Plant based Herbal Products and their Dermatological Effects

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Abstract

Skin conditions causing discomfort are of common occurrence. Dermatology is a branch of western medicine dedicated to the study of skin complications which is complimented with medicine to provide symptomatic treatment. These skin disorders have also been mentioned in Ayurveda as the disease of 'Kustha' which is caused by the imbalances in tridoshas and dhatus (bodily elements). Ayurvedic texts describe the use of plant derived polyherbal medicines and other products of common use in an Indian kitchen with potential to provide relief and treat a variety of skin conditions. Despite their diverse uses, they are known to impart adverse effects and interfere with the metabolome of the cells. This chapter outlines different skin conditions and an integrated approach of western and Ayurvedic medicines to treat them, some plant derived products of common usage and their associated side effects.

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1. Introduction

Plants have been used for their medicinal properties since ancient times to treat many different health conditions of the human body, such as digestive disorders, disorders of the eye, skin associated conditions etc. Their therapeutic potential can be attributed to the diversity of metabolites that are synthesised in the plants depending upon their geography, environmental conditions, and the genome. The heterogeneity of phytochemicals available in different plant species make them suitable to be used together in different proportions to target specific disease conditions and their associated complications. Some of the common plant products used in an Indian kitchen for everyday cooking are also known to have medicinal properties and many other health benefits, for example, cloves which are used in many different recipes is a rich source of manganese which is known to promote healthy brain function. They are also high in eugenol, an antioxidant that is known to reduce oxidative stress and promote overall good health (Cortés-Rojas et al. 2014; Pham-Huy et al. 2008). Similarly, cinnamon is known for its antidiabetic and anticancer activity (Rao and Gan 2014) and is also known to have anti-ageing skin benefits. The active ingredient, cinnamaldehyde is known to promote the biosynthesis of type I collagen, thus reducing the hypoactive changes in the ageing skin (Takasao et al. 2012).

Dermatology is a branch of western medicine that deals with the study of skin, its anatomy, disorders and their respective symptomatic treatments via ingestion and topical uses of synthetic medicines. On the other hand, Ayurveda, the traditional Indian medicinal system that follows the concept of the ratio of different energies in the body, namely Vatta, Pitta and Kapha uses plant derived herbal medicines to restore the balance of these energies, known as the tridosha (three vital humours) (Parasuraman et al. 2014). The Ayurvedic system defines skin and their associated disorders and treatments in a branch called ‘Kushta rog’ (Kushta = skin, rog = disease). The western medicine takes an observational approach by tracking the phenotypic and genotypic changes occurring in the patient. Contrary to that, Ayurveda

works holistically by observing the disbalanced doshas and restoring them back using a combination of various approaches, such as yoga, meditation, oil massages, diet and lifestyle modifications and using combination of different herbal drugs.

The basis for understanding Ayurvedic approach of tridoshas can be dated back to approximately 400 C.E., mentioned in the three scriptures, namely, Charaka, Sushruta and Vagbhata Samhitas. According to these texts, Ayurvedic theory stems from a great sage, named Sankhya who explained the journey of consciousness into matter. According to this philosophy, there are two concepts, *Purusha* and *Prakruti*, where *Purusha* is defined as the pure formless energy that can exist independently whereas *Prakruti* is defined as the divine mother who exists with the help of *Purusha* (Jaiswal and Williams 2016; Larson 1987). The integration of *Purusha* and *Prakruti* gives rise to *Mahad* or *Buddhi*, the supreme awareness which further creates *Ahamkara* or ego. It is this *Ahamkara* that gives rise to the three universal qualities, i.e., *Sattva*, *Rajas* and *Tamas*. These three qualities or *gunas* have different natures. *Sattva guna* represents the spiritual or pure essence, *Rajas guna* represents the movement whereas the *Tamas guna* represents the darkness and inertia. Out of the three, *Rajas* represents the kinetic energy and upon combination with *Sattva* and *Tamas*, the organic and inorganic counterparts of matter are formed respectively. The inorganic counterpart is further constituted by five elements: Earth, Air, Water, Fire and Ether or the *Panchmahabhuta*. These *Panchmahabhutas* in different combinations give rise to the tridoshas, Vatta (Air and Ether), Pitta (Fire and Water) and Kapha (Water and Earth). It is the disruption of equilibrium between these doshas that give rise to different disease conditions and upon restoring the equilibrium, the body attains the original state of harmony and constant practise of Ayurvedic principles prevents the disruption of equilibrium state of tridoshas (Jaiswal and Williams 2016; Larson 1987).

Though, both the medicinal systems work towards treating the same skin condition, they use different terminology and different philosophies of approaching a disease but shows similar behaviour at the cellular and molecular levels. This fact is supported by the research being carried out at the molecular level for both kinds of medicinal systems. In modern times, where it is difficult to find Ayurvedic practitioners with multitude of knowledge and the original Ayurvedic texts, many people turn to self-treat their disease conditions using local knowledge available from various reliable and unreliable sources without the information about the associated side effects. This chapter outlines the Ayurvedic and western medicine approach to understand

the structure of skin, associated disease conditions, use of various Ayurvedic and synthetic drugs and their side effects or toxicity and plants of common use.

