

NATURAL PRODUCTS FOR TREATMENT OF SKIN AND SOFT TISSUE DISORDERS

The background of the cover is a light blue gradient with vertical stripes. In the center, there is a large, faint illustration of a skin cross-section showing various layers and structures. Overlaid on this are several green leaves of varying sizes and orientations, some appearing to grow from the bottom left. A complex molecular structure, consisting of interconnected spheres and lines, is positioned in the middle of the skin cross-section. The overall aesthetic is clean, scientific, and natural.

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Natural Products for Treatment of Skin and Soft Tissue Disorders

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FOREWORD

I am very happy and honored to write a foreword for the book titled "Natural Products for Treatment of Skin and Soft Tissue Disorders" which will be edited by three prestigious scientists, Dr. Heba Abd El-Sattar El-Nashar, Dr. Mohammed El-Shazly, and Dr. Nouran Mohammed Fahmy and published by Bentham Science Publishers.

The book will be very useful as an important textbook and guideline in the field of natural products for skin care and disorders. It is a comprehensive book with content from tiny acne to serious cancer, from natural products to nanoparticle formulation, as well as from protection to clinical treatment. In addition to professional editing, many distinguished professors will be involved and contribute their knowledge and promising ideas to this cherished book.

I am very honored to introduce and recommend this book edited by my good friends. They are not only excellent scientists but also professional and talented in scientific writing that will fulfill readers' expectations.

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PREFACE

Mother Nature has always been the treasure trove for biologically active compounds that helped humanity to survive and thrive. Medicinal plants have played a major role in the development of human civilizations. Since antiquity, humans searched for natural sources to cure diseases, and they found their target in medicinal plants. The Egyptian, Greek, Indian, Chinese, and Aztec civilizations relied heavily on the use of medicinal plants to cure human and animal ailments. Medicinal plants have been used to treat all types of disorders, including cardiovascular, digestive, skin and kidney disorders. Skin disorders differ from other disorders by being external, can be detected by the naked eye, medicinal plant extracts can be easily applied to the disorders and the healing effect can be easily tracked. Skin is the largest organ in the human body and the first line of defense against traumas, infections and radiation. Skin is a dynamic organ with millions of cells dying and regenerating regularly. It is affected by a plethora of disorders and should be treated to avoid the spread of invasion to internal organs.

Medicinal plants have been used to treat skin disorders and to improve skin condition. They have also been used in cosmetic preparations to remove wrinkles, black spots and provide a radiant appearance. In the current book, we take the reader on an enjoyable journey of medicinal plants treating skin-related disorders. The first chapter deals with “Eczema, etiology and treatment”. Eczema is not a condition but a group of skin diseases that cause skin inflammation and irritation. It exists in seven different forms with different signs and symptoms. Eczema, also called Atopic dermatitis (AD), is its most prevalent and popular form, with a high global burden in morbidity and health-care costs. It is a chronic recurrent skin inflammatory disorder characterized by itching, redness, and burning sensation of dark or light patches or crusting eruptions of the skin. The second chapter discusses “Superficial mycoses as a challenging skin disorder”. Superficial mycoses of skin, nails and hair caused by dermatophytes, non-dermatophyte molds, yeasts and yeast-like fungi are among the common morbidities that invade particularly in tropical countries. Various antifungal agents, including polyenes, fluoropyrimidines, echinocandins, and azoles, have been commonly used, topically and/or orally, for the treatment of superficial mycoses. The third chapter focuses on “Acne and current possible treatments”. Acne vulgaris is one of the skin diseases related to the sebaceous gland, characterized by multiple pathogenic factors. The treatment strategies involve the blockage of these pathological factors. Conventional therapies for the treatment of Acne vulgaris in controlling its pathological factors are still inadequate in providing therapeutic effectiveness and exhibit remarkable side effects. The fourth chapter concentrates on “Vitiligo and treatment protocols”. Vitiligo is an abiding acquired skin disorder caused by the epidermal disappearance of pigment cells of localized and general skin mucosa, characterized by the appearance of symmetrical patches on the skin. The exact cause of this disorder is unknown, but genetic susceptibility, melanocyte growth factor deficiency, autoimmunity, and some neurological and environmental factors are believed to play a triggering role. The fifth chapter summarizes “Atopic Dermatitis Prevalence and How to manage it”. Atopic dermatitis is a common inflammatory skin disorder characterized by recurrent eczematous lesions and intense itch. The disorder affects people of all ages and ethnicities, has a substantial psychosocial impact on patients and relatives, and is the leading cause of the global burden of skin disease. Moreover, the persistence of atopic dermatitis has been reported in 60% of adults who had the disease as children. The sixth chapter deals with “Epidemiology, diagnosis, and policy framework for prevention and treatment schemes of skin infections in developing countries”. Skin disease (SD) infections are a common public health problem in developing countries. The prevalence is universal and can cause a significant economic burden. Besides, it is considered an essential source of morbidity among

special groups like children and affects all ages and ethnicities globally. However, the impact of SD on the national public healthcare system is complex and poorly studied up-to-date, especially in developing countries. Moreover, the trends of SD have changed due to population aging, genetic and environmental factors. The seventh chapter discusses “Skin cancer as an emerging global threat and potential natural therapeutic”. Global advancement is facing a huge threat due to rising cases of skin cancer and potential health-system costs. Perception of skin cancer prevalence is important for the treatment, prevention strategies, and administration of medical allowances. In addition to fair and tanned skin being a risk factor for the development of disease, sedentary lifestyle habits and reduction in physical activities have increased the mortalities worldwide. This effort signifies information on the incidence, risk factors and mortality rates across six continents. The eighth chapter summarizes “Skin ulcers as a painful disorder with limited therapeutic protocols”. A skin ulcer is a type of open wound on the skin caused by injury, poor circulation, pressure, or infection. Specific forms of wounds are described using distinct terms, such as surgical incision, burn, and laceration. Skin ulcers can be extremely painful and take a long time to heal. They can become infected and cause other medical complications if left untreated. Treatment for skin ulcers is diagnosed on the basis of the ulcer as well as the underlying cause. However, there is still a shortage of efficient medicine in the skin ulcer treatment guidelines since wound management consists only of wound dressing, antibiotics, and pain control.

We covered in this book a wide array of skin disorders and how to treat them using medicinal plants. We included researchers from different countries to discuss their experience in using medicinal plants for the treatment of skin disorders. This book will guide researchers all over the world to understand the value of medicinal plants in treating skin disorders and how to move forward in their research.

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Dedication

To

THE SOUL OF MY FATHER,

Who taught me to trust in ALLAH,

encouraged me to believe in myself.

MY MOTHER,

A strong woman whose loving spirit always sustains me.

&

MY HUSBAND AND MY LITTLE ANGLE LAYLA

A constant source of love, concern, support, strength, never-ending motivation, and patience.

