CHAPTER 1

INTRODUCTION

1.1 Research in natural products:

One of the most important areas of chemical research in modern organic chemistry is natural products. This is easily understandable from the fact that many of the important chemicals, the life saving drugs and medicines are natural products. For example, the drug taxol, **paclitaxel (1),** a powerful anticancer drug known, isolated from the bark of the yew tree *Taxus brevifolia* has yielded two approved drugs for breast and ovarian cancer ***(Pazdur and Kudelka, 1993)***. Paclitaxel is a mitotic inhibitor used in cancer chemotherapy.

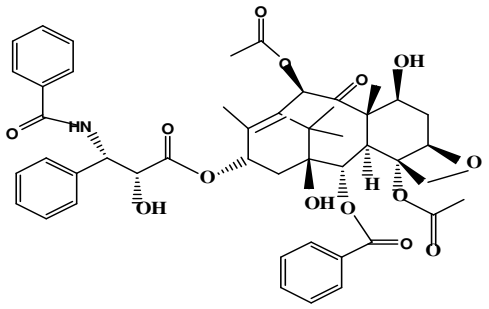
Rein anthraquinone (2) is an antineoplastic anticancer drug found in rhubarb (*Rheum* sp.) and other purgative ***(Iosi et al., 1993).***

Arteether (3), an antimalarial agent, has been developed from artemisinin, a sesquiterpene lactone isolated from *Artemisia annua* (Asteraceae), a plant used in traditional Chinese medicine as a remedy for chills and fevers. Other derivatives of artemisinin are in various stages of clinical trial as antimalarial drugs in Europe ***(Balunas and Kinghorn, 2005, Van et al., 1999).***

Quinine (4), natural white cryatalline alkaloids from the cinchona bark is used for the effective treatment for malaria caused by *Plasmodium falciparum* ***(Dorndorp et al., 2005).***

Exenatide (5) ***(Malhotra et al., 1992, Keating, 2005)*** is a synthetic analog of exenadin-4, which is originally isolated as a 39

amino acid peptide from the saliva of the Gila monster (*Heloderma suspectum*), and the first insulin mimetic found to improve glycemic control.



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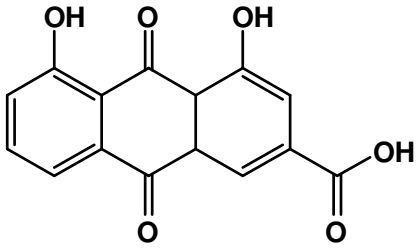

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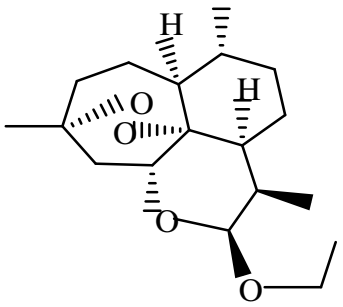

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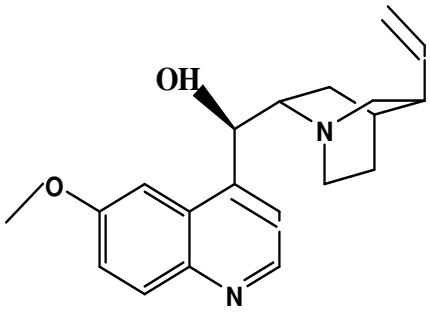

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L-His-L-Gly-L-Glu-Gly-L-Thr-L-Phe-L-Thr-Ser-L-Asp-L-Leu-L-Ser-L-Lys-L-Gin-L-Met-L-Glu-L-Glu-L-Glu-L-Alv-L-Val-L-Arg-L-Leu-L-Phe-IIe-L-Glu-L-Trp-L-Leu-L-Lys -L-Asn-Gly-Gly-L-Pro-L-Ser-L-Ser-L-Ser-Gly-L-Ala-L-Pro-L-Pro-L-Pro-L-Ser-NH_2

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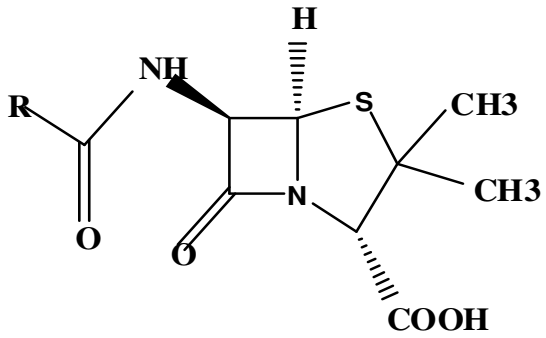
The natural products may also be obtained from microorganisms, animal sources, marine life origin, and the plants.

1.1.1 Natural products from microorganisms:

Terrestrial microorganisms are very good sources of structurally different bioactive substances, and have contributed to the discovery of antibacterial agents such as penicillins, cephalosporins, aminoglycosides, tetracyclines, and polyketides ***(Dewick, 2002).***

The discovery of **Penicillin (6),** a powerful antibiotic by Alexender flaming in 1928 from *Penicillin fungai* gave a boosf towards the area of drug discovery from microorganisms.



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Current therapeutic uses of metabolites from microorganisms have played an excellent role in the development of immunosuppressive agents (eg, cyclosporins and rapamycin), cholesterol-lowering agents (eg, lovastatin and mevastatin), antihelmintic agents (eg, ivermectin), an antidiabetic agent (acarbose), and anticancer agents (eg, pentostatin, peplomycin, and epirubicin) ***(Newnam et al., 2000, Butler, 2005, Sneader, 2005).***

Tigecycline (7) is the 9-*tert*-butyl-glycylamido derivative of minocycline, which is a semi-synthetic product of chlortetracycline

isolated from *Streptomyces aureofaciens*. Tigecycline exhibited antibacterial activity similar to other tetracyclines and typically active against tetracycline-resistant organisms ***(Zhanel et al., 2004).***

