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CHAPTER

Omprakash H. Nautiyal, The *Experiment, 2013, May, Vol.10. (1), 611-646*

NATURAL PRODUCTS FROM PLANT, MICROBIAL AND MARINE SPECIES

ABSTRACT

Natural products are quite complex constituents and falls in the category of alkaloids, terpenoids, carotenoids etc are yielded from the various sources with the prominent medicinal and healing values. In this text the discussion is made about their constituents along with their structures and interestingly it is very challenging to understand their role in healing various diseases without any major side effects. The alkaloids like caffeine, morphine, hyosamine etc are explained and sources from which they are obtained are also mentioned. Ongoing researches do get innovative claims about the new natural products entities employing sophisticated instrumentations.

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1. Introduction

A natural product is a chemical compound produced by a living organism found in nature that usually has a pharmacological or biological activity for use in pharmaceutical drug discovery. Natural products are ubiquitous in our everyday life. Some are active constituents of many medicines, vitamins, food activities, flavour and fragrances, agrochemicals and pesticides used for plant protection. With the advent of improved chromatographic separation techniques, the separation of various natural products including positional and stereoisomer is achieved routinely. Natural products provided the only source of pharmaceuticals for thousands of years, and natural products have made enormous contributions to human health through compounds such as quinine, morphine, aspirin and many others. Major reasons why natural products are so important are: (1-10)

1) There is a strong biological and ecological rationale for plants and marine invertebrates to produce novel bioactive secondary metabolites.

2) Natural products have historically provided many major new drugs.

3) Natural products provide drugs that would be inaccessible by other routes. Thus, compounds such as paclitaxel (taxol) (figure 1) would never be prepared by standard medicinal chemistry approaches to drug discovery even including newer methods of combinatorial chemistry.

1.1 Natural products and various sources

A natural product is a chemical compound or substance produced by a living organism found in nature that usually has a pharmacological or biological activity for use in pharmaceutical drug discovery and drug design. A natural product can be considered as such even if it can be prepared by total synthesis. (10-15)

These small molecules provide the source of inspiration for the majority of FDA-approved agents and continue to be one of the major sources of inspiration for drug discovery. In particular, these compounds are important in the treatment of life-threatening conditions. (15-20)

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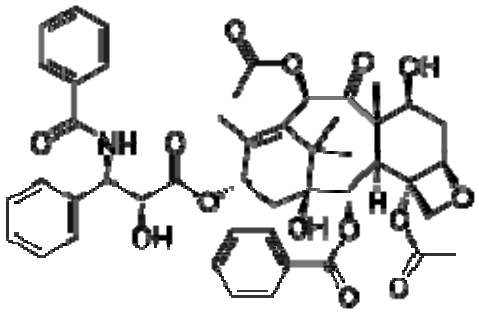

Figure.1 Taxol

1.2 Natural sources

Natural products may be extracted from tissues of terrestrial plants, marine organisms or microorganism fermentation broths. A crude (untreated) extract from any one of these sources typically contains novel, structurally diverse chemical compounds, which the natural environment is a rich source of. Chemical diversity in nature is based on biological and geographical diversity, so researchers travel around the world obtaining samples to analyze and evaluate in drug discovery screens or bioassays. This effort to search for natural products is known as bio prospecting.

1.3 The plant kingdom

Plants have always been a rich source of lead compounds (e.g. morphine, cocaine, digitalis, quinine, tubocurarine, nicotine, and muscarine). Many of these lead compounds are useful drugs in themselves (e.g. morphine and quinine), and others have been the basis for synthetic drugs (e.g. local anaesthetics developed from cocaine). Clinically useful drugs which have been recently isolated from plants include the anticancer agent paclitaxel (Taxol) from the yew tree, and the ant malarial agent artemisinin from Artemisia annua. (15-20)

Plants provide a large bank of rich, complex and highly varied structures which are unlikely to be synthesized in laboratories. Furthermore, evolution has already carried out a screening process itself whereby plants are more likely to survive if they contain potent compounds which deter animals or insects from eating them. Even today, the number of plants that have been extensively studied is relatively very few and the vast majority have not been studied at all. (20-25)

1.4 The microbial world

Microorganisms such as bacteria and fungi have been invaluable for discovering drugs and lead compounds. These microorganisms produce a large variety of antimicrobial agents which have evolved to give their hosts an advantage over their competitors in the microbiological world. (26-30)

The screening of microorganisms became highly popular after the discovery of penicillin. Soil and water samples were collected from all over the world in order to study new bacterial or fungal strains, leading to an impressive arsenal of antibacterial agents such as the cephalosporin's, tetracycline's, amino glycosides, rifamycins, and chloramphenicol.

Although most of the drugs derived from microorganisms are used in antibacterial therapy, some microbial metabolites have provided lead compounds in other fields of medicine. For example, asperlicin - isolated from Aspergillus alliaceus is a novel antagonist of a peptide hormone called cholecystokinin (CCK) which is involved in the control of appetite. CCK is also acts as a neurotransmitter in the brain and is thought to be involved in panic attacks. Analogues of asperlicin may therefore have potential in treating anxiety. Other examples include the fungal metabolite lovastatin, which was the lead compound for a series of drugs that lower cholesterol levels,

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and another fungal metabolite called cyclosporine which is used to suppress the immune response after transplantation operations. (26-30)

1.5 The marine world

In recent years, there has been a great interest in finding lead compounds from marine sources. Coral, sponges, fish, and marine microorganisms have a wealth of biologically potent chemicals with interesting inflammatory, antiviral, and anticancer activity. Curacin A (figure 2) is obtained from a marine cyano bacterium that shows potent antitumor activity. Other antitumor agents derived from marine sources include eleutherobin, discodermolide, bryostatins, dolostatins, and cephalostatins. (26-30)

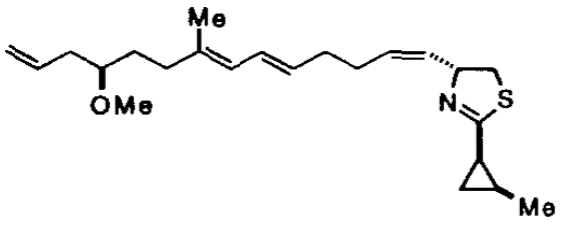

Figure.2 Curacin A cyano bacterium that shows potent antitumor activity

[1]1.6 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. (26-30)

1.7 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 cobras). However, non-peptide toxins such as tetrodotoxin from the puffer fish are also extremely potent. (26-30)

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 agents cilazapril and captopril. (26-30)

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 eyelid) to prevent muscle spasm. These toxins prevent cholinergic transmission and could well prove a lead for the development of novel ant cholinergic drugs. (26-30)

1.8 History of Development of Natural Products

1868-Way back in 1868, JR Watkins formulated a liniment product he called Red Liniment and he began selling it door to door. Fast – forward 140 years and the company he started is a multi-million dollar company that appears to remain committed to product excellence.

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1936-The Natural Products Association (NPA), founded in 1936 is the largest and oldest non-profit organization dedicated to the natural products industry. The Natural Products Association represents more than 1000 retailers, manufacturers, wholesalers.

1968-Established in 1968, now manufactures a complete line health and natural products, including vitamins, dietary supplements, natural foods, sports nutrition, herbs, essential oils, personal care products and more, utilizing natural and organic raw materials.

December 1998- Technical Services offers innovative technical solutions and has developed expertise in natural products isolation, pharmaceutical development, and food products and nutraceuticals.

January 1, 1999- A natural products pharmaceuticals is a drug that has been obtained from, or based on, naturally occurring materials, throughout history, people have collected wild plants and cultivated them near their homes with the intentions of maintaining and restoring good health.

February 25, 2000- The chapter thus provides a powerful incentive to emulate these indefatigable pioneers as well as an excellent overview of the history of natural products and it is warmly recommended, although it is not clear why the publishers chose to include it in each volume.

January 1, 2004-Provisions in the Natural Health Product Regulations, (part of the food and Drug Act) which came into effect on January 1, 2004, saying that all products that makes claims aboyt their effects, must apply for a Natural Products Number (NPN) from Health.

August 10, 2006- David Seckman this year celebrated two major milestones in the association's history. He being the Association's executive director and CFO first celebrated their 70th anniversary and took a look back at what has made their association great.

May 16, 2007- Lastly, considering what a strong factor risk is for all cancers, prostate cancer may also increase in men who have a family history of breast cancer. Other potential risk factors of this nature were not accounted for in the study.

May 1, 2008- The group represents more than 10000 retailers, manufacturers, wholesalers, and distributers of natural products, including foods, dietary supplements, and health and beauty aids

1.9 Natural Products as Medicinally Useful Products

The use of natural products as medicinal agents presumably predates the earliest recorded history as the earliest humans used various, but specific plants to treat illness. Natural products, as the term implies, are those chemical compounds derived from living organisms, plants, animals, insects, and the study of natural products is the investigation of their structure, formation, use, and purpose in the organism. Drugs derived from natural products are usually secondary metabolites and their derivatives, and today those must be pure and highly characterized compounds. (27-30)

The treatment of diseases with pure pharmaceutical agents is a relatively modern phenomenon. However, as European explorers and merchants spread out to the Western and Eastern parts of the world, some of the benefits they would bring back were newly discovered pharmaceutical preparations of natural origin. One of the earliest success stories in developing a drug from a natural product was aspirin. The Ebers papyrus indicates the use of willow leaves as an antipyretic treatment, and early English herbals also recommend the use of teas made from willow bark for this use. Following on these folk treatments, chemists and pharmacists began to isolate the compounds responsible for the remedy. Among the earliest pure compounds discovered was salicin, isolated from the bark of the white willow, Salix Alba, in 1825-26. It was subsequently converted to salicylic acid via hydrolysis and oxidation, and proved as successful as an antipyretic (fever reducing) that it was actively manufactured and used worldwide. The use of salicylic acid, however, often led to severe gastrointestinal toxicity. This was overcome when Felix Hoffmann of Bayer Company converted salicylic acid into acetylsalicylic acid (ASA) via acetylation. Bayer then began marketing ASA under the trade name aspirin in 1899. Today, aspirin is (figure 3) still the most widely used analgesic and antipyretic drug in the world. (27-30)

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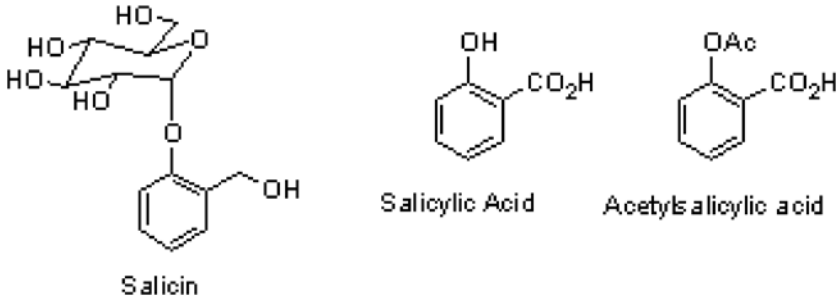

Figure.3 salicin and derivatives

1.10 Alkaloids

Many of the earliest isolated pure compounds with biological activity were alkaloids. This was due to the ease of isolation. The nitrogen generally makes the compound basic and the compound exists in the plant as a salt. Thus, alkaloids are often extracted with water or mild acid and then recovered as crystalline material by treatment with base. (31-35)

Isolated originally from Cinchona succirubra, quinine is one of 31 alkaloids with related structures, and the principal ant malarial compound, in the plant. (Alkaloids have been defined in various ways, but one definition comes fairly close to actuality. An alkaloid is a plant-derived compound that is toxic or physiologically active, contains nitrogen in a heterocyclic ring, is basic, has a complex structure, and is of limited distribution in the plant kingdom.) Malaria is still a major problem throughout the world, and, although synthetic ant malarial drugs largely supplanted quinine as the treatment for malaria during World War II, quinine is often once again the drug of choice as strains of malaria have become resistant to the synthetic drugs. However, the search for other ant malarial drugs from natural sources has also continued. One of the most promising new drugs is qinghaosu, (figure 4 & 5) isolated from Artemisia annua, a sesquiterpene (see below) which contains a unique trioxane structure. Among the most famous of the alkaloids are the Solanaceae or tropane alkaloids.

