CHAPTER-2
2.0 REVIEW OF LITERATURE

2.1 Asclepiadaceae R.Br. ~ Apocynaceae

Habit and leaf form; Herbs, or lianas, or shrubs, or trees (rarely); laticiferous. ‘Normal’ plants, or switch-plants, or plants of very peculiar vegetative form; sometimes ‘cactoid’; with leaves modified as ‘pitchers’ in Dischidia rafflesiana. Leaves well developed, or much reduced. Plants succulent, or non-succulent; autotrophic (usually), or ‘carnivorous’ (D. rafflesiana). Trapping mechanism if the ‘pitchers’ of D. rafflesiana function as such, passive. The traps consisting of ‘pitchers’. Perennial. Self supporting, or climbing; when climbing, stem twines, or root climbers, or scrambling; the twiners twining anticlockwise (Araujia, Ceropogia, Stephanotis). Mesophytic, or xerophytic. Leaves opposite (decussate, usually), or whorled (rarely, and rarely spiral); ‘herbaceous’, or fleshy, or membranous, or modified into spines; simple. Lamina entire (often reduced); one-veined, or pinnately veined, or pinnately veined to palmately veined. Leaves stipulate, or extstipulate (or reduced to colleters). Stipules with colleters (and colleters usually present in the stipular position). Domatia recorded (in 3 genera); represented by pits, or hair tufts.

General anatomy; Plants with laticifers (non-articulated, branched or not).

Leaf anatomy; Stomata anomocytic, or anisocytic, or paracytic. Minor leaf veins without phloem transfer cells (Hoya).

Stem anatomy; Cork cambium present; initially superficial. Nodes unilacunar, or trilacunar (associated with one or three petiolar traces, not gutter-shaped). Primary vascular tissue often bicollateral. Internal phloem usually present. Secondary thickening developing from a conventional cambial ring, or anomalous; from a single cambial ring. ‘Included’ phloem present, or absent. Xylem with fibre tracheids, or without fibre tracheids; with vessels. Vessel end-walls simple. Vessels with vestured pits. Wood
Reproductive type: pollination. Plants hermaphrodite. Entomophilous; often via diptera.

Pollination mechanism conspicuously specialized (involving trapping of insects' legs or proboscis between the osmotically elastic anther wings, and withdrawal entailing capture of the pollinia by means of 'sutured corpuscular pollen carriers').

Inflorescence, floral, fruit and seed morphology. Flowers solitary, or aggregated in 'inflorescences'. The terminal inflorescence unit usually cymose (often umbelliform), or racemose (rarely). Flowers fragrant, or malodorous, or odourless; regular; 5 merous; cyclic; tetracyclic. Hypogynous disk absent. Perianth with distinct calyx and corolla; 10; 2 whorled; isomerous. Calyx 5; 1 whorled; usually gamosepalous (at the base). Calyx lobes markedly longer than the tube. Calyx regular; imbricate, or valvate; with the median member posterior. Corolla 5; 1 whorled; appendiculate (with a corona, simple or of separate scales, in only Gymnema, Leptadenia, Oxystelma), or not appendiculate (mostly); gamopetalous (the tube short). Corolla lobes about the same length as the tube, or markedly longer than the tube. Corolla contorted; regular. Androecium 5. Androecial members adnate; united with the gynoecium (forming a gynostegium with it); coherent (via the filaments, forming a short sheath around the style — by contrast with Periplocaceae); 1 adelphous; 1 whorled. Androecium exclusively of fertile stamens. Stamens 5; inserted near the base of the corolla tube (at the base); isomerous with the perianth; oppositipetalous; alternating with the corolla members; filantherous to with sessile anthers. Filaments appendiculate (nearly always, the short filaments ornamented from their external bases with the nectariferous components of an androecial corona of variable form, which is incorporated in the gynostegium), or not appendiculate (Orthanthera only). Anthers connivent (distinct from one another, but individually
attached adaxially to the stylehead; basifixed; intorse; bilocular (nearly always), or four locular (Secamoneae only); bisporangiate (usually). or tetrasporangiate (in Secamoneae): appendaged (provided with horny wings and membranous connective appendages contributing to the coronal complex). Endothelium developing fibrous thickenings (rarely), or not developing fibrous thickenings (a thick, undifferentiated wall being common). Microsporogenesis successive, or simultaneous. The initial microspore tetrads linear. Anther wall initially with one middle layer; of the ‘basic’ type, or of the ‘dicot’ type. Tapetum glandular. Pollen shed in aggregates; in the form of pollinia (one or two per theca). Pollen grains 2-celled, or 3-celled.

*Gynoecium* 2 carpelled. Carpels reduced in number relative to the perianth. The pistil 2 celled. *Gynoecium* syncarpous (but the carpels united only by their styleheads); synstylous; superior. Carpel (1–)5–50 ovuled (generally numerous). Placentation marginal (ventral). Ovary alternatively interpretable as 2 locular (the separate ovaries being viewed as the ‘locules’ of a ‘syncarpous’ gynoecium). Gynoecium median; stylate. Styles 2; partially joined (free below, but united by the dilated stylehead, which has lateral stigmatic surfaces alternating with the stamens). Stigmas wet type, or dry type; papillate, or non-papillate; Group II type and Group IV type. Placentation interpretable as axile (ventral in the discrete ‘loculi’, corresponding with ‘axile’ in *Apocynaceae*). Ovules (1–)5–50 per locule (generally more or less numerous); pendulous; anatropous; unitegmic; pseudocrassinucellate. Embryo-sac development *Polygonum*-type. Polar nuclei fusing prior to fertilization. Antipodal cells formed; 3; not proliferating; ephemeral (usually), or persistent (*Ceropegia, Cynanchum*). Synergids pear-shaped (sometimes with filiform apparatus). Endosperm formation nuclear. Embryogeny solanad.