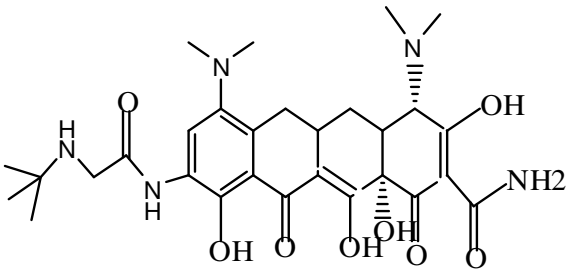
Miglustat (8) is a therapeutic drug in lies of enzyme replacement therapy. Miglustat is an analog of nojirimycin. It is obtained from the broth filtrate of *Streptomyces lavendulae.* It inhibits reversibly glucosylceramide synthase, a ceramide-specific glucosyltransferase that catalyzes the formation of glucocerebroside, and thereby decreases tissue storage of glucosyl ceramide ***(Pastores et al., 2005, Weinreb et al., 2005).***

Biapenem (9), isolated from *Streptomyces cattleya*, is an antibacterial agent effective against both Gram-negative and Gram-positive bacteria including species producing β-lactamases ***(Perry and Ibbotson, 2002).***

Ertapenem (10), isolated from *Streptomyces cattleya* is a new 1β-methylcarbapenem based on thienamycin. It possesses broad-spectrum antibacterial activity and improved the stability to hydrolysis by renal dehydropeptidase enzymes located in the brush border of the kidneys ***(Sader and Gales, 2001*)*.***

A novel analog of ascomycin, isolated as a fermentation product of *Streptomyces hygroscopicus* var *ascomyceticus* is **Pimecrolimus (11).** This can prevent the dephosphorylation of the cytoplasmic component of the nuclear factor of activated T cells ***(Gupta and Chow., 2003*)*.***

A α-bromoacryloyl derivative of distamycin A is **Brostallicin (12),** which was isolated from the culture mycelium of *Streptomyces distallicus*. This is a DNA minor groove binding anticancer agent ***(DiMacro et al., 1962, Broggini et al., 2004)***.



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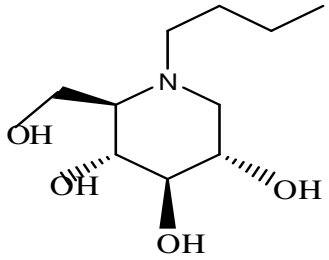

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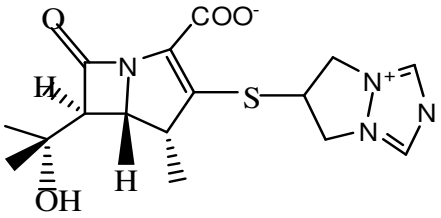

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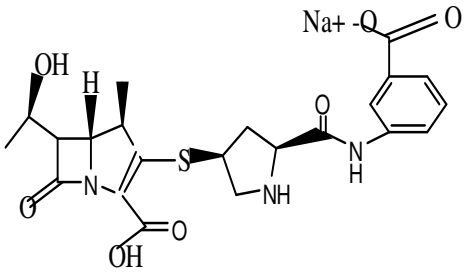

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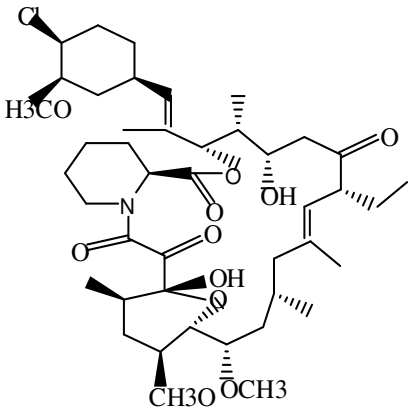

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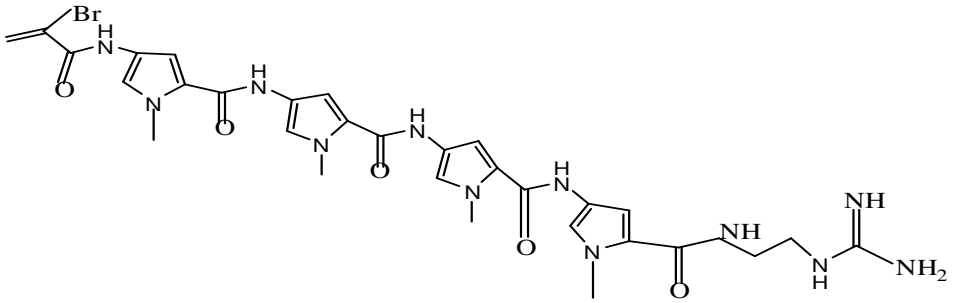

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1.1.2 Natural products from animal sources:

Animals can sometimes be a source of new lead compounds. For example, a series of antibiotic peptides were extracted from the skin of the African clawed frog and a potent analgesic compound called epibatidine was obtained from the skin extracts of the Ecuadorian poison frog ***(Dossey and Aaron, 2010).***

1.1.3 Natural products from venoms and toxins:

Venoms and toxins from animals, plants, snakes, spiders, scorpions, insects, and microorganisms are extremely potent because they often have very specific interactions with a macromolecular target in the body. As a result, they have proved important tools in studying receptors, ion channels, and enzymes. Many of these toxins are polypeptides (e.g. α-bungarotoxin from cobra). However, non-peptide toxins such as tetrodotoxin from the puffer fish are also extremely potent.

Venoms and toxins have been used as lead compounds in the development of novel drugs. For example, teprotide, a peptide isolated

from the venom of the Brazilian viper, was the lead compound for the development of the antihypertensive agent's cilazapril and captopril.

The neurotoxins from *clostridium botulinum* are responsible for serious food poisoning (botulism), but they have a clinical use as well. They can be injected into specific muscles (such as those controlling the eyelids) to prevent muscle spasm. These toxins prevent cholinergic transmission and could well prove a lead for the development of novel anticholinergic drugs ***(Dossey and Aaron, 2010).***

1.1.4 Natural products from marine life origin:

There has been a great interest in finding lead compounds from marine life origin. Natural products obtained from marine life origin are utilized in the treatment and/or prevention of human disease.