Plants containing these alkaloids have been used throughout recorded history as poisons, but many of the alkaloids do have valuable pharmaceutical properties. Atropine the racemic form of hyoscyamine comes from Atropa belladonna (deadly nightshade) and is used to dilate the pupils of the eye. Atropine is also a CNS stimulant and is used as a treatment for nerve gas poisoning. Scopolamine, another member of this class is used as a treatment for motion sickness. Cocaine, from Erythroxylum coca, is closely related in structure, is also a CNS stimulant, and has been used as a topical anaesthetic in ophthalmology. It is also a drug of abuse. Cocaine was found in very small amounts in the original Coca-Cola formula, but was not the main concern of the USDA at the time. Caffeine was considered to be the major problem with the drink. Datura stramonium (Jimsonweed), a plant found in Virginia contains similar compounds. (31-35)

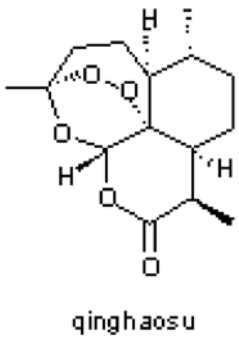

Figure.4 Qinghaosu

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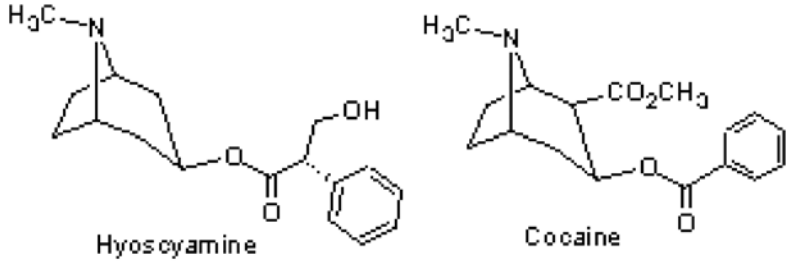

Figure.5 Hyoscyamin and cocaine

The morphine alkaloids, (figure 6) derived from the opium poppy, Papaver somniferum, are powerful pain relievers and narcotics. The narcotic activity of P. somniferum was noted on Sumerian tablets in 3500 B.C., making it one of the oldest drugs known. Opium is the dried latex of the seed heads of P. somniferum and has been used as an analgesic (eliminates or relieves pain) and narcotic (induces sleep or drowsiness) in preparations such as laudanum and paregoric. Morphine is the principal alkaloid and was first isolated between 1803 and 1806. It was widely used for pain relief beginning in the 1830's, but was also recognized as being addictive. In an attempt to make morphine less addictive, Bayer chemists acetylated the hydroxyl groups to produce diacetylmorphine. This was marketed as a non-addictive pain reliever under the trade name Heroin for about two years in the early 1900's, until it was recognized to be more addictive than morphine. Other derivatives of morphine have been developed and found use as opiate antagonists or as animal tranquilizers. (31-35)

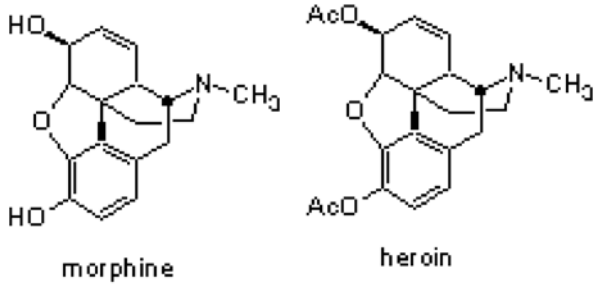

Figure.6 Morphine and Heroin

1.11 House Cleaning With Natural Products

[2]In the past, natural ingredients were the only option for housecleaning. The trend is now turning back towards using non-poisonous, natural cleaning products. There are many benefits to switching, here are some of them: (36-40)

- save money, especially when buying in bulk
- avoid accidental poisoning
- protect the environment

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- protect the water supply
- less plastic containers to recycle
- reduce risk to children and pets
- no exposure to harmful fumes caused by chemical product combining

1.12 Tools and Equipment for Natural Home Cleaning

- cotton cloths or rags (worn out socks make "handy" dusters)
- inexpensive spray bottles (do not re-use ones which previously contained chemical cleaners)
- distilled white vinegar
- baking soda
- liquid castile soap
- fresh lemons
- tea tree essential oil
- lavender essential oil
- fresh air

1.13 Distilled White Vinegar

Distilled white vinegar is a natural disinfectant and as such it is a wonderful ingredient in the natural housecleaning kit. It is readily available and inexpensive. A mixture of 1/3 vinegar and 2/3 water in a spray bottle can be used to clean windows, mirrors and things such as sliding glass shower doors. Spray on; allow sitting for a moment and then wiping or washing off thoroughly. (36-40)

1.14 Baking Soda

Baking soda is a mildly abrasive, non-toxic, multi-use powder. Used in baking and cleaning, it is also found in some toothpaste, and can in fact be sprinkled on to a toothbrush (occasionally) to clean teeth. Save even more money by buying in bulk and storing in air-tight glass containers. Sprinkle baking soda in sinks, tubs or toilet bowls, and then scrub with a cloth or sponge. It is also effective as a gentle scrub for tiles, faucets and fixtures. Rinsing away thoroughly will remove residue and as a side benefit, will freshen drains as well. (36-40)

1.15 Fresh Lemons

Convenient and good smelling lemons pack an invigorating scent along with their ability to clean tiles and faucets. Lemons are a good source of natural aromatherapy. Make a lemony scrubber sponge by dipping a half cut lemon into a saucer of baking soda and using it to scour tiles, tubs or sinks. Rinse well.

1.16 Tea Tree and Lavender Essential Oils

While there are many essential oils on the market, Tea Tree and Lavender essential oils are good choices for the natural housecleaning basket. Both have anti-bacterial properties and so are excellent choices for bathroom cleaning take a spray bottle, fill to almost full with water, add 15-20 drops of either (or a combination) oil, add a drop of liquid castille soap, and shake well. Use as a general countertop or bathroom cleanser spray. (Caution, essential oils are not recommended for use by pregnant women).

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1.17 Value of Natural Seaweed Products in a Healthy Diet

Land plants require a rigid structure to withstand the constant pull of gravity, which marine plants do not need. Instead, they do need a flexible structure to accommodate the varying stresses as result of currents and wave motion. Seaweed and algae have, unlike their earthly cousins, no roots, leaves, or vascular systems. They nourish themselves through osmosis, attracting gases and nutrients dissolved in the watery environment that is their home. Because of the lack of a vascular system, the minerals/nutrients in seaweeds are in colloidal form, able to retain their molecular identity in liquid suspension. The micronutrients and electrolytes in seaweed are bio available, in a form that human cells need to mesh with their metabolisms. Not surprising really, because the composition of human blood plasma, or fluid surrounding cell membranes, is similar to that of seawater. (41-45)

Seaweed itself constitutes a source of dietary fibber that differs chemically and physically from those of land plants and induces different physiological effects. Referenced data indicates that algal dietary fibber may show important functional activities, such as antioxidant, anti-mutagen and anticoagulant effect, anti-tumour activity, and an important role in the modification of lipid metabolism in the human body. An increase in their consumption would elevate the foods offered to the population. (41-45)

Many physical ailments in both humans and their companion animals can be regularly resolved with the simple addition of a little seaweed to their respective diets. However you have to act in the here and now to reap the benefits later. People consider themselves healthy unless they are ill or overweight, a kind of borderline health. Optimum health is more. For optimum health you need to achieve vitality, mental clarity, and improved digestion. Most of us need to consider weight loss as a reduced risk for development of serious diseases. (41-45)

Sea vegetables are virtually fat-free, low calorie and one of the richest sources of minerals and fibber in the vegetable kingdom. They have ready access to the abundance of minerals found in the ocean. Coastal peoples all over the world have prized seaweed as a source of valuable nutrients, primarily minerals, for eons. Ancient tradition: the power of the Earth (plants) to be combined with products of the sea (flexibility), key to a long and healthy life. (41-45)

Seaweed is used to help to build and sustain the broad nutritional balance of vitamins, minerals, and vital nutrients on which optimum health and vitality depend. They are low-calorie foods, with a high concentration of minerals, vitamins, proteins (digestible and indigestible), carbohydrates, and lipids. (Figure 7) (41-45)

Figure.7 Natural sea weed

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Sea plants are regarded as more potent than land plants because they contain a great number of organic compounds known as phyto (plant) chemicals. Many of these organic compounds are necessary, but missing in our modern food supply. This mineral content of seaweed, vegetables, and fibber is extraordinary, and lies at the root of many of their reputed healing properties. The major minerals are instrumental in all kinds of life-sustaining activities in your body. Although therapeutic seaweed constituents can be extracted and are available and used in cases of chronic conditions, it is easier and cheaper to use whole seaweeds, not extracts. (46-50)

1.18 Natural Products in the Pharmaceuticals Industry

Natural products have traditionally been an important source of pharmaceuticals. Although synthetic chemistry has also produced many new bioactive substances and combinatorial techniques have considerably expanded the number of compounds available for tests, there are still a relatively high number of natural products and their derivatives among the best selling drugs and there has been a renewed interest in natural products as a source of pharmaceuticals. It has been recently shown that the types of natural products that evidence biological activity are quite different from their synthetic counterparts and statistical evaluations show a clear difference between the structural properties of natural products and synthetic compounds. As the degree of differences between natural products of different sources is also very high and there many sources of natural products are relatively untapped, interest in developing active principles from biodiversity will probably continue for a long time. (46-50)

Drawbacks in the use of natural products in large-scale screening projects derive from the uncertainties in obtaining sufficient amounts of material, the variability in composition of samples and in tracing some form of activity to certain structures contained in extracts. It would appear that these uncertainties, associated with the risks that are inherent to new product introduction in the pharmaceutical industry, should make isolation of active principles from natural product quite unattractive. However, the efforts to shorten research times have increased the degree of specialization required for research, discovery and development of candidates for exploratory development and provide powerful incentive for outsourcing development programs. Whereas until recently nearly all pharmaceutical research was conducted internally, modern strategy now endorses research portfolios that include projects or technology partly provided extramurally by biotechnology companies and academic groups. Many of the uncertainties in collection, identification and screening are significantly reduced when these activities are coordinated by specialized companies or academic groups. Two of the world's largest pharmaceutical companies have negotiated agreements that would provide an access to compounds isolated from Brazilian natural products though arrangements of this type. (46-50)

The introduction of new chemical entities (NCEs) for human therapeutically use may be indicative of trends and perspectives in the pharmaceutical industry. Data on the last five years, collected from Annual Reports in Medicinal Chemistry is very illustrative. An increasing number of NCEs originate in firms that are not among the major pharmaceutical companies, some of them in countries that are new to the area. In the last two years, a rather large number of new biological entities (NBEs) were launched along with the NCEs. In 1998 there was roughly one NBE for 3 NCEs and in 1999 this proportion remained significant. It is also noteworthy that other biological entities, not considered NBEs, obtained from natural products were also launched in 1999 and that Arglabin, a new anti neoplastic agent with promising response to "difficult-to-treat" cancers can be obtained by extraction from a plant from Kazakhstan. (46-50)

