CHAPTER 1

INTRODUCTION
Pharmaceutics occupies an important place in Ayurveda, the medicinal heritage of our country. It has a vast literature describing hundreds of useful medicinal plants covering all aspects of disease, therapeutics and pharmacy. Earliest references to such plant are in the Rig Veda and Atharva Vada, dating back to second millennium BC. Charka Samhita (~900 BC)\(^1,2\) is the first recorded treatise fully devoted to concepts and practice of Ayurveda. Since the primitive days of human existence man had always been depend upon the plants not only for the daily needs but also for the treatment of illness as well. Fortunately India has been the land of almost all privileged medicinally potent-plants. 

Plants are unlimited source of natural products. The therapeutic use of plants for the treatment of human sufferings is known since the days of antiquity. There are more than 350 thousand species of higher plants out of which a small portion has been investigated for their biologically active constituents. There have been continuous reports on biologically active principles from plants.

Herbalism has been one of the main branch of medicine for centuries in all part of the world. There are ample proof for the application of the crude plant extracts and decoctions in the therapy world over as well as in India. But the rationalization of the science of therapeutics as we know is comparatively of recent origin. Thus chemical investigation along with the pharmacological examination of the chemical constituents from plants of medicinal value has gained much importance in the therapeutic world. This idea has encouraged me to take up the phytochemical and pharmacological investigations incorporated in the present thesis.

Since the dawn of human creation, man had to suffer from various ailments and diseases. His worries to be relieved of diseases led to search for remedies that could provide cures for them. His attention was naturally diverted towards the plants since they were easily and abundantly available. It was therefore natural that in its
early stages, medicinal science developed around such plants as were observed to have some therapeutic properties. The search for medicinal plants have continued through centuries. It goes to credit of the people of India that they were acquainted with a far larger number of medicinal plants than the natives of any other country on the face of the earth.

The plants and their products are the greatest gift of nature for the service of mankind. The use of the plants to prevent and cure diseases goes for back in the history of man. The plants have been used for defense, protection and nourishment by human beings with the dawn of civilization. The primitive man used the raw materials and raw extracts of the plants to help those in sorrows, needs and sickness without the knowledge of their chemical composition. With the growth of civilization, the multifarious use of plant products began to be appreciated for their uses in medicine, flavours, perfumes, dyeing, cosmetics, edible fats etc. More than in any other branch of science, empeiricism have been developed in medicinal chemical research. As such, the plants have been thoroughly investigated throughout the ages and their importance understood either for beauty or vigour.

Chemistry has to play a vital role in improving the material life of the people at large. Phytochemistry, a dynamic science, plays an important role in medicine. It helps in determining the chemical constituents and structure of active principles and opens the door for newer synthetic analogue. The isolation of active principles which possess the physiological and pharmacological activity from the medicinal plants and their successful utilization to alleviate human sufferings have encouraged researchers to continue the investigation of new drugs from natural sources.

The last decade has witnessed numerous changes in the use of botanical products having medicinal values. In India, a number of issues connected with the international agreement on Trade Related Aspects of Intellectual Property Rights
(TRIPS) have been discussed with particular emphasis on drugs and pharmaceutical industry. The year 1994-95 saw the beginning of the era of changed National and International scenario in new drug development. International Intellectual Property Rights (IRP) was effective in India from January 1995, India being on of signatories. As a result of which some of the Research and Development Institutes have redefined various long term projects and aimed towards product or technology development⁴.

- Medicinal plants need to be redefined. A workshop on utilization of medicinal plants organized by UNIDO asserts that an aggressive and systematic application of scientific knowledge and modern technology in the development of plants derived botanicals and medicinals, especially in China, India and Korea has led to the global resurgence in the use of plant based products⁵. Also, advances in the development of new assay technologies and automated screening techniques, have made natural products screening an economically viable approach to the drug industry.⁶

Over the past 10 years, there has been a resurgence of interest in the investigation of natural materials as a source of potential, new chemotherapeutic agents, but there are now signs that this interest is once more waning in favour of new approaches to drug discovery, such as combinatorial chemistry and computer-based molecular modeling designs. In order to provide a more solid basis for the claims made for the importance of natural products in drug discovery and development, data on new drugs approved by either the United States Food and Drug Administration (FDA) or comparable entities in other countries, and reported mainly in the Annual Reports of Medicinal Chemistry⁷.

