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

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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

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Introduction

An extensive research work is available on isolation and characterization of flavonoids from plants[1-8]. Flavonoids possess potential pharmacological activities such as antioxidant activity, vitamin C sparing activity[9], and the activities of 5-lipoxygenase, cyclo-oxygenase[10], protein kinase C, tyrosine kinase, genetic toxicity[11] 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[11], antileukemic properties[12], and mild vasodilators properties useful for the treatment of heart diseases[12]. 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[11–13]. Several furanocoumarins were also found to alter hexobarbitol-induced sleeping time comparable with the model drug[14], and showed cytotoxic action and significantly inhibited the growth of tumor in mice[15]. Some coumarins such as columbianetin, columbianadin, osthol, etc. have been reported to inhibit ADP – induced platelet aggression[11]. Furanocoumarins, psoralen and xanthotoxin, were found to be toxic to human lung, breast and colon cancer cell lines[16].

Research in Chemistry of Natural Products and Drug Development

Phytochemistry reports thousands of newer organic molecules or compounds every year[17-20]. Pharmacological testing, modifying, derivatising and research on these natural products represent a major strategy for discovering and developing new drugs[17-20]. 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[20]. 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

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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[21] shows antibacterial activity against some bacteria and fungi[11]. Flavonoids (rutin, naringin, baicalin) possess antibacterial activity[11]. Rutin shows antiviral and anti-inflammatory properties and weak antibacterial activity[22]. Baiculin showed good antibacterial properties[11]. Chalcones, 1–(2–hydroxyphenyl)–3–(3–chlorophenyl)–2–propen–1–one and 1–(2 hydroxyphenyl)–3–(–iodophenyl)–2–propen–1-one, showed inhibition (>90%) of *Mycobacterium tuberculosis* H 37 Rv[23]. Some chalcone like compounds with heterocyclic rings showed even higher inhibition (>95%) as an anti-tuberculosis agent.[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 (isogancaonin C), 7, 2'–dihydroxy–4'–methoxy–isoflav–3–ene (bolusanthin III), 6, 6'–dihydroxy–4'–methoxy–2–arylbenzofuran (bolusanthin IV) in addition to some known flavonoids (derrone, medicarpan, genistein, weighteone, lupiweighteone, gancaonine C etc.), isolated from the roots of woody biomass of *Bolusanthus speciosus*, showed strong antimicrobial activity against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus* and *Candida mycoderma*. These compounds also showed radical scavenging properties[24], which may be helpful in anti-ageing studies as well.

Flavonoids[25], kaemferol 3–O–β–D–galactopyranoside, kaemferol 3–O–β–D–glucopyranoside, isorhamnetin 3–O–β–D–glucopyranoside, quercetin 3–O–β–D–glucopyranoside, quercetin 3–O–β–D–glucopyranosyl (6→1)-α-L–rhamnophyranoside, isolated from leaves of *Diospyros kaki* and tested on the stimulus induced superoxide generation and phosphorylation of tyrosine residues of protein in human neutrophilis, showed suppression activities. A protective effect for blood vessels may be expected from these flavonoids. "Kaki yo", a traditional medicine in Japan, is reported as a hyposensitive drug[25].

Extracts from Ginkgo leaves (*Ginkgo biloba* L.), one of the top selling plant derived medicines in the USA and Europe[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[26], besides biflavonoids. A validation method based on GC-MS for simultaneous identification and quantification of marker compounds in *G. biloba* extract and pharmaceutical preparations have been developed and reported[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[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

the search for newer molecules or compounds from other antimicrobial substances from other sources such as plants. Traditionally used medicinal plants in local folk medicines or in Ayurvedic or Unani system of medicines contain the compounds of known therapeutic properties. The natural products from medicinal herbs, shrubs, trees, including aquatic biomass, etc. which can either inhibit the growth of disease causing microbes or effects or kills the pathogens and may have no or least and manageable toxicity to host cells are the potential candidates for the systematic studies on the development of antimicrobial drugs to replace antibiotics or other drugs for which microbes have developed resistance.

