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.

Keywords: skin diseases; herbal medicine; ethnobotany; granzyme B; human leukocyte elastase; molecular docking

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   | *Achyranthes aspera* Prickly chaff flower Family Amaranthaceae | Used to treat boils and scabies | [18] |
| 2   | *Aconitum chasmanthum* Gaping monkshood Family Ranunculaceae | Used to treat mumps and measles | [19] |
| 3   | *Butea monosperma* Flame of forest Family Fabaceae | Used to treat skin diseases such as inflammation | [20] |
| 4   | *Boerhavia diffusa* Tar vine, wine flower Family Nyctaginaceae | Used to treat abscesses | [21] |
| 5   | *Curcuma longa* Turmeric Family Zingiberaceae | Used to treat skin inflammation | [22] |
| 6   | *Crocus sativus* saffron Family Iridaceae | Used to treat psoriasis | [23] |
| 7   | *Commelina benghalensis* Tropical spiderwort Family Commelinaceae | Used to treat wound infection | [24] |
| 8   | *Cyperus difformis* Family Cyperaceae | Used to treat skin infections | [25] |
| 9   | *Cassia tora* Stinking cassia Family Caesalpiniaceae | Used to treat psoriasis | [26] |
| 10  | *Capsicum frutescens* Chilli Family Solanaceae | Used to treat psoriasis | [27] |
| 11  | *Dalbergia sissoo* North Indian rosewood Family Fabaceae | Used to treat abscesses | [28] |
| 12  | *Eucalyptus globulus* Eucalyptus Family Myrtaceae | Used to treat acne, fungal infections, and heal wounds | [29] |
| 13  | *Euphorbia wallichii* Wallich spurge Family Euphorbiaceae | Used to treat skin infections and warts | [30] |
| 14  | *Ficus carica* Fig Family Moraceae | Used to treat itching, pimples, and scabies | [31] |
| 15  | *Fagopyrum tataricum* Tartary buckwheat Family Polygonaceae | Used to treat erysipelas | [32] |
| 16  | *Gnaphalium affine* Cotton weed Family Asteraceae | Used to treat weeping pruritus of skin | [33] |
| 17  | *Juniperus excelsa* Eastern savin Family Cupressaceae | Used to treat skin infections | [34] |
| No. | Botanical Source (Latin Name, Common Name, Family) | Uses | References |
|-----|-----------------------------------------------|------|------------|
| 18  | *Lens culinaris*  
Lentil  
Family Fabaceae | Used to treat skin infections and acne | [35] |
| 19  | *Marsilea quadrifolia*  
Water clover  
Family Marsileaceae | Used to treat abscesses | [36] |
| 20  | *Mahonia aquifolium*  
Oregon grape  
Family Berberidaceae | Used to treat psoriasis | [37] |
| 21  | *Pleurotus bromius*  
Brown’s paper cup flower  
Family Apiaceae | Used to treat skin infections | [38] |
| 22  | *Pinus roxburghii*  
Chir pine  
Family Pinaceae | Used to treat pruritus, inflammation, and other skin diseases | [39] |
| 23  | *Pinus wallichiana*  
Bhutan pine  
Family Pinaceae | Used to treat wound infection | [40] |
| 24  | *Rubia cordifolia*  
Common madder  
Family Rubiaceae | Used to treat psoriasis | [41] |
| 25  | *Solanum nigrum*  
Black nightshade  
Family Solanaceae | Used to treat pimples, pustules, ringworms, eczema, syphilitic ulcers, and leukoderma | [42,43] |
| 26  | *Simmondsia chinensis*  
Jojoba  
Family Buxaceae | Used to treat acne and psoriasis | [44] |
| 27  | *Taxus wallichiana*  
Himalayan yew  
Family Taxaceae | Used to treat psoriasis and ringworm | [45] |
| 28  | *Tectona grandis*  
Teak  
Family Lamiaceae | Used to treat pruritus and heal wounds | [46,47] |
| 29  | *Thespesia populnea*  
Indian tulip tree  
Family Malvaceae | Used to treat psoriasis | [48] |
| 30  | *Wrightia tinctoria*  
Sweet indrajao  
Family Apocynaceae | Used to treat psoriasis | [49] |