1.19 Legume Natural Products

Leguminosae have long been studied as important taxonomic markers and economically important family. In the face of the vast number of natural products collectively produced by plants, the study of specific pathways had been viewed as somewhat esoteric, and attempts to obtain a more global understanding of natural product biosynthesis seemed beyond easy grasp. Those views have been changing in recent years due to the realization of the importance of natural products for plant, animal, and human health, and

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the impact of genomics technologies on all areas of biology. At least 25% of the genome of Arabidopsis encodes enzymes of metabolism, and the number may be similar or even higher in legumes, several of which now have extensive genomics resources. Whole genome-level DNA sequence information, coupled with improved methods for profiling natural products, now make possible combined genetic and biochemical approaches for addressing natural product function, deciphering biosynthetic pathways, and engineering novel pathways in transgenic plants. Several of the following case studies highlight these approaches. (51-55)

1.20 Alkaloids and Non protein Amino Acids (NPAAs)

Within the approximately 650 genera and more than 18,000 species of legumes, quinolizidine (characteristic of Lupinus species; (figure 6) dipiperidine, pyrrolizidine, β-carboline, phenyl ethylamine, and indole alkaloids have been reported. The Tyr-derived Erythrina alkaloids appear to be found only in the large genus Erythrina. NPAAs are also common within the Leguminosae, with canavanine, pipecolic acid, and djencolic acid derivatives the most important groups. NPAAs are often highly toxic, and are responsible for several serious human toxicoses, among the best known of which is lathyrism, a non progressive motor neuron disease associated with high consumption of grass peas. As early as the 5th century BC, writers described the irreversible weakness in the legs of the inhabitants of ancient cities during times of war and starvation, when they were forced to eat a diet containing a high proportion of pulses. Grass peas, which are ideally suited to arid regions such as Ethiopia and the Indian subcontinent, contain high levels of ODPA. In their seeds, and this compound is responsible for the neurological symptoms and also for deleterious effects on bone formation, particularly in children. Although low-ODPA lines of grass pea have been developed through traditional breeding and selection that appear suitable as supplementary material for animal feeds, removal of the neurotoxin from the seed by transgenic approaches is yet to be reported. More work is needed on the molecular biology of the biosynthetic pathways leading to the many nitrogen-containing natural products of the Leguminosae. (51-55)

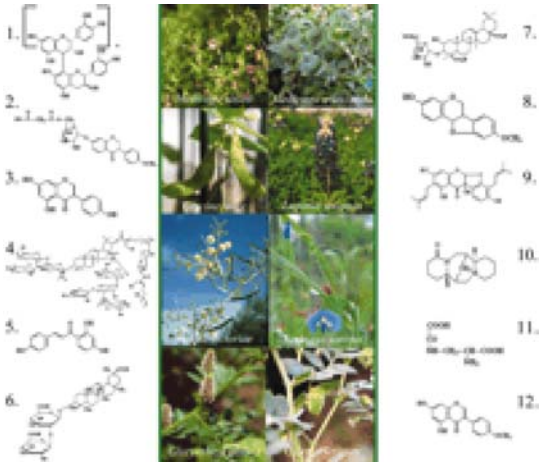

Figure.8 A small fraction of the biochemical diversity of legumes is shown in this selection of natural products from eight species. The compounds are seed coat proanthocyanidin from alfalfa (Medicago sativa; 1); formononetin malonyl glucoside, a constitutive isoflavone conjugate from roots of alfalfa and barrel medic (Medicago truncatula; 2); genistein, an isoflavone from seeds of soybean (Glycine max; 3); avicin D, a complex triterpene saponin from seed pods of Acacia victoriae (4); isoliquiritigenin, a chalcone from roots of liquorice (Glycyrrhiza galbra; 5); glycyrrhizin, a triterpene saponin from : acid glucoside, a triterpene saponin from roots of alfalfa and barrel medic (7); medicarpin,

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a pterocarpan phytoalexin from fungally infected barrel medic and alfalfa (8); a prenylated isoflavone (lupinol A) from roots of Lupinus species (9); lupanine, a quinolizidine alkaloid from roots of Lupinus species (10); 3-N-oxalyl-L-2,3-diaminopropanoic acid (ODPA) from seed of grasspea (Lathyrus sativus; 11); and biochanin A, an isoflavone from seeds of Chicken pea (Cicer arietinum)

1.21 Isoflavonoids: Natural Products for Plant and Human Health

Flavonoids (figure 8) are found throughout the plant kingdom, whereas isoflavonoids are more restricted Isoflavonoids are particularly prevalent in the Papilonoideae subfamily of the Leguminosae, wherein they are widely distributed, and function as preformed or inducible antimicrobial, or anti-insect compounds, as inducers of the nodulation genes of symbiotic Rhizobium bacteria, or as allelopathic agents. Pterocarpan-type phytoalexins such as medicarpin and constitutive isoflavone malonyl glycosides shown above in are typical of the isoflavonoids from these species. A large body of literature has reported temporal and spatial correlations between phytoalexin accumulation and disease resistance in legumes, but a role for isoflavonoids in disease resistance has only recently been confirmed by genetic approaches. (51-55)

Isoflavonoids are formed from flavanones (ubiquitously present in plants) by an unusual aryl migration reaction catalyzed by the cytochrome P450 enzyme CYP93C1 (2-hydroxyisoflavanone synthase, commonly termed isoflavone synthase [IFS]. It would appear that the IFS gene has arisen independently during evolution in taxonomically distinct families, because, in addition to their general occurrence in papilonoid legumes, isoflavonoids have also been reported in a few members of other families, including the Rosaceae, Chenopodiaceae, Apocynaceae, and Pinaceae. (51-55)

Isoflavones exhibit estrogenic, antiangiogenic, antioxidant, and anticancer activities, and are now popular as dietary supplements. Genistein (figure 9) has been the subject of over 3,600 published studies (listed in Biological Abstracts) in the last 10 years. Major sources of isoflavones for humans are seed products of soybean (daidzein and genistein) and chickpea (biochanin A,), and the health-promoting activity of high-soy diets is believed to reside in their isoflavone components. Epidemiological

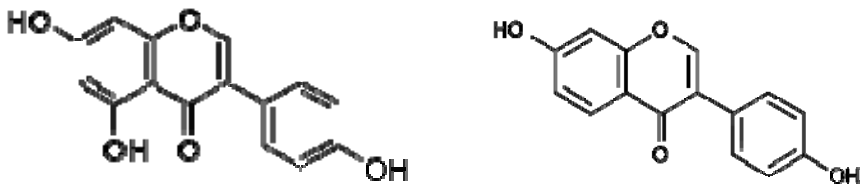

Figure.9 Genistein and Daidzein

studies suggest a link between consumption of soy isoflavones and reduced risks of breast and prostate cancers in humans. (51-55)

Isoflavones may possess other health-promoting activities, including chemoprevention of osteoporosis, and prevention of other postmenopausal disorders and cardiovascular disease. A recent study indicated that a high-soy diet may even help improve cognitive function in students presented with a variety of complex mental tasks. Plants containing certain prenylated isoflavones have been used by the Zulus of South Africa for the treatment of impotency, and they appear to be active in improving erectile dysfunction (a kind of"phytoviagra"). (51-55)

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Is it possible to introduce genistein or other isoflavones into vegetables, grains, and fruits for dietary disease prevention? Soybean IFS has been expressed in Arabidopsis, corn (Zea mays), and tobacco (Nicotiana tabacum). However, in all cases, only small amounts of genistein glycoconjugates were formed. Limiting factors for obtaining significant isoflavone accumulation in a heterologous target plant include limitation of IFS activity itself, limitation of precursor pools, and, most importantly, competition between IFS and other enzymes, such as flavanone 3-hydroxylase, that use the same substrate (naringenin; . This competition may be indicative of metabolic channeling at the branch points for the formation of the various classes of flavonoids. Armed with this knowledge, it should now be possible to optimize isoflavonoid biosynthesis in nonlegumes to expand the delivery of dietary isoflavones and to develop new sources for the more complex bioactive isoflavonoids. (51-55)

Important areas for future research on isoflavonoids include understanding flux control between isoflavonoid biosynthesis and competing pathways, deciphering the physical basis for association of biosynthetic enzymes in metabolic channels, and validating the various health-promoting effects ascribed to dietary provision of isoflavones. The latter point is of great importance if transgenic foods with value added health benefits are ever to make it to the market place. (51-55)

1.22 Triterpene Saponins: Complex Molecules with Complex Activities

All known classes of terpenoids have been reported within the Leguminosae. Particularly interesting are the triterpene saponins, whose biological activities can positively and negatively impact plant traits. Some saponins display allelopathic, antimicrobial, and anti-insect activity, but they can also be toxic to monogastricanimals, act as antipalatability factors, or reduce forage digestibility in ruminants. Monogastric animals often avoid consuming foods that contain saponins, and, therefore, development of saponin-free alfalfa is an agronomic target. (51-55)

Saponins also have useful pharmacological activities. Many are anticholesterolemic or can act as adjuvants. The roots of the licorice plant (Glycyrrhiza glabra) are one of the oldest known botanicals in Chinese medicine. Health beneficial activities include anti-inflammation, antiulcer, antiallergy, and anticarcinogenesis, and the triterpene saponin glycyrrhizin may account for many of these properties, although liquorice also contains bioactive chalcones), isoflavans, diketones, and hydroxy-phenols. Desert shrubs of the genus Acacia contain complex triterpene saponins, known as avicins, within the developing seedpods, where they presumably protect the seeds from predation. These compounds, which consist of an acacic acid triterpene skeleton conjugated to eight sugars and two linear monoterpenes, are now under development as anticancer agents in view of their ability to induce cell cycle arrest in mammalian cells. Their mode of action in target cells appears to involve induction of apoptosis by mitochondrial perturbation. (51-55)

Most of the steps in the biosynthesis of triterpene saponins remain uncharacterized at the molecular level. The model legume barrel medic contains a complex mixture of saponins, including glycosides of medicagenic acid, some of which have also previously been found in soybean. The first committed step in their biosynthesis is catalyzed by a specific oxidosqualene cyclase, β-amyrin synthase. β-Amyrin synthase has been functionally characterized from several plants, including pea (Pisum sativum;) and barrel medic, and is closely related to plant cycloartenol synthase involved in sterol biosynthesis. The steps between β-amyrin and the various saponin aglycones produced in Medic ago and soybean involve a series of oxidative reactions that, by analogy to similar reactions in brassinosteroid biosynthesis, probably are catalyzed by cytochrome P450 enzymes. The aglycones are subsequently converted to the saponins by the action of series of glycosyl transferases (GTs). To date, only a single GT involved in saponin biosynthesis in soybean has been characterized biochemically. This pathway is a prime candidate for functional genomics approaches (see below). (51-55)

Important areas for future research on triterpene saponins for legume improvement and commercial exploitation include obtaining a basic understanding of their biosynthesis from initial cyclization to final conjugation, discovering regulatory genes for coordinated up-

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regulation of triterpene pathways, and using transgenic approaches to learn more about triterpene function as a basis for genetic modification studies.

