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Natural Products with Special Reference to Pharmacological Effects of Flavonoids : A Mini Review

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Abstract: Natural products once served as the only source of medicines for mankind. The structure determination and biological activity screening of natural products, especially those with a history of medicinal use taking clues form folklore medicine, Ayurveda, siddha, tribal medicine etc., has been an important activity in medicinal chemistry. Flavonoids are a group of polyphenolic compounds found in plant kingdom.To date about 3000 varieties of flavonoids are known. Many have low toxicity in mammals and some of them are widely used in medicine for maintenance of capillary integrity.
Key words: Natural products, flavanoids, pharmacological properties.

Introduction

Over three quarters of the world population relies mainly on plants and plant extracts for health care. Natural products once served as the only source of medicines for mankind. The structure determination and biological activity screening of natural products, specially those with a history of medicinal use taking clues form folkore medicine, Ayurveda, siddha, tribal medicine etc., has been an important activity in medicinal chemistry. These natural products are having varied biological activity. Discovery and development of new therapeutic agent is a continuing process. Inspite of the fact, at present we have at present we have at our command a formidable array of modern drugs[1], the need to discover and invent new agents is genuine and primordial. It has been estimated[2] that only about one third of all know diseases have satisfactory therapy. In addition, drug resistant strains of microbes are throwing challenges to the drug development. It is being predicted that, clue to several other reasons including global warming; infectious diseases may become one of the main scourges of mankind in the near future. Several strategies have been or being exploited to discover and invent new therapeutic agents[3]. More than 120 important prescription drugs are derived from plants[4]. Most of these drugs were developed because of their use in traditional medicine. Recent WHO studies indicate that over 30 percent of the worlds plant species have at one time or another been used for medicinal purposes. Of the 2,50,000 higher plant species on Earth, more than 80,000 species are medicinal. About 8000 herbal remedies have been codified in Ayurveda, which is still in use in may dispensaries today.

For a long time, the only way to use plant medicine was either direct application or the used of crude plant extracts. Now it is possible to rapidly build up extensively libraries of certain classes of organic compounds by the method of combinatorial chemistry. The structure determination and synthesis of natural products has received attention only during the early 19th century and extensive investigation of medicinally useful natural products is still in progress. Exploratory screening of medicinal or poisonous plants of Tropical

forests, marine flora and fauna, soil samples, fungi and microbes is conducted either to discover a new drug or a lead structure. A lead is a prototype compound for a given biological activity, for example, for antitumor activity, a natural product lead structure is subjected to chemical modification to arrive at the therapeutically important molecular fragment, the pharmacophore. Only a few natural products are directly used as drugs but in many cases the chemical modification of the lead structure gave a more potent synthetic or semi synthetic analogs. Table-1 presents some of the clinically very important natural product drugs, lead structures. Synthetic or semi synthetic analogs.

Table-1: Natural Products drugs, Leads and their Semi synthetic or synthetic analogs.

Natural Product drugs or Lead	Source	Drug Activity	Synthetic or Semisynthetic analogs
Atopine	Atropa belladonna	Anticholinergic	-
Benzyl penicillin	Penicillium Chrysogenum	Antibiotic	Ampicillin Amoxycillin
Codeine	Papaver somniferum	Analgesic	Nalarphine Meperidine
Cephalosporin	Cephalasporium acremonium	Antibiotic	Cephalexin Cephadroxil Cefachlor Cephatrioxone
Camptothecin	Camptotheca accumnata	Anticancer	10-hydroxy comptothesin, 9-amino camptothesin, Topotecan Ironotecan
Digoxin	Digitalis Lantana	Cardiovascural	-
Ephedrine	Ephedra Vulgaris	Antiasthama	Salbutamol Salmeterol
Khellin	Amni visinaga	Brochias asthama	Sodium chromoglycate
Lovastatin	Aspergillus terreus	Hypercholesterolemia	Prarastatin
Morphine	Papaver somniferum	Analgesic	Herion Naxoxane
Podophyllotoxin	Podophillum peltatum	Anticancer	Etopside TEniposide
Quinine	Cinchona succirubra	Antimalarial	Chloroquine Meploquine Pamaquine Primaquin
Reserpine	Rauwolfia serpentina	Hypotensive Anticholinergic	-
Tubacurarine	Tubocurare	Neuromuscular blocking agent	Decamethoxium Soxamethonium Laudexim
Teprotide	Bothrops Javaraca	Antihypertension	Captropril Enalapril Lisinopril Ramipril
Vinblastin	Catharanthus roseus	Anticancer	Vindesine
Vincristine	Catharanthus roseus	Anticancer	-