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Eczema, Etiology and Treatment

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Abstract: Eczema is not a condition but a group of skin diseases that causes skin inflammation and irritation. It exists in several different forms, and each form has its signs and symptoms. Eczema is also referred to as Atopic dermatitis (AD), which is its most prevalent and popular form, with a high global burden in morbidity and health-care costs. It is a chronic recurrent skin inflammatory disorder that is characterized by itching, redness, burning sensation of dark or light patches, papular bumps and weeping or crusting eruptions of the skin. Pathophysiology of AD is complex and multifactorial, involving genetic predisposition, skin barrier defects, immunological dysfunction and regulation, microbial colonisation, neuroinflammation, altered lipid composition, food allergies and other environmental risk factors. Currently, available treatment regimens, which include corticosteroids, calcineurin inhibitors, antibiotics, immunomodulatory agents, UV therapy, may offer some relief to patients, but there is no permanent cure for the disease. Specific cases may additionally need psychosomatic counselling (in stress induces exacerbations), Monoclonal antibodies targeting T-helper 2 pathways and aeroallergens, which may improve the condition of associated asthma or rhinitis. To minimize the side-effects caused by conventional treatments such as skin atrophy, telangiectasia, lymphomas and malignancies, Novel jakus kinase (JAK) receptor inhibitors are under development which are believed to show promising effects in treating AD. Traditional Chinese herbs, used widely, have revealed some supplementary activity in reducing the severity of AD. Tapinarof, a naturally derived stilbene that activates aryl hydro carbon receptor (AHR) and triggers inflammation, has shown significant results in AD and psoriasis patients. Homeopathy, aroma therapy, essential oils, essential fatty acids, vitamins and minerals, have also been exemplified to aid clinical AD treatment.

Keywords: Atopic dermatitis, Calcineurin inhibitors, Corticosteroids, Cutaneous microbiome, Dupilumab, EASI, Eczema, Filaggrin, Immune dysregulation, JAK receptor inhibitors, Monoclonal antibodies, Phototherapy, SCORAD, Traditional herbs.

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INTRODUCTION

Eczema is not a condition but a reaction pattern associated with a group of skin diseases that causes skin inflammation and irritation [1]. Eczema is also referred to as Atopic dermatitis (AD), which is its most prevalent and popular form, with a high global burden in morbidity and health-care costs [2]. AD may or may not occur as Triad, *i.e.*, in association with asthma and hay-fever (Atopic march). It starts at an early age and thus predominantly affects children and infants more than adults. About 1/3rd of children with AD develop asthma in later life [3]. It is a non-contagious, chronic recurrent skin inflammatory disorder, which is characterized by intense itching, redness, and burning sensation of dark or light patches, or popular bumps [4], and is associated with a dramatic decrease in the quality of life and high sleep disturbances [5]. It can exacerbate exposure to different things, including allergens, such as pet dander or dust mites and other common triggers, like harsh soaps, detergents, chemicals, perfumes, *etc.*

The pathophysiology of AD is complex and multifactorial. Immunologic findings in AD include raised immunoglobulin E (IgE), eosinophils, spontaneous histamine release from mast cells, and T-helper 2 (Th2) cells secreting interleukin-4 (IL-4) and IL-5, and decreased numbers of Th1 cells secreting interferon- γ [6]. The “inside-out” hypothesis suggests that the disease is primarily cytokine-driven, with resultant reactive epidermal hyperplasia caused by immune activation. Corticosteroids and Calcineurin inhibitors are still the mainstays of treatment. However, novel treatment modalities along with herbal treatment, can provide alternate options for reducing disease progression.

Diagnosis

Diagnosis is mainly based on examining the patient skin and reviewing medical history. Following tests that detect specific IgE levels to allergins are conducted on patients to rule out other skin diseases or identify conditions that accompany eczema [6].

Atopy Patch Test (APT)

The APT is based on T cell–a specific response to the application of allergens on the healthy skin of the patient's back or forearm, where an eczematous reaction is read after 48 and 72 hours when it is positive. That method is used to assess sensitization for aeroallergens in AD patients and is not aimed for healthy individuals, asthmatic patients, or patients with rhinitis.

Skin Prick Tests (SPT)

The SPT value is variable in diagnosing food allergies. The history of the disease and the SPT values of specific IgE are important in the diagnosis of early sensitization, but the diagnosis is more problematic for the late type of allergic manifestation, especially to food allergens.

The late type requires a patch test, an APT skin application food test (SAFT), and an exposition test such as the open test, single-challenge test, or double-blind placebo-controlled food challenge test (DBPCFC). The latter is the gold standard procedure for diagnosing food allergies. A combination of SPT and APT significantly enhance the accuracy in the diagnosis of specific food allergies in infants with AD or digestive symptoms [7]. These methods are costly, time-consuming and often inconvenient to patients.

Severity Scoring of Atopic Dermatitis (SCORAD)

This method is used to detect the severity of AD, and it's useful for clinical trials. In this method, three elements of eruptions, *i.e.*, erythema/acute papules, exudation/ crusts, chronic papules/lichenification/nodules, are measured in the five areas of eruption head/neck, anterior trunk, posterior trunk, upper limbs and lower limbs. The severity score for each body region is given as 0 (for absent), 1 (for mild), 2 (for moderate), 3 (for severe) and 4 (very severe). The highest possible score is 20 (5 areas and 4 degrees). When the evaluation of the area of eruption is done considering all three elements for all five body regions, the highest score is 60 points [8].

Modern image processing and computer algorithm have also been used for automatic eczema detection and severity measurement models. This system can successfully detect regions of eczema and classify the identified region accordingly based on image color and texture features. Then the model automatically measures “Eczema Area and Severity Index (EASI),” by computing skin parameters - eczema affected area score, eczema intensity score, and body region score of eczema, allowing both patients and physicians to accurately assess the affected skin [9]. This method is non-invasive, fully automatic, precise, accurate, and efficient in diagnosing AD.

TYPES OF ECZEMA

The earliest classification of eczema was based on the presence/detection of IgE antibodies and was of 2 types intrinsic or non-allergic form and extrinsic or allergic form [10]. Later, Kursel *et al.* conducted a study in support of two variants of eczema, by providing generalised risk factors [11]:

Superficial Mycoses as a Challenging Skin Disorder

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Abstract: Superficial mycoses of the skin, nails and hair caused by dermatophytes, non-dermatophyte molds, yeasts and yeast-like fungi are among the most common morbidity of the skin, especially in tropical regions of the world. Various antifungal agents, including polyenes, fluoropyrimidines, echinocandins, and azoles, have been commonly used, topically and/or orally, for the treatment of superficial mycoses. Nevertheless, the conventional treatment guideline is not always successful due to drug resistance as well as the possibility of drug interactions and side effects. Recently, the search for new antifungal compounds, such as naphthoquinones, anthraquinones, terpenoids, saponins and flavonoids from medicinal plants toward novel drug development, has attracted a lot of attention. This chapter describes the common superficial mycoses as well as their pathophysiology, epidemiology and current treatment options. Promising herbal extracts or phytochemicals and their products used as therapeutic alternatives for combating superficial mycosis are also highlighted.