In India, several CSIR institutes and government laboratories, like Central Council for Research in Ayurveda and Siddha (CCRAS), Central Council for Research in Unani Medicine (CCRUM), Indian Council of Agriculture Research (IARI) and universities are conducting screening of plant products. Central Institute of Medicinal
and Aromatic Plants (CIMAP) accord high priority in increasing the production of medicinal and aromatic plants and processing technologies. Indian Institute of Chemical Technology (IICT) entered into an agreement with M/s. Parke Davis, Philadelphia, U.S.A. for the evaluations of Indian medicinal plants\(^7\).\(^8\).

Several higher plants extracts are under investigation for drug development in Central Drug Research Institute (CDRI), fixation of toxic limits of crude herbal extracts and pharmacological screening and tissue culture techniques of introducing indigenous plants growing at higher altitudes are under investigation in Homeopathic Pharmacopoeia laboratory.

Many multinational companies (MNCs) have been engaged in natural product research for the isolation of active principles. These would be then chemically synthesized and patented. According to new patents laws, a patented product can be manufacturered either by the patent holder or the MNCs which secure a license from the patent holder. In this context, the Indian manufacturers may lose the right to make the drugs containing the ingredients, which are patented by the foreign firm or MNCs.

Phytochemistry has not only enriched modern medicine but has also provided valuable leads for drug designing. The medicinal property of plants depends upon the presence of pharmacological and physiological active compounds. Therefore, it becomes necessary to isolate the active compounds from plants in pure form and to study their structure by means of physico-chemical examination and then subject them to pharmacological and physiological tests. Further by slightly modifying the composition of natural drug it may be possible to increase the physiological activity of the drug.

Various plant product posses significant physiological and pharmacological activities for example: Rhinacanthin-E and Rhinacanthin-F isolated from the aerial
parts of the Rhinacanthus nasutus showed significant antiviral activity against influenza virus type A$^9$. A bioactivity-guided fractionation of an extract of Terminalia bellerica fruits led to the isolation of two new lignans named termilignan and thannilignam, together with 7-hydroxy-3', 4'-(methylenedioxy)-flavan and anglignan. All four compounds possessed anti-HIV-1, antimalarial and antifungal activities in vitro$^{10}$. Lycorine, an alkaloid isolated from the roots and leaves of Clivia miniata showed antiviral activity$^{11}$ against semliki forest herpes and poliomyelitis virus. Hypnea musciformis wulfen showed antispasmodic activity and antiinflammatory activity against rats hind paw oedema induced by commercial carrageenan$^{12}$. (+) - Odorinol is the first natural product displaying strong short lived antiviral activity against RDV in chick embryos$^{13}$. Extracts from seeds of Areca catechu, bark of Eugena jambolana, bark of Saraca indica and stem bark of Terminalia arjuna exhibited the HIV-1 PR activity$^{14}$. Carnosic acid isolated from leaves of Rosmarinus officinalis showed strongest inhibitory effect against HIV-1 virus$^{15}$. Suberosol, isolated from the leaves and stem of Polyalthia suberosa showed anti–HIV replication activity in H-9 lymphocyte cells$^{16}$. Extracts of Scaevola sericea, Psychotria haw aiiensis, Pipturus albidus and Eugenia malaccensis showed selective antiviral activity$^{17}$ against HSV-1, HSV-2 and vesicular stomatitis virus. Inhibitory effect from extracts of Phyllanthus urinaria against duck hepatitis B virus (DHBV) DNA replication has been reported$^{18}$. The extracts of fruits of Quercus pedunculata, Rumex cytrius, Terminalia bellerica, Terminalia chebula and Terminalia horrida showed significant inhibitory activity on human immunodeficiency virus-1$^{19}$. Antiviral activity of Aloe extracts against cytomegalo virus$^{20}$ has been reported in the leaves of Aloe barbadensis. Extracts of Rhus acuminata, Saraca indica and Strychnos potatrum were found to possess inhibitory effects against herpes simplex virus of type-1$^{21}$. HSV – 1 inhibitory effects$^{22-24}$ were also observed in
the plants extracts of *Hamamelis virginiana*, *Rhinacanthus nasutus* and *Magnolia officinalis*.

