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Chemistry and Utilization of Phenylpropanoids Including Flavonoids, Coumarins, and Lignans

Tom J. Mabry* and A. Ulubelen

Phenylpropanoids are perhaps the most widespread types of natural products occurring in nature. In this account of the chemistry and utilization of phenylpropanoids we emphasize a few of the useful physiological, pharmacological, and chemical properties of flavonoids, lignans, and coumarins which are three of the major classes of compounds containing the C_6–C_3 phenylpropanoid moiety.

FLAVONOIDS

With the exception of most algae[1] flavonoids are found throughout the plant kingdom, and within individual plants they may occur in every organ but are usually concentrated in leaves and flower parts. Except for the well-known pollinator-attracting red and blue anthocyanins and yellow aurones and chalcones, most flavonoids absorb light between 240–370 nm, an ultraviolet spectral region also visible to many pollinators.

Many flavonoids including those which are phytoalexins[2,3] provide plants with a defense against viral infections.[4-7] Others exhibit antitumor[8-11] and general antiinflammatory[12,13] activity. The estrogenic action of many isoflavones is well known,[14] and mixtures of flavonoids are commonly used commercially to reduce capillary fragility.[15]

Since most flavonoids are isolated in only small amounts, their structures are primarily determined by spectral methods, especially UV,[16-18] ^1H[16,17] and ^{13}C[19-23] NMR, and MS.[24-26]

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Flavonoids are biogenetically formed from a malonate-derived C_6 unit and a shikimic acid-derived C_6–C_3 phenylpropanoid moiety to give initially the chalcones. The chalcone–flavanone isomeric pair then undergoes further transformations (see Figure 1) including oxidations, rearrangements, alkylations, acylations, and glycosylations all of which give structural diversity to the thousands of distinct flavonoids known at the present time.

Isolation of Flavonoids. Flavonoid isolation remains the most time-consuming aspect of research in this field. Most isolations involve extracting air-dried ground plant material with methanol–water (80:20) and then partitioning the material obtained from this extract between water and a series of organic solvents: hexane, methylene dichloride, and ethyl acetate. The hexane and methylene dichloride layers yield mostly aglycons, especially highly methoxylated types, while the ethyl acetate yields some aglycons but mostly mono- and diglycosides. The remaining water layer contains glycosides, especially di-, tri-, and tetraglycosides, as well as sulfated flavonoids.

Flavonoids may be obtained in large quantities by column chromatography using such supports as polyamide, cellulose, Sephadex, and silica gel and by preparative high-pressure liquid–liquid chromatography.[27-30] Flavo-

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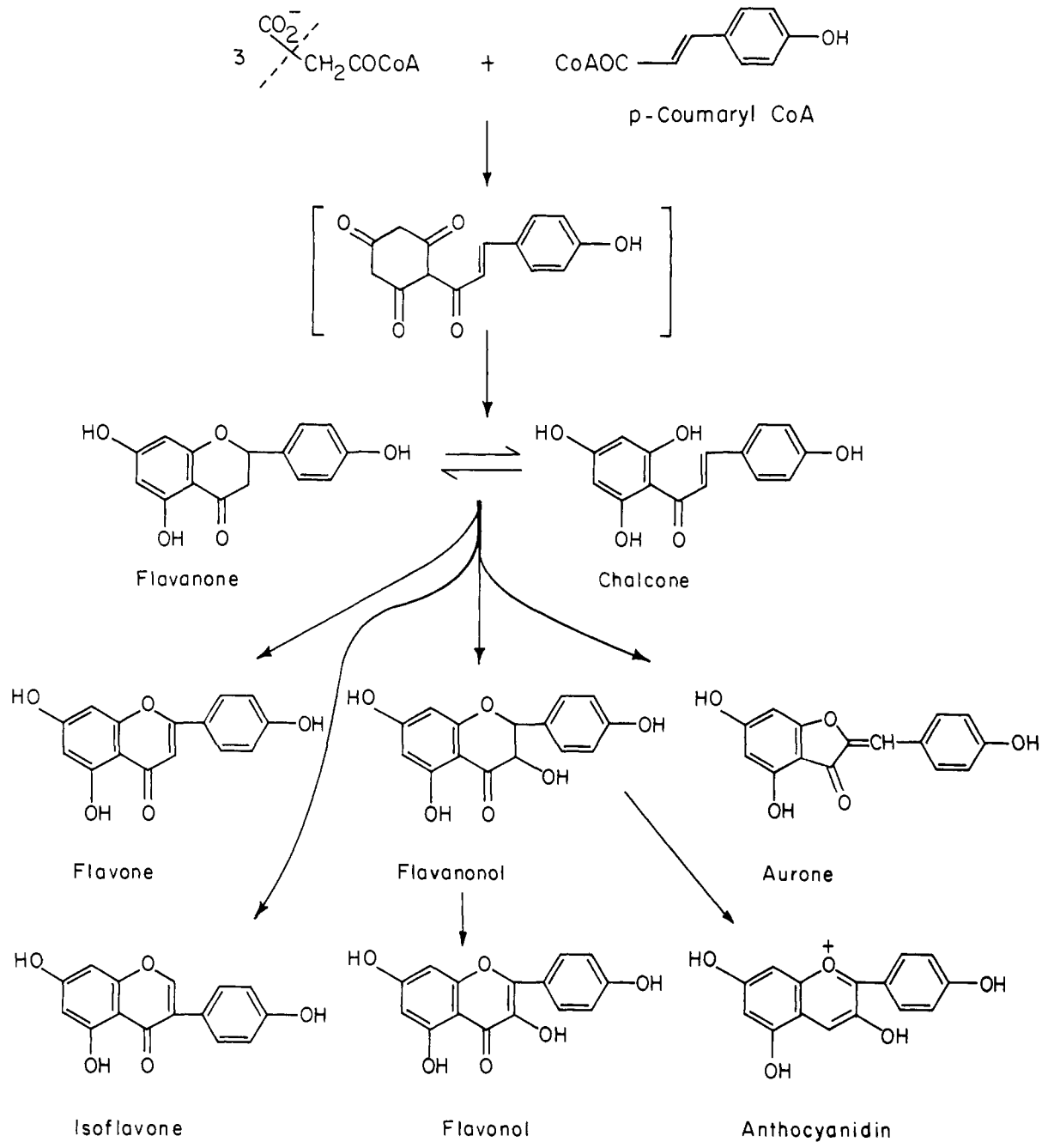
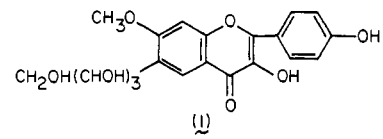