Keywords: Antifungal, Candidiasis, Dermatophytes, Phytochemicals, Superficial mycoses, Tinea versicolor.

INTRODUCTION

Fungi are microorganisms in a group of eukaryotes characterized by a complex cellular organization. Notable examples of fungi include organisms such as yeasts, rusts, smuts, mildews, molds, and mushrooms [1, 2]. Fungi can infect and are capable of causing diseases in plants, animals and humans. More than 100,000 species of fungi have been identified as the cause of various diseases [3]. Superficial fungal infections or superficial mycoses is a common skin, nail, and hair diseases caused by pathogenic fungi. The major pathogenic agents of superficial fungal infections consist of dermatophytes, non-dermatophyte molds,

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yeasts, and yeast-like fungi [4]. Dermatophytes are fungi that use keratin for growth. Three genera of dermatophytes, namely *Trichophyton*, *Microsporum*, and *Epidermophyton*, are commonly found to be the major cause of superficial fungal infections. Less commonly found in superficial mycoses are the non-dermatophyte fungi, including *Cladosporium* spp., *Neoscytalidim dimidatum*, and *Alternaria* spp. Additionally, yeasts and yeast-like fungi are accounted as a cause of superficial mycoses. Among the yeasts, *Candida* spp. and *Malassezia* spp. are considered to be the most common fungal infectious diseases in humans. Yeast-like fungi such as *Kodamaea ohmeri*, *Geotrichum* spp. and *Cryptococcus* spp. have also been reported as another common cause of superficial mycoses [5, 6].

Superficial mycoses do not only cause cosmetic disfigurement, but also affect the function of infected organ systems. Although superficial mycoses rarely induce life-threatening symptoms, they are still a major problem globally due to their high worldwide incidence rate, particularly in tropical countries [6]. Generally, topical and systemic antifungal agents, including polyenes, fluoropyrimidines, echinocandins, and azoles along with good personal hygiene practices, are commonly recommended as standard treatment guidelines for superficial mycoses [7]. However, these treatment guidelines are not always successful, because of the increasing incidence of anti-fungal drug resistance as well as the possibility of side effects and drug interactions [8]. Recently, the use of natural compounds, particularly phytochemicals, has attracted intense research interest and proposed as pragmatic alternative antifungal agents due to their unique and diverse mechanisms of action along with lower adverse effects. Various phytochemicals, including naphthoquinones, anthraquinones, terpenoids, saponins and flavonoids, have been reported for their anti-fungal potential in drug development [9].

This chapter aims to describe the common characteristics of superficial mycoses as well as their pathophysiology, epidemiology, and current treatment options. Furthermore, the recent targeted drug development from herbal extracts and the promising phytochemicals as well as their innovative products potentially used as alternative therapeutic agents for superficial mycoses treatment, are also highlighted.

SUPERFICIAL MYCOSES AND PATHOPHYSIOLOGY

Superficial mycoses are conditions of fungal infections of the skin, hair, and nail that are usually limited to the stratum corneum and the superficial layers of the skin, and infrequently invade the dermis. It can be classified into two main groups according to its pathogenesis, *viz*: non-inflammatory infections (pityriasis versicolor, tinea nigra, piedra) and inflammatory infections (dermatophytosis, tinea capitis, tinea corporis, tinea cruris, tinea pedis, tinea unguium, tinea barbae,

tinea imbricata, and candidiasis) [6, 10]. Generally, superficial mycoses are not life-threatening diseases. However, it may affect internal organs in exceedingly rare cases. Pathophysiology of the most common superficial mycoses, including pityriasis versicolor, dermatophytosis, and candidiasis, is summarized as follows.

Pityriasis Versicolor

Pityriasis versicolor is mainly caused by *Malassezia*, a genus of yeast that is normally found on the superficial area of humans. Recently, more than ten species of *Malassezia* have been reported as the main cause of most cases of pityriasis versicolor, particularly *Malassezia furfur*, *M. globosa*, and *M. sympodialis*. Transformation of *Malassezia* from normal skin flora to its pathogenic counterpart is a key pathway toward the development of superficial mycoses [11, 12].

Due to the general lipophilic properties of *Malassezia*, the seborrheic areas of the body, such as the upper back and chest, face and forehead, are usually colonized by the yeasts [13]. Overgrowth of the yeasts, particularly in hot, humid conditions, hyperhidrosis, and the use of topical skin oils, promote the production of dicarboxylic acids such as azelaic acid. This suppresses the activity of the tyrosinase enzyme, thereby causing depigmentation [14]. Pityriasis versicolor occurs more commonly in immunocompromised hosts, indicating that a patient's immune system may be another important factor in the pathogenesis of this disease [15].

Dermatophytosis

Dermatophytosis is a fungal infection of the cutaneous area that is normally caused by a dermatophyte. The categorization of dermatophytes is dependent on their normal habitat, including human (anthropophilic species) animals (zoophilic species) or soil (geophilic species), and site of infection, for example, scalp hair (tinea capitis), beard hair (tinea barbae) and nails (tinea unguium or dermatophyte onychomycosis). Three main genera of dermatophytes, *i.e.*, *Trichophyton*, *Epidermophyton* and *Microsporum*, commonly invade human keratin and cause dermatophytosis [6, 16].

The process of dermatophyte infection in humans consists of three major steps, namely adherence, invasion, and development of a host response, respectively. In the beginning, dermatophytes contact and adhere to keratinized tissue, then degrade keratin and penetrate into the stratum corneum area by producing a variety of virulence factors. After the invasion step, antigenic compounds such as chitin and glucan, as well as the metabolites produced by dermatophytes-induced host cells, *e.g.*, glycopeptides, peptides and carbohydrates, stimulate the response

Acne and Current Possible Treatments

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Abstract: Acne vulgaris is one of the most skin diseases related to the sebaceous gland, characterized by multiple pathogenic factors. The treatment strategies involve the blockage of these pathological factors. Conventional therapies for the treatment of Acne vulgaris in controlling its pathological factors are still inadequate in providing therapeutic effectiveness and exhibit remarkable side effects. New therapeutic agent development for acne treatment is still stagnant. Recently, researchers have been focusing and seeking great interest in the treatment of acne through natural products – as a new therapeutic option. In this regard, multiple natural products have been evaluated for their potential to treat acne, including berberine, α -mangostin, curcumin, ampelopsin, fustin, ellagic acid, gallic acid, myricetin, lupeol and many more. These natural products have been reported as suitable candidates for blocking multiple pathogenic factors associated with acne. In addition, the nanotechnology-based delivery of natural products is a new platform and treatment option for Acne vulgaris. Natural products nano-based delivery resolves many other issues concerned with natural products apart from treatment aid. Natural products, therefore, pose a precious source in determining new agents for the treatment of acne. However, reported studies are preclinical, and to obtain reliable and conclusive results, further clinical studies are required to uplift natural products from bench top to clinical setup in treating the worst consequences of Acne vulgaris.

