1. INTRODUCTION

1.1 PHYTOCHEMISTRY OR PLANT CHEMISTRY

"is concerned with the enormous variety of organic substances that are elaborated and accumulated by plants and deals with the chemical structures of these substances, their biosynthesis, turnover and metabolism, their natural distribution and their biological function

(Harborne, 1998)"

Nature always stands as a golden mark to exemplify the outstanding phenomena of symbiosis. Natural products from plant, animal and minerals have been the basis of the treatment of human disease. According to World Health Organization (WHO) estimate that about 80% of people in developing countries still relays on traditional medicine based largely on species of plants and animals for their primary health care[1].

Natural products have been a major source of drug for centuries. Ever since the birth of mankind there has been a relationship between life, disease and plants. Natural products and their derivatives represent more than 50% of the drugs in clinical use in the world[2, 3]. Medicinal plants as a group comprises approximately 8000 species. Millions of rural household's use medicinal plants in a self-help mode. The WHO estimates that about three-quarters of the world population currently use herbs and other forms of traditional medicines to treat their diseases.

During thousands of years of human existence, many natural materials were identified for combating human ailments either by instinct or intuition or trial and error. The indigenous system of medicine in the Indian sub-continent is known as Aryuveda. Ayurveda, the 'Science of Life' is an ancient medicine system which is popularly known as the art of healing and prolonging life. It is an asset of our culture, civilization and science. Ayurveda is not only the oriental science of medicine but

also rich store house of principles and practices of medicine, which can be of great value to all system of medicine. The oldest religious book of the world "Rigveda" provides information about the use of the plant 'Soma' as a medicinal agent by Indo-Aryans[2]. The plant Soma is known to have intoxicating properties. Aryan used the plant for sacrificial purposes, and its juice is described as a stimulating beverages[3]. Apparently the Aryans also had a vast knowledge of the therapeutic properties of other medicinal herbs and plants. The works of Charak and Sushruta also describe that Aryans were aware of large number of medicinal plants[4]. The systemization of medicinal plants is attributed mostly to Charak and Sushruta, who have cited about 700 medicinal plants. The book "Sushruta Samhita" compiled in 1000 B.C. includes a comprehensive chapter on herbal therapeutic and contains remarkable information about the use of medicinal plants[5].

This is widely accepted to be true in olden times, before the advent of high-throughput screening and the post-genomic era more than 80% of drug substances were natural products or inspired by a natural compounds[6].

Herbs have been an integral part of human life before learned to hunt animal primitive man, had depended on plants for both food and medicine. Medicines from plants used to cure but simultaneously magic spell were intoned as the plant material was applied. This was the usual method for healing power of plant based materials for many reasons-availability, affordability, or their belief in traditional cures[7].

Natural products have been the single most productive source of leads for the development of drugs. Since antiquity natural products have been used by man for a number of applications. Drugs derived from plant sources have been empirically used in the treatment of various human disorders for thousands of years in the form of the traditional medicine. The various systems of medicine like Ayurveda, Siddha, Unani and Allopathy used several plant species to treat different ailments[8]. In India around 20,000 medicinal plant species have been recorded[9].

Medicinal plants have curative properties due to presence of various complex chemical substances of different composition, which are found as secondary plant

metabolites in one or more parts of these plants. These plant metabolites, according to their composition, are grouped as alkaloids, glycosides, flavonoids, corticosteroids, essential oils, etc.[10].

India being a tropical country is rich in vegetation with a wide diversity. India is one of the world's 12 mega diversity centers having rich vegetation with 47,000 plant species and a wide variety of medicinal plants along with tradition of plant based knowledge distributed among the vast numbers of ethnic groups. There are many medicinally important species which are used to produce various types of drugs and medicines to treat many ailments in India since the time of the Rig-Veda.

India has one of the richest plants medical traditions in the world. These are estimated to be around 25,000 effective plant-based formulations, used in folk medicine and known to rural communities in India. There are over 1.5 million practitioners of traditional medicinal system using medicinal plants in preventive, promotional and curative applications. It is estimated that there are over 7800 medicinal drug-manufacturing units in India, which consume about 2000 tones of herbs annually[11].

Herbal medicines are also in great demand in the developed world for primary health care because of their efficacy, safety and lesser side effects. They also offer therapeutics for age-related disorders like memory loss, osteoporosis, immune disorders, etc. for which no modern medicine is available. Herbal medicine is still the mainstay of about 75–80% of the world population, mainly in the developing countries, for primary health care because of better cultural acceptability, better compatibility with the human body and lesser side effects[12].