2. Skin Anatomy and Associated Disorders

The skin is the largest organ of the body, responsible for almost 15% of the total adult body weight. Skin has various vital functions which includes gathering sensory information from the environment, protection against external factors (physical, chemical, and biological), maintenance of body homeostasis, thermoregulation and storage of water, fat, and vitamin D.

2.1. Western medicine perspective/Conventional anatomy

According to the modern medicine practise, the skin is composed of three primary layers: the epidermis, the dermis, and the subcutaneous tissue (Kanitakis 2002). The epidermis is the outermost layer which is made up of special cells known as the keratinocytes, whose function is to produce keratin, which is a long, filament like protein with a protective role. The middle layer of the skin is known as dermis. It is made-up of a fibrillar protein, collagen which belongs to the class of structural proteins. The deeper layer of the skin is the subcutaneous tissue. This layer contains small lobes of fat cells known as lipocytes. The thickness of these layers varies depending on the location on the body. For example, the eyelids have the thinnest epidermal layer measuring less than 0.1 mm, whereas it is thickest, measuring up to 1.5 mm in the soles of the feet and in the palms (Rustin 1990).

2.1.1. Epidermis

The epidermis, the outermost layer of the skin is a continuously renewing stratified, squamous epithelium that keratinizes and gives rise to derivative structures – the pilosebaceous apparatus, nails and sweat glands. The epidermis is composed of four cell types– keratinocytes, melanocytes, langerhans cells and merkel cells. The epidermis can be divided into 4 distinct layers depending upon morphology and position of keratinocytes– the outermost cornified layer (*stratum corneum*), the granular cell layer (*stratum granulosum),* the squamous cell layer (*stratum spinosum)* and the basal cell layer (*stratum germinativum*) (O'Keefe 2005; Rustin 1990). The basal cells of the epidermis undergo proliferation to form new outer epidermis.

2.1.2. Dermis

The dermis is the second layer of the skin and is composed of fibrous, filamentous, and a tough supportive connective tissue matrix, which contain specialised structures

including collagen, elastin fibres, nerve, and vascular networks, fibroblasts, macrophages, and mast cells. The dermis provides elasticity, pliability, and tensile strength. It guards the body against mechanical injury, binds water, aids in thermal regulation, and includes special receptors for various sensory stimuli.

2.1.3. Subcutaneous fat (Hypodermis)

Beneath the dermis lies the subcutaneous tissue or panniculus, composed of lobules of fat cells/lipocytes separated by fibrous septa composed of collagen and large vessels. The subcutaneous fat acts as a storehouse of energy.

2.2. Ayurvedic perspective of skin anatomy (Twacha sharir rachna)

According to the Ayurvedic concept, the skin consists of 7 layers, namely, *avabhasini*, *lohita*, *shweta*, *tamra*, *vedini*, *rohini*, and *mansdhara* (Badhoria et al. 2020). The first 4 layers represents the epidermis, i.e., *avabhasini* represents stratum corneum; *shweta* represents stratum lucidum, and *tamra* represents stratum granulosum. The *avabhasini* is known to reflect individual's health by maintaining the health of layers underneath and is also known to protect plasma or *rasa dhatu*. The *lohita* is known to support the *avabhasini* and provides an indication of the quality of *rakta dhatu* (blood). *Shweta* layer is known to balance the skin colouration, i.e., melanin formaion, and *tamra* is known to be responsible to support, protect and nourish the upper layers. *Vedini*, and *Rohini* makes the two layers of dermis, i.e., the papillary and the reticular layers with sensation and healing and regeneration as respective functions, and the last layer *Mansdhara* refers to the hypodermis or the subcutaneous fat layer and is known to provide firmness and flexibility to the skin (Badhoria et al. 2020).

2.3. Skin disorders of common occurrence, their treatments and associated toxicity

The disease burden due to skin conditions is usually underestimated even though it is the fourth major cause of human diseases and affects one-third population globally (Flohr and Hay 2021). It largely remains underrepresented due to many unreported cases, both fatal and non-fatal. The most common skin conditions of high global disease burden are atopic dermatitis, acne, and psoriasis. Western medicine classifies skin diseases in two categories, i.e., either caused by an external/environmental factor or by a micro-organism (bacteria, fungi, or virus). Contrary to this, Ayurveda uses many different causes to classify the disease conditions in two categories, namely, *mahakushta* (major skin disease) and *kshudra kushta* (minor skin disease) (Badhoria et al. 2020). The classification in Ayurveda describes symptoms associated

to all different kinds of skin conditions based on the imbalance in any one or multiple tridoshas which shows a great degree of overlap with the western medicine description of the same conditions. Therefore, it is of immense difficulty to correlate specific kushta names with each skin condition described by the western medicine system (Krishna Kumar and Chacko 2019). Two skin conditions of common occurrence, psoriasis and eczema has been outlined here with reference to both medicinal systems.