Keywords: Acne, Pathological factors, Treatment, Natural products, Nano-delivery.

INTRODUCTION

Acne vulgaris is a disease of pilo-sebaceous follicles characterized by chronic inflammation. It's a multi factorial and most prevalent skin disorder affecting people of all ages and ethnic [1, 2]. Acne vulgaris, irrespective of nationality, sex and socioeconomic status, is mostly concerned with adolescence, which is attribu-

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ted to androgen production during puberty [3]. Acne incidence is greater in women (12%) than in men, and in the US, the cost of acne treatment is about 3 billion dollars per year [4, 5]. However, acne vulgaris is not a life-threatening complication since it leads to normal activities disturbances like anxiety and lack of self-confidence [6].

Multiple pathological factors are involved in the development of acne, including colonization and proliferation of *Propionibacterium acnes*, excessive production of sebum, acquired and innate immunity and abnormal hyperkeratinization of follicles [7]. In addition, acne lesions are developed and affected by family history and diet as well [8]. It is very necessary to develop a new pharmacological intervention for the management of acne to cope with current related problems like lack of confidence, to improve quality of life, to boost the lack-response, and more specifically, to bypass the problems and complications associated with drug therapy [9].

Among conventional therapies, hormonal therapy is one of them. Spironolactone, flutamide and cyproterone acetate were used as androgen receptor blockers for the treatment of acne [10]. Laser and light-based therapies have been explored for acne treatment along with pharmacological measures to synergize the effect [11]. Topical, systemic and antibacterial conventional therapies were carried out for the treatment of acne; however, age, site of acne lesion and types as well are risk factors for consideration. In addition, different barriers in conventional therapies have made it quite challenging, and failure of therapy has been observed [12]. Thus there is a need to select alternate therapy choices for acne treatment that might be effective with clinical significance and reduced side effects.

It is obvious that phytochemicals used for the treatment of acne are hydrophobic, and mostly that exhibit low penetration as well as reduced bioavailability or/and low availability at the target side [13]. Some of them are concerned with worse adverse effects. All these barriers are associated with conventional therapy for acne as well. To overwhelm these problems, nanotechnology is an effective platform that deals effectively with them [14]. In acne treatment, topical formulations from nanoplatforms were evaluated mostly, showing clinical significance with reduced side effects. Nano gels and emulsions have shown optimal therapeutic outcomes topically with efficient penetration. Phytochemical nanoparticles have also shown remarkable outputs in the form of nano structure lipid carriers and niosomes as well [15, 16]. Therefore in recent research, nanoformulations for phytochemicals were extensively carried out and evaluated.

In addition to nano-based formulations, phytochemicals were directly employed for the treatment of acne. Different classes of phytochemicals, mostly in topical

gels and cream form, showed desired therapeutic outcomes. This book chapter highlights the role of phytochemicals as a source of current possible treatments for acne. Apart from it, phytochemicals in nano form also act as a newer approach for the treatment of acne that covers prominent problems associated with phytochemical therapy and provides certain effective outcomes to phytochemical-based therapy that pave the way for acne treatment.

Conventional Therapies for Acne

Focusing lesions associated with acne vulgaris were treated in women with oral contraceptives containing a combination of progestin and estrogen. Results of a meta-analysis study revealed that using combination hormonal therapy for acne lesions, a 62% reduction in inflammation related to acne was observed [17]. Due to optimal therapeutic outcome, FDA has approved combination hormonal therapy for acne treatment, *i.e.*, ethinyl estradiol–drospirenone, ethinyl estradiol–norgestimate, ethinyl estradiol–norethindrone [18]. Spironolactone, due to its antiandrogen activity, has been evaluated for anti-acne potential. Observational and retrospective data showed that it is effective in the treatment of acne, particularly in females [19].

In case of moderate to severe acne problems, oral antibiotics were used to deal with the concerned inflammation however, due to increased oral antibiotic resistance, the therapy was switched to systemic therapy [20]. The systemic administration of antibiotics for acne treatment was favored by using benzoyl peroxide and retinoids as a part of combination therapy. Such a combination therapy in clinical trials was assessed and resulted in a 60% reduction in acne lesion inflammation within a time period of three months [21]. The concentration of Cutibacterium acne was effectively reduced after treatment with tetracycline. So tetracycline is another alternative and can be prescribed for acne treatment [22]. However, it needs to be taken on an empty stomach and inconsistent bioavailability limit its use in acne treatment. In addition to tetracycline, other antibiotics used for the treatment of acne include macrolide, penicillin, cephalosporin, and trimethoprim–sulfamethoxazole [23].

Topical retinoid is another choice for the treatment of acne vulgaris however, it still has taken the tag of underprescribing by dermatologists and health care providers. Topical retinoid can be used in combination with isotretinoin and tazarotene. Such a combination exhibit photosensitizing activity, however, it can be overcome by the use of sunscreen [24]. In addition to topical retinoids, topical antimicrobial agents are also used for the treatment of acne vulgaris [25]. Clindamycin and erythromycin are effective as topical antimicrobial agents. However, its worth to mention that individual antibiotics face the problem of

Vitiligo and Treatment Protocols

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Abstract: Vitiligo is an abiding acquired skin disorder caused by the epidermal disappearance of pigment cells of localized and general skin mucosa, characterized by the appearance of symmetrical patches on the skin. The exact cause of this disorder is unknown, but genetic susceptibility, melanocyte growth factor deficiency, autoimmunity, and some neurological and environmental factors are believed to play a triggering role. Although no drugs are completely successful in managing this disorder, many different approaches, such as topical corticosteroids, calcineurin inhibitors, transplantation, newly emerged phototherapy, or the combination approaches, however, have shown positive results and have helped to restore skin tone in people with small areas of depigmentation. The association of the adverse effects such as redness, itching, burning, pruritis, xerosis cutis, or potential risk of skin cancer and the high treatment cost with these therapies has necessitated the development of other newer treatment approaches such as phytotherapy for vitiligo. Also, novel drugs are being developed that either stimulate the melanocytes, like afamelanotide, or help control or protect the melanocytes. Many herbal drugs have been reported beneficial in the treatment of vitiligo, which has been shown to stimulate melanogenesis, proliferation or migration of melanocytes or have immunomodulatory properties. Further research on herbal drugs should be extended to develop safe, effective and affordable treatments for vitiligo.

Keywords: Afamelanotide, Corticosteroids, Depigmentation, Herbal drugs, Melanocyte growth factor, Phytotherapy, Skin patches, Vitiligo.

