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Chapter 1

1. Introduction

1.1 Introductions of Herbal medicines:

All plants produce chemical compounds as part of their normal metabolic activities. These include primary metabolites, such as sugars and fats, found in all plants, and secondary metabolites found in a smaller range of plants, some useful ones found only in a particular genus or species.

Plants up-regulate and down-regulate their biochemical paths in response to the local mix of herbivores, pollinators and microorganisms [1]. The chemical profile of a single plant may vary over time as it reacts to changing conditions. It is the secondary metabolites and pigments that can have therapeutic actions in humans and which can be refined to produce drugs.

Plants synthesize a bewildering variety of phyto-chemicals but most are derivatives of a few biochemical motifs such as Alkaloids, Phenols and their derivatives, Terpenoids, Glycosides and others. These secondary metabolites possess some therapeutic properties therefore, some plants are also classified as Herbs.

Herbs, and substances derived from natural sources (spices), [2] would have been one of the only treatments for diseases in all prehistoric cultures. However, because herbs will rot away in most conditions and because no written notes could have been made about them or their uses, historians are unlikely ever to know exactly, which herbs were used in prehistoric medicine. Of course an idea of which herbs they used has been obtained by looking at the area in which the prehistoric tribes lived in and the herbs that grow there naturally, [3] and of course through anthropological studies of existing indigenous peoples; [4] unlike the Ancient Civilizations who were able to transport and trade herbs from across their own and others empires, prehistoric people would have relied on locally sourced herbs.

Our ancient religious texts and epics give a good insight into the applications of naturally occurring plant products, useful in the curing of several diseases. One of the documentations is "Ayurveda". Some well-known examples of herbs medicines are incorporated here.
1.2 Ayurveda:

Ayurveda (Devanagari: आयुर्वेद or Ayurvedic medicine) is an ancient system of health care that is native to the Indian subcontinent. Ayurveda is a science of life and life according to Ayurveda is a combination of senses, mind, body and soul. Ayurveda (Sanskrit for "knowledge of life" or "knowledge of longevity") is a comprehensive system of traditional health care that emphasizes the relationship among body, mind, and spirit. It is also considered to be the traditional system of medicine of India. So it is clear from this definition that Ayurveda is not only limited to body or physical symptoms but also gives a comprehensive knowledge about spiritual, mental and social health. Ayurveda is a science in the sense that it is a complete system. It is a qualitative, holistic science of health and longevity, a philosophy and system of healing the whole person, body and mind. Historians have not pinpointed the exact time Ayurveda came into being. Most agree that Ayurvedic classical texts were written in India between 3,500 and 5,000 years ago. At this time, philosophy and medicine were not separated. Therefore, philosophical views have strongly influenced the Ayurvedic way of thinking. There are several aspects to Ayurveda that are quite unique: Ayurveda provides reference points for managing treatment decisions specific to each case. Ayurvedic theory is profoundly useful in analyzing individual patient constitution and understanding variations in disease manifestation. The Ayurvedic framework can be used to structure working models of the unique state of each patient, and to project a vision or goal for a whole state of health, again unique to each case. Ayurveda provides specific Do's and Don'ts to each individual on lifestyle, diet, exercise and yoga, herb therapy, and even spiritual practices to restore and maintain balance in body and mind. This understanding that we are all unique individuals enables Ayurveda to address not only specific health concerns but also provides explanation as to why one person responds differently than another.

The philosophy of Ayurveda

The emergence of different schools of Sanskrit philosophy like Nyaya, Vaisheshika, Sankhya, Yoga, Vedanta and Mimamsa was another landmark in the history of Indian medicine. The principles expounded in these philosophies facilitated the development within Ayurveda of its theory of humoral pathology which propounds that the human body is composed of Tridoshas, the three humors – Vata, Pitta and Kapha. When these are in equilibrium they are called the
Tridhatus. The body in which these three humors are in a state of equilibrium enjoys perfect health; their disequilibrium causes ill health.

**Tridosha system**
The most fundamental and characteristic principle of Ayurveda is called "tridosha" or the Three Humours. Doshas are the physiological factors of the body. They are to be seen as all pervasive, subtle entities, and are categorized into vata, pitta and kapha. *Vata* is the impulse principle necessary to mobilize the function of the nervous system. *Pitta* is the energy principle which uses bile to direct digestion and hence metabolism into the venous system. *Kapha* is the body fluid principle which relates to mucous, lubrication and the carrier of nutrients into the arterial system. All Ayurvedic physicians believe that these ancient ideas, based in the knowledge discovered by the Rishis and Munis, exist in harmony with physical reality. These Ayurvedic concepts allow physicians to examine the homeostasis of the whole system. People may be of a predominant dosha or constitution, but all doshas have the basic elements within them.

**Disease management in Ayurveda**
The principles of Ayurvedic pharmacology are fundamentally different from those of other systems of medicine, especially evidence-based medicine. *Shamana* and *Shodhana* are the two concepts of disease management in Ayurveda. *Shamana* means alleviation. Shamana methods mitigate the disease and its symptoms. *Shodhana* means elimination and Shodhana methods aim at the elimination of the basic cause of disease.

1.3 **Global scenario of Herbal medicine:**
There is currently a large and ever-expanding global population base that prefers the use of natural products in treating and preventing medical problems. At present, plant and herb resources are unlimited, as far as the search for useful phyto-chemicals is concerned; but these resources are dwindling fast, due to the onward march of civilization. This has influenced many pharmaceutical companies to produce new formulations extracted from plants or herbs. Although a significant number of studies have used known purified plant chemicals, very few screening programmes have been initiated on crude plant materials. Virtually all cultures around the globe have relied historically, and continue to rely on medicinal plants for primary health care. There is currently a worldwide upsurge in the use of herbal preparations and the active ingredients isolated from medicinal plants in health care. Natural products from plants traditionally have provided the
pharmaceutical industry with one of its most important sources of lead compounds and up to 40% of modern drugs are derived from natural sources, using either the natural substance or a synthesized version. Herbs are still widely used today is not a throwback to the Dark Ages but an indication that herbs are a growing part of modern, high-tech medicine: about 25-30 percent of today's prescription drugs contain chemicals derived from plants. Some 119 chemical substances from 91 plants are now used in Western medicine. Of these, 74 percent were folk medicines brought to our pharmacies through scientific research. Researchers today examine folk or historical uses of plants to find new drugs for cancer, AIDS, and even the common cold [5]. There is accumulating scientific evidence that many of the natural herbs have medicinal properties that can alleviate symptoms or prevent disease. A growing number of researches have demonstrated that commonly used herbs such as green tea, licorice, Curcuma rhinocerous Nakai, cloves, Terminalia arjuna Linn., Euphorbia jolkini Bioss, Polygonum cuspidatum, Myrica rubra Sieb Zuce, Centella asiatica, Belasturum kavi, Ochrosia elliptica Labill, Stephania ierandrea, and Rhei Rhizoma possess chemopreventive properties that, in some cases, can be used therapeutically. These herbs have been found to possess significant antiproliferative activity against various cancer cells and this activity is supposed to be associated with the modulation of cell cycle progression and induction of apoptosis. Po-Lin Kuo et al. and his group summarize their findings from studies performed to date regarding the chemopreventive activities of the above-mentioned herbs and their ingredients on the various types of cancer cells [6].

Teresa Peccere. M. et al. and his group reported that aloe-emodin (AE), a hydroxyanthraquinone present in Aloe vera leaves, has a specific in vitro and in vivo antineuroectodermal tumor activity. The growth of human neuroectodermal tumors is inhibited in mice with severe combined immunodeficiency without any appreciable toxic effects on the animals. The compound does not inhibit the proliferation of normal fibroblasts or that of hemopoietic progenitor cells. The cytotoxicity mechanism consists of the induction of apoptosis, whereas the selectivity against neuroectodermal tumor cells is founded on a specific energy-dependent pathway of drug incorporation. Taking into account its unique cytotoxicity profile and mode of action, AE might represent a conceptually new lead antitumor drug [7].

Several hundred plant and herb species that have potentials novel antiviral agents have been studied, with surprisingly little overlap. A wide variety of active phytochemicals, including the
flavonoids, terpenoids, lignans, sulphides, polyphenolics, coumarins, saponins, furyl compounds, alkaloids, polyines, thiophenes, proteins and peptides have been identified. Some volatile essential oils of commonly used culinary herbs, spices and herbal teas have also exhibited a high level of antiviral activity. However, given the few classes of compounds investigated, most of the pharmacopoeia of compounds in medicinal plants with antiviral activity is still not known. Several of these phytochemicals have complementary and overlapping mechanisms of action, including antiviral effects by either inhibiting the formation of viral DNA or RNA or inhibiting the activity of viral reproduction. Assay methods to determine antiviral activity include multiple-arm trials, randomized crossover studies, and more compromised designs such as nonrandomized crossovers and preened post-treatment analyses. Nevertheless, the relative success achieved recently using medicinal plant/herb extracts of various species that are capable of acting therapeutically in various viral infections has raised optimism about the future of phyto-antiviral agents. From the literature there are innumerable potentially useful medicinal plants and herbs waiting to be evaluated and exploited for therapeutic applications against genetically and functionally diverse viruses' families such as Retroviridae, Hepadnaviridae and Herpesviridae.

Before 20th century, crude and semi-pure extracts of plants, animals, microbes and minerals represented the only medications available to treat human and domestic animal illnesses. The 20th century revolutionized the thinking in the use of drugs, as the receptor theory of drug action was postulated in. The idea that effect of drug in human body are mediated by specific interactions of the drug molecule with biological macromolecules, (proteins or nucleic acids in most cases) led scientists to the conclusion that individual chemical compounds in extracts, rather than some mystical “power of life” are the factors required for the biological activity of the drug. This made for the beginning of a totally new era in pharmacology, as pure, isolated chemicals, instead of extracts, became the standard treatments for diseases. Indeed, many bioactive compounds, responsible for the effects of crude extract drugs, and their chemical structure was elucidated. Classical examples of drug compounds discovered this way are morphine, the active agent in opium, and digoxin, a heart stimulant originating from flower Digitalis lanata. The evolution in synthetic chemistry also led to chemical synthesis of many of the elucidated structures.
Until the 1970s, the new drug compounds were almost solely of natural origin. However, as the fields of synthetic chemistry became more and more powerful, the pharmaceutical industry started to prefer synthetic compounds instead of natural products as drug candidates. The following reasons for the decline in interest in natural products as drug candidates have been suggested [8] introduction of high-throughput screening (HTS) as the standard method for hit discovery. The traditional natural product libraries were poorly suitable for HTS environment. The pressure to faster generation of lead compounds. The process in natural product drug discovery usually required several separation circles and structure elucidation (see below) and was thus time-consuming. Rise of combinatorial chemistry and thus the generation of synthetic compound libraries in a screening friendly format general decline in interest towards developing new antibiotic drugs, a traditionally strong area of natural product drug discovery.