**B**  
Medicinal Plants Used to Treat Eczema

| No. | Botanical Source (Latin Name, Common Name, Family) | Uses | References |
|-----|-----------------------------------------------|------|------------|
| 31  | *Abrus precatorius*  
Rosary pea  
Family Fabaceae | Used to treat eczema | [50] |
| 32  | *Avena sativa*  
Oat  
Family Poaceae | Used to treat eczema, wounds, inflammation, itching, burns, and irritation | [51] |
| 33  | *Arnebia euchroma*  
Pink arnebia  
Family Boraginaceae | Used to treat burns, eczema, and dermatitis | [52,53] |
| No. | Botanical Source (Latin Name, Common Name, Family) | Uses | References |
|-----|---------------------------------------------------|------|------------|
| 34  | *Actinidia deliciosa*  
Kiwi fruit  
Family Actinidiaceae | Used to treat inflammation and eczema | [54] |
| 35  | *Aristolochia indica*  
Indian birthwort  
Family Aristolochiaceae | Used to treat eczema and wounds | [55] |
| 36  | *Betula alba*  
Paper birch  
Family Betulaceae | Used to treat eczema, psoriasis, and acne | [56] |
| 37  | *Cannabis sativus*  
Charas, ganja  
Family Cannabaceae | Used to treat sores, eczema, dermatitis, psoriasis, seborrheic, and lichen planus | [57] |
| 38  | *Matricaria chamomilla*  
Chamomile  
Family Asteraceae | Used to treat eczema and skin inflammation | [58,59] |
| 39  | *Sarco asoca*  
Ashoka  
Family Caesalpiniaceae | Used to treat skin diseases, inflammation, eczema, and scabies | [60] |
| 40  | *Saponaria officinalis*  
Soapworts  
Family Caryophyllaceae | Used to treat eczema, acne, boils, and psoriasis | [61,62] |
| 41  | *Vitex negundo*  
Nirgundi  
Family Verbenaceae | Used to treat skin diseases such as eczema, acne, pimples, ringworms, etc. | [35] |

