STATEMENT OF THE PROBLEM

Emergence of new diseases, re-emergence of old, development of resistant strains, side
effects of some currently available drugs including toxicity and other undesirable effects in
allergic patients are a few major problems which require immediate attention to combat these
diseases with effective drugs of high therapeutic index. Furthermore, effective drugs are also
needed for immune compromised patients who are at great risk by opportunistic pathogens that
normally do not pose any major threat in the normal population. Therefore, there is an immense
need for the development; and discovery of new and safer bioactive compounds.

Natural products are usually derived from microorganisms, plants or animals. Plants continued
to remain a rich source of therapeutic substances since extinct civilization. Moreover, even
today, a major portion of new drugs (~60%) are obtained from natural products or their

About 80% of the world’s populations rely for their primary health care on traditional
medicine, most of which are prepared from plants (Alves and Rosa, 2007). It is strongly believed
that remedies based on these medicinal plants often have no or minimal side effects, secondly
these traditional herbal medicines are available at an affordable price. Increasingly, global
market for herbal medicines has reached to over US $ 60 billion annually, and is growing
steadily (Kartal, 2006). There are at least 120 distinct chemical substances derived from plants
are considered important herbal drugs.

The identification of plants useful to human beings from natural commenced in prehistoric times.
Experiments and trials were the two main ways through which humans have learnt the various
uses of plants. The use of plant resources for medicinal and other purposes is one of a number of practices developed by ancient people.

Currently, a lot of efforts are underway to identify novel substances derived from the natural sources that exhibit a range of clinical and pharmaceutical activities (Lewis and Ausubel, 2006). Most of the laboratories and research institutes are working on isolation of organic substances synthesized by various medicinal plants.
Like bacteria, fungi are also responsible for a variety of infections in human beings. Fungi are a large group with about 250,000 species which are major pathogens of agricultural plants and important opportunistic pathogens of humans recently ranking as the seventh most common cause of infectious disease–related deaths in the United States (Odds, 2000). More than 300 species have been reported to be potentially pathogenic to humans (Guarro and Barradell, 1997). The infections caused by fungi are generally referred as Mycoses. These can further be classified into four groups’ viz. Superficial, Subcutaneous, Systemic and Opportunistic. Fungal infections in humans are generally confined to superficial areas such as skin infections, however in immunocompromised people mild or nonpathogenic fungi can prove to be fatal. Opportunistic fungal pathogens cause a variety of invasive or systemic fungal infections in immunocompromised or immunosuppressed individuals. Fungal infections have been gaining prime importance because of the morbidity of hospitalized patients. Fungi previously thought to be non-pathogenic for humans or sporadically associated with human diseases. Approximately 90% of human fungal infections are caused by Aspergillus, Candida, Cladosporium, Epidermophyton, Microsporum and Trichophyton species.

The prevalence of invasive or systemic fungal infections has increased significantly during the past decades (Walsh et. al., 1996). These have become one of leading cause of death among patients due to greater use of broad spectrum antibiotics, immunosuppressive agents, intensive care of low birth weight infants, organ transplantation & the acquired immunodeficiency syndrome (AIDS) epidemic (Graybill, 1996).
Today, fungal infections are a real problem, having doubled in number from the 1980’s to the 1990’s, and with bloodstream infections increasing five-fold with an observed mortality of 55% (Torres et al., 1995). Candidiasis, Cryptococcosis and Aspergillosis have been frequently reported in persons suffering from Acquired Immune Deficiency Syndrome (AIDS) (White, 1997). Systemic candidiasis has been reported to occur in up to 10% of infants weighing less than 1kg; the greatest increases in surgical patients & 78% of fungal infections are due to Candida spp. (Beck-Sague and Jarvis, 1993)
1.1: FUNGAL INFECTIONS

The human body is covered with a vast amount and diverse range of germs. These germs live harmlessly within the body and on the skin. However, certain types of fungus can build up on the skin and cause infections. A fungal infection usually appears on the skin, as the organisms live on a protein called keratin. This protein makes up the nails, skin and hair. The various symptoms of a fungal infection depend on the type of the fungus that has caused the infection. Symptoms and appearance also depend on the part of the body infected.