However, more recent evolvements in techniques involved in natural product research, as well as the observation of the chemical complementarily of natural and synthetic compounds, have restored the interest in natural compounds as drug candidates. The declining trend in patents on natural products has turned as a slight increase in the beginning of the 21st century.

Despite the rise of combinatorial chemistry as an integral part of lead discovery process, the natural products still play a major role as starting material for drug discovery [9]. David Newman and Gordon Cragg have made a remarkable contribution to evaluation of the significance of natural products in drug discovery via their analysis of the sources of approved drugs. The latest update of the report is published in 2007 [10], covering years 1981-2006. According to their report, of the 974 small molecule new chemical entities, 63% were natural derived or nature-inspired (semi-synthetic derivatives of natural products, compounds synthesized by use of natural product pharmacophore or compounds otherwise designed to mimic the natural ligand/substrate of the target). For certain therapy areas, such as antimicrobials, antinecancer antihypertensive, anti-inflammatory drugs and the numbers were even higher for instance; approximately 75% of all approved small molecule new chemical entities were derived from nature.

Role of WHO in herbal medicine

Two decades ago, WHO referred to traditional health systems (including herbal medicine) as ‘holistic’ that of viewing man in his totality within a wide ecological spectrum, and of emphasizing the view that ill health or disease is brought about by an imbalance or disequilibrium
of man in his total ecological system and not only by the causative agent and pathogenic evolution (WHO), probably implying that the indigenous system drugs (including herbal medicine) restore the imbalance or disequilibrium leading to the cure of ill health or disease. Such an attitude sent signals that WHO as an organization has failed to provide leadership to establish traditional systems of medicine which provide health care to about 80% of the world population. However, it helped the inclusion of proven traditional remedies in national drug policies and regulatory approvals by developing countries. The World Health Assembly continued the debate and adopted a resolution (WHA 42.43) in 1989 that herbal medicine is of great importance to the health of individuals and communities. The redefined definition of traditional medicine thus issued in the early nineties is given vide supra (see herbal medicine). Consequently, in 1991 WHO developed guidelines for the assessment of herbal medicine, and the same were ratified by the 6th International Conference of Drug Regulatory Authorities held at Ottawa in the same year. The salient features of WHO guidelines are: (i) **Quality assessment:** Crude plant material; Plant preparation; Finished product. (ii) **Stability:** Shelf life. (iii) **Safety assessment:** Documentation of safety based on experience or/and; Toxicology studies. (iv) **Assessment of efficacy:** Documented evidence of traditional use or/and; Activity determination (animals, human). To the best of my knowledge, WHO has not systematically evaluated any traditional medicine [7].

*The global markets of herbs*

The largest global markets for MAPs are China, France, Germany, Italy, Japan, Spain, the UK and the US. Japan has the highest *per capita* consumption of botanical medicines in the world (Laird 1999). In the US and Europe, the trade has typically been growing at an average of 10 percent per annum, partly because of the popularity of alternative treatments and partly because there is increasing official recognition of the benefits of traditional medical systems involving herbal preparations. The International Council for Medicinal and Aromatic Plants expects world growth during 2001 and 2002 to be approximately 8-10 per cent a year (Srivastava 2000). The US has recently been an exception, with a sharp drop in sales. In 1997, the five top-selling species in the US were echinacea, garlic, ginkgo, golden seal and saw palmetto (Laird 1999). In 1999, the world market for herbal remedies was US$19.4 billion, with Europe in the lead (US$6.7 billion), followed by Asia (US$5.1 billion), North America (US$4.0 billion), Japan (US$2.2 billion) and the rest of the world (US$1.4 billion) (Laird and Pierce 2002). The market in China is large and
shared between public and private ownership. Thirteen of the top companies producing Traditional Chinese Medicines (TCMs) are listed publicly on the domestic stock exchange. China’s total output of medicinal plants from both cultivated and wild-harvested sources is 1.6 million tonnes (Kuipers 1997). The total value of the finished TCM sector in 1996 was US$3.7 billion. This estimate excludes domestic consumption, the inclusion of which would result in a far higher figure. Overall, sales of botanical medicine products in China in 1995 were estimated at US$5 billion (Laird 1999). The botanical medicine market in Japan in 1996 was estimated at US$2.4 billion. Japan has the highest per capita consumption of botanical medicines in the world, and sales have grown rapidly in recent years, in part because doctors increasingly incorporate TCM as a complement to western medicine. In 1983, 28% of doctors used TCM, but by 1989 this figure had risen to 69 per cent (Laird 1999). India is a major exporter of raw MAPs and processed plant-based drugs. Exports of crude drugs from India in 1994-95 were valued at US$53,219 million and of essential oils US$13,250 million (Lambert et al. 1997:31, Table 9). Important crude drugs included Plantago ovata (psyllium), Panax spp. (ginseng), Cassia spp. (senna) and Catharanthus roseus (rosy periwinkle). Essential oils included Santalum album (sandalwood), Mentha arvensis (peppermint) and Cymbopogon flexuosus (lemongrass). Seventy-five percent of total exports from India are sent to six countries – France, Germany, Japan, Switzerland, the UK and the US. Other major importers are Bangladesh, Pakistan and Spain (Lambert et al. 1997).

1.4 Herbal medicine scenario in India:

It is evident that the Indian people have tremendous passion for medicinal plants and use them for wide range of health relates applications from a common cold to memory improvement and treatment of various diseases [11-14]. In the old traditions local communities in every ecosystem from the Trans-Himalayas down to the coastal plains have discovered the medical uses of thousands of plants found locally in their ecosystem. India has one the richest plants medical culture in the world. It is a culture that is of the tremendous contemporary relevance because it can on one hand ensure health security to millions of people and on the other hand it can provide new and safe herbal drugs to the entire world. Demand for medicinal plant is increasing in both developing and developed countries due to growing recognition of natural products. Being non-narcotic, having no side-effects, easily available at affordable prices and sometime the only source of health care available to the poor. Medicinal plant sector has traditionally occupied an
important position in the socio-cultural, spiritual and medicinal arena of rural and tribal lives of India. The turnover of herbal medicines in India as over the counter products, ethical and classical formulations and have remedies of Ayurveda, Unani and Siddha systems of medicine is about $1 billion with a meager export of $80 million. 80% of the exports to developed countries are of crude drugs and not finished formulations leading to low revenue for the country. The list of medicinal plants exported from India are Aconitum species (root), Acorus calamus (rhizome), Adatoda vasica (whole plant), Berberis aristata (root), Cassia augustifolia (leaf and pod), Colchicum luteum (rhizome and seed), Hedychium spicatum (rhizome), Heracleum candicans (rhizome), Imula racemose (rhizome), Juglans regia (husk), Juniperus communis (fruit), Juniperus macropoda (fruit), Picrorhiza kurrooa (root), Plantago ovata (seed and husk), Podophyllum emodi (rhizome), Pinica granatum (flower, root and bark), Rauwolfia serpentina (root), Rheum emodi (rhizome), Saussurea lappa (rhizome), Swertia shirayita (whole plant), Valeriana jatamansi (rhizome), Zingiber officinale (rhizome). Five of these, i.e. Glycrrhiza glabra, Commiphora mukul, Plantago ovata, Aloe barbadensis and Azardica indica are used in modern medicine. Others are used in 52 to 141 herbal formulations and Triphala (Terminalia chebula, Terminalia bellerica and Embelica officinalis) along is used in 219 formulation. And India is one of the 12 mega biodiversity centres having over 45,000 plant species. Its diversity is unmatched due to the presence of 16 different agro-climatic zones, 10 vegetative zones and 15 biotic provinces. The country has 15,000-18,000 flowering plants, 23,000 fungi, 2500 algae, 1600 lichens, 1800 bryophytes and 30 million micro-organisms. India also has equivalent to 3/4 of its land exclusive economic zone in the ocean harbouring a large variety of flora and fauna, many of them with therapeutic properties. About 1500 plants with medicinal uses are mentioned in ancient texts and around 800 plants have been used in traditional medicine. According to an all India ethnobiological survey carried out by the ministry of environment of India, there are over 8000 species of plants being used by the people of India.

1.5 Survey of Plant-derived Drugs:

An increasing number of modern drugs have been isolated and purified from plant extracts. Well-known examples of plant-derived medicinal agents include the antimalarial drug quinine, isolated from the bark of Cinchona officinalis, the analgesics codeine and morphine from Papaver somniferum, the cardiac glycoside digoxin from Digitalis purpurea, the antihypertensive reserpine from Rauwolfia serpentina [15], and the anticancer drugs vinblastine 2 and vincristine 3, isolated
from the Madagascar periwinkle, *Catharanthus roseus* [8], to name a few. Of the established plant-
derived anticancer drugs, vinblastine 2 and vincristine 3 are still produced by their direct isolation
from the plant material [9] and *Catharanthus*, laxative anthraquinone glycoside from the plants of
*Cassia* family.