We defined alkaloids as natural products that contain an amino group. The name is derived from the fact that aqueous solutions of these compounds are slightly basic, i.e. alkaline, due to the presence of the amino group. The reactions that produce alkaloids generally involve the secondary metabolism of amino acids. In particular, most alkaloids are derived from four different amino acids; lysine, phenylalanine, tyrosine, and tryptophan. Most alkaloids are derived from a few common amino acids. Most have physiological activity. Most are basic, but have non-basic forms, such as quaternary compounds and N-oxides. Many alkaloids give simple colour and precipitation reactions, such as with Dragendorf's reagent that makes it relatively easy to determine their presence or absence in plant material. Many alkaloids and neurotransmitters found in many animals, alkaloids often interact with the nervous system. Among these neurotransmitters are acetylcholine, nor adrenaline, dopamine, serotonin, and GABA. These involve both CNS-ANS sites. (Figure 9 & 10) (51-55)

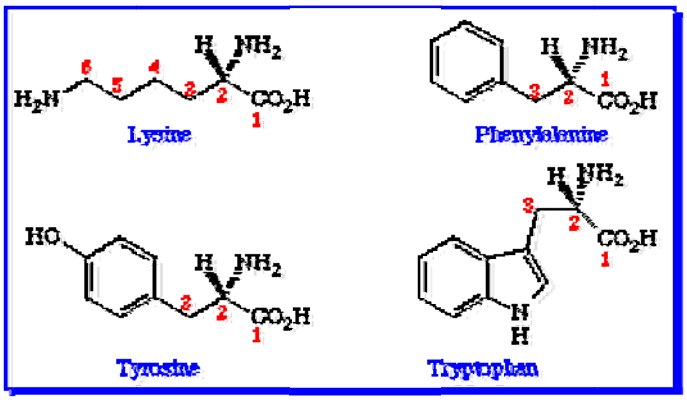

Figure.10 Amino Acids as Alkaloid Precursors

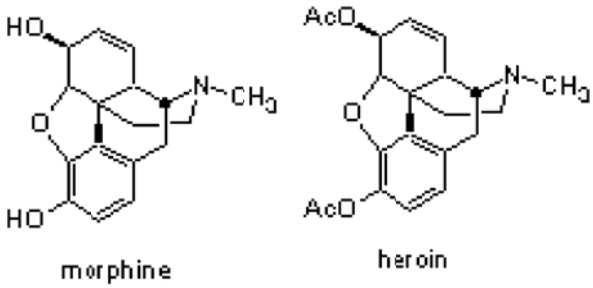

Figure.11 Morphine and Heroin

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1.23 Alkaloids

Alkaloids (figure 12) are naturally occurring chemical compounds containing basic nitrogen atoms. The name is derived from the word alkaline, and is used to describe any nitrogen-containing base. A heterocyclic compound containing nitrogen with an alkaline pH, it has a marked physiological action on animal physiology. There are exceptions to each of these criteria. Alkaloids are produce by a large variety of organisms, including bacteria, fungi, plants, and animals and are part of the group of natural products (also called secondary metabolites). Many alkaloids can be purified from crude extracts by acid-base extraction. Many alkaloids are toxic to other organisms. They often have pharmacological effects and are used as medications as recreational drugs, or in entheogenicrituals. Examples are the local anaesthetic and stimulant cocaine, the stimulant caffeine nicotine, the analgesic morphine, or the anti malarial drug quinine. Most alkaloids have a bitter taste. (56-60)

The classification of the alkaloids is complex and may be guided by a set of rules that take into account the structure and other chemical features of the alkaloid molecule, its biological origin, as well as the biogenetic origin where known. (56-60)

For example

Pyridine group: piperine, coniine, trigonelline, arecoline, arecaidine,cytisine, obeline, nicotine, anabasine, sparteine, pelletierine.
[3]Pyrrolidine group: hygrine, cuscohygrine, nicotine.
Tropane *group:* atropine, cocaine, ecgonine, scopolamine catuabine
Indolizine group: senecionine, *swainsonine*
Quinoline group: quinine, quinidine, dihydroquinine, dihydroquinidine, strychnine, brucine, veratrine, cevadine

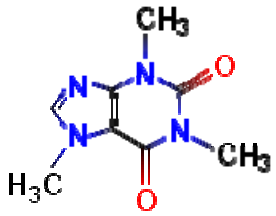

Figure 12 Caffine a purine alkaloid

1.23.1 Classification of Alkaloids

The classification of the alkaloids is complex and may be guided by a set of rules that take into account the structure and other chemical features of the alkaloid molecule, its biological origin, as well as the biogenetic origin where known. For example, where the biosynthesis pathway of an alkaloid is unknown, it may be grouped based on structural similarities with known compounds, including non-nitrogenous compounds, or by the organism(s) from which the alkaloid was isolated. (56-60)

- Pyridine group: piperine, coniine, trigonelline, arecoline, arecaidine, guvacine, cytisine, lobeline,nicotine, cotinine, anabasine , sparteine, pelletierine.
- Pyrrolidine group: hygrine, cuscohygrine, nicotine
- Tropane group: atropine, cocaine, ecgonine, scopolamine, catuabine

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- Indolizine group: senecionine, swainsonine
- Quinoline group: quinine, quinidine, dihydroquinine, dihydroquinidine, strychnine, brucine,veratrine, cevadine
- Isoquinoline group: opium alkaloids
  (papaverine, narcotine, narceine), pancratistatin,sanguinarine, hydrastine, berberine, emetine
- Phenanthrene alkaloids: opium alkaloids (morphine, codeine, thebaine, oripavine)
- Phenethylamine group: mescaline, ephedrine, dopamine
- Indole group:
- Tryptamines: serotonin, DMT, 5-MeO-DMT, bufotenine, psilocybin
- Ergolines (the ergot alkaloids): ergine, ergotamine, lysergic acid
- Beta-carbolines: harmine, harmaline, tetrahydroharmine
- Vinca alkaloids: vinblastine, vincristine
- Kratom (Mitragyna speciosa) alkaloids: mitragynine, 7-hydroxymitragynine
- Tabernanthe iboga alkaloids: ibogaine, voacangine, coronaridine
- Strychnos nux-vomica alkaloids: strychnine, brucine
- Purine group:
- Xanthines: caffeine, theobromine, theophylline
- Terpenoid group:
- Aconitum alkaloids: aconitine
- Steroid alkaloids (containing a steroid skeleton in a nitrogen containing structure):
- Solanum (e.g. potato and tomato) alkaloids (solanidine, solanine, chaconine)
- Veratrum alkaloids (veratramine, cyclopamine, cycloposine, jervine, muldamine)
- Quaternary ammonium compounds: muscarine, choline, neurine
- Miscellaneous: capsaicin, cynarin, phytolaccine, phytolaccotoxin
-

1.23.2 Medicinal uses of Alkaloids

A number of alkaloids are used as drugs. Among the oldest and best known of these is quinine, derived from the bark of the tropical cinchona tree. Indians of South America have long used cinchona bark to reduce fever, much as willow bark was used in Europe as a source of aspirin. In the 1600s Europeans discovered that the bark could actually cure malaria one of the most debilitating. Many medically useful alkaloids act by way of the peripheral nervous system; others work directly on the brain. Prominent among the latter are the pain relievers morphine and codeine, derived from the opium poppy (Papaver somniferum). Morphine is the stronger of the two, but codeine is often prescribed for moderate pain. Codeine is also an effective cough suppressant; for years it was a standard component of cough syrups. Now, however, it has been replaced for the most part by drugs that do not have the psychological side effects of codeine. (56-60)

1.23.2.1 Qunine

Quinine(figure 13) is a natural white crystalline alkaloid having antipyretic (fever reducing) , antimalarial, analgesic (painkilling), and anti-inflammatory properties and a bitter taste. It is a stereoisomer of quinidine which, unlike quinine, is an anti-arrhythmic. Though it has been synthesized in the lab, the bark of the cinchona tree is the only natural source of quinine. Quinine was the first effective treatment for malaria. (56-60)

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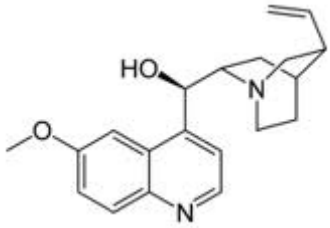

Figure 13 quinine

1.23.2.2. Cocaine:

Cocaine (figure 14) is a crystalline terpane alkaloid that is obtained from the leaves of the coca plant. The name comes from "coca" in addition to the alkaloid suffix -ine, forming cocaine. It is a stimulant of the central nervous system and an appetite suppressant. Specifically, it is a serotonin-norepinephrine-dopamine reuptake inhibitor, which mediates functionality of such as an exogenous catecholamine transporter ligand. Because of the way it affects the mesolimbic reward pathway, cocaine is addictive.

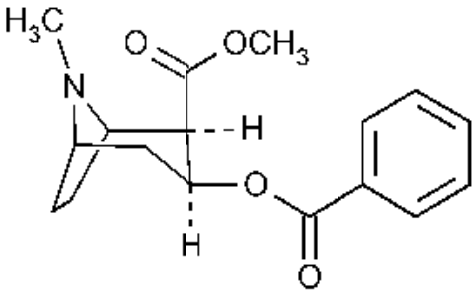

Figure.14 Cocaine

1.23.2.3 Cinchona

Cinchona bark (figure 15) also produces quinidine. It is used primarily to control abnormalities of heart rhythm such as fibrillation, a series of rapidly quivering beats that do not pump any blood, and heart block, a condition in which electrical currents fail to coordinate the contractions of the upper and lower chambers of the heart.

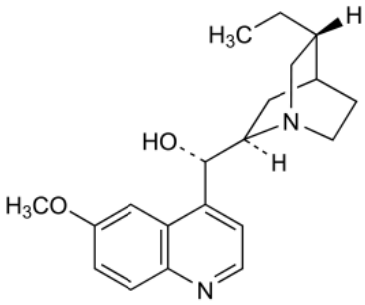

Figure.15 Cinchona

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1.23.2.4 Vincaleukoblastine

Vincaleukoblastine (figure 16) and vincristine, two alkaloids derived from the periwinkle plant (Catharanthus roseus), are used effectively for the treatment of white-blood-cell cancer. Vincaleukoblastine is especially useful against lymphoma (cancer of the lymph glands), while vincristine is used against the most common form of childhood leukemia. (56-60)

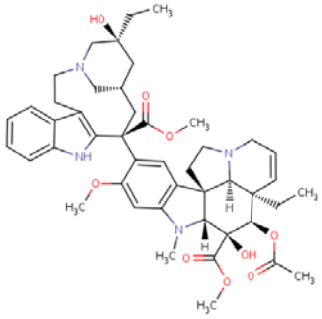

Figure.16 Vincaleukoblastine

1.23.2.5 Atropine

Atropine (figure 17) is an alkaloid produced by several plants, including deadly nightshade (Atropa belladonna), Jimson weed (Datura stramonium), and henbane (Hyoscyamus Niger). It has a variety of medical uses, as it is able to relax smooth muscle by blocking action of the neurotransmitter acetylcholine. Atropine is most commonly used to dilate the pupil during eye examinations. Atropine also relieves nasal congestion and serves as an antidote to nerve gas and insecticide poisoning. (56-60)

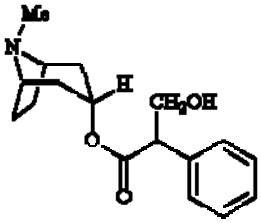

Figure.17 Atropine

1.23.2.6 Pilocarpine

Pilocarpine, (figure 18) derived from several Brazilian shrubs of the genus Pilocarpus, is another alkaloid used in ophthalmology, the medical specialty that treats the eye. This drug stimulates the drainage of excess fluid from the eyeball, relieving the high pressure in the eye caused by glaucoma. If untreated, glaucoma can lead to blindness. (56-60)