*Fruit*: non-fleshy; an aggregate (of two carpels), or not an aggregate (of one only, by abortion); dehiscent; *comprising a pair of ‘follicles’ with thin papery placental flaps, or*
commonly only one of the pair developing. Seeds endospermic. Endosperm oily. Seeds
conspicuously hairy (with a terminal coma of long, silky hairs); winged (usually, all
round), or wingless (Secamoneae). Cotyledons 2. Embryo chlorophyllous (4/7); straight.
Seedling: Germination phanerocotylar, or cryptocotylar. Physiology, biochemistry.
Cyanogenic (very rarely), or not cyanogenic. Alkaloids present, or absent. Iridoids
seemingly not detected. Proanthocyanidins absent. Flavonols present, or absent.
kaempferol, or kaempferol and quercetin. Ellagic acid absent (4 species, 4 genera).
Arbutin absent. Saponins/sapogenins usually absent. Aluminium accumulation not found.
C₃ and CAM. C₃ physiology recorded directly in Asclepias — Krenzer et al. 1975. CAM
Hoodia, Hoya, Huernia, Sarcostemma, Stapelia. Trichocaulon: Anatomy non-C₄ type
(Asclepias, Caralluma). Geography, cytology. Temperate (rarely), or sub-tropical to

Taxonomy: Subclass Dicotyledonae; Tenuinucelli. Dahlgren’s Superorder Gentianiflorae:
Gentianales. Cronquist’s Subclass Asteridae; Gentianales. APG (1998) Eudicot; core
Eudicot; Asterid; Euasterid I; Gentianales (as a synonym of Apocynaceae). Species 2000.
Genera 280; Absolmsia, Adelostemma, Aidomene, Amblyopetalum. Amblystigma,
Brachystelma, Calotropis. Campestigma, Carallum, Ceropgia, Cibirhiza, Cionura.
Clemensiella, Conomitra, Cordylogyne, Corollonema, Cosmostigma. Costantina.
Ditassa, Dittoceras, Dolichopetalum, Dolichostégia, Dorystephania, Dregea.
Drepanostemma, Duvalia, Duvaliandra, Echidnopsis, Edithcoele, Emicocarpus.
## Comparison of *Calotropis* and *Asclepias* species

<table>
<thead>
<tr>
<th>Species</th>
<th>Common name(s)</th>
<th>Origin</th>
<th>Height (ft.)</th>
<th>Leaf arrangement</th>
<th>Flower Size (inches)</th>
<th>Color</th>
<th>Leaves</th>
<th>Fruits</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Calotropis gigantea</em></td>
<td>Gigantic swallow wort, Madar</td>
<td>India</td>
<td>8-10</td>
<td>Opposite</td>
<td>2</td>
<td>White to purple, rarely light green yellow or white. Flowers not scented</td>
<td>Sessile</td>
<td>Follicles recurved, 2 or 1 follicles, second more often suppressed, 3-4&quot; long</td>
</tr>
<tr>
<td><em>Asclepias tuberosa</em></td>
<td>Butterfly weed</td>
<td>South America</td>
<td>2-3</td>
<td>Alternate</td>
<td>0.5</td>
<td>Corolla greenish-orange, scented</td>
<td>Sessile or very short petiolated</td>
<td>Follicles finely pubescent, 4-5&quot; long</td>
</tr>
<tr>
<td><em>Asclepias syriaca</em></td>
<td>Common milkweed Sikweed</td>
<td>South America</td>
<td>Up to 5</td>
<td>Opposite or verticillate</td>
<td>0.5</td>
<td>Corolla greenish to purplish white, scented.</td>
<td>Petiolated</td>
<td>Follicles tomentose and echinate, 3-5&quot; long.</td>
</tr>
<tr>
<td><em>Calotropis procera</em></td>
<td>Swallow-wort</td>
<td>India</td>
<td>3-6</td>
<td>Opposite</td>
<td>1.5</td>
<td>White to pink, scented.</td>
<td>Sub-sessile</td>
<td>Follicles 3-4&quot;, recurved</td>
</tr>
</tbody>
</table>
Treutlera, Trichocalon, Trichosacme, Trichosandra, Tridentea, Tromotriche, Tweedia.
Tylophora, Tylophoropsis, Vailia, Vincetoxicopsis, Vincetoxicum, Voharanga.
Vohemaria, White-Sloanea, Widgrenia, Woodia, Xysmalobium.
Economic uses, etc. Prized cultivated succulents or vines from Asclepias, Hoya, Aruajia.
Ceropogia, Stapelia, Caralluma, Decabelone, etc. (Watson and Dallwitz. 2000)

2.2 Calotropis gigantea

Synonym Asclepias gigantea.

Vernacular Sanskrit; Alarka, Hindi; Madar safed, English; Mudar, bow string hemp.

Names Bengali: Akanda, Nepalese: Baramadhaka, Sinhalese: Elawara. French:
Herbe Liron-delle, Unani: Aak Safed, Arabian: Ushar-e-Abyaz, Persian:
Khark-safed, Pastu, Spalwek, Tamil: Yerukki.

Parts used Root, root bark, leaves, juice and flower.

Habitat Frequently met with throughout India as a weed on fallow land and in waste grounds.

Description A stout, hairy tomentose shrub 4-10 ft height with milky juice leaves sessile, thick, glaucous green, 4-8 inch in length, elliptic or obovate-oblong clothed beneath with fine cottony tomentum. Flowers; 1.5 to 2.0 inch in diameter. Not scented: Corolla; purplish or white, lobes spreading, coronal scales hairy with two obtuse auricles just below the rounded apex. Follicles; 3-4 inch long curved turgid. Seeds; with a tuft of silky hair. Leaf; The epidermis of the leaf lamina is followed by three layers of closely packed palisade cells filled with chloroplasts. Multicellular thin-walled trichomes are distributed throughout the leaf. A rubiaceous type of stomata is found in the lower epidermis. Epidermal cells contain starch grains. fats and oil in parenchyma but tannin is absent (Duke, 1985).
Ayurvedic Descriptions Rasa-katu ticta, Guna-rooiksha, laghu, teekshna, Veerya-Ushna, Vipak, katu.