**C Medicinal Plants Used for Wound healing**

| No. | Botanical Source (Latin Name, Common Name, Family) | Uses | References |
|-----|---------------------------------------------------|------|------------|
| 42  | *Achillea millefolium*  
Common Yarrow  
Family Asteraceae | Used to treat burn wounds | [63] |
| 43  | *Albizia lebbeck*  
Siris  
Family Fabaceae | Used for wound healing, leucoderma, itching, and inflammation | [64] |
| 44  | *Allium sativum*  
Garlic  
Family Alliaceae | Used to treat psoriasis, scars, and heal wounds | [65] |
| 45  | *Aloe barbadensis*  
Aloe vera  
Family Aloeaceae | Used to treat skin injuries | [66] |
| 46  | *Alternanthera brasiliana*  
Brazilian joyweed  
Family Amaranthaceae | Used to heal inflammation wounds | [64] |
| 47  | *Abelmoschus esculentus*  
Okra  
Family Malvaceae | Used to cure pimples and wounds | [67] |
| 48  | *Adiantum venustum D*  
Himalayan maidenhair  
Family Pteridaceae | Used to heal wounds | [68] |
| 49  | *Argemone Mexicana*  
Mexican poppy  
Family Papaveraceae | Used to treat wounds | [69] |
| No. | Botanical Source (Latin Name, Common Name, Family) | Uses | References |
|-----|--------------------------------------------------|------|------------|
| 50  | *Alkanna tinctoria* Alkanet Family Boraginaceae   | Used to treat itching, skin wounds, and rashes | [70] |
| 51  | *Brassica oleracea* Red cabbage Family Brassicaceae | Used to treat dermatitis and wounds | [71] |
| 52  | *Berberis lycium* Indian lycium Family Berberidaceae | Used to heal wounds | [72] |
| 53  | *Bergenia ciliata* Winter begonia Family Saxifragaceae | Used to heal wounds | [73,74] |
| 54  | *Bergenia ligulata* Asmabhedaka Family Saxifragaceae | Used to heal wounds and treat boils | [75] |
| 55  | *Bauhinia purpurea* Orchid tree Family Fabaceae | Used to heal wounds and treat inflammation | [76] |
| 56  | *Carissa spinarum* Bush plum Family Apocynaceae | Used to heal wounds and treat boils | [77] |
| 57  | *Cannabis sativa* Marijuana, hemp Family Cannabaceae | Used to treat dandruff and heal wounds | [78] |
| 58  | *Capparis decidua* Bare caper Family Capparaceae | Used to heal wounds | [79] |
| 59  | *Cynodon dactylon* Bermuda grass Family Poaceae | Used to heal wounds and skin problems | [80,81] |
| 60  | *Cocos nucifera* Coconut Family Arecaceae | Used to treat skin wounds | [82] |
| 61  | *Euphorbia helioscopia* Sun spurge Family Euphorbiaceae | Used to heal wounds | [83,84] |
| 62  | *Ferula foetida* Asafoetida, Hing Family Apiaceae | Used to heal wounds | [85] |
| 63  | *Ficus benghalensis* Banyan tree Family Moraceae | Used to treat skin injuries | [86] |
| 64  | *Gerbera gossypina* Hairy gerbera daisy Family Asteraceae | Used to heal wounds | [87] |
| 65  | *Galium aparine* Goosegrass Family Rubiaceae | Used to treat wounds as an antiseptic | [88] |
| 66  | *Hackelia americana* 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  | Hypericum perforatum Perforate john’s wort Family Hypericaceae | Used to treat wounds, abrasions, inflammatory skin disease, and burns | [90] |
| 68  | Isodon rugosus Wrinkled leaf isodon Family Lamiaceae | Used to heal wounds | [91] |
| 69  | Launaea nudicaulis Bhatal Family Asteraceae | Used to heal wounds | [92] |
| 70  | Momordica charantia Bitter gourd Family Cucurbitaceae | Used to heal wounds | [93] |
| 71  | Micromeria biflora Lemon savory Family Lamiaceae | Used to heal wounds and treat skin infections | [94] |
| 72  | Nigella sativa Black cumin Family Ranunculaceae | Used to heal wounds | [95,96] |
| 73  | Plantago major Great plantain Family Plantaginaceae | Used to treat wounds | [97] |
| 74  | Plantago lanceolata Ribwort plantain Family Plantaginaceae | Used to heal wounds | [98] |
| 75  | Rumex dissectus Arrowleaf dock Family Polygonaceae | Used to stop wound bleeding | [99] |
| 76  | Salvia moorcroftiana Kashmir salvia Family Lamiaceae | Used to treat skin itching and wound healing | [100] |
| 77  | Trigonella foenum-graecum Fenugreek Family Fabaceae | Used to heal wounds | [101,102] |
| 78  | Tephrosia purpurea Wild indigo Family Fabaceae | Used to heal wounds | [103] |
| 79  | Urtica dioica Stinging nettle Family Urticaceae | Used to heal wounds | [104,105] |
| 80  | Verbascum Thapsus 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  | Astilbe thunbergii Astilbe Family Saxifragaceae | Used to treat burns | [107] |
| 82  | Anaphalis margaritacea Pearly everlasting Family Asteraceae | Used to treat sunburn | [108] |
Table 1. Cont.

| No. | Botanical Source (Latin Name, Common Name, Family) | Uses | References |
|-----|-------------------------------------------------|------|------------|
| 83  | Aquilegia pubiflora Himalayan columbine Family Ranunculaceae | Used to heal wounds and treat skin burns | [109] |
| 84  | Amygdalus communis Almonds Family Rosaceae | Used to treat burn wounds | [53] |
| 85  | Bergenia stracheyi Himalayan Bergenia Family Saxifragaceae | Used to treat sunstroke and heal wounds | [110] |
| 86  | Calendula officinalis Marigold Family Asteraceae | Used to treat burns and bruises | [111] |
| 87  | Cucumis melo Muskmelon Family Cucurbitaceae | Used to treat skin burns | [112] |
| 88  | Corydalis govaniana Govan’s corydalis Family Papaveraceae | Used to treat skin burns | [113] |
| 89  | Carica cadamarcensis Mountain papaya Family Caricaceae | Used to treat burn wounds | [114] |
| 90  | Chitoria ternatea Butterfly pea Family Fabaceae | Used to treat boils, acne, and skin outbreaks | [115] |
| 91  | Datura stramonium Jimsonweed, thornapple Family Solanaceae | Used to treat boils | [116] |
| 92  | Dodonaea viscosa Hop bush Family Sapindaceae | Used to treat skin burns and heal wounds, acne, pimplles, rashes, itching, and pustules | [117–119] |
| 93  | Echinacea angustifolia Purple coneflower Family Asteraceae | Used to treat psoriasis, burns, acne, ulcers, and skin wounds | [120] |
| 94  | Ginkgo biloba Maidenhair tree Family Ginkgoaceae | Used to treat skin burns | [121] |
| 95  | Hippophae rhamnoides Sea buckthorn Family Elaeagnaceae | Used to treat rashes and skin burns | [122,123] |
| 96  | Impatiens edgeworthii Edgeworth Balsam Family Balsaminaceae | Used to treat skin burns | [124] |
| 97  | Mangifera indica Mango Family Anacardiaceae | Protect skin from sun damage | [125] |
| 98  | Malus pumila Apple Family Rosaceae | Used to treat boils | [126] |
| 99  | Malva sylvestris High mallow Family Malvaceae | Used to treat burn wounds | [53] |
### Table 1. Cont.