Natural products when directly used as drugs are highly effective, free from side effects and chronic toxicity. The main disadvantage in the use of natural product drugs is that of short or limited supply and the complex chemical structure, which makes their manufacture impossible. Hence, semisynthetic analogs are being synthesized. Analog design includes synthesis of analogs, structures of lead with variation of branches, chain length increase or decrease, variation of the kind and position of the substituents, the replacement of rings by similar cyclic structures and empirical modification within the frame work of reasonably close analogy. Functional groups in the lead are replaced by similar size, shape and reactive groups, the changes are known as biosteric replacements[5]. ASAR studies are made to find the relationship between the substituent introduced and the drug potency of the analog. Many of the structure alterations are dictated by synthetic accessibility in a given lead series. The same technique of analog design are followed even in the case of a synthetic lead structure modification. In the studies the success rate to discover any new drug is 1:10,000. However, the modification of the natural or synthetic lead by design of analogs is still the principal approach by the pharmaceutical companies to discover a new drug structure. It is a monument to human patience that many valuable drugs have been discovered by this method.

In India about 20% of the drugs sold are plant derived and are particularly useful to treat chronic diseases of liver, kidney and skin. People prefer Ayurvedic or heral medicines, as they have practically no side effects, cheaper and equivalent medicines in allopathy are not available. There is a renewed interest world wide and in India in particular after the GATT agreement to discover new plant based drugs in view of diverse vegetation here. Several major Indian pharmaceutical companies have embarked on ambitious programmes to screen indigenous plants with a view to discover new drugs or lead structures and develop their synthetic analogs as drugs. There are 119 drugs of known structure that are still extracted form higher plants and used globally. It is estimated that 60% of anti-tumor and anti-infectious drugs already in the market or under clinical trial are of natural origin and the vast majority of these molecules cannot yet be synthesized economically and are still obtained from wild or cultivated plants[6]. The isolated compounds artemisinin, taxol and camptothecin are examples of natural products that are undergoing clinical trial and commercial development. Several natural products isolated form plants used in traditional medicine have potent antiplasmodial action in vitro and represent potential sources of new antimalarial drugs[7]. In addition to above all a good number of novel plant derived substances have entered into western drug markets and clinical plant based research has made a rewarding progress in the important fields particularly in anticancer and antimalarial therapies[8].

Over the last decade, interest in drugs of plant origin has been growing very fast and currently, there is a world-wide upsurge in the use of herbal preparations and active ingredients of medicinal plants in health care. The consumption of medicinal plants has almost doubled in Western Europe in recent years. The ecological awareness and an increased demand for one-classical therapies may be invoked as the main reasons for this renewal. Equally, the efficacy of a number of phytopharmaceutical preparations, such as aloe, ginko, garlic or valerian, has been demonstrated by studies that applied the same scientific standards as for synthetic drugs. As a result of all these reasons, there is enormous market for crude herbal medicines in addition to purified plant derived drugs[9]. The clinical applications of taxol, etoposide and artemisinin have helped to revive an interest in higher plants as sources of new drugs. Though there is a considerable development in medicinal field there still remains an urgent need to develop new clinical drugs for numerous diseases which result from the malfunction of the central nervous systems (CNS), e.g. Parkinson's disease, Alzeimers, epilepsy, migraine, pain, schizophrenia, sleeping disorders, ets. Natural products have already proven a track record for CNS activities, e.g. caffeine, codeine, morphine, nicotine, reserpine and it is possible that there are further such drugs still to be found from nature[10]. During recent years the attention of pharmaceutical industry has switched once more to natural world and this may be illustrated by reference to three clinical drugs taxol, etoposide and artemisinin. They are giving much importance to natural product research especially herbal products to find the lead molecules for various diseases. Besides, these industrial research, many institutes and Universities are also concentrating much on herbal product research e.g., National Cancer Institute, USA[6].

Large pharmaceutical companies are studying new drugs from natural sources[6]. Glaxo company is well known for the production of drugs in bulk which are identified as drugs from natural products e.g. penicillin, vitamin B_{12}, etc., and it is giving much importance to further natural product research[11]. The potential use of higher plants as source of new drugs is still poorly explored. Of the estimated 250,000-500.000 plant species, only a small percentage has been investigated. it is estimated that only 5000 species have been studied for medicinal use[6,9]. It is logical to presume that many more useful drugs will be found in the plant kingdom if the search for these entities is carried out in a logical and systematic manner[12].

Flavanoids

Flavonoids are a group of polyphenolic compounds found in plants. So far about 3000 varieties of flavonoids are known[13]. Many have low toxicity in mammals and some of them are widely used in medicine for maintenance of capillary integrity[14].

Pharmacological effects of flavonoids:

1. CNS activity:

Synthetic flavonoids like-6 bromoflavone and 6-bromo-3-nitro-flavones were shown to displace [3H] flumazenil binding to membranes from rat cerebellum but not from spinal cord, indicating selectivity for the Bz-Omega receptor subtype, but later was very potent than 6-bromoflavone. These synthetic flavonoids possess anxiolytic like properaties similar or superior to that of diazapam[15].