Actions and Uses Badona as tapan sothlar, barna sodhan, kustaghana, dipan, pachan, krimighna

Chemical Constituents The leaves of *Calotropis gigantea* contain an active principle, mudarine. Besides this a yellow bitter acid and resin were also found. In addition, the leaves contain three glucosides viz. calotropin, uscharin and calotoxin. Singh and Rao, 1991 observed that asclepin isolated from calotropis spp. was found to be 3-o-acetyl-calotropin by various chemical and physical tests. It will be seen that the root bark from the older plants has a higher percent of acrid and bitter resinous matter than that from the younger plants. After quantitative experiment s on the powdered bark the following results were obtained (Umberto Quattrochi, 2000).

*Calotropis gigantea* an indigenous plant is known to have cardiac actions as mentioned by Nadkarni in Indian Materia Medica. Parts of the plant, which grows wild in most developing countries, are used for medicinal (Chopra, et al., 1958) and other purposes (Satyawati, et al., 1976). The effect of *Calotropis gigantea* on dog ECG had been studied in 1976 (Kulkarni, et al.,). The isolated proteinases calotropain F₁ and F₂ of *Calotropis gigantea* latex had been studied in detail, simultaneously a comparative study of the esterase, amidase, milk clotting and caseinolytic activities were also studied (Abraham and Joshi, 1979). The milky sap of *Calotropis gigantea* was studied in blood group serology as a proteolytic enzyme (Patil, et al., 1993). Isorhamnetin-3-O-rutinoside, Isorhamnetin-3-O-glucopyronoside, taraxasterol acetate and flavonol trisaccharide were isolated and characterized from the aerial part of *Calotropis gigantea* and their structures were established by combination of fast atom bombardment mass spectroscopy, $^1$H and $^{13}$C NMR spectra and some chemical degradations (Sen, et al.,
Autodigestion of the cysteine proteinases, calotropins D₁ and D₂ isolated from the latex of *Calotropis gigantea*, had been studied at pH 7.5 and 37 C in the presence of an activating agent (Sen Gupta, et al., 1984). The plant is considered to be crude drug of Bangladesh (Kitagawa et al., 1992) and medicinal plant of Indonesia (Kiuchi et al., 1998). Pal and Sinha in 1980 isolated, crystallized and studied the properties of Calotropins D₁ and D₂ from *Calotropis gigantea* (Pal and Sinha, 1980). Two new oxiopregnane-oligoglycosides named calotropis A and B have been isolated from the root of *Calotropis gigantea* and their chemical structures have been elucidated by chemical spectroscopy methods (Kitagawa et al., 1992). The cytotoxic principles of ‘Akond mul’ (root of *Calotropis gigantea*) cardenolide glycosides, calotropin frugoside and 4-O-Beta-D-Glucopyranosyl frugoside were obtained as the cytotoxic principles (Kiuchi, et al., 1998). Development-inhibiting activity against *Sitophilus zeamais* Motschulsky (Coleoptera: Curculionidae) (Haque and Nakita, 2000).

<table>
<thead>
<tr>
<th></th>
<th>% of contents from young plants</th>
<th>From old Plants</th>
</tr>
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<tbody>
<tr>
<td>Moisture</td>
<td>12.1</td>
<td>10.2</td>
</tr>
<tr>
<td>Spirit extract</td>
<td>15</td>
<td>16.2</td>
</tr>
<tr>
<td>Soluble in water</td>
<td>7.2</td>
<td>7.5</td>
</tr>
<tr>
<td>Resins</td>
<td>7.8</td>
<td>8.7</td>
</tr>
<tr>
<td>Total ash</td>
<td>7.0</td>
<td>12.2</td>
</tr>
<tr>
<td>Sand</td>
<td>2.8</td>
<td>7.2</td>
</tr>
<tr>
<td>Pure ash</td>
<td>4.2</td>
<td>5.0</td>
</tr>
</tbody>
</table>

**Medicinal properties and uses**

Root bark is alternative tonic, antispasmodic, expectorant, emetic. It is also recommended in leprosy, hepatic and splenic enlargements, dropsy and worms (Nadkarni, 1954; Chopra et al., 1956). The milky juice of *Calotropis gigantea* showed marked stimulant action on
the spontaneous activity of the isolated non gravid rat uterus (Dhawan and Saxena, 1968). The alcoholic extracts of the roots and leaves of *Calotropis gigantea* were found to have anticancer activity against human epidermal carcinoma of the nasopharynx in tissue culture (Bhakuni et al., 1969; Dhar et al., 1968).

The medicinal properties of the plant are similar to those of *Calotropis procera*. The milky juice is used as a blistering agent. The root bark is very useful in acute and subacute dysentery. Its tincture and powder were used in bronchitis and dysentery and were found efficacious. (Nadkarni, 1954; Chopra et al., 1958). The drug acts like digitalis on the heart. The taste of root bark of both species is mucilaginous and bitter and the odor is peculiar. Flower are digestive, stomachic and tonic. The milky juice is a violent purgative and gastrointestinal irritant. All parts of the plant have alternative properties when taken in small doses (Nadkarni, 1954; Chopra et al., 1958; Chopra, et al., 1956; Kartikar and Basu, 1984).

**Preparation and Dose**  
Tincture – 4-28 ml/day in divided doses  
Powder – 0.5-1 g/day in divided doses

**Antidotes** - As an antidote to poisoning atropine may be administered. In severe cases the stomach pump may be used and chloral or chloroform administered. Amyl nitrite may also be useful.