| No. | Botanical Source (Latin Name, Common Name, Family) | Uses | References |
|-----|---------------------------------------------------|------|------------|
| 100 | *Matricaria chamomilla*<br>Chamomile<br>Family Asteraceae | Used to treat burn wounds | [127] |
| 101 | *Onosma hispida*<br>Bristly onosma<br>Family Boraginaceae | Used to treat skin burns | [128] |
| 102 | *Portulaca oleracea*<br>Purslane, little hogweed<br>Family Portulacaceae | Used to treat burns, skin eruptions, rashes, skin inflammation, eczema, abscesses, and pruritus | [129–131] |
| 103 | *Pisum sativum*<br>Garden pea<br>Family Fabaceae | Used to treat skin burns | [132] |
| 104 | *Picrorhiza kurroa*<br>Kutki<br>Family Plantaginaceae | Used to treat burning sensation | [133] |
| 105 | *Rumex dentatus*<br>Toothed dock<br>Family Polygonaceae | Used to treat boils | [134] |
| 106 | *Rubus abchasiensis*<br>Akhray<br>Family Rosaceae | Used to treat boils and wounds | [135] |
| 107 | *Solanum virginianum*<br>Thorny nightshade<br>Family Solanaceae | Used to treat swelling of skin | [136] |
| 108 | *Scrophularia deserti*<br>Desert figwort<br>Family Scrophulariaceae | Used to treat burn wounds | [53] |
| 109 | *Sesamum indicum*<br>Sesame<br>Family Pedaliaceae | Used to treat burn wounds | [137] |
| 110 | *Silybum marianum*<br>Blessed thistle<br>Family Asteraceae | Used to treat burn wounds and improve skin health | [138] |
| 111 | *Tamarix aphylla*<br>Athel<br>Family Tamaricaceae | Used to treat skin burns and wounds | [139] |
| 112 | *Tridax procumbens*<br>Coatbuttons, tridax daisy<br>Family Asteraceae | Used to treat burn wounds | [140] |
| 113 | *Zanthoxylum armatum*<br>Winged prickly ash<br>Family Rutaceae | Used to treat skin burns | [141] |
| **E** | **Medicinal Plants Used to Treat Miscellaneous Disorders** | | |
| 114 | *Allium cepa*<br>Garden onion<br>Family Alliaceae | Used to treat skin lesions | [142] |
| 115 | *Azadirachta indica*<br>Neem<br>Family Meliaceae | Used to treat acne and protect skin from UV rays | [143] |
| No. | Botanical Source (Latin Name, Common Name, Family) | Uses | References |
|-----|--------------------------------------------------|------|------------|
| 116 | *Anethum graveolens*  
Dill  
Family Apiaceae | Used to treat pimples | [144] |
| 117 | *Androsace rotundifolia lehm.*  
Rock jasmine  
Family Primulaceae | Used to treat skin problems | [145] |
| 118 | *Arnica montana*  
Mountain arnica  
Family Asteraceae | Used as anti-inflammatory to treat boils and acne eruptions | [146,147] |
| 119 | *Bauhinia variegata*  
Kachnar, orchid tree  
Family Fabaceae | Used to treat skin disease and skin ulcers | [148] |
| 120 | *Beta vulgaris*  
Beetroot  
Family Brassicaceae | Used to treat tumors | [149] |
| 121 | *Brassica juncea*  
Mustard  
Family Brassicaceae | Used against skin eruptions and ulcers | [150,151] |
| 122 | *Berberis aquifolium*  
Oregon grape  
Family Berberidaceae | Used to treat acne scars | [152] |
| 123 | *Camellia sinensis*  
Green Tea  
Family Theaceae | Used to treat skin tumors and cancer | [153] |
| 124 | *Coriandrum sativum*  
Dhaniya  
Family Apiaceae | Used to treat pimples | [154,155] |
| 125 | *Calotropis procera*  
Giant milkweed  
Family Apocynaceae | Used to treat inflammation | [156] |
| 126 | *Cerastium fontanum*  
Mouse ear chickweed  
Family Caryophyllaceae | Used to treat skin diseases; also acts as anti-inflammatory | [157] |
| 127 | *Citrus medica*  
Citron  
Family Rutaceae | Used to treat skin irritation | [158,159] |
| 128 | *Citrus sinensis*  
orange  
Family Rutaceae | Used to treat pimples | [160] |
| 129 | *Catharanthus roseus*  
Periwinkle  
Family Apocynaceae | Used to cure pimples | [161] |
| 130 | *Carthamus tinctorius*  
safflower  
Family Asteraceae | Used to treat eruptive skin problems | [162] |
| 131 | *Clerodendrum viscosum*  
Hill glory bower  
Family Verbenaceae | Used as antiseptic skin wash | [163] |
| 132 | *Equisetum arvense*  
Field horsetail  
Family Equisetaceae | Used to treat skin allergy | [164] |
| No.  | Botanical Source (Latin Name, Common Name, Family) | Uses                                      | References |
|------|---------------------------------------------------|-------------------------------------------|------------|
| 133  | *Lavendula officinalis* Lavender Family Labiatae | Used to prevent and heal acne             | [165]      |
| 134  | *Lawsonia inermis* Henna Family Lythraceae        | Used to treat inflammation and tumors     | [166]      |
| 135  | *Lycopersicon esculentum* Tomato Family Solanaceae| Used to treat acne and sunburn            | [167]      |
| 136  | *Ledum groenlandicum oedar* Labrador tea Family Ericaceae | Used to treat itching, acne, and redness | [61]       |
| 137  | *Mirabilis jalapa* Four o’clock Family Nyctaginaceae | Used to treat allergic skin disorders     | [168]      |
| 138  | *Melia azedarach* Persian lilac Family Meliaceae  | Used to treat pimples and inflammation    | [169]      |
| 139  | *Myrsine Africana* Cape myrtle Family Myrsinaceae | Used to treat skin disorders              | [170]      |
| 140  | *Melaleuca alternifolia* Tea tree Family Myrtaceae | Used to treat acne                        | [171]      |
| 141  | *Olea europaea* Olive tree Family Oleaceae        | Used as skin cleanser                     | [172]      |
| 142  | *Octium sanctum* Tulsi Family Lamiaceae           | Used to treat acne and inflammation       | [173,174]  |
| 143  | *Plumbago zeylanica* Doctor bush Family Plumbaginaceae | Used to treat skin diseases such as sores, acne, and dermatitis | [31] |
| 144  | *Prunus persica* Peach Family Rosaceae            | Used to treat skin disorders              | [175]      |
| 145  | *Piper nigrum* Black pepper Family Piperaceae     | Used to treat acne                        | [176]      |
| 146  | *Pterocarpus santalinus* Red sandalwood Family Fabaceae | Used to treat skin inflammation and acne | [177]      |
| 147  | *Rosmarinus officinalis* Rosemary Family Lamiaceae | Used to block skin tumor cells            | [178]      |
| 148  | *Ricinus communis* Castor oil plant Family Euphorbiaceae | Used in children for skin diseases       | [179]      |
| 149  | *Rheum officinale* Rhubarb Family Polygonaceae    | Used to treat acne                        | [180]      |
Table 1. Cont.