Herbal medicines are currently in demand and their popularity is increasing day by day. Herbal medicines are in great demand in the developed as well as developing countries for primary health care because of their wide biological and medicinal activities, higher safety margins, lesser costs and fear of side effects of modern medicine[13]. About 500 plants with medicinal use are mentioned in ancient literature[14].

Despite the use of herbal medicines over many centuries, only a relatively small number of plant species have been studied for possible medical applications. Safety and efficacy data are available for an even smaller number of plants, their extracts and active ingredients and preparations containing them[15, 16].

Phytochemical's are defined as the substances found in edible fruits and vegetables that exhibit a potential for modulating human metabolism in a manner beneficial for the prevention of chronic and degenerative diseases[17].

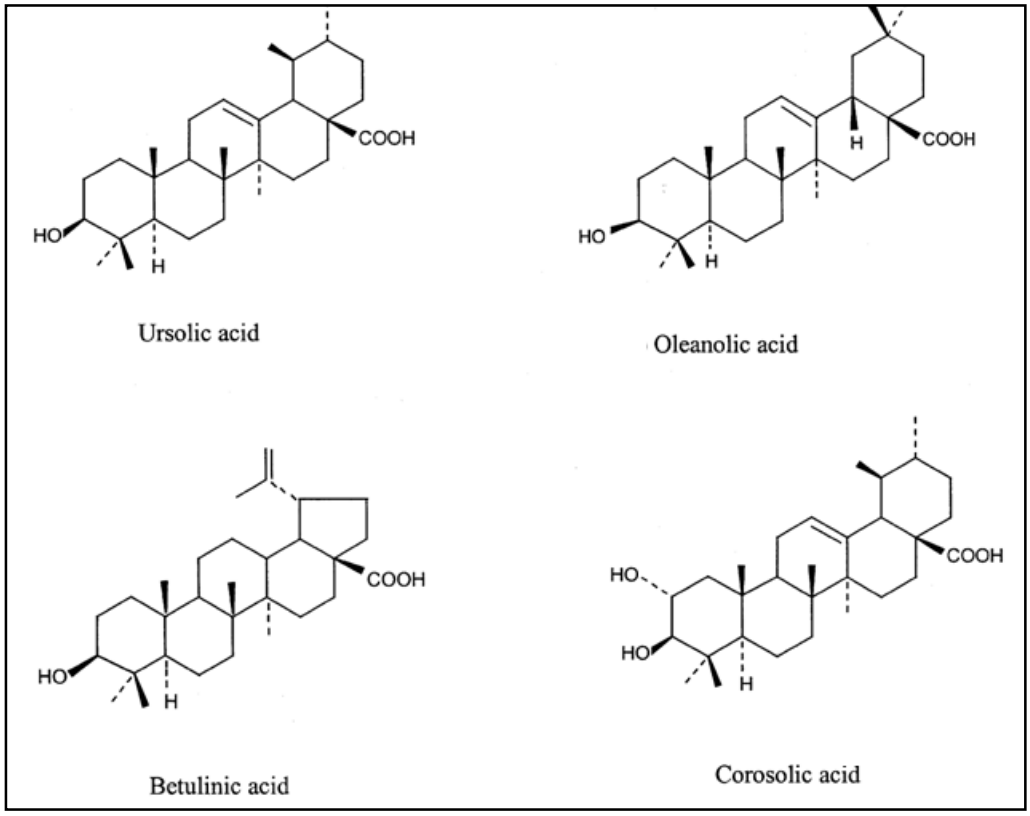
TRITERPENOIDS

The chemistry of oleanane- and ursane-type triterpenoids has been actively explored in recent years, and their biological and pharmacological activities of these compounds have been found to span a variety of properties. These include antitumor, anti-viral, anti-inflammatory, hepatoprotective, gastroprotective, antimicrobial, antidiabetic, and hemolytic properties as well as many others[18]. The isolation and structure modifications of these triterpenoids as well as the biological and pharmacological activities discovered in the past ten years, with an emphasis on their structure-activity relationships. Oleanolic acid (OA) (3β-hydroxy-olea-12-en-28-oic acid) and its isomer, ursolic acid (UA) (3β-hydroxy-urs-12-en-28-oic acid) are triterpenoid compounds which exist widely in nature in free acid form or as aglycones for oleanane- and ursane-type triterpenoid saponins[18]. Oleanane and ursane are also called β-amyrane and α-amyrane, respectively. Saponins glycosylated at either C-3 or C-28 are termed monodesmosides, and those glycosylated at both C-3 and C-28 are termed bisdesmosides. These types of triterpene saponins exhibit diverse activities, which may be attributable to the different substructures in the A-, C-, E-rings or other positions. Many comprehensive reviews of two type triterpenoids have been published covering different areas of interest, such as isolation and structure[19,20,21,22,23,24,25,26], and pharmacological activities [18,27,28,29,30], but reviews of structure-activity relationships are scarce.