Alcohol extracts[27] of 45 Indian medicinal plants were tested against following multi drug resistant bacteria: *S. aureus, Salmonella paratyphi, E. coli, Shigella dysenteriae* and *C. albicans*. Some of the plants were *Allium cepa.* L. (payaz), *Allium sativum* L. (lehsun), *Azadirachta indica* A. Juss (neem), *Emblica officinalis* Gaerth (amla), *Ficus religiosa* L. (pipal), *Eucalyptus sp.* (safeda), *Lantana camara* L. (ghaneri), *Hemidesmus indicus* R. Br. (anantamul), *Syzygium cuminii* L. (jamun), *Terminalia chebula* Retz. (harad), *Calotropis procera* L. (aak/madar), *Camellia sinensis* L. (chai), *Citrus sinensis* L. (musambi) and *Sapindus sp.* (ritha). About 40 alcoholic extracts showed antibacterial activity against one or more test bacteria. About 24 extracts showed anticandidal activity[27]. *Eucalyptus, L. inermis, H. antigysentrica, H. indicus, C. equisetifolia, T. belerica, E. officinalis, C. sinensis, S. aromaticum, P. grantum, Nigella sativa, Plumbago zeylanica, Allium sativum, Azadirachta indica, Lantana camara, Psidium guajava, Camellia sinensis, T. belerica, Zizyphus jujuba, Acorus calamus* and *O. sanctum* showed antimicrobial activity[27]. Presence of flavonoids along with other natural products has been reported from these plant extracts[27]. *Aloe vera* may be used against *Salmonella*, *Staphylococcus*, etc. It may also help in strengthening the immune system. Basil (*O. sanctum* L.), tulsi, leaves may be studied for antiviral, antibacterial and other medicinal activities. The study of synergistic interaction of active phytochemicals with antibiotics is required to be done[27]. This may help in exploiting their potential in the combination therapy for infectious diseases caused by multi-drug-resistant microbes.

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 didemethoxymatairesinol, and flavonoids, coumestrol, luteolin and kaemferol were found to decrease the aromatase activity[28]. Consumption of lignan and flavonoid-rich plant foods may contribute to the reduction of estrogen dependent disease, such as breast cancer[28]. 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[29], may be incorporated in a cosmetic, pharmaceutical, dietetic or food composition. Some medicinal properties of lemon are due to flavonones, hisperidin and eriocitrin, and flavone, diosmin[30]. Effect of plant flavonoids on immune and inflammatory cell functions[31,32] and the role of phytochemicals in improving age-related neurological dysfunctions[31] have been studied.

Flavonolignans result by coupling of a flavonoid with a C_9 precursor like coniferyl alcohol[33-38]. Silymarin was the first member of this new class of compounds isolated from seeds of *Silybum marianum*[39]. The other flavonolignans identified were silydianin[40], silychristin[41] dehydro-silymarin[42] and 2, 3-dehydrosilychristin[43] Wagner *et al*[34-38] studied antihepatotoxic effects of silymarin on lipid metabolism in rats disturbed by phalloidin intoxication. Silymarin-N-methyl gluconin 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[8,44-48] of *Hydnocarpus wightiana* contain flavonolignans: hydnocarpin, 0.08; methoxyhydnocarpin, 0.03; isohydnocarpin, 0.03; hydnowightin, 0.05; and neohydnocarpin, 0.04%. Hulls[47] 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[49-57] as biodiesel directly or through trans-estrification or as a renewable source of lubricating oil. Flavonolignans, hydnowightin, hydnocarpin and neohydnocarpin, showed potent hypolipidemic activity in mice,

lowering both serum cholesterol and triglyceride levels[58], besides good activity against human KB nasopharynsc, colon adenocarcinoma and Hela S uterine growth. Hydnowightin 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 neohydocarpin 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 xylose 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 benthamanianus*[61]. Pharmacokinetic study on silibinins and the effect of silymarin on bile salt secretion in rat has been found[62]. Cytotoxic flavonolignans and flavones from *Verbascum sinaiticum* 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[66,67]. Further studies may be extended by either isolating or synthesizing the flavonolignans such as hydnocarpin, hydnowightin, neohydnocarpin, etc. Pharmacological properties of these flavonolignans along with antimicrobial properties may be studied. There is also a scope for chrial 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. wighitiana, 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 pharmocopoeia[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 antisickling 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[80]. A bioactive coumarin from the bark of *Sonneratia apetela* has been isolated[81]. COX-1 and COX-2 inhibitory flavonoids were isolated from *Indigofera aspalathoides*[82]. T Cell suppression by a fraction from *Euphorbia tirucalli* has been reported[83]. These studies were directed to investigate the effects of the biopolymeric fraction of this plant on the immune system in experimental animals[83]. This plant is a petrocrop and contains bicoumarins. Few flavonoids and flavonoid glycoside dirhamnoside and a disaccharide galactomannan have been isolated from *I. tinctoria*[84]. Vast literature is available on traditional medicinal plants[77,85-90] 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[91].