2.3.1. Psoriasis

Psoriasis is a chronic, inflammatory disorder which chiefly affects the skin, joints, and other systems of the body. It is a common disorder affecting approximately 2-3% of the world population. The etiopathogenesis of the disease is not yet clear. It is predominantly a T cell mediated disorder which occur commonly in genetically susceptible individuals, influenced by environmental factors (Griffiths and Barker 2007). Psoriasis is characterized by erythematous, raised plaques with silvery shiny scales. These lesions tend to be symmetrical and may involve nails and joints. Treatment for psoriasis includes topical agents like corticosteroids, tazarotene, vitamin D analogues, salicylic acid, coal tar, calcineurin inhibitors, etc. Other drugs such as methotrexate, acitretin, and cyclosporine are the cornerstones of psoriasis treatment. Nowadays, various biologicals are approved for the treatment for psoriasis such as apremilast, etanercept, infliximab, and secukinumab (Kanwar et al. 2010). The side effects of the treatment include local skin changes, tachyphylaxis (decrease in response to a drug) and hypothalamic-pituitary-adrenal axis suppression, i.e., tertiary adrenal insufficiency due to discontinuation of corticosteroids after a long-term administration of the drug (Papp et al. 2011). Other drug specific side effects include dryness of the mucosal layer, joint stiffness (arthralgia), gastrointestinal upset, photosensitivity, and elevated triglyceride levels (Menter et al. 2010). Hepatotoxicity is another side effect along with nausea, vomiting, diarrhoea and fatigue reported to be associated with the drug methotrexate (Malatjalian et al. 1996). Similarly, the drug cyclosporine is known to impart nephrotoxicity with other side effects, such as hypertension, tremors, gingival hyperplasia (gums overgrowth) etc. Another important and serious side effect of the drug is the trigger of different malignancies, such as different skin cancers and lymphoma. This suggests that the treatment using these drugs comes at a cost and therefore the pros and cons of using western approach should be weighted before commencing the treatment.

Ayurveda, on the other hand, describe psoriasis as a disease of imbalance between the tridoshas, specifically the increase in vatta and kapha doshas. It has been described to share symptoms with 2 shudrakushtas (*kitibh kushta* and *ekakushta*) and one mahakushta (*sidhmakushta*) (Krishna Kumar and Chacko 2019). It has been described in Charaka samhita that *Psoriasis vulgaris* is a disease that affects 7 different factors in the body, namely, the two doshas (vatta and kapha), *dhatus* (the body tissue elements), *lasika* (blood plasma), *mamsa* (muscle tissue), *rakta* (blood) and *twak* (skin). It is the derangement of these factors that affect the functioning of *srotas* or the transporting channels in the skin. Drugs such as *Patolakaturohinyadi kashaya, Kaishor guggulu, Mahatiktaka ghrita, Gandhaka rasayana, Khadirarishta* and *Winsoria oil* have been reported to be used in the treatment of psoriasis (Nille and Chaudhary 2021). All these drugs are polyherbal composition and for each of the constituent plants, there is no evidence that supports the toxic behaviour of these species (Chandrasekaran et al. 2009; Hemanth Kumar et al. 2014; Khandaker et al. 2018; Wang et al. 2018).

But contrary to this, the medicine *Kaishor guggulu* contains extract from the plant *Commiphora wightii* (guggulu) for which, it has been reported that if used in pure form, guggulu resin is known to cause a variety of discomforts, such as diarrhoea, headache, nausea, irregular menstruation, and skin rashes but if consumed in large doses, it has been reported to impart hepatotoxicity due to the presence of many different phytochemical species, such as myrecene and its dimeric and polymeric forms and the phytosteroid guggulustreone in both E and Z forms (Satyavati 1988). Therefore, if a plant has been classified to be toxic but still need to be used in an Ayurvedic drug preparation, the plant undergoes the process of purification (*Shodhana vidhi*). The process of shodhana is very exhaustive and starts with removing the raw impurities by hand from the resin afterwards which, it is broken down and tied in a cloth which is hanged into a container which contains either of the recommended media, such as cow urine, cow milk, water, decoction of Triphala (*Emblica officinalis*) and decoction and aqueous extract of Malabar nut (*Adhatoda vasica*) leaves. The guggulu is boiled until all the insoluble fractions get separated which are then discarded. The soluble fraction of gugullu remains in the media which is further boiled to get a soft mass which is further smeared with cow ghee over a wooden board and is dried under the sun. The dried mass which is the purified guggulu is then used in drug preparations (Biswas et al. 2016).

2.3.2 Eczema

Eczema or atopic dermatitis is a condition associated with the inflammation of the skin. It is more prevalent in children than adults and is more common in rural areas. It is characterized by erythema (skin rash), edema (swelling), papulo-vesicle rash oozing in acute stage, with crusting and scaling in subacute and lichenification (hard and thick skin) in the chronic stages. Histologically, it is characterized by spongiosis, i.e., abnormal accumulation of fluid in epidermis. They are classified broadly depending upon the etiology into exogenous eczemas (when external cause for the eczema is identifiable) and endogenous eczemas (an internal cause or an inherent property of the skin is responsible) (Nemeth and Evans 2021). The pathogenic mechanism involves the activation of keratinocytes and the secretion of interleukin-1 and 8 which infiltrate the neutrophiles. Due to hyperproliferation of keratinocytes and the production of cytokines, the epidermal layer thickens and develops oedema and itching with blisters (Neelam et al. 2016). The treatment for eczema includes topical application of low potency steroids usually under occlusion, i.e., applying the medicine on affected area and covering it with a cloth to restrict the perspiration locally to hydrate the epidermal layer, stratum corneum for better absorption; intralesional injection in the dermal layer. Other drugs include topical application of calcineurin inhibitors, use of oral drugs for systemic therapy, such as azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil (Lee et al. 2016).