![Reserpine 1](image)

Vinblastine 2 R = CH$_3$

Vincristine 3 R = CHO

1.5.1 Infectious Diseases Area:
The occurrence of new bacterial and viral pathogens and the increasing clinical importance of drug-
resistant variants of well-known pathogens have given additional urgency to anti-infectious diseases
research in the last decades. Many effective antibacterial, antimicrobial, antiviral or antifungal agents
have been isolated from various plant species. (+)-Calanolide A 4 (phase I clinical trials) is a reverse
transcriptase inhibitor discovered from the Malaysian rainforest tree *Calophyllum lanigerum*
(Chusiaeaceae) by the U. S. National Cancer Institute. In vitro studies of this compound demonstrated its
effectiveness against the Human Immunodeficiency Virus Type 1 (HIV-1), including strains resistant
to AZT and other non-nucleoside reverse-transcriptase inhibitors. It also exhibited synergistic anti-
HIV activity in combination with nucleoside reverse-transcriptase inhibitors, including AZT, ddl, and
ddC. In an effort aiming at the discovery of more potent anti-HIV pyranocoumarins of the (+)-
calanolide A [15] type from plants of the genus *Calophyllum*, 31 species have been analyzed and their
anti-HIV activity tested [16]. In addition to isomers of (+)-calanolide A, more than 10 other
pyranocoumarins were isolated, among which soulattrolide 5 (from *C. teysmannii*), which was found
to be also a potent inhibitor of HIV-1 reverse transcriptase (*IC*$_{50}$ of 0.34 µM) [16, 28]. Two isomers of
this last compound, inophyllum B [8] and inophyllum P [17] were isolated from *C. inophyllum*, and
inhibited HIV reverse transcriptase with *IC*$_{50}$ values of 38 and 130 nM, respectively [19].
Another class of anti-HIV natural products, the atropisomeric naphthylisoquinoline alkaloids dimers, michellamines A, B, and C, were isolated from *Ancistrocladus korupensis* (Ancistrocladaceae), an extremely rare tropical rainforest plant of Cameroon [20]. The most potent and abundant member of the series, michellamine B [21], inhibited the enzymatic activities of reverse transcriptases from both HIV-1 and HIV-2. Enzymatic assays showed michellamine B [21] to inhibit drug-sensitive and drug-resistant HIV-1 and HIV-2 reverse transcriptases, including the AZT-resistant strain G910-6 [20, 22].

From the root bark of *Schumanniaphyton magnificum* was isolated the chromone secondary amine, schumannificine 9, which displayed activity against HIV, whereas potent anti-Herpes simplex (anti-HSV) activity was also observed for a number of its derivatives [23, 24]. Pancratistatin 10 is an Amaryllidaceae isoquinoline alkaloid isolated from the bulbs of the Hawaiian *Pancratium litorale* Jacq. [25], and which exhibited consistent *in vitro* activity against flaviviruses (Japanese encephalitis, yellow fever, and dengue viruses) and the bunyaviruses (Punta Toro and Rift Valley fever virus) [26].
In the early 1970's, the antimalarial artemisinin 11 was isolated [27, 28] from *Artemisia annua* L. (Asteraceae plant family), a plant used in traditional Chinese medicine for the treatment of febrile diseases. The drug is effective in treating chloroquine-resistant malaria and other severe cases without major toxicity. Its synthetic and fat-soluble analogue, artemether, which is a methyl ether of the corresponding lactol, is as effective as quinine in the treatment of severe malaria. The *in vitro* concentration at which artemisinin can inhibit 50% of the growth of *Plasmodium falciparum* ranges from 3 to 30 μg/L, while artemether is approximately twice as active. Artemisinin 11 and its derivatives have found their way into clinical use in many areas where malaria is endemic [21, 29].

Various tropical species from the Malpighiaceae plant family, which are used regularly by tropical tribe groups in South America, contain β-carboline alkaloids [30, 31]. In an *in vitro* test against epimastigotes of *Trypanosoma cruzi* (Costa Rica strain), one of these alkaloids, harmine 12, was effective in reducing growth for more than 90% at a concentration of 50 μg/mL, and showed significant activity at 5 μg/mL as an anti-Leishmanial compound [32].

### 1.5.2 Neurological Diseases Area:

Natural products research afforded some interesting compounds which are effective medicines for neurological diseases. Galanthamine 13, a natural product originally isolated from Caucasian snowdrop *Galanthus woronowii* [33], and the common snowdrop *Galanthus nivalis* [34] in the 1950s, is a long-acting, centrally active competitive cholinesterase inhibitor. It has also been found in several South African *Amaryllidaceae* [35]. *Galanthus* species have been used for hundreds of years in traditional medicine to treat painful neurological conditions such as facial neuralgia, with such treatment being essentially topical [21]. Galanthamine 13 has been used extensively as a curare reversal agent in anaesthetic practice in Eastern bloc countries [36]. In the 1990s, preliminary clinical trials have claimed that Galanthamine 13 has some beneficial effects in restoring cholinergic transmission in patients with Alzheimer's disease [37-39]. Phase II clinical trials carried out in
patients with senile dementia of Alzheimer’s type have shown a statistically significant improvement in cognitive performance [40].

Another example of a plant derived candidate for the treatment of Alzheimer’s disease is huperzine A 14. For several centuries, elderly people in some parts of mainland China have brewed Huperzia serata (Lycopodiacae) for improvement of their memory. In the early 1980’s, huperzine A 14 was isolated from this traditional medicinal plant [41-43] as a potent, reversible, and selective inhibitor of acetylcholinesterase [44]. In a prospective, multicenter, double-blind trial with 103 patients, huperzine A 14 induced improvement in memory cognition and behaviour in about 58% of patients with Alzheimer’s disease [45]. Because of the fact that the compound is produced at very low levels in nature, its total synthesis has been developed [46, 47].

1.5.3 Cardiovascular and Metabolic Diseases Area:

Recently, research efforts have been focussed on the discovery of oral antihyperglycemic agents for the treatment of Type II diabetes primarily from the screening of medicinal plants in animal models. A number of orally active natural products were shown to reduce blood glucose in these in vivo models [48]. An example of an active cardiovascular and metabolic plant-derived compound is forskolin (colforsin) 15, which is a labdane-type diterpene isolated from the Indian Coleus forskohlii (Lamiaceae) [49, 50]. The compound was first found to have blood pressure lowering and cardioactive properties [21, 51]. Due to its powerful and direct action on adenylate cyclase, therapeutic benefit in various diseases, such as congestive heart failure, hypertension, and asthma, has been expected. However, because of its low water solubility (0.0026%), the usage of forskolin 15 as a drug has been limited. To overcome this problem, semisynthetic efforts generated a water-soluble forskolin derivative, colforsin daproate (NIK-477) 16 which exhibited reversible effects on the respiratory, circulatory, and autonomic nervous systems. Its preliminary clinical trials demonstrated beneficial hemodynamic effects in heart failure patients. The compound was then brought into phase
II trials in Japan for treatment of asthma and phase III clinical trials for treatment of cardiac insufficiency [25, 56].

\[ \text{Forskolin 15} \]

\[ \text{Coforsin daproate 16} \]

1.5.4 **Immunological, Inflammatory, and Related Diseases Area:**

Interesting compounds with effective activity against immunological and inflammatory diseases have been isolated from some Chinese medicinal plants. Triptolide 17 is a major active component isolated from *Tripterygium wilfordii* (Celastraceae), a plant traditionally used in China for the treatment of rheumatoid arthritis. A variety of formulations of the plant extract was developed in mainland China and was shown to be effective in the treatment of patients with inflammatory and autoimmune diseases. The compound was demonstrated to significantly inhibit arthritis in animal models. The immunosuppressive effect is mediated by inhibition of IL-2 signal transduction [21].

\[ \text{Triptolide 17} \]

\[ \text{Ginkgolide B 18} \]

\[ \text{Gomisin A 19} \]

*Ginkgo biloba* (Ginkgoaceae) is a Chinese tree which has been used therapeutically for thousands of years. Ginkgolides, a class of unique diterpene cage-like compounds, are among the natural products isolated from the leaves. In the late 1980's, it was demonstrated that the ginkgolides were highly active as selective platelet-activating factor (PAF) receptor antagonists. One of them, ginkgolide B (BN-52021) 18, has been advanced to phase III clinical trials for the treatment of septic shock in patients with severe sepsis caused by Gram-negative bacterial infections. Good results were also found in inflammatory and autoimmune disorders [53, 54]. Another plant-derived drug of immunological
activity is gomisin A [24], a lignan derivative isolated from the dry fruits of *Schisandra chinensis*, a plant used in Chinese traditional medicine for the treatment of liver intoxication. Gomisin A [24] was found to protect against hepatocarcinogenesis and liver damage in various animal models. Its mechanism of action includes induction of hepatic metabolizing enzyme systems, increase in the proliferation of the endoplasmic reticulum of liver cells, and antioxidant activity [55].

1.5.5 Oncological Diseases Area:

Plants have a long history of use in the treatment of cancer [56], although many of the claims for the efficacy of such treatment should be viewed with some skepticism because cancer, as a specific disease entity, is likely to be poorly defined in terms of folklore and traditional medicine [1]. Of the plant-derived anticancer drugs in clinical use, the best known are the so-called *Vinca* alkaloids, vinblastine 2 and vincristine 3, isolated from the Madagascar periwinkle, *Catharanthus roseus* [14] in the early 1960's. In the 1970's, combretastatin A-4 [24] was isolated from *Combretum caffrum* (Combretaceae), an African willow tree that has a history of being used by the Zulu for various purposes. The compound 20 has proved to be a powerful inhibitor of tubulin assembly and a variety of human cancer cell lines [57]. The toxicity of European yew trees has been known for thousands of years [58] and the use of various parts of some of the species (e.g., *Taxus brevifolia*, *T. canadensis*, *T. baccata*) by several native American tribes for the treatment of some non-cancerous conditions has been reported [56]. However, it was only in the 1960's, that laboratory tests demonstrated that the extracts of the Western Pacific Yew, *Taxus brevifolia* (Taxaceae), could kill cancer cells [59]. The active compound, the diterpenoid paclitaxel (Taxol®) 21, was initially isolated from a species collected in USA, Washington State [60]. In test systems using human tumor cell lines, paclitaxel 21 showed distinct activity against several types of cancer, while phase I clinical studies have shown that this compound has significant clinical benefit for the treatment of ovarian and breast cancer (46). As paclitaxel 21 occurs in low yield in the bark of the Western Pacific yew, its production as a clinical drug is problematic. A related diterpenoid, baccatin III, and other key precursors (the baceatins) occur in higher yields in the needles (which represent a renewable source for the tree) of several species of *Taxus*. Semisynthetic modification of baccatin III readily led to the paclitaxel analogue docetaxel (Taxotere) 22, which proved to be a serious rival of paclitaxel 21 [58, 61].
1.6 Agrochemicals of Plant Origin