Fungal diseases are called mycoses and those affecting humans can be divided into following groups on the basis of level of penetration in to the body tissues:

- Mycotic infections are classified by the tissue levels that are colonized.
  - Superficial infections are generally limited to the outer layers of the skin and hair.
  - Cutaneous infections are located deeper in the epidermis, hair and nails.
  - Subcutaneous infections involve the dermis, subcutaneous tissues and muscle.
- In addition, mycotic infections may be systemic, generally originating in the lungs.
- Finally, some mycoses are termed as opportunistic, and these may involve a variety of body sites.

Figure 1.1: Outlines these different types of mycotic infections (Dermatomycosis), giving examples of representative agents.
1.2: DERMATOMYCOSIS

Dermatomycosis includes dermatophytosis, sporotrichosis and cryptococcosis commonly occurring in humans and animals and are considered to be zoonotic diseases. The dermatophytosis is classified in three anamorphic (asexual or imperfect) genera, *Epidermophyton, Microsporum*, and *Trichophyton*, of anamorphic class *Hyphomycetes* of the Deuteromycota (Fungi imperfecti).

Dermatophytosis is a clinical condition caused by fungal infection of the skin in humans, pets and domestic animals. It is caused by fungi of several different species. The fungi that causes parasitic infection (dermatophytes) feed on keratin, the material found in the outer layer of the skin, hair and nails. These fungi thrive on skin that is warm and moist but may also survive directly on the outsides of hair shafts or in their interiors.

This condition has been prevalent since before 1906, at which time ringworm was treated with compounds of mercury, or sometimes sulphur or iodine. Hairy areas of skin were considered too difficult to treat, so the scalp was treated with X-rays and followed up with anti-parasitic medication. It has been estimated that in current times, up to twenty percent of the population is infected by ringworm or one of the other dermatophytoses.

1.3: DERMATOPHYTES

Dermatophytes (name based on the Greek for ‘skin plants’) are a common label for a group of three types of fungus that commonly causes skin diseases in animals and humans. These anamorphic (asexual or imperfect fungi) genera are: *Microsporum, Epidermophyton* and
Trichophyton. There are about 40 species in these three genera which are classified on the basis of the infection site. (Figure 1.3.1)

Dermatophytes love to grow at low temperature up to 30°C. Higher temperature of the hot spot cause the fungus to move towards the periphery of the lesion where the temperature is comparatively low, thus producing concentric ring shaped lesions; the name “ring worm diseases” is derived from such lesions. The centre of the ring contains dead and desquamated cells that matt by oozing secretions while the peripheral zone may contain actively multiplying fungi. The virulence of the infecting strain or species, the anatomic location of the infected site and local environmental factor determine the severity of infection (Soltys, 1963).

Dermatophytes colonize the superficial dead and desquamating layers of skin and appendages and cause infections of the skin, hair and nails due to their ability to obtain nutrients from keratinized material. The organisms colonize the keratin tissues and inflammation is caused by the host response to metabolic by-products. They are usually restricted to the non living cornified layers of the epidermis because of their inability to penetrate viable tissue of an immune-competent host. Invasion does elicit a host response ranging from mild to severe. Acid proteinases, elastase, keratinase and other proteinases reportedly act as virulence factor. The development of cell mediated immunity corelated with delayed hypersensitivity and an inflammatory response is associated with clinical culture, whereas the lack of or a defective cell-mediated immunity predisposes the host to chronic or recurrent dermatophytic infection. Some of these infections are known as ringworm or tinea. Toenail or fingernail infections are referred to as Onychomycoses.
On the basis of host preference and natural habitat, dermatophytes are also classified as geophilic (soil associated), zoophilic and anthropophilic.

i. **Geophilic:** This category includes the fungal species that normally inhabit in soil but may accidentally infect animals and man. *Microsporum gypseum* is a typical example of this group.

ii. **Zoophilic:** Zoophilic dermatophytes include fungi that are primarily pathogenic for animals and rarely man. *Trichophyton mentagrophytes* is an example of this group.

iii. **Anthropophilic:** Anthropophilic fungi include species pathogenic to man. Human beings are the main reservoir of this category of dermatophytes.
1.4: CLASSIFICATION OF DERMATOPHYTOSIS

A number of different species of fungi are involved. Dermatophytes of the genera *Trichophyton* and *Microsporum* are the most common causative agents. These fungi attack various parts of the body and lead to the following conditions:

**Table 1.4.1.** Body parts affected by Dermatophytosis

<table>
<thead>
<tr>
<th>Dermatophytosis</th>
<th>Affected Body Parts</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Tinea pedis</em> (Athlete’s foot)</td>
<td>Feet</td>
</tr>
<tr>
<td><em>Tinea unguium</em></td>
<td>Finger nails and toenails</td>
</tr>
<tr>
<td><em>Tinea corporis</em></td>
<td>Arms, legs and trunk</td>
</tr>
<tr>
<td><em>Tinea cruris</em> (Jock itch)</td>
<td>Groin area</td>
</tr>
<tr>
<td><em>Tinea manuum</em></td>
<td>Hands and palm area</td>
</tr>
<tr>
<td><em>Tinea capitis</em></td>
<td>Scalp</td>
</tr>
<tr>
<td><em>Tinea barbae</em></td>
<td>Facial hair</td>
</tr>
<tr>
<td><em>Tinea faciei</em> (Face fungus)</td>
<td>Face</td>
</tr>
<tr>
<td><strong>Other superficial mycoses</strong></td>
<td><strong>Caused by</strong></td>
</tr>
<tr>
<td><em>Tinea versicolor</em></td>
<td><em>Malassezia furfur</em></td>
</tr>
<tr>
<td><em>Tinea nigra</em></td>
<td><em>Hortaea werneckii</em></td>
</tr>
</tbody>
</table>

1.5: CURRENTLY USED ANTIFUNGAL AGENTS

In the past few decades, a worldwide increase in the incidence of fungal infections has been observed as well as a rise in the resistance of some species of fungus to different fungicidal used in medicinal practice. Fungi are one of the most neglected pathogens, as demonstrated by the fact that the amphotericin B, a polyene antibiotic discovered as long ago as 1956, is still used as a "gold standard" for antifungal therapy. The last two decades have witnessed a dramatic rise in the incidence of life threatening systemic fungal infections. The
challenge has been to develop effective strategies for the treatment of candidiasis and other fungal diseases, considering the increase in opportunistic fungal infections in human immunodeficiency virus-positive patients and in others who are immunocompromised due to cancer chemotherapy and the indiscriminate use of antibiotics. These antifungal agents have a wide application in human medicine, agriculture and veterinary medicine (Vandamme, 1984).

Five major classes of systemic antifungal compounds are currently in clinical use:

- The polyene antibiotics (Amphotericin B),
- The azole derivatives (Fluconazole & Itraconazole),
- The allylamines (Terbinafine) and thiocarbamates,
- The morpholines and
- The nucleoside analogs (Georgopapadakou and Walsh, 1996).

The first three are targeted against ergosterol, the major fungal sterol present in the plasma membrane. The fourth inhibits sterol biosynthesis and the fifth class targets the DNA synthesis. Griseofulvin, a nuclear division and membrane tubule inhibitor, and lipopeptides that are known to act on *Pneumocystis carinii* belong to a miscellaneous class of compounds (Morris *et al.* 1994). But these antifungal antibiotics are becoming resistant. More recently new antifungals have been introduced by the Merck R&D, which is known as Echinocandins (Caspofungin).
1.5 a. Antifungal agents affecting fungal sterols

The major groups of antifungal agents that affect fungal growth by either interacting with or inhibiting synthesis of ergosterol, a key component of fungal cell wall, include the polyenes, the azoles and the allylamines (Ghannoum and Rice, 1999).

![Diagram of antifungal agents targeting fungal sterols]

**Figure 1.5.1:** Target of antifungal agents

**Polyenes**

Polyenes antifungal agents are useful for the treatment of systemic fungal infection. It binds to a sterol moiety, especially ergosterol, which is present in the membrane of the sensitive fungi. Polyene makes channels or pores in the membrane, which increase the permeability of cell membrane. It results in the leakage of variety of small molecules.
Amphotericin B was discovered in 1956 by Gold and coworkers (Bennett, 2001) which belongs to family of some 200 polyene macrolide antibiotics. Interaction of amphotericin B with membrane sterol results in the production of aqueous pores consisting of annulars of eight amphotericin B molecules linked hydrophobically to the membrane sterols. This configuration forms pores resulting in an increased permeability, leakage of vital cytoplasmic components, and eventually death of the organisms (Kerridge, 1985).

