Pharmacological properties of flavonoids including flavonolignans – Integration of pетrocrops with drug development from plants

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Received 10 September 2004; revised 15 March 2005; accepted 16 February 2006

Flavonoids possess antioxidant, radical scavenger, antileukemic and vasodilator activity. These may be useful for improving blood circulation in brain and in Alzheimer disease. Flavonoids also show anti-cancer, anti-ageing and antibacterial properties. Flavonolignans are a class of compounds where the properties of flavones and lignans may synergise. The review presents the pharmacological activities of some of the flavonolignans including author’s research work in this area. There may be a wide scope of integrating the pharmaceutical industries especially those based on natural products, with the fuel and energy industries dealing with the production of petroleum hydrocarbons, biodiesel, lubricating oils, alcohols, glucose and glucose based value added chemicals and materials, xylose and xylose based value added chemicals and materials, lignin based aromatic and heterocyclic chemicals etc.

Keywords: Drugs, Flavonoids, Flavonolignans, Medicinal plants, Natural products, Petrocrops

IPC Code: A61K31/60

Introduction

An extensive research work is available on isolation and characterization of flavonoids from plants. Flavonoids possess potential pharmacological activities such as antioxidant activity, vitamin C sparing activity, and the activities of 5-lipoxygenase, cyclo-oxygenase, protein kinase C, tyrosine kinase, genetic toxicity etc. Flavonoids have free radical scavenging and antioxidation properties, which are useful for their pharmacological activities including anticancer and anti-ageing properties.

Flavonoids show interactions with cytochrome P 450, antileukemic properties, and mild vasodilators properties useful for the treatment of heart diseases. The leaf extract of Ginkgo biloba containing flavonoids (including biflavones) was used for improving blood circulation in brain varix and several isoflavones were also used for improving blood circulation. Several furanocoumarins were also found to alter hexobarbitol-induced sleeping time comparable with the model drug, and showed cytotoxic action and significantly inhibited the growth of tumor in mice. Some coumarins such as columbianetin, columbianadin, osthol, etc. have been reported to inhibit ADP – induced platelet aggregation. Furanocoumarins, psoralen and xanthotoxin, were found to be toxic to human lung, breast and colon cancer cell lines.

Research in Chemistry of Natural Products and Drug Development

Phytochemistry reports thousands of newer organic molecules or compounds every year. Pharmacological testing, modifying, derivatising and research on these natural products represent a major strategy for discovering and developing new drugs. The use of medicinal plants for the treatment of human diseases is well known and is practiced in Ayurveda since ancient times.

Pharmacokinetics and pharmacodynamics are important studies from the drug development to clinical trials. However, studies on toxicity, chiral separation and activity and development of convenient synthesis and cleaner manufacturing process are also important. Traditionally, medicinal plants have already provided leads for potential antiparasitic, antifungal, antiviral and antibacterial compounds including flavonoids, coumarins, naphthoquinones, terpenoids, alkaloids, steroids, etc. Combinatorial chemistry has helped in development...
of a series of similar but homologous structural compounds for testing.

Synthetic chemistry, catalysis, fermentation, enzymology, chiral chemistry and engineering, molecular reaction dynamics, quantum chemistry, high temperature and high pressure induced catalytic reactions afford the development of novel and unique chemical compounds with novel structures, conformations and configurations. Such compounds and their modified derivatives may be studied for pharmacological properties and may form basis for novel drugs. A mixture of different plant extracts and even a mixture of different potent compounds may also prove to be a different wonder drug and research may be extended in this direction. Discovering newer molecular structures from natural biomass sources from nature remains a major challenge and source of novel opportunity in combinatorial chemistry, drug designing, bioinformatics, genomics and bioenergetics, etc. Biosynergistic use of these compounds formulations may lead to fight different diseases through a series of metabolic biochemical reactions including bioenergetics. Synthetic chemistry, manufacturing engineering and process development engineering work may be required for the commercialization of the drug.

Antibacterial Activities of Flavonoids and Related Compounds

Coumarin osthol\textsuperscript{21} shows antibacterial activity against some bacteria and fungi\textsuperscript{11}. Flavonoids (rutin, naringin, baicalin) possess antibacterial activity\textsuperscript{11}. Rutin shows antiviral and anti-inflammatory properties and weak antibacterial activity\textsuperscript{22}. Baiculin showed good antibacterial properties\textsuperscript{11}. Chalcones, 1–(2-hydroxyphenyl)–3–(3–chlorophenyl)–2–propen–1–one and 1–(2 hydroxyphenyl)–3–(iodophenyl)–2–propen-1-one, showed inhibition (\textgeq 90\%) of \textit{Mycobacterium tuberculosis} H 37 Rv\textsuperscript{23}. Some chalcone like compounds with heterocyclic rings showed even higher inhibition (\textgeq 95\%) as an anti-tuberculosis agent.\textsuperscript{23} Flavones and flavonones were found to show lesser anti-tuberculosis activity.