The *Calotropis gigantea* has been studied extensively for its various properties. The effect of rare earth elements on growth and nutrition of coconut palm and root competition for these elements has been studied between the palm and *Calotropis gigantea* (Wahid and Valiathan, 2000). Sugarcane press mud cake: Accelerator of biogas production in *Calotropis gigantea* biomass (Abubacker and Rao, 1999). Use of this plant has been studied in Cross-cultural ethnobotanical studies of Santhal Pargana (Eastern India) and Western Ghats (Southern India) (Goel and Rajendran 1999). The evaluation of
plant lattice against Heterodera cajani on greengram was studied by Gupta and Sobita, 1999. Importance of the plant in traditional and homeopathic systems of medicine in India was studied by Pal, 1999. Studies on the uptake of heavy metals by the plant species on chromite minespoils in sub-tropical regions of India (Samantaray and Rout, 1999). The use of medicinal plants by tribals of Chotanagpur with other tribals of India was correlated in 1999 (Topno and Ghosh). In comparison of allelopathic potential of Datura stramonium L. was also studied (Oudwhia and Tripathi 1998). An effect of extract of Calotropis gigantea stem on the heart beat of Lamellidens marginalis had been elaborated (Pillay and Azariah, 1997). Plant-insect-predator interactions: Reference to Aphis nerii Boyr (Homoptera; Aphidae) and Menochilus sexmaculatus Fabr (Coleoptera: Coccinellidae) on the milkweed, Calotropis gigantea L. (Asclepiadaceae) (Pugalenthhi and Livingstone 1997). This plant was found useful in tribals during in search for antibacterial and antifungal activity of some plants of Kerala (Sasidharan, 1997). This plant was also found useful in tribals during in search of antiviral and cytotoxic activities of some plants used in Malaysian indigenous medicine (Ali and Mackeen, 1996). The effect of plant extracts and systemic fungicide had been studied on the pineapple fruit-rotting fungus (Damayanti and Susheela, 1996). The morphology and biochemical aspects of starch grains in latex sera of plant were also studied (Dc. 1996). A non-chemical approach was applied to control Fusarium diseases of mulberry (Gupta and Govindaiah, 1996). The antimalarial effect of plant extracts was studied on post-embryonic development of the mosquito Culex quinquefasciatus (Neraliya and Srivastava 1996). This plant was studied while in the chemical study of Indonesian medicinal plants (Shibuya and Kitagawa 1996). On Hyphomycetes: LXXII. Further novel leaf spot-inducing species of Phaeoramularia from the Indian subcontinent (Singh and Chaudhary, 1996). The nature of the plant as cardenolides (heart poisons) had been studied in the
painted grasshopper Plocilocus pictus F. (Orthoptera: Pyrgomorphidae) feeding on the milkweed *Calotropis gigantea* L. (Asclepiadaceae) (Pugalenthi and Livingstone 1995). The utility of this plant in U.P. was found in search of some interesting plant records after a gap of more than one century from the district of Lucknow, U.P. (Singh. 1995). Discovered as herbal drugs used by the tribal people of Lohit district of Arunachal Pradesh for abortion and easy delivery-A report (Bhuyan 1994). The *Calotropis gigantea* in Israel was considered as new arrival or new discovery (Dagan and Eissikowitz 1994).

The plant was studied extensively in 1993 including quantitative microscopy and varietal differentiation (Chaudhary, 1993), histo-pharmacognostic evaluation (De. and Datta 1993), on the physical properties (Iizuka and Kawano, 1993). An ethnobotanical as remedies for scorpion sting and snake bite (Jain and Sahu, 1993). The effect of certain leaf extracts on hatching and mortality of the root-knot nematode, *Meloidogyne incognita*, infesting mulberry (Philip and Govindaiah, 1993), in the population drift and seed resource utilization of spilostethus hospes (Fab.) (Sanjayan, 1993).

The effect of drug and extract on mitochondrial malate dehydrogenase and malic enzyme of a filarial worm *Setaria digitata* (Banu and Nellaiappen, 1992), taxonomic account in Australia (Forster, 1992) biology on the basis of its nutritional ecology (Livingstone and Pugalenthi, 1992) was elaborated. Studies on differentiation of laticifers through light and electron microscopy (Roy and De 1992), chemical constituents flavonol glycosides (Sen and Sahu, 1992), chemical structures of calotroposides C. D. E. F. and G: Five additional new oxypregnane-oligoglycosides from the root (Asclepiadaceae) (Shibuya and Zhang, 1992), a report on flavonoid investigation (Rahman and Wilcock 1991) was given in detail. The plant has also been studied for its air pollution tolerance of (Singh and Rao, 1991), and antifeedant properties against second stage larva of *Henosepilachna vigintioctopunctata* Fabricius (Rao and Chitra, 1990). The field
Analysis of numbers of papers/mentions over time (Source: Agricola database 1970-1996)
evaluation of plant extract for the control of brinjal spotted leaf beetle, *Henosepalachna vigintioctopunctata* Fab (Reddy and Chitra, 1990) has also shown the usefulness of this plant.

*Calotropis* yields a durable fiber (commercially known as Bowstring of India) useful for ropes, carpets, fishing nets, and sewing thread. Floss, obtained from seeds, is used for stuffing purposes. Fermented mixture of *Calotropis* and salt is used to remove the hair from goat skins for production of "nari leather" and of sheep skins to make leather which is much used for inexpensive book-binding (Singh, et. al. 1996). Fungicidal and insecticidal properties of *Calotropis* have been reported (Oudhia, 2001).

Allelopathic effects of *Calotropis* on different agricultural crops have not been well studied. Extracts of different plant parts viz. root, stem, leaf, and stem - leaf of *Calotropis* affect germination and seedling vigor of many agricultural crops have been reported (Oudhia and Tripathi 1997, 1999; Oudhia et al. 1997, 1998a,b). However, extracts of *Calotropis* failed to produce any detrimental effects on weeds such as *Chenopodium album* *Melilotus alba*, *Melilotus indica*, *Sphaeranthus indicus*, and *Phalaris minor* (Oudhia and Tripathi 1997).