Azole

The azole group of drugs can be classified into two subclasses: imidazole and triazole. The mechanism of action of these two subclasses are same i.e. ergosterol synthesis inhibitor. The systemic triazoles are more slowly metabolized and have less effect on human sterol synthesis than that of the imidazoles. Few examples of imidazoles include clotrimazole, miconazole, ketoconazole, econazole, butoconazole, oxiconazole and sulconazole, whereas, the commonly used triazoles are teraconazole, itraconazoles and fluconazole (Gupta, et al., 2003).

Allylamines and Thiocarbamate

Naftifungin and terbinafine are allylamines, and tolnaftate is tricarbamate group of drugs. These drugs are functionally and chemically distinct from other major classes of ergosterol-inhibiting antifungal agents. Allylamines act by inhibiting early steps of ergosterol biosynthesis at the step of squalene epoxidation. This inhibition results in the accumulation of squalene which consequently results in fungal cell death. It is speculated that the increase concentration of squalene may increase membrane permeability, leading to disruption of cellular
organization and then death. Interestingly, fungal death is not associated with the ergosterol
deficiency due to inhibition of its synthesis (Bennett, 2001).

1.5. b. Compounds active against fungal cell wall component α- and β-glucans

The fungal cell wall has a unique composition and contains mannan, chitin and α- and β-glucans. The cellular pathways for the synthesis of unique fungal molecule are, therefore, an attractive target to control fungal growth. A number of compounds, which have the ability to affect cell walls of fungi, have been reported in literature (Hector, 1993; Ghannoum and Rice, 1999). For example, aculeacins, echinocandins, and papulacandins are specific inhibitors of fungal 3 β-glucans synthetase (Balashov, et al., 2006).

Echinocandins

Echinocandins inhibit the synthesis of glucan in the cell wall, probably via the enzyme 1,3-β glucan synthase:

- Anidulafungin
- Caspofungin
- Micafungin

These drugs are administered parenterally only, not orally. They may be used for systemic fungal infections in immunocompromised patients.
1.5. c. Compounds inhibiting Nucleic Acids

Flucytosine and Griseofulvin are nucleic acid inhibitor. Flucytosine, a fluorinated pyrimidine has inhibitory activity against many types of yeast. This drug is clinically useful against *Cryptococcus neoformans*, *Candida* sp. and the agents of chromomycosis.

Griseofulvin is fungistatic in vitro for various species of the dermatophytes *Microsporum*, *Epidermophyton* and *Trichophyton*. This drug inhibits mitosis. Griseofulvin causes disruption of the mitotic spindle by interacting with polymerized microtubules by binding to both microtubule associated protein and tubulin (*Kidwai, et al., 2003*)
1.6: ANTIFUNGAL MEDICATIONS AND THEIR SIDE EFFECTS

Some antifungal drugs with their trade names, uses and side effects are discussed as:

Table 1.6.1: Antifungal medications their uses and side effects

<table>
<thead>
<tr>
<th>Drug with trade names</th>
<th>Common uses</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B (Fungizone)</td>
<td>Wide variety of fungal infections</td>
<td>Chills, fever, headache, vomiting, lowered potassium levels in blood, kidney damage and anemia</td>
</tr>
<tr>
<td>Andulafungin (Eraxis)</td>
<td><em>Aspergillus, Candidal</em> and possibly other infections</td>
<td>Fever, nausea and inflammation of veins</td>
</tr>
<tr>
<td>Caspofungin (Cancidas)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Micafungin (Mycamine)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluconazole (Difulcan)</td>
<td><em>Candidal</em> and other fungal infections, including <em>Cryptococcal</em></td>
<td>Liver inflammation (Hepatitis) but less than that with Ketoconazole (Nizoral)</td>
</tr>
<tr>
<td>Flucytosine (Ancobon)</td>
<td><em>Candidal</em> and <em>Cryptococcal</em> infections</td>
<td>Bone marrow and kidney damage</td>
</tr>
<tr>
<td>Itraconazole (Sporanox)</td>
<td><em>Candidal</em> and other fungal infections</td>
<td>Nausea, diarrhea and liver inflammation but less than that with Ketoconazole (Nizoral)</td>
</tr>
<tr>
<td>Ketoconazole (Nizoral)</td>
<td><em>Candidal</em> and other fungal infections</td>
<td>Nausea and vomiting, blocked production of <em>ANDRODERM DELATESTRYL</em> and cortisol CORTEF, and liver inflammation</td>
</tr>
<tr>
<td>Posaconazole (Noxafil)</td>
<td><em>Aspergillus, Candidal</em> and many other fungal infections</td>
<td>Nausea, vomiting and rarely liver inflammation</td>
</tr>
<tr>
<td>Voriconazole (Vfend)</td>
<td><em>Aspergillus and Candidal</em> infections</td>
<td>Visual disturbances that are reversible</td>
</tr>
</tbody>
</table>
1.7: NEED FOR NEW ANTIFUNGALS