Figure 1. Biogenesis of flavonoids.

noids are visualized on paper and on TLC plates over UV light with and without ammonia and with spray reagents, including Naturstoffreagenz A (NA) and $FeCl_3$–MeOH.

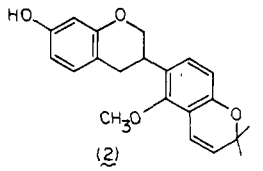
Uses and Functions of Flavonoids. No attempt is made here to discuss all the uses of plant extracts containing flavonoids when the exact role of the flavonoids is obscure. The examples treated in this account of phenylpropanoids represent the more established uses of flavonoids.

Flavonoids as Fungicides. A relationship appears to exist in plants between the presence of phenolics and the plant's ability to resist viral and fungal infections. For example, the presence of apigenin 7- and 4′-glucosides, luteolin 7- and 4′-glucosides and 7-rhamnoglucoside and quercetin 3-glucosides has been correlated with fire-blight (a pathogen) resistence in eight species of *Pyrus*.[31] In general, resistance may be imparted to a plant by the synthesis and storage of phenolics or by de nova synthesis (of phytoalexins) in response to fungal or viral infections.[32,33] The fungicidal property of flavonoids contributes to the durability of lumber. For example, potent antifungal compounds include dihydroquercetin in Douglas fir and dihydrorobinetin and keyakinin (1) and keyakinol (corresponding flavone) in *Robinia pseudoacacia*.[34]

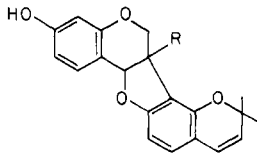


(1) keyakinin

Naringenin, nobiletin, tangeritin, and 5,4′-dihydroxy-6,7,8,3′-tetramethoxyflavone protect the leaves of some citrus plants against "mal secco" disease which is caused by the pathogenic fungus *Deuterophoma tracheiphila*.[35,36] The isoflavan phaseollinisoflavan and its methyl ether (2) obtained from diseased tissue of *Phaseolus vulgaris* (French bear) inhibited the growth of the fungus of *Fu-*

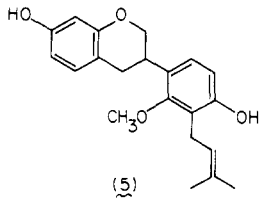


(2)
phaseollinisoflavanmethyl ether

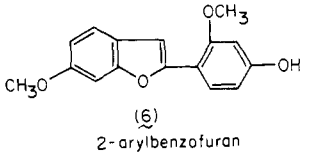


(3) R=H
(4) R=OH

sarium solani (Mart) Appel.[32] Two isoflavan derivatives (**3**, **4**) from *Collecotrichum lindemuthianum* are also antifungicides.[3] After inoculation of this same species[37] to the cowpea (*Vigna unguiculata*), seven antifungal phytoalexins of the isoflavonoid type (**5**) as well as 2-aryl-



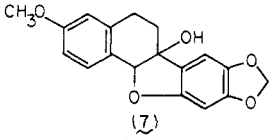
(5)



(6)
2-arylbenzofuran

benzofuran (**6**) (38) were produced.

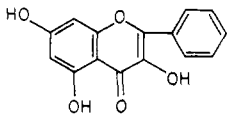
Some fungi can degrade phytoalexins; for example, *Fusarium solani*, the pathogen fungi of the pea, metabolizes pisatin (**7**), a pterocarpanoid phytoalexin produced by the



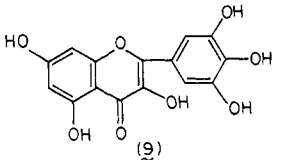
(7)
pisatin

plant.[37]

Antidiarrhetic Activity of Flavonoids. The presence of galangin (**8**), myricetin (**9**), kaempferol, quercetin, and



