REVIEW

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An update on bioactive plant lignans

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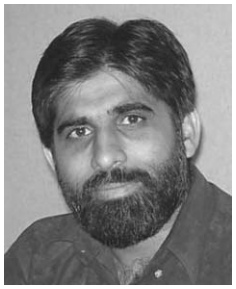
Lignans are a class of secondary plant metabolites produced by oxidative dimerization of two phenylpropanoid units. Although their molecular backbone consists only of two phenylpropane (C_6–C_3) units, lignans show an enormous structural diversity. There is a growing interest in lignans and their synthetic derivatives due to applications in cancer chemotherapy and various other pharmacological effects. This review deals with lignans possessing anticancer, antioxidant, antimicrobial, anti-inflammatory and immunosuppressive activities, and comprises the data reported in more than 100 peer-reviewed articles, so as to highlight the recently reported bioactive lignans that could be a first step towards the development of potential new therapeutic agents.

Muhammad Saleem obtained his M.Sc. degree from Islamia University, Bahawalpur (Pakistan) and his Ph.D. degree from the HEJ Research Institute of Chemistry at the University of Karachi, where he worked with Dr Muhammad Shaiq Ali on the isolation and biological evaluation of natural products from marine and terrestrial sources. He was appointed to the Pakistan Council of Scientific and Industrial Research laboratories, Karachi in 2000 and served as Senior Scientific Officer. This was followed by his appointment as a Korea Science and Engineering Foundation postdoctoral fellow at the Korea Institute of Science and Technology (KIST), where he worked with Dr Yong Sup Lee on natural products research. Afterwards, he was appointed as a visiting scientist at KIST and is still engaged in R&D activities.

Hyoung Ja Kim received her MSc degree in Chemistry from the University of SangMyung, Korea, in 1993. She is currently working as a research scientist on the isolation, structure elucidation, and modification of natural products at the Life Sciences Division of Korea Institute of Science and Technology (KIST). She is also undergoing a Ph.D. course at the College of Pharmacy, Kyung Hee University under the supervision of Professor Yong Sup Lee.

Muhammad Shaiq Ali did his M.Sc. at the University of Karachi. He obtained his M.Phil. degree in microbiological transformation from the University of Sussex (UK) and his doctoral degree in marine chemistry in 1992 under the supervision of Professor Viqar Uddin Ahmad of the HEJ Research Institute of Chemistry at the University of Karachi. In 1994, he was appointed as an Assistant Professor at the HEJ Research Institute of Chemistry, and presently he is working as Associate Professor. His research interests are marine and terrestrial natural product chemistry and the microbiological transformation of organic molecules.

Yong Sup Lee received his B.En. degree from Seoul National University in 1983. He obtained his M.Sc. and Ph.D. degrees in organic chemistry from the Korea Advanced Institute of Science and Technology (KAIST) under the supervision of Dr Hokoon Park. He worked in the fields of medicinal chemistry and natural products chemistry at KIST as a principal research scientist from 1985 to 2004. He undertook postdoctoral research at North Carolina State University in 1994 with Professor Daniel L. Comins, and was a visiting scientist at the University of Illinois at Chicago with Professor John M. Pezuuto in 2001. In 2004, he was appointed as an Associate Professor at the College of Pharmacy, Kyung Hee University (Korea). His research interests are development of new drug candidates from natural products or by organic synthesis.


Muhammad Saleem


Hyoung Ja Kim


Muhammad Shaiq Ali


Yong Sup Lee

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1 Introduction

In spite of the impressive progress that has been made in organic chemistry, about 25% of all prescription medicines to date are of plant origin. When we look at the influence of natural products upon anticancer drug discovery and design, the percentage is even higher. Approximately 60% of all drugs now in clinical trials for the multiplicity of cancers are either natural products, compounds derived from natural products, or contain pharmacophores derived from natural products.[1,2] In recent decades, renewed interest in investigating natural products has led to the advent of several important anticancer substances such as vinblastine, vincristine, paclitaxel, and the semi-synthetic drugs Etoposide™, Etopophos™ and Teniposide™. The latter three compounds are chemical derivatives of podophyllotoxin, a natural product belonging to the lignan group of compounds.

Lignans are a class of secondary plant metabolites produced by oxidative dimerization of two phenylpropanoid units. The term *lignan* is applied to the optically active dimers of phenylpropanoids linked by the central carbon atoms of their side chains. Lignans are mostly present in nature in the free form, while their glycoside derivatives are only a minor form. They are widely distributed in the plant kingdom and have been found in species belonging to more than seventy families. Lignans are found in roots, rhizomes, stems, leaves, seeds and fruits. With some exceptions, these sources do not provide commercially useful quantities. The exception could be the wound resins of trees, since lignans occur here in simple mixtures with other natural products, and are readily separated in substantial quantities. To some extent, this is also true for heartwood sources.[3] Extraordinarily high concentrations of lignans (6–24%, w/w) have been recently found in wood knots of *Picea abies*.[4] Flax is one of the richest sources of plant lignans.[5] Flax is particularly rich in the lignan secoisolariciresinol diglycoside (SDG), and it also contains small amounts of the lignans matairesinol, pinoresinol and isolariciresinol.[6,7] Lignans are found in most fibre-rich plants, including grains such as wheat, barley and oats; legumes such as beans, lentils and soybeans; and vegetables such as garlic, asparagus, broccoli and carrots.

In spite of their extensive distribution, their biological functions in plants are as yet unclear. Because some lignans have potent antimicrobial, antifungal, antiviral, antioxidant, insecticidal and antifeeding properties, they probably play an important role in plant defense against various biological pathogens and pests. Furthermore, they may participate in plant growth and development.[3] In addition to their purpose in nature, lignans also possess significant pharmacological activities, including antitumor, anti-inflammatory, immunosuppressive, cardiovascular, antioxidant and antiviral actions.[8–14]

From a chemical point of view, lignans show an enormous structural diversity, although their molecular backbone consists only of two phenylpropane (C_6–C_3) units. Nature itself offers a huge library of compounds, which can hardly be surpassed even by modern combinatorial chemistry techniques. Many types of biological activity have been reported for members of this group of natural products. In many cases, lignans have served as a lead compound for the synthesis of derivatives to optimize their activity, and to study structure–activity relationships. The aim of this review is not to give a complete listing of all biological activities reported for lignans, but to highlight the recent pharmacological studies which could be a first step towards the development of potential new therapeutic agents. The discussion extends to lead compounds with anticancer, antioxidant and antimicrobial activities, and covers the literature between 2002 and 2004.

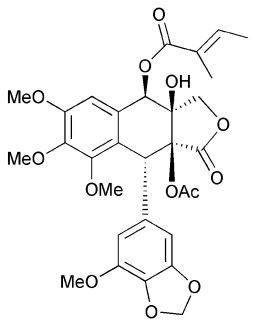
2 Anticancer plant lignans

Cancer is a disease of worldwide importance. Its incidence in the developed countries is rising, and it occupies second place in the order of causes of death. A similar tendency can be observed in the developing world: the gradual improvement in life expectancy is associated with elevated cancer incidence and mortality. Accordingly, we might assume that malignancy will be soon a global problem, with its associated burden. Therefore, it is easy to understand that cancer therapy is a focus of common interest.

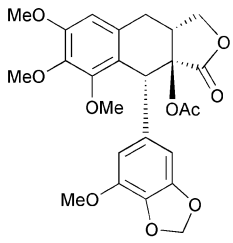
Cancer chemotherapy started with the discovery of the cytostatic effect of nitrogen mustard and its derivatives more than five decades ago. This observation opened the way for the synthesis of various alkylating agents and antimitotics with antitumor activity against several human malignancies. However, the considerable toxicity of these drugs limited their application, and only hormone-active products were relatively well-tolerated. Besides, the majority of human malignant tumors proved to be chemoresistant. Consequently, there was still an urgent need for finding less toxic compounds possessing a broader antitumor spectrum.

Cancer chemotherapy involves the use of anticancer drugs, which may be obtained from natural or synthetic sources. It is noteworthy that most of these anticancer agents are structurally so complex that they would never have emerged from a synthetic program alone or from a combinatorial approach to drug discovery. Thus, the natural products approach to discovery and development of new anticancer drugs is attractive in that it is complementary to synthesis and biosynthesis.