The chemistry and biology of oleanane- and ursane-type triterpenoids discovered in the past ten years, with an emphasis on the relationships between their

structures and activities. These triterpenoids are often mentioned simultaneously because they share similar structural features and pharmacological activities. In addition, other pentacyclic triterpenoids such as those of the corosolic and betulinic type are often cited in order to compare their structures and activities with those of oleanane and ursane type triterpenoids.

Structures of common dietary Triterpenoids:

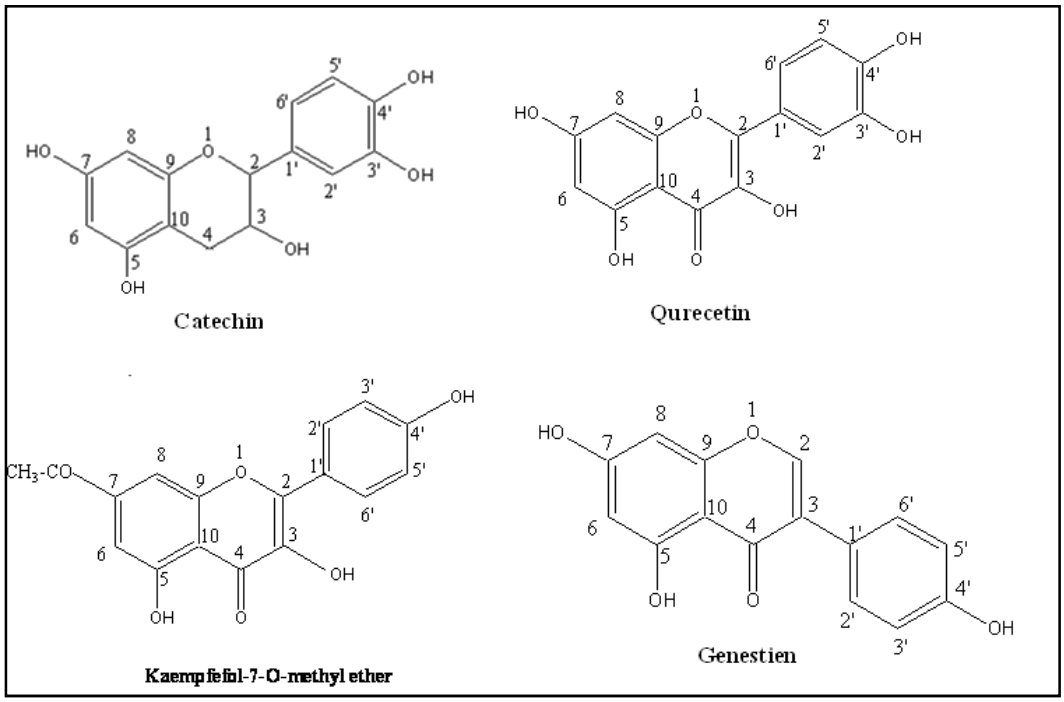


FLAVONOIDS

Flavonoids are low molecular weight [31, 32] bioactive polyphenols[33] which play a vital role in photosynthesizing cells[34]. The original "flavonoids" research apparently began in 1936, when Hungarian scientist Albert Szent-Gyorgi was uncovering a synergy between pure vitamin C and as yet unidentified co- factors from the peels of lemons, which he first called "citrin," and, later, "vitamin P" [35].

Flavonoids are secondary metabolites characterized by flavon nucleus and C6-C8-C6 carbon-skeleton [36, 37]. These are group of structurally related compounds with a chromane-type Skelton having phenyl substituent in C2-C3 position. The basic structural feature of flavonoid is 2-phenyl-benzo-γ-pyrane groups bound to carbon of aglycone usually 6-C or 8-C[38].