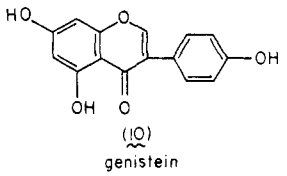
(8)
galangin



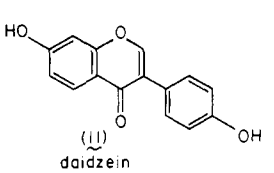
(9)
myricetin

gallic acid in the fruits of *Comptonia peregrina*[39] appears to be related to the use of these fruits against diarrhea in central Europe since the early 19th century.[40]

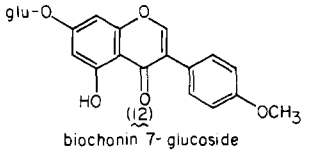
Estrogenic Activity. Bennetts et al. reported[41] a serious decline in lambing rates in Australia; it was later shown to be caused by the isoflavone genistein (**10**) in the clover plant *Trifolium subterraneum*.[42,43] Isoflavones are structurally similar to stilbestrols and have similar estrogenic activity.[14] In addition to genistein, many other isoflavones including daidzein (**11**), tectorigerin 7-glucoside, irigenin, irilone 4'-glucoside, and biochanin 7-glucoside (**12**) also exhibit estrogenic activity; of these, daidzein (**11**) is



(10)
genistein



(11)
daidzein



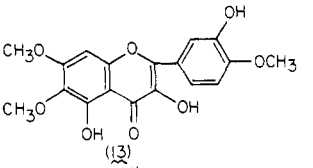
(12)
biochonin 7- glucoside

the most active estrogenic flavonoid in mouse-uterine weight assays.[44-48]

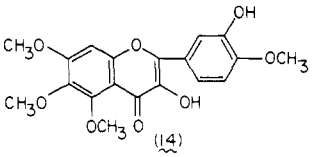
A mixture of synthetic phosphorylated hesperidins produced a definite antifertility effect in some rats and no effect in others; however, only one of the phosphorylated compounds was found to possess the antifertility action.[44]

Molluscacidal Activity. 2',4'-Dihydroxy-3',6'-dimethoxychalcone from the East African plant *Polygonum senegallense* is used as a molluscacide in Kenya.[49]

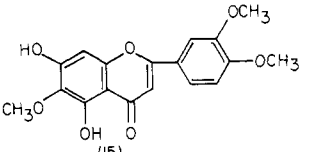
Antitumor Activity. The flavonols eupatin (**13**) and



(13)
eupatin



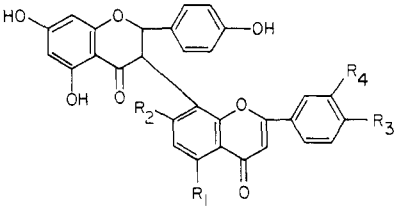
(14)
eupatoretin



(15)
eupatilin

eupatoretin (**14**) and the flavone eupatilin (**15**) from *Eupatorium semiserratum* all exhibited moderate cytotoxicity when tested against human carcinoma of nasopharynx.[8,9] Two methoxylated flavonols (5,7,3'-trihydroxy-3,4'-dimethoxyflavone and 5,7,3'-trihydroxy-3,6,4'-trimethoxyflavone) from *Baccharis sarothroides* were found to be active against the human carcinoma 9KB system.[9]

Apigenin and the biflavonoids morelloflavone (**16**),

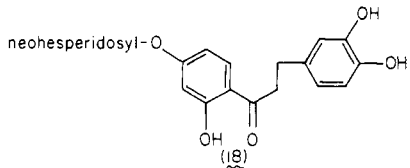


(16) $R_1=R_2=R_3=R_4=OH$, morelloflavon
(17) $R_1=R_2=R_3=OH$; $R_4=H$, volkensiflavon

volkensiflavone (**17**), and fugugelin were also found to have antitumor activity.[10] Quercetagetrin and patuletrin are active against Lewis lung carcinoma (in vivo).[11] Nevertheless, no flavonoids are currently used in cancer treatments.

Feeding Stimulants and Insecticidal Properties of Flavonoids and Pterocarpans. 6-Methoxyluteolin 7-rhamnoside is a feeding stimulant for the *Agasicles beetles* in alligator weed[50] while various pterocarpans including pisatin and phaseollin give plants resistance to insect attack.[3]

Dihydrochalcones as New Sweetening Agents. The dihydrochalcones of naringin and neohesperidin (and other synthetic dihydrochalcones) have considerable potential as commercial sweeteners.[51] The dihydrochalcones are prepared by ring opening and catalytic hydrogenation of the bitter flavanone glycosides. Naringin is available in large quantities as a byproduct of the processing of citrus fruits and a procedure is now available to convert it in 80% yield to neohesperidin dihydrochalcone (**18**);[52,53] the latter compound is sweeter by a factor of 10 relative to naringin dihydrochalcone and 1000–2000 times sweeter than sucrose.[51] Because these dihydrochalcones are poorly soluble in acidic media and have an aftertaste resembling licorice,



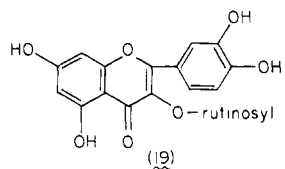
(18)
neohesperidin dihydrochalcone

more commercially suitable dihydrochalcones have been prepared from them such as 4′-NaO_3S-$(CH_2)_3$-hesperetin dihydrochalcone. Since some dihydrochalcones may soon be added to citrus products, as LC procedure to detect them in the mixture of flavonoids present in citrus extracts has been developed.[54] To our knowledge, the FDA has not yet approved the use of any dihydrochalcones.