For example**, Ziconotide (13)** is currently used in Pain Management ***(Schroeder et al., 2004)***. This is one of the ω-conotoxins isolated from cone snail (*Conus magus*) venom, and are 24–27residue peptides members of the cyclic cysteine knot family was developed for the treatment of severe chronic pain.

HTI-286 (14), a synthetic analog of the tripeptide, hemiasterlin, originally isolated from the South African sponge *Hemiasterella minor*, has shown antitumor activity in human tumor xenograft murine models ***(Newman and Cragg,2004, Loganzo et al.,2004).***

Spisulosine (15) has been isolated from *Spisula polynyma*, Spisulosine shows antiproliferative activity against various human cancer cell lines (colon, gastric, pancreas, pharynx, and renal tumors), and inhibits tumor growth of human renal tumors, melanoma and

prostate tumors in vivo mouse studies **(*Jimeno et al, 1999, Cuadros et al, 2000).***

Squalamine (16) is an aminosterol. It isobtained from the dogfish shark, *Squalus acanthias.* This is a protect inhibitor of growth factor-mediated endothelial cell proliferation and migration and angiogenesis ***(Moore et al, 1993, Hao et al, 2003)***

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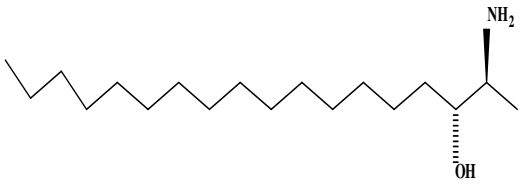

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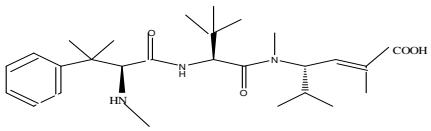

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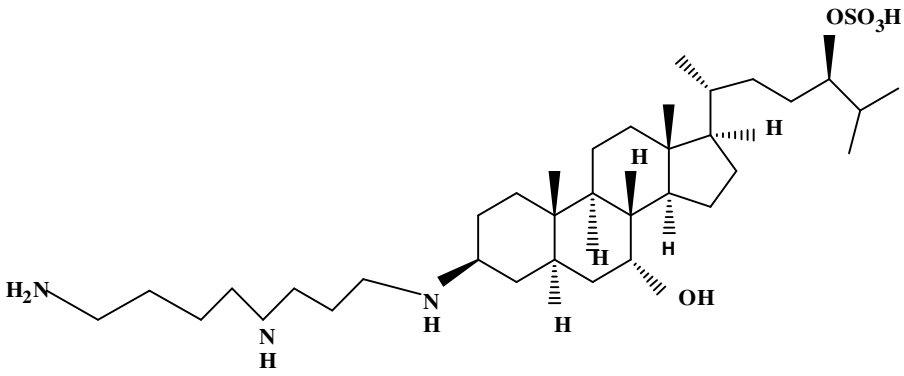

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1.1.5 Natural products from plant kingdom:

Plant kingdom has been the major source of natural products. Chinese, Indian, Arabian and other traditional systems of medicines make extensive use of about 5000 plants. India is proud to be rich in biological diversity and tenth among the plant rich countries of Asia, sixth as far as centers of diversity especially agro diversity are concerned. Nearly, three fourth of the drugs and perfumery products used in the world are available in natural state in the country ***(Sharma et al., 1991).***

India possesses almost 8% of the estimated biodiversity of the World with around 1, 26,000 species. There are about 400 families in the world of flowering plants; at least 315 are represented in India. According to WHO, around 21,000 plant species have the potential for being used as medicinal plants ***(Sharma et al., 1991)***. Some of the plant species with their therapeutic value under different plant groups are given below the table.

Table 1.1.5(a). Plant species with therapeutic value under different plant groups ***(Jiaxiang, 1997).***

Thalophytes	230
Bryophytes	39
Pteridophytes	382
Gymnospermae	55
Angiospermae	
a)Monocotyledones	676
b) Dicotyledones	3495
Total	4877

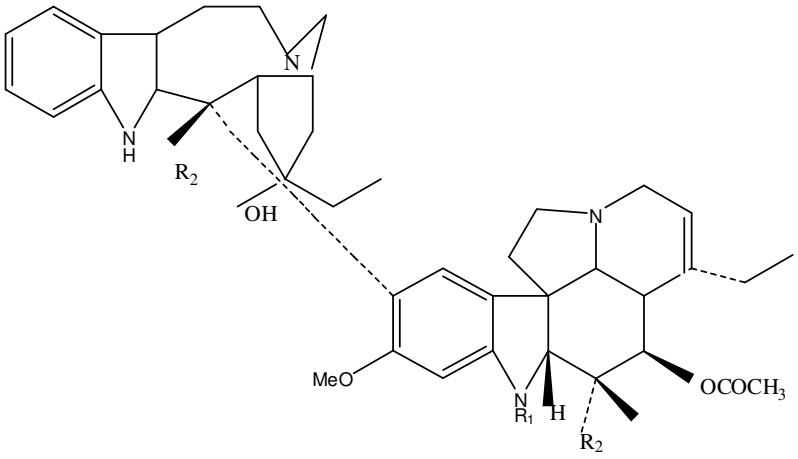
Table 1.1.5(b): Plant families containing over 100 species with therapeutic value ***(Jiaxiang, 1997).***

Family	Genera	Species
I. Monocot		
Liliaceae	45	165
II. Dicots		
Compositae	89	331
Leguminosae	91	313
Ranuculaceae	31	208
Laminaceae	46	189
Rosaceae	28	146
Umbelliferae	34	123
Rubiaceae	35	118
Euphorbiaceae	30	104
Asclepiadaceae	29	101