1.6.1 General Overview:

Enhancement of health quality by fighting against endemic and novel diseases is certainly one of the major challenges for the whole world today. However, pest management is also an important and vital component in actual production of food, which is needed in increasing quantities to meet the demands of the world’s burgeoning population. The main important strategy of this management is the use of chemicals to control insect (but also bacteria, fungi and viruses) pests, which not only attack plants and plant products at various stages of production, but also destroy structures and transmit human and livestock diseases. There are approximately one million insect species in the world, representing 70% of all species in the animal kingdom. Of these, around 10,000 have been recognized as harmful. It has been estimated that 14% of crop losses worldwide are caused by insect pests. Thus, control of harmful insects is a must for mankind [62]. But there is an enormous scope for the discovery of safer, more potent, and environmentally non-polluting insecticides. Because biologically derived chemicals are perceived by consumers as having less environmental toxicity and lower mammalian toxicity, chemical companies currently tend to have a greater desire to discover and develop natural product-based plant pesticides [63]. At present, the commercial success is below the results expected. Of the various strategies used for developing new biologically active compounds for specific applications, probing nature’s bounty of so-called secondary metabolites has proved quite effective in the past, and promises to remain so in the future. These secondary metabolites are now thought to mediate plant defense mechanisms by producing chemical barriers against animal and microbial
predators. Plants must also compete with other plants (allelopathic interactions), often of the same species, for sunlight, water and nutrients. This chemical warfare between plants and their pathogens consistently provides new natural product leads [62]. Plant-derived substances have been used as botanical pesticides since ancient times, as attested by the so-called “Persian dust” or “Persian insect powder” (Pyrethrum) [63]. However, from early Roman times to the mid-20th century, only pyrethrins, rotenone, nicotine, sabadilla and quassin were widely used as insect repellents and toxicants in the Western hemisphere [64]. Over 2000 plant species belonging to some sixty families (Table 1.1) are now known to possess insecticidal properties. Of these, the following families have provided plants of commercial value, both present and past: Asteraceae (Compositae), Flacourtiaceae, Fabaceae (Leguminosae), Liliaceae and Solanaceae [62].

1.6.2 Few Examples of Plant-derived Insecticides:
Currently and commercially, the most important insecticidal plant widely used is pyrethrum [65], which consists of the fried flower-heads of any of the two species of the genus Chrysanthemum (Family: Asteraceae) now revised to the genus Tanacetum [66]: the Persian insect flower (red flower), T. coccineum Willd and the Dalmatian insect flower (white flower) T. cinerariaefolium Vis. Of the two species, T. cinerariaefolium, a native to former Yugoslavia, is commercially the most important and is cultivated on a large scale in Kenya, Tanzania, Ecuador, Brazil, Russia, Japan and India. The insecticidal principles of pyrethrum have been fully characterized [65, 67] and consist of six esters, namely pyrethrins 23a-f belonging to the two series I, II. Esters of Series-I is derivatives of (+)-Trans-chrysanthemiacid and have excellent insect killing properties, while series-II, derived from pyrethric acid, has high knock-down activity. Products based on pyrethrum are essentially used for indoor applications.

![Chemical structure of pyrethrins](pyrethrin.png)
Pyrethrins are quite photolabile and their half-life in open environment is such that their use on agricultural crops is excluded essentially on economic grounds. On the other hand, they have a high safety margin for mammals (LD50 for pyrethrin I 23a: 260-400 mg/kg, rat, oral), chiefly because of their rapid metabolic disposal. Thus, there has been a distinct need to develop pyrethrin analogues, which would be photostable, safe and environmentally nonpersistent [62, 63]. Intense efforts aiming at the latter goal led, in between the late 1940's and the late 1960's, to the synthesis of several very effective household insecticides, namely the so-called pyrethroids [68-70], opening a major area of industrial and academic research. The development of pyrethroids has been one of the major success stories in the use of natural products as a source of leads for novel compounds possessing useful insecticidal activity. Their synthesis strategies lay in the modulation of the natural pyrethrins, both in the carboxylic acid as well as in the alcohol moieties. The neem tree or margosa, *Azadirachta indica*, A. Juss (Meliaceae) is widespread in many Asian and African countries. Centuries before synthetic insecticides became available, farmers in India protected crops with natural repellents found in neem fruits and leaves [71]. The active principles or “bitters” have been identified as limonoids, a group of stereochemically homogenous tetratorniterpenoids. The most potent and chemically the most important of them is azadirachtin 24, although some 64 triterpinoids have been reported from the seeds, wood, bark, leaves, and fruit of the neem tree [72, 73]. Neem derivatives have diverse behaviour and physiological effects ranging from repellency to feeding deterrence, growth disruption, sterilizing effects, mating disruption, oviposition inhibition, etc. [74, 75].

Two other phytoinsecticides [76], sabadilla [77, 78] and ryania [77, 79] may be mentioned. Sabadilla is the dried powdered barley-like ripe seeds of the South and Central American plant *Schoenocaulony officinale* Gray (Liliaceae), also known as *Sabadilla officinalis* Brant, and *Veratrum sabadilla* Retz
which the local people had been using for a long time to control insect-infestation. The major insecticidal components of Sabadilla are veratridine 25, the 3-veratronyl [3-(3,4-dimethoxybenzoyl)], and cevadine 26, the 3-angenoyl [3-(Z)-2-methylbut-2-enoyl] derivative of veracevone 27. These alkaloids are highly poisonous (e.g., LD_{50} for veratridine 25: 1.35 mg/kg, mouse, intraperitoneal) [62, 74]. Veratridine 25 is one of several alkaloids identified as neurotoxins that affect sodium ion channels in excitable membranes [78]. An extensive study on the effect of varying the nature of the acyl group, attached to the 3-position (sixty-five 3-acyl derivatives tested) of veracevone 27, on insecticidal activity and toxicity to mice has been reported. Of all the derivatives, the naturally occurring veratridine 25 and cevadine 26 were near optimal in potency [78]. Ryania consists of the powdered roots and stems of the South American plant *Ryania speciosa* Vahl (Flacourtiaeae) and has been used as a contact and stomach poison to insects [62, 75]. The active principle is the diterpene ryanodine 28 which is present in the roots with a yield of 0.1-0.25%. It is less photolabile than pyrethrum and its mammalian toxicity is also low (LD_{50}: 750 mg/kg, rat, oral) [62]. Dehydroryanodine 29 was also isolated from Ryania. The two compounds were found essentially equipotent and accounted for almost all of the biological activity of Ryania insecticide [60c].

![Chemical structures of ryanodine and dehydroryanodine.](image)

The sesquiterpene polyol ester angulatin A 30 is claimed to be strongly antifeedant (and insecticidal) against a variety of insects [80]. Angulatin A 30 and close antifeedant analogues [81] are derived from the root bark of *Ceiba angulatus* Max. (Celastracae), which is used, in China, to protect plants from insects [75]. From the seeds of *Croton tiglium* L. (Euphorbiaceae) was isolated the tigliane diterpene ester 31 which showed both growth inhibitory and insecticidal activities in diet against newly hatched larvae of *Pectinophora gossypiella* (100% kill at 20 ppm) [82]. It also gave 100% kill of *Culex pipiens* larvae at 0.6 ppm but was ineffective against *Oncopeltus fasciatus* and *Tribolium confusum*. Esters of this type are also well-known for their vesicant and tumorpromoting properties.
Several quassinoid drugs have been used for a long time for their tonic and insecticidal properties [31]. A series of antileukemic and cytotoxic quassinoids, isolated from Simaba multilora Juss and Soulaunea soulaneoides (Gray) Nootboom (Simaroubaceae), were evaluated in diets for their growth-inhibitory and insecticidal activities against the tobacco budworm Heliothis virescens and for their antifeedant activity against H. virescens and the fall armyworm Spodoptera frugiperda [83]. The most effective quassinoid was 6a-senccioyloxychaparrinone 32 which was equivalent to azadirachtin 24 as a growth inhibitor of newly hatched H. virescens but was, at an LDso of 7 ppm, 2.5-3.5 times less toxic [75].

\[ \text{[Image of chemical structures]} \]

**1.7 Medicines for dermatological disorder:**

Several molecules are available for the treatments of the skin disease. Some of them are described bellow.

**Impetigo:** This is a common skin condition and is characterized by superficial bacterial infection caused by Staphylococcus aureus or streptococci. Generally, it is a mixed infection. The primary lesion is a superficial pustule that ruptures and forms a typical yellow brown crust. The lesion may occur on normal skin or may be superimposed upon another skin disease such as pediculosis. The condition usually responds well to topical antibiotic therapy but systemic antibiotics are preferred in certain circumstances. Improvement of personal hygiene is important in therapy. After gentle cleaning and debridement of the adherent crusts, application of an ointment containing neomycin 1%, framycetin 1.5% bacitracin 1% or mupirocin 2% is recommended. Topical use of antibiotics such as gentamicin and penicillin, which are valuable for the treatment of systemic illnesses, should be avoided, as they are liable to sensitize the skin. Systemic therapy is also recommended in patients with renal and heart disease, with coexisting eczema and in those on immunosuppressive drugs.
Furuncle or Boil: This is an acute infection of the hair follicle commonly caused by staphylococci. In healthy individuals, it responds to fomentation and the use of anti-septic drugs like chlorhexidine. In severe cases and in those with persistent lesions, cream containing neomycin, framycetin or mupirocin may be applied. Patients who develop boils frequently may require long term treatment with an appropriate antibiotic. In such cases, an underlying systemic disease like diabetes mellitus or uremia should be excluded.

Herpes simplex and Herpes zoster: Herpes simplex can be treated by topical application of 5% acyclovir or of 1% penciclovir. Both these drugs are applied 4 to 5 times a day. Topical acyclovir is, however, less effective than systemic acyclovir, and it offers no significant clinical advantage in acyclovir genital herpes. In severe cases involving the mucosae, acyclovir is given by the oral or IV route. The oral dose of acyclovir is 200 mg. five times a day for 10 to 14 days. Infections due to herpes zoster also respond to acyclovir and idoxuridine, but to a lesser extent than herpes simplex. In severe cases of herpes zoster, acyclovir is administered IV in dose of 5 mg/kg every 8 hours for 5 days. Alternatively, vidarabine can be infused IV in the dose of 15 mg/kg once daily, over 12 hours, at a concentration of 0.5 mg/ml. Use of corticosteroids in herpes zoster is controversial.

Post-herpetic neuralgia may respond to local application of 2% capsaicin, and to analgesics. Drugs like amitryptyline, gabapentine and carbamazepine are also beneficial.