Flavonoids as Co-pigments. Flavonoids such as quercetin glucosides exhibit a co-pigmentation effect on the adsorption characteristics of cyanidin glucosides;[55] similarly apigenin 7-glucuronide serves as a co-pigment with aureusin[56] and apigenin 4′-glucoside 7-glucuronide is a co-pigment in *Centaurea cyanus*.[57]

Antiinflammatory Activity. In 1936 Szent-Gyorgyi observed that certain pathological conditions characterized by increased permeability or fragility of capillary walls could be cured by lemon extractives, and the factor which increased the capillary resistance was called vitamin P.[12] Although other workers obtained contradictory results which led to the abandoning of the vitamin designation[58] work in this field continued and the term bioflavonoids subsequently was coined to denote flavonoids having biological activity. Since 1948 an increasing number of reports have appeared which describe the therapeutic use of the water-soluble citrus flavonoids. When the citrus flavonoid mixture was separated into three fractions by differential solubility in methanol, ethyl acetate, and water and each assayed for antiinflammatory activity by the modified[59] method of Ungar,[60] 65% of the activity was found in the water-soluble fraction. The citrus flavonoid complex displayed broader inflammation inhibition than either cortisone or ACTH.[61] Hesperidin, naringin, and a small amount of nobiletin, together with 5,6,7,8,3′,4′-hexamethoxyflavone were found in the active water extract.[13]

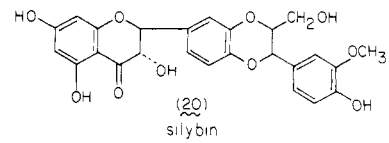
Increased capillary permeability is the initial manifestation of inflammation and most methods devised for measuring inflammation are based on the loss of plasma into the inflammated tissue; however, Ungar[62] reported a bioassay based on direct measurement of the edema formation. The results with Ungar's method clearly demonstrated that citrus peel extracts inhibit increased capillary permeability.[13] Srinivasan (1971)[63] found that flavonoids appear to play an important role in the circulatory system. Benko (1970)[64] found that severe brain edemas and subpleural hemorrhages in rats were significantly reduced when rats were given 50 mg/kg of derivatives of rutin or hesperidin. One medication (Essaven) containing the methylated chalcone of hesperidin along with other flavonoid derivatives is said to be so effective as an antiphlogistic agent that if applied to a bruise one can immediately observe reduction in the swelling. β-Hydroxyethyl rutin (see **19**) is widely used (e.g., Venoruton) to treat hemmoroids, cataracts, varicose veins, and



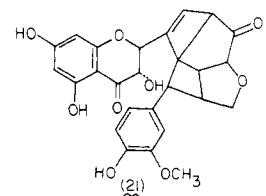
(19)
rutin

other general problems of capillary fragility. When applied as a gel to swollen varicose veins, the β-hydroxyethyl rutin can reduce the pain and swelling within a few minutes. Tons of rutin are derivatized every year mostly in Switzerland; the rutin is obtained in India by the extraction of the rutin-rich flowers of *Sophora japonica* L. (Leguminosae) (13–30% rutin).

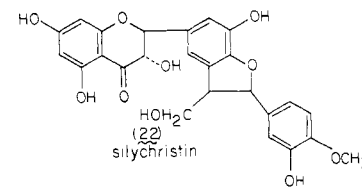
Antihepatotoxic Agents. Medicinal properties have been attributed to the water-soluble extract of the fruits of the milk thistle (*Silybum marianum* (L.) Gaertn., Family Compositae) for over 2000 years. The active component is a mixture of flavanonol–lignans, namely silybin (**20**), silydianin (**21**), and silychristin (**22**), referred to



(20)
silybin



(21)
silydianin



(22)
silychristin

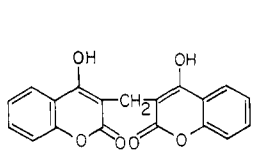
collectively as silymarin.[65] These isomeric compounds each represent the condensation of a molecule of taxifolin and coniferylic alcohol and they each possess antihepatotoxic activity as established by animal studies. Silymarin is one of the few nonimmunosuppressant drugs available for treating liver diseases, especially cirrhosis caused by alcohol.[66,67] Commercial products containing silymarin (e.g., Legalon) have a stabilizing effect on the outer hepatic plasma membrane and prevent the action of several liver poisons. Silymarin can also cause displacement of some liver toxins and has a cell-regenerating activity, promoting ribosomal-RNA and protein synthesis. The overall effect of silymarin is to stabilize the liver cell membranes and render them impermeable to toxins.