Flavonoids, 5, 7, 4–trihydroxy–6–[1–hydroxyl–2–methylbuten–2–yl] isoflavone (isogannaconin C), 7, 2′–dihydroxy–4′–methoxy–isoflav–3–ene (bolusanthin III), 6, 6′–dihydroxy–4′–methoxy–2–arylbenzoferan (bolusanthin IV) in addition to some known flavonoids (derrone, medicarpin, genistein, weighteone, lupiweighteone, gancaonine C etc.), isolated from the roots of woody biomass of \textit{Bolusanthus speciosus}, showed strong antimicrobial activity against \textit{Escherichia coli}, \textit{Bacillus subtilis}, \textit{Staphylococcus aureus} and \textit{Candida mycoderma}. These compounds also showed radical scavenging properties\textsuperscript{24}, which may be helpful in anti-ageing studies as well.


Extracts from Ginkgo leaves (\textit{Ginkgo biloba} L.), one of the top selling plant derived medicines in the USA and Europe\textsuperscript{26}, are widely used for treating cerebral insufficiency, against memory loss and as a potential drug for Alzheimer’s disease. The major markers in Ginkgo are gingolides, bilobalide and flavonoids\textsuperscript{26}, besides biflavonoids. A validation method based on GC-MS for simultaneous identification and quantification of marker compounds in \textit{G. biloba} extract and pharmaceutical preparations have been developed and reported\textsuperscript{26}.

Infectious diseases are world’s leading cause of premature deaths and the number of such diseases keep on increasing. In fact, once a few diseases are eradicated or eliminated, others are added such as HIV-AIDS, SARS, etc. Almost 50,000 people die every day\textsuperscript{27}. In recent years, drug resistance to several human pathogenic bacteria has been reported world over for various diseases. The situation may become more alarming due to indiscriminate use of antibiotics for a different length of time. Thus there is a need for newer antimicrobial compounds having broad-spectrum activity.

The drug resistant bacteria and fungal pathogens may further complicate the treatment of infectious diseases in immuno compromised, AIDS, cancer, chronically weak patients. The emergence of multiple drug resistance to human pathogens has necessitated
Pharmacological Properties of Flavonolignans

Lignans and flavonoids are found in high concentration in whole grains, legumes, fruits, vegetables, seeds etc. The lignan enterolactone and its precursors, 3′–dimethoxy–3-O-dimethyl matairesinol and didemethoxyxymatairesinol, and flavonoids, coumestrol, luteolin and kaempferol were found to decrease the aromatase activity. Consumption of lignan and flavonoid-rich plant foods may contribute to the reduction of estrogen dependent disease, such as breast cancer. The micro-capsules, prepared by interfacial cross-linking of flavonoids for preventing discoloration, while maintaining both the anti-free radical and antioxidative activity of the flavonoids may be incorporated in a cosmetic, pharmaceutical, dietary or food composition. Some medicinal properties of lemon are due to flavonones, hesperidin and eriocitrin, and flavone, diosmin. Effect of plant flavonoids on immune and inflammatory cell functions and the role of phytochemicals in improving age-related neurological dysfunctions have been studied.

Flavonolignans result by coupling of a flavonoid with a C9 precursor like coniferyl alcohol. Silymarin was the first member of this new class of compounds isolated from seeds of Silybum marianum. The other flavonolignans identified were silydianin, silychristin, dehydro-silymarin, and 2,3-dehydro-silychristin. Wagner et al. studied antihepatotoxic effects of silymarin on lipid metabolism in rats disturbed by phalloidin intoxication. Silymarin-N-methyl glucoun unit 51148-13-1 when administered to rats with phalloidin prevented liver disturbances in liver lipid metabolism produced by phalloidin. Silymarin was marketed in West Germany as a drug against liver diseases.

