CHAPTER 1: INTRODUCTION

This chapter gives an introduction to the research thesis “Development and evaluation of herbal formulation for dermatological use”.

1.1 Rationale

Skin is the largest organ which covers and protects the body. A person suffering from skin disease may tend to have depression and psychological trauma, or encounter embarrassing situations in additions to physical discomfort, as the society generally tries to avoid people suffering from visible skin disorders. One such skin disease is psoriasis (Benjamin B and Joel DK, 2002).

1.2 Psoriasis

Psoriasis is a common, chronic, inflammatory, recurrent, genetically determined disorder of the skin. It is non-contagious, usually inherited, autoimmune disorder with red lesions appearing on the skin covered with silvery scales. Psoriasis Greek word- *so ri a sis* means itching. There is no known cure and it is possible only to control. The effective management of psoriasis can be achieved by traditional medicines and need to be investigated and documented scientifically. Here is an attempt to scientifically formulate and evaluate a herbal drug for the management of psoriasis.
1.3 Psoriasis and its distribution

Psoriasis is a chronic inflammatory immune-mediated disease of skin and joints affecting around 0.5-1% of children and 2-3% of adults. Typically, the patients develop erythematous scaly papules and plaques. Up to 20 or 30% of patients with psoriasis develop psoriatic joint involvement, which may result in severe joint destruction and (in rare cases) mutilating arthritis. Both psoriasis of the skin and psoriatic arthritis are frequently accompanied by impairment of quality of life (Parisi R et al., 2013).

1.4 Histopathological changes on the skin associated with psoriasis

(Nestle et al., 2001)

The histopathological changes that normally take place on the skin and its layers with the development of psoriasis include, parakeratosis (presence of nucleated cells of the stratum corneum), stratum granulosum (its thickness decreases with increased disease), spongiform pustule (degree of infiltration of polymorphs in the epidermis), Munro’s microabscesss (infiltration of neutrophils in the epidermis), acanthosis (elongation of rete ridges), dermal vessel tortuosity (degree of tortuosity of dermal vessels).
1.5 Treatment for psoriasis in classical medicine

Psoriasis (*Da-al-sadaf*) has not been mentioned in any of classical medical literature. However, it was mentioned in Unani medicine and in Ayurveda as *Kust Kutam*. In recent times, psoriasis has been identified as an independent disease or skin disorder. *Da-al-sadaf* is derived from two Arabic words *Daun* (= disease) and *Al-Sadaf* (= oyster shell) while psoriasis is derived from a Greek words *so ri a sis* which means itching. Technically it may be defined as a common genetically determined inflammatory and proliferative disease of the skin.

1.6 Traditional oral therapies

Most clinicians initiate methotrexate as first-line systemic therapy for patients with psoriasis or psoriatic arthritis. Others use cyclosporine, which induces general immunosuppression by preventing T cell activation and cytokine expression. Both compounds are effective in psoriasis and psoriatic arthritis (Heydendael VMR *et al.*, 2003). However, their long-term use is complicated by several toxicities. Patients suffering from pustular psoriasis can also benefit from oral retinoids, while patients with psoriasis vulgaris respond better to oral retinoids when receiving additional phototherapy (Sbidian E *et al.*, 2011). In some countries fumaric acid esters (FAEs) are used for treating psoriasis. FAEs seem to improve psoriasis by acting on the immune response and
inhibiting the production of pro-inflammatory cytokines like IL-12 and IL-23 (Litjens NHR et al., 2004, Ghoreschi K et al., 2011) FAE therapy is regarded as an anti-psoriatic therapy with limited toxicity. Because rare reports on progressive multifocal leukoencephalopathy (PML) exist in patients with severe lymphopenia under FAE treatment, severe and long-lasting lymphopenia should be avoided when patients are treated with this drug (Sweetser MT et al., 2013).