Use of these drugs has also some associated side effects, for example, topical glucocorticoids cause skin atrophy, perioral dermatitis and adrenal suppression or reduction in cortisol biosynthesis. Drug specific side effects are also observed, for example long term use of azathioprine can cause hepatotoxicity and kidney damage but less severe effects include fever, fatigue, and nausea (Espín and García-Fernández 2014). Similarly, methotrexate shows similar side effects like that of azathioprine but is also known to cause more adverse effects, such as interstitial pneumonitis, pancreatitis, and renal failure (Hannoodee and Mittal 2021).

The Ayurvedic view of this disease is different and the doshic theory suggests that eczema or *vicharachika* occurs due to an increase in the kapha dosha. The major causative factors attributed to this dosha imbalance is the consumption of incompatible food items known as *virudha ahar* and the holding of natural urges, known as *vegadharana*. These two factors are known to trigger the pathogenesis that first affect the digestive fire or *Jamharagni* leading to dyspepsia or *Agnimandya*

which in turn lead to tridosha imbalance and derangement of the factors or *dravyasangrah* for *kushta rog*. As these factors are disrupted, the symptoms begin to appear such as itching (*kandu*), blackish discoloration (*pidika*), burning sensation (*daha*), pain (*ruja*), profuse discharge (*strava*) and dryness (*rukhata*) (Girbide et al. 2019). The treatment for eczema or *vicharachika* includes the use of the drugs *Triphala kashaya*, *Lodhradi kashaya*, *Nalpamardi taila*, *Arogyavardhini rasa*, *Bilwadi Agada*, *Punarnavaasava* and *Patolakaturohinyadi kashaya* (Savalagimath et al. 2018) . The drug Lodhradi kashaya contains the rhizome extracts of *musta* or the plant *Cyperus rotundus* (Singh and Reddy 2017). The plant has been reported to contain teratogenic phytochemical such as β-D-glucopyranoside, β-sitosterol and p-hydroxybenzoic acid that have been reported to be linked to abortion in mice (Saraswathy and Vidhya 2013). Recently, it has also been reported that another phytochemical in *C. rotundus*, coumarin is also responsible to impart hepatotoxicity in both humans and animals (Malik et al. 2021). Apart from this, no other plants used in any of these preparations has been reported to be toxic. This suggests that herbal medicines should also be taken under the supervision of a certified ayurvedic practitioner.

3. Plants of everyday use and their role in dermatology

Many plants are used on everyday basis in homes that hold great therapeutic potential. A few of them are used in cooking as spices, like turmeric and coriander powder, whereas, others are used as mouth fresheners, for example fennel and cardamom. All of these have been known from an ancient time to provide health benefits. Although, they are also known to cause some cutaneous side effects, listed in Table 1.

Table 1: Plant products used in dermotology under self-treatment regine and their side-effects

Name	Mode of application	Adverse effects	References
Aloe vera	Topical	Severe and prolonged allergic dermatitis	(Hunter and Frumkin 1991)
Tea tree oil	Topical	Allergic contact dermatitis	(Hausen 1994)
Capsaicin	Topical	Dermatitis, anaphylaxis	(Foti et al. 1997; Williams et al. 1995)
Curcumin	Topical	Allergic contact dermatitis	(Hata et al. 1997)

Camphor	Topical	Erythematous, Papulous oedematous pruriginous eruptions	(Marguery et al. 1995)
Balsam of Peru	Topical	Allergic contact dermatitis	(Hausen et al. 1995)
Kava	Oral	Contact type dermatitis	(Süss and Lehmann 1996)
Garlic	Oral	Urticaria, Angioedema	(Asero et al. 1998)
Echinacea	Oral	Generalised urticaria anaphylaxis	(Mullins 1998)

Here, we outline 5 different plant and their products in everyday use, their beneficial effects and associated toxicity.

3.1. Oatmeal

Avena sativa, commonly known as Oat is a member of the plant family Poaceae. The cereal is known for its multifunctional characteristics and nutritional profile. Oatmeal has been used in households as a natural remedy for soothing dry, itchy, or irritated skin and due to its coarse nature, it has also been used for cleansing, moisturising, and for reducing inflammation. Oatmeal has been extensively used for treating dermatological conditions; it is believed that its anti-inflammatory properties can aid in reducing the symptoms of conditions like eczema and psoriasis. Oat bran is rich in vitamin B complexes, vitamin E, beneficial fats, proteins, and several minerals. Such chemical polymorphism lends several uses to concoctions of oatmeal for therapeutic purposes (Hausen et al. 1995).

Oatmeal contains several key components – 60% polysaccharides (starch), 10-18% proteins, 3-11% lipids, 5% fiber, 5% b-glucans, trace amounts of vitamins, flavonoids, and phenolic acids (Cerio et al. 2010). Of note are phenols, of which avenanthramides are present in oats at approximately 300 ppm (Pazyar et al. 2012). Oat lipids are primarily composed of triglycerides and unsaturated fatty acids (Nollent et al. 2020). The former is rich in omega-3 linoleic and omega-6 linolenic acids, which have been known to aid normal skin barrier function (Mao-Qiang et al. 1996).

