elastase (HLE) is a serine proteinase involved in inflammation and tissue degradation. HLE inhibitors are believed to treat a number of diseases, such as emphysema and cystic fibrosis [220].

Natural products can have enzyme inhibitory potential for the management of different disorders [226]. According to the *in silico* study results, cyclamin, a saponin, is suggested to be a successful constituent for treating most underlying skin diseases owing to its chemical structure that possesses aliphatic rings, richness in oxygen atoms, and the ability to bind effectively with key amino acids of the binding sites of both granzyme B and HLE.

7. Conclusions

Herbs have great potential to treat various kinds of skin problems. Compared to various allopathic drugs, they have a comparatively low cost and can be of great benefit to many patients, especially poor people. Herbs are rich sources of active ingredients and can be a safer and cost-effective method for the management of skin ailments, ranging from rashes to skin cancer. FDA-approved formulas containing natural sources such as honey and biological cellulose are available and aid greatly in the treatment of skin diseases. Different mechanisms are displayed by such phytochemicals, such as inhibition of multiple inflammatory mediators, ranging from NF- κ , TNF- α , IL-1, TXB2, to COX-2. Their mechanism of action was elucidated via molecular modeling studies that were performed on the active sites of two essential proteins: granzyme B, which is a serine protease found in the granules of natural killer cells (NK cells) and cytotoxic T cells; and human leukocyte elastase (HLE), which is a serine proteinase involved in inflammation and tissue degradation. Molecular docking studies have confirmed that phytoconstituents of natural origin have potential beneficial effects on various skin disorders, especially those containing saponin. Owing to the aliphatic chains and structure rich in oxygen atoms, cyclamin saponin was able to display a comparable and stable complex with both enzymes. C-docker interaction energy expressed by saponin was -28.10 Kcal/mol for granzyme B and -48.50 Kcal/mol for HLE. Saponin bounded to granzyme B similarly to complexed reference via two H-bonds with Ser 100 and three H-bonds with Asn 101, Asp 176, and Thr178. It displayed van der Waals force attraction with Asn 93, Asn 95, Asn 98, and Ile 179, while it bounded to the strategic binding site of HLE via two H-bonds with Ala 60 and two H-bonds with Asn 61 and Arg 63, Pi—Pi bonds with Leu 35, and van der Waals interaction with Arg 36, Gly 39, His 40, Val 59, Val 62, Asn 62 Chain A, Val 62 Chain B, Ile 88, and Glu 90.

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List of Abbreviations

DNA	Deoxyribonucleic acid
UV	Ultraviolet radiation
NF- κ B	Nuclear factor-kappa enhancer binding protein
TNF- α	Tumor necrosis factor alpha
C3b	Complement component 3
NO	Nitric oxides
IL-1 β	Interleukin 1 beta
TXB2	Thromboxane B2
COX-2	Cyclooxygenase-2
FDA	Food and Drug Administration
BC	Bacterial cellulose

PC	Plant cellulose
NK	Natural killer
HLE	Human leukocyte elastase

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