Structures of common dietary flavonoids

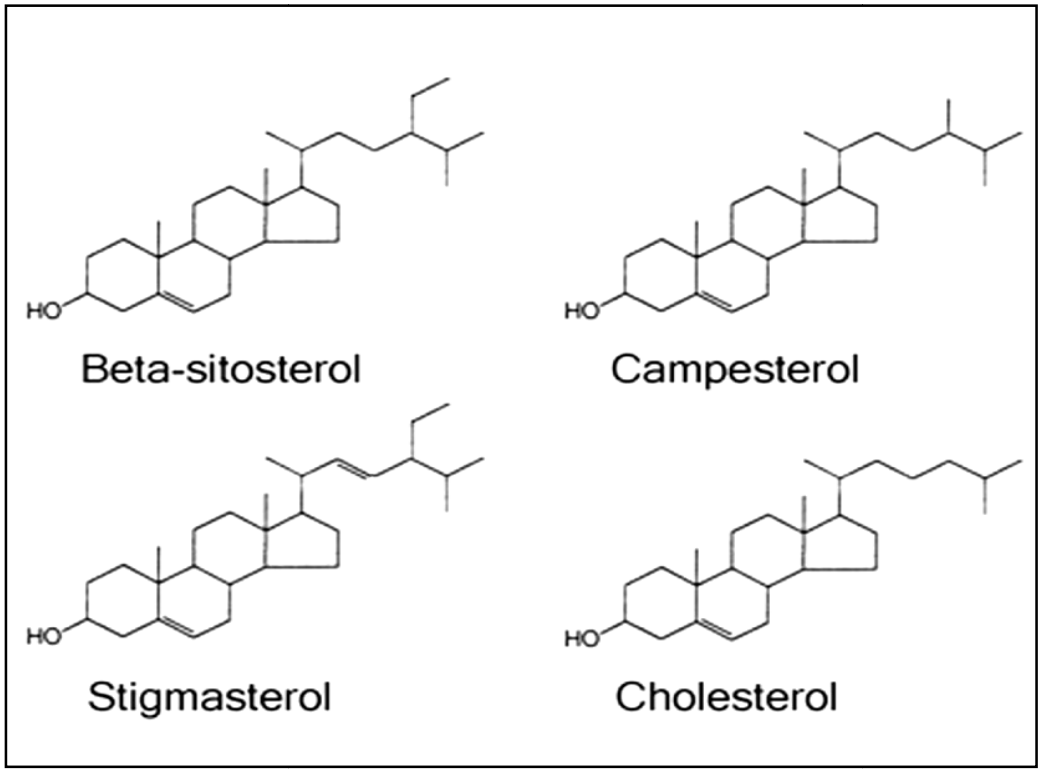


Flavonoids are powerful antioxidants against free radicals and are described as free-radical scavengers. This activity is attributed to their hydrogen- donating ability. Indeed, the phenolic groups of flavonoids serve as a source of a readily available ‘‘H” atoms such that the subsequent radicals produced can be delocalized over the flavonoid structure[17]. Free radical scavenging capacity is primarily attributed to high reactivity’s of hydroxyl substituent’s that participate in the reaction [31].

PHYTOSTEROLS

Phytosterols (also called plant sterols) are specific phytochemical's that resemble cholesterol in structure but are found exclusively in the plants. Phytosterols are derivatives of the parent molecules 4-des-methyl sterol [40]. Phytosterols exit within the plant in both esterifies and free alcohol forms. More than 200 phytosterols exit naturally in the plant kingdom and many are found in food stuff [41]. Phytosterols are absorbed from the diet in small but significant amounts and may reach serum concentrations in the low micro molar range. Epidemiological data suggest that phytosterols in the diet are associated with a reduction in common cancers including cancers of the colon, breast, and prostate[42]. The most common phytosterols in the human diet are ß-sitosterol, stigmasterol and campesterol. The concentration of these phytosterols vary among food groups but typical distribution of phytosterols in common plant foods as reported in Food Chemical Codex monograph for sterols consists of 50-65% ß-sitosterol, 10-40% campesterol and 0-35% stigmasterol [43]. These compounds are white powders with mild, characteristic odor, insoluble in water and soluble in alcohols. These have many applications, for instance as food additive taken to lower cholesterol, as well as in medicine and cosmetics. Phytosterols have also been reported for the cholesterol lowering and the anticancer properties. Influences of phytosterols on the immune and hormone systems may also contribute to their health effects.

Structures of common dietary phytosterols



The main health concern is atherosclerosis and the vulnerable plaques, which produce heart attacks, stroke, and other cardiovascular and cerebrovascular events[44]. Stigmasterol and ß-sitosterol are the phytosterols with a molecular weight of 412.691 and a formula of $C_{29}H_{48}O$ and 414.707 and $C_{29}H_{50}O$ respectively. Stigmasterol is also known as Wulzen anti-stiffness factor.