Botanically the plant has been considered for its tissue culture and plant regeneration from immature embryo explants (Roy and De 1990), DNA, RNA and protein contents during rhizogenesis in tissue culture (De. 1989). Structural, developmental and histochemical studies in the colleters (Kuriachen and Dave 1989). The laticiferous taxon was studied as a source of energy and hydrocarbon (Marimuthu and Subramanian, 1989). The surface and internal lipids of leaves (Lakshminarayana and Rao, 1988) and the effect of seed treatment with this plant latex on the root-knot development and plant growth of some vegetables (Siddiqui and Alam 1988a) was also studied. The effect of seed dressing with plant latex on *Tylenchorhynchus brassicae* and
plant growth of cabbage and cauliflower (Siddiqui and Alam 1988b) was extensively studied.

Characterization of extracellular lipase produced by *Aspergillus japonicus* in response to *Calotropis gigantea* latex (Vora and Bhandare, 1988), chemical modification and amino terminal sequence of calotropin D₁ (Bhattacharya and Sengupta, 1985). Effects on hard coated seeds of Trichosanthes anguina: Plant extract (Datta, 1987). A simple TLC method for detection of cardiac glycosides (cardenolides) from *Calotropis gigantea* (Linn) R Br. ex Ait both in situ and in vitro (De and Datta 1987) was developed successfully. The Gamma activity of plant from monazite-bearing soils of the West Coast of Sri Lanka was elaborated (Hewamanna and Ranawake, 1987). Organ specific chemodifferentiation of cardenolides in vitro (Datta and De 1986a), Laticifer differentiation in cultures (Datta and De 1986b), histochemistry and in vitro study on the pollinium (Viswanathan and Lakshmanan 1984, 1986) will help in understanding the properties of this plant. Phenolic hydroxyl ionization in calotropins from *Calotropis gigantea* latex (Bhattacharya and Sengupta, 1985), inheritance and frequency of a color polymorphism in *Danaus plexippus* (Lepidoptera: Danaidae) on Oahu, Hawaii (USA) (Stimson and Meyers 1984). The environmental implications of the use of *Calotropis gigantea* as a textile fabric (Tuntawiroon and Samootsakorn, 1984), effects of Calotropis leaf extract on mitosis of Allium sativum root tips (Vivekanandan, 1984) and found one of the useful plant in search for antifeedants in some botanicals for desert locust, *Schistocerca gregaria* (Singh, 1983).

### 2.3 Pathophysiology of inflammation

Inflammation is the response of living tissue to damage. The acute inflammatory response has 3 main functions.
The affected area is occupied by a transient material called the acute inflammatory exudate. The exudate carries proteins, fluid and cells from local blood vessels into the damaged area to mediate local defenses.

- If an infective causitive agent (e.g. bacteria) is present in the damaged area, it can be destroyed and eliminated by components of the exudate.

- The damaged tissue can be broken down and partially liquefied, and the debris removed from the site of damage.

The cause of acute inflammation may be due to physical damage, chemical substances, micro-organisms or other agents. The inflammatory response consist of changes in blood flow, increased permeability of blood vessels and escape of cells from the blood into the tissues. The changes are essentially the same whatever the cause and wherever the site. Acute inflammation is short-lasting, lasting only a few days. If it is longer lasting however, then it is referred to as chronic inflammation. Various examples of acute inflammation that includes sore throat, reactions in the skin to a scratch or a burn or insect bite, and acute hepatitis and so on. However, there are occasional historical exceptions such as pneumonia, inflammation of the lung rather than pneumonitis and pleurisy, inflammation of the pleura, rather than pleuritis.

If the agent causing acute inflammation is not removed, the acute inflammation may progress to the chronic stage. In addition to organisation of the tissue just described, the character of the cellular exudate changes, with lymphocytes, plasma cells and macrophages (sometimes including multi nucleate giant cells) replacing the neutrophil polymorphs. Often, chronic inflammation occurs as a primary event, there being no preceding period of acute inflammation.
The ability to mount an inflammatory response is essential for survival in the face of environmental pathogens and injury, although in some situations and diseases the inflammatory response may be exaggerated and sustained for no apparent beneficial reasons. Several classes of leukocytes play an essential role in inflammation. Although earlier ideas emphasized the promotion of migration of cells out of the microvasculature, recent studies have examined the role of the endothelial cells and of cells adhesion molecules, including E-,-, P-,-, and L- selectins, intracellular adhesion molecules-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and leukocyteintegrins in the adhesion of leukocytes, platelets and endothelium at the site of inflammation activated endothelial cells play a key role in ‘targeting’ circulating cells to inflammatory sites. Expression of the various adhesion molecule (Gallin, et al., 1992).

Besides the well-known NSAID for the treatment of rheumatic pain, herbal medicine can also be applied successfully. Plants with antirheumatic efficacy include Fraxini cortex, Populi cortex folia and Solidaginis herba (Klein, Galezinsky, 1999). Most of the species belonging to Scrophularia genus had been used as antiinflammatory drugs by the folk medicine (Garcia, et al., 1996). One hundred and seventy-seven plant extracts, representing 163 species of plants and/or fungi, were evaluated in rats to determine their antiinflammatory activity using the carrageenin-induced pedal oedema assay. Of the 163 species of plants and/or fungi tested, 17 exhibited between 30-39 per cent inhibition of inflammation, 21 between 40-49 per cent on chronic and acute inflammation models (Benoit, et al., 2001). Antiinflammatory effect of Forsythia suspensa Vahl, its active fraction, Curcuma xanthorrhiza Roxb, and its active principles (Ozaki. 1990). Graptophyllum pictum (L.) Griff (Ozaki, et al., 1989a). Myristica fragrans Houtt, and its active principles (Ozaki, et al., 1989b). The aqueous and methanolic extracts of Hypoxis hemerocallidea corm, locally known as 'African potato' in South Africa, were examined
on rat paw oedema induced by subplantar injections of fresh egg albumin (0.5 ml/kg) (Ojewole, 2002). In detail the pharmacological and clinical effectiveness of a fixed phytogenic combination trembling popular (Populus tremula), true goldenrod (Solidago virgaurea) and ash (Fraxinus excelsior) in mild to moderate rheumatic complaints (Kim and Kim, 2000) were studied. Antiinflammatory effects of triterpenes isolated from Leptadenia hastata latex on keratinocyte proliferation (Nikiema, et al., 2001), the aqueous and ethanol extracts from the leaves of Giochnatia polymorpha and further fractions obtained from the latter extract using solvents with increasing polarity, including its aqueous residue and the amino acid, 4-hydroxy-N-methyl-proline were investigated by carrageenan-induced pedal oedema formation (Jachak, 1999).