The molecular mechanism of action involves avenanthramide phenols, which inhibits the NF-kappa B luciferase activity induced by TNF-α (Cerio et al. 2010). These are also known to reduce the secretion of an inflammatory cytokine, IL-8. Interleukins and TNF-α are both implicated in several autoimmune and inflammatory skin

disorders such as atopic dermatitis and eczema. Generally, oatmeal extract is also seen to decrease the production of arachidonic acid, TNF-α, and cytosolic phospholipase A2 – all components of inflammation pathways in various cell types in the body (Alexandrescu et al. 2007).

3.1.1. Therapeutic applications and toxicity

Oatmeal has been traditionally used in decreasing itching symptoms in a variety of skin conditions. An *in vitro* study has demonstrated that avenanthramides aid in reducing the secretion of inflammation-inducing histamines in mast cells (Cerio et al. 2010). This is directly implicated in reducing associated itching, as seen in other conditions as urticaria and dry-skin disorders, such as xerotic dermatoses (Sur et al. 2008). Avenanthramides have been seen to have an alleviating effect on eczema as well. Findings have demonstrated that colloidal oatmeal preparations can have ameliorative effects on chronic hand eczema (Sobhan et al. 2020). Similar studies have also shown that adding 1% colloidal oatmeal to moisturisers gives better results in treatment of dry skin compared to standard moisturisers. Colloidal oatmeal-including moisturisers are also seen to improve skin appearance and discomfort associated with psoriasis. As molecular pathways are shared between pro-inflammatory skin conditions, it is hypothesized that a similar mechanism of action is enacted by avenanthramides in this condition (Nollent et al. 2020).

Despite great therapeutic potential, oatmeal has also been reported to impart toxicity. The major toxic effect of oatmeal preparation and products on the skin stems from allergies. Oat sensitivity and allergy can trigger an immune system response which may manifest in the form of localised rashes at the area of application. Accidental application or ingestion can cause other side effects like mucosal irritation, itchy eyes, nausea, diarrhoea, or anaphylaxis in severe allergic reactions. Mild allergic reactions can often be stopped by taking oral antihistamines.

3.2. Aloe Vera

Aloe vera, scientifically known as *Aloe barbadensis* Miller, belongs to the Asphodelaceae family. Parts of the plant have been historically used for medicinal purposes in many countries: India, China, Greece, and Egypt. The ability of Aloe vera in therapeutic treatment came to light after it was successfully used to treat chronic and severe radiation dermatitis (Bharadwaj et al. 2018). Anatomically, the Aloe vera leaf consists of three layers: an inner gel-like layer which contains water (99%), amino acids, sterols, lipids, and vitamins; a middle latex layer which contains

anthraquinones and glycosides, and a thin outer layer (rind) which acts as a protective sheath over the leaf and synthesises carbohydrates and proteins (Szapary 2000).

Aloe vera contains a plethora of 75 potentially active constituent biomolecules. These include vitamins (vitamins A, C, E, B_{12}, folic acid, and choline), enzymes (alkaline phosphatase, amylase, catalase, cellulase, aliiase, peroxidase, bradykinase, and carboxypeptidase), sugars (mono- and poly-saccharides), minerals (trace levels of calcium, copper, selenium, magnesium, potassium, sodium, zinc), anthraquinones (aloin and emodin), hormones (trace auxins and gibberellins), and fatty acids (cholesterol, β-sisosterol, lupeol, and campesterol) (Kumar et al. 2019; Nalimu et al. 2021).

3.2.1. Therapeutic applications and toxicity

It has been observed through various studies that Aloe vera has therapeutic value in treating several dermatological conditions. Topical application of Aloe vera gel is observed to significantly increase collagen synthesis in case of wound healing. The mechanism of action here involves two key Aloe vera components– glucomannan (a manose-rich polysaccharide) and gibberellin which interact with growth factor receptors on fibroblasts, in turn stimulating their proliferation and activity (Chithra et al. 1998). In addition to increasing the extent of collagen cross linking, *Aloe* gel also changes the composition of collagen to have more type 3 collagen, thus aiding in accelerated wound healing and stronger scar tissue (Heggers et al. 1996). A novel anti-inflammatory compound, C-glucosyl chromone, was isolated from *Aloe* gel extracts. *Aloe* preparations are seen to help with reducing inflammation by inhibiting the cyclooxygenase pathway, which in turn reduces prostaglandin E2 production from arachidonic acid (Hutter et al. 1996).

Aloe vera gel is also reported to help protect the skin against radiation damage (Roberts and Travis 1995). A suggested mechanism of action is the generation of metallothionein, an antioxidant protein, following application of the gel. The protein scavenges hydroxyl radicals, which in turn reduces the production and release of cytokines such as interleukin-10 in skin kerationcytes. This helps prevent UV-induced suppression of delayed type hypersensitivity (Byeon et al. 1998). Mucopolysaccharides, a key component of Aloe vera, help in binding moisture into the skin. This lends to its popular use as a moisturizer. In addition to these protective effects, Aloe vera also acts as an antiseptic due its components lupeol, salicylic acid, urea nitrogen, cinnamomic acid, phenols, and sulphur. These compounds have a detrimental action on fungi, bacteria, and some viruses (Surjushe et al. 2008).