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[85-93] 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[49-58]. 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[85-93].

India is among 18 mega diverse countries[94], which control almost 70 percent of world bioresources. It seems that bioresources may replace oil as the most sought after natural resource[94]. 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[94].

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[95]. The studies of bioinformatics, protein-protein interactions, drug-drug interactions, genetic mutations (influencing infections and diseases in individuals), molecular finger printing 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[95]. 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[96-106]. The studies of chemistry, biochemistry and pharmacological properties of flavonoids may be important[101-104]. These also possess antimicrobial properties[99-100] against bacteria[21-24,27,96,97] but virus and fungi[98] as well and have broad spectrum of activities against not only cancer[105] but ageing as well[106].

Nandave *et al*[107] 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-arhythmic, 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.

References

1 Iwashuta K, Kobori M, Yamaki K & Tsushiba T, Flavonoids inhibit cell growth and induce apoptosis in B16

Melanoma 4A5 cells, *Biosc Biotechnol Biochem*, **64** (2000) 1813-1820.

2 Murti V V S, Raman, P V & Seshadri T R, Cupressuflavonone, A new biflavonyl pigment, *Tetrahedron*, **23** (1967) 397-404.

3 Bandopadhyaya M, Malik S B & Seshadri T R, Candicanin, A novel bicoumarin derivative from the roots of *Heracleum candicans*, *Tetrahed Lett*, (1971) 4221-4222.

4 Bandopadhyaya M, Pardeshi, N P & Seshadri, T R, Experiments towards the synthesis of Lasiocephalin and its constituents, *Indian J Chem*, **12** (1974) 295-297.

5 Natarajan S, Murti V V S & Seshadri T R, Some pharmacological properties of flavonoids and biflavonoids, *Curr Sci*, **23** (1970) 533-534.

6 Chandramouli N, Murti V V S, Natarajan S & Seshadri T R, Synthesis of Eucomin, 4'-Demethyleucomin & 5, 7, Di-O-methyleucomol, *Indian J Chem*, **10** (1972) 1115.

7 Sharma D K & Seshadri T R, Oxidative coupling of esculetin and isoscopoletin by $Fe(DMF)_3Cl_2(FeCl_4)$, Potassium Hexacyno-Ferrate (III) and Manganese tris Acetyl Acetonate, *Indian J Chem*, **15** (1977) 939-941.

8 Sharma D K, Ranganathan K R, Bhushan B, Parthasarathy M R & Seshadri T R, Flavonolignans from *Hydnocarpus wightiana*, *Planta Med*, **37** (1979) 79-83.

9 Middleton E Jr & Kandaswami, C, Effects of flavonoids on immune and inflammatory cell functions, *Biochem Pharmacol*, **43** (1992) 1167-1179.

10 Sankawa U & Chun Y T, Anti-allergic substances from Chinese medicinal plants, in *Advances in Chinese Medicinal Materials Research*, edited by H M Chang, H N Yeung, W W Tsu & A Koo (World Scientific Publ Co, Singapore) 1985, 171-180.

11 Ng T B, Ling, J M L, Wang Z-T, Cai J N, & Xu G J, Examination of coumarins, flavonoids and polysachharopeptides for antibacterial activity, *Gen Pharmac*, **27** (1996) 1237-1240.

12 Hodek, P, Trefil, P & Stiborova M, Flavonoids-potent and versatile biologically active compounds interacting with cytochromes P450, *Chemico-Biological Interact*, **139** (2002).

13 Yoshimoto T, Furukawa M, Yamamoto S, Horie T & Watanabe – kono S, Flavonoids: potent inhibitors of arachidonate 5-lipoxygenase*, Biochem Biophys Res Comm*, **116** (1983) 612-618.

14 Li R Z, He Y Q, Chiao M Xu, Y, Zhang, Q B, Meng J R, Gu Y & Ge, L P, Studies of the active constituents of the Chinese drug "Du-huo", *Angelica pubescens*. *Acta Pharmac Sin*, **24** (1989) 546-551.