Warts: Warts are human papilloma-virus induced benign proliferation of the skin and mucosa. Most of the patients do not need any treatment as warts are known to undergo spontaneous regression within 1 to 2 years. Several methods are used to treat warts. These range from cryotherapy and electro-desiccation to carbon dioxide laser ablation. Warts can also be treated by local application of keratolytic agents like salicylic acid in flexible collodion. Other topical drugs include podophyllin 15 to 25% solution, trichloracetic acid and phenol. Formaldehyde (5% solution) and podophyllin are particularly useful in the management of plantar warts. Silver nitrate in the form of pencil may be used to cauterise the warts. Care must be taken to protect the surrounding skin.
1.7.1 Drug Therapy of Fungal Skin Infections:

For therapeutic purposes, fungus infections (mycoses) have been classified as superficial (affecting the skin, and its appendages hair and nails), subcutaneous and deep. The common fungi, which cause superficial skin infection are:

- The dermatophytes (trichophyton, microsporon and epidermophyton) which cause ringworm (dermatophytosis).
- The candida species which cause mucocutaneous candidiasis; and
- Pityrosporon orbiculare, also known as Malassezia furfur, which causes tinea versicolor.

Majority of superficial fungal infections can be treated by local antifungal agents. Only chronic, resistant infections may need systemic antifungal therapy with griseofulvin or an azole. Because tinea infections of the foot are often complicated by bacterial infections and other factors, an ideal antifungal medication for the foot should have antifungal and antibacterial properties and a drying effect. A solution or a cream containing an azole such as clotrimazole and miconazole meets these requirements and also covers the candida; such a preparation is suited for treating tinea pedis. For systemic antifungal agents,

**Topically useful antifungal agents:**

Benzoic acid and Salicylic acid: These agents possess antifungal properties. Salicylic acid is a comparatively weak antifungal agent but has keratolytic properties. Benzoic acid compound ointment (Whitfields ointment) contains 6% of benzoic acid and 3% of salicylic acid in an emulsifying ointment. This is a commonly employed and effective preparation in the treatment of dermatophytosis. Sometimes it may cause local irritation.

**Miconazole (Daktarin, NuFunge):** Miconazole nitrate is a synthetic imidazole compound, effective topically against dermatophyte infections, candidiasis and gram-positive bacteria. Applied as a 2% cream, twice daily for 2-4 weeks, it is effective in the treatment of fungal skin infections such as tinea cruris (groin) and tinea pedis (foot). It produces prolonged remission and the incidence of recurrence is claimed to be low. The drug is well tolerated and does not stain skin and clothes. It may be used in resistant cases. Miconazole has been used IV and intrathecally in the treatment of systemic fungal infections

**Clotrimazole (Imidi):** This synthetic, imidazole antimycotic agent is effective against a variety of human pathogenic fungi including Histoplasma capsulatum, Coccidioides immitis, Cryptococcus
neof Funeral, Sporotrichum schenckii, Candida and Aspergillus. It is effective as a systemic antifungal agent on oral administration. Topically, it is useful in treating skin and vaginal infection due to M. furfur and C albicans. The drug may rarely cause local erythema and blistering.

Ketoconazole (Fungicide): This imidazole, antifungal drug is chemically related to miconazole. It has similar broad spectrum, antifungal actions and can also be given orally to treat superficial and deep fungal infections. The drug is toxic to the liver and should be used orally, only to treat extensive or resistant dermatophytosis of the trunk, dermatophytosis of scalp and nails, and persistent and distressing superficial candidiasis Fluconazole is an alternative to ketoconazole and is claimed to be safer. The other imidazole drugs available for topical antifungal therapy are butoconazole, econazole, oxiconazole, sulconazole and terconazole.

Tolnaftate (Tinaderm): This drug is effective in the treatment of superficial fungal infections of the skin caused by trichophyton and epidermophyton though its superiority over the older antifungal preparations is not established. The drug is not effective against fungal infection of nails and hair, and relapses are frequent when it is employed in the treatment of Trichophyton rubrum of the trunk. It is used as 1% solution or cream, and is nonirritating, nonstaining and odourless.

Undecylenic acid: This drug is applied to the skin in the concentrations of 2 to 15 per cent, sometimes in combination with zinc undecylenate in the treatment of dermatophytoses, particularly tinea pedis. For application to mucous surfaces, a concentration exceeding 1 per cent should not be used as it may cause burning.

Ciclopirox olamine (Loprox, Batrafen): This drug not related chemically to the imidazole is as effective as the imidazoles in the treatment of cutaneous candidiasis and dermatophytoses, as well as in tinea versicolor. It causes minor local but no systemic adverse effects. It is available as 1% cream.

Terbinafine: Terbinafine is an allylamine. Applied as 1% cream or solution daily for 1-2 weeks, it is effective in dermatophyte infections. It may cause local irritation. Naftifinene 1% also has similar activity.

Selenium sulfide (Selsun): This drug has been used in the treatment of tinea versicolor, a chronic fungal infection, caused by Malassezia furfur. It is also temporarily effective in the treatment of
dandruff. It has mild toxicity but possesses unpleasant odour. It is irritant to the eyes. The drug is commonly used as a 2.5% suspension: the preparation is applied once daily for 5 days to the wet skin, lathered in place for 15-20 minutes and then washed thoroughly. After that, one application once a month is continued to prevent re-infection.

Ichthammol (Ammonium ichthosulfonate): Ichthammol consists of the ammonium salts of the sulfonic acids in an oily substance prepared from the distillate of butuminous schist or shell or from other sources, together with ammonium sulfate and water. It is an almost black, viscid liquid with a strong and a characteristic odour, soluble in water. It is slightly irritant to the skin. Ichthammol is used as 10% cream and ointment in the treatment of resistant dermatomycoses and other chronic skin diseases.

Other topical fungicidal agents: include tincture iodine, iodophors, haloprogin, phenol, oxidising agents e.g. potassium permanganate and dyes like gentian violet. Fungicidal actions of iodochlorhydroxyquinoline 3% and nystatin have already been discussed. It must be emphasized that fungal skin infections and scabies (discussed later) are common among the population from warm and humid climate, particularly in those with unhygienic habits. Simple personal hygiene and environmental control measures usually suffice to limit the infection and hence, preventive measures such as cleanliness and mass education are far more important than any drug.

1.8 Herbs medicine for dermatological disorder:

Over viewing to the present trend of using herbal medicinal plants as medicines, the present investigational study for the dermatological disorder [84-86] and other biological activity for the plants of cassia family and rubiaceae have been carried out. After studying the literature regarding the plant it was seen that this plant is efficacious for the treatment of skin disease. The role of plants in the protection of the skin may be come from a number of perspectives. Plants oils may be used to form a protective emollient layer that reduces transepidermal water loss and so increase the hydration of the straturn corneum. This not only forms a lubricious layer of fatty acids on the skin but also increases the “plumping” of the tissue, so contributing to a smoothing of the wrinkles. The presence of reactive free radicals can be ‘mopped up’ by the use of antioxidants and free-radical scavengers. The use of sunscreens will also reduce the potential of solar damage. There is an increasing body of evidence to suggest that some plants can provide a prophylactic function. The need to tan seems to be an irrepressible desire for many people and though one can tan safely
without erythema and dangerous cellular damage, it is the feeling of most dermatologists that the ageing process is accelerated by tanning, regardless of the precautions that have been taken. The provision of cellular regeneration from plant sources is theoretically possible through the use of phytosterols and phytohormones and there are many other chemical entities within plants that can reduce erythema, reduce swelling and repair skin damage. Skin care today is big and growing business. If one peruses the cosmetics section of any departmental store, one can easily become overwhelmed, not only with the choices offered, but also with the prices. For example, American people spend more than 45 billion dollars annually on cosmetics and 6,000 to 10,000 new products are introduced every year. The similar situation is in India. In India and in some other countries, people are using chamomile, fennel, lavender, aloe vera, lemon balm, pot marigold, red clover, rose, and plants of cassia family for the preparation of herbal products. Plants from cassia family and its related family are identified as a potential source for herbal medicine. This family contains anthraquinone derivatives in their structures and are potentially using in skin diseases like Acne, Eczema, Herpes, Psoriasis, Ringworm. Herbs have been used in clinical medicine for thousands of years. Our ancient identified very reach tradition about the uses of Herbs in the curing of several diseases. In this context we have chosen some medicinally important plants according to their utility.

1.8.1 Skin Order:
In zootomy and dermatology, skin is an organ of the integumentary system made up of multiple layers of epithelial tissues, which guard underlying muscles and organs [87]. As the interface with the surroundings, it plays the most important role in protecting against pathogens. Its other main functions are insulation and temperature regulation, sensation and vitamin D and B synthesis. Skin is considered one of the most important parts of the body. Skin has pigmentation, or melanin, provided by melanocytes, which absorb some of the potentially dangerous ultraviolet radiation in sunlight. It also contains DNA repair enzymes which help to reverse UV damage, and people who lack the genes for these enzymes suffer high rates of skin cancer. One form predominantly produced by UV light, malignant melanoma, is particularly invasive, causing it to spread quickly, and can often be deadly. Human skin pigmentation varies among populations in a striking manner. This has sometimes led to the classification of people on the basis of skin color. Mammalian skin often contains hairs, which in sufficient density is called fur.
The hair mainly serves to augment the insulation the skin provides, but can also serve as a secondary sexual characteristic or as camouflage. On some animals the skin is very hard and thick, and can be processed to create leather. Reptiles and fish have hard protective scales on their skin for protection, and birds have hard feathers, all made of tough β-keratins. Amphibian skin is not a strong barrier to passage of chemicals and is often subject to osmosis. A frog sitting in an anesthetic solution will quickly go to sleep. Damaged skin will try to heal by forming scar tissue, often giving rise to discoloration and depigmentation of the skin.

The skin is often known as "the largest organ of the human body". This applies to exterior surface, as it covers the body, appearing to have the largest surface area of all the organs. Moreover, it applies to weight, as it weighs more than any single internal organ, accounting for about 15 percent of body weight. For the average adult human, the skin has a surface area of between 1.5-2.0 square meters; most of it is between 2-3 mm thick. The average square inch of skin holds 650 sweat glands, 20 blood vessels, 60,000 melanocytes, and more than a thousand nerve endings. The use of natural or synthetic cosmetics to treat the appearance of the face and condition of the skin (such as pore control and black head cleansing) is common among many cultures.
Skin is composed of three primary layers: the epidermis, which provides waterproofing and serves as a barrier to infection; the dermis, which serves as a location for the appendages of skin; and the hypodermis (subcutaneous adipose layer), which is called the basement membrane.