INTRODUCTION

Vitiligo is a progressive disorder of the skin characterized by delineated white lesions of inconstant size and shape. The appearance of these patches has been attributed to the selective loss of skin pigment cells (melanocytes), which in turn makes skin more prone to sunburn, aging and cancer. Although the exact etiology

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of the disease is unknown, the progression of the disease might be due to some autoimmune, neural and biochemical mechanisms. It affects nearly 1-2% of the world population, mostly before adulthood, with high psychiatric morbidity and can be socially distressing for the affected individuals [1, 2]. The incidence of vitiligo in India has been reported between 0.25-4% in dermatology outpatients across India and up to 8.8% in Rajasthan and Gujarat [3]. With proper management and supervision, disease progression can be abated, and patients may attain repigmentation in order to restore the functional deficiencies and morphology of the depigmented areas [1]. Topical corticosteroids and calcineurin inhibitors have proved effective first-choice treatments for localized forms of this disease. However, in generalized form, phototherapy has revealed exceptional efficacy [4]. Light therapy (UVB) alone has shown better repigmentation rates and safety profiles in comparison to topical or oral psoralen and UVA combination (PUVA). Alternative treatment options include transplantation methods, depigmentation therapies, and other novel therapeutic approaches such as focused microphototherapy, systemic antioxidant therapy, *etc.* [1]. Many herbal drugs have been reported beneficial in the treatment of vitiligo, which has been shown to stimulate melanogenesis, proliferation or migration of melanocytes or have immunomodulatory properties [5]. In recent years, efforts to discover and develop new, safe, affordable, and effective vitiligo drugs from natural sources have gained much attention among researchers due to the recognition of the worldwide importance of fighting vitiligo disease.

ETIOLOGY

Despite the numerous efforts, the exact etiology underlying the disease is still unclear. However, several hypotheses regarding the loss of melanocytes have been put forth, but none of these hypotheses could clearly explain the complete spectrum of this disorder. The key factors that might play a triggering role in the progression of disease include genetic factors, neural factors, autoimmune factors, some self-destructing precursors of melanogenesis and defective melanocyte growth factor [1]. Nearly one-third of vitiligo-affected individuals have reported close family members affected by the disorder signifying that genetic factors have very important role in the pathogenesis of the disease [6]. Most recent theories in the pathophysiology of vitiligo include oxidative stress and accumulation of hydrogen peroxide (H_2O_2) in the epidermal layer of depigmented area. Oxidative stress theory states that oxygen radicals are the main reason for the apoptosis of melanocytes. Free radical levels may rise either due to an increase in the rate of their production or the reduced ability of cells to neutralize them [7]. In addition, accumulation of high levels of H_2O_2 in the epidermis is destructive for melanocytes, inhibits tyrosinase enzyme, and also disables catalase which is a

peroxisomal enzyme catalyzing the reduction of H_2O_2 to water and oxygen. Such disparity between oxidative stress and antioxidant enzyme systems plays a significant role in the destruction of melanocytes [8, 9].

TYPES

The main types of vitiligo include [1, 10, 11]:

- i. **Segmental/Localized Vitiligo:** It is the least common pattern, which mainly includes focal, segmental (limited to a particular section of the integument), and mucosal lesions often following the distribution of trigeminal nerve but do not progress to a generalized form.
- ii. **Generalized/Non-Segmental Vitiligo:** It is the most common pattern which corresponds to all generalized symmetrical forms, including acrofacial, vulgaris and mixed acrofacialis and/or vulgaris and/or segmentalis form.
- iii. **Universal Vitiligo:** It is a rare type of vitiligo, and comprises >80% depigmentation.

TREATMENT

In spite of tremendous efforts, vitiligo treatment modalities are still derisory for the patients as most physicians contemplate it as a trivial form of the disease, which cannot be completely treated, and the patient has to live with it for a lifetime. This approach towards the disease makes the patient feel discouraged from seeking therapy. There must be a proper approach to explaining the disease and its treatment to the patient. Although there is no appropriate therapeutic cure for the disease, several conventional (Fig. 1), novel treatment protocols (Fig. 2) and herbal drugs which are being used for the treatment of vitiligo have revealed promising results in most patients.

Atopic Dermatitis Prevalence and How to Manage It

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Abstract: Atopic dermatitis (AD) is a common inflammatory skin disorder characterized by recurrent eczematous lesions and intense itch. More precisely, the earliest lesion is a small erythematous papule or papulovesicle. These papules may then later become erythematous plaques with clinical features of weeping, crusting, or scaling, depending on the severity of the lesions. The most problematic symptom of AD is itch. The “itch-scratch” cycle involves the act of scratching affected areas of the skin to relieve AD-associated itch, which can further worsen the disease.

This skin disorder affects people of all ages and ethnicities, has a substantial psychosocial impact on patients and relatives, and is the leading cause of the global burden of skin disease. Moreover, AD persistence has been reported in 60% of adults who had the disease as children.

AD is associated with an increased risk of multiple comorbidities, including food allergy, asthma, allergic rhinitis, and mental health disorders. The pathophysiology is complex and involves a strong genetic predisposition, epidermal dysfunction, and T-cell-driven inflammation. There is increasing evidence that AD involves multiple immune pathways. Currently, there is no cure, but increasing numbers of innovative targeted therapies hold promise for achieving disease control. As effective medical treatments for this condition are limited in number, many patients have turned to alternative therapies, including so-called natural products, such as herbs and algae. In this chapter, we summarized and discussed advances in the understanding of the disease and its implications for prevention, management, and future research, with a focus on natural solutions.

Keywords: Atopic dermatitis, Filaggrin, Genetic, IgE, Microbiota, Natural solutions, Skin barrier, Treatment, Th2.

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INTRODUCTION

Prevalence and Economic Impact

Atopic dermatitis (AD) is one of the most common inflammatory skin diseases, often of early-life onset, for which the prevalence continues to increase in industrialized countries [1]. The prevalence of AD in adults ranges from 2% to 10% (reported by the World Allergy Organization), and from 15% to 20% in children [2, 3]. Both sexes are affected, and the prevalence varies among races and ethnic groups. While the majority of patients (>85%) develop AD within the first 5 years of life, only half achieve significant improvement by 7 years of age [4]. It is important to note that the risk of atopic eczema is 40% for children with one atopic parent. When both parents are affected by the same manifestation of atopy (*i.e.*, father and mother with atopic eczema), the risk is between 70% and 80%. This prevalence has increased by 2 to 3-fold during the past decade in Western countries [5]. Although the cause of this increase remains unknown, the role of the microbiome in the pathogenesis of AD has been suggested [6].

It is well established that AD has large cost implications, as the disease clearly causes a major financial burden to both individual families and national healthcare systems. Aside from its economic cost, this skin disease bears a significant burden on society. However, assessing the economic burden of AD is complex as it consists of costs for medical care and non-medical care as well as indirect costs (*i.e.*, loss of education and workdays), given that the degree to which medical costs are an individual (out-of-pocket) burden or a collective burden largely depends on each country's respective healthcare system. More precisely, direct costs include prescription medicines, visits to health care providers, hospitalizations, and transportation. Indirect costs include missed days or lost productivity at work or school, career modification, and reduced quality of life [7].