1 Lee K H, Tagabara K, Suzuki, H, Wu RY, Haruna, Hall I H, Huang H C, Ito K, Iida T & Lai J S, Antitumour agents 49. Tricin, kaempferol-3-0-β-D-glucopyranoside and (+) – nortrachelogenin, anti-leukemic principles from *Wikstroemia indica.J Nat Prod*, **44** (1981) 530-535.

16 Saqib Q N, Hui, Y H, Anderson J E & McLaughlin, J L, Bioactive furanocoumarins from the berries of *Zanthoxylum americanum, Physiotherapy Res*, **4** (1990) 216-219.

17 Ferriola P C, Cody Y & Middleton E Jr, Protein kinase C inhibition by plant flavonoids. Kinetic mechanisms and structure-activity relationships, *Biochem Pharmac*, **38** (1989) 1617-1624.

18 Grazini Y, Erikson E & Erikson R L, The effect of quercetin on the phosphorylation activity of the Rous Sarcoma virus transforming gene product *in vitro* and *in vivo*, *Eur J Biochem*, **135** (1983) 583-589.

19 Ammon H P T & Handel T, Crataegus, toxikologie and pharmakologie teil III. Pharmakodynamic and pharmokokinetik, *Planta Med*, **43** (1981) 313-322.

20 Kayser O, Kidderlen A F & Croft S L, Natural products as potential anti-parasitic drugs, *Acta Tropica*, **77** (2000) 307-314.

21 Honda G, Tabata M, Baba K & Kotawa M, On the antidermatophytic constituents and the original plants of the traditional Chinese drug She Chuang Zi, *Shoyakugaku Zasshi*, **38** (1984) 221-226.

22 Jiang, J W & Xiao Q X, *Handbook of Bioactive Constituents in Plant Drugs,* (People's Health Press, Beijing, China), 1986.

23 Lin Y-M, Zhou Y, Flavin M T, Zhou L M Nie, W & Chen F-C, Chalcones and flavonoids as anti-Tuberculosis agents, *Bioorg Medicin Chem*, **10** (2002) 2795-2802.

24 Erasto P, Bojase-Moleta, Gomotsang & Majinda, RT, Antimicrobial and antioxidant flavonoids from the root wood of *Bolusanthus speciosa*, *Phytochemistry*, **65** (2004) 875-880.

25 Chen G Lu, H, Wang, C, Yamshita K, Manabe, M, Meng, Z, Xu, S, & Kodama H, Effect of five flavonoid compounds isolated from leaves of *Diospyros kaki* on stimulus-induced superoxide generation and tyrosyl phosphorylation of proteins in human neutrophils, *Clinica Chimica Acta*, **326** (2002) 169-175.

26 Deng F & Zito S W, Development and validation of a gas chromatographic-mass spectrometric method for simultaneous identification and qualification of marker compounds including bilobalide, ginkgolides and flavonoids in *Ginkgo biloba* L. extract and pharmaceutical preparations, *J Chromatograp*, **986** (2003) 121-127.

27 Ahmed I & Beg A Z, Antimircobial and phytochemical studies on 45 Indian medicinal plants against multi-drug resistant human pathogens, *J Ethnopharmacol*, **74** (2001) 113-123.

28 Wang C W, Makela T, Hase, T, Adiercrutz & Kruzer, MS, Lignans and flavonoids inhibit aromatase enzyme in human preadipocytes, *J Steroid Biochem Molecul Biol*, **50** (1994) 205.

29 Levy M C, & Andry M C, (Centre National de la Rechersche Scientifque, France) French Patent Application **FR2 715 582** [In French].

30 Del Rio J A, Fuster M D, Gomez, P Poraz, I, Garcia-Lidon, A & Ourtuno, A, *Citrus limon* : a source of flavonoids of pharmaceutical interest, *Food Chem*, **84** (2004) 457-461.

31 Youdim K A & Joseph J A, A possible emerging role of phytochemicals in improving age related neurological dysfunctions : A multiplicity of effects, *Free Radic Biol Med*, **30** (2001) 583-584.

32 Middleton E Jr, Effect of plant flavonoids on immune and inflammatory cell function, *Adv Exp Med Biol*, **439** (1998) 175-182.