The outermost epidermis consists of stratified squamous epithelium with an underlying connective tissue section, or dermis, and a hypodermis, or basement membrane. The epidermis contains no blood vessels, and cells in the deepest layers are nourished by diffusion from blood capillaries extending to the upper layers of the dermis. The main types of cells make up the epidermis, which are keratinocytes, with melanocytes and Langerhans cells also present. The epidermis can be further subdivided into the following strata (beginning with the outermost layer): corneum, lucidum, granulosum, spinosum, basale. Cells are formed through mitosis at the basale layer. The daughter cells, (see cell division) move up the strata changing shape and composition as they die due to isolation from their blood source. The cytoplasm is released and the protein keratin is inserted. They eventually reach the corneum and slough off (desquamation). This process is called keratinization and takes place within about 30 days. This keratinized layer of skin is responsible for keeping water in the body and keeping other harmful chemicals and pathogens out, making skin a natural barrier to infection.

Blood capillaries are found beneath the epidermis, and are linked to an arteriole and a venule. Arterial shunt vessels may bypass the network in ears, the nose and fingertips. The dermis lies below the epidermis and contains a number of structures including blood vessels, nerves, hair follicles, smooth muscle, glands and lymphatic tissue. It consists of loose connective tissue otherwise called areolar connective tissue - collagen, elastin and reticular fibers are present. Erector muscles, or arrector pili muscles attached between the hair papilla and epidermis, can contract, resulting in the hair fibre pulled upright and consequentially the formation of goose bumps. Sebaceous glands are exocrine glands which produce sebum, a mixture of lipids and waxy substances: lubrication, water-proofing, softening and antibacterial actions are among the many functions of sebum. Sweat glands open up via a duct onto the skin by a pore.

The dermis can be split into the papillary and reticular layers. The papillary layer is the outermost and extends into the epidermis to supply it with nutrients. It is composed of loosely arranged fibres. Papillary ridges make up the lines of the hands and feet, producing individually unique
finger prints and foot prints. The reticular layer is denser and is continuous with the hypodermis. It contains the bulk of the structures (such as sweat glands). The reticular layer is composed of irregularly arranged fibres and resists stretching. The hypodermis is not part of the skin, and lies below the dermis. Its purpose is to attach the skin to underlying bone and muscle as well as supplying it with blood vessels and nerves. It consists of loose connective tissue and elastin. The main cell types are fibroblasts, macrophages and adipocytes (the hypodermis contains 50% of body fat). Fat serves as padding and insulation for the body.

1.8.1.2 Types of the skin:

Skin can be divided into two types thick and thin. Thick skin is present on the soles of the feet and the palms of the hands. It has a larger stratum corneum with higher keratin content. Thick skin does not grow hair; its purpose is to help grip. Thin skin is present on the bulk of the body and has a smaller stratum corneum and fewer papillae ridges. It has hair and is softer and more elastic. The characteristics of the skin, including sensory nerve density and the type of hair, vary with location on the body [87].

1.8.1.3 Function of the skin:

1. Protection: an anatomical barrier between the internal and external environment in bodily defense; Langerhans cells in the skin are part of the adaptive immune system
2. Sensation: contains a variety of nerve endings that react to heat, cold, touch, pressure, vibration, and tissue injury; see somatosensory system and touch.
3. Heat regulation: the skin contains a blood supply far greater than its requirements which allows precise control of energy loss by radiation, convection and conduction. Dilated blood vessels increase perfusion and heat loss while constricted vessels greatly reduce cutaneous blood flow and conserve heat. Erector pili muscles are significant in animals.
4. Control of evaporation: the skin provides a relatively dry and impermeable barrier to fluid loss. Loss of this function contributes to the massive fluid loss in burns.
5. Aesthetics and communication: others see our skin and can assess our mood, physical state and attractiveness.
6. Storage and synthesis: acts as a storage centre for lipids and water, as well as a means of synthesis of vitamin D and B by action of UV on certain parts of the skin. This synthesis
is linked to pigmentation, with darker skin producing more vitamin B than D, and vice versa.

7. Excretion: The concentration of urea is 1/130th that of urine. Excretion by sweating is at most a secondary function to temperature regulation.

8. Absorption: Oxygen, nitrogen and carbon dioxide can diffuse into the epidermis in small amounts, some animals using their skin for their sole respiration organ. In addition, medicine can be administered through the skin, by ointments or by means of adhesive patch, such as the nicotine patch or iontophoresis. The skin is an important site of transport in many other organisms.

1.8.1.4 Hygiene:
The skin must be regularly cleaned. Unless enough care is taken it will become cracked or inflamed. Unclean skin favors the development of pathogenic organisms. The constantly peeling off dead cells of the epidermis mix with the secretions of the sweat and sebaceous glands and the dust found on the skin to form a filthy layer on its surface. If not washed away, the dirt and dead skin slurry begins to decompose emitting a foul smell. Functions of the skin are disturbed when it is dirty and it becomes more easily damaged because the release of antibacterial compounds decreased. Dirty skin is more prone to develop infections. Cosmetics should be used carefully because these may cause allergic reactions. Each season requires suitable clothing in order to facilitate the evaporation of the sweat. Sunlight, water and air play an important role in keeping the skin healthy.

The skin supports its own ecosystems of microorganisms, including yeasts and bacteria, which cannot be removed by any amount of cleaning. In general these organisms keep one another in check and are part of a healthy skin. When the balance is disturbed, e.g., by antibiotics which kill bacteria, there may be an overgrowth and infection by yeasts. The skin is continuous with the inner epithelial lining of the body at the orifices, each of which supports its own complement of flora.
1.8.1.5 Skin Disorder:

There are many types of skin disorders reported some of them are very common like Scabies, Herpes, Dandruff, Acne, Psoriasis, Ringworm, etc.

![Figure 1.2](image)

**Figure 1.2** Photograph of Scabies infected human skin and Electron Micrograph of scabies mite

1.8.1.5.1 Scabies:

Scabies also known as "the itch" is an intensely itching rash caused by a tiny mite (bug) that lives in the skin. Since it is only $\frac{1}{60}$th inch long, the scabies mite is almost impossible to see without magnification. The rash usually involves the hands, wrists, breasts, genital area, and waistline. In severe cases scabies can spread to almost the entire body, but rarely the face. Scabies often resembles other rashes. The only way to find out whether you have scabies is for a doctor to scrape off a piece of skin and examine it under a microscope.

**Causes:**

- Scabies is caused by a little mite.
- Scabies is transmitted by close personal contact.
- Scabies is very contagious.

**Treatment:** Treatment consists of applying a mite-killing medication. The usual treatment is either a cream containing permethrin or a lotion containing malathion. These kill the mite. Apply the medicine before bed to all of your skin from the neck down, not just to the itching areas. Rub the medicine thoroughly into your hands, wrists, body folds, and under the fingernails. Do not wash your hands for eight hours. Wash the medicine off the next morning. Repeat the application
as above exactly one week after the first treatment. Wash all linen and cloths in hot water. itching and rash may continue even though all the mites have been killed. This results from allergy to the mites and is called postscabetic dermatitis. Postscabetic dermatitis is not scabies, and requires special treatment. Don't try to treat it with the mite-killing medicine. The itching rash of scabies usually clears up in 2-6 weeks if you carry out your treatment exactly as instructed and all close personal and sexual contacts are treated at the same time.

1.8.1.5.2 Herpes:
The word "herpes" is taken from the Greek word "herpein" which means "to creep." The herpes simplex viruses are double-stranded DNA viruses that only infect humans. There are two types of herpes simplex viruses:

- Herpes simplex virus type 1 (HSV-1)
- Herpes simplex virus type 2 (HSV-2)

![A Course of Shingles](image)

**Figure 1.3** 3D-Photograph of the HSV-infected human Skin, lip and Palm

The figure No 1.3 shows that The reawakened virus generally causes a vague burning sensation or tingling over an area of skin. A painful rash usually occurs two to five days after the first
symptoms appear. A cluster of small bumps (1) turns into blisters (2) that resemble chickenpox lesions. The blisters fill with pus, break open (3), crust over (4), and finally disappear. This process takes four to five weeks. A painful condition called post-herpetic neuralgia can sometimes occur. This condition is thought to be caused by damage to the nerves (5), and can last from weeks to years after the rash disappears.

Herpes Simplex Virus Infections: A person can be infected with one or both herpes viruses. It has generally been believed that HSV-1 infections occurred in the mouth and HSV-2 infections occur in the genital area. Now it has been shown that either type of virus can infect either site.

How the Herpes Simplex Virus Works:

⇒ The virus comes in contact with broken skin or the lining of the mouth, vagina, or anus.
⇒ The virus goes to the nuclei of the cells and tries to reproduce itself, or replicate.
⇒ Though the cells are infected, most people do not get symptoms.
⇒ Sometimes the virus's replication process destroys the cells it has invaded causing blisters or ulcers to form on the skin.
⇒ The blisters or ulcers crust over and heal without scarring.
⇒ The virus is transported back through the nerve to important nerve branching points called ganglia deep in the body.
⇒ The virus stays in the ganglia in an inactive, or latent, form. During this time, the virus does not replicate. It stays in this latent form for varying amounts of time.
⇒ Certain triggers may cause the virus to travel back down the nerve to the skin and cause symptoms again. This is known as recurrence.

Causes of Herpes Simplex Virus Recurrences

Even with a normal immune system, recurrences can happen. Sometimes the recurrence occurs spontaneously. However, the following are known triggers that can stimulate a recurrence:

- Physical stress
- Poor emotional coping style
- Persistent stressors for greater than 1 week
- Anxiety
- Fever
- Exposure to ultraviolet light
- Nerve damage

**Figure 1.4** 3D-Photograph of healthy and infected skin.[inflamed hair follicle]

- Tissue damage
- A suppressed immune system
- Heat
- Cold
- Menstruation
- Other infections
- Fatigue

1.8.1.5.3 Acne:

Acne is a common skin disorder characterized by clogged pores and pimples. Acne is not a serious health threat but, it can cause scars. Acne is most common during adolescence, affecting more than 85% of teenagers, and frequently continues into adulthood [88]. For most people, acne diminishes over time and tends to disappear, or at least decrease, after one reaches his or her early twenties. There is, however, no way to predict how long it will take for it to disappear entirely, and some individuals will continue to suffer from acne decades later, into their thirties and forties and even beyond. Acne is the most common skin disease. Nearly 17 million people in the United States have it. People of all races and ages get acne. But it is most common in teenagers and young adults.