1.2 Natural product as antineoplastic agent:

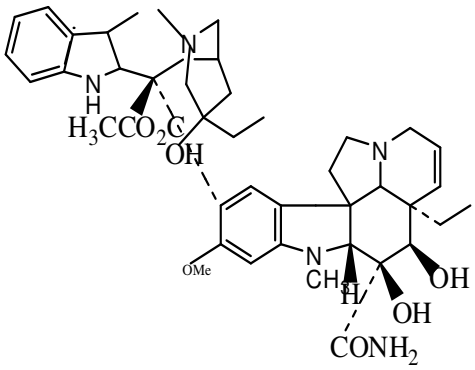
The plant kingdom has prospective and fruitful hunting grounds for new tumor inhibitors. This has been illustrated by the isolation of vinka alkaloids **vinblastine (17), vincristine (18) Vindesine (19)** from the Madagascar periwinkle, *Catharanthus roseus* (Linn.) G. Don, Apocynaceae, known in Thailand as Phaeng phuai farang ***(Cragg et al., 1993*)**. The epipodophyllotoxins **[Etoposide (20), Teniposide (21)],** the taxanes **[Taxotere (22)],** and the camptothecin derivatives **[Camptothecin (23)** and **Irinotecan (24)]** ***(Evans, 2002).*** So far,

pharmaceutical companies have screened more than 25,000 plants for anti-cancer drugs ***(Saxe, 1987)***



Vinblastine **(17)** R1=CH_3, R2=CO_2CH_3

Vincristine **(18)** R1=CHO, R2=CO_2CH_3



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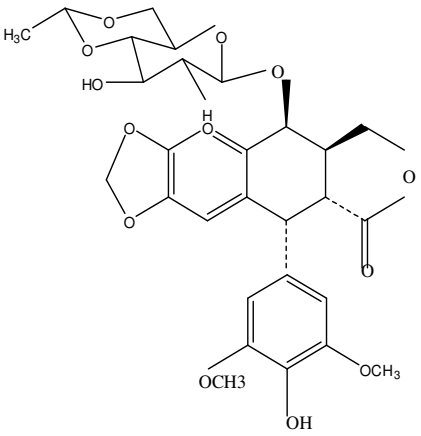

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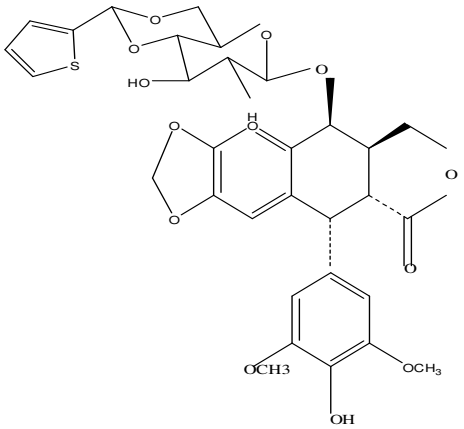

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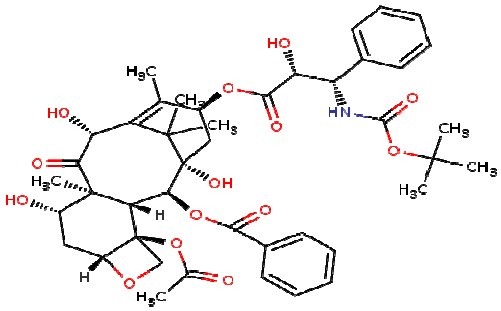

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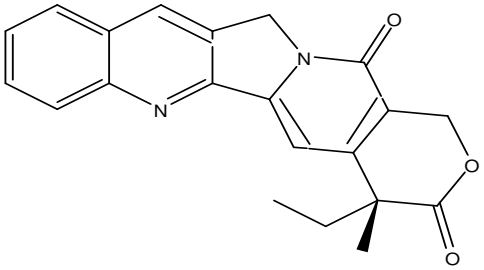

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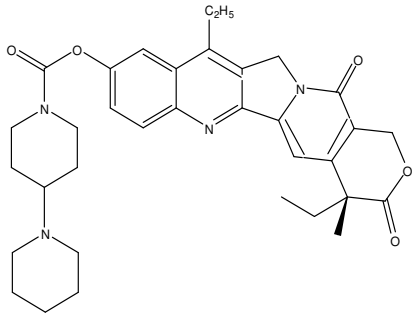

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Phytoconstituents derived from the herbs/plants have been used in various formulations to enhance activity of immune cells of the body that promotes production of cytokines including interleukin, interferon, tumor necrosis factor and colony stimulating factor.

For example, **Homoharringtonine (25)**, a cephalotaxus alkaloid from the tree *Cephalotaxus harringtonia* ***(Powell et al., 1970*)**, is an inhibitor of protein synthesis and is reported to have activity against hematologic malignancies ***(Kantarjian et al., 2001).***

Ingenol 3-O-angelate (26), which was obtained from *Euphorbia peplus* (known as "petty spurge" in England), is a potential topical chemotherapeutic agent for skin cancer and exhibits its action through activation of protein kinase***(Kedei et al., 2004, Ogbourne et al., 2004).***

Phenoxodiol (27), a synthetic analog of daidzein, a well known isoflavone from soybean (Glycine max) and found in several other folk-medicines, is being developed as a therapy for cervical, ovarian, prostate, renal, and vaginal cancers ***(Kamsteeg et al., 2003).***

Phenols and polyphenols, the flavonoids and their derivatives, are ubiquitous in plants and more than 8,000 different compounds are included in this group and many of them are antioxidants.They have been associated with the inhibition of atherosclerosis and cancer (***Martinez-Valverde et al., 2000***) and other biological activities.