Tremendous advancement in the field of instrumental techniques coupled with sophistication of spectroscopic methods made it possible to isolate and elucidate the therapeutically active constituents contained in plants. A number of natural products still continue to be important drugs even today of which well known are: codeine (antitussive / analgesic), colchicine (antigout), physostigmine (cholinergic), atropine (anticholinergic), quinine, artemisin (antimalarials), digitoxin, digoxin (cardiotonics) and morphine (analgesic).

The great diversity and complexity of the chemical nature of the natural products and their presence some times in very poor amount in plants, provide a major obstacle in the progress of the phytochemistry. More recent scientific pursuits have explored a vast number of plant based active principles which is increasing day by day\textsuperscript{25-28}. Application of powerful analytical tools like chromatography,\textsuperscript{29-34} paper electro phoresis,\textsuperscript{35-37} radioactive tracers, electrophoresis, IR, \textsuperscript{1}H-NMR, \textsuperscript{13}C-NMR and mass spectroscopy\textsuperscript{38-44} has greatly widened the horizon of natural products chemists in establishing the structure of the higher molecules such as alkaloids, steroids, mucilage, tannins, waxes and essential oils\textsuperscript{45,46}. This has given a significant impetus to the development of drugs from plant sources. Plant based natural products are now in routine use either directly or as a precursor for the synthesis of many synthetic drugs\textsuperscript{47-49}.

Unfortunately a single test can not be applied for the determination of the medicinal value of the plants. A test for antibacterial activity for example will not reveal the presence of a substance possessing narcotic effect or having action on the heart. There are certain constituents like 'Hasish' and 'Opium' which are not distributed in the plant tissues uniformly. Further, it is also possible that substance may not be
present in the plant at all the stages to its growth. Climatic conditions also affect the chemical constituents in the plants.

The important field of research in phytochemistry lies in the investigation and modification of drugs and the relationship between chemical structure and physiological action. When the mechanism of drug action is known, it becomes possible to synthesise the relative new drugs possessing greater therapeutic value and less toxicity. The development of 'Aspirin' is a classical example of this fact. 'Aspirin' is a modified drug of the natural drug 'Salicin' and is used in the treatment of rheumatic and neuralgic pains. As a further example, the knowledge of the mechanism of the action of 'Connine' led chemists to synthesise a wide range of new drugs 'Procaine' and 'Novacaine' which possess local anaesthetic properties.

A systematic examination of the plants for getting the new drug is obviously an arduous task for the plant biochemists. Nevertheless, many notable drugs already recorded to give encouragement for the continuation of the work. Plants and other natural sources can provide thousands of substances of which a few can reasonably be considered useful as drugs. Thus the science of medicine has developed on the basis of curative and preventive properties on diseases of different plant products. This was the main reason for the investigation of all the types of plants for achieving success in the utilization of natural products for benefit of mankind.

The most common biologically active constituents of plants belong under the following groups of the compound:

1. Anthraquinones  
2. Lactones and coumarins  
3. Terpenoids  
4. Tannins  
5. Glycosides  
6. Alkaloids  
7. Enzymes  
8. Proteins and amino acids  
9. Steroids  
10. Saponins and sapogenins
11. Flavonoids
12. Carotenoids
13. Fatty acids
14. Essential oils
15. Esters
16. Resins
17. Lignans etc.

The description of all the groups of the organic substance mentioned above is not possible and is beyond the scope of this thesis. However a brief description of the terpenoids, flavonoids, steroids and tannins have been given here as the author has been engaged mainly in the study of the compounds belonging to these chemical groups.
TERPENOIDS

The terpenoids represent a compound which has a carbon skeleton (i) either \( C-C-C \) or (ii) has at some stage in its biogenesis a carbon skeleton so constructed.