Seed hulls of Hydnocarpus wightiana contain flavonolignans: hydncarin, 0.08; methoxyhydncarin, 0.03; isohydncarin, 0.03; hydnowighton, 0.05; and neohydncarin, 0.04%. Hulls also contain flavonoids, apigenin, chrysoeriol and luteolin, besides β-sitosterol, lupeol, β-amyrin, betulinic acid and sitosterol-β-D-glucoside. H. wightiana oil (non edible) may be studied for use as biodiesel directly or through trans-estrichification or as a renewable source of lubricating oil. Flavonolignans, hydnowighton, hydncarin and neohydncarin, showed potent hypolipidemic activity in mice.
lowering both serum cholesterol and triglyceride levels\(^{58}\), besides good activity against human KB nasopharynx, colon adenocarcinoma and Hela S uterine growth. Hydnocarpin demonstrated the best lipid lowering effect moderately active against murine L-1210 leukemia growth\(^{58}\). Good anti-inflammatory and antineoplastic activity were demonstrated by hydnocarpin in mice in vivo. Cytotoxicity against the growth of murine and human tissue cultured cells was shown. Pharmacological activities of flavonolignans may be due to the fact that both flavonoids as well as lignans had demonstrated pharmacological activities individually as the class of compounds separately. Hydnocarpin was found active against glioma growth. Hydnocarpin and neohydncarpin demonstrated significant activity against Tmolt, leukemia cell growth\(^{58}\).

Petrocrops such as *Calotropis procera*, *Euphorbia lathyris*, etc. may not only afford the production of flavonoids and other natural products but petroleum hydrocarbons also\(^{49-57}\). The residual lignocellulosic biomass of petrocrops and biodiesel producing seeds, remaining after the extraction of flavonoids, coumarins, etc., consists of biopolymers such as hemicellulose, cellulose, lignin, etc., which may be exploited to yield xylose and xylene based value added chemicals, furfural, alcohols, glucose and glucose based value added chemicals, products such as alcohols, acetone, laevulenic acid, aromatic alcohols, dimethyl sulphoxide, heterocyclic compounds etc\(^{49-57}\).

**Future Scope of Flavonolignans**

Flavonolignans have been identified in *Sasavetchi Rehder*\(^{59}\), *Hyparrhenia hirta*\(^{60}\) and *Distemonanthus benthamianus*\(^{61}\). Pharmacokinetic study on silybinins and the effect of silymarin on bile salt secretion in rat has been found\(^{62}\). Cytotoxic flavonolignans and flavones from *Verbascum sinaicum* leaves have been reported\(^{63}\). This has shown that there is still a considerable interest in the pharmacological studies of flavonolignans\(^{8,64,65}\) and further studies in this direction may be undertaken which may include the studies on antimicrobial properties of flavonolignans and their derivatives. Flavonolignans may be synthesized by oxidative coupling reactions\(^{56,67}\). Further studies may be extended by either isolating or synthesizing the flavonolignans such as hydnocarpin, hydnowightin, neohydncarpin, etc. Pharmacological properties of these flavonolignans along with antimicrobial properties may be studied. There is also a scope for chiral engineering in the chiral separation of flavonolignans by using lipase enzyme or by column chromatography or chiral synthesis. The S-, N- and O-heterocyclic compounds present in lignins or other sulphonates, lignites, coals and crude oil may be studied for their pharmacological and antimicrobial properties.

**Integrated Process to obtain Petroleum and Medicines from Petrocrops**

Petrocrops (laticiferous and resinous plants) and seeds and seed coats are storehouses of flavonoids, coumarins, flavonolignans, lignans, alkaloids, etc. Some of these had already been used as local folk medicines\(^{33}\). Studies may be extended on the potential petrocrops and non-edible seeds for exploring the possibility of obtaining not only petroleum, lubricating oil, biodiesel but also medicines\(^{33,51,55,56,68}\). Petrocrops such as *C. procera*, *E. lathyris*, *Jatropha curcas*, *H. wightiana*, *L. camara*, *C. gigantea*, etc. may be studied further for obtaining petroleum hydrocarbons, lubricants, biodiesel, materials, value added chemicals and fuels along with medicinal products. *Spirulina* seems to be a good candidate for further research in the production of hydrogen, pharmaceuticals and other value added chemicals etc\(^{69}\).