| No. | Botanical Source (Latin Name, Common Name, Family) | Uses | References |
|-----|--------------------------------------------------|------|------------|
| 150 | *Salix babylonica*  
Weeping willow  
Family Salicaceae | Used as skin cleanser | [181] |
| 151 | *Serenoa repens*  
Saw palmetto  
Family Arecaceae | Used to treat acne and inflammation | [182] |
| 152 | *Thymus vulgaris*  
Thyme  
Family a | Used to treat cellulitis | [153] |
| 153 | *Taraxacum officinale*  
Common dandelion  
Family Asteraceae | Used to treat pimples | [183] |
| 154 | *Tussilago farfara*  
coltsfoot  
Family Asteraceae | Used to treat sores and inflammation of skin | [184] |
| 155 | *Valeriana jatamansi*  
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-κB, 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 *Rosmarinus 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-1β, 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.         | Abrus precatorius          | Stigmasterol, β-sitosterol, and abrusogenin        | Abrusogenin         | [200]|
| 2.         | Achillea millefolium       | Chlorogenic acid, apigenin-7-glucoside, and luteolin-7-glucoside | Chlorogenic acid    | [201]|
| 3.         | Achyranthes aspera         | Rutin, chlorogenic acid, and genistein             | Genistein           | [202]|
| 4.         | Allium cepa                | Quercetin, S-methyl-L-cysteine, cycloalliin, N-acetylcysteine, S-propyl-L-cysteine sulfoxide, and dimethyl trisulfide | Cycloalliin, N-acetyl cysteine, S-methyl-L-cysteine | [203]|
| 5.         | Azadirachta indica         | Nimbin, nimbanene, ascorbic acid, n-hexacosanol, nimbolide, 17-hydroxy azadiradione, 6-desacetyl nimbinene, and nimbandiol | Nimbin              | [204]|