Terpenoidal chemistry has an attraction for the organic chemists because of its use in the preparation of perfumes, flavours, protective coatings, pharmaceuticals, insecticides and condensation catalysts etc.

Terpenes are classified as: monoterpenes \((C_5H_8)_2\), sesquiterpenes \((C_5H_8)_3\), diterpenes \((C_5H_8)_4\), triterpenes \((C_5H_8)_6\), tetraterpenes \((C_5H_8)_8\) and polyterpenes \((C_5H_8)_n\).

Most of the known triterpenoids have been found to have either tetracyclic or pentacyclic structure.

TETRACYCLIC TRITERPENOIDS

The interest in the chemistry of the tetracyclic triterpenoids has grown chiefly because of the resemblance with and probable biogentic relationship to the steroids. Some of the tetracyclic terpenoids have been found to be monoisoprenoid (e.g. Lanosterol and Agnosterol)\(^{50}\) and still more observed in Eburioic acid\(^{51}\) and Polyporenic acid \(^{52}\). The two main families in the group of terpenoid to which most are related can be represented by the two substances, lanosterol and euphol:

[Diagram of Lanosterol and Euphol]
In addition to this the other families are dammarane, cycloartane, euphane, protostane, eburicane and cucurbitacin etc.

**DAMMARANE**

**CYCLOARTANE**

**EUPHANE**

**PROTOSTANE**

**EBURICANE**

**CUCURBITACIN**

**PENTACYCLIC TRITREPENOIDS**

Pentacyclic triterpenes occur in the plant as a glycoside (saponin) or as a free from. The non glycoside triterpenoids are frequently found as excretions or in the cuticles, where they may have a protective or water proofing function. This class can further be divided into the following series on the basis of the chemical structures:
1. Lupane (e.g. Lupeol)
2. Oleanane (e.g. β-amyrin) and
3. Ursane (e.g. α-amyrin).

The lupane, oleanane and ursane series are the most widespread pentacyclic triterpene found in nature. The other series are the hopane (e.g. mollugogenol), teraxerane (e.g. teraxerol) and friedelane (e.g. friedelinol). The nor group of these series are of rare occurrence in nature for example nor-lupane and nor-oleanane.
Physiological Activity of the Terpenes

Triterpenoids have been observed to have very interesting physiological activities. Cephalosporin, helvolic acid and fusidin with penicillin shows a remarkably high antistaphylococcal activity$^{53}$. Glycyrrhetic acid is used in the treatment of Addison’s disease, asiaticoside, leprosy and tuberculosis$^{54}$. Nimbin shows potent antiinflammatory, antipyretic and analgesic activity$^{55}$. α- and β-amyrin acetates both have antiinflammatory activity$^{56}$. New triterpenoids namely meliavolkinin and melianin reported recently in the root bark of *Melia volkensii* showed marginal cytotoxicities against certain human tumor cell lines$^{57}$.

The friedelanes constitute an important class of triterpenes, member of which have shown interesting biological activity$^{58}$. A new friedelan triterpenoid isolated from *Maytenus macrocarpa* showed significant activity against aldose reductase$^{59}$. The triterpenes reported in the plant, *Inonotus obliquus* exhibited antitumor activity$^{60}$. The pentacyclic triterpenes betulinic acid has been shown to exhibit a variety of biological activities, including inhibition of human immunodeficiency virus (HIV) replication in H-9 lymphocyte cells, blockage of HIV-1 entry into cells and cytotoxicity against a variety of cultured human tumor cells$^{64}$. Recently betulinic acid was identified as a melanoma-specific cytotoxic agent in both *in vitro* cell and *in vivo* studies$^{65}$.
Triterpenoid glycosides reported in the Mussaenda macropylia and Cyclamen mirabile showed antimicrobial, uterocontractile and inhibitory activities against a periodontopathic bacterium and porphyromonas gingivalis\textsuperscript{66,67}. Limonoids reported in the Melia azedarach showed antimicrobial\textsuperscript{68,69} and antileukemic\textsuperscript{70} activities. A novel triterpene from Rudgea viburnioides exhibited moderate antifungal activity against Cladosporium cladosporioides\textsuperscript{71}.