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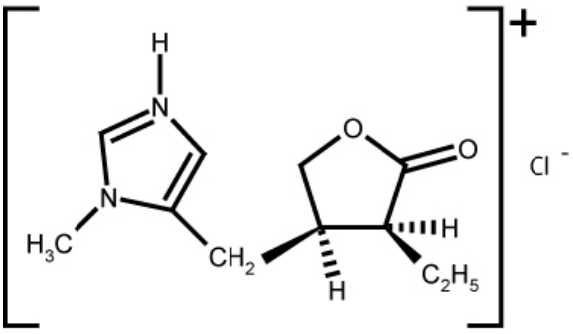

Figure.18 Pilocarpine

1.23.2.7 Reserpine

Reserpine (figure 19) in the 1950s revolutionized high blood pressure treatment and brought new hope to those suffering from this previously untreatable and life-threatening condition. Derived from tropical trees and shrubs of the genus Aauwolfia, reserpine works by depleting the body's stores of the neither neurotransmitter nor epinephrine. Among its other functions, nor epinephrine contracts the arteries and thereby contributes to high blood pressure. Unfortunately, reserpine also causes drowsiness and sometimes severe depression. Medications without these side effects have been developed in recent decades, and reserpine is rarely used. (56-60)

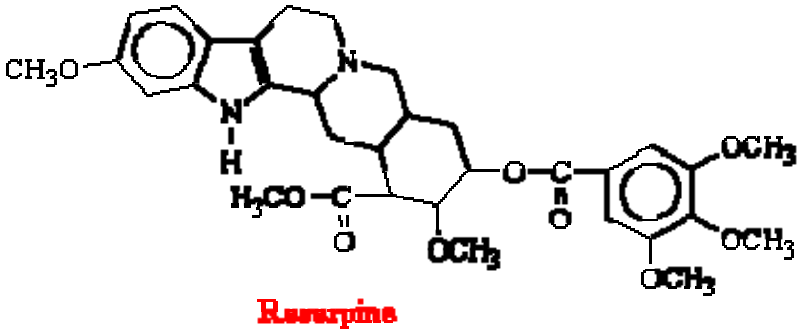

Figure.19 Reserpine

1.23.2.8 Solanceae

Among the most famous of the alkaloids are the Solanaceae or tropane alkaloids. Plants containing these alkaloids have been used throughout recorded history as poisons, but many of the alkaloids do have valuable pharmaceutical properties. Atropine (figure 20) the racemic form of hyoscyamine, comes from Atropa belladonna (deadly nightshade) and is used to dilate the pupils of the eye. Atropine is also a CNS stimulant and is used as a treatment for nerve gas poisoning. Scopolamine, another member of this class is used as a treatment for motion sickness. Cocaine, from Erythroxylum coca, is closely related in structure, is also a CNS stimulant, and has been used as a topical anaesthetic in ophthalmology. It is also a drug of abuse. Cocaine was found in very small amounts in the original Coca-Cola formula, but was not the main concern of the USDA at the time. Caffeine was considered to be the major problem with the drink. Datura stramonium (Jimsonweed), a plant found in Virginia contains similar compounds. (56-60)

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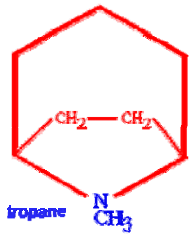

Figure.20 Tropane

1.23.2.9 Ergot

Ergot alkaloids come from a fungus, Claviceps purpurea, which is a parasite on rye and wheat. The ergot alkaloids are responsible for ergotism (St. Anthony's fire), which manifests itself as gangrenous ergotism, resulting in loss of limbs, or convulsive ergotism, resulting in hallucinations. In both cases, death usually follows and outbreaks of ergotism caused 11,000 deaths in Russia as late as 1926. Today the problem is recognized and controlled. Some of the ergot alkaloids have been used to treat migraine headaches and sexual disorders in clinical applications. The most famous of these alkaloids is lysergic acid diethylamide, LSD, (figure 21) powerful hallucinogen that is a synthetic derivative of the natural products. Similar alkaloids, particularly ergine, are also found in Mexican morning glories, such as Ipomeoa tricolor. (56-60)

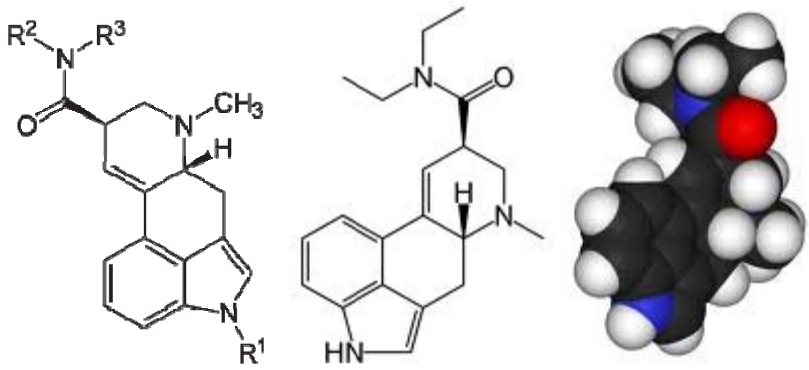

Figure.21 Lysergine and Lysergic acid diethylamide (LSD)

1.23.2.10 Morphine

Morphine alkaloids, derived from the opium poppy, Papaver somniferum, are powerful pain relievers and narcotics. The narcotic activity of P. somniferum was noted on Sumerian tablets in 3500 B.C., making it one of the oldest drugs known. Opium is the dried latex of the seed heads of P. somniferum, and has been used as an analgesic (eliminates or relieves pain) and narcotic (induces sleep or drowsiness) in preparations such as laudanum and paregoric. Morphine is the principal alkaloid and was first isolated between 1803 and 1806. It was widely used for pain relief beginning in the 1830's, but was also recognized as being addictive. In an attempt to make morphine less addictive, Bayer chemists acetylated the hydroxyl groups to produce diacetylmorphine. This was marketed as a non-addictive pain reliever under the trade name Heroin for about two years in the early 1900's, until it was recognized to be more

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addictive than morphine. Other derivatives of morphine have been developed and found use as opiate antagonists or as animal tranquilizers. (56-60)

1.23.2.11Vincristine

Vincristine, (figure 22) one of the most potent antileukemic drugs in use today, was isolated in a search for diabetes treatments from Vinca rosea (now Catharanthus roseus) in the 1950's along with vinblastine, a homologue in which the N-methyl group is oxidized to an aldehyde moiety. This is such a complex structure that it is still isolated from the plant (the Madagascan periwinkle) today rather than prepared by synthesis. The small change in structure, however, causes a significant change in pharmoacological efficacy. Vincristine (leurocristine, VCR) is most effective in treating childhood leukemias and non-Hodgkin's lymphomas, where vinblastine (vincaleukoblastine, VLB) is used to treat Hodgkin's disease.

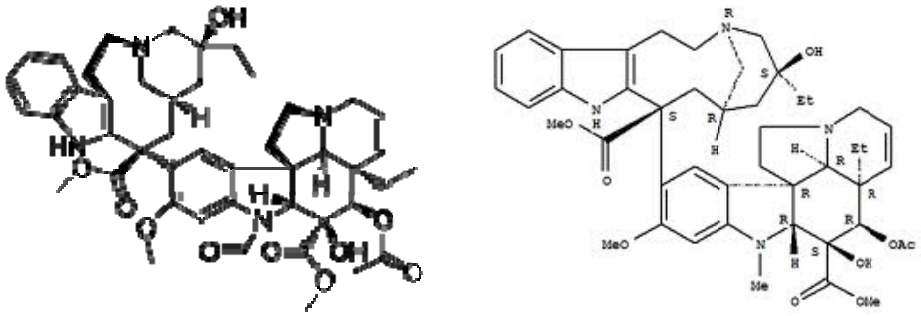

Figure.22 Vincristine and Vinblastine

1.23.2.12 Rauvolfia serpntina

Rauvolfia serpentina or Sarpaghandha plant is widely used medicinally both in the Modern Western Medical system and also in Ayurvedic, Unani and folk medicine. Sarpagandha is an important medicinal plant distributed in the foot-hills of Himalayan range, up to the elevation of 1300-1400 m. and almost all over the country. It is used in traditional medicine in India, China, Africa and many other countries. It helps to reduce blood pressure, depresses activity of central nervous system and acts as a hypnotic. In India and Nepal, it is a common treatment for hypertension and insomnia. Hindus used this plant for centuries as a febrifuge and as an antidote to the bites of poisonous reptiles like snakes. Now its medicinal value has been accepted by the allopathic system.

1.23.2.13 Moringa oleifera lam

Moringa oleifera Lam (Moringaceae) (figure 23) is a highly valued plant, distributed in many countries of the tropics and subtropics. It has an impressive range of medicinal uses with high nutritional value. Different parts of this plant contain a profile of important minerals, and are a good source of protein, vitamins, β-carotene, amino acids and various phenolics. The Moringa plant provides a rich and rare combination of zeatin, quercetin, α-sitosterol, caffeoylquinic acid and kaempferol (figure 24). In addition to its compelling water purifying powers and high nutritional value, M. oleifera is very important for its medicinal value. Various parts of this plant such as the leaves, roots, seed, bark, fruit, flowers and immature pods act as cardiac and circulatory stimulants, possess antitumor, antipyretic, antiepileptic, anti-inflammatory, antiulcer, antispasmodic, diuretic, antihypertensive, cholesterol lowering, antioxidant, anti diabetic, hepatoprotective, antibacterial and antifungal activities, and are being employed for the treatment of different ailments in the indigenous system of medicine, particularly in South Asia.

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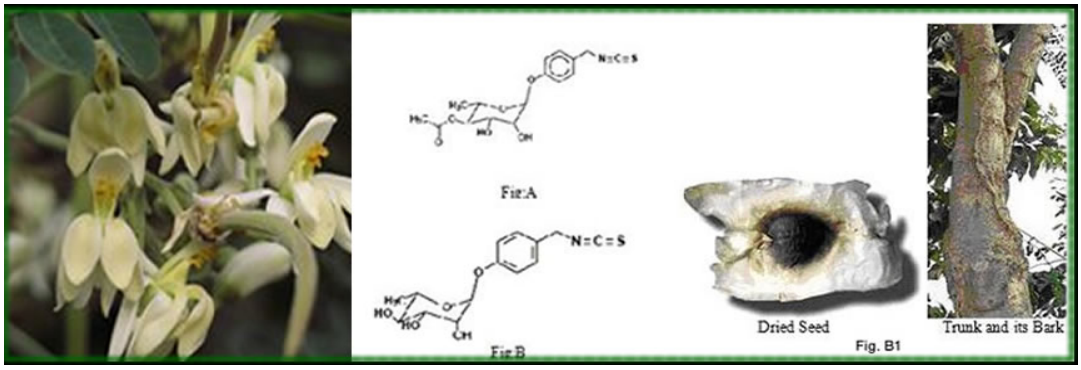

Figure.23 Source of Moringa oleifera Lam (Moringaceae)