While Aloe vera is not a specifically toxic plant, users may observe side effects of its topical and oral applications. Sensitive individuals may have a stinging sensation in addition to burning and redness at the area of application. Such allergic reactions are mostly due to the component anthraquinones (Surjushe et al. 2008) . It is best to do a patch test to determine any allergies to Aloe vera.

3.3. Neem

Neem (*Azadirachta indica*), a member of the Meliaceae family, has a rich history in traditional Chinese, Ayurvedic, and Unani medicine worldwide. The tree is found in abundance in countries like India, Bangladesh, Nepal, and Pakistan. Traditionally, various parts of the neem tree including bark, leaves, flowers, fruit, gum, and oil are all associated with therapeutic benefit for a range of ailments. Apart from consumption, topical application of several preparations of the plant is also known to have beneficial effects (Islas et al. 2020).

A key active constituent of the neem plant is azadirachtin, while some others are nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, salannin, and querctin. Neem leaves contain nimbin, nimbanene, 6-desacetylnimbinene, nimbandiol, nimbolide, ascorbic acid, n-hexacosanol and amino acids and also 7-desaetyl-7-benzoylazadiradione, 7-desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione, and nimbiol (Seth and Shah 2010). Fresh leaves are additionally seen to contain quercetin and ß-sitosterol, both polyphenolic flavonoids known to have antibacterial and antifungal properties (Govindachari et al. 1998), and seeds hold valuable constituents including gedunin and azadirachtin.

The anti-pathogenic effects of neem are primarily attributed to a high antioxidant content and the presence of active components aforementioned. While the exact molecular mechanisms are not yet elucidated, studies in insects have shown that neem's antifeedant effect is caused by a complex limonoid called azadirachtin which is present inside the seeds. It is also seen that an ethanol extract of neem leaves shows *in vitro* antimicrobial activity against methicillin-resistant *Staphylococcus aureus* at high concentrations (Hossain et al. 2013; Sarmiento et al. 2011).

Active components nimbolide, azadirachtin, and ascorbate show, in decreasing order, concentration-dependent anti-radical scavenging (antioxidant) activity and reductive potential. This property makes neem a rich source of antioxidants. Specifically, chloroform crude extracts of neem could be used as a natural antioxidant (Kiranmai et al. 2011). One study has looked at the use of root bark extract and found that it

exhibits higher free radical scavenging effect with a high 50% activity at a concentration of 27.3 mg/mL. This is contracted with an equivalent activity from ascorbic acid at 0.58 mM (Alzohairy 2016). Neem also plays a role in regulating inflammation via regulation of proinflammatory enzymes such as cyclo-oxygenase (COX) and lipo-oxygenase (LOX) (Chattopadhyay 1998).

3.3.1. Therapeutic applications and toxicity

In a study on rats, is seen that neem leaf extracts at a dosage of 200 mg/kg show significant anti-inflammatory activity (Kaur et al. 2004). Another study has shown that the function of macrophages and neutrophils is suppressed by nimbidin. These are the cell types that are known to be critical in the inflammation pathway helping control general inflammation (Barua et al. 2010).

Another study conducted on rats looked at the wound healing potential of neem extract and found that in cases of both excision and incision wounds, application of extracts significantly promoted healing activity (Chinedu Ugoeze et al. 2021). Leaf extracts of the plant are also seen to promote wound healing through increased neovascularization and modulation of the inflammatory response.

In addition to its anti-microbial activity, methanol and ethanol extract of neem is known to exhibit antifungal activity by inhibiting growth of *Aspergillus flavus*, *Alternaria solani*, and *Cladosporium* (Natarajan et al. 2003). Various studies have also shown that aqueous extracts and neem oil also have antifungal properties (Amadioha and Obi 1998). Because of its insecticidal properties, it is widely used in Indian villages to kill head lice, which is a serious dermatological condition (Anon 1992).

3.4. Curcumin

Curcumin was first isolated by Vogel and Pelletier. This spice comes from the plant *Curcuma longa*. Lampe and Milobedeska introduced the structure of the active component, a diferuloylmethane in 1910 (Bandyopadhyay 2014). It is known to exists in two isomeric forms, i.e., the keto-enol tautomeric forms. The neutral and acidic conditions support the keto form, while the enol form is seen in alkaline conditions. In terms of its solubility, it is readily soluble in organic substances, such as methanol, ethanol and acetone whereas insoluble in water (Prasad et al. 2014; Trujillo et al. 2013).

The intestinal metabolism of curcumin includes conjugation and reduction, which yield derivatives like curcumin glucuronide, curcumin sulphate, tetrahydrocurcumin and hexahydrocurcumin. It is metabolized in the liver rapidly

with its excretion taking place mainly via gall bladder and minimally via kidneys (Esatbeyoglu et al. 2012).

Oral consumption of curcumin results in lower clinical efficacy. This is attributed to its poor bioavailability and an extensive metabolism in the body. A consequence of the poor absorption is seen in the therapeutic potential of curcumin. *In-vitro* studies have reported that the active compounds of curcumin are of more relevance at concentrations in the micromolar range, whereas after oral intake, the plasma concentration has been reported to be only in the nanomolar range (Burgos-Morón et al. 2010). Recent technologies such as the use of nanoparticles, micelles, liposomes, and phospholipid complexes are under evaluation to increase the oral bioavailability of curcumin. Active ingredients in curcumin are known to influence multiple cellular signalling pathways and is also known to have anti-inflammatory, antioxidant, and antimicrobial properties along with chemosensitising and radiosensitising properties. Other uses include wound healing, and hypoglycemic effect in diabetes (Prasad et al. 2014).