Spasmolytic Agents. Liquirtin, 7,4′-dihydroxyflavanone 4′-glucoside, from *Glycyrrhizae radix*, has no spasmolytic effects; however, both its aglycon and the chalcone obtained from the aglycon have activity similar to papaverin.[63] In addition to these, luteolin and its derivatives are also known as spasmolitic agents.[68,69]

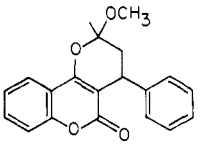
COUMARINS

Like flavonoids, coumarins (Figure 2) are widespread in higher plants, especially in grasses, orchids, legumes, mints, and umbellifers, and rutaceous plants. Some coumarins have been used as anticoagulants[70] and as a treatment for Parkinson's syndrome[71] and leucoderma.[72] Other coumarins exhibit antibacterial,[73] antitumor,[74] and vasodilatory (in coronary vessels)[75] activities. Most structure determinations of coumarins rely heavily upon spectral methods.[20,75–79]

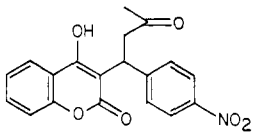
Anticoagulant Activities of Coumarins. The most important pharmacological activity of coumarins is the anticoagulant property. The toxic material in spoiled sweet clover which causes serious hemorrhages in cattle was found to be dicumarol [3,3′-methylenebis(4-hydroxycoumarin)] (**23**) by Stahmann et al.[80] Today synthetic dicumarol is used extensively as an anticoagulant along with a number of other related synthetic coumarins including cyclocoumarol (**24**), acenocoumarol (**25**), and sodium warfarin (**26**).



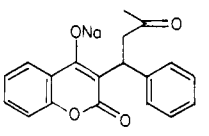
(23)
dicumarol



(24)
cyclocoumarol



(25)
acenocoumarol

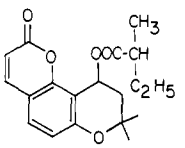


(26)
sodium warfarin

Most coumarins are free from toxic side reactions and may be given for years without negative side effects; however, overdoses cause hemorrhages.[81] The activity of sodium warfarin[26] is so high that it was employed as an effective hemorrhagic rodenticide for years before its acceptance into human therapy.

When the anticoagulant activity of dicoumarol, warfarin, and other coumarins was tested on rats, the blood rate returned to normal only after 3 weeks.[70] Recent investigations of coumarin anticoagulants showed that pretreatment of rats with barbiturates reduces the prothrombin response to coumarin anticoagulants, presumably by stimulating the metabolic breakdown of the drug. In contrast, compounds of the morphine type were found to enhance the response to coumarins presumably by inhibiting enzymes which metabolize the coumarins in the liver.[82-84]

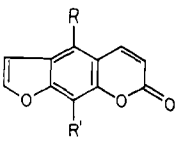
A rare complication from the use of dicumarol and its congeners is characterized by sudden, localized hemorrhagic skin lesions, culminating in hemorrhagic gangrenous necrosis.[85] The vasodilatory activity of visnadine (27) is



(27)
visnadine

especially pronounced in the coronary vessels.[75] In addition, visnadine was shown to inhibit spasms of smooth muscles and to protect animals against the effects of digitoxin. Visnadine has no pronounced toxicity and it has been used in the treatment of patients suffering from chronic myocardial lesions[86] and Parkinson's syndrome.[71] Mono- and disubstituted coumarins have been used as diuretics and as antialdosterone drugs.[87]

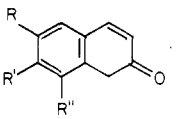
Leucodermic and Antipsorasis Activity. Furanocoumarins have long been used for the treatment of vitiliginous areas.[88,89] Some of the plants known to contain dermal photosensitizing agents include parsley, celery, figs, and parsnip. After contact with juices from such plants, the skin can develop erythema, hyperpigmentation, and occasionally vesiculation upon exposure to sunlight.[90] All furanocoumarins capable of inducing photosensitization such as psoralen (28) from *Psoralea corylifolia*, xanthotoxin (29), imperatorin (30), and bergapten (31) from *Ammi majus* L. have absorption peaks in two spectral regions: 320–360 nm and 420–460 nm. In addition to their use in the treatment of vitiligo, furanocoumarins such as 8-methoxypsoralen are one of the few successful treatments for psorasis. After taking the furanocoumarins orally, patients are exposed to longwave ultraviolet radiation



(28) R = R' = H, psoralen
(29) R = H; R' = OCH_3, xanthotoxin
(30) R = H; R' = O-CH_2-CH=C(CH_3)(CH_3), imparatorin
(31) R = OCH_3; R' = H, bergapten

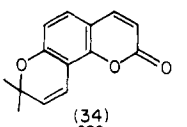
(320–400 nm) to effect relief from the psorasis rash.

Antibacterial and Antifungal Activity. Dicumarol[23] exhibits excellent activity against many bacteria including *Bacillus anthraus*, *Staphylococcus aureus*, *S. albus*, *Streptococcus pyogenes*, and *Pasteurella avicida*.[91-93] Some coumarins, including umbelliferrone (32), scopoletin

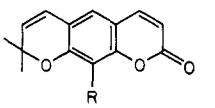


(32) R = R'' = H; R' = OH, umbelliferrone
(33) R = OCH_3; R' = OH; R'' = H, scopoletin
(37) R = $CH_2CH=C(CH_3)(CH_2)_2CH=C(CH_3)_2$; R' = OH; R'' = H, ostruthin
(38) R = H; R' = R'' = OH, daphnetin
(39) R = R' = OH; R'' = H, esculetin

(33), and furanocoumarins, inhibit the growth of the yeast *Saccharomyces cerevisiae* and at higher concentrations retard the germination of the spores of *Aspergillus niger* and *Penicillium glaucum*. Seselin (34), xanthyletin (35),