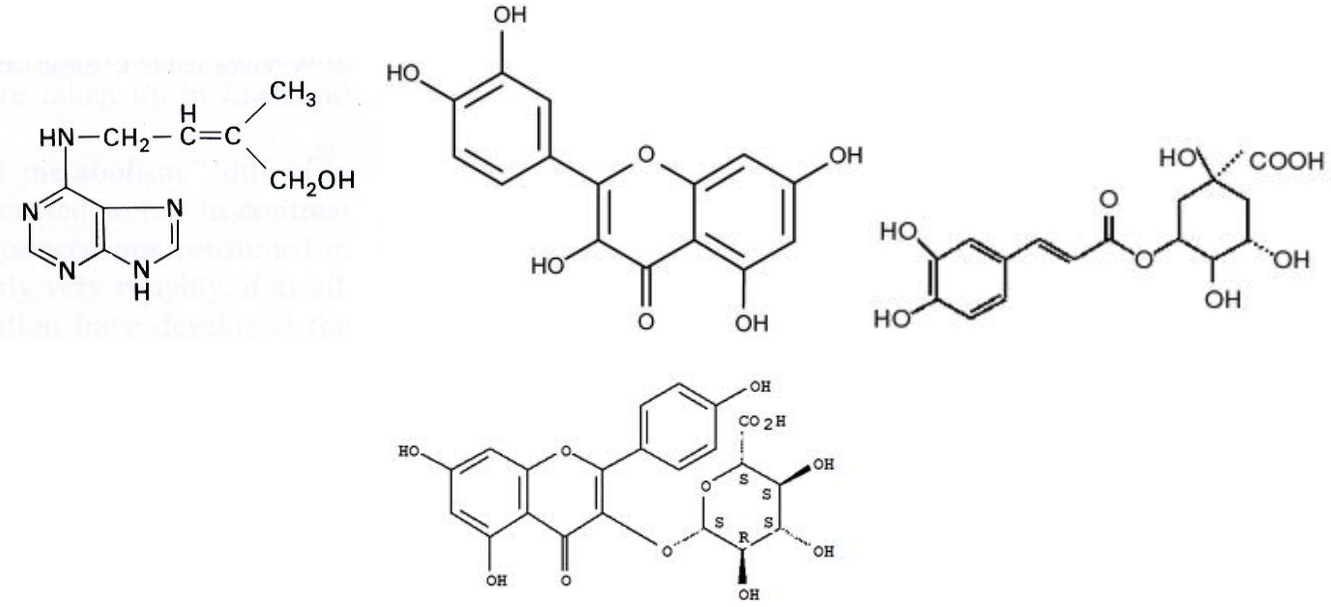

Figure.24 Structures of Zeatine, Quercitine, Caffeoylquinic acid, Kaempferol

1.23.2.14 Colchicine

Colchicine (figure 25) won Food and Drug Administration (FDA) approval in the United States as a stand-alone drug for the treatment of acute flares of gout and familial Mediterranean fever. It had previously been approved as an ingredient in an FDA-approved combination product for gout. The approval was based on a study in which two doses an hour apart were effective at combating the condition.It is also used as an anti-inflammatory agent for long-term treatment of Behcet's disease. The Australian biotechnology company Giaconda has developed a combination therapy to treat constipation-predominant irritable bowel syndrome which combines colchicine with the anti-inflammatory drug olsalazine. The British drug development company Angiogene is developing a pro-drug of a colchicines congener, ZD6126 (also known as ANG453) as a treatment for cancer.Colchicine has a relatively low therapeutic index. Long term (prophylactic) regimens of oral colchicine are absolutely contraindicated in patients with advanced renal failure (including those on dialysis). 10-20% of a colchicine dose is excreted unchanged by the kidneys. Colchicine is not

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removed by haemodialysis. Cumulative toxicity is a high probability in this clinical setting. A severe neuromyopathy may result. The presentation includes a progressive onset of proximal weakness, elevated creatine kinase, and sensorimotor polyneuropathy. Colchicine toxicity can be potentiated by the concomitant use of cholesterol lowering drugs (statins, fibrates). This neuromuscular condition can be irreversible (even after drug discontinuation). Accompanying dementia has been noted in advanced cases. It may culminate in hypercapnic respiratory failure and death. Colchicine is "used widely" off-label by naturopaths for a number of treatments, including the treatment of back pain.

The goal of most colchicine research is a more thorough understanding of the cause of gout, which is often thought of as a disease of rich living. However, as many victims will testify, the affliction does not limit itself to this lifestyle. Gout, from the Latin gutta, meaning drop, was used to describe the symptoms because physicians presumed the disease was caused by the dropping of phlegm into the big toe. Hyperurecosia or elevated blood levels of uric acid, causes the common symptoms of gout. In humans and other primates, uric acid is the final metabolite in the breakdown of purines. When this metabolic pathway becomes overwhelmed, from either an enzymatic deficiency or an increase in dietary purines, uric acid cannot be efficiently eliminated from the body. The poorly soluble uric acid crystallizes, initiating a response from macrophages and leukocytes. The phagocytosis of urate crystals by the macrophages and leukocytes stimulates the release of cytokines and interleukins, leading to inflammation and the distinctive symptoms. (61-68)

The precise mechanism by which colchicine relieves the intense pain of gout is not known. However, it is believed that the major relief of pain involves colchicine's major pharmacological action: binding to tubulin dimers. Tubulin (MW approximately 10,000 Dalton) is a protein consisting of two forms, alpha and beta. Alpha and beta tubulin form dimers, and these dimers polymerize to form long filaments of microtubules. When colchicine binds to the tubulin dimers, the dimers are unable to form the microtubules. The microtubules are vital for formation of spindle fibers during mitosis and meiosis, intracellular transport of vesicles and proteins, flagella reassembly, ameboid motility, and other cellular processes. Inhibition of ameoboid motility prevents macrophage and leokocyte migration and phagocytosis, thereby presumably preventing the inflammation and pain of gout. Because colchicine disrupts mitosis, halting the process at metaphase, scientists have also evaluated colchicine as an anticancer agent. However, serious toxicities prevent the use of colchicine in antineoplastic therapies.

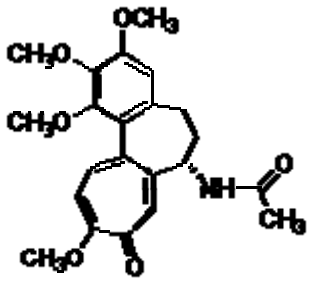

Figure.25 Colchicne

The single bond between the A and C rings (figure 26) are rotationally restricted, in a similar manner to certain substituted biphenyls. This restriction adds a degree of asymmetry to the molecule. In 1933, Kuhn designated this type of stereoisomerism as atropisomerism (from Greek - "a" meaning not; "tropos" meaning turn). The designation of this asymmetry is "aS or aR," according to the rules of molecular asymmetry, in which the "a" stands for axial chirality. In colchicine, the C-C bond between the A and C

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rings is the chiral axis.

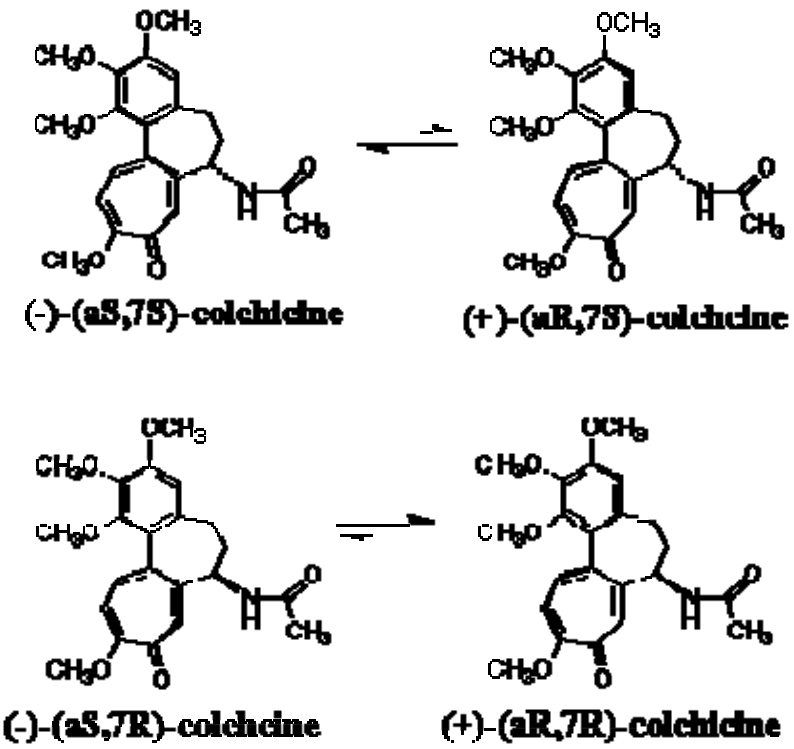

Figure.26 Stereoisomer of Colchcicine

In light of this molecular asymmetry, colchicine has four stereoisomers, as shown in Figure 26. Each pair has either the R or S configuration at C-7. (-)- (aS, 7S)-Colchicine, the natural isomer, can interconvert between the two conformational isomers aR and aS, given enough energy. The energy barrier of rotation in colchicine, approximately 22-24 kcal/mol, is large enough to allow the synthesis and isolation of the conformations as stereoisomers. The research of many medicinal chemists, in particular Arnold Brossi, has led to the conclusion that the counter clockwise an S conformation is that of the naturally occurring alkaloid. Shown in Figure 25 are energy-minimized models of the atropisomers of (7S)-colchicine (Constructed using Sybyl 6.4. Note the very different arrangement of the acetamide group in the two conformations.

In the search for more effective agents than those provided by Mother Nature, medicinal chemists have synthesized hundreds of analogous of colchicine and colchicine-like compounds. Analysis of these data has yielded information about the optimal structural requirements for binding to tubulin and inhibiting tubulin polymerization. The basic, although not comprehensive, structure-activity relationships (SARs) are summarized in (figure 27) adapted from Boye and Brossi. (+)- (aR,7R)-Colchicine, the unnatural enantiomer of (-)-colchicine, is devoid of tubulin binding activity. The appropriate torsion angle (about 53 degrees) between rings A and C is required for tubulin binding ability. Removal or demethylation of the methoxy groups decreases potency. On the B ring, the acetamide can be replaced by other alkyl amides with retention of potency; however, the free amine has decreased antitubulin activity. The

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acetamide can be elimated altogether, and activity is retained. On the C ring, demethylation to the 10 -OH (i.e., colchiceine) destroys activity. Replacement of the 10-methoxy with SCH3 or NR2 leads to increased potency. Reversal of the oxygen pattern (i.e., 9-methoxy and 10-keto) produces isocolchicine, which is inactive. It is apparent that the tropolonic functionality contributes to activity. This seven membered C ring can, however, be replaced with a an anisole ring, producing a bridged biphenyl, which retains tubulin binding activity, as long as the torsion angle between the rings A and C is acceptable.