Fungal resistance has received little attention in contrast to the critical importance of bacterial resistance. Clinical resistances to the antifungal agents were rare till 1980’s. The incidence of fungal infections including resistant infections has increased during 1990’s reflecting increased incidence of Immunodeficiency associated cancer chemotherapy, organ and bone marrow transplantation and HIV epidemic (Iwamoto, et.al, 1994b; Hosoe et. al., 2000). Antifungal resistance may be defined as a stable inheritable adjustable by a fungal cell to an antifungal agent resulting in less than normal sensitivity to the antifungal agent. There are 3 factors contribute to antifungal drug resistance (White et al., 1998):

- Many clinical factors that contribute to resistance are associated with the pharmacology of drugs, or type of fungal infections present
- Cellular factors associated with a resistance fungal strain.
- Molecular factors that is ultimately responsible for resistance phenotype in the cell. The molecular mechanism of resistance that have been identified to date in Candida albicans include over expression or mutation of target enzyme & alteration of the enzyme in same biosynthetic pathway as target enzyme.

The rise in the incidence fungal infections has exacerbated the need for next generation of antifungal agents, since many of currently available drugs have undesirable side effects, are ineffective against new or re-emerging fungi or lead to rapid development of resistance (Vanden Bossche et.al, 1994; Graybill et.al., 1988). This drug resistance has resulted in drastic increase in incidence of opportunistic & systemic fungal infections. Resistance is considered as primary when an organism is resistant to drug before exposure, whereas, secondary resistant is
that which develops in response to the drug. The latter mechanism of resistance accounts for the emergence of resistant fungi to azoles & polyenes seen over last few years (White et al., 2002).

The prevalence of resistant strains is due to

- An increased reliance on antimicrobial medication, giving resistant strains a selective advantage
- The recent trend towards aggressive resuscitation & invasive surgery, favouring infection.
- The treatment of more immunocompromised patients such as very elderly, the HIV positive & intentionally immunodepressed.

There are only few available drugs for treatment of fungal infections in immunocompromised patients or in severe systemic pathology i.e. therapeutic choices for treatment of fungal infections are limited. So, search for new compound with low toxicity & stability is a priority in field of anti-fungal therapy.

Antifungal drugs basically belong to two broad categories:

(a) Those made synthetically.

(b) Those produced by various organisms.

Most people become interested in synthetic drugs because of their quick action as compared to traditional medicines & secondly because of their bulk production in industries. New microbes and their products are discovered for medicinal uses. Their products were extracted & then synthesized in the laboratory since 1970 almost 75% of such medicines are of synthetic origin or products of fermentation (Brewer, 2000).
1.8: TARGET FUNGAL SPECIES

The cutaneous mycosis, unlike other fungal infections, is becoming more common and mainly caused by Microsporum species (Mayers et al, 2004; Gupta et al, 2004). Microsporum spp. mostly infects the hair and skin. The genus Microsporum includes 17 conventional species. Some of these are:


Following two species have been selected for the present study:

**Microsporum canis**

*Microsporum canis* is a zoophilic dermatophyte of world-wide distribution which is a frequent cause of ringworm in humans, especially children. Invades hair, skin and rarely nails. On SDA, colonies are flat, spreading and white to cream coloured, with a dense cottonty surface which may show some radial grooves. Macroconidia are typically spindle shaped with 5-15 cells, verrucose, thick-walled and often have a terminal knob. Microconidia are sparse clavate and smooth walled.

**Microsporum fulvum**

*Microsporum fulvum* is a geophilic fungus of world-wide distribution which may cause occasional infections in humans and animals. Colonies are fast growing, flat, suede-like,
tawny- buff to pinkish-buff in colour and frequently have a fluffy white advancing edge. Abundant thin- walled, elongate, ellipsoidal macroconidia and microconidia are formed with 3 to 6 septa.