3.4.1. Therapeutic applications and toxicity

Curcumin has been proven to have a great potential in treating inflammatory and malignant disorders of the skin. A few of its uses are described here. Curcuminoids in high dose of such as 6 g per day can show improvement in the signs and symptoms of oral lichen planus. Most common reported side effect of such high doses is diarrhoea (Chainani-Wu et al. 2012).

Various *in vivo* and *in vitro* studies are done to establish the role of curcumin in treatment of psoriasis. Curcumin acts by inhibiting the NF-κB pathway, thus reducing inflammation caused by Th1 cytokines. However, a small study about the use of curcumin for treating moderate to severe psoriasis showed low efficacy of oral curcumin due to reduced oral availability (Kurd et al. 2008). Curcumin has also been shown effective in 1% topical gel form in chronic plaque psoriasis. It inhibits local phosphorylase kinase activity (Heng et al. 2000).

In burns, it has been reported to inhibit the activity of phosphorylase kinase and subsequently the NF-κB/TGF-β signalling pathways, thus, promote healing while simultaneously preventing scarring. In malignancy, active component of curcumin inhibits the activity of NF-κB and leads to apoptosis in basal carcinoma and melanoma cells in humans and is also known to cause upregulation of p53 (Jee et al. 1998; Marín et al. 2007; Siwak et al. 2005). This inhibition of NF-κB also helps

in reducing the growth and proliferation of squamous cell carcinoma (Aggarwal et al. 2004). Also, in topical form curcumin reduces the carcinogenesis of the skin (Sharma et al. 2005). Curcumin also downregulates STAT-3 pathway along with the NF-κB pathway, thus inducing selective apoptosis in cutaneous T cell lymphoma (Zhang et al. 2010).

In wound healing, curcumin is beneficial in various ways because of its antioxidant properties. It accelerates wound healing by increasing granulation in tissues, neovascularization, and enhancing collagen synthesis. It also inhibits the functions of the enzymes COX and LOX. This reduces the concentration of inflammatory cytokines from being released by macrophages and monocytes (Merrell et al. 2009). Curcumin has antifungal properties against *Candida* (Martins et al. 2009). Its active components also possess antimicrobial, antiviral and antiparasitic properties (Marathe et al. 2011).

As a dietary component in many cuisines, curcumin has regularly been used with an approximate dosage of 100 mg/day (Jee et al. 1998). The bioavailability of active components when curcumin is ingested orally is poor, and so acute toxicity is unlikely for a short-term use of up to 8 g per day. Mild toxicity may lead to nausea, abdominal discomfort, dyspepsia and diarrhoea. Contraindications for the use of curcumin are hypersensitivity to its components, biliary tract obstruction and gall stones. It exhibits the antioxidant role at low cellular levels while higher levels may lead to oxidative stress attributed to increased amount of reactive oxygen species (ROS) (Gupta et al. 2011). These high levels can contribute to increases oxidative stress in vitiligo (Schallreuter and Rokos 2006). Curcumin in moderate doses leads to inhibition of apoptosis caused by cytotoxic chemo-therapeutic agents used routinely in breast cancer treatment (Somasundaram et al. 2002). Curcumin may show antiplatelet effects on oral ingestion (Brown et al. 2015). Topical curcumin is frequently associated with both immunologic and non-immunologic contact urticaria (Liddle et al. 2006). It can also lead to allergic contact dermatitis which is detected by positive patch testing (Calapai et al. 2014).

3.5. Tea tree oil (TTO)

Tea tree oil (TTO) is obtained from the plant *Melaleuca alternifolia* that belongs to the Myrtaceae family. TTO (melaleuca oil) is effective in various skin infections, and inflammatory skin disorders (Pazyar and Yaghoobi 2012). It is also known to be an anti-skin cancer agent (Greay et al. 2010).

TTO contains around a hundred chemical components, mainly terpenes and their corresponding alcohols (Papadopoulos et al. 2008). The major component of TTO is terpinen-4-ol, which has strong antimicrobial and anti-inflammatory properties (Mondello et al. 2006). The major component terpinen-4-ol is known to reduce the production of inflammatory factors such as TNF-, IL- 8, and IL-10, and prostaglandin E2. Also, the water-soluble fractions, i.e., terpinen-4-ol and a-terpineol are known to suppress signalling radicals produced by monocytes. Additionally, terpinen-4-ol also modulates vasodilation and plasma extravasation (Carson et al. 2006).

TTO is known to exhibit diverse activities, such as antioxidant activity due to several antioxidants, such as α-terpinene, α-terpinolene, and γ-terpinene which have been seen to be present in crude TTO (Kim et al. 2004). TTO also shows antibacterial activity. Terpinen-4-ol has been reported to show antibiotic behaviour against methicillin resistant *Staphylococcus aureus* (MRSA) bacterium and coagulase negative *staphylococcus* (CoNS) bacterium. A 5% TTO solutions added into washing agents show effectiveness in removing MRSA from the skin (Thompson et al. 2008). TTO has also been found to be effective against oral bacteria. Mouth washing with TTO has been reported to reduce the amount of oral and dental plaque (Soukoulis and Hirsch 2004). TTO has also been reported to act as an antiviral agent. It has been shown to have potent killing action against Herpes Simplex Virus 1 (HSV-1) and Herpes Simplex Virus 2 (HSV-2)(Schnitzler et al. 2001).

In terms of anti-viral therapeutic prospects, a study showed that TTO can be an economic alternative to treat recurrent herpes labialis (Carson et al. 2001). The oil also has been shown to be effective against the Human Papilloma Virus (HPV) that causes hand warts. It works by mechanistically facilitating epithelialization over infected areas completely (Millar and Moore 2008).

TTO has also been shown to have antifungal and antiprotozoal activities. A double blinded randomized controlled trial (RCT) study with 25% and 50% TTO formulations reported a good clinical response for the treatment of tinea pedis, an interdigital fungal foot infection (Satchell et al. 2002b). A multicentre RCT showed good clinical improvement in patients with distal subungual onychomycosis upon topical TTO for six months. It showed statistically significant improvement in appearance and symptoms of the disease (Buck et al. 1994). TTO has also been suggested to be active against the fungus *Madueralla mycetomatis* for the treatment of eumycetoma as it can easily penetrate through the skin (van de Sande et al. 2007). TTO has been found to be effective against the parasite *Trichomonas vaginalis* (Carson et al. 2001).

In another study, an *in vitro* analysis showed that mites of *Sarcoptes scabiei* var. hominis were not able to survive after exposure to 5% TTO (Walton et al. 2000). A similar study with 5% TTO reported terpinen-4-ol, a major component of TTO to be highly effective in reduction of survival time for *Sarcoptes scabiei* var. hominis (Walton et al. 2004). TTO has also been used as an additive agent in various preparations for head lice infestations as an alternative and natural treatment for children and adults.

Another study revealed that TTO can be used as an alternative to pyrethrin-based products. A combination of TTO and lavender oil has been reported to show great effectiveness towards live head lice (Barker and Altman 2010). In addition, a study exerted effectiveness of TTO in eradicating eyelid demodex by using 50% TTO and tea tree shampoo-based lid scrubs (Gao et al. 2007).

3.5.1. Therapeutic applications and toxicity

Tea tree oil has broad spectrum antimicrobial and anti-inflammatory properties. Due to these properties, tea tree oil is used in various therapeutics like treatment of acne (Enshaieh et al. 2007). Various studies have also proved that 5% TTO gel has efficacy against *Propionibacterium acnes* and can be used in the treatment of acne vulgaris. In 1990, a study with 124 patients with acne showed a comparison between 5% tea tree oil in water-based gel and 5% benzoyl peroxide. TTO showed statistical improvement in the number of acne lesions at the end of 3 months. The effects were not produced as quick as benzoyl peroxide, but there was significantly lower incidence of side effects like xerosis, irritation, itching, and burning with TTO (Bassett et al. 1990).

Various other studies also proved that TTO has antifungal activity against the fungal species of *Malassezia*, that might be helpful in the treatment of seborrheic dermatitis (Gupta et al. 2004; Waldroup and Scheinfeld 2008). Similarly, a study by Satchell et al. (2002a) revealed that 5% TTO is useful in the management of dandruff. TTO has also been reported to be effective on tumour cells by inducing the reorganisation of the lipid structure of plasma membrane (Giordani et al. 2006).

Topical 10% TTO/dimethyl sulfoxide (DMSO) significantly slows down the growth of subcutaneous melanomas (Greay et al. 2010). Bozzuto et al. (2011) demonstrated that TTO is also able to inhibit the growth of melanoma cells and is also helpful to overcome multidrug resistance in such cases. TTO also has special role in wound healing. TTO hydrogel application can increases the rate of burn wound healing by reducing the inflammation (Jandera et al. 2000).

Sustained topical application of highly concentrated TTO can result in adverse reactions to the skin. These adverse effects include both allergic and irritant contact dermatitis, systemic contact dermatitis and hypersensitivity reactions, erythema multiforme like reactions, idiopathic male prepubertal gynecomastia and linear IgA disease (Crawford et al. 2004; Henley and Korach 2010). A study with estimating the toxicity of TTO reported that its components were not genotoxic (Hammer et al. 2006).

4. Conclusion

Dermatology is a vast field with great potential to explore in developing new treatment regimes. With digitisation of Ayurvedic texts and the biochemical and molecular research complementing our previous knowledge, new doors are being opened in the field of computational and molecular Ayurveda with its application in dermatology. From the literature review conducted, it seems that both western and Ayurvedic medicine practices follow different routes to treat the same skin abnormalities but also show a significant overlap in describing the disease conditions. Therefore, it would be interesting to try and integrate our ancient Ayurvedic knowledge with western medicine system and try to practise a new approach of mixopathy, i.e., mixing the two treatment plans together for better and more effective treatment of the diseases with least side effects. Another very interesting addition to the research in Ayurvedic dermatology would be to conduct toxicology studies at tissue, cellular and molecular levels to understand their correlation at the organismal level. With advancement in new technologies, this could be realised easily and will prove to be very interesting and helpful in developing more new and effective therapies.

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