(34)
seselin

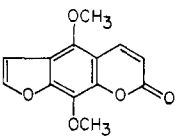


(35) R = H, xanthyletin
(36) R = OCH_3, luvangetin

psoralen (28), and luvangetin (36) all inhibit the growth of *A. niger*.[88] Ostruthin (37) inhibits the growth of Gram-positive bacteria while daphnetin (38), esculetin (39), and scopoletin (33) act as neutral plant fungicides. The concentration of these latter compounds tends to increase at the site of the plant wound or infection. The glycosides of these same coumarins were inactive.[94]

Vasodilatory Activity. Dicumarol (23) and warfarin (26) show vasodilatory activity on swine coronary arteries[95] at a level comparable to that exhibited by aminophylline and nitroglycerine. Ptryxin and suksdorfin have an even more potent action.[96] Visnadine is widely employed in Europe for the treatment of angina pectoris.[75]

Molluscacidal Activity. Schönberg and Latif[97] demonstrated the potential of snail control with furanocoumarins; they found that bergapten (31) and isopimpinellin (40) exert a molluscacidal activity comparable to



(40)
isopimpinellin

some of the most powerful synthetic agents, including dinitro-*O*-dicyclohexylphenol and sodium pentachlorophenate.

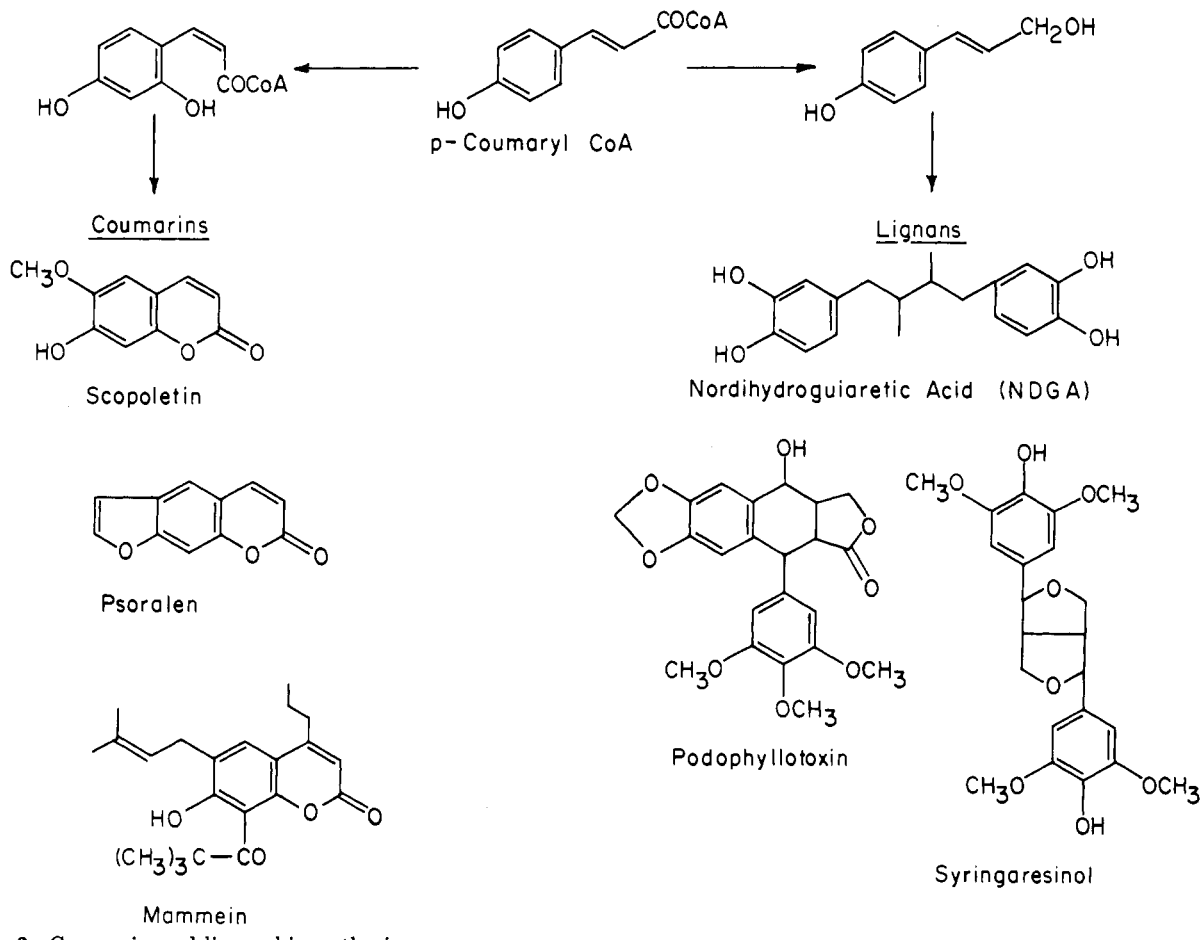
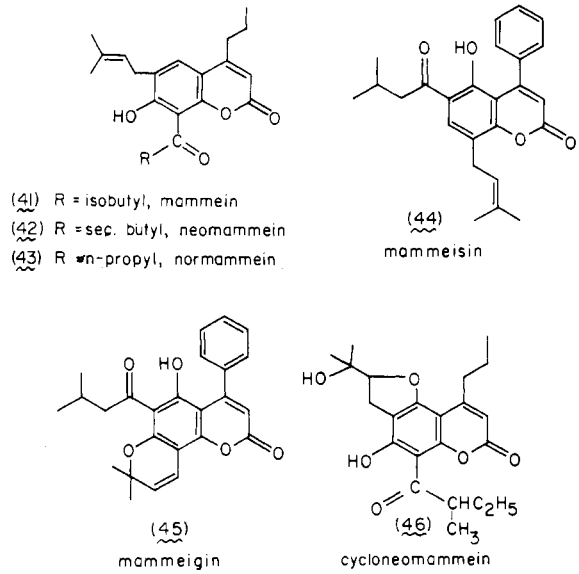