Stigmasterol is used as a precursor in the manufacture of synthetic progesterone, a valuable human hormone that plays an important physiological role in the regulatory and tissue rebuilding mechanisms related to estrogen effects, as well as acting as an intermediate in the biosynthesis of androgens, estrogens, and corticoids. Alone and in combination with similar phytosterols, ß-sitosterol reduces blood levels of cholesterol. In Europe ß-sitosterol plays a major role in treatment of herbal therapy of benign prostatic hypertrophy (BPH). It is also used for the treatment of prostatic carcinoma and breast cancer[45, 46]. ß-sitosterol has shown to reduced carcinogen-

induced cancer of colons in the rats as well asexhibiting anti-inflammatory, anti-pyretic, anti-complementary activity and insulin releasing activity[47, 48,49,50].

1.2 HISTORICAL GLANCE OF NATURAL PRODUCTS FOR DRUG DISCOVERY

Natural product derived from microorganism, plant and animal Sources have crucial role for treatment of diseases. In the areas of cancer and infectious disease, 60% and 75% of new drugs, respectively, originated from natural sources between 1981 and 2002[51]. As well as natural product drug discovery also has several limitations when compared to synthetic chemical drug discovery[52].

a. Lack of skill for high-quality natural product library.

b. Natural products are often synthesized in small quantities and present as mixtures in extracts, which require labor-intensive and time-consuming purification procedures. Obtaining further quantities for preclinical development requires large-scale reacquisition or fermentation that would have a substantial impact on the development time line.

c. Rediscovery of known compounds is a major problem when screening natural product libraries. This is caused by a lack of efficient de-replication methodologies for both natural product sourcing and compounds in the natural product libraries (De-replication is the process by which the chemical and biological characteristics of the unknown compounds are compared with the chemical and biological characteristics of known compounds from the databases to eliminate those that have been identified previously). Some natural products were discovered more frequently than others during screening programs. As the number of described natural products increased, so did the probability of rediscovering known compounds.

d. The time-consuming processes of de-replication and purification are not compatible with the present regime of blitz screening campaigns in which assay support is only available for a limited duration (three months).

e. Natural products are often structurally complex. Modification of complex natural products using organic chemistry is frequently challenging. Medicinal and combinatorial chemists prefer not to work with natural products because of the large size and complexity of the compounds, which have too many functional groups to protect. It is difficult to prepare as many natural product analogs as synthetic chemicals in the same amount of time.

1.3 RECENT SUCCESS OF NATURAL PRODUCTS

Although pharmaceutical Industries have decline keen into the natural products but it still show a substantial impact on the drug discovery process. About 136 natural product and natural-product-derived drugs have undergone various stages of clinical development in all major therapeutic areas[53]. Recent technological advances and the development of new methods have revolutionized the screening of natural products and offer a unique opportunity to re-establish natural products as major source of drug leads. The new methods and technologies can address the aforementioned limitations of screening of natural products. Examples of recent advances in the application of these technologies that have immediate impact on the discovery of novel drugs are: (i) development of a streamlined screening process for natural products; (ii) improved natural product sourcing; and advances in (iii) organic synthetic methodologies; (iv) combinational biosynthesis; and (v) microbial genomics.

1.4 INTERNATIONAL SCENARIO

International market of medicinal plants is over US $ 60 billion per year, which is growing at the rate of 7% and expected to be US $ 5 trillion by 2035.

In the first International congress on Medicinal plants held at the university of Munich, Germany in 1976, it was estimated that 6,66,000 plant species existed on the earth and only 5% of them had been specially investigated chemically and pharmacologically[54]. Therefore, there is an urgent need to evaluate the therapeutic potential of the drugs as per WHO guidelines. The importance of adequate

pharmacognostical, phytochemical and pharmacological evidence of crude drug used in various medicinal systems is becoming increasingly recognized and in this respect the present work will be useful. The Satpuda region is estimated to contain 10,000 species of plants, of which more than 1,000 have medicinal values.

1.5 FUTURE PROSPECT IN HERBAL MEDICINES

Scientific research on medicinal plants is being carried out most intensely in research institutes, universities and pharmaceutical laboratories as well as in the clinics of many developed countries. The research on medicinal plants has in two important directions. Firstly, the active gradients of plant that have long been known for their healing properties are investigated. The second sphere of basic research is directed towards the discovery of new kinds of medicinal plants and new drugs from the more remote regions of the world, which have not been explored so far.

The investment in plant-derived products by small to medium scale commercial enterprises has thus significantly increased. It is also apparent that the delicate balance of cultivation, collection and production of new products requires careful consideration with greater investment in infrastructure to provide a larger skills base for the conservation aspects of this trade. For future sustainability, this communication strongly endorses as a requisite a concerted input into research and development implemented at a greater scale for product development. This needs to be linked to extension services where plant extracts used in the production of phytomedicines are tested for efficacy and safety.

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