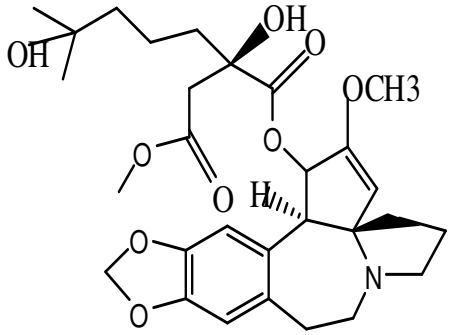
Solanum pseudocapsicum L. (Solanaceae) leaves have been reported to have antitumor activity for the total alkaloid fraction of this plant ***(Badami et al., 2003).***

Anthraquinone (28), natural products like rubidianin, isolated from alcoholic extract of *Rubia cordifolia* has demonstrated significant antioxidant activity. It prevented lipid peroxidation induced by ferrous sulphate and t-butylhydroperoxide ***(Tripathi et al., 1997).***

Withanolides (29), the active phytochemical constituents of *Withania somnifera Dunal* (Solanaceae) are group of pharmacologically active compounds present in the whole plant. Withanolides are similar to ginsenosides (the active constituents of

Panax ginseng) in structure and activity. They are believed to be immunomodulator having anticancer activity. **(*Ali and Shuaib, 1997).***

Protopanaxadiol (30), a derivative of a triterpene aglycone of several saponins from ginseng (*Panax ginseng*), and exhibits its apoptotic effects oncancer cells through various signaling pathways, and is also reported to be cytotoxic against multidrug resistant tumors ***(Jia et al., 2004, Kiviharju et al., 2002).***



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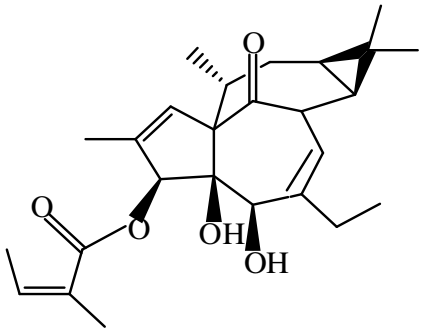

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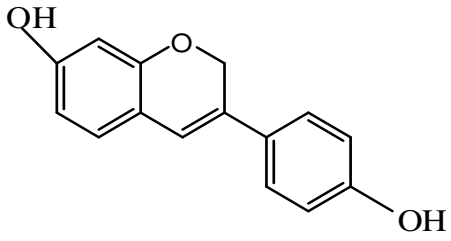

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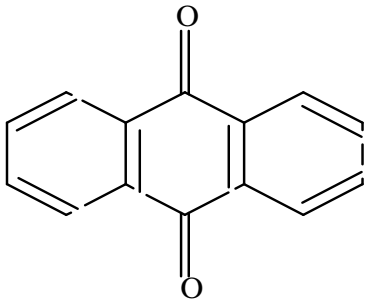

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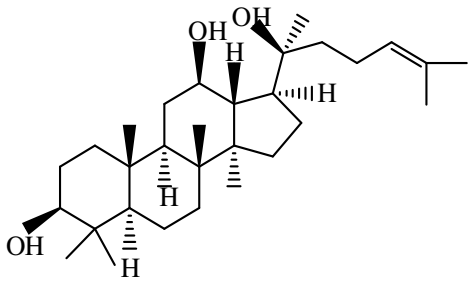

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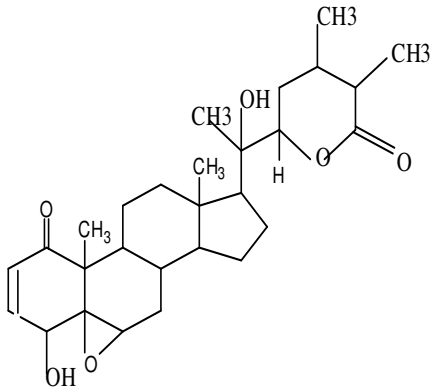

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Some of the plants/herbs with their antineoplastic/anticancer activity are given below the table which helps the body to fight cancer more effectively and toxic side effects of chemotherapy and radiotherapy stages of cancer ***(Farnsworth et al, 1985).***

Table1.2: Some of the plants/herbs with their antineoplastic/anticancer activity.

Botanical Name	Common Name	Active constituents and properties
Allivum sativum	Garlic	S-allylcysteine (SAC), diallyldisulphide (DADS) diallyltrisulphide (DATS) have anticarcinogenic property. ***(Lau et al., 1990, Steinmetz et al., 1994, Milner, 1996.)***

Aloe ferox, Aloe arbadenis	Aloe vera	Aloe vera found to contains Aloe-emodin, emodin, aloin acemannan,which activates the macrophase to fight cancer and enhance the activity of the immune system and found to inhibit metastages ***(Pecere et al.,2000*)**.
Catharanthus roseus	Vinca	Vinblastine, vincristine (leurocrystine), alstonine, ajmalicine and reserpine used in the treatment of cancers of the breast, lung, bladder and the cervix ***(Jean Bruncton, 1993).***
Camellia sinensis	Green tea	*Camellia sinensis* contains polyphenolics which are known to possess antimutagenic and anticanceractivity. Some evidence suggests that tea has a protective effect against stomach and colon cancers ***(Dreosti, 1996).***

Curcuma longa Linn.	Turmeric	*Curcuma longa* contains curcumin, which inhibits the growth of cancer by preventing production of harmful eicosanoid such as PGE-2 ***(Kikuzaki and Nakatani, 1993).***
Glycine max	Soyabean	Genistein, one of the isoflavones found in higher concentrations in soya products, strengthening immune system of the body and reducing toxic effects of chemotherapy and radiotherapy **(*Kleijnen and Knipschild, 1992*).**
Gyrophora esculenta	Mushroom	Contains Polysaccharides β-glucans, α-glucans, and galactomannans *Gyrophora esculenta* is a mushroom that inhibits growth of cancer by enhancing activity of the natural killer cells. A study revealed that it inhibits carcinogenesis and metastases ***(Ambasta et al., 2000).***

Mentha species	Pudina	*Mentha species* such as *Mentha piperita*, *Mentha longifolia* and *Mentha aquatica* contain phenolic antioxidants that prevent recurrence of cancer ***(Attele et al., 1999*)**.
Zingiber officinale	Ginger	Ginger rhizomes offer a rich package of gingerols-phenolic antioxidants that possess pronounced anti-inflammatory activity-that inhibit various cancers. ***(Katiyar et al.,1996*)**

1.3 Natural products in Medicine:

The importance of natural products, the plant kingdom derived medicines in modern medicine is often underestimated. Fossil records date human use of plants as medicines at least to the Middle Paleolithic age some 60,000 years ago ***(Solecki and Shanidar,1975*).** From that point, the development of traditional medical systems incorporating plants as a means of therapy can be traced back only as far as recorded documents of their likeness.