Oleanolic acid, pomolic acid, ursolic acid and their derivaties were identified as anti-HIV principle from several plants, including Rosa woodsii (leaves), Prosopis glandulosa (leaves and twigs), Phoradendron juniperinum (whole plant), Hyptis capitata (whole plant), Ternstromia gymnanthera (aerial part) and Geum japonicum (whole plant)\textsuperscript{72,73}. Among the oleanolic acid derivatives demonstrated most potent anti-HIV activity, with an EC\textsubscript{50} value of 0.0005 \(\mu\)g/ml and a T.I. value of 22400\textsuperscript{72}.

Terpenoidal saponins have been reported to possess antifungal properties\textsuperscript{74,75}. The magnitude of the hemolytic activity of saponins has often been linked with the antifungal and antiinflammatory activities of the saponins\textsuperscript{76}. In recent years, natural occurring compounds including terpenoidal saponins have been reported to inhibit the effect of diverse environmental mutagens and carcinogens\textsuperscript{77,78}. From a bioassay-guided fractionation procedure using herpes simplex virus type-1 (HSV-1) as the target model, a virucidal saponin mixture (maesasaponin mixture B) was isolated from the MeOH extract of leaves of Maesa lanceolata\textsuperscript{79}. Four triterpenoids saponins (from seeds of Aesculus chinensis) were evaluated for their inhibitory activity against HIV-1 protease\textsuperscript{80}. Biologically active triterpene saponins from callus tissue of Polygala amarella showed significant immunological properties based on the enhancement of granulocyte phagocytosis \textit{in vitro}\textsuperscript{81}. 
FLAVONOIDS

The term flavonoids is applied to include a large number of naturally occurring plant pigments in which two benzene rings are linked by a propane bridge (C₆-C-C-C₆), except in the isoflavone in which the arrangement is C₆-C-C. The skeleton structure and numbering system in the various flavonoids are as follows:

FLAVONES

AURONES

CHALCHONES

The flavonoids have been divided into several groups on the basis of their structures. Some of the important groups of the flavonoidal compounds along with their examples are mentioned below:

(I) FLAVANONES

Example: Sakuronetin

(II) FLAVANONOLS

Example: Taxifolin
(III) FLAVONES

Example: Apigenin

(IV) FLAVONOLS

Example: Quercetin

(V) ISOFLAVONES

Example: Daidzein

(VI) ANTHOCYANIDINS

Example: Cyanidin

(VII) LEUCOANTHOCYANIDINS

Example: Melacocidin

(VIII) CHALCHONES

Example: Lanceolin
(IX) DIHYDROCHALCHONES

Example: Salipurposide

(X) AURONES

Example: Auresidine

(XI) CATECHINS

Example: Gallocatechin

Physiological Activity of the Flavonoids

Flavonoids are phenolic pigments of plants which are widespread natural products as secondary plant metabolite which have a broad spectrum of biological activity. Interest in the physiological action of the flavonoids and their possible application to clinical therapy has been long existence. The well known ability of ‘Phlorizin’ to induce glucosuria has made it a widely used compound in experimental physiological and pharmacology.

The bacteriostatic action of anthocyanins and chalcones, the insecticidal action of polyhydroxy flavones and their ethers and the action of flavones and chalcones on isolated enzyme systems have been studied.

3- and 7- hydroxy flavones were shown to be highly effective in inhibiting the reverse transcriptase activity on moloney murine leukemia virus. Pelargonidin,
quercetin and procyanidin were found to be virucidal activity against herpes simplex virus (HSV). Methylated flavone, acacetin isolated from Scoparia inhibits HSV-1 replication. The flavonoids namely galangin, kaemferol and quercetin showed in vitro activity against HSV-1. Antirhinovirus activity is also exhibited by 5, 4'-dihydroxy -3, 7, 3'-trimethoxy flavone. Two 3-methoxy flavones such as ternatin isolated from Evodia madagascariensis and melaternatin isolated from Melicop indica showed antiviral activity against DNA and poliovirus.