33 The Wealth of India, *Raw Materials*, CSIR, New Delhi, 1959.

34 Wagner H, Diesel, P & Seitz, M, Arzneim Forsch. (Drug Research), **24** (1974) 466.

35 Wagner H, Hoerhammer L & Muenster R, *Naturwissenschaften,* **52** (1965) 305.

36 Wagner H, Hoerhammer, L & Muenster, R, *Arzneimittel-Forsch*, **18** (1968) 688.

37 Ruen H M, Schriewer H, Tegtbaver U & Lasana J E, *Experientia*, **29** (1973) 1372.

38 Wagner H, Bull Liaison, *Groupe Polyphenols*, **5** (1974) 1, 24.

39 Abraham, D J, Tagaki, S, Rosenstein R D, Shino, R, Wagner H, Hoeshammer, L, Saligmann O, & Farnsworth N R, *Tet Lett*, (1970) 2675.

40 Harkin J M, *Forschr Chem Forsch*, **6** (1966) 100.

41 Wagner H, Seligmann O, Hoerhammer L, Seitz M, & Sonnenbichler, J, *Tel Lett*, (1971) 1895.

42 Bandopadhyaya M, Pardeshi N P & Seshadri T R, Compounds of *Silybum marianum, Indian J Chem,* **10** (1972) 808-809.

43 Takemoto T, Ikegawa S & Kyosuke N, *Yakugaku Zasshi*, **95** (1975) 1017.

44 Ranganathan K R & Seshadri T R, *Tet lett*, (1973) 3481.

45 Ranganathan K R & Seshadri T R, *Indian J Chem*, **12** (1974) 888.

46 Ranganathan K R & Seshadri T R, *Indian J Chem*., **10** (1972) 1115.

47 Sharma D K, *Two new flavonolignans from Hydnocarpus wightiana and syntheses of some naturally occurring dimers*, Ph D Thesis, Univ of Delhi, 1976.

48 Parthasarathy M R, Ranganathan K R & Sharma D K, 13-CNMR of flavonolignans from *Hydnocarpus wightiana*, *Phytochem*, **18** (1979) 506-508.

49 Behera B K, Arora M, & Sharma D K, Studies on biotransformation of *Calotropis procera* latex – A renewable source of petroleum, value added chemicals and products, *Ener Sources***, 22** (2000) 781-807.

50 Sharma D K, Process technology development for degrading natural polymers and polymeric organic wastes, Reviews in Process *Chem Engin*, **2** (1999) 111.

51 Sharma D K, Tiwari M, Arora M, & Behera BK, Microbial transformation and biodegradation of *Calotropis procera* latex towards obtaining value added chemicals, pharmaceuticals and fuels*, Petrol Sci Technol*, **15** (1977) 137-169.

52 Sharma D K, Potential of biomass utilization, *Ind Prod Finder*, **25** (1996) 324.

53 Sharma D K, Tiwari M, & Behera B K, Solid State fermentation of new substrates for production of cellulase and other biopolymer hydrolyzing enzymes, *Appl Biochem Biotech*, **51**/52 (1996) 495-500.

54 Sharma D K, Dastidar M G, & Chahar S, Studies on treatment of black liquor from small paper industries, *IPPTA J***, 4** (1995) 37-42.

55 Behera B K, Midha N, Arora M, & Sharma D K, Production of petroleum hydrocarbons, fermentable sugars and ethanol from *Tabernaemontana divaricata, Ener Conv Mgmt*, **36** (1995) 281-288.

56 Sharma D K, Tiwari M & Behera B K, A review of integrated processes to get value added chemicals and fuels from petrocrops, *Biores Technol*, **49** (1994) 1-6.

57 Singh A, Das K & Sharma D K, Integrated process for production of furfural, xylose, glucose, and ethanol by two step acid hydrolysis, *Ind Eng Chem Prod Res Dev*, **23** (1984) 257-262.

58 Sharma D K & Hall I H, Hypolipidemic, anti-inflammatory and antineoplasmic and cytoxicity of flavonolignans isolated from *Hydnocarpus wightiana* seeds, *J Nat Prod*, **54** (1991) 1298-1302.

59 Nakajima Y, Yun Y S, & Kumugi A, Six new flavonolignans fro *Sasa* veitchii (Carr.) Rehder, *Tetrahedron*, **59** (2003) 8011-8015.

1 Seidlova-Wuttke D, Becker T, Christoffel V, Jarry H, & Wuttke W, Silymarin is a selective estrogen receptor β (ERβ) agonist and has estrogen effects in metaphysis of the femur but no or antiestrogenic effects in the uterus of ovariectomized (ovx) rats*, J Steroid Biochem Molecul Biol*, **86** (2003) 179-188.