Medicinal herbs of folk-origin are significant sources of synthetic and herbal drugs. In the commercial market, folk-medicinal

herbs are used as raw drugs, extracts or tinctures. Natural products or related substances or extracts of folk medicine accounted for 30% of the top 35 worldwide natural product-based drugs sold ***(Butler, 2004***) in recent years. Isolated active constituents are used for applied research for finding their bioactivity.

In many countries modern medicines have replaced plants with many synthetic products but almost 30% pharmaceutical preparations are still obtained directly or indirectly from plants, majority of them based on ethnobotanical information ***(Marino-Bettolo, 1980)*.**

There are 121 drugs in current use in the USA derived from plant, with 95 species acting as sources, more than one drug being obtained from some species. Approximately 25% of all prescriptions dispensed in the United States contain plant extracts or active ingredients obtained from, or patterned after, plant materials ***(Anonymous, 1994).***

Over three-quarters of the world population relies mainly on plants and plant extracts for health care. More than 30% of the entire plant species, at one time or other was used for medicinal purpose. Of the 2, 50,000 higher plant species on earth, more than 80,000 are medicinal ***(Thomas, 1997*).** Most of the powerful drugs used in modern medicines originated in plants. ***Oliver-Bever (1986)*** has cited several examples of West African species of plants, including *Erythroxylum coca*, whose traditional therapeutic properties were evaluated pharmacologically.

Rauvolfia serpentina, Cannabis sativa, Papaver somniferum, Gymnema sylvestre, Picrorrhiza kurrooa, Azadirachta indica,

Curcuma longa, etc., are some Indian examples of modern pharmacological confirmation of traditional uses of plants. Discovery of reserpine from a traditional medicinal plant (*Rauvolfia serpentina*) is very interesting. This plant which is called Chotachand in Hindi, have been used by local people of Himalayan Mountains for snakebite ***(Balick and Cox., 1996).***

The Male fern (*Dryopteris filix-mas*) in Europe, the *Kamala* dye tree (*Mallotus philippinensis*, Euphorbiaceae) in South Asia, the Gemma Agrimoniae (winter bud tree) (*Agrimonia pilosa*, Rosaceae) in East Asia, and the *Flores Koso* tree, (*Hagenia abyssinica*, Rosaceae) in East Africa, are all botanically unrelated; yet they were used as teaniafuge in the traditional medical systems of these far off regions of the globe ***(Xiao, 1981).***

A crude drug from even a single plant species used in traditional medicine, simultaneously contains several chemical compounds, each with a different therapeutic effect. For example, neem or gingers have many different chemical compounds which exert over a dozen different therapeutic effects ***(Sharon, 1994, Shubharani, 1995).*** The Indian Ayurvedic Formulary ***(Anonymous, 1978)*** lists about 350 single plant drugs and the rest are formulations that contain several species of plants. For example, *Dashamoolaristha* has 68 species, *Mahaavishagarbhataila* 64 species, *Mahaanaarayanataila* 55 species and *Karpuraadiyarka* 52 species ***(Anonymous, 1978).*** WHO has estimated conservatively that between 60 and 90 percent of the population of the non-industrialized countries rely on medicinal plants to meet their health care needs, either totally or partially and 80% of

the world's populations rely primarily on traditional medicine ***(WHO,1978, Okerele, 1992.).***

With the scarcity of doctors and paucity of hospitals and clinics, the large majorities of these populations have to rely on sources other than allopathic medicine for their health care. For example, in Ghana there is one traditional doctor for approximately every 400 people, while the ratio of allopathic doctors to patients is 1 for 12,000 **(*Joyce, 1992, Boye and Oku, 1987).***

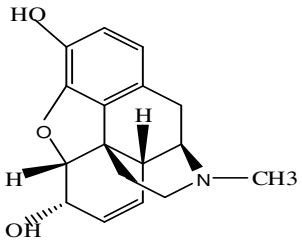
Various reports from the United Nations (UNCTAD and GATT) have indicated that 33 percent of drug products in the highly industrialized countries are derived directly from higher plants; most of these are tropical plants growing in equatorial countries. The market for plant-based drugs is growing every year throughout the world. These drugs now account for over $US 50 billion of the total worldwide drug market now totaling over $US 173 billion ***(UNEP, 1992)***. Today's plant based drugs treat a range of diseases from headache to cancer. The CDRI (Central Drug Research Institute, Lucknow, India) evaluated approximately 2,000 plant species for several biologic activities, including antibacterial, antidiabetic, antifungal, antifertility, antihypercholesteremic, anti-inflammatory, antitumor, cardiovascular, central nervous-system depressant, cytotoxicity, diuretic, and others ***(Dhar et al., 1968).***

*F*or example, the alkaloids drug morphine **(31)** derived from *Papaver somniferum* L, is regarded as the gold standard, or benchmark, in clinical medicine, is used as analgesics to relieve severe or agonizing pain and suffering. Like other opioids, such as

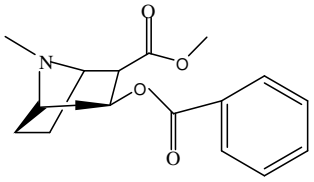
oxycodone, hydromorpone, and diacetylmorphine (heroin), morphine acts directly on the central nervous system (CNS) to relieve pain ***(Solecki and Shanidar, 1975).***

Cocaine (32) (benzoylmethylecgonine) is a crystaline tropane that is obtained from the leaves of the coca plant ***(Aggrawal and Anil, 1995).*** Cocaine is a powerful nervous system stimulant, increases alertness, feelings of well-being and euphoria, energy and motor activity, feelings of competence and sexuality. Athletic performance may be enhanced in sports where sustained attention and endurance is required ***(WHO, 2004, WHO, 2007).***