A number of cytotoxic flavonoids from the roots of Mountinga calabura showed significant cytotoxic activity when tested against P-388 cells. A new flavonoid glycoside isolated from the stem bark of Sapium sebiferum showed antileukemic and antimicrobial properties. A new flavonoid glycoside from the roots of Mella azedarach showed antineoplastic activity. 5, 7, 2', 4'-tetrahydroxy flavanone isolated from Sophora exigua showed antibacterial activity against methicillin resistant staphylococcus aureus.

Antiinflammatory activity of taxifolin, santin and ermanin has been reported in literature. Some flavonoidal and chalcone glycosides isolated from Clerrdendrom plomidis showed pronounced antifungal property.

Certain flavonols isolated from Chrysoplenium grayanum exhibited activity against KB cells in vitro. A moderate inhibitory effect on viral replication was exerted by a new chalcone ester glycoside isolated from the leaves of Bidens leucanthe. A new bioactive flavanone, dioclen isolated from the root bark of Dioclea grandiflora, a new flavonol glycoside gallate ester isolated from the leaves of Acer okamotoanum were shown its inhibitory activity against HIV-1 integrase. Antiinflammatory and analgesic activities of amentoflavone (isolated from Selaginella tamariscina and Ginkgo biloba) have been reported. Four new O-acylated flavonol glycoside isolated from leaves of Stenochlaena palustris showed significant
antibacterial activity against gram-positive strains\textsuperscript{107}. The anthocyanins and cyanidin isolated from Tart cherries exhibited \textit{in vitro} antioxidant and antiinflammatory activities comparable to commercial products\textsuperscript{108}. 
**STEROIDS**

Sterols are polycyclic hydroaromatic secondary alcohols and may occur in the free state or as esters. Invariably they occur whenever life exists and are found associated with fats and oils of both vegetables and animals origin. The sterols have been mainly divided into three groups according to their occurrence.

1. **PHYTOSTEROLS** – obtained from plant kingdom
2. **ZOOSTEROLS** – obtained from animals and
3. **MYCSTEROLS** – obtained from micro-organisms including fungi

Sterols have been divided into various groups according to their structural pattern in their skeleton as given below:

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<tr>
<th>Series</th>
<th>Ring A/B transfused</th>
<th>Rings A, B and C are fused</th>
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<tr>
<td>C 19</td>
<td><strong>ANDROSTANE</strong></td>
<td><strong>ISO-ANDROSTANE</strong></td>
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<td><img src="image" alt="Androstane" /></td>
<td><img src="image" alt="Iso-Androstane" /></td>
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<tr>
<td>C 21</td>
<td><strong>ALLOPREGNANE</strong></td>
<td><strong>PREGNANE</strong></td>
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<td><img src="image" alt="Pregnane" /></td>
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Physiological Activity of the Steroids

Sterols seem to have an important function in animal metabolism, as hormones, co-enzymes, bile acids and vitamins-D. β-sitosterol present in many plant shows significant antipyretic and antiinflammatory activities\textsuperscript{110}. Plant steroids have used as raw material for the pharmaceutical industry, tissue culture and \textit{in vitro} use of enzymes to increase the yield of sapogenins from plant material. Capsimine and isocapsicatrone, new steroidal alkaloids, isolated from the roots of \textit{Solanum capsicastrum} exhibited strong activity against liver damage induced by carbon tetrachloride\textsuperscript{111}. Steroids called ecdysones (20-desoxyecdysterone), isolated for the first time from pupae of silkworm, \textit{Bombyx mori}, induces moulting activity in insects and crustaceans\textsuperscript{112}. 19 steroids, isolated from Antarctic starfish, \textit{Acodonta stercoratus conspicuus} were evaluated for their ability to inhibit growth in Antarctic marine bacteria\textsuperscript{113}. Six new steroidal glycosides from \textit{Allium chinense} exhibited anticoagulation and anticancer activities\textsuperscript{114}.