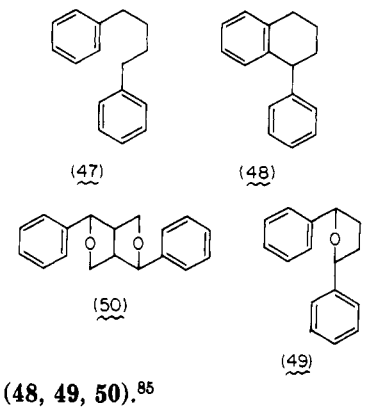
Figure 2. Coumarin and lignan biosynthesis.

Antitumor Activity. Several coumarins obtained from *Mammea americana* L. exhibit antitumor activity against the sarcoma 180 in vivo test system;[74] these include memmein (**41**), neomammein (**42**), normammein (**43**), mammeisin (**44**), mammeigin (**45**), and cycloneomammein (**46**).

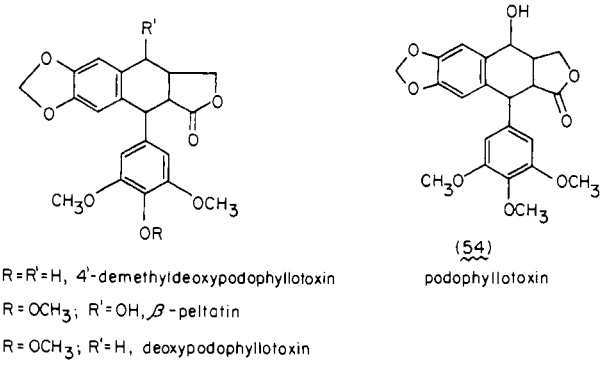


LIGNANS

Lignans are also rather widely distributed in higher plants, although fewer structural types are known relative to the number of flavonoids and coumarins. They are biogenetically derived by the oxidative dimerization of two C_6–C_3 units[98-100] (Figure 2). The term lignan was introduced in 1936[101] to include natural products characterized by the β,γ-dibenzbutane skeleton (**47**) or modifications thereof (**48**, **49**, **50**).[85]

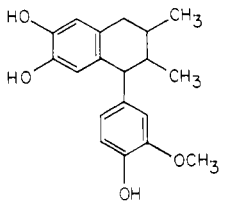


Antitumor Activities. The lignans 4′-demethyldeoxypodophyllotoxin (**51**) and β-peltatin (**52**) from *Hyptis*

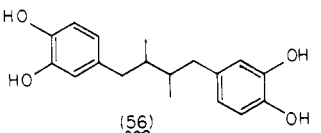


verticillata Jaca (Labiatae) serve as antimitotic agents.[102] 3-Demethylpodophyllotoxin and α- and β-peltatin from *Linum album* (Linaceae) are moderately active against 9KB cell culture and lymphocytic leukemia.[103] Deoxypodophyllotoxin (**53**) is the cytotoxic principle of *Libocedrus decurrens* (Pinaceae) against 9KB in vitro test system.[104] Podophyllotoxin (**54**) is active against sarcoma 37 in mice.[105]

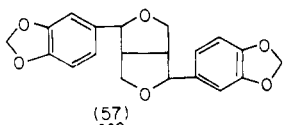
Antibacterial Activity. Norisoguaiacin (**55**) showed



(55)
Norisoguaiacin



(56)
nordihydroguaiaretic acid

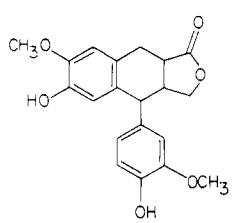


(57)
sesamin

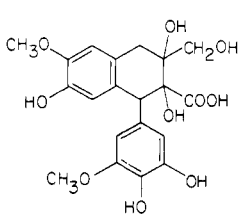
inhibitory action against several *Streptococcus* species.[106]

Antioxidant Activity. Nordihydroguaiaretic acid (NDGA) (**56**) from the resinous exudates of the members of creosote bush (*Larrea*, Fam. Zygophyllaceae)[107-110] is a potent antioxidant which has been used to prevent rancidity in many materials including vegetable and animal fats,[111,112] fishes,[112] and fish oils.[113] NDGA is also a protective agent against the oxidation of vitamins A[111,114] and E.[115] Scientists in Centro de Investigacion en Quimica Aplicada (CIQA) Saltillo, Mexico, have a major program underway presently to develop the NDGA-flavonoid resin on the leaf surface of *Larrea tridentata* as an antioxidant for oil, rubber, pharmaceuticals, and foodstuffs, as a fungicide, and as a stabilizing agents for polymers such as adhesives and plastics. Sesamin (**57**) and conidendrin[58] are also used as antioxidants. Sesamin is an insecticide[116] and it is used as an synergist with other insecticides such as pyrethrins.[117,118]

Commercial Extraction Processes. Lignans are extractable from wood with hot water and various organic solvents in yields of from 1 to 30% of dry heartwood. Readily recoverable lignans related to conidendrin (**58**) are



58



59

present in hemlock and spruce species while important types related to plicatic acid (**59**) are present in western red cedar (*Thuja plicata*). Although high-yield commercial extraction processes have been developed for both the conidendrin and plicatic acid types (see ref 119, 120) in a number of laboratories including MacMillan Bloedel, Ltd., Rayonier Canada Ltd., Crown Zellerbach Corporation, and the Western Forests Products Laboratory (now Forintek Canada Corp.), no favorable markets have been established for these natural lignans or their derivatives.