- Symptoms
The most common form of acne is known as "acne vulgaris", meaning "common acne." Many teenagers get this type of acne. The face and upper neck are the most commonly affected, but the chest, back and shoulders may have acne as well. The upper arms can also have acne, but lesions found there are often keratosis pilaris, not acne. The typical acne lesions are comedones and inflammatory papules, pustules, and nodules. Some of the large nodules were previously called "cysts" and the term nodulocystic has been used to describe severe cases of inflammatory acne. Aside from scarring, its main effects are psychological, such as reduced self-esteem [89] and, according to at least one study, depression or suicide. Acne usually appears during adolescence, when people already tend to be most socially insecure. Early and aggressive treatment is therefore advocated by some to lessen the overall impact to individuals [89].

- **Causes of Acne**

The small holes in your skin (pores) connect to oil glands under the skin. These glands make an oily substance called sebum. The pores connect to the glands by a canal called a follicle. Inside the follicles, oil carries dead skin cells to the surface of the skin. A thin hair also grows through the follicle and out to the skin. When the follicle of a skin gland clogs up, a pimple grows. Most pimples are found on the face, neck, back, chest, and shoulders.

- **Types of acne [Pimples]**

There are many types of pimples. The most common types are [90]:

- **Whiteheads.**
  - These are pimples that stay under the surface of the skin.
  - They occur when the openings of hair follicles become clogged and blocked with oil secretions and dead skin.

- **Blackheads.**
  - These pimples rise to the skin's surface and look black.

- **Papules.**
  - These are small pink bumps that can be tender.

- **Pustules.** These pimples are red at the bottom and have pus on top.

- **Nodules.**
  - These are large, painful, solid pimples that are deep in the skin.

- **Cysts.**
These deep, painful, pus-filled pimples can cause scars.

They are formed by the buildup of secretions deep within hair follicles.

1.8.1.5.4 Dandruff:

Figure 1.5 Photograph of infected hair with dandruff

Dandruff (also called scurf and historically termed Pityriasis capitis) is due to the excessive shedding of dead skin cells from the scalp. As it is normal for skin cells to die and flake off, a small amount of flaking is normal and in fact quite common. Some people, however, either chronically or as a result of certain triggers, experience an unusually large amount of flaking, which can also be accompanied by redness and irritation. Most cases of dandruff can be easily treated with specialized shampoos. Dandruff is not an organism like lice; it is just dead skin that accumulates in the scalp. Dandruff is unlikely to be the cause of hair loss. Excessive flaking can also be a symptom of seborrhoeic dermatitis, psoriasis, fungal infection or excoriation associated with infestation of head lice. Dandruff is a global phenomenon and many people find that dandruff can cause social or self-esteem problems. Treatment may be important purely for psychological reasons.

Causes

As the epidermal layer continually replaces itself, cells are pushed outward where they eventually die and flake off. In most people, these flakes of skin are too small to be visible. However, certain conditions cause cell turnover to be unusually rapid, especially in the scalp. For people with dandruff, skin cells may mature and be shed in 2 - 7 days, as opposed to around a month in people
without dandruff. The result is that dead skin cells are shed in large, oily clumps, which appear as white or grayish patches on the scalp skin and clothes.

Dandruff has been shown to be the result of three required factors: [91]

1. Skin oil commonly referred to as sebum or sebaceous secretions [92]
2. The metabolic by-products of skin micro-organisms (most specifically Malassezia yeasts) [93-95]
3. Individual susceptibility

Common older literature cites the fungus Malassezia furfur (previously known as Pityrosporum ovale) as the cause of dandruff. While this fungus is found naturally on the skin surface of both healthy people and those with dandruff, it was discovered that a scalp specific fungus, Malassezia globosa, is the responsible agent [96]. This fungus metabolizes triglycerides present in sebum by the expression of lipase, resulting in a lipid byproduct oleic acid (OA). Penetration by OA of the top layer of the epidermis, the stratum corneum, results in an inflammatory response in susceptible persons, which disturbs homeostasis and results in erratic cleavage of stratum corneum cells. Rarely, dandruff can be a manifestation of an allergic reaction to chemicals in hair gels/sprays, hair oils, or sometimes even dandruff medications like ketoconazole.

There is no convincing evidence that food (such as sugar or yeast), excessive perspiration, or climate have any role in the pathogenesis of dandruff.

Seborrheic dermatitis

Flaking is a symptom of seborrheic dermatitis. Joseph Bark notes that "Redness and itching is actually seborrheic dermatitis, and it frequently occurs around the folds of the nose and the eyebrow areas, not just the scalp." Dry, thick, well-defined lesions consisting of large, silvery scales may be traced to the less common psoriasis of the scalp. Seasonal changes, stress, and immuno-suppression seem to affect seborrheic dermatitis [97].

Treatment

There have been many strategies for the control of dandruff. Simply increasing shampooing will remove flakes. However, elimination of the fungus results in dramatic improvement. Regular shampooing with an anti-fungal product can reduce recurrence. Some common anti-dandruff shampoos are classified according to their active ingredient.
\[\text{Zinc pyrithione shampoos (Selsun Salon, Head \& Shoulders). These contain the antibacterial and antifungal agent zinc pyrithione, which has been shown to reduce the fungus that causes dandruff and seborrheic dermatitis.}\]

\[\text{Tar-based shampoos (Neutrogena T/Gel). Coal tar, a byproduct of the coal manufacturing process, helps conditions such as dandruff, seborrheic dermatitis and psoriasis by slowing cell turnover.}\]

\[\text{Shampoos containing salicylic acid (Ionil T). These "scalp scrubs" help eliminate scale, but they may leave your scalp dry, leading to more flaking. Using a conditioner after shampooing can help counter dryness.}\]

\[\text{Selenium sulfide shampoos (Selsun Blue). These shampoos help prevent cell turnover and may also reduce the number of malassezia. Because they can discolor blonde, gray or chemically colored hair, be sure to use them only as directed and to rinse well after shampooing.}\]

\[\text{Ketoconazole shampoos (Nizoral). The newest addition to the dandruff armamentarium, ketoconazole is a broad-spectrum antifungal agent that may work when other shampoos fail. It's available over-the-counter as well as by prescription.}\]

1.8.1.5.5 \textit{Psoriasis} ("itch" in Greek):

Psoriasis is a chronic skin disease that generally appears as patches of raised red skin covered by a flaky white buildup. In some cases, psoriasis is very mild and people don't know they have it. In other cases, it is very severe and covers large areas of the body. Psoriasis is not contagious. You can not "catch" it from another person and a person cannot "catch" it from you.

\[\text{Causes of Psoriasis}\]

The exact cause of psoriasis is unknown. However, researchers believe psoriasis is related to

\[\text{Figure 1.6 3D-Photograph of healthy and psoriasis}\]
faulty signals sent by the body's immune system. The faulty signals accelerate the growth cycle in skin cells, which pile up on the surface when the body can't shed them fast enough. In the United States two out of every hundred people have psoriasis (four to five million people). Approximately 150,000 new cases occur each year.

Psoriasis is probably one of the longest known illnesses of humans and simultaneously one of the most misunderstood. Some scholars believe psoriasis to have been included among the skin conditions called tzaraat in the Bible [98]. In more recent times psoriasis was frequently described as a variety of leprosy. The Greeks used the term "lepra" for scaly skin conditions. They used term psora to describe itchy skin conditions. It became known as Willan's lepra in the late 18th century when English dermatologists Robert Willan and Thomas Bateman differentiated it from other skin diseases. They assigned names to the condition based on the appearance of lesions. Willan identified two categories: leprosa graecorum and psora leprosa.

While it may have been visually, and later semantically, confused with leprosy it was not until 1841 that the condition was finally given the name psoriasis by the Viennese dermatologist Ferdinand von Hebra. The name is derived from the Greek word psora which means to itch [99]. It was during the 20th century that psoriasis was further differentiated into specific types.

Types of psoriasis

The symptoms of psoriasis can manifest in a variety of forms. Variants include plaque, pustular, guttate and flexural psoriasis. This section describes each type [100].
Plaque psoriasis (psoriasis vulgaris) is the most common form of psoriasis. It affects 80 to 90% of people with psoriasis. Plaque psoriasis typically appears as raised areas of inflamed skin covered with silvery white scaly skin. These areas are called plaques.

- Flexural psoriasis (inverse psoriasis) appears as smooth inflamed patches of skin. It occurs in skin folds, particularly around the genitals (between the thigh and groin), the armpits, under an overweight stomach, and under the breasts (infra mammary fold). It is aggravated by friction and sweat, and is vulnerable to fungal infections.

- Guttate psoriasis is characterized by numerous small oval (teardrop-shaped) spots. These numerous spots of psoriasis appear over large areas of the body, such as the trunk, limbs, and scalp. Guttate psoriasis is associated with streptococcal throat infection.

- Pustular psoriasis appears as raised bumps that are filled with non-infectious pus (pustules). The skin under and surrounding pustules is red and tender. Pustular psoriasis can be localised, commonly to the hands and feet (palmoplantar pustulosis), or generalised with widespread patches occurring randomly on any part of the body.

- Nail psoriasis produces a variety of changes in the appearance of finger and toe nails. These changes include discoloring under the nail plate, pitting of the nails, lines going across the nails, thickening of the skin under the nail, and the loosening (onycholysis) and crumbling of the nail.

- Psoriatic arthritis involves joint and connective tissue inflammation. Psoriatic arthritis can affect any joint but is most common in the joints of the fingers and toes. This can result in a sausage-shaped swelling of the fingers and toes known as dactylitis. Psoriatic arthritis can also affect the hips, knees and spine (spondylitis). About 10-15% of people who have psoriasis also have psoriatic arthritis.

- Erythrodermic psoriasis involves the widespread inflammation and exfoliation of the skin over most of the body surface. It may be accompanied by severe itching, swelling and pain. It is often the result of an exacerbation of unstable plaque psoriasis, particularly following the abrupt withdrawal of systemic treatment. This form of psoriasis can be fatal, as the extreme inflammation and exfoliation disrupt the body's ability to regulate temperature and for the skin to perform barrier functions.
A diagnosis of psoriasis is usually based on the appearance of the skin. There are no special blood tests or diagnostic procedures for psoriasis. Sometimes a skin biopsy, or scraping, may be needed to rule out other disorders and to confirm the diagnosis. Skin from a biopsy will show clubbed Rete pegs if positive for psoriasis.