1.7 Available classical allopathic therapies (Katharina B et al., 2014)

- Topical—emollients, moisturizers, tars and anthralins
- Topical corticosteroids, vitamin A analogs, and vitamin D analogs
- Systemic treatments—corticosteroids, methotrexate, cyclosporine etretinate, retinoids and other immunomodulators, and hydroxyurea
- Phototherapy
- Photo-chemotherapy

1.8 Latest anti-psoriatic oral compounds and biologicals

(Katharina B et al., 2014)
A list of latest anti-psoriatic oral compounds and biologicals are given below:

<table>
<thead>
<tr>
<th>Category</th>
<th>Therapeutic drug</th>
<th>Target, mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional oral compounds</td>
<td>Methotrexate</td>
<td>Folic acid antagonist, inhibits cell activation</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
<td>Inhibits T cell activation and cytokine secretion</td>
</tr>
<tr>
<td></td>
<td>Retinoids</td>
<td>Vitamin A analogs inhibiting epidermal proliferation and differentiation</td>
</tr>
<tr>
<td></td>
<td>Fumaric acid esters</td>
<td>GSH conjugation, changes in cytokine production</td>
</tr>
<tr>
<td>Established Biologics</td>
<td>Infliximab</td>
<td>Antibody neutralizing TNF</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td>TNFR fusion protein</td>
</tr>
<tr>
<td></td>
<td>Adalimumab</td>
<td>Antibody neutralizing TNF</td>
</tr>
<tr>
<td></td>
<td>Ustekinumab</td>
<td>Antibody neutralizing IL-12/IL-23 p40</td>
</tr>
<tr>
<td>Modern oral compounds (phase 3 development)</td>
<td>Dimethyl fumarate</td>
<td>GSH conjugation, Nrf2 activation, inhibition of IL-12 and IL-23, induction of IL-10 and Th2</td>
</tr>
<tr>
<td></td>
<td>Apremilast</td>
<td>PDE4 inhibitor, increase of cAMP, inhibition of IL-12,IL-23,TNF and IFN-γ</td>
</tr>
<tr>
<td></td>
<td>Tofacitinib</td>
<td>JAK inhibitor silencing cytokine receptor signaling, inhibiting Th1 and Th17 responses</td>
</tr>
<tr>
<td>New biologics (phase 3 development)</td>
<td>Brodalumab</td>
<td>Antibody binding IL-17 receptor</td>
</tr>
<tr>
<td></td>
<td>Ixekizumab</td>
<td>Antibody neutralizing IL-17A</td>
</tr>
<tr>
<td></td>
<td>Secukinumab</td>
<td>Antibody neutralizing IL-17A</td>
</tr>
<tr>
<td></td>
<td>MK-3222</td>
<td>Antibody neutralizing IL-23p19</td>
</tr>
</tbody>
</table>

1.9 *Wrightia tinctoria* (Srivastava R, 2014)

*Wrightia tinctoria* (Roxb.) R.Br (Apocynaceae) is a small deciduous tree widely distributed all over India in tropical areas like Madhya Pradesh, Rajasthan, Tamil Nadu and Peninsular India. The plant bark is used as a galactagogue to treat abdominal pain, as an antipyretic, as an antidote for snake poison, as an
antidysenteric, antidiarrhoeal, haemorrhagic agent and to treat skin diseases and wounds. The seeds are carminative, astringent, aphrodisiac and tonic and are given for infections of the chest, asthma, colic and diuresis.

1.9.1 Ancient utility of Wrightia tinctoria

Wrightia tinctoria is commonly called as Sweet Indrajao, Pala Indigo plant, Dyer's Oleander, Jaundice curative tree in South India. Sweet Indrajao is a small, deciduous tree with a light gray, scaly smooth bark. Native to India and Burma, Wrightia is named after a Scottish physician and botanist William Wright (1740-1827). Sweet Indrajao is called dhudi in Hindi language because of its preservative nature. The juice of the tender leaves is used efficaciously in jaundice. Crushed fresh leaves when filled in the cavity of decayed tooth relieve toothache. In Siddha system of medicine, it is used for the treatment of psoriasis and other skin diseases (Srivastava R, 2014).

1.9.2 Chemical constituents of Wrightia tinctoria (Srivastava R, 2014)

The plant is reported to contain flavanoid, glycoflavones-iso-orientin, and phenolic acids. The various chemical constituents isolated from various parts of the plant are reported as 3,4-Seco-lup-20 (29)-en-3-oic acid, lupeol, stigmasterol and campetosterol, indigotin, indirubin, tryptanthrin, isatin, anthranillate and rutin. Triacontanol, wrightial, cycloartenone, cycloecalenol, β-amyrin,
α-amyrin, and β-sitosterol, 14α-methylzymosterol, four uncommon sterols, desmosterol, clerosterol, 24-methylene-25-methylcholesterol, and 24-dehydropollina-stanol, were isolated and identified in addition to several more common phytosterols. The triterpinoids components of the leaves and pods of Wrightia tinctoria were also isolated.