61 Bouaziz M, Veich N C, Grayer R J, Simmonds S J, & Damak M, Flavonolignans from *Hyparrhenia hirta, Phyotchem*, **60**(5) (2002) 515-520.

62 Grocenzi F A, Pellegrino J M, Pozzi E J S, Mottino A D, Garay E A R & Roma M G, Effect of silymarin on biliary bile slat secretion in the rat, *Biochem Pharmacol*, **59** (2000) 1015-1022.

63 Mohammed S A, Afifi M S A, Ahmed M M, Pezzuto J M, & Kinghornt A D, Cytotoxic flavonolignans and flavones from *Verbascum sinaiticum* leaves, *Phytochem*, **34** (1993) 839-841.

64 Skottova N, Vagera Z S, Vecera R, Urbanek K, Jegorov A & Samanek V, Pharmacokinetic study of iodine-labeled silibinins in rat, *Pharmacol Res*, **44** (2001) 247-253.

65 Malan E, Swinny E & Ferreira D, A 3-oxygenated flavonolignoid from *Distemonanthus benthamianus*, *Phytochem*, **37** (1994) 1771-1772.

66 Sharma D K & Parthasarathy M R, Novel oxidative coupling reactions of vanillin and ferulic acid, *J Inst, Chem,* **60** (1988) 103.

67 Datta P K, Banerjee D & Datta N L, *Tet Lett* (1972) 601.

68 Sharma D K & Prasad R, Oil and non-polluting fuel from latex bearing plants, *Biomass*, **11** (1986) 75-79.

69 Balasundaram R, Gadgil K, Behera B K & Sharma D K, Photobiological production of hydrogen from *Spirulina* for fueling the fuel cells*, Ener Sources*, In press.

70 Durbin R D, *Toxins in Plant Diseases* (Academic Press, New York) 1981.

71 Southon I W & Buckingham J D, *Dictionary of Alkaloids*, **Vol 2**,(Chapman and Hall, London) 1989.

72 Harborne J B, *The Flavonoids: Advances in Research since 1986* (Chapman and Hall, London) 1993.

73 Harborne J B, *In Chemicals from Plants Perspectives on Plant Secondary Products,* Walton N J & Brown D E eds, 2, (Imperial College Press) London, 1999.

74 Hill R A & Connolly J D, *Dictionary of Terpenoids* (Chapman and Hall, London) 1991.

75 Dewick D M, *Medicinal Natural Products: A Biosynthetic Approach* (John Wiley and Sons, England) 1997.

76 Cordell G A, Changing strategies in natural products chemistry, *Phytochem*, **40** (1995) 1585-1612.

77 *A Selection of Prime Ayurvedic Plant Drugs: Ancient – Modern Concordance*, Sukh Dev (Anamaya Publishers, New Delhi) 2005.

78 Saxena B B, Garcia C, Bohmstein A, Rathnam P & Haller I, *Proc. Chemistry Biology Interface: Synergistic New Frontiers*, *An International Conf*, New Delhi, Nov 21-26, 2004.

79 Pandey R C, Tripathi P, Mishra R, Gillette P N & Asakura T, *Proc. Chemistry Biology Interface: Synergistic New Frontiers – An International Conf*, New Delhi, Nov 21-26, 2004.

80 Misra N, Acharya R, Gupta A P, Singh B, Kaul V K & Ahuja P S, *Proc Chemistry Biology Interface: Synergistic New Frontiers – An International Conf,* New Delhi, Nov 21-26, 2004.

81 Maurya B R & Jadhav B L, *Proc Chemistry Biology Interface : Synergistic New Frontiers – An International Conf,* New Delhi, Nov 21-26, 2004.

82 Brahmbhall K, Sevam C, Oli R G, Sarade K & Jachak S M, *Proc Chemistry Biology Interface: Synergistic New Frontiers – An International Conf,* New Delhi, November 21-26, 2004.

83 Bani S, Kaul A, Ahmad S F, Khan B, Suri K A, Satti N K & Qazi G N, *Proc Chemistry Biology Interface: Synergistic New Frontiers – An International Conf,* New Delhi, Nov 21-26, 2004.

84 Khaliq T & Narender T, *Proc Chemistry Biology Interface: Synergistic New Frontiers – An International Conf,* New Delhi, Nov 21-26, 2004.

85 *Neem: Research and Development*, Randhawa, N S & Parmar, B S, Society of Pesticide Science (India), New Delhi, India, 1993.