In order to fully utilize the bioactivities of medicinal plant extracts, detailed knowledge of their phytochemical constituents is required.
| Serial No. | Botanical Name       | Some Phytoconstituents and/or Classes of Compounds                                                                 | Selected Structures | Ref. |
|-----------|----------------------|---------------------------------------------------------------------------------------------------------------|---------------------|------|
| 6.        | Albizia lebbeck      | 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 | Lupeol              | [205]|
| 7.        | Allium sativum       | Alliin, allicin, S-allyl cysteine, diallyl sulfide, diallyl trisulfide, diallyl disulfide, and ajoene         | Alliin              | [206]|
| 8.        | Aloe barbadensis     | Aloesin, cinnamic acid, isoaloresin D, caffeic acid, chlorogenic acid, aloin A and B, emodin, isovitexin, and orientin | Aloin               | [207]|
| 9.        | Alternanthea brasiliana | Amaranthine, iso amaranthine, betanin, isobetanin, hydroxybenzoic acid, hydroxycinnamic acid, kaempferol glucoside, rhamnoside, and dirhamnosyl-glucoside | Amaranthine         | [208]|
| 10.       | Anethum graveolens   | Limonene, carvone, α-phellandrene, β-phellandrene, and p-cymene                                             | Limonene            | [209]|
| 11.       | Avena sativa         | Proteins, lipids, polysaccharides, β-glycan, dietary fibers, avenanthramides, gramine alkaloid, flavonolignans, flavonoids, saponins, and sterols | Avenanthramide A    | [210]|

Table 2. Cont.
| Serial No. | Botanical Name          | Some Phytoconstituents and/or Classes of Compounds                                                                 | Selected Structures | Ref.   |
|-----------|-------------------------|----------------------------------------------------------------------------------------------------------------------|---------------------|--------|
| 12        | *Arnebia euchroma*      | Shikonin, methylasiodiplodin, euchroquinols A-C, and 9,17-epoxy arnebinol                                               | Shikonin            | [211]  |
| 13        | *Astilbe thunbergii*    | Eucryphin, astilbin, and berginin                                                                                   | Eucryphin           | [107]  |
| 14        | *Actinidia deliciosa*   | Rutin, quercitrin, quercetin, chrysin, and syringic acid                                                           | Quercetin           | [212]  |
| 15        | *Anaphalis margaritacea*| Volatile oil contains E-caryophyllene, and its oxide, δ-cadinene, γ-cadinene, cubenol, ledol, and α-pinene       | E-caryophyllene     | [213]  |
| 16        | *Abelmoschus esculentus*| Quercetin-3-glucoside, diglucoside, catechins, and hydroxyl cinnamic acid derivatives                               | Quercetin-3-glucoside| [214]  |
| 17        | *Adiantum venustum* Don | Norlupane, noroleanane, lupane triterpenoids, adiantone, and 21-hydroxyadiantone (Norhopane) triterpenes            | Adiantone           | [215]  |
| Serial No. | Botanical Name          | Some Phytoconstituents and/or Classes of Compounds                                                                 | Selected Structures | Ref. |
|-----------|-------------------------|-------------------------------------------------------------------------------------------------------------------|---------------------|------|
| 18.       | *Saponaria officinalis* | Saponins                                                                                                         | Cyclamin            | [62] |
| 19.       | *Aquilegia pubiflora*   | Orientin, coumaric acid, sinapic acid, chlorogenic acid, ferulic acid, vitexin, isoorientin, and isovitexin   | Orientin            | [216]|
| 20.       | *Argemone mexicana*     | Berberine, oxyberberine, arginine, higenamine, pancorine, sanguinarine, β-amyrin, trans-phytol, luteolin, quercetin, quercitrin, and rutin | Berberine           | [69] |
| 21.       | *Arnicamontana*         | 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 | Solaniol            | [217]|
| 22.       | *Alkannatinctoria*      | Alkaloid, bufadienolides, carbohydrate, flavonoids, saponins, and tannins                                         | Bufadienolide       | [218]|