The diversity of the healthcare system of each country is reflected in several studies. Two studies from the USA reported direct and indirect costs of approximately USD 3300 per person per year (PPPY) for children [8] and adults [9]. Three European studies reported out-of-pocket costs for medical care as €351 PPPY for French adults and €927 for adults with moderate-to-severe AD in nine European countries [10, 11]. The burden of AD can also be evaluated using the disability-adjusted life-years (DALYs), a measure of the difference between living a life in perfect health *versus* living with the disease. This measure is the sum of the years of life lost due to premature death and the years lived with a disability within a given population [12]. These authors noted that AD has the highest DALY burden of all skin diseases and ranks 15th among all nonfatal diseases

globally. A total of five European countries rank top in age-standardized DALYs: Sweden, the UK, Iceland, Finland and Denmark. However, it appears that the global burden of AD expressed in DALYs remained stable during the data collection period from 1990 to 2017 [12].

Generally, healthcare costs continue to rise around the world. Finding ways to reduce costs by more efficiently managing AD will continue to be important for physicians, patients and society. By reducing the incidence of AD, it is possible that fewer patients will require more expensive interventions, which is of particular concern as emerging biologics become available for this disorder.

ETIOLOGY AND PATHOGENESIS

AD is an inflammatory, chronically relapsing, intensely pruritic skin disease characterized by dry skin [13]. Furthermore, it is the highest-ranked skin disease with respect to DALYs and years lived with a disease. This pathology is characterized by eczematous, pruritic skin patches and plaques as well as itching that can severely affect quality of life [14]. Furthermore, the itch has been associated with mental distress and increased risk for suicidal ideation in those with AD [15]. Of note, emotional stress has also been shown to increase itching, implying a bidirectional relationship between these features [16].

Nevertheless, AD is a “diffuse” skin condition. The definition of the whole disease seems as imprecise as the limits of the affected skin areas. Sometimes the term “involved” skin is questionable, especially when dermato-histopathological investigations show signs of inflammation in also clinically “uninvolved” skin areas. The susceptibility to environmental influences, especially on the psychosocial level, underlines the strong variability of this dermatosis. In addition, this disease manifests itself differently in different age groups and different body regions.

AD is often accompanied by other atopic disorders, such as allergic rhinoconjunctivitis, asthma, food allergies, and less often, eosinophilic esophagitis. These conditions may appear simultaneously or develop in succession.

AD is also associated with sleep disruption (mainly due to pruritus), with worse sleep disruption observed in more severe diseases. In addition, AD is associated with decreased work productivity, depression, and anxiety, all of which carry additional health and economic burdens for patients and their families.

It is also important to note that there is a link between AD and obesity [17]. Indeed, the few investigations addressing AD and obesity in infancy or early

Epidemiology, Diagnosis, Prevention, Policy and Treatment Schemes of Skin Infections in Developing Countries

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Abstract: Skin diseases are common public health problems in developing countries. The prevalence is universal and can cause a significant economic burden. Additionally, it is a common cause of morbidity among vulnerable groups, such as children, and affects people of all ages and ethnicities. However, the impact of skin disease on the national public healthcare system is complex and poorly studied, particularly in developing countries. A number of factors, including population aging, genetics, and environment, have contributed to the change in skin disease trends. The combined effects of these factors have severe health implications for people, and their dynamics are not fully understood. It is thus necessary to improve diagnostic techniques in order to provide new therapeutic resources in dermatology in the wake of the scientific revolution and technological innovations. To understand the changes in the prevalence of skin disease age-specific distributions and associated mortality, this study provides comprehensive information on vulnerable populations, epidemiological characteristics, and geographic distributions. Furthermore, the study provides a baseline for the management of skin disorders using medicinal plants. Surveillance, burden, diagnostics, and treatments of skin disease are essential components of developing measurable, influential, and sustainable intervention programs to reduce disease infections. Furthermore, these approaches assist in understanding the pathogenesis and disease process and assist with the development of new therapeutic strategies and prev-

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entive measures against morbidity in underdeveloped and developing countries, as well as establishing a baseline for medicinal plants that contribute significantly to the treatment.

Keywords: Skin diseases, epidemiology, diagnosis, treatment, quality of life, prevention, herbal plants, developing countries.

INTRODUCTION

The skin is a vital organ in human anatomy and performs essential functions crucial for optimal health. Skin functions are critical for human survival: organ protection, regulating the optimal performance of organs, excretion, and electrolyte balance, among other indispensable roles it plays [1]. The skin composition consists of three layers, such as the Epidermis, Dermis, and Fat layer. While the epidermis is a thin keratinocytes cell composite, the dermis is relatively thick and consists of nerve endings, sweat and oil glands (sebaceous glands), hair follicles, and blood vessels. The fat layer, however, has other peculiar functions equally vital for overall health. The impairment or damage to the skin has general implications for health in the human body. Thus, varying conditions may expose the skin to a degenerative state that subsequently results in skin diseases.

Skin disease is a health problem that has triggered severe public health concerns in developing countries [2] and has been plaguing the region for more than a century. The prevalence has consistently affected livelihood, mental health, and overall quality of life in the region [3 - 5]. It is also considered the most common dermatological problem aggravated by migration due to overexposure to the sun and insect bites. Consequently, there are shreds of evidence of considerable morbidity and mortality globally [6]. They are by far the leading cause of an increase in the death rate in developing countries compared with developed countries. Advancements in technology and medical discovery have made it possible to put numerous infectious diseases under control, coupled with improvements in hand and personal hygiene and nutrition and the availability of anti-infective chemotherapy and preventive measures, such as the discovery of vaccines for different skin diseases [7]. There is various evidence of skin diseases affecting all genders, and ages from different countries and ethnic groups; approximately 70% of people in developing countries suffer from skin diseases at some time in their lives [8]. The majority seek medical consultation because of the self-limiting nature of disease or self-treatment options for many people. The prevalence of skin diseases significantly impacts individuals, families, and patients' social lives, and the heavy economic burden on the health community and public health. The prevalence of skin diseases is associated with people's

socioeconomic status globally [9], and there is a need to craft a road map and improve on early detection, treatment, and control, especially in the resource-poor region [10, 11].

This chapter explored the epidemiology of skin diseases and the various forms of manifestation evidenced in developing countries. The epidemiology expanded on the most common skin diseases and among whom they are most prevalent. The part consolidated on the risk factors of skin diseases, beginning from bacteria-associated skin diseases and down to autoimmune and environmental-triggered skin diseases. Other parts explored various options available for diagnosing and treating skin diseases and the implementation modality in practice. The later part of the chapter focuses on skin disease patients' quality of Life (QoL), telemedicine, and other technology applications in skin diseases. Policy implications for skin diseases to improve approaches to skin disease were included to facilitate the improvement of health delivery for skin diseases in developing countries.

EPIDEMIOLOGY OF SKIN DISEASES

The most common manifestations of skin diseases in developing countries are pyoderma, anthrax, cutaneous diphtheria, cutaneous tuberculosis, Buruli ulcer, leprosy, scabies, and pediculosis capitis, leishmaniasis, and cutaneous larva migrans [12]. These skin diseases are further categorized as infectious and noninfectious [13, 14]. Similarly, skin disease prevalence in developing countries is rampant among infants, young and old, males and females alike, depending on their circumstances and experiences.