2. Cardiotonic Activity:

Flavonoids have been reported to have action on the heart. The unsubstituted parent flavones exerts coronary dilatory activity and was commercially available under the name 'chromocor' and its combination with routine and isoquercetin was also available with brand name 'flavoc' usful in the treatment of atherosclerosis. 3-methyl quercetin has positive chronitropic effect on guinea pig right atrium and anti arrhythmic effect on left artium[16]. In recent report the carditoxicity (negative inotropic effect) of doxorubicin on the mouse left atrium has been inhibited by flavonoids, 7-mono hydroxyl ethyl rutoside and 7,3',4' trihydroxy ethyl rutoside. Huesken et al. gave detailed discussion on the cardioprotective effects of flavonoids[17]. Different flavonoids were tested for a positive inotropic effect on guinea pig papillary muscle. Quercetin showed the most potent intrinsic activity and produced the strongest inotropic response among the different flavonoids. The relative order of potency of the tested lavonoids was, quercetin, morin, kaempferl, luteolin, apigenin, fisetin, galangin[18].

3. Lipid lowering Activity:

Oxidative modification of low-density lipoproteins (LDL) by free radicals is an early event in the pathogenesis of atherosclerosis. A number of mechanisms are likely to contribute to inhibition of LDL oxidation by quercetin glycoside flavonoids[19].

4. Antioxidant activity:

Free radical production in animal cells can either be accidental or deliberate. With the increasing acceptance of free radicals as common place and as important biochemical intermediates, they have been implicated in a large number of human diseases[20]. Quercetin and silybin are found to be free radical scavangers[21]. The scavenging activity of flavonoids has been reported to be in the order: myrecetin > quercetin > rhamnetin > morin > diosmetin > naringen > apigenin > catechin > 5,7 – dihydroxy -3',4',5' trimethoxyflavone > quercetin have also been suggested as stabilization for fish oil, an alternative to synthetic antioxidants[23].

5. Antinflammatory acivity:

A number of flavonoids are reported to possess anti-inflammatory activity. Hesperidin possess significant anti- inflammatory and analgesic effects[24]. Recently, apigenin, luteolin and quercetin have been reported to exhibit anti- inflammatory activity. Treatment with silymarin demonstrated reversal of the carrageenin induced biochemical changes. Detailed biochemical studies to establish mechanism of action of flavonoids have been carried out[25].

6. Antineoplastic activity:

Quite a number of flavonoids have exhibited antineoplastic activity. Recent reviews highlighted this activity[26]. Quercetin exerted a dose dependent inhibition of cell growth and colony formation. Kaempferol, fisetin, catechin, toxifolin also suppressed cell grouth[27].

7. Hepatoprotective activity:

Many flavonoids like silymarin, apigenin, quercetin and naringenin have also been found to posses hepatoprotective activity[28].

8. Antimicrobial Activity:

Quercetin and kaempferol are known to be the most common flavonols present in many plants and have been proved to possess antimicrobial activity[29,30,31] . chrysin[33,34,35] were found to be active against streptococcus species. Antifungal activity was exhibited by quercetin[36] against Candida albicans and Candida tropicalis. Where as rutin[37] apigenin[38] were active against other fungal species.

Antiviral, including anti-HIV activity was also displayed by flavonoids. It has been found that flavonols are more active than flavones against herpes simplex virus type-I and the order of importance was galangin>kaempferl>quercetin[39]. Recently, a natural plant flavonoid polymer of molecular weight 2100 Daltons was found to have antiviral activity against two strains of type-I herpes type simplex virus, including a thymidine – kinase deficient strain and type-II herpes simplex virus[40]. Out of the flavonoids tested, flavan-3-ol was more effective than flavones and flavonones in selective inhibition of HIV [41].

9. Biochemical effects of flavonoids:

Flavonoids are known to inhibit a number of enzymes such as aldose reductase[42], lipo-oxygenase[43], and cyclo-oxygenase[44]. Myricetin, and kaempferol inhibit the activity of the adenosine deaminase[45]. Quercetin, morin, myricetin and kaempferol are effective in antagonizing bradykinin responses[46].

10. Antiulcer activity:

Some recent repors have indicated that many flavonoids possess antiulcerogenic activity. B hygroxy ethyl rutosides, gossypin, naringin, naringenin and (+) cyanidanol-3 were shown to exhibit antiulcer activity. Particular interest has been accorded to the gastric antiulcer action of flavonoids. It has been shown that hypolactin-8- glucoside[47], amentoflavone[48] and quercetin[49] possess decrease histamine secretion form mast cell by inhibition of histidine decarboxylase[50].

Table 2. Subclasses of Flavonoids[32]

Flavonoid subgroup	Representative flavonoids
Flavonols	Kaempherol, myricetin, quercetin, rutin
Flavones	Apigenin, chrysin, luteolin
Isoflavones	Daidzein, genistein, glycitein,formonone
Flavanols	Catechin, gallocatechin
Flavanones	Eriodictyol, hesperitin, naringenin
Flavanonols	Taxifolin

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