2.4 Pathophysiology of pain

The boundaries between normal discomfort and pathologic pain are often obscure. The intensity of pain suffered differs enormously with the personality, intelligence and culture of the individual. Protracted severe pain can become so dominant factor in a patients life that it can eventually lead to both physical and psychological exhaustion. The relief of pain by the use of appropriate drugs forms an important aspect of therapeutic skills in practice. The choice of treatment would depend upon:

- The nature of the painful disease,
- The mechanism by which it produces pain
- Other associated complications and conditions; and
- The risk of toxicity involved due to the drug so selected

An attempt should always be made to find out the probable cause. Where the cause is obvious, therapy should be directed to treat it. Thus, pain due to an abscess can
be relieved by appropriate chemotherapy and surgery. Whereas that due to a bony metastasis can be relieved by local radiotherapy.

In patients in whom, for some reason, the cause cannot be treated, immediate relief of pain can be obtained by modifying the mechanism by which pain is produced e.g. use of nitrates in angina pectoris, miotics in glaucoma and muscle relaxants in certain musculoskeletal disorders. Mechanism of production of abdominal pain is many times obscure and a demonstrable cause is absent in many cases. It is a common experience that a few seeds of cardamom, fennel or a little ginger can make the stomach comfortable after a sumptuous meal. These agents form the traditional ingredients of many stomachache powders and gripe waters sold in the market. Opioid and non-opioid analgesics are the most commonly employed agents for symptomatic relief of pain without affecting any other aspect of the clinical condition (Satoskar, et al., 1999).

Mankind has always given himself means to fight pain by using at first, means offered to him by his environment particularly the plants. A drug that selectively relieves pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness are called analgesics. Analgesics relieve pain as a symptom, without affecting its cause. Pain that accompanies inflammation and tissue injury probably results from local stimulation of pain fibers and enhanced pain sensitivity, in part a consequence of increased excitability of central neurons in the spinal cord (Konttinen et. al, 1994).

Despite the progress that has occurred in recent years in the development of therapy, there is still a need for effective and potent analgesics, especially for the treatment of chronic pain. One of the most important analgesic drugs employed in clinical practice today continues to be the alkaloid morphine. Recently discovered antinociceptive substances include alkaloids, terpenoids and flavonoid. Plant-derived substances have,
and will certainly continue to have a relevant place in the process of drug discovery, particularly in the development of new analgesic drugs (Calixto, et al., 2000). Several hundreds of plants have been screened so far to find the alternative to the existing drugs to overcome the undesirable effects. The analgesic components were isolated from a Bornean medicinal plant, *Tabernaemontana pauciflora Blume* (syn. Ervatamia blumeana Mark gr.), and the major components were identified as coronaridine and 3-(2-oxopropyl) coronaridine (Okuyama, et al., 1992). Seventeen medicinal plants used popularly in Brazil for their reputed analgesic properties were tested in mice by the writhing and tail flick methods. All extractions were made in 50% aqueous ethanol at low temperatures (Costa, et al., 1989). Analgesic effect of *Pilostigma reticulatum* (nguiguis) (Diallo and Diouf, 2000), selected species of *Phyllanthus* in mice (Santos, 1994), lemon grass tea (Lorenzetti, et al., 1991), leaves of *Vernonia condensate* (Fruotosa, et al., 1994), hydroalcoholic extract of *Siphocampylus verticillatus* (Trentin, 1997), Peruvian medicinal plant, *huanarpo* (*Jatropha ciliata*) (Okuyama, et al., 1996), *Chasmanthera* dependents leaf methanol extract (Morebise, 2001), root extract of *Tragia involucrata* Linn (Dhar, et al., 2000), *Boerhaavia diffusa* L. (Nyctaginaceae) (Hiruma-Lima, et al., 2000), *Randia siamensis* extract (Reanmongkol, 1994) and *Phyllanthus corcovadensis* (Gorski. et al., 1993) had been studied but only few of them has been developed successfully as formulations.

### 2.5 Pathophysiology of fever

Fever, which means a body temperature above the usual range of normal, can be caused by abnormalities in the brain itself or by toxic substances that affect the temperature-regulating centers. Some causes of fever includes bacterial diseases, brain tumors and environmental conditions that may terminate in heatstroke.
Many proteins, breakdown products of proteins, and certain other substances, especially lipopolysaccharide toxins released from bacterial cell membranes, can cause the set-point of the hypothalamic thermostat to rise. Substances that cause this effect are called pyrogens. It is pyrogens released from toxic bacteria or pyrogens released from degenerating tissues of the body that cause fever during disease conditions. When the set-point of the hypothalamic temperature-regulating center becomes increased to a higher level than normal, all the mechanisms for raising the body temperature are brought into play, including heat conservation and increased heat production. Within a few hours after the set-point has been increased to a higher level, the body temperature also approaches this level.

Experiments in animals have shown that some pyrogens, when injected into the hypothalamus, can act directly and immediately on the hypothalamic temperature-regulating center to increase its set-point. Other pyrogens function indirectly and may require several hours of latency before causing their effects. This is true of many of the bacterial pyrogens, especially the endotoxins from gram-negative bacteria, as follows.

When bacteria or breakdown products of bacteria are present in the tissues or in the blood, these are phagocytized by the blood leukocytes, by tissue macrophages and by large granular killer lymphocytes. All these cells in turn digest the bacterial products and then release into the body fluids the substance interleukin-1, also called leukocyte pyrogen or endogenous pyrogen. The interleukin-1, on reaching the hypothalamus, immediately activates the processes to produce fever, sometimes increasing the body temperature a noticeable amount in only 8 to 10 min. As little as one ten-millionth of a gram of endotoxin lipopolysaccharide from the bacteria, acting in this manner in concert with the blood leukocytes, tissue macrophages and killer lymphocytes, can cause fever.
The amount of interleukin-1 that is formed in response to the lipopolysaccharide to cause the fever is only a few nanograms.