A bioactive secosterol with an unusual A - and B - ring oxygenation pattern isolated an Indonesian soft coral \textit{Lopophytum sp.} was found to have activity against human ovarian tumor and human leukemia cell lines\textsuperscript{115}. Two new sterols from the soft coral \textit{Nephthea erecta} exhibited significant cytotoxicity toward the growth of KB and P-388 cells\textsuperscript{116}. New cytotoxic oxygenated fucosterols from the brown algae \textit{Turbinaria conoides} displayed cytotoxicity against various cancer cell lines\textsuperscript{117}. Four new steroids from two \textit{Octocorals} showed no antifouling activity against barnacle larvae, but lethality to barnacle at a concentration of 100 μg/ml (LD\textsubscript{100})\textsuperscript{118}. 
TANNINS

The term tannins denote the substances responsible for the conversion of raw animal skins into leather. The natural tannins are the plant products of a phenolic nature which are employed in tanning leather and also as mordant in dyeing. Tannins occur in many shrubs and trees, particularly in leaves, fruits and bark. The vegetable tannins are polyphenols with a molecular weight in the range of 500 - 3000\textsuperscript{119}. Although tannins have several other industrial and technological applications such as in the manufacture of inks and plastics in the preparation of fish nets and in the oil well drilling.

The most acceptable division of the vegetable tannins is (I) the hydrolysable and (II) condensed tannin, as originally suggested by Freudenberg\textsuperscript{120} which is a classification based on structural types. The main distinction between the two arise from their action towards hydrolytic agent, particularly acids. The hydrolysable tannin has been considered under two headings: (1) those which give a sugar and gallic acid on acid hydrolysis and (2) those which give ellagic acid as one of the products on acid hydrolysis. Thus on hydrolysis the gallotannins give gallic acid, (1) and the ellagittannins yielded hexahydroxy diphenic acid, (2) isolated normally as its stable dilactone ellagic acid, (3) or an acid which can be considered to be derive by simple chemical transformation of (2) such as oxidation, reduction and ring fission. Schmidt's\textsuperscript{121} elegant schemes of biosynthesis of the ellagittannins link the two groups since he considered the hexahydroxy diphenyl group,(4) characteristic of ellagittannins to be derived by oxidative coupling of two suitable disposed galloyl residue in a gallotannin.

The condensed tannins in contrast do not readily break down with acids, instead they under progressive polymerization under the action of acids to yield the amorphous phlobaphens or tannins red. The derivation of the tannins themselves is a
matter of some conjecture although most workers agree that they are formed by a similar self condensation or polymerization of monomeric flavan 3,4 diol or flavan 3-precursors. Freudenberg has suggested that their formation is a purely post-mortem process occurring over a long period of time and if this view is held then the condensed tannin, unlike the gallotannins and ellagitannins are not direct products of plant metabolism. Other workers, whilst agreeing that further tannin polymerization may occur as a post-mortem process in the heartwood and the bark, favour the view that the tannins are formed in living tissues under enzymatic control and the consensus of opinion and such evidences as there is probable supports this idea.
INTER - RELATIONSHIP OF THE GALLOTANNINS AND ELLAGITANNIN

Physiological Activity of the Tannins

The compounds which give more or less firmly bound colloidal precipitate with albuminoidal portion of epithelial cells and with cell secretions can counteract diarrhoea by their astringent action. The most important therapeutic agent of this type, is the tannins. Tannins are used as contracting drugs on inflammed, chafed surface, mucous membrane and also in the protein coagulant treatment of burns.

Tannins are known to possess a variety of biological activities, such as lowering the level of blood urea nitrogen,\textsuperscript{122,123} inhibiting the activity of angiotensin converting enzyme,\textsuperscript{124} antiviral and anti-HIV activities,\textsuperscript{125,126} inhibition of lipid peroxidation,\textsuperscript{127,128} antimutagenic effects,\textsuperscript{129} DNA breaking activity\textsuperscript{130,131} and psychotropic activity\textsuperscript{132}.