**Trichophyton species**

The genus *Trichophyton* has several species. Most common are *T. mentagrophytes*, *T. rubrum*, *T. schoenleinii*, *T. tonsurans*, *T. verrucosum*, and *T. violaceum*. *T.* frequently causes chronic infections of skin, nails and rarely scalp. *T. mentagrophytes* is the target species in present study.

**Trichophyton mentagrophytes**

*Trichophyton mentagrophytes* is a keratinophilic fungus belonging to a homogeneous group of fungi called the dermatophytes. This is an anthropophilic and zoophilic fungus. The growth rate of colonies is slow to moderately rapid. The texture is waxy, glabrous to cottony. From the front, the color is white to butter yellowish. Reverse is pale, yellowish, brown, or reddish-brown. Microscopically, the most consistent feature of *T. mentagrophytes* is the production of globose microaleuriospores arranged in grape-like clusters. Macroconidia are thin-walled and cigar shaped.

**Aspergillus species**

*Aspergillus* a filamentous cosmopolitan and ubiquitous fungus found in nature. *Aspergillus* is well known to play a role in three different clinical settings in man:
Opportunistic infections; Allergic states; and Toxicoses immunosuppression are the major factors predisposing to development of opportunistic infections. Among all the filamentous fungi, *Aspergillus* is in general the most commonly isolated one in invasive infections.

The genus *Aspergillus* includes over 185 species. Around 20 species have so far been reported as causative agents of opportunistic infections in man. Among these, *Aspergillus fumigatus* is the most commonly isolated species, followed by *Aspergillus flavus* and *Aspergillus niger*.

Following two species are selected for present study:

**Aspergillus niger**

*Aspergillus niger* colonies consist of a compact white or yellow basal felt covered by a dense layer of dark-brown to black conidial heads. Conidial heads are large up to 3 mm x 15-20 um in diameter, globose, dark brown. Conidiophores are smooth-walled, hyaline or turning dark towards the vesicle. Conidial heads are biseriate with the phialides borne on brown, often septate metulae. Conidia are globose to subglobose (3.5-5.0 µm in diameter), dark brown to black and rough-walled. This is the third most common species associated with invasive pulmonary aspergillosis. It is also often a causative agent of aspergilloma and is the most frequently encountered agent of otomycosis.

**Aspergillus fumigatus**

It is the most common *Aspergillus* species to cause disease in an individual with an immunodeficiency. *A. fumigatus*, a saprotroph widespread in nature, is typically found in soil and
decaying organic matter, such as compost heaps, where it plays an essential role in carbon and nitrogen recycling. Colonies of the fungus produce from conidiophores thousands of minute grey-green conidia (2–3 μm) that readily become airborne. For many years, A. fumigatus was not thought to only reproduce asexually, as neither mating nor meiosis had ever been observed. The fungus is capable of growth at 37 °C/99 °F (normal human body temperature), and can grow at temperatures up to 50 °C/122 °F, with conidia surviving at 70 °C/158 °F. Its spores are ubiquitous in the atmosphere, and it is estimated that everybody inhales several hundred spores each day; typically these are quickly eliminated by the immune system in healthy individuals. In immunocompromised individuals, such as organ transplant recipients and people with AIDS or leukemia, the fungus is more likely to become pathogenic, over-running the host's weakened defense and causing a range of diseases generally termed aspergillosis.
1.9: INTRODUCTION OF PLANT \textit{CALOTROPIS PROCERA} (Ait.)

\textit{Calotropis procera} (Ait.) R.Br. (Figure 1.4) is a widely used medicinal plant in Indian sub-continent (Kumar and Roy, 2007; Sehgal, \textit{et al.}, 2005; Akinloye, \textit{et al.}, 2001; Zafar, \textit{et al.}, 2006). It has long ethnobotanical history in traditional medicine and grows in abundance in this geographical region.