Several experiments have suggested that interleukin-1 causes fever by first inducing the formation of one of the prostaglandin's, mainly prostaglandinE2, or a similar substance, and this in turn acts in the hypothalamus to elicit the fever reaction. When prostaglandin formation is blocked by drugs, the fever is either completely abrogated or at least reduced. In fact, this may be the explanation for the manner in which aspirin reduces fever, because aspirin impedes the formation of prostaglandin’s from arachidonic acid. Drugs such as aspirin that reduce the level of fever are called antipyretics (Guyton and Hall, 2000).

2.6 Pathophysiology of ulcer

Peptic ulcer is one of the common gastrointestinal disorders in clinical practice. The common forms of peptic ulcer are:

- Duodenal ulcer (DU)
- Gastric ulcer (GU)
- NSAID induced ulcer; and
- Stress ulcer(s)

Of these, gastric ulcers occur most frequently in the older age group and in the lower socioeconomic class of individuals. The exact cause of ulceration is not known. The gastric acid and pepsin, however, are definitely known to be responsible for maintaining the lesion, once it is produced. Peptic ulceration occurs only in areas which are bathed by an acid juice and it is true to say, ‘No acid, no ulcer’. In certain individuals, there is a constitutional tendency to produce an excess of gastric juice and acid. As this tendency persists even after the ulcer heals, there is always a tendency to recurrence.

The gastric acid and pepsin are secreted by the main gastric glands, present all over the body and fundus of the stomach. The rate and the composition of secretion of main gastric glands vary considerably, depending upon the number of acid secreting cells (the perietal cell mass), emotional factors, digestive state at a given time, hormonal status and the presence of extrinsic chemical stimuli such as caffeine and histamine. The parietal (oxyntic) cells are located in the walls of the mid section of the oxyntic glands, the secretory unit of the gastric mucosa. In addition to parietal cells, these glands consist of chief, mucous, endocrine and somatostatin cells. Gastric acid secretion is regulated by intrinsic central and peripheral mechanisms. The central mechanism acts through the
vagus nerve. In addition, Ach liberated from the postganglionic nerve fibers directly stimulates the parietal cells.

Parietal cells respond to histamine and acetylcholine. The presence of pharmacologically typical H₂-receptors on human parietal cells has been demonstrated. The response of parietal cells to gastric, however, varies among different species. Combination of histamine with both gastric and acetylcholine causes potentiating effect on parietal cell function. The tubulovesicular and canalicular structures of the parietal cells possess specific hydrogen-potassium-ATPase enzyme (proton pump), which is responsible for the exchange of H⁺ for K⁺ ions across the apical surface. The final process of acid transport per se is the property of this gastric H⁺-K⁺ ATPase. The enzyme is stimulated by protein kinases, activated by histamine and by protein kinases, activated by histamine and by acetylcholine and gastrin.

The fundic mucosa also contain numerous cells with a potential paracrine role, such as cells containing somatostatin, histamine, and serotonin (5-HT). Such cells possess several receptors that may regulate acid secretion by modulating the release of the paracrine transmitters. Thus, acetylcholine may enhance the secretion of acid not only by stimulating the parietal cell directly, but also by reducing the level of somatostatin, a potent inhibitor of acid secretion. Prostaglandin E is produced by cells throughout the G.I.tract, which inhibits the secretion of gastric acid in humans, particularly food stimulated acid secretion.

Control of gastric acidity may be achieved by neutralizing gastric acid using antacids and by inhibiting the gastric acid secretion with drugs. Gastric antacids are substances which, on ingestion, react with gastric acid and lower the acidity of gastric contents. The drugs act as weak bases. They raise the gastric pH to above 4. The non-systemic antacids are insoluble till they come into contact with the gastric acid. Some of
the antacid which escapes the reaction with the acid remains in the stomach and reacts with the acid subsequently secreted. The duration of action of such insoluble antacid is, therefore generally longer than that of soluble antacids. They have no effect on the volume of gastric juice nor on the total output of the hydrogen ion. The systemic antacids have to be administered frequently and in sufficient quantity. The output of the gastric juice and acid far exceeds the basal secretion. However, the release of carbon dioxide with resultant belching, flatulence, feeling of fullness, nausea and exacerbation of esophageal reflux are the common side-effects. Systemic alkalosis and possibility of oedema due to sodium retention are its other disadvantages.

An ideal antacid should; act quickly and should have a prolonged action; not interfere with the digestion of food; not interfere with the digestion of food; not cause alkalosis; be nontoxic, palatable, cheap and easily available. The drugs available to reduce the gastric acidity can acts as antimuscarinics, histamine receptor antagonists or proton-pump inhibitors (Satoskar, et al., 1999).

Gastric ulcers occur most frequently in the older age group and in the lower socio-economic class of individuals. Several anti-ulcer drugs are available in the market but there are only few drugs of plant origin, which are effective in the treatment of ulcer along with inflammation, pain and fever. Anti-inflammatory and antiulcer activity of *Teucrium buxifolium* (Fernandez_Puntero, et al., 1997), *Piper longum* Linn, *Zingiber officianalis* Linn and *Ferula* species (Agrawal, et al., 2000), neem tree (Garg, et al., 1993), *Pongamia pinnata* roots (Singh, et al., 1997), *Rhamnus procumbens* (Goel, et al., 1988), *Curcuma longa* (Rafatullah, et al., 1990). The active constituents of the plants have been isolated and studied for gastroprotective activity of triterpenoids (Gupta, et al., 1981) and the constituents of *Rhigiocarya racemifera* (Menispermaceae) (Aguwa, 1985), *Centella asiatica* (Linn.) (Chatterjee, et al., 1992), *Styrax camorum* and *Caesalpinia