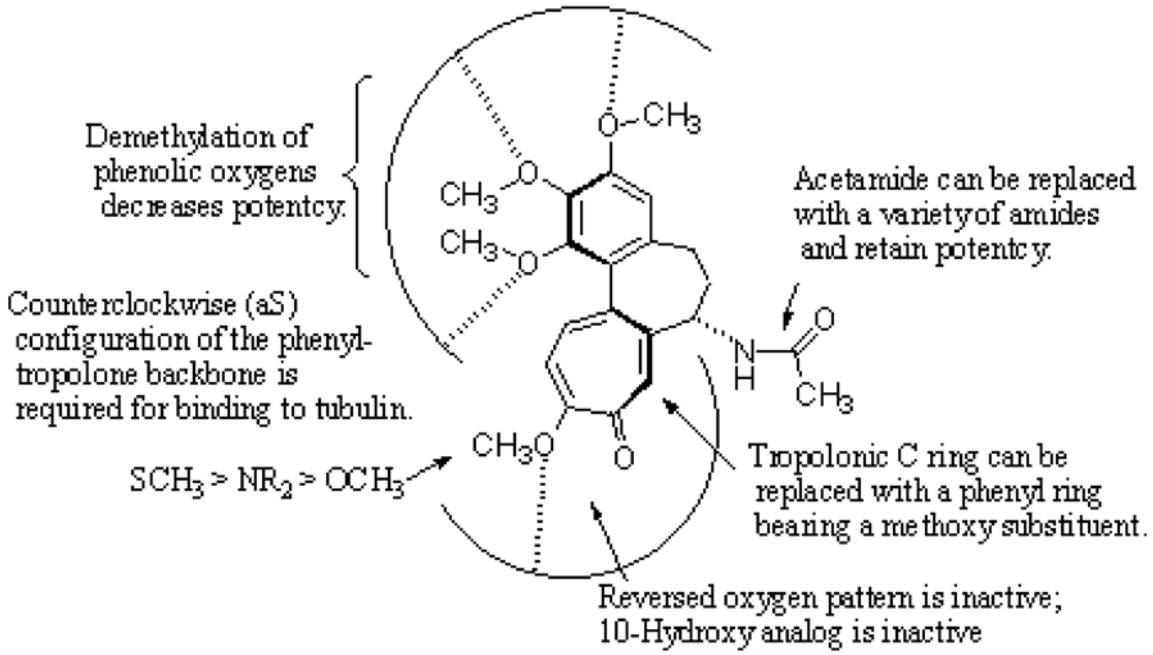

Figure.27 Structure-activity relationships of Colchicine analogous

1.23.2.15 Belladonna

Belladonna is a very poisonous plant species. A common name for Belladonna is deadly nightshade. The plant species is distributed throughout Europe, West Asia, North America and North Africa. The plant grows berries which are extremely poisonous. The berries are attractive and pose a threat to children who may try to eat them. A child eating 5 Belladonna berries may die. This plant species when eaten is also toxic to certain animals such as domestic animals and livestock. Cattle and rabbits can eat Belladonna without any issues. The principal alkaloids contained in Atropa Belladonna, as atropine, hyoscyarnine, hyoseine, and belladonnine, also atropamine, (figure 28) are substances which bear a close chemical relationship to one another, being partly isomeric and capable of being transformed into one another, e. g., and hyoscyamine into atropine.

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[4]Atropine and hyoscyamine, both of the formula, $C_{17}H_{23}NO_3$, are capable of being resolved into the alkaloid tropine ($C_8H_{15}NO$) and tropic acid ($C_9H_{10}O_3$) by treatment with baryta-water, while hyoscine, under these conditions, is split into pseudotropine ($C_8H_{15}NO$), melting at 106° C. (232.2° F.), and tropic acid.

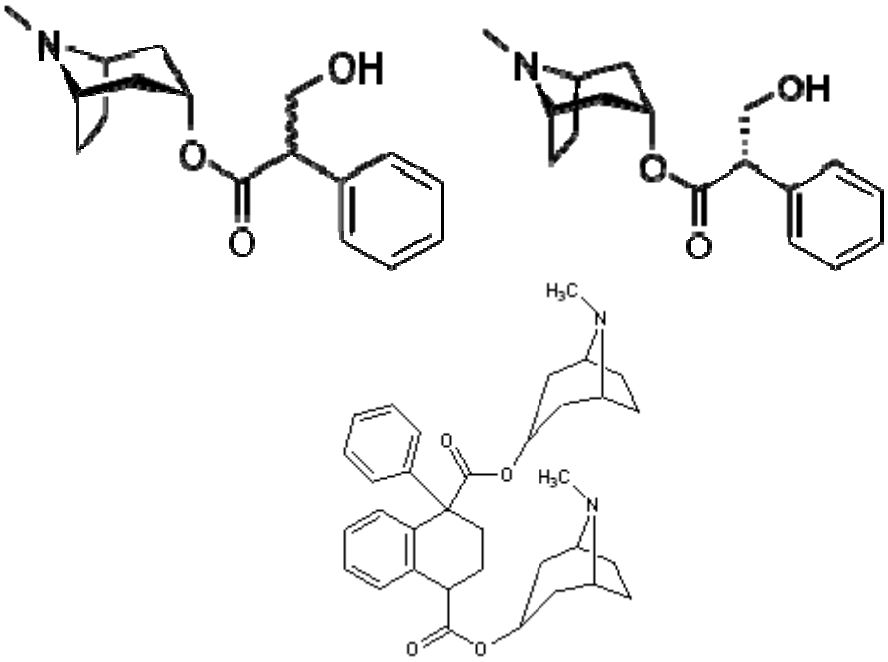

Figure.28 Major constituents Atropine, Hyocyamine and Belladonnine

If in these processes concentrated hydrochloric acid is employed atropic acid ($C_9H_8O_2$) and its polymer, isatropic acid ($C_{18}H_{16}O_4$) are formed, besides tropic acid. These reactions were first established by Kraut, in 1863, and Lossen, in 1866, find subsequently studied in detail by Ladenburg and other investigators. Tropine was found to be a pyridine derivative, viz.: oxy-ethyl-methyl tetra hydropyridine (C_5H_7N. $[C_2H_4OH].CH_3$). It is a strong, tertiary base, forming hygroscopic crystals, which melt at 62° C. (143.6° F.) and boil at 229° C. (445° F.). They are easily soluble in alcohol and water; also soluble in ether. Heated with fuming hydrochloric acid to 180° C. (356° F.) or acted upon by sulphuric acid and glacial acetic acid, the base tropidine, containing 1 molecule less of water, is formed, having the composition $C_5H_6(C_2H_4)N.CH_3$, boiling at 162° C. (323.6° F.), and resembling coniine in odor. In 1880 Ladenburg recognized tropic acid to be A-phenyl-B-oxypropionic acid ($CH_2OH.CHC_6H_5.COOH$). It is soluble in alcohol and ether, to some extent in water, from which solvent it crystallizes in needles or plates, melting at from 117° to 118° C. (242.6° to 246.2° F.). Ladenburg, in 1884, succeeded in obtaining atropine by synthesis from its products of decomposition by evaporating a mixture of tropic acid and tropine with hydrochloric acid. By substituting other aromatic acids for tropic acid Ladenburg, in 1884, made known a series of synthetical alkaloids, to which he gave the name tropeïnes, of this series tropine being the common basic constituent. Homatropine ($C_{16}H_{21}NO_3$) he obtained by the action of tropine upon mandelic acid ($C_6H_5.CHOH.COOH$) in the presence of hydrochloric acid

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1.23.2.16 Caffeine

Caffeine is a bitter, white crystalline xanthine alkaloid that is a psychoactive stimulant drug. Caffeine was discovered by a German chemist, Friedrich Ferdinand Runge, in 1819. He coined the term kaffein, a chemical compound in coffee (the German word for which is Kaffee), which in English became caffeine. Caffeine is found in varying quantities in the beans, leaves, and fruit of some plants, where it acts as a natural pesticide that paralyzes and kills certain insects feeding on the plants. It is most commonly consumed by humans in infusions extracted from the cherries of the coffee plant and the leaves of the tea bush, as well as from various foods and drinks containing products derived from the kola nut. Other sources include yerba mate, Guarana berries, and the Holly. In humans, caffeine is a central nervous system (CNS) stimulant, having the effect of temporarily warding off drowsiness and restoring alertness. Beverages containing caffeine, such as coffee, tea, soft drinks, and energy drinks, enjoy great popularity. Regular users develop a strong tolerance to this effect, and studies have generally failed to support the common notion that ordinary consumption of caffeinated beverages contributes significantly to dehydration.

1.23.2.17 Lotus

Lotus seeds are classified as astringents, being sweet and neutral, and benefiting the spleen, kidney, and heart. The sweet taste and nourishing qualities of the seed are responsible for the benefit to the spleen; this helps stop diarrhoea associated with qi deficiency. The astringent quality helps prevent loss of kidney essence, so the seeds are used to treat weak sexual function in men and leucorrhoea in women. The seed also has calming properties that alleviate restlessness, palpitations, and insomnia. As an example of a therapy for diarrhoea, one ounce of lotus seed is soaked in warm water for a few hours, then an adequate amount of rock sugar is added (to taste), and the mixture is simmered until the lotus seeds are well done. To this thick soup a cup of tea-made by steeping 5 g of black tea in boiling water-is added to yield the medicinal food. Inside the seed there is a green embryo that is quite bitter; it is usually removed before the seed is provided as a food product. The embryo (lianzixin; heart of the lotus seed), is classified as bitter and cold and benefiting the heart; it dispels pathogenic heat from the heart to treat fidgets and spontaneous bleeding due to heat. The bitter components are isoquinoline alkaloids with sedative and antispasmodic effects. The alkaloids dilate blood vessels and thereby reduce blood pressure. (68-74)

Small amounts of the alkaloids are found in the seeds with embryo removed, and these may contribute an antispasmodic action for the intestines, helping to alleviate diarrhoea. The lotus leaves (heye) are also bitter, but neutral, and are said to benefit the stomach, spleen, and liver. They are used for treatment of summer heat syndrome and dampness accumulation; they also contain the lotus alkaloids with hypotensive effect. Lotus leaf has become popular for lowering blood lipids and treating fatty liver; it is commonly combined with crataegus, which promotes blood circulation and lowers blood fats, for that purpose. Lotus stems (hegeng) are used medicinally in the same way as the leaves for treatment of summer heat and are used also to treat tightness in the chest due to obstruction of qi circulation. Lotus stamen (lianxu) is sweet, astringent, and neutral, benefiting the heart and kidney; it is mainly used for preventing discharge, such as treatment of leucorrhoea or for frequent urination. It contains flavonoids and a small amount of alkaloids. Lotus nodes, the rhizome nodes (oujie), are astringent and neutral, benefiting the liver, lung, and stomach. They are mostly used to control bleeding. All the parts of the lotus have some ant hemorrhagic effect, but the rhizome nodes are relied upon for that purpose specifically. The active component for reducing bleeding is not yet established, though quercetin and other flavonoids (figure 29) may play a role by improving capillary wall strength. By charcoaling the lotus plant parts, as is sometimes done, a haemostatic effect is assured, as charcoal itself has this effect (it promotes blood coagulation).

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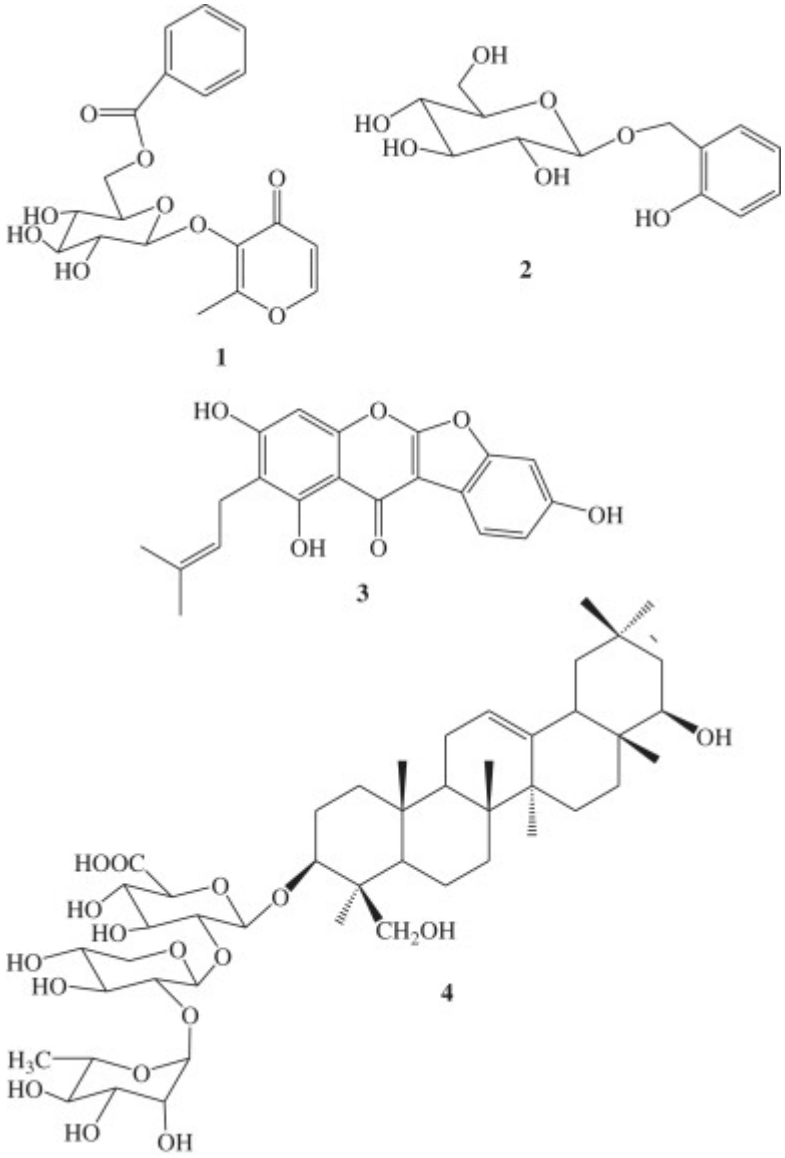

Figure.29 Chemical constituents of lotus Pusillus medic

1.23.2.18 Nicotine

Nicotine (figure 29) is an alkaloid found primarily in leaves of the tobacco plant (Nicotiana tabacum). Although it is a stimulant, it can produce either relaxation or arousal, depending on the user's state. Users commonly burn the leaves and inhale the smoke; some, however, may chew the leaves, while others either "snuff" finely ground leaves into their noses or place them between their cheeks and gums.