Severity: Psoriasis is usually graded as mild (affecting less than 3% of the body), moderate (affecting 3-10% of the body) or severe. Several scales exist for measuring the severity of psoriasis. The degree of severity is generally based on the following factors: the proportion of body surface area affected; disease activity (degree of plaque redness, thickness and scaling); response to previous therapies; and the impact of the disease on the person. Pie chart showing the distribution of severity among people with psoriasis and data from the study of 278 people.

The Psoriasis Area Severity Index (PASI) is the most widely used measurement tool for psoriasis. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease) [101]. Nevertheless, the PASI can be too unwieldy to use outside of trials, which has led to attempts to simplify the index for clinical use [104].
Treatments

The most common treatments for psoriasis are Medicines, Phototherapy and Surgery. Medicines are preferable options for the treatments of psoriasis. In this treatment Mild forms of psoriasis are usually treated with medicines, such as tar, that are applied on the skin (topical medicines). More serious forms of psoriasis, like those involving the entire body, may need medicines taken by mouth or given as a shot. Some examples of these medicines include steroids, salicylic acid, and medicines that regulate the immune system. In some cases, bandages that already have medicine on them are also used [102].

Effect on the quality of life

Psoriasis has been shown to affect health-related quality of life to an extent similar to the effects of other chronic diseases such as depression, myocardial infarction, hypertension, congestive heart failure or type-2 diabetes. Depending on the severity and location of outbreaks, individuals may experience significant physical discomfort and some disability. Itching and pain can interfere with basic functions, such as self-care, walking, and sleep. Plaques on hands and feet can prevent individuals from working at certain occupations, playing some sports, and caring for family members or a home. The frequency of medical care is costly and can interfere with an employment or school schedule.

Individuals with psoriasis may also feel self-conscious about their appearance and have a poor self-image that stems from fear of public rejection and psychosexual concerns. Psychological distress can lead to significant depression and social isolation.
1.8.1.5.6 **Ringworm:**

Ringworm is a contagious fungus infection that can affect the scalp, characterized by a reddish to brownish raised or bumpy patch of skin that may be lighter in the center, giving the appearance of a 'ring.' Contrary to its name, ringworm.

It's not caused by a worm but by parasitic fungi (Dermatophytosis). It can exist anywhere on the body. Ringworm is also called Tinea. It can exist anywhere on the body [103].

Infectious agent that causes Ringworm

Ringworm is caused by several different fungus organisms that all belong to a group called "Dermatophytes." Different Dermatophytes affect different parts of the body and cause the various types of Ringworm:

- Ringworm of the scalp
- Ringworm of the body
- Ringworm of the foot (athlete's foot)
- Ringworm of the nails

Ringworm is widespread around the world and in the United States. The fungus that causes scalp Ringworm lives in humans and animals. The fungus that causes Ringworm of the body lives in humans, animals, and soil. The fungi that cause Ringworm of the foot and Ringworm of the nails live only in humans.

Causes
Ringworm is spread by either direct or indirect contact. People can get Ringworm by direct skin-to-skin contact with an infected person or pet. People can also get Ringworm indirectly by contact with objects or surfaces that an infected person or pet has touched, such as hats, combs, brushes, bed linens, stuffed animals, telephones, gym mats, and shower stalls. In rare cases Ringworm can be spread by contact with soil.

- Signs and symptoms of Ringworm
  - Ringworm of the scalp usually begins as a small pimple that becomes larger, leaving scaly patches of temporary baldness. Infected hairs become brittle and break off easily. Yellowish crusty areas sometimes develop.
  - Ringworm of the body shows up as a flat, round patch anywhere on the skin except for the scalp and feet. The groin is a common area of infection (groin Ringworm). As the rash gradually expands, its center clears to produce a ring. More than one patch might appear, and the patches can overlap. The area is sometimes itchy.
  - Ringworm of the foot is also called athlete's foot. It appears as a scaling or cracking of the skin, especially between the toes.
  - Ringworm of the nails causes the affected nails to become thicker, discolored, and brittle, or to become chalky and disintegrate.

- Exposure and symptoms
  Scalp Ringworm usually appears 10 to 14 days after contact, and Ringworm of the skin 4 to 10 days after contact. The time between exposure and symptoms is not known for the other types of Ringworm.

- Diagnosis and Treatment for Ringworm
  A health-care provider can diagnose Ringworm by examining the site of infection with special tests.

  Ringworm can be treated with fungus-killing medicine. The medicine can be in taken in tablet or liquid form by mouth or as a cream (antifungal creams, such as miconazole or clotrimazole) applied directly to the affected area. Although Ringworm is not tracked by health authorities, infections appear to be increasing steadily, especially among pre-school and school-age children. Early recognition and treatment are needed to slow the spread of infection and to prevent re-infection.
1.9 From the literature: (Dermatological work using herb):

Carle Paul et al and his group have been reported the main biological effect of ascomycins is an inhibition of the synthesis of both Th-1 and Th-2 type cytokines in target cells. Several compounds are being developed with SDZ ASM 981 being at the most advanced stage. It has high anti-inflammatory activity in animal models of skin inflammation and does not induce skin deterioration. Topical application of SDZ ASM 981 was shown to be effective in atopic dermatitis (AD), allergic contact dermatitis and also in psoriasis under semi-occlusive conditions. Yadav P, Dubey N. K. et al. found the fungicidal activity during screening of 12 essential oils of higher plants against two ringworm fungi Trichophyton mentagrophytes and microsporum audouini by poisoned food technique, the oils of plants viz. Cinnamomum tamala, Citrus maxima, Cymbopogon citratus, Eucalyptus citriodora, Eupatorium cannabinum, Nepeta hindostana Ocimum canum showed absolute toxicity against both the test fungi. The minimum inhibitory concentration of the oils of Cinnamomum tamala and Citrus maxima was 500 ppm against both the test fungi and these oils showed superiority in efficacy over some synthetic antifungal agents. The oils exhibited fungicidal or fungistatic nature of toxicity.

V. S. Nikitina and his coworkers studied Polyphenolic compounds present in extracts of plants belonging to the families Geraniaceae (blood-red cranesbill, wood cranesbill, meadow cranesbill, and alfilaria) and Rosaceae (red raspberry, European dewberry, and tormentil) have been tested for their activity against gram-positive and gram-negative bacteria of the genera Azotobacter, Bacillus, and Pseudomonas. And they found the bacteriostatic activity exhibited some species-related features and depended on the polarity of the extracting agent. The bacteriostatic activity of plant-derived phenolic compounds correlated with their antioxidant potential. The plants of the families Geraniaceae and Rosaceae offer promise as a source of raw material for isolation of polyphenolic compounds exhibiting bactericidal activity, including against opportunistic pathogens (B. cereus, E. coli, P. aeruginosa, and S. aureus strains).

V. G. premkumar and D. Shyamsunder et al reported antidermatophytic activity against dermatophytes belonging to the three genera, Trichophyton, epidermophyton and microsporon affect the keratinous tissue of humans and other vertebrates, causing superficial fungal infection and the present study reports the in vitro antidermatophytic activity of Methanolic leaf extract of Pistia stratiotes against a battery of dermatophytes. And the results indicate that P. stratiotes
Methanol extracts was found to be the most active against the dermatophytes T. rubrum, T. mentagrophytes and E. floccosum with MIC & MFC values of 250 μg/mL, while against M. gyseum and M. nanum, the values were 125 μg/mL same for all the 15th replicates experiments. C. Pieyrard-Franchimont, had concluded that, Dandruff is a reactive response of the epidermis of the scalp to various stimuli. Of these, set of converging features altogether supports the role of Malassezia spp. as the main causative agent. Some environmental factors such as ultraviolet light and airborne irritant agents or those applied deliberately to the scalp are also potential protagonists, which must not be overlooked. Irrespective of the causative factor, the physiopathological events in dandruff could be summarized into a few successive steps involving the intervention of the triggering agent, particularly the increased Malassezia load over some corneocytes, discrete subclinical inflammation, parakeratosis and scale formation. The process can also ensue in hair cycle disturbance.

Loknath Ghoshal and his group carried out studied entitled comparative evaluation of effectiveness of Adapalene and Azithromycine, alone or in combination in acne vulgaris and present study they used methods for a total of 61 newly attending cases of inflammatory acne vulgaris were considered the study. They were randomly allocated into three groups. Group 1 received topical adapalene (0.01%) gel; group 2 received oral azithromycin, whereas group 3 was given a combination of these two. The patients were treated for a period of 12 weeks, being reviewed every fortnightly. The results obtained were analyzed using statistical methods, and they concluded At the end of 12 weeks of treatment, the three treatment groups showed no statistically significant difference in the efficacy in inflammatory acne.

M. Rajbhandari et al, and his groups studied Methanolic extracts of 41 plant species belonging to 27 families used in the traditional medicine in Nepal have been investigated for in vitro antiviral activity against Herpes simplex virus type 1 (HSV-1) and influenza virus A by dye uptake assay in the systems HSV-1/Vero cells and influenza virus A/MDCK cells. The extracts of Astilbe rivularis, Bergenia ciliata, Cassiope fastigiata and Thymus linearis showed potent anti-herpes viral activity. The extracts of Allium oreoprasum, Androsace strigilosa, Asparagus filicinus, Astilbe rivularis, Bergenia ciliata and Verbascum thapsus exhibited strong anti-influenza viral activity.
1.10 Aim and significance of the work:

Plants from the Cassia family (Cassia tora, and Cassia fistula) are identified as a potential source for herbal medicine. These families contain anthraquinone glycosides and its derivatives in their structures. And it’s potentially useful for their laxative [104-106] property. Hence, we focused on the presence anthraquinone derivatives constituents and it’s responsible for the biological properties. Present work is carried out on the basis of literature skin diseases like Acne, Eczema, Herpes, Psoriasis, and Ringworm. In present study, we have selected medicinally useful three plants from cassia family and one from rubiaceae, which having anthraquinone ingredient, known for their potential against many diseases like diabetes mellitus, cancer, tuberculosis, psoriasis, ringworm antiviral and antifungal disease and many other chronic diseases.

In the present study we would like to check its impact on the skin diseases and also identify the active ingredient responsible for it. Validate the identity of the active ingredient through its characterization by using HPLC [FT-IR, UV/Visible, Mass and NMR spectroscopy] and other spectral techniques and screen through the biological activity.