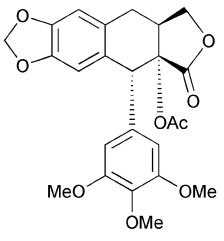
The resin of *Commiphora erlangeriana* is known to be poisonous to humans and animals, and has traditionally been used as an arrow poison.[15] Since phytochemical studies on this plant material resulted in the isolation of four major lignans **1–4** that closely relate to the structure of podophyllotoxin **5**, it was hypothesized that the well-known poisoning effect of the resin could in part be due to direct toxicity to mammalian cells.



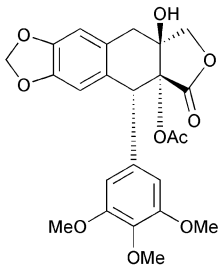
Erlangerins A (**1**)



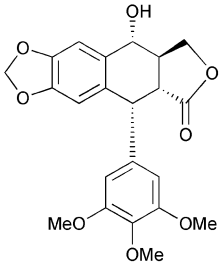
Erlangerins B (**2**)



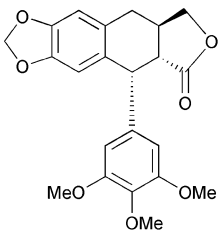
Erlangerins C (**3**)



Erlangerins D (**4**)



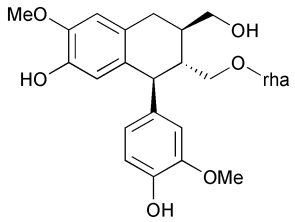
Podophyllotoxin (**5**)



4-Deoxypodophyllotoxin (**6**)

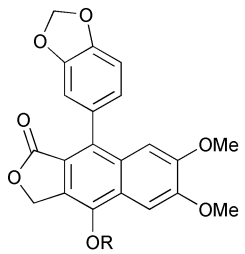
Hence, the toxicity of **1–4** was studied by measuring the viability of two human (HeLa and EAhy926) and two murine (L929 and RAW264.7) cell lines. As assessed by the MTT assay, the effects of **3** and **4** closely follow the activity profile of **5**.[15] In contrast, **1** and **2** suppressed cell viability only at higher concentrations. The structures, as well as the observed biological activity, of **3** and **4** closely relate to podophyllotoxin **5** and 4-deoxypodophyllotoxin **6**, and hence may indicate a similar mechanism of action.[15]

Aviculin **7** is a lignan glycoside which exhibited a more potent inhibitory effect on cancer cell invasion in an *in vitro* study.[16] Ohashi *et al.* examined **7** with respect to its effects on cancer cell invasion through a rat mesothelium monolayer using an MM1 cell line isolated from rat ascites hepatoma AH130 cells.[16]



Aviculin (**7**)

The lignans **8–11** were explored for their anticancer activities against a number of cancer cells *in vitro*. Justicidin A **9** has shown significant cytotoxic activities against Hep3B, HepG2, MCF-7 and MCF-7-*ras*. Compound **11** showed almost the same cytotoxic potencies against these cancer cell lines as **9**, with stronger cytotoxic activities against Hep3B, SiHa, HepG2, HT-29, HCT 116, MCF-7 and MCF-7-*ras* than its aglycon **10**. Compound **8** showed significant cytotoxic activity against the Hep3B and HepG2 cell lines.[17] Compounds **9** and **11** also strongly enhanced tumor necrosis factor R (TNF-R) generation from mouse macrophage-like RAW264.7 cells stimulated with lipopolysaccharide (LPS). These results revealed that *O*-methylation or *O*-glycosylation at C-4 of **10** enhanced the cytotoxic activity towards several of the cell lines used, while *O*-glycosylation with more than one sugar unit at C-4 of **10** led to less cytotoxic activity.[17]



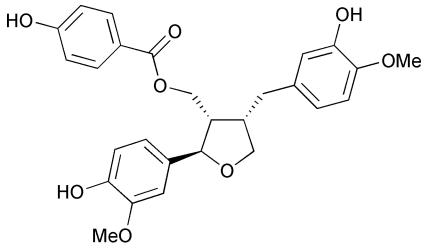
R = 4-O-α-L-arabinopyranosyl-(1'''-2'')-β-D-apiofuranosyl, procumbenoside A (**8**)

R = Me, Justicidin A (**9**)

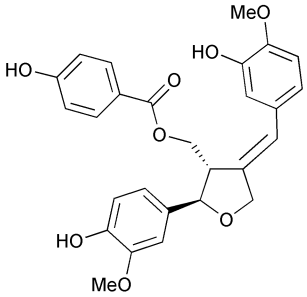
R = H, Diphyllin (**10**)

R = β-D-apiofuranosyl, Tuberculatin (**11**)

The lignan compounds **12** and **13** isolated from *Agastache rugosa* inhibited etoposide-induced apoptosis in U937 cells with IC_{50} values of 15.2 and 11.4 μg mL^{-1}, respectively. From these results, **12** and **13** seem to be worthy candidates for further research as potential anti-apoptotic agents.[18]

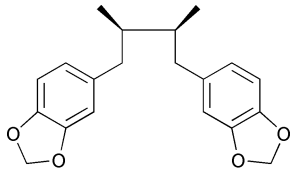


Agastinol (**12**)

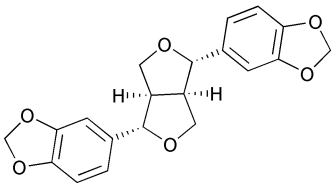


Agastenol (**13**)

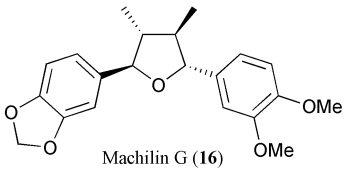
Several reports have suggested that PLCγ1† plays a key role in the proliferation and progression of human cancer.[19–21] Lee *et al.* evaluated **14–17** for their abilities to inhibit PLCγ1 *in vitro*.[22] These compounds **14–17** exhibited dose-dependent inhibitory activities on PLCγ1 with IC_{50} values of 8.8–18.5 μM. Accordingly, the antiproliferative activities of **14–17** were tested on three human cancer cell lines, A549 (lung), MCF-7 (breast), and HCT-15 (colon), and showed good inhibitory activities (IC_{50} = 1.4–8.3 μM).[22] The structure–activity relationship of **14–17** suggested that the benzene ring with the methylene dioxy group is responsible for the expression of inhibitory activities against PLCγ1. These results suggest that inhibition of PLCγ1 may be an important mechanism for antiproliferative effect on the human cancer cells. Therefore, these PLCγ1 inhibitors may be worthy candidates as cancer chemopreventive and chemotherapeutic agents, and as a new class of PLCγ1 inhibitors.



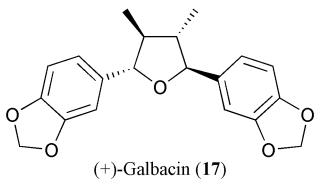
Machilin A (**14**)



(-)-Sesamin (**15**)



Machilin G (**16**)

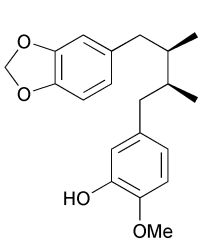


(+)-Galbacin (**17**)

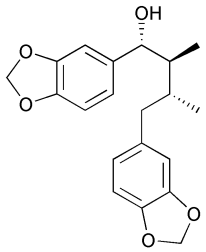
Park *et al.* isolated **18–21** from *Machilus thunbergii*, and assessed their ability to activate caspase-3 activity in human promyeloid leukemic HL-60 cells.[23] These compounds induced an apoptotic effect in HL-60 cells in a caspase-3 activation manner. It is possible that these compounds may be valuable as

† Phospholipase Cγl (PLCγl) is a substrate for several receptor tyrosine kinases and its catalytic activity is increased by tyrosine phosphorylation.