There are reports of skin diseases such as staphylococcal scalded skin Syndrome in neonates [15, 16]. Of 340 pediatric patients in Tanzania recruited for a study, at least 16.5% reported having at least one skin condition affecting boys and girls. The majority of the skin diseases were due to infections, while 28.5% reported eczematous dermatitis and pigmentary disorders (7.4%) [17]. In the same study, 50.7 were fungal infections, bacterial (29.6%), and viral (19.7%) among those with infectious skin diseases. Other evidence shows an increased prevalence of skin diseases like scabies, impetigo, warts, and tinea capitis among male children than among female school children [18]. Similarly, among outpatients in a Bangladesh health complex, among about 2000 patients enrolled for investigation for skin diseases, approximately 33.02% had a parasitic infection, 28.3% suffered from fungal infection, 20.1% bacterial infection and 43% from some noninfectious skin diseases among them 37.79% had eczema, 17.87% had a papulosquamous disease, 14.25% had acne, 14.01% had urticaria, and 8.7% had vitiligo [19].

Skin Cancer as an Emerging Global Threat and Potential Natural Therapeutic

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Abstract: Background and Aim: Global advancement is facing a huge threat due to the increased number of skin cancer cases and potential health-system costs. Perception of skin cancer prevalence is important for the treatment, prevention strategies, and administration of medical allowances. In addition to fair and tanned skin, the risk factor for the development of disease is sedentary lifestyle habits, and the reduction in physical activities has risen the mortalities worldwide. This effort signifies information on incidence, risk factors, and mortality rates across six continents.

Methodology: The scientific literature was illustrated to find the correlation between the risk factors and resulting data to map, the approaches practiced concerning certain prevention strategies, in particular to alteration in behaviors such as reduction to UV-light exposure, screening and prevention in the progression of the disease.

Results: The incidence of the disease is highest in Australia and New Zealand and lowest in Asian countries. A global survey was done on disease burden in 2018, in which signposts Incidence and mortality are 33.3 ASR and 4.8 ASR, respectively, in New Zealand and 33.6 ASR and 3.2 ASR, respectively, in Australia for melanoma skin cancer. The resistance of skin cancer to topical chemotherapy has turned the attention to natural therapeutics, including herbs, plant extracts and nutraceuticals.

Conclusion: In difficult circumstances, a change in adaptive behavior and cognitive development can reduce the disease burden worldwide. Natural therapeutics can be used to exert anti-inflammatory, anti-proliferative and anti-tumorigenic by modulating the signaling pathways and other physiological effects.

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Keywords: Apoptosis, Anti-inflammatory, Incidence, Melanoma skin cancer, Mortality, Melanocytes, Non- melanoma skin cancer, Natural therapeutics, preventive approaches, Signaling pathways, Risk factors, UV- radiation exposure.

INTRODUCTION

The biggest organ in the human body is skin, which plays an essential role in human health and survival by providing a physical obstruction between humans and the outer environment. This physical barrier formulates a critical first-line defense counter by attacking pathogens and must also protect against a variety of physiochemical factors [1]. Skin cancer is considered the most important type of cancer in Canada which is considered a noteworthy and emergent issue for public health. The Canadian Cancer Society has paid exceptional attention to the statistics report on cancer for 2014. For non-melanoma cancer, 76,100 cases and 440 deaths were calculated, and for melanoma skin cancer, there were about 6,500 new cases and 1,050 deaths [2].

Principal factors of risk for the advancement of numerous kinds of skin cancer include genetic constituents, nature of skin (associated with the capability to tan or burn), and ethnicity or race (strictly connected with melanoma). Compounding the elementary aspects is the extreme exposure to ultraviolet rays, which is among the big physical threats to the advancement of skin cancer in certain racial assemblages. Being the chief professional risk aspect, outdoor employees are more susceptible to emerging skin cancer [3].

Skin cancer has advanced as the most communal malignant disease accounting for 4.5% of all novel cancer cases with an average addition of about a million new cases annually. This prevalence is more supplementary than any other cancer category. It is a life frightening lethal disease whose risk and prevalence has been growing over the last three decades, triggering substantial cost to human well-being and the economy throughout the globe [4].

The highest prevalence of cases of skin cancer in Asia is documented in Kazakhstan, with a population of 23.3 per 100,000 [5]. The approximation for the United States is that one out of five Americans will diagnose with skin cancer throughout their lifespan. In the year 2012, approximately 5.4 million basal cell carcinomas (BCC) and spinocellular carcinomas (SCC) were diagnosed [2]. Every year the appearance of additional cases of skin cancer occurs than all the collective incidences of cancers of the lungs, breast, colon, and prostate. The latest study in the US predicted that in 2012, 5.4 million new cases were spotted among more than 3.3 million individuals [6].

The incidence of skin cancer is very high in many countries, out of which most cases are avoidable. Regardless, the struggles of addressing skin cancer risk factors like intentional tanning activities, insufficient sun protection, rates of skin cancer, and rates of melanoma skin cancer have continued to escalate worldwide. It is important to work with a unified approach, adequate support, and comprehensive and communitywide struggles to eliminate this cancer. Through this kind of commitment and coordination, there can be an achievement in the significant reduction of illness, death rates, and healthcare costs.

Variants of Skin Cancer

Skin cancer is typically assembled into non-melanoma (NMSC) and melanoma (MM). NMSC is further divided into squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Both types of carcinomas advance from the epidermis and contribute 25% and 70%, correspondingly [5].

The (NMSCs) non-melanoma skin cancers include basal cell carcinoma (BCC), which is the most common human cancer in white people. Non-melanoma skin cancer is most commonly diagnosed in men instead of women, and its chances increase with growing age [7]. In the year 2017, there were almost 24.5 million occurrences of cancer cases globally (16.8 million cases without non-melanoma skin cancer (NMSC) and 9.6 million cases of cancer expiries [8].

Melanoma is a destructive malignancy that emerges from the unrestrained division of melanocytes. It contributes to the greater part of skin cancer deaths [9]. A study illustrated that 1% deaths (3000/ annum) were caused by skin cancer in Germany in both men and women, out of which 80% deaths were caused by melanoma cancer [10].

Melanocytes are neural apex-derived pigment cells that are inherent at the dermal–epidermal interface and make straight contact with just about 20–30 keratinocytes *via* the nerve, for instance, dendritic projections. Melanocytes protect the keratinocytes from UV radiation *via* the amalgamation of the melanin polymer in particular organelles which are labelled as melanosomes and are shifted to related keratinocytes *via* the dendritic processes. Malignant alteration of melanocytes gives intensification to the most violent form of skin cancer, melanoma [1]. Fig. (1) demonstrates the types of skin cancer.