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Potential Utilization of Brazilian Wood Extractives

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Attention is called to the potentialities of Brazilian trees in offering compounds of biological interest. The chemical knowledge which has been acquired about phenolics (arylpyrones, benzophenones, neolignans, xanthones, coumarins, isocoumarins, flavonoids), polyketides, terpenoids (sesqui-, di-, triterpenoids, prenylnaphthoquinones), and alkaloids is reviewed, provided a group of biogenetically related compounds has been isolated and biodynamic activity can be pointed out.

A conservative estimate situates the number of plant species native to Brazil close to 120000. An ever increasing number of Brazil's wood-producing species is constantly being absorbed into the mainstream of international commerce. Their utilization for uses other than construction and carpentry, charcoal, and cellulose manufacture constitutes a challenge which chemists and pharmacologists have only recently started to meet. It is true that interest in the natural wealth of the country reaches back to the time of its discovery by Portuguese seafarers in the year 1500. The first orderly description of plants used for medicinal purposes by the inhabitants was undertaken by a scientific mission brought to the northeastern part of the country by Maurice of Nassau during the time of its occupation by the Dutch (1630–1654). It was Willem Pies, a physician, who described the most important indigenous drugs, among which were jaborandi, ipecac, and tobacco.

One hundred and seventy years later, another mission played a decisive role in the beginnings of scientific activity in Brazil. Brought to the recently independent monarchy by princess Leopoldina of Austria, the bride of Pedro I, the country's first emperor, its most famous members, Johann Baptist von Spix, zoologist, and Karl Friedrich Phillip von Martius, botanist, exhaustively documented their thorough observations on the country's natural wealth. It was upon Martius' encouragement that Theodor Peckolt, an obscure pharmacist from Silesia, arrived in Brazil in 1847. With admirable drive and enthusiasm Peckolt analyzed by methods available to him at the time over 6000 plants, publishing the results of his studies in more than 150 papers. Although his analyses were necessarily crude by present-day standards, he nevertheless described a number of chemical entities which have withstood the rigor of modern scrutiny. Thus, Peckolt (1870) was probably the first to isolate, describe, and name an iridoid. He extracted the bitter principle of agoniada bark (*Plumeria lancifolia* Mart., Apocynaceae) and accordingly called it agoniadin. Twenty-five years later Boorsma (1894) isolated the same substance from *P. acutifolia* Poir. and, unaware of Peckolt's work, named it plumierid. Shortly afterward Franchimont (1899, 1900) recognized the identity of the two compounds. The name plumierid or plumieride has been maintained in the literature, but precedence actually belongs to agoniadin. The structure (Figure 1, **1**) was elucidated, 88 years after isolation, by Halpern and Schmid (1958).

The properties of specific pure iridoids have been investigated only in a few cases (Sticher, 1977). Plumieride exhibits a weak activity against fungi, while several nonglucosidic iridoids from *Plumeria* species were shown to possess antimicrobial properties (Jewers et al., 1975).

Iridoids, both nonglucosidic and in the form of glucosides, have also been found in another Brazilian tree, the genipapo (*Genipa americana* L., Rubiaceae). Genipic acid and genipinic acid (Figure 1, **2**) are also antimicrobial (Tallent, 1964), whereas the glucosides geniposide and geniposidic acid (Figure 1, **3**) exhibit purgative activity (Yamaguchi et al., 1974, 1976; Inouye et al., 1974).

These and investigations on many other natural compounds have been sparked by indigenous use of their plant hosts, a topic which we brought recently into historical focus with respect to Amazonian species (Gottlieb and Mors, 1978). The best known outcomes of such studies concern emetine from ipecac, pilocarpine from jaborandi, and curarizing alkaloids from several Loganiaceae and Menispermaceae, classical drugs originally introduced from Brazil and supplied from the mentioned plant sources to this day (Mors and Rizzini, 1966; Valle, 1978).

In more recent times, particularly during the last 20 years, considerable activity in the field of phytochemistry has been going on in Brazil. Hundreds of compounds have been isolated from plants and their structures have been established. Brazilian pharmacologists have, nevertheless, only very recently begun to undertake a purposeful study of plant products, concentrating to this day on the so-called etiotropic properties, i.e., activity against organisms which are the causative agents of diseases. Outstanding among these are schistosomiasis and Chagas' disease, nonexistent in the more developed countries of Europe and North America. The systematic study of organotropic properties, i.e., those manifest on higher animals and man, is just now being initiated. It is to be expected that many of these investigations will lead to interesting practical applications.

We shall now endeavor to convey, in a number of charts, the chemical knowledge which has been acquired about

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