Nicotine (33) is an alkaloids found in the nightshade family of plants (Solanaceae) that constitutes approximately 0.6–3.0% of the dry weight of tobacco ***(Solecki and Shanidar, 1975).*** It can be quantified in blood, plasma, or urine to confirm a diagnosis of poisoning or to facilitate a medicolegal death investigation. Careful interpretation of results is important, since passive exposure to cigarette smoke can result in significant accumulation of nicotine, followed by the appearance of its metabolites in various body fluids ***(Benowitz et al., 2009, Baselt, 2008).*** Nicotine use is not regulated in competitive sports programs, yet the drug has been shown to have a significant beneficial effect on athletic performance ***(Mündel and Jones, 2006).***



(31)



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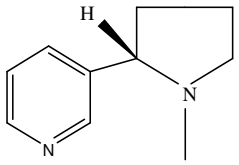
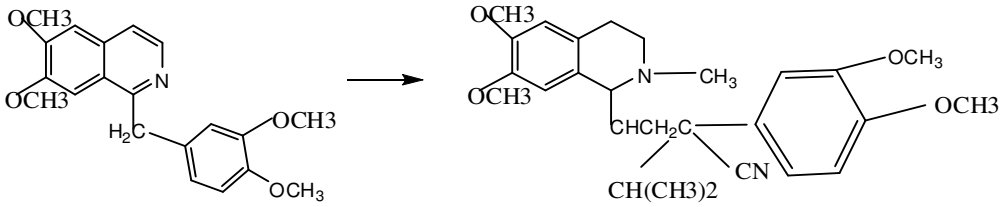


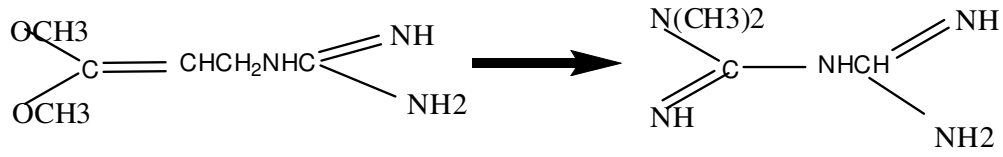
(33)

Some drugs from plants that served as model for the next generation drugs. For examples, **Papaverine (34),** useful as a smooth muscle relaxant, provided the basic structure for verapamil, a drug used to treat hypertension ***(Sneader, 1985*****). Galegine (35)** was isolated as an active antihyperglycemic agent from the plant *Galega officinalis* L. This plant was used ethnomedically for the treatment of diabetes. Galegine provided the template for the synthesis of metformin and opened up interest in the synthesis of other biguanidine-type antidiabetic drugs ***(Sneader, 1985).***



Papaverine Verapamil

(34)



Galegine Metformin

(35)

Some drugs derived from plant with their clinical action and plant sources are given below ***(Farnsworth et al., 1985).***

Table1.3: Drugs derived from plants, with their ethnomedical correlations and sources. Drug Action or clinical use Plant source.

Drugs	**Clinical action**	**Plant source**
Adoniside	Cardiotonic	*Adonis vernalis* L.
Aescin	Anti-inflammatory	*Aesculus hippocastanum* L.
Agrimophol	Anthelmintic	*Agrimonia eupatoria* L.
Anisodine	Anticholinergic	*Anisodus tanguticus* (Maxim.) Pascher
Atropine	Anticholinergic	*Atropa belladonna* L.
Berberine	Bacillary dysentery	*Berberis vulgaris* L.
Bromelain	Anti-inflammatory; proteolytic agent	*Ananas comosus* (L.) Merrill
Caffeine	CNS stimulant	*Camellia sinensis* (L.) Kuntze
(+)-Catechin	Haemostatic	*Potentilla fragaroides* L.
Cocaine	Local anaesthetic	*Erythroxylum coca* Lamk.

Codeine	Analgesic; antitussive	*Papaver somniferum* L.
Deserpidine	Antihypertensive; tranqulizer	*Rauvolfia canescens* L.
Digitalin	Cardiotonic	*Digitalis purpurea* L.
Digoxin	Cardiotonic	*Digitalis lanata* Ehrh
Gitalin	Cardiotonic	*Digitalis purpurea* L.
Hydrastine	Hemostatic; astringent	*Hydrastis canadensis* L.
Khellin	Bronchodilator	*Ammi visnaga* (L.) Lamk.
Kawain	Tranquilizer	*Piper methysicum* Forst. f.
Kainic Acid	Ascaricide	*Digenea simplex* (Wulf.) Agardh
Lobeline	Smoking deterrent; respiratory stimulant	*Lobelia inflata* L.
Morphine	Analgesic	*Papaver somniferum* L.
Noscapine	Antitussive	*Papaver somniferum* L.
Ouabain	Cardiotonic	*Strophanthus gratus* Baill.

Papain	Proteolytic; mucolytic	*Carica papaya* L.
Pseudoephedrine	Sympathomimetic	*Ephedra sinica* Stapf.
Quisqualic Acid	Anthelmintic	*Quisqualis indica* L.
Rhomitoxin	Antihypertensive	*Rhododendron molle* G. Don
Rotenone	Pisticide	*Lonchocarpus nicou* (Aubl.) DC
Rotundine	Analgesic; sedative	*Stephania sinica* Diels
Santonin	Ascaricide	*Artemisia maritima* L.
Silymarin	Antihepatotoxic	*Silybum marianum* (L.) Gaertn.
Stevioside	Sweetener	*Stevia rebaudiana* Bertoni
Strychnine	CNS stimulant	*Strychnos nux-vomica* L.
Teniposide	Antitumor agent	*Podophyllum peltatum* L.
Tetrahydropalmatine	Analgesic; sedative	*Corydalis ambigua* (Pallas) Cham. & Schltal
Theophylline	Diuretic; bronchodilator	*Camellia sinensis* (L.) Kuntze

Valepotriates	Sedative	*Valeriana officinalis* L.
Vincamine	Cerebral stimulant	*Vinca minor* L.
Xanthotoxin	Leukoderma; vitiligo	*Ammi majus* L.
Yohimbine	Aphrodisiac	*Pausinystalia yohimbe* (K. Schum.) Pierre
Yuanhuacine	Abortifacient	*Daphne genkwa* Seib. & Zucc.
Yuanhuadine	Abortifacient	*Daphne genkwa* Seib. & Zucc.