CHAPTER 8**Skin Ulcers as a Painful Disorder with Limited Therapeutic Protocols****Thongtham Suksawat¹ and Pharkphoom Panichayupakaranant^{1,*}**¹ *Department of Pharmacognosy and Pharmaceutical Botany, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat-Yai 90112, Thailand*

Abstract: A skin ulcer is a type of open wound on the skin caused by injury, poor circulation, pressure, or infection. Specific forms of wounds are described using distinct terms, such as surgical incision, burn, and laceration. Skin ulcers can be extremely painful and take a long time to heal. They can become infected and cause other medical complications if left untreated. Treatment for skin ulcers is determined on the basis of the ulcer condition as well as the underlying cause. However, there is still a shortage of effective and safe medications for skin ulcer since current treatment guidelines for wound management consists only of wound dressing, antibiotics, and pain control. Wound healing and anti-inflammatory agents used for treating skin ulcers are quite limited. Recent revelations about natural compounds and their multifunctional pharmacological attributes, especially those with anti-inflammatory, antibacterial, antioxidant and wound-healing activities, have been very encouraging for therapeutic skin ulcer development. Various phytochemicals, such as curcuminoids, flavonoids, xanthenes, polyphenolic compounds, saponins, and terpenoids, were reportedly used as alternative agents for the treatment of skin ulcers. This chapter describes skin ulcers, their pathophysiology, as well as current therapeutic protocols. In addition, some selected phytochemicals and herbal extracts with strong prospects as well as their commercially available products for the treatment of skin ulcers, are highlighted.

Keywords: Anti-inflammation, Antimicrobial, Antioxidant, Skin ulcer, Wound healing.

INTRODUCTION

Skin is the largest organ that covers the entire external surface of the human body and serves a significant biological function. The skin helps to maintain fluid homeostasis, regulates temperature and chemical metabolism, provides sensory

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messages to the brain, and acts as the first line of the body's defense mechanism against pathogens, stress from the environment, and mechanical injury. Wounds are physical injuries that cause an opening or breaking of the skin or a break in the epithelial integrity of the skin, which may be accompanied by disruption of the structure and function of the underlying normal tissue. Wound infection is one of the most frequent illnesses in the world as a result of inadequate sanitary settings [1]. As a result, adequate healing procedures are required for the restoration of the skin and normal physiological conditions. Depending on the level of injury, the self-wound healing process begins with four stages, including hemostasis, inflammation, proliferation, and remodeling, and ultimately decides the look and strength of the tissue recovered [2].

Herbal medications have been traditionally used in wound therapy for disinfection, dressing, and debridement. All of which aid in the formation of an adequate physical healing process. A variety of plants are used in folklore cultures to cure incisions, wounds, and burns [3]. Recently, the mechanism of herbal extracts and phytochemicals in the wound healing process has attracted more attention since they can work *via* many mechanisms and demonstrate therapeutic characteristics at various phases of the wound healing process [4]. Various plant extracts have shown the ability to treat and cure skin ulcers through their biological effects, *i.e.*, wound healing, antimicrobial, and anti-inflammation, antioxidants and occasionally anti-allergy. Antimicrobial agents help in reducing tissue injury and inflammation caused by wound infection, while anti-inflammatory and antioxidant agents are capable of enhancing wound healing and protect tissues from oxidative damage. Therefore, phytochemicals that possess all these biological properties have a high potential to accelerate wound healing [5, 6].

This chapter aims to elucidate alternative skin ulcer therapy by describing targets for innovative pharmacological approaches against skin ulcers, herbal extracts or phytochemicals with high prospects, and their patented products that might be utilized as therapeutic alternatives. The typical features of skin ulcers, their pathogenesis, as well as current therapies are also described.

SKIN ULCERS AND PATHOPHYSIOLOGY

A skin ulcer is defined as any damage to the skin and, in most cases, to the epidermis of the skin that disturbs its regular function. Skin ulcers are classified as open or closed ulcers according to the etiology of ulcer formation, which is categorized by acute and chronic ulcers [7]. Acute ulcers, which consist of surgical and accidental ulcers, involve regular processes of inflammation, tissue proliferation, and remodeling. All of these processes take place on time [8].

Chronic ulcers are usually prolonged to heal because the healing process does not progress normally, and there is local infection. The most serious causes of chronic ulcers are diabetes mellitus, hypoxia, trauma, and inadequate treatment in the early stages of wounding [9]. Since chronic ulcers are frequently exposed to bacteria as a result of delayed wound healing, they progress to the infection stage. The pathogenic bacteria found in ulcers are *Staphylococcus aureus*, *S. epidermidis*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Escherichia coli*, and *Enterococcus faecalis*, as well as pathogenic fungi such as *Candida albicans*, have been implicated as primarily responsible for chronic ulcer infections [10].

Skin, the largest organ in the human body, is vital to life's nourishment by regulating water and electrolyte balance, body temperature, and functioning as a frontier to external pathogens such as microorganisms. These functions are no longer efficiently performed when this shield is damaged due to ulcers or burns. As a result, restoring its integrity as quickly as feasible is critical [11]. A skin ulcer is an interruption in the skin's epithelial integrity. The disruption can also affect the dermis and subcutaneous tissue. Normal skin ulcer healing necessitates a complicated series of processes that culminate in the repair of wounded tissues. A healed wound can be defined as restoring to its normal anatomical structure and function within a regular period of time, usually following a small insult. Skin ulcer pathophysiology is thus a bodily wound-healing process that keeps skin functioning normally [12].

Based on the conventional classification, wound healing is classified into four processes, namely hemostasis, inflammation, proliferation, and remodeling. These stages usually happen in this order, with occasional overlap. Normally, an ulcer will heal within 4 to 6 weeks [13]. When part of the skin is damaged, the hemostasis phase is established. At this stage, a number of significant events occur. Vasoconstriction is initially used to keep the body from bleeding out rapidly. Platelets are infused into the wound to halt bleeding and create a clot. As a result, during the coagulation cascade, a fibrin mesh forms around the platelet plugs, assisting in clot formation. Subsequently, platelets start to release cytokines and growth factors that aid in the wound-healing process. Platelets also have dense compartments that store amines that improve microvascular permeability, such as serotonin. The inflammatory response is triggered, and inflammatory cells are activated. Angiogenesis and epithelization are promoted by neutrophils and cytokines. The ulcer starts to seal during the inflammatory phase. Bacteria and debris are eliminated, and the migration of cells is boosted. After granulocytes or polymorphonuclear leukocytes (PMNLs) infiltrate the wound, they phagocytose bacteria and other foreign particles in the wound environment and eliminate them by secretion of degrading enzymes and oxygen-derived free radical species.

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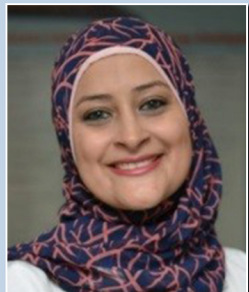
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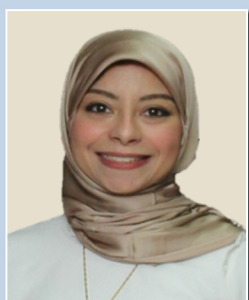
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