*Table 2. Cont.*
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-[[2-[(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 Asp 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 (1IAU) compared to reference complexed ligand.

| Serial No. | Compound        | (C-Docker Interaction Energy) | 2D Interaction Diagram * | Type of Binding |
|------------|-----------------|-------------------------------|--------------------------|-----------------|
| 1          | Ligand (reference) | −27.55                       | ![Diagram](image1.png)   | **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                       | ![Diagram](image2.png)   | **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                       | ![Diagram](image3.png)   | **H-bond**: Asn 95, Asn 98, His 173 (×2)  
**Pi-Pi**: Tyr 174  
**Van der Waals**: Lys 97 |
| 4          | Alliin           | −18.53                       | ![Diagram](image4.png)   | **H-bond**: Ser 100 (×2)  
**Pi-Pi**: Asp 176  
**Van der Waals**: Asn 95, Asn 98, Asn 101, Ile 179  
**Unfavorable**: Asp 176 |
| Serial No. | Compound             | (C-Docker Interaction Energy) | 2D Interaction Diagram * | Type of Binding            |
|-----------|----------------------|------------------------------|--------------------------|----------------------------|
| 5         | Quercetin-3-glucoside| −17.59                       | ![Diagram](image_url)     | **H-bond:** Asn 95, Asp 176, Thr 178  
  **Van der Waals:** Asn 98, Ile 179 |
| 6         | Aloin                | −17.35                       | ![Diagram](image_url)     | **H-bond:** Ser 100, Asp 176 (×2)  
  **Van der Waals:** Asn 95, Asn 98, Asn 101, Thr 178, Ile 179 |
| 7         | Berberine            | −15.12                       | ![Diagram](image_url)     | **Pi-Pi:** Asp 176  
  **Van der Waals:** Asn 95, Asn 98, Ser 100, Ile 179 |
| 8         | Chlorogenic acid     | −14.09                       | ![Diagram](image_url)     | **H-bond:** Asp 176, Thr 178 (×2)  
  **Van der Waals:** Ile 179 |
| 9         | Avenanthramide A     | −14.03                       | ![Diagram](image_url)     | **H-bond:** Asn 95, Asn 98, Asp 176  
  **Van der Waals:** Ser 100, Ile 179 |
| Serial No. | Compound | (C-Docker Interaction Energy) | 2D Interaction Diagram * | Type of Binding |
|-----------|----------|-------------------------------|--------------------------|-----------------|
| 10        | Adiantone | $-12.76$                      | ![Diagram](image1.png)   | H-bond: Asn 101  
PI-Alkyl: Ile 179  
Van der Waals: Ala 93, Asn 95, Asn 98, Ser 100, Asp 176 |
| 11        | Orientin  | $-11.89$                      | ![Diagram](image2.png)   | H-bond: Asn 98, Ser 100, Asp 176  
Van der Waals: Asn 95, Ile 179 |
| 12        | Eucryphin | $-11.34$                      | ![Diagram](image3.png)   | H-bond: Ala 93, Ser 100  
Van der Waals: Tyr 94, Asn 95, Asn 98, Ser 100, Asn 101 |
| 13        | Lupeol    | $-11.15$                      | ![Diagram](image4.png)   | Van der Waals: Ala 93, Asn 95, Asn 98, Ser 100, Asn 101, Asp 176, Ile 179 |
| 14        | Quercetin | $-11.02$                      | ![Diagram](image5.png)   | H-bond: Asn 98, Ser 100, Asp 176  
Van der Waals: Ile 179 |