Enzymes and proteins from plant origin also have been used as drugs since ancient times and many of them were available before the development of biotechnology. Proteins and enzymes used as drugs fit into many therapeutic categories ***(Kokate et al., 2001).***

Name of drugs	Chemical constituents	uses
Papain	Papain and chymopapain	Proteolytic, meat tenderizer, clarification of beverages.
Bromelin	Mixture of proteolytic enzymes	Anti inflammatory for soft tissues, and clotting agents.

1.4 Natural products with hepatoprotective activity:

Liver is the main organ which regulates many important metabolic functions. Hepatic injury is directly associated with these altered metabolic functions (***Mitra et al., 1998).*** Several studies have been carried out to examine the effect of plants used to support normal liver function and treat diseases of liver.

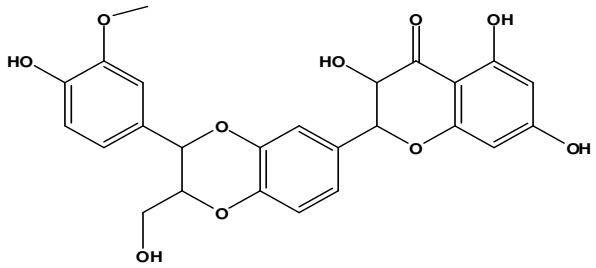
About 600 commercial preparations with claimed liver protecting activity are available all over the world.About 100 Indian medicinal plants belonging to 40 families are used for herbal formulation (***Handa et al.,1986***).

For example, plants such as *Silybum marrium* (milk thistle), *Curcuma longa* (turmeric) (***Luper, 1999***), *Nymphea stellata* (***Bhandarkar and Khan, 2004***). *Andrographis lineate,* ***(Sangameswaran et al., 2008),*** Andrographis *paniculata* ***(Handa and Sharma, 1990),*** *Azadirachta indica* ***(Chattopadhyay et al., 1992),*** *Careya arborea* (***Senthilkumar et al., 2008),*** *Cassia fistula* (***Senthilkumar et al., 2008),*** *Cleome viscosa* (***Gupta and Dixit, 2009)***, *Fumaria indica* (***Saxena et al., 1993)*** Linn are safe for effective treatment of liver disorders.

Liver protective plants contain a variety of chemical constituents like phenols, coumarins, lignans, essential oil, monoterpenes, carotinoids, glycosides, flavanoids, organic acids, lipids, alkaloids and xanthenes.Recent experience has shown that plant drugs are relatively non-toxic, safe and even free from serious side effects (***Momin, 1987***).

Silymarin **(36**), a flavonolignan isolated from *Silybum marianum* .is the single herbal drug formulation which is mostly used in liver diseases amounts to about 180 million US dollars in Germany alone. It is interesting to note that herbal drug sale are tripled between 1992 and

1996 in Germany and nearly one third of out-patients attending liver clinics use natural remedies ***(Schuppan et al., 1999).***



(36)

1.5 Medicinal plants of Manipur:

Manipur, a state in North East India ($23^0$50' to $25^0$42' N latitudes and $92^0$58' to $94^0$45'longitudes) being a part of Indo-Myanmar Hot spots of bio-diversity ***(Myers et al., 2000*)**, possesses rich of flora and fauna. The flora of this region includes aromatic and medicinal plants with a number of bioactive compounds ***(Myers et al., 2000).***

In Manipur, plants have been the source of medicine from time immemorial to treat different ailments and are associated with various folklore and ritual, which is performed by *Maiba* (traditional herbal healer or priest). History reveals that in the beginning of the 14^{th} century there has been a good description of medicinal plants and herbal treatment for many diseases. A number of works on ethno botany of Manipur has been done since **1980s**. For example, work done by ***Sinha, 1987, Devi, 1990, Ghosh, 1994, Sinha, 1996, Singh, 1997, Sharma et al.,1999, Ghosh, 2000, Singh et al., 2000, Sharma et al.,2003, Sharma et al., 2004, Sharma et al., 2005, Warjeet et al., 2006, Potsangbam et al., 2008*** **etc.**

The Manipuri people even now, use some of the plants, plant products, animal products minerals etc for domestic purposes for utilizing their traditional knowledge, which had been developed by their forefather through trial and error methods and passed on to them through oral tradition from one generation to another. Unfortunately, due to lack of written documents, most of the traditional knowledge about medicinal plants and their uses survived only by words of mouth from generation to generation and are being slowly lost. For example, *Terminalia citrina* Roxb.ex Flem, *Glycasmis arborea* Roxb(DC), *Achyranthus aspera* Linn**,** *Melothria maderaspatana* Linn, Cogn.and *Costus specious* (koenig) Sm, are used especially for the treatment of dog bites ***(Singh and Singh, 2000)***.

The products of *Flacourtia jangomas* (Lour). Rauch and *Gardenia campanulata* are used for the preparation of traditional soap and detergents by people of Manipur **(*Singh and Singh, 2002)***.

The exploration of the plant kingdom and research in natural products has been going on in various part of the globe (***Akpulu et al., 1994, Balasooriya et al., 1982, Edeoga et al., 2005, Faraz et al., 2003, Atata et al., 2003****.)* and in different laboratories of our country ***(Perumalsamy and Ignacimuthu, 2000, Vedavathy and Rao, 1991. Jayashree and Maneemegalai, 2008, Devi, S and Paul, S.B, 2011, Choudhury et al., 2011, Paul et al., 2010, 2009, 2007 Nath et al., 2011, Choudhury et al., 2011, 2007, Paul and Roy, 2009)*.** The forest of Manipur and Silchar, Assam remains to be explored at least from the point of view of chemical research. Whereas some ethno botanical works had been done in the region by some botanists, the chemical investigation of these plants is yet to be done in the real sense.

The present investigation is an attempt to put a step forward towards the chemical and biological examination of the plants for their natural products. So, some plants are collected and have been subjected to preliminary examinations for their medicinal properties. From these, a few are selected, among these plants ***Phyllanthus acidus*** **(L)Skeel** and ***Croton caudatus*** **Geiseler** assumes an important significance and selected for exhaustive investigation.

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