\textbf{Family:} Asclepiadaceae

\textbf{Common name:}

\textbf{English:} Calotrope, \textit{Calotropis}, Dead Sea Fruit, Desert Wick, Giant Milk Weed, Mudar Fibre, Rubber Bush, Rubber Tree, Sodom Apple, Swallow- Wart

\textbf{Hindi:} Aak, Akada, Akado, Madar

\textbf{Classification:}

\textbf{Taxon:} \textit{Calotropis procera} (Aiton) W. T. Aiton

\begin{itemize}
  \item \textbf{Kingdom:} \textit{Plantae} – Plants
  \item \textbf{Subkingdom:} \textit{Tracheobionta} – Vascular plants
  \item \textbf{Superdivision:} \textit{Spermatophyta} – Seed plants
  \item \textbf{Division:} \textit{Magnoliophyta} – Flowering plants
  \item \textbf{Class:} \textit{Magnoliopsida} – Dicotyledons
  \item \textbf{Subclass:} \textit{Asteridae}
  \item \textbf{Order:} \textit{Gentianales}
  \item \textbf{Family:} \textit{Asclepiadaceae} (Milkweed family)
  \item \textbf{Genus:} \textit{Calotropis} \textit{R. Br.} – \textit{Calotropis}
  \item \textbf{Species:} procera
\end{itemize}

\textbf{Figure 1.9.1:} \textit{Calotropis procera} (Ait.)
a. BOTANICAL DESCRIPTION:

*Calotropis procera* is a shrub or small tree up to 2.5 m (max. 6m) high.

**Stem:** Stem usually simple, rarely branched, woody at the base and covered with a fissured, corky, branches somewhat succulent and densely white tomentose, early glabrescent.

**Leaves:** Leaves are opposite, simple, subsessile, stipule absent; blade oblong-obovate to broadly obovate, 5-30x 2.5-15.5 cm, apex abruptly and shortly acuminate to apiculate, base cordate, margins entire, succulent. They are white tomentose when young, later glabrescent and glaucous.

**Inflorescences:** Dense, multiflowerd, umbellate cyme arising from the nodes and appearing axillary or terminal.

**Flower:** Hermaphrodite, pentamerous, pedicle 1-3 long; calyx 5-lobed, shortly united at the base, lobes ovate, 4-7x 3-4 mm, glabrescent.

**Fruit:** Simple, fleshy, inflated, subglobose to obliquely ovoid follicle up to 10 cm or more in diameter.

**Seed:** Numerous, flat obovate, 6x 5 mm, with silky white pappus 3 cm or more long.

b. Ecology and Distribution

*Calotropis procera* is drought-resistant, salt-tolerant, to a relatively high degree, and through its wind and animal dispersed seeds, it quickly becomes established as a weed along degraded roadsides, lagoon edges and in overgrazed native pastures. It has preference for and is often dominant in areas of abandoned cultivation especially sandy soils in areas of low rainfall; assumed to be indicator of over-cultivation.
c. Geographical Distribution

Native: Afghanistan, Algeria, Burkina Faso, Cameroon, Chad, Cote d’Ivoire, Democratic Republic Of Congo, Egypt, Eritrea, Ethiopia, Gambia, Gana, Guinea-Bissau, India, Iran, Iraq, Israel, Kenya, Kuwait, Lebanon, Libyan Arab Jamahiria, Mali, Mauritania, Morocco, Mozambique, Myanmar, Nepal, Niger, Oman, Pakistan, Sudia Arabia, Senegal, Sierra Leone, Somalia, Sudan, Syrian Arab Republic, Tanzania, Thailand, Uganda, United Arab Emirates, Vietnam, Yemen and Republic Of Zimbabwe.

d. Biophysical Limits

These plants grow at altitude up to 1300 m where a mean annual rainfall ranges, 300-400mm. They are preferably distributed in sandy soils.

e. Reproductive Biology

These plants are reproduced via cross pollination through insect such as monarch butterflies. However, both animals and wind also dispers seeds. Progeny are genetically divergent from its parents (chromosome number 2n = 22).

f. Medicinal Use:

Compounds derived from the plant have been found to have emeto-cathartic and digitalic properties. The principal active medicinal compounds are asclepin and mudarin. Other compounds have been found to have bactericidal and vermicidal properties. The latex contains a proteolytic enzyme called calotropaine. An infusion of bark powder is used in the treatment and cure of leprosy and elephantiasis (Singh, et al., 2002). The root bark is an emetic, the flower a digestive, and a tonic is used for asthma and catarrh. Bark and wood stimulate lactation in cattle. Roots (extremely poisonous) are applied for snakebite. The latex is used for treating ringworm, guinea worm blisters, scorpion stings, venereal sores and ophthalmic disorders; also used as a laxative. Its use in India in the treatment of skin disease has caused severe bullous dermatitis leading some times to hypertrophic scars.