**Emerging Trend of Research on Medicinal Plants and Need for Integration with Biofuels and Biomass Conversion**

It is estimated that plants produce at least 100,000 secondary constituents during their growth and development from more than 200,000 species of flowering plants\(^{70}\). The structure of more than 10,000 alkaloids\(^{71}\), 4,000 flavonoids\(^{72}\), 8,000 polyphenols\(^{73}\), 20,000 terpenoids\(^{74}\) etc. has already been elucidated. The progress of the discovery of new biological and medicinal agents from natural products has been reviewed\(^{75,76}\). In Ayurveda, plants form a dominant segment of pharmacopoeia\(^{77-90}\). Betulin from the bark of white-birch tree and its structurally modified analogues are being studied for the prostate cancer therapy\(^{78}\). NICOSAN/HEMOXIN, a formulation of four plants, showed a strong antiscickling effect\(^{79}\). *Podophyllum hexandrum* Linn (*Berberi daceae*), a
perennial herb, contains several lignans possessing anti-tumour activity and also used for the semi-synthesis of potent anti-cancer drugs. A bioactive coumarin from the bark of Sonneratia apetela has been isolated. COX-1 and COX-2 inhibitory flavonoids were isolated from Indigofera aspalathoides. T Cell suppression by a fraction from Euphorbia tirucalli has been reported. These studies were directed to investigate the effects of the biopolymeric fraction of this plant on the immune system in experimental animals. This plant is a petrocrop and contains bicoumarins. Few flavonoids and flavonoid glycoside dirhamnoside and a disaccharide galactomannan have been isolated from I. tinctoria. Vast literature is available on traditional medicinal plants which may be used for the drug discovery research. Curcumin from turmeric (Curcuma domestica) has been found to check the accumulation of β-amyloids that build up in the brains of Alzheimer’s disease–afflicted persons.

Thus plants can be put to medicinal use and also as petrocrops as a source of biodiesel and biolubricants. In fact, the residual or spent biomass (> 90%) obtained after the extraction or recovery of medicinal products may be used as a source of xylose, glucose, ethanol, aromatic chemicals, hydrogen, cellulosic, hemicellulosic and lignin products and chemicals etc. through biomass conversion technologies. Thus, future may see an integration of petrocrops, biodiesel (Jatropha curcas), biolubricants, hydrogen or cellulosic, hemicellulosic and lignin chemicals production with the recovery of drugs from the medicinal plants.

India is among 18 mega diverse countries, which control almost 70 percent of world bioresources. It seems that bioresources may replace oil as the most sought after natural resource. The present trade in bioresources plant genetic resources is estimated to be around 60 billion dollars and this may touch 1 trillion dollars by 2020. Medicines may be grown into plants in future directed natural photobiosynthesis in the farms in vegetables and fruits through genetic engineering. The spectacular research in medicinal field is progressing from human genome project to systems biology and employing nanosystems biotechnology towards individual (personal) medication. The studies of bioinformatics, protein-protein interactions, drug-drug interactions, genetic mutations (influencing infections and diseases in individuals), molecular fingerprinting of cell from a single drop of a blood, genes directed natural products based drugs etc. may help in controlling diseases in human and increase the human life span. There may be a different medicine for the same disease for different individuals dictated by examination of genetic, metabolic systems, natural and other drug reaction etc. Flavonoids may play an important role directly through derivatisation or functional or medicinal foods. The studies of chemistry, biochemistry and pharmacological properties of flavonoids may be important. These also possess antimicrobial properties against bacteria, but virus and fungi as well and have broad spectrum of activities against not only cancer but ageing as well.

Nandave et al reviewed cardioprotective property of flavonoids that possess wide spectrum of biological activities in cardiovascular and cancer, which include, free radical scavenging, antioxidant, anti-thrombic, antiapoptic, anti-ischemic, anti-arthrythmic, anti-hypertensive and anti-inflammatory activities. Major dietary sources of flavonoids in the form of flavonols, flavones, isoflavones, flavonones and flavononols are tea, red wine, apple, tomato, cherry, onion, thyme, parsley, soya beans and other legumes, grape fruit, orange, lemon and several other vegetables and fruits and trees such as Ginkgo and neem. There is still wide scope of research in finding out the beneficial effects of flavonoids. Research in author’s laboratory is underway to study the effect of different flavonoids in diseases such as pneumonia, prostate cancer and amoebic dysentery through bioinformatics studies of docking flavonoids on different protein structures involved in these diseases.

Conclusions
Flavonoids and flavonolignans may offer a great scope for the drug development in future. Production of medicines from plant biomass may also be integrated with biodiesel, alcohols, glucose, xylose, furfural, aromatic chemicals, hydrogen, etc. from the lignocellulosic biomass and plant extractives. Further R & D work may be extended to make the integrated processes cost effective.

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