2.7 Pathophysiology of diarrhea

Diarrhea is a conditional disorder associated with excess of water and electrolytes loss. Diarrhea occurs as a sign of an underlying disease condition usually reflects a disruption in the bi-directional transport of Na⁺ and Cl⁻ ions through intestinal epithelial cells. A decrease in net ion absorption or an increase in net secretion without a proportional change in the opposing flux can result in diarrhea of luminal ions cannot be absorbed in sufficient amounts by the intestinal mucosa distal to the site of transport impairment. Most secretory diarrhea results in a stool volume exceeding one liter/day in non-fasting patients. Alteration in gut motility or blood flow also may play some role in the pathogenesis of diarrhea, but their involvement is not well defined (Peskar, et al, 1986).
Diarrhea may also occur as a manifestation of non-infectious disease. First, the malabsorption of nutrients as occurs in celiac disease, may lead to the accumulation of osmotically active particles or prosecretory substances in the intestinal lumen, water may diffuse into the lumen as a result of standing osmotic gradient. Second, the immune system of the gut may be activated, as in cases of food allergy or chronic inflammation, resulting in the release of histamine, eicosanoids and other prosecretory substances from mucosal mast cells and immunocytes. Third, diarrhea can occur secondary to disturbances in the endocrine system. Tumors involving endocrine type cells may produce excessive amounts of circulatory hormones that can subsequently act on the intestinal mucosa to promote secretory malignant carcinoid tumors for example, may release 5-HT, Substance P or related peptides and other gut secretagogues. Tumors involving the GI tract, pancreas, adrenal glands, lungs or thyroid gland may secrete such diverse substances as gastrin, prostanoids and other substances known to stimulate intestinal secretion (Sellin and Field, 1981).

An antidiarrheal drug effective in non infectious diarrheas would inhibit secretion or promote absorption and produce some decrease in intestinal motility to permit a longer contact time of luminal fluids with epithelial cells. On the other hand, it is desirable that a drug capable of inhibiting intestinal secretion produced by enteric microorganisms have little or no effect on gut motor function (Tatsume, et al, 1990).

Drugs designed to tip the balance of intestinal ion transport selectively in favor of net absorption could potentially act at a variety of intestinal and extraintestinal sites to inhibit diarrhea. The sites includes; 1 nervous pathway underlying the intestinal mucosa that serve to regulate epithelial functions; 2 the immune cells synthesizing and releasing inflammatory and allergic mediators; 3 the epithelial cell receptors for humoral substances, immune mediators and luminal enterotoxins; 4 elements of the intracellular
signal transduction pathways, linked to these receptors and five the ion-transporting processes themselves. Although some drugs act at one or two of these sites, no antisecretory drug yet identified fulfill the criteria of an ideal broad spectrum anti-diarrheal agent (David, 1995).

An estimate of the purgative activity of unknown compound has frequently been based on the observation that administration of the compound to rats or mice has caused a more frequent passage of fecal pellets and that the character of these changed from formed and relatively solid pellets to unformed semi fluid collagenous masses. Most of the methods used were chemically induced (Bonny castle, 1964).

The mode of action of the unknown drug to involve in the secretory mechanism of intestine is one the field of challenge? However, some procedures have been developed to determine the secretion of intestine and also the changes induced by various form of treatment, but these methods are entirely not satisfactory. Effort to clarify the position has been made and is continuing. Now the methods developed to study the electrolyte secretion are by means of potential difference across the circular smooth muscle.

The problems encountered in determining drug and the effects of various physiological conditions on gastrointestinal motility are many. Procedures have been developed to estimate motility changes induced by various forms of treatment, but they are not entirely satisfactory efforts to clarify the position have been made and are continuing.

Methods used in the analysis of GI propulsive function are of several types, One approach entails study of the transit of unabsorbed marker substances. The most direct approach for assessment of changes in propulsion. Other techniques involve analysis of the pressure in the gut lumen with a variety of devices used in the monitoring of pressure changes. Most direct analysis of the properties of the smooth muscle of the gut is
achieved by quantification of its contractile activity or its electrical activity, which may be determined in-vivo or in-vitro (Carol, 1994).

Recurrent diarrhea is prevalent in developing countries, particularly in tropical regions. A natural based antidiarrheal home remedy can serve as an ideal health tool to limit diarrhea-related morbidity and mortality. In the traditional Indian medical science of Ayurveda, nutmeg is one such plant said to possess antidiarrheal activity. According to indigenous criteria a plant is used in the treatment of a certain illness because of the plant's characteristic smell and taste. Plants with astringent properties are particularly valued to treat diarrhea and dysentery. Bitter, aromatic and bitter-aromatic plants are especially employed to treat gastrointestinal cramps and pain. Additionally, the efficacy of these plants was evaluated using ethnobotanical, phytochemical and pharmacologic information on the plants. The majority of the plants contain chemicals that may produce the effects desired by the Mixe. Frequently tannin-containing drugs are used to treat diarrhea and dysentery. A large number of the plants used by the Mixe in the treatment of gastrointestinal pain contain essential oil or bitter principles (Heinrich, at al., 1992).

There are large numbers of epidemiological and experimental evidence pertaining to world-wide acute-diarrheal disease, which is one of the principal causes of death in the infants, particularly in malnourished and which is of critical importance in developing countries (Snyder and Merson, 1982; Lutterodt, 1989). It thus becomes important to identify and evaluate commonly available natural drugs as an alternative to currently used anti-diarrheal drugs, which are not completely free from adverse effects (Hardman and Limbird, 1992). Several studies have evaluated the effectiveness of some traditional medicines in treating diarrhea, in all different continents (Offiah, V.N. and Chikwender, 1999; Mukherjee, et al., 1998; Rani, et al., 1999; Zavata, et al., 1998). India has a great environmental and biological diversity compared with the rest of the world. A range of
medicinal plants with anti-diarrheal properties has been widely used by the traditional healers; however, the effectiveness of many of these anti-diarrheal traditional medicines has not been scientifically evaluated.