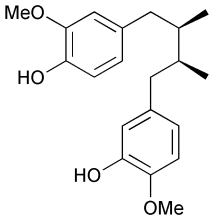
cancer chemopreventive agents. In DNA topoisomerase I and II assays *in vitro* at a concentration of 100 μM, **20** showed the most potent inhibitory activity, with 93.6 and 82.1% inhibition, respectively, and weak cytotoxicity against HT-29 and MCF-7.[24] In a similar study, Li *et al.* reported that two more lignans, **22** and **23**, showed inhibition of topoisomerase I and II. The transportation of these lignans through cell and nuclear membranes, in order to reach the target DNA topoisomerases I and II, could be possible barriers in the MTT assay.[24]



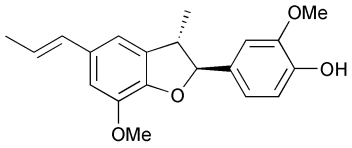
Macelignan (**18**)



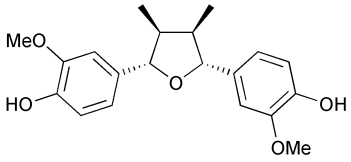
Oleiferin C (**19**)



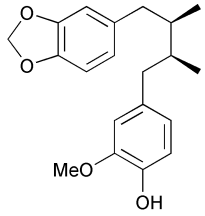
Meso-dihydroguaiaretic acid (**20**)



Licarin A (**21**)

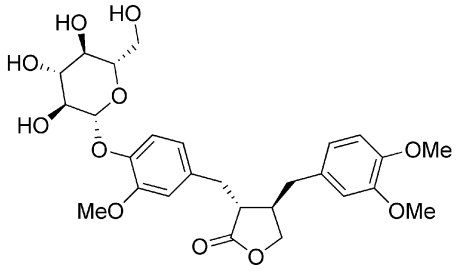


Nectandrin B (**22**)



Erythro-austrobailignan-6 (**23**)

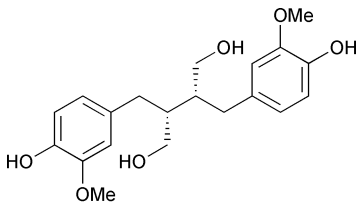
Although lignans have been reported to possess antitumor activity in various cancer cells, their anticancer effects in human prostate cancer have rarely been established. Chueh *et al.* examined the effect of **24** on growth regulation in prostate cancer PC-3 cells.[25] Treatment of PC-3 cells with **24** decreased the cell number in a concentration- and time-dependent manner. Arctiin **24** preferentially induced cell detachment, but did not have antiproliferation or cytotoxic effects in PC-3 cells. This investigation revealed that **24** significantly induces cell detachment and decreases the cell numbers by the up-regulation of MUC-1 mRNA and protein in PC-3 cells.



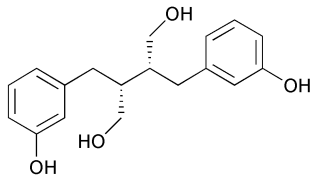
Arctiin **(24)**

Metastasis is a major cause of morbidity and mortality in breast cancer, with tumor cell invasion playing a crucial role in the metastatic process. Some lignans were investigated for their effects on the invasion of a breast cancer cell line (MDA-MB-231) through Matrigel.[30] Among the tested lignans, **25** and its metabolite enterodiol **26** induced a significant decrease in cell invasion, however, this only occurred at the highest concentration tested (50 μM).[26]

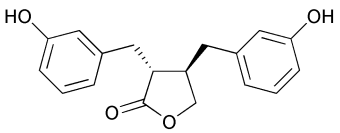
The mammalian lignans enterodiol **26** and enterolactone **27** have been shown to inhibit breast and colon carcinoma. In addition, Lin *et al.* were the first to report the effect of lignans on prostatic carcinoma.[27] At 10–100 μM concentration, **27** significantly inhibited the growth of PC-3, DU-145 and LNCaP cell lines, whereas **26** only inhibited PC-3 and LNCaP cells. While **27** was a more potent growth inhibitor than **26**, both were less potent than genistein. These studies revealed that **26** and **27** suppress the growth of prostate cancer cells, and may do so *via* hormonally dependent and hormonally independent mechanisms.[27]



Seco-isolariciresinol (**25**)

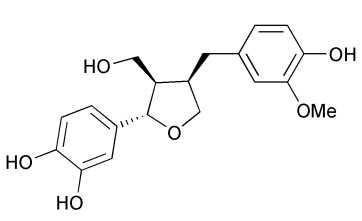


Enterodiol (**26**)

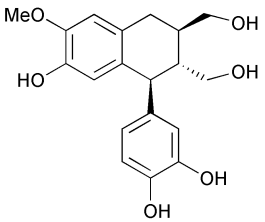


Enterolactone (**27**)

The lignans **25**, **28** and **29** from *Taxus wallichiana* were explored for anticancer properties. It was found that all three lignans were active against colon adenocarcinoma cell lines in the MTT assay. However, **25** and **29** were most active against the Caco-2 cell line in a clonogenic assay. Compound **29** was equal to or even better than standard reference compounds such as taxol and doxorubicin against colon adenocarcinoma (Caco-2) in both assay systems. Taxiresinol **28** was active against ovary teratocarcinoma and breast adenocarcinoma cell lines, albeit at higher concentration.[28]

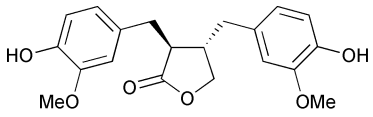


(+)-Taxiresinol (**28**)

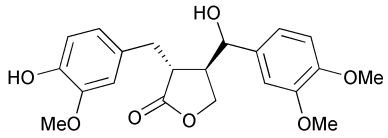


Isotaxiresinol (**29**)

Kim *et al.* isolated **30** and **31** from safflower seeds, and reported their potent cytotoxic effect on human promyleocytic leukemia HL-60 cells.[29] They investigated whether mechanisms of matairesinol-induced cell death are associated with apoptosis (programmed cell death). Matairesinol **30** dose-dependently reduced viability of HL-60 cells. The results indicate that **30**-induced HL-60 cell death was due to DNA damage and apoptosis.

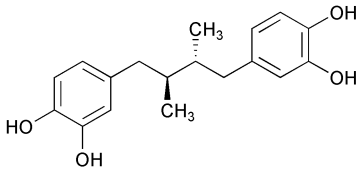


Matairesinol (**30**)

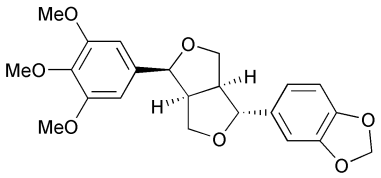


2-Hydroxyarctigenin (**31**)

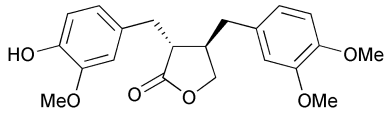
Nordihydroguaiaretic acid **32**, commonly used for the inhibition of lipoxygenase isoenzymes, showed the strongest growth inhibition, followed by **33** and **34**.[30] These lignans caused a time- and dose-dependent loss of mitochondrial membrane potential (MMP), down-regulation of the anti-apoptotic protein bclxL and an increase of the apoptotic index. With respect to these results, naturally occurring lignans could be useful in the therapy and chemoprevention of colorectal tumors.



Nordihydroguaiaretic acid (**32**)

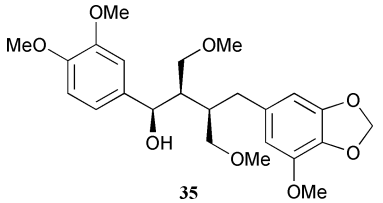


(+)-Epiaschantin (**33**)



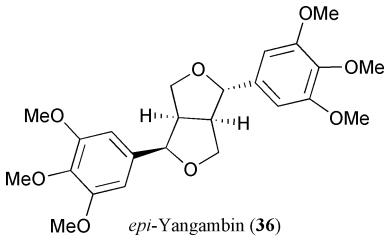
Arctigenin (**34**)

Lignan **35** showed antiproliferative activity against specific markers of apoptosis, such as bcl2, c-myc and caspases, and effects on telomerase.[31] Four specific cancer cell lines (HepG2, EL-1 monocytes, HeLa and MCP7) were used in this study. The results indicate that **35** was capable of inhibiting telomerase activity, and could also inhibit bcl2 and activate caspase 3 and caspase 8, whose significance in the induction of apoptosis is well-known. It was suggested that this compound could serve as a valuable chemotherapeutic drug after further evaluation.