86 Vander Nat J M, Vander Sluis W G, De Silva K T D & Labadie R P, *J Ethnopharmacol*, **35** (1991) 1.

87 Kinghorn A D & Balandrin M F (Ed) Human Medicinal Agents from Plants, *ACS Symp Ser,* **534,** ACS, Washington, 1992.

88 Chopra R N, Nayar S L & Chopra I C, *Glossary of Indian Medicinal Plants*, CSIR, New Delhi, 1992.

89 Govil J N, Singh V K & Hashmi S, *Glimpses in Plant Research Vol X, Medicinal Plants: New Vistas of Research* (Part I) (Today and Tomorrow Printers & Publishers, New Delhi) 1993.

90 Rastogi R P, Mehrotra B N Sinha, S, Pant P & Seth R, *Compendium of Indian Medicinal Plants*, **Vol 2**, 1970-79, CDRI, Lucknow and Publication and Information Directorate (CSIR), New Delhi, 1991.

91 The Hindustan Times, January 5, 2005.

92 Gabon R, *Plant Flavonoids in Biology and Medicine II. Biochemical*, *Cellular and Medicinal Properties* (Alan R Liss Inc, New York, USA) 1988, 1.

93 Nostro A, Germano M P, D'Angelo V, Manno A & Cannatelli M A, Extraction methods and bioautography for evaluation of medicinal plant antimicrobial activity, *Lett Appl Microbiol*, **30** (2000) 379.

94 Bio Wars, The Hindustan Times, January 9, 2005.

95 Cohen J, 'Big-Picture Biotech', *Span*, **46** (2005) 46.

96 Li Y-L, Ma S-C, Y, Y-T Ye, S-M & But P, P-H, Antiviral activities of flavonoids and organic acid from *Trollius chinesis* Bunge, *J Ethnopharmacol,* **79** (2002) 365-368.

97 Sample S J, Nobbs S F, Pyke S M, Reynolds G D & Flower R L P, Antiviral flavonoids from *Pierocaulon sphacelatum*, An Australian Aboriginal medicine, *J Ethnopharmacol*, **68** (1999) 283-288.

98 Tomas – Berberan, F A, Msonthi J D & Hostettmann, Antifungal epiruticular methylated flavonoids from *Helichrysum nitens*, *Phytochem*, **27** (1988) 753-755.

99 Sohn H-Y, Son K H, Kiwon C S, Kwon C-S & Kang S S, Antimicrobial and Cytotoxic activity of 18 prenylated flavonoids isolated from medicinal plants : *Morus alba L, Morus mangolica Schneider, Broussnetia papyrifera (L.) Vent, Sophora flavescens Ait and Echinosphora korensis* Nakai, *Phytomedicine*, **11** (2004) 666-672.

100 Hernandez N E, Tereschuk M L & Abdala L R, Antimicrobial activity of flavonoids in medicinal plants from Tafi del Valle (Turuman Agrentina), *J Ethnopharmacol*, **73** (2000) 317-322.

101 Plant flavonoids in biology and medicine II. biochemical, cellular and medicinal properties : ed. By Cody, V, Middleton E, Jr, Harborne J B & Beretz A, Alan R Liss Inc, New York, 1988, Book Review, *Phytochem,* **28** (1989) 22-26.

102 Plant flavonoids in biology and medicine : biochemical, pharmacological and structure activity relationships, Miscellaneous, *Biochimie*, **66** (1984) 19.

103 Havsteen B H, The biochemistry and medical significance of flavonoids. Review article, *Pharmacol Therapeut,* **96** (2002) 67-202.

104 Winkel-Shirley B, Biosynthesis of flavonoids and effects of stress. Review article, *Curr Opinion in Plant Biol,* **5** (2002) 218-223.

105 Sannomiya M, Fonseca V B, Da Silva M A, Rocha L R M, Dos Santos L C, Hiruma Lima C A, Souza Brito A R M & Vilegas W, Flavonoids and antiulcerogenic activity from *Byrosonima crassa* leaves extracts, *J Ethnopharmacol,* **97** (2005) 1-6.

106 Montoro P, Braca A, Pizza C & De Tommasi N, Structure antioxidant activity relationships of flavonoids isolated from different plant species, *Food Chem*, **92** (2005) 349-355.

107 Nadave M, Ojha S K & Arya D S, Protective role of flavonoids in cardiovascular diseases, *Nat Prod Rad*, **4** (2005) 166-175.