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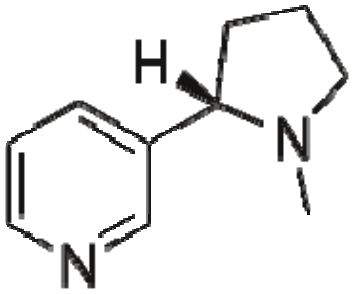

Figure.30 Nicotine

Nicotine (figure 30) is so highly addictive that the American Psychiatric Association includes it in their diagnostic manual under substance dependence. Nicotine addiction is also very difficult to break. To relieve the physical and psychological symptoms of nicotine withdrawal restlessness, anxiety, irritability, depression, difficulty in concentrating, and a craving for the drug, Pharmaceutical companies now offer nicotine replacement systems such as the nicotine "patch" and gum. These systems deliver nicotine in a less addicting pattern that allows the dose to be gradually decreased and eventually eliminated. Two drugs clonidine, and the antidepressant bupropion (Wellbrutin) have been approved by the Food and Drug Administration to help people quit. Like most alkaloids, nicotine exerts its effects at receptors for chemicals that transmit nerve impulses. Nicotine acts at the nicotinic receptor class for the transmitter acetylcholine. These effects largely account for nicotine's unfavorable impact on the user's health. People pay a great deal of attention to the danger of lung cancer, which results when smokers inhale cigarette smoke. While nicotine in itself is not carcinogenic, cigarettes and tobacco products contain more than 4,000 different chemicals, 60 of which are known carcinogens, and account for approximately one in every seven deaths in the United States, and one in three between the ages of 35 and 70 primarily due to cancers and cardiovascular diseases. Nicotine does, however, constrict small arteries, which raises the blood pressure and makes the heart work harder. It also makes the heart beat faster, yet, because it constricts the arteries supplying the heart muscle, the organ receives less blood. When build-ups of fatty plaque have already narrowed heart arteries, this may be enough to trigger heart pain (angina) or heart attack. Also, elevated blood pressure greatly increases the risk of stroke. Nicotine causes circulatory problems, particularly affecting the hands and feet, and causes some men difficulty in obtaining an erection. On the other hand, nicotine may have beneficial properties: for some users, it inhibits the appetite and slightly speeds up the body's metabolic rate, helping to keep weight down. Also, research has shown smokers appear to have a decreased risk of Parkinson disease

1.24 Allopathic uses for Belladonna

Belladonna is given in small amounts for over the counter flu and cough medicines .Eye doctors also use this drug in small amounts to dilate pupils. Belladonna is often combined with other drugs to treat patients. Examples of this are Donnatal. Donnatal is a prescription drug that provides peripheral anticholinergic/antispasmodic action and mild sedation. It contains natural belladonna alkaloids combined with Phenobarbital. The drug is considered possibly effective for the treatment of irritable bowel syndrome and acute enter colitis and as an adjunctive therapy in the treatment of duodenal ulcers.

1.25 Homeopathic uses for Belladonna

Hanhemann proved this remedy in 1799 and used it to treat scarlet fever. Belladonna is used to treat conditions with a sudden onset. The types of conditions Belladonna treatments are similar to the symptoms if someone is poisoned with Belladonna. Belladonna poisoning results in people getting a high fever, sore throat or loss of voice, nausea, delirium, muscle spasms, flushed skin and dilated pupils. Homeopathic Belladonna is used to treat these types of conditions in a person.

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[5]Homeopathic Belladonna is also used to treat cold and flu symptoms, infections with inflammation, intense pounding headaches, boils, earaches, seizures, labor pain, pink eye, nose bleeds, nephritis(inflammation of the kidneys) restless sleep, teething pain, tonsillitis, acne and sunburn. Female use Belladonna to treat breast infections, urinary bladder infections, menstrual cramps, and irritated nipples due to breast feeding.

Natural Products in Medicine

Because natural products are most important in the areas of anti-infective and anticancer agents, some of the important contributions to these drug classes are worth closer inspection. In particular the anticancer drugs will be examined, as that is the area of research that the Kingston group is concerned with. (75-77)

Natural Products and Anti-infective

The first real breakthrough in the field of anti-infective was the discovery of the β-lactam antibiotics such as penicillin G (figure 31). After its discovery it was suddenly possible to treat diseases that before had been untreatable and sometimes even deadly. The next breakthrough was the discovery of streptomycin. Streptomycin (figure 32) was the first antibiotic treatment for tuberculosis. These discoveries were followed by the discovery of the tetracyclines, chlortetracycline (figure 33), and the macrolide, which are best represented by erythromycin A (figure 34).

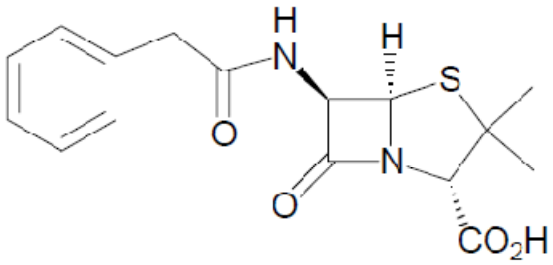

Figure.31 Penicillin G

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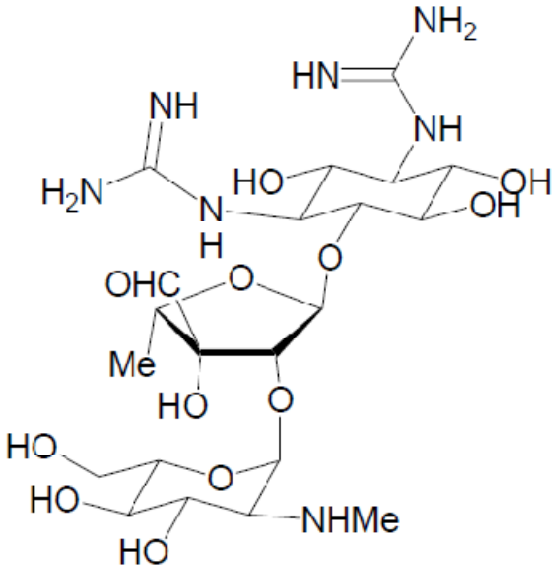

Figure 32 Streptomycin

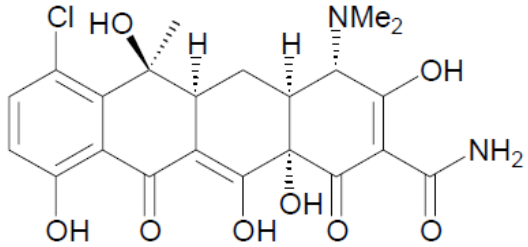

Figure.33 Chlortetracycline

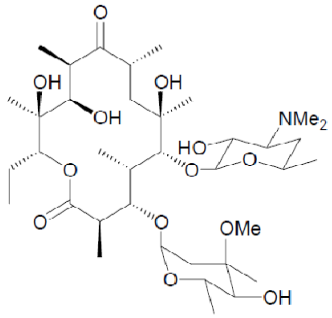

Figure.34 Erythromycin A

Natural products have also made an important impact in the area of ant malarial drugs. The first ant malarial drug was quinine (figure 35), which led to the development of other ant malarial drugs such as chloroquine (figure 36). The newest class of potential anti malarials are Peroxy Bridge containing compounds. The first compound of this class to be discovered was artemisinin (figure 37),

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which has been used for over 2000 years by the Chinese to treat malaria. The peroxy-bridge compounds, artemisinin in particular, show promise in treating cases of malaria that have become resistant to treatment with chloroquine.

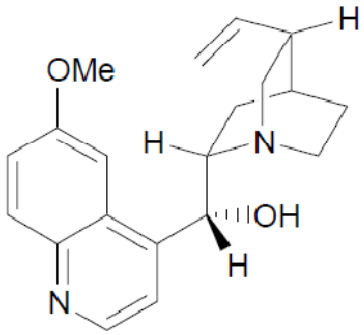

Figure 35Quinine

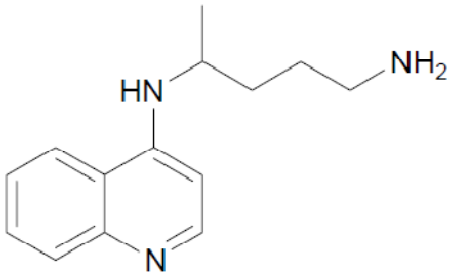

Figure 36Chloroquine

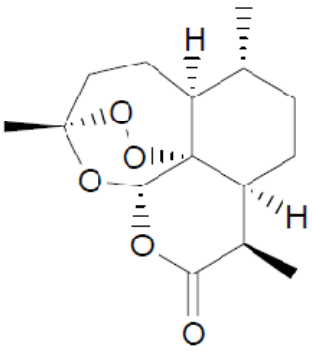

Figure.37 Artemisnin

Antiviral drugs have also relied heavily on natural products as drugs and/or leads. Spongouridine (figure 38) and spongothymidine (figure 38) led to the discovery of the anti-HIV drug AZT (figure 38). In fact spongouridine and spongothymidine can be thought of as the precursors of all nucleoside drugs. (75-77)

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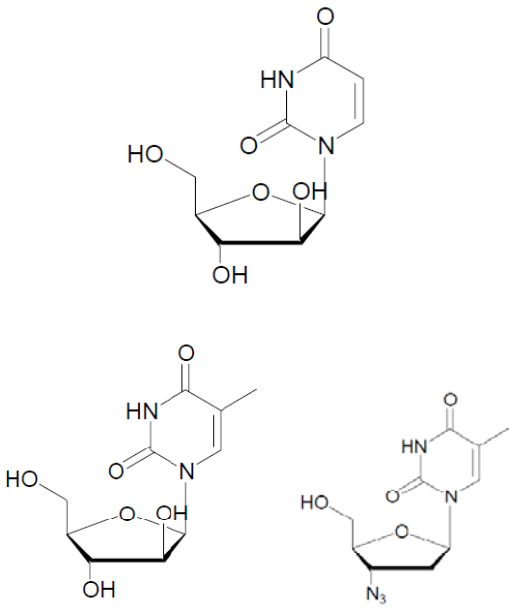

Figure.38 Spongouridine, spongothymidine, AZT

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