Eschweilenol A, (5) isolated from \textit{Eschweileria coriacea}\textsuperscript{133} is a new bioactive ellagic acid derivative. Fifty seven tannins and related compounds, including gallotannins, ellagitannins, and condensed and complex tannins were evaluated for their cytotoxicities against human tumor cell. Among them, chebulagic acid (isolated from \textit{T. chebula}), geraniin (isolated from \textit{G. thunbergii}) and sanguin H-11 (isolated
from *S. officinalis*) exhibited moderate selective cytotoxicity against PRMI-7951 melanoma cells with ED$_{50}$ values in the range of 0.1-0.8 µg/ml$^{134}$. 

Nine tannins, including gallo- and ellagitannins were evaluated as potential inhibitors of HIV replication. Among them, 1, 3, 4-tri-O-galloylquinic acid, (6) and 3, 5-di-O-galloylshikimic acid, (7) were more active inhibitors of HIV replication in H-9 lymphocyte cells$^{135,137}$. 

(6) 

(7)
Ellagic acid isolated from *Fragaria ananassa* and two new synthetic derivatives of ellagic acid: 3, 3'-di-O-β-D-glucopyranosylellagic acid decaacetate, (8) and 3, 3'-di-n-octyl-4, 4'-dihexanoyllelgic acid, (9) were effective as inhibitors of benzo-α-pyrene tumorigenesis in the lungs of strain A/J mice\textsuperscript{138}.

![Diagram of ellagic acid](image)

(8) \[ R_1 = -O\text{-tetra-O-acetyl-β-D-glucopyranosyl}, \quad R_2 = OAc \]

(9) \[ R_1 = -O\text{-n-octyl}, \quad R_2 = \text{Hexanoyloxy} \]
NATURE OF THE COMPOUNDS ISOLATED BY THE AUTHOR

The author has been able to isolate and characterize the following compounds from three selected Combretaceous Indian medicinal plants. A brief idea is mentioned herein.

1. **Terminalia alata**: The roots of *Terminalia data* yielded nine compounds. Among them, four are new compounds which have been reported for the first time in nature. The isolated compounds belong to the following chemical groups.
   (i) **TERPENOIDS**: Four known terpenoids and two new terpenoid glycosides.
   (ii) **FLAVONOIDS**: A known anthocyanidin, a new flavanone and a new chalcone glycoside.

2. **Terminalia arjuna**: The roots of *Terminalia arjuna* yielded five compounds. Among them, one is a new compound which has been reported for the first time in nature. The isolated compounds belong to the following chemical groups.
   (i) **TERPENOIDS**: Two known terpenoids and a new terpenoid glycoside.
   (ii) **STEROL**: A known sterol.
   (iii) **TANNIN**: A known tannin.

3. **Terminalia catappa**: The roots of *Terminalia catappa* yielded four compounds. Among them, one is a new compound which has been reported for the first time in nature. The isolated compounds belong to the following chemical groups.
   (i) **STEROL**: A known sterol.
   (ii) **TERPENOIDS**: A known terpenoid and a new terpenoid glycoside.
   (iii) **FLAVONOID**: A known flavonoid glycoside.

In addition to this, the ethanolic extracts and the new compounds - E, F, G, and H isolated from the roots of *T. alata* and the new compound - D isolated from the roots of *T. arjuna* exhibited antifungal, antibacterial and antiinflammatory activities respectively which are discussed in the **CHAPTER-5**.
SPECTRAL RECORDING AND PLANT MATERIALS

The plant materials: *Terminalia alata* (roots), *Terminalia arjuna* (roots) and *Terminalia catappa* (roots) were procured from the United Chemicals and Allied Products, Calcutta and authenticated by the Botany Department of this University. The voucher specimens are deposited at the ethnobotanic collection of the supplier. The melting points of the compounds were determined in an open capillary tubes and are uncorrected.

The UV spectra were recorded on a Perkin-Elmer 202 spectrophotometer. The IR spectra were taken in KBr disc on a Shimadzu 8201 PC FTIR spectrophotometer ($\nu_{\text{max}}$ in cm$^{-1}$).

The $^1$H-NMR and $^{13}$C-NMR spectra were recorded on Brucker WM / DRX 200 and 90.56 MHz instruments respectively using TMS an internal standard (chemical shifts $\delta$ in ppm). The mass spectra were recorded on Jeol D-300 spectrometer.