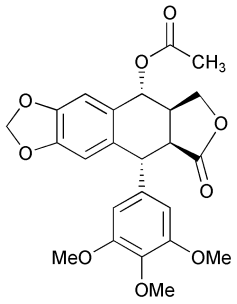


35

Compounds **36** and **37** were isolated from the EtOAc extract of the twigs of *Hernandia ovigera*, using a soft agar assay with JB6 murine epidermal cells. Both **36** and **37** exhibited significant inhibition of the transformation of murine epidermal JB6 cells.[32] These two compounds were also tested at higher concentrations to check their cytotoxic effects against JB6 cells; they showed IC_{50} values of 1.2 and 5.7 μg mL^{-1}, respectively. This 10-fold difference in activity provides some indication that **36** and **37** may be suitable as potential cancer chemopreventive agents, but further testing will be required to establish their efficacy.

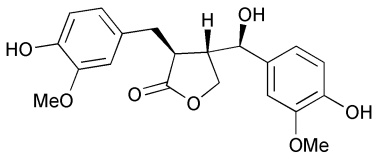


epi-Yangambin (**36**)



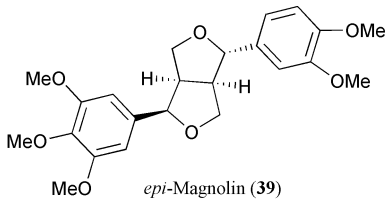
(+)-7'-Acetylpicropodophyllin (**37**)

The antitumor activity of hydroxymatairesinol (**38**) was studied in 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced rat mammary cancer.[33] **38** had a statistically significant inhibitory effect on tumor growth. Prevention of tumor formation was also evaluated in the Apc(Min) mice model, which develops intestinal polyps spontaneously. In short-term toxicity studies (up to 28 days), **38** was essentially non-toxic when given to rats and dogs (daily doses up to 2000 and 665 mg kg^{-1}, respectively). In human studies, **38** has been given in single doses up to 1350 mg to healthy male volunteers without treatment-related adverse events. In another study, **38** was explored for its chemopreventive effects on the development of mammary carcinoma induced by DMBA in rats.[34] Compound **38** reduced tumor volume and tumor growth, but no significant reduction in tumor multiplicity (no. of tumors per rat) was observed. Anticarcinogenic effects of dietary **38** were also evident when administration started after DMBA induction, as growth inhibition of established tumors. Saarinen *et al.* further explored **38** for its metabolism and biological actions in animals.[35] Compound **38** decreased the number of growing tumors and increased the proportion of regressing and stabilized tumors in the rat DMBA-induced mammary tumor model. At 50 mg kg^{-1}, **38** had no estrogenic or anti-estrogenic activity in the uterine growth test in immature rats.

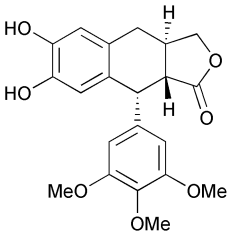


Hydroxymatairesinol (**38**)

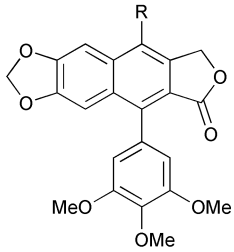
Ito *et al.* isolated antitumor compounds from the seeds of *Hernandia ovigera* and tested them for their inhibitory effects on Epstein-Barr virus early antigen activation induced by 12-*O*-tetradecanoylphorbol 13-acetate (TPA) in Raji cells.[36] The antitumor activity of each of the seven lignans **6** and **39–44** was tested in a short-term *in vitro* assay of TPA-induced EBV-EA activation in Raji cells. All compounds tested showed inhibitory effects on EBV activation, exhibited significant inhibitory effects at high concentration (1×10^3 mole ratio), and were found to be slightly weaker than that of β-carotene, a vitamin A precursor that has been used commonly in cancer prevention studies.[37] These results suggest that lignans might be valuable as antitumor compounds in chemical carcinogenesis.



epi-Magnolin (**39**)

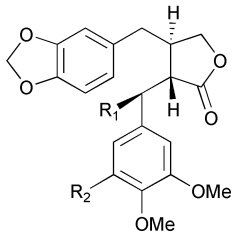


6,7-Demethylenedeoxypodophyllotoxin (**40**)



1,2,3,4-Dehydrodeoxypodophyllotoxin (**41**), R = H

Dehydropodophyllotoxin (**42**), R = OH



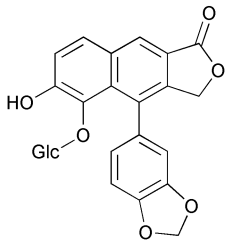
Bursehernin (**43**), $R_1 = R_2 = H$

Podorhizol (**44**), $R_1 = OH$, $R_2 = OMe$

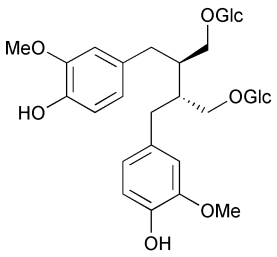
Takasaki *et al.* explored the lignans **24** and **34**, obtained from the aerial part of *Saussurea medusa*, for their antitumor effects.[38] These compounds exhibited a remarkable antitumor effect in the two-stage carcinogenesis test of mouse skin tumors with DMBA as an initiator and TPA as a promoter, by both topical application and oral administration. Furthermore, **34** exhibited potent antitumor activity in the two-stage carcinogenesis test of mouse pulmonary tumors with 4-nitroquinoline-*N*-oxide as an initiator and glycerol as a promoter.[38]

The acute toxicity (24 h) and general behavior in mice of elenoside (**45**), from *Justicia hyssopifolia*, was studied. Compound **45** showed moderate cytotoxicity and central depressive properties.[39] It also displayed cytotoxic activity towards the human tumor cell line panel of the US National Cancer Institute (NCI). The results indicated that **45** had central depressant effects, and its cytotoxic activity suggested that **45** and its genin derivatives merit further investigation as antitumor drugs. In another study, the cytotoxic effect of **45** towards human cancer cell lines was investigated.[40] An examination of the general pharmacological effects of **45** using the Irwin test[41] showed a decrease in the motor affective response which, in part, reflects the effect of **45** on social behavior. These results suggest that **45** has a similar action to the sedative-hypnotic effect of the barbiturates. Compound **45** was compared with a major tranquilizer (chlorpromazine), and it was found that administration of **45** resulted in loss of spontaneous movements, muscular tone and righting reflex. Thus, **45** exhibits CNS-depressant action similar to that of other psychopharmacological agents. It was also found to be cytotoxic to leukemia cell lines (CCRFCEM, K-526, MOLT-4, RPMI-8226), and some activity was also observed against specific melanoma cell lines (M19-MEL, SK-MEL-2), a CNS cancer cell line (SNB-19), a renal cancer cell line (UO-31) and a colon cancer cell line (HCC-2998). These data revealed that **45** appears to be a sedative with a broad-spectrum cytotoxicity.

Increased plasma insulin-like growth factor I (IGF-I) concentrations are associated with increased breast cancer risk. Rickard *et al.* studied the effects of flaxseed and its constituent lignan **46** on plasma IGF-I levels in rats treated with or without *N*-methyl-*N*-nitrosourea (MNU).[42] In MNU-free rats, both flaxseed and **46** reduced plasma IGF-I levels, which were inversely related to urinary lignan excretion. Flaxseed and its constituent **46** inhibit mammary tumor development in rats. The anticancer effect of flaxseed and **46** may be related, in part, to reductions in plasma IGF-I.[42]

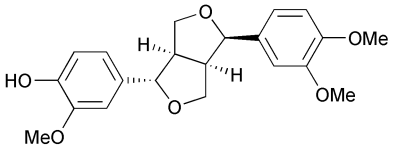


Elenoside (**45**)

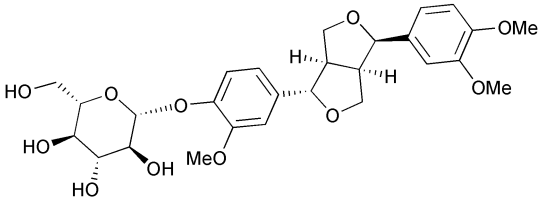


Secoisolariciresinol diglycoside (SDG, **46**)

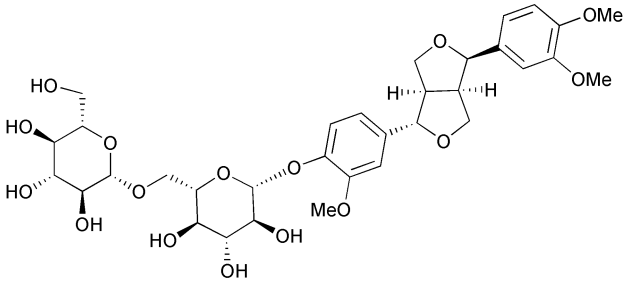
The furan lignans **47**–**49** were isolated from *Lancea tibetica*, and their antitumor activities on human hepatoma cell SMMC-7721, human uterine cervix carcinoma cell HeLa, hamster lung fibroblast cell V79 and mouse melanoma cell B16 *in vitro* were studied by using an MTT calorimetric assay with vincristine as the positive control.[43] The results showed that **47** had strong cytotoxicities on the four tested cell lines when compared to that of vincristine, whereas **48** and **49** had little effect on the proliferation of the tested cell lines. The loss of antitumor activity of **48** and **49** may be due to the substitution of the hydrogen of the phenolic hydroxyl group.



Phillygenol (**47**)



Phillyroside (**48**)



Phillygenoldiglycoside (**49**)

These studies suggested that lignans might be valuable as antitumor compounds in chemical carcinogenesis and as chemopreventing agents. Lignans can be sedative non-toxic agents for the inhibition of apoptotic agents. PLCγ1 inhibitory

Table 1 Summary of the lignans possessing anticancer activities

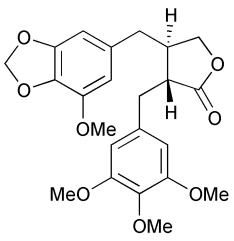
Compound	Name	Plant source	Target	Ref.
1	Erlangerin A	*Commiphora erlangeriana*	HeLa, EAhy926, L929, RAW 264.7	15
2	Erlangerin B	*Commiphora erlangeriana*	HeLa, EAhy926, L929, RAW 264.7	15
3	Erlangerin C	*Commiphora erlangeriana*	HeLa, EAhy926, L929	15
4	Erlangerin D	*Commiphora erlangeriana*	HeLa, EAhy926, L929	15
6	4-Deoxypodophyllotoxin	*Hernandia nymphaeifolia*, *Hernandia ovigera*	Inhibition of TPA-induced EBV-EA activation	15, 40
7	Aviculin	*Mallotus furetianus*, *Chaenomeles sinensis*	MM1 cell line	16
8	Procumbenoside A	*Usticia procumbens*	212, Hep3B, HepG2 cell lines	17
9	Justicidin A	*Usticia procumbens*	Hep3B, HepG2, MCF-7, MCF-7-*ras*, TNF-R	17
10	Diphyllin	*Usticia procumbens*	Hep3B, HepG2, MCF-7, MCF-7-*ras*, SiHa, HT-29, HCT 116	17
11	Tuberculatin	*Usticia procumbens*	Hep3B, HepG2, MCF-7, MCF-7-*ras*, SiHa, HT-29, HCT 116, TNF-R	17
12	Agastinol	*Agastache rugosa*	Apoptosis in U937	18
13	Agastenol	*Agastache rugosa*	Apoptosis in U937	18
14	Machilin A	*Machilus thunbergii*	PLCγ1 *in vitro*	22
15	(−)-Sesamin C	*Machilus thunbergii*	PLCγ1 *in vitro*	22
16	Machilin G	*Machilus thunbergii*	PLCγ1 *in vitro*	22
17	(+)-Galbacin	*Machilus thunbergii*	PLCγ1 *in vitro*	22
18	Macelignan	*Machilus thunbergii*	Promyeloid leukemic HL-60 cells	23
19	Oleiferin	*Machilus thunbergii*	Promyeloid leukemic HL-60 cells	23
20	*meso*-Dihydroguaiaretic acid	*Machilus thunbergii*	Promyeloid leukemic HL-60 cells, HT-29, MCF-7	23, 24
21	Licarin A	*Machilus thunbergii*	Promyeloid leukemic HL-60 cells	23
22	Nectandrin B	*Machilus thunbergii*	HT-29, MCF-7	24
23	*erythro*-Austrobailignan-6	*Machilus thunbergii*	HT-29, MCF-7	24
24	Arctiin	*Saussurea medusa*	PC-3 cells, mouse skin tumors	25, 38
25	*seco*-Isolariciresinol	*Sarcomelicope megistophylla*, *Taxus wallichiana*	MDA-MB-231, Caco-2	26, 28
26	Enterodiol	Mammalian lignana	MDA-MB-231, PC-3, DU-145, LNCaP	26, 27
27	Enterolactone	Mammalian lignana	PC-3, DU-145, LNCaP	27
28	Taxiresinol	*Taxus wallichiana*	Caco-2	28
29	Isotaxiresinol	*Taxus wallichiana*	Caco-2	28
30	Matairesinol	Safflower seeds	HL-60 cells	28
31	2-Hydroxyarctigenin	Safflower seeds	HL-60 cells	29
32	Nordihydroguaiaretic acid (NDGA)	—	Lipoxygenase isoenzymes	30
33	Epiashantin	*Hernandia ovigera*	Lipoxygenase isoenzymes	30
34	Arctigenin	*Saussurea medusa*	Lipoxygenase isoenzymes, mouse skin tumors	30, 38
35	7′-Hydroxy-3′,4′,5,9,9′-pentamethoxy-3,4-methylene dioxy lignan	*Phyllanthus urinaria*	HepG2, EL-1 monocytes, HeLa, MCP7	31
36	*epi*-Yangambin	*Hernandia nymphaeifolia*, *Hernandia ovigera*	JB6 cells	32
37	(7R,8S,7′R,8′R)-(+)-7′-Acetylpicropodophyllin	*Hernandia ovigera*	JB6 cells	32
38	Hydroxymatairesinol (HM-3000)	*Picea abies*	Rat mammary cancer	33–35
39	*epi*-Magnolin	*Hernandia nymphaeifolia*, *Hernandia ovigera*	Inhibition of TPA-induced EBV-EA activation	36
40	6,7-Demethylenedeoxypodophyllotoxin	*Hernandia ovigera*	Inhibition of TPA-induced EBV-EA activation	36
41	1,2,3,4-Dehydrodeoxypodophyllotoxin	*Hernandia ovigera*	Inhibition of TPA-induced EBV-EA activation	36
42	Dehydropodophyllotoxin	*Hernandia ovigera*	Inhibition of TPA-induced EBV-EA activation	36
43	Bursehernin	*Hernandia ovigera*	Inhibition of TPA-induced EBV-EA activation	36
44	Podorhizol	*Hernandia ovigera*	Inhibition of TPA-induced EBV-EA activation	36
45	Elenoside	*Justicia hyssopifolia*	Human tumor cell line panel NCI, leukemia cell lines (CCRFCEM, K-526, MOLT-4, RPMI-8226)	39, 41
46	Secoisolariciresinol diglycoside (SDG)	Flaxseed	IGF-I	42
47	Phillygenol	*Lancea tibetica*	Hepatoma cell SMMC-7721, human carcinoma of uterine cervix cell HeLa, hamster lung fibroblast cell V79 and mouse melanoma cell B16	43
48	Phillyroside	*Lancea tibetica*	Hepatoma cell SMMC-7721, human carcinoma of uterine cervix cell HeLa, hamster lung fibroblast cell V79 and mouse melanoma cell B16	43
49	Phillygenoldiglycoside	*Lancea tibetica*	Hepatoma cell SMMC-7721, human carcinoma of uterine cervix cell HeLa, hamster lung fibroblast cell V79 and mouse melanoma cell B16	43

lignans were also suggested as worthy candidates for cancer chemopreventive and chemotherapeutic agents.

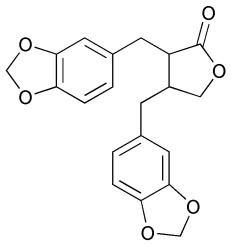
3 Anti-inflammatory plant lignans

Prostaglandins are a related family of chemicals that are produced within the cells of the body by the cyclooxygenases COX-1 and COX-2. They have several important functions, including the promotion of inflammation, pain, and fever. COX-2 is one of the key enzymes that help the body produce the inflammatory hormone-like prostaglandins and cytokines. COX-2 is essential – without it, we wouldn't be able to fight infections or heal injuries – but when the body overproduces COX-2, the result is chronic inflammation and pain. Inhibitors of COX-1 and COX-2 can help in the treatment of inflammatory disorders.

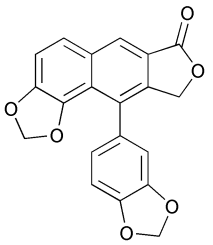
The lignan **50** has been shown to be a valuable inhibitor of both COX-1 and COX-2.[44] Ban *et al.* investigated **51–54** for their inhibitory effects on the production of prostaglandin E_2 (PGE_2) stimulated by 12-*O*-tetradecanoylphorbol 13-acetate (TPA) in rat peritoneal macrophages.[45] Among these compounds, **53** was found to be most potent, followed by **52**, **54** and **51**, whereas **53** showed no inhibitory effect on the release of radioactivity from [^{3}H]arachidonic acid-labeled macrophages and the expression of COX-2 protein induced by TPA. However, the activities of isolated COX-1 and COX-2 were inhibited by **53**, reflecting the inhibition of both COX-1- and COX-2-dependent PGE_2 production in the cell culture system. These findings suggest that the mechanism of action of **53** in the inhibition of PGE_2 production is the direct inhibition of COX enzymatic activity.



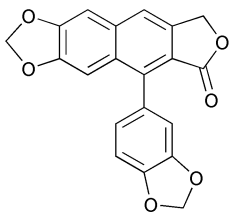
5'-Methoxyyatein (**50**)



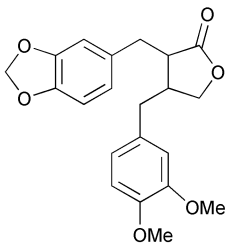
Savinin (**51**)



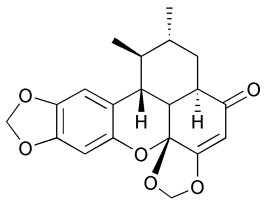
Helioxanthin (**52**)



Taiwanin C (**53**)



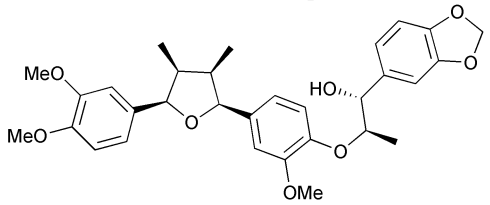
cis-Dibenzylbutyrolactone (**54**)



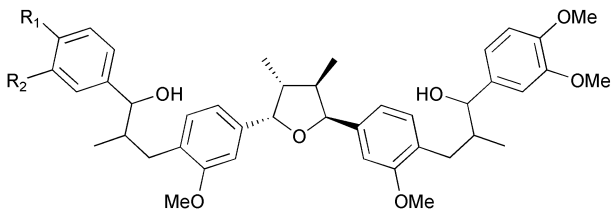
Sauchinone (**55**)

Lipopolysaccharide (LPS), an endotoxin associated with septic shock syndrome, stimulates the production of inflammatory mediators such as NO, TNF-α, interleukins, prostanoids and leukotrienes.[46–48] The effects of arctigenin **34** on mitogen-activated protein (MAP) kinase activation in Raw264.7 cells and MAP kinase kinase (MKK) activity were examined.[49] The effect of **34** on activator protein 1 (AP-1) activation was also studied in association with tumor necrosis factor α (TNF-α) expression. Immunoblot analysis showed that **34** inhibited phosphorylation of MAP kinases ERK1/2, p38 kinase and JNK, and their activities in Raw264.7 cells treated with LPS. Arctigenin **34** potently inhibited the activity of MKK1 *in vitro*. Arctigenin **34** blocked TNF-α production and decreased the level of TNF-α mRNA in the cells exposed to LPS. These results showed that **34** inhibited activation of MAP kinases, including ERK1/2, p38 kinase and JNK through the inhibition of MKK activities, leading to AP-1 inactivation, which might, at least in part, contribute to the inhibition of TNF-α production. Lignan **34** also inhibited LPS-inducible nuclear NF-κB activation and nuclear translocation of p65,[50] which was accompanied by inhibition of I-κB-α phosphorylation. Immunoblot analysis revealed that **34** potently inhibited the induction of iNOS by LPS. The potent inhibition of LPS-inducible NO production in macrophages may constitute anti-inflammatory effects of the dibenzylbutyrolactone lignans.[51] Sauchinone **55** is another lignan isolated from the root of *Saururus chinensis* as an active principle responsible for inhibiting the production of NO in LPS-stimulated RAW264.7 cells by activity-guided fractionation.[52] Furthermore, **55** prevented LPS-induced NF-κB activation, which is known to play a critical role in iNOS expression, assessed by a reporter assay under the control of NF-κB. However, an electrophoretic mobility shift assay (EMSA) demonstrated that **55** did not suppress the DNA-binding activity of NF-κB or the degradation of I-κB-α induced by LPS. Compound **55** was also found to exert its inhibitory effects on iNOS, TNF-α and COX-2 gene expression and on the activation of transcription factors, NF-κB, CCAAT/enhancer-binding protein (C/EBP), AP-1 and cAMP-response element-binding protein (CREB) in Raw264.7 cells as part of the studies on its anti-inflammatory effects.[53]

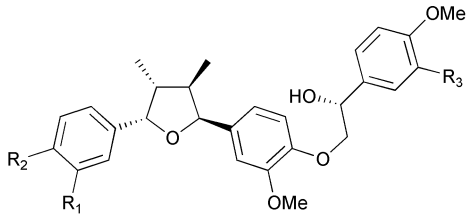
Lee *et al.* isolated **56–58** from the methanol extracts of the root of *Saururus chinensis*, and evaluated them for their inhibitory activities against hACAT-1 and hACAT-2.[54] Saucerneol B **56** inhibited hACAT-1 three times more strongly than hACAT-2, whereas **57** was more potent against hACAT-2 than hACAT-1. However, **58** mainly inhibited hACAT-1, not hACAT-2.[54] Manassantin A **57** and B **58**, along with other compounds of the same series, **59–62**, were isolated from the roots of *Saururus chinensis*, and were studied using HeLa cells transfected with NF-κB reporter construct.[55] Compounds **56–58** showed the most potent inhibitory activity, whereas **59–62** exhibited relatively low inhibitory effects. The relative potency of these compounds on the inhibition of NF-κB activation was dilignan > sesquineolignan > lignan, suggesting that the phenylpropanoid moiety attached to C-4 and/or C-4′ was important for the inhibition of the stimuli-induced NF-κB activation process.



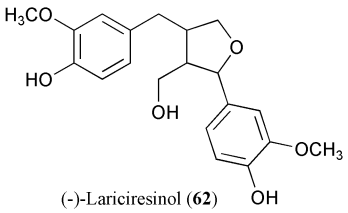
Saucerneol B (**56**)



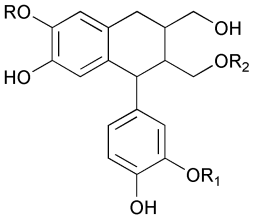
Manassantin A (**57**) $R_1 = R_2 = OMe$
Manassantin B (**58**) $R_1 = R_2$ -OCH_2O-

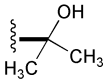


	R_1	R_2	R_3
Saucerneol D (**59**)	$-OCH_2O-$	$-OCH_2O-$	$-OCH_3$
Saucerneol E (**60**)	$-OCH_2O-$	$-OCH_2O-$	-OH
(-)-Saucerneol methylether (**61**)	$-OCH_3$	$-OCH_3$	$-OCH_3$



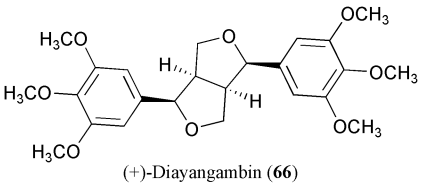
(-)-Lariciresinol (**62**)



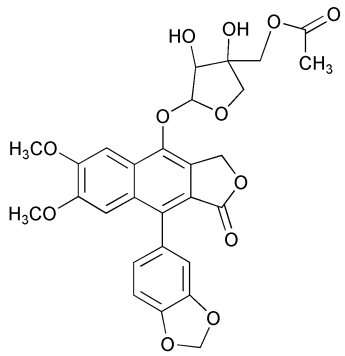
	R	R_1	R_2
(-)-3'-demethylisolariciresinol-9'-hydroxyisopropylether (**63**)	CH_3	H	
Isolariciresinol (**64**)	CH_3	CH_3	H
(-)-3-Demethylisolariciresinol (**65**)	H	CH_3	H

Kuepeli *et al.* investigated five lignans **28** and **62–65** for their anti-inflammatory activities, in which the lignans significantly inhibited carrageenan-induced hind paw edema in mice.[56] These results (and some previous studies on biological activities of these lignans), showed that lariciresinol **62** and isolariciresinol **64** possess a potent *in vitro* inhibitory effect on the production of TNF-α, a pro-inflammatory cytokine.[57] Therefore, lignan derivatives in the present study might show their anti-inflammatory effects *via* the same mode.

(+)-Diayangambin **66** was evaluated *in vitro* and *in vivo* for its immunomodulatory and anti-inflammatory efficacy.[58] Human mononuclear cell proliferation was inhibited by **66**, and the compound reduced PGE_2 generation in the stimulated RAW264.7 macrophage cell line. A clear reduction of ear swelling was observed when **66** was administered orally to 2,4-dinitrofluorobenzene-treated mice. These findings indicate the potential of **66** for the treatment of immune and inflammatory responses. 5-Lipoxygenase (5-LOX) is the key enzyme for the biosynthesis of leukotrienes (LTs) from arachidonic acid (AA);[59] LTs are important mediators in inflammatory, allergic and obstructive processes.[60] Therefore, inhibitors of 5-LOX, which might represent putative remedies for the treatment of topical chromic inflammatory disorders such as dermatitis and psoriasis, have become the subject of intensive research. Jose *et al.* evaluated diphyllin acetylapioside **67** as a main inhibitor of 5-LOX,[61] and found that it had an IC_{50} much lower than that of apigenin.



(+)-Diayangambin (**66**)



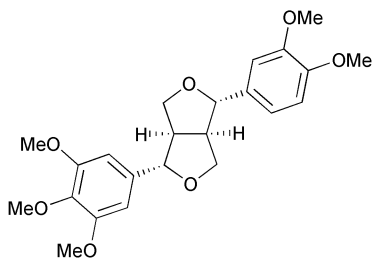
Diphyllin acetylapioside (**67**)

The inhibitory activity of lignans isolated from *Magnolia fargesii* were accessed on cell adhesion molecules on the surface of THP-1 human monocytic cell lines.[62] The six lignans **68–73** displayed relatively strong inhibitory activities on ICAM-1 expression induced by TNF-α. Similarly, the inhibitory activities of these six lignans on VCAM-1 expression were also potent. Among them, the activity of **70** and **71** were relatively strong but less than that of dexamethasone. It was recently reported that **71** and **72** displayed anti-PAF activity,[63] and **71** and **75** had TNF-α-suppressing activity in LPS-stimulated macrophages.[64] Additionally, the anti-PAF activity of magnolin **68** from *Magnolia biondii* was reported.[65] In view of these results, it is likely that these bioactive lignans are compounds worth developing as novel anti-inflammatory drugs.

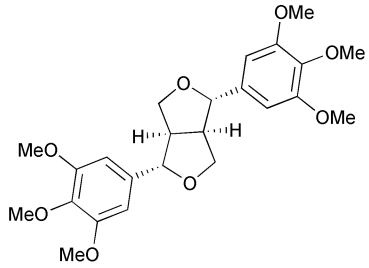
The lignans **64** and **74–77**, isolated from the rhizomes of *Coptis japonica*, were tested to evaluate their *in vitro* anti-inflammatory effects.[57] Compounds **64** and **75** showed higher inhibitory effects on TNF-α production, whereas **77** strongly suppressed lymphocyte proliferation. The results indicate that the lignans may differentially modulate inflammatory cell responses, suggesting that these compounds may participate in anti-inflammatory processes mediated by *C. japonica*.[57]

Macrophages and lymphocytes play an important role in host immune responses such as acute or chronic inflammation.[66] Under these conditions, they are proliferated and activated by inflammatory signals, *e.g.* some bacterial products, including LPS. As a result, they secrete a number of pro-inflammatory mediators such as cytokines (TNF-α, interleukin-1 and -6) and eicosanoids (prostaglandin E_2 and leukotriene B_4), as well as reactive oxygen and nitrogen intermediates, including NO. The compounds **64** and **74–77** from *C. japonica* were first examined in activated macrophages; it was found that these compounds significantly inhibited TNF-α production from mouse macrophages.[67] In addition, compounds such as **75** and **77** showed significant suppressive effects on NO production triggered by LPS but not by IFN-γ, although the activity was weaker than for TNF-α production. It can be speculated that the lignan compounds may interfere with a biosynthetic pathway for TNF-α production, rather than NO, in activated macrophage cells.

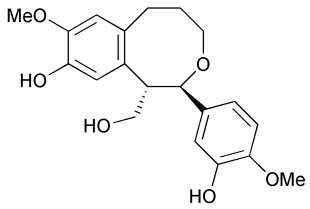
It is generally known that the proliferation of T lymphocytes is an initial stage in the enhancement of chronic inflammatory conditions *via* activation of inflammatory cells such as neutrophils and macrophages, resulting in a massive production of chemical mediators and pro-inflammatory cytokines.[66] This is the reason why potent immunosuppressive agents such as cyclosporin A are reported to have a curative effect in chronic inflammatory diseases.[68] To check if these compounds block lymphocyte



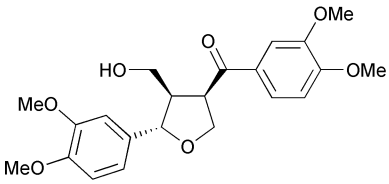
Magnolin (**68**)



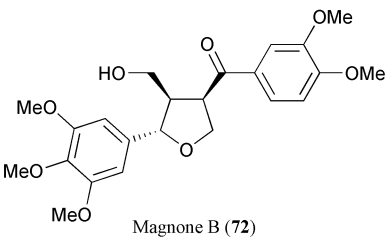
Lirioresinol-B dimethyl ether (**69**)



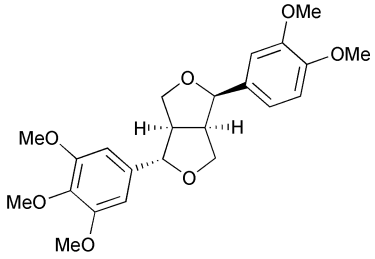
4' -*O*-demethylbiondinin A (**70**)



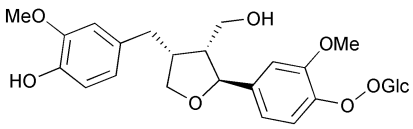
Magnone A (**71**)



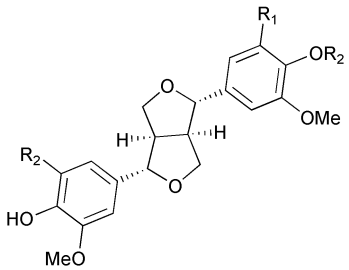
Magnone B (**72**)



Epimagnolin A (**73**)



Lariciresinol glycoside (**74**)

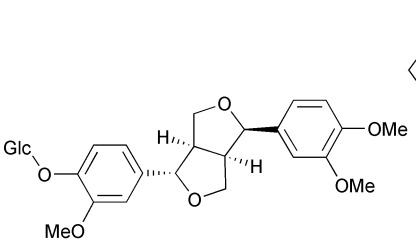


Pinoresinol (**75**), $R_1 = R_2 = H$
Pinoresinol glycoside (**76**), $R_1 = Glc$, $R_2 = H$
Syringaresinol glycoside (**77**), $R_1 = Glc$, $R_2 = OCH_3$

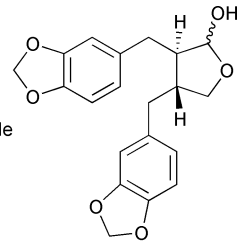
proliferation, mitogenic proliferation elicited by Con A (for CD4 + T-cells) or IL-2 (CD8 + T-cells, CTLL-2) was evaluated, and compared with the normal proliferation of the CD4 + T lymphocyte cell line (Sup-T1).[69] Interestingly, the results indicate that only compound **77** potently inhibited both types of T lymphocyte proliferation. The compound seems to selectively suppress CD8 + T lymphocyte (CTLL-2) proliferation 3–4 times more strongly than CD4 + T lymphocytes and Sup-T1 cells, as shown in the pharmacology of ginkgetin, which showed a 4-fold higher suppression of ovarian adenocarcinoma cell proliferation as compared to other cell lines.[70] However, compound **75** displayed an opposite effect, by which the compound suppressed concanavalin (Con A)-induced T lymphocyte proliferation.

Compound **78** was isolated from the leaves of *Phillyrea latifolia*, and was explored for interactions with the cyclooxygenase and 5-lipoxygenase pathways of arachidonate metabolism in calcium-stimulated mouse peritoneal macrophages and human platelets, and for its effects on cell viability.[71] This compound is capable of exerting inhibitory actions on enzymes of the arachidonate cascade. Phillyrin **78** exerts a preferential effect on the cyclooxygenase pathway, inhibiting release of the cyclooxygenase metabolites PGE_2, and to a lesser extent reducing thromboxane B_2 levels.

Cubebin **79**, isolated from the crude hexane extract of the leaves of *Zanthoxylum naranjillo*, showed a significant anti-inflammatory activity on the paw edema induced by carrageenin in rats, but did not provide a significant reduction in the cell migration for the acute carrageenin-induced inflammatory reaction in the peritoneal cavity of rats. In addition, it was effective in reducing neither the edema induced by dextran nor the edema induced by histamine, but it partially reduced the edema induced by serotonin. Moreover, **79** significantly reduced the edema induced by PGE_2, and the number of writhings induced by both acetic acid and PGI_2 in mice. Therefore, it may be suggested that the mechanism of action of **79** is similar to that observed for most of the non-steroidal drugs.[72]



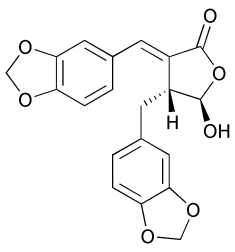
Phillyrin (**78**)



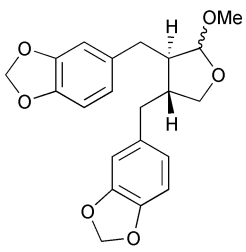
Cubebin (**79**)

Savinin **57** and calocedrin **80**, dibenzyl butyrolactone-type lignan compounds having an α-arylidene γ-lactone structure, significantly inhibited TNF-α production in LPS-stimulated RAW264.7 cells, and T-cell proliferation elicited by Con A, without displaying cytotoxicity.[73]

Cubebin **79** and methylcubebin **81** exerted a significant analgesic activity in the acetic acid-induced writhing in mice.[78] The results also showed that the analgesic activity of **79** was slightly more pronounced than that observed for **81**.



Calocedrin (**80**)



Methylcubebin (**81**)

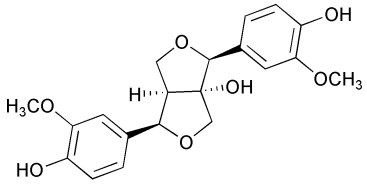
Table 2 Summary of the lignans possessing anti-inflammatory activities

Compound	Name	Plant source	Target	Ref.
28	Taxiresinol	*Taxus baccata*	Carrageenan-induced hind paw edema	56
34	Arctigenin	*Bardanae fructus*, *Saussurea medusa*, *Arctium lappa*, *Torreya nucifera*, *Ipomea cairica*	MAP kinases ERK1/2, p38 kinase, JNK TNF-α mRNA, and iNOS mRNA	49
50	5′-Methoxyyatein	—	COX-1, COX-2	44
51	Savinin	*Pterocarpus santalinus*	PGE_2, TNF-α	45, 73
52	Helioxanthin	*Pterocarpus santalinus*	PGE_2	45
53	Taiwanin C	*Pterocarpus santalinus*	PGE_2, COX-1, COX-2	45
54	*cis*-Dibenzylbutyrolactone	*Pterocarpus santalinus*	PGE_2	45
55	Sauchinone	*Saururus chinensis*	NO in LPS-stimulated RAW264.7, NF-κB, LPS-inducible iNOS, TNF-α, COX-2	52
56	Saucerneol B	*Saururus chinensis*	hACAT-1, hACAT-2	54
57	Manassantin A	*Saururus chinensis*	hACAT-1, hACAT-2, NF-κB	54, 55
58	Manassantin B	*Saururus chinensis*	hACAT-1, NF-κB	54, 55
59	Saucerneol D	*Saururus chinensis*	NF-κB	55
60	Saucerneol E	*Saururus chinensis*	NF-κB	55
61	(−)-Saucerneol methyl ether	*Saururus chinensis*	NF-κB	55
62	Lariciresinol	*Taxus baccata*	Carrageenan-induced hind paw edema	56
63	3′-Demethylisolariciresinol 9′-hydroxy isopropyl ether	*Taxus baccata*	Carrageenan-induced hind paw edema	56
64	Isolariciresinol	*Taxus baccata*, *C. japonica*	Carrageenan-induced hind paw edema, TNF-α	56, 57
65	3-Demethylisolariciresinol	*Taxus baccata*	Carrageenan-induced hind paw edema	56
66	(+)-Diayangambin	*Piper fimbriulatum*	Carrageenan mouse paw edema model, PGE_2	58
67	Diphyllin acetylapioside	*Haplophyllum hispanicum*	5-LOX	61
68	Magnolin	*Magnolia fargesii*, *Magnolia biondii*	ICAM-1, VCAM-1, anti-PAF	62, 64
69	Lirioresinol-B dimethyl ether	*Magnolia fargesii*	ICAM-1, VCAM-1, TNF-α	62
70	4′-*O*-Demethylbiondinin A	*Magnolia fargesii*	ICAM-1, VCAM-1	62
71	Magnone A	*Magnolia fargesii*	ICAM-1, VCAM-1, anti-PAF	62, 64
72	Magnone B	*Magnolia fargesii*	ICAM-1, VCAM-1, anti-PAF	62, 64
73	*epi*-Magnolin A	*Magnolia fargesii*, *Magnolia biondii*	ICAM-1, VCAM-1, TNF-α	62
74	Lariciresinol glycoside	*Coptis japonica*	TNF-α	57
75	Pinoresinol	*Coptis japonica*	TNF-α	57
76	Pinoresinol glycoside	*Coptis japonica*	TNF-α	57
77	Syringaresinol glycoside	*Coptis japonica*	TNF-α, CD8 + T lymphocyte, CD4 + T lymphocytes	57
78	Phillyrin	*Phillyrea latifolia*	PGE_2, thromboxane B_2	71
79	Cubebin	*Zanthoxylum naranjillo*	PGE_2, PGI_2, carrageenan mouse paw edema	72, 74