Table 3. Cont.
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, 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 |
| Serial No. | Compound            | (C-Docker Interaction Energy) | 2D Interaction Diagram * | Type of Binding                                      |
|-----------|---------------------|-------------------------------|--------------------------|------------------------------------------------------|
| 19        | Genistein           | −7.64                         | ![Image](image1.png)     | **H-bond**: Asn 98, Ser 100<br>**Van der Waals**: Asn 95, Asp 176, Ile 179 |
| 20        | Solaniol            | −7.28                         | ![Image](image2.png)     | **H-bond**: Asn 98<br>**Van der Waals**: Asn 95, Ser 100, Asn 101, Asp 176, Ile 179 |
| 21        | E-caryophyllene     | −3.25                         | ![Image](image3.png)     | **Van der Waals**: Asn 98, Ser 100, Asn 101, Asp 176, Ile 179 |
| 22        | Limonene            | −2.48                         | ![Image](image4.png)     | **Van der Waals**: Asn 98, Ser 100, Asn 101, Asp 176, Ile 179 |
| 23        | S-methyl-L-cysteine | −1.79                         | ![Image](image5.png)     | No interaction                                       |
| 24        | N-acetyl cysteine   | −1.05                         | ![Image](image6.png)     | 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       | Interaction Energy | 2D Interaction Diagram * | Type of Binding                               |
|------------|----------------|--------------------|--------------------------|-----------------------------------------------|
| 1          | Ligand (reference) | −33.57             | ![2D Interaction Diagram](image1.png) | 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             | ![2D Interaction Diagram](image2.png) | 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                        | ![Amaranthine Diagram](image1) | 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                        | ![Chlorogenic Acid Diagram](image2) | 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                       | ![Quercetin-3-glucoside Diagram](image3) | 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                        | ![Orientin Diagram](image4) | 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 |
| Serial No. | Compound       | (C-Docker Interaction Energy) | 2D Interaction Diagram * | Type of Binding |
|------------|----------------|-------------------------------|--------------------------|-----------------|
| 7          | Abrusogenin    | −26.39                        | H-bond: Asn 62A, Val 62B | Van der Waals: Leu 35, Arg 36, Ala 60, Asn 61 |
|            |                |                               |                          |                 |
| 8          | Alloin         | −24.93                        | H-bond: Asn 61, Val 62, Asn 62A(×2) | Pi-alkyl: 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 |
| Serial No. | Compound     | (C-Docker Interaction Energy) | 2D Interaction Diagram * | Type of Binding |
|-----------|--------------|-------------------------------|--------------------------|----------------|
| 11        | Eucryphin    | −22.47                        | ![Diagram](image1)       | 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                        | ![Diagram](image2)       | H-bond: Ala 60, Asn 61, Asn 62A, Pi-amide: Val 62, Van der Waals: Val 62B, Ile 88 |
| 13        | Shikonin     | −19.80                        | ![Diagram](image3)       | 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                        | ![Diagram](image4)       | 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                        | ![Genistein Diagram](image) | 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                        | ![Lupeol Diagram](image)  | H-bond: Ala 60  
Van der Waals: Leu 35, Asn 61, Val 62, Asn 62A, Val 62B |
| 17         | Adiantone  | −17.99                        | ![Adiantone Diagram](image) | H-bond: Arg 36  
Pi-alkyl: Ala 64  
Van der Waals: Leu 35, Asn 61, Val 62, Asn 62A |
| 18         | Solaniol   | −17.44                        | ![Solaniol Diagram](image) | H-bond: Asn 61, Asn 62A, Val 62  
Van der Waals: Ala 60, Val 62B |
| Serial No. | Compound                  | (C-Docker Interaction Energy) | 2D Interaction Diagram * | Type of Binding                           |
|-----------|---------------------------|-------------------------------|--------------------------|-------------------------------------------|
| 19        | N-acetyl cysteine         | $-17.25$                      | ![Diagram](image1)       | H-bond: Asn 61, Asn 62A ($\times 3$)\nVan der Waals: Val 59, Ala 60, Val 62, Val 62B |
| 20        | Berberine                 | $-16.59$                      | ![Diagram](image2)       | H-bond: Val 59, Asn 61, Val 62B\nVan der Waals: Ala 60, Val 62, Asn 62A |
| 21        | Alliin                    | $-15.63$                      | ![Diagram](image3)       | H-bond: Asn 61, Val 62, Asn 62A\nVan der Waals: Val 59, Ala 60, Val 62B |
| 22        | S-methyl-L-cysteine       | $-14.29$                      | ![Diagram](image4)       | H-bond: Asn 61, Asn 62A, Val 62           |
Table 4. Cont.

| Serial No. | Compound          | 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 | 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

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