1.10 Reverse pharmacological correlation of ayurvedic plants

(Vaidya ADB, 2006)

Ayurveda in India dates back to 3000 BC. It has a connotation of revealed knowledge, complete within itself and as some say, it has hardly any need for research. Sri Ram Nath Chopra (1882-1973) was a pioneer in the field of experimental pharmacology of indigenous drugs of India. Most of the medicinal plants he studied were in use, in Ayurveda, for thousands of years. Reverse pharmacology would indicate the research process from the robust clinical base of documented therapeutic or other effects of plants and formulations. Reverse pharmacology, for drug development has been highly productive and cost effective in the recent past. Globally, this approach has now generated greater interest in Ayurveda and Indian pharmacology.
**Topical application** (Shailesh S *et al.*, 2008)

1.11.1 Definition

Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes.

1.11.2 Advantages

The topical route of application offers several advantages over systemic administration, like avoidance of systemic toxicity and side effects, decreased induction of resistance, and a high concentration of active agent at the site of action, to bypass first pass metabolism, avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time etc.

1.11.3 Disadvantages

The disadvantages mainly include skin irritation of contact dermatitis which may occur due to the drug and/or excipients, poor permeability of some drugs through the skin and possibility of allergenic reactions. This can be used only for drugs which require very small plasma concentration for action where enzyme in epidermis may denature the drugs. Drugs of larger particle size are not easy to absorb through the skin.
1.11.4 Permeation through skin

Most of topical preparations are meant to be applied to the skin. So basic knowledge of skin and its physiology function and biochemistry is very important for designing topicals. The skin is the heaviest single organ of the body which combines with the mucosal lining of the respiratory, digestive and urogenital tracts to form a capsule, which separates the internal body structures from the external environment. The pH of the skin varies from 4 to 5.6. Sweat and fatty acids secreted from sebum influence the pH of the skin surface. It is suggested that acidity of the skin helps in limiting or preventing the growth of pathogens and other organisms.

1.11.5 Physiology of the skin

The skin has several layers. The overlaying outer layer is called epidermis; the layer below epidermis is called dermis. The dermis contains a network of blood vessels, hair follicle, sweat gland and sebaceous gland. Beneath the dermis are subcutaneous fatty tissues. Bulbs of hair project into these fatty tissues.

1.11.6 Absorption through skin

Two principal absorption routes are identified:

Transepidermal absorption

It is now generally believed that the transepidermal pathway is principally responsible for diffusion across the skin. The resistance encountered along this
pathway arises in the stratum corneum. Permeation by the transepidermal route first involves partitioning into the stratum corneum. Diffusion then takes place across this tissue. The current popular belief is that most substances diffuse across the stratum corneum via the intercellular lipoidal route.

Transfollicular (shunt pathway) absorption

The skin’s appendages offer only secondary avenues for permeation. Sebaceous and eccrine glands are the only appendages, which are seriously considered as shunts bypassing the stratum corneum since these are distributed over the entire body. Though eccrine glands are numerous, their orifices are tiny and add up to a miniscule fraction of the body’s surface. Moreover, they are either evacuated or so profusely active that molecule cannot diffuse inwardly against the glands output.

1.11.7 Ointment as a topical drug delivery system

Ointments are semisolid preparations intended for external application to the skin or mucous membranes. Typical ointments are based on petrolatum. An ointment does not contain sufficient water to separate into a second phase at room temperature. Water-soluble ointments may be formulated with polyethylene glycol. Ointments are ideal emollients with good skin penetration and adherence to surfaces.
1.11.8 Types of ointment bases

Occlusive ointments:

- Hydrophobic base (e.g. petrolatum)
- Anhydrous absorptive / humectant (e.g. lanolin)
- W/O absorptive: contains H₂O e.g. (cold cream)

Non-Occlusive ointments:

- Water-removable O/W (e.g. hydrophilic ointment)
- Water-soluble (e.g. PEG)

1.11.9 Method of ointment preparation

We prepare ointments of smooth consistency, non-grittiness, and pharmaceutical elegance. We use geometric dilution when manually compounding with a spatula or mortar and pestle. For larger quantities, a mixer is utilized. The final procedure involves a brass mill to reduce particle size and to produce a non-irritating ointment.

1.11.10 Packaging of ointments

Ointments are packaged in convenient containers such as tubes or jars.

1.11.11 Evaluation of ointments

The parameters of evaluation include penetration, rate of release of medicaments, irritant effect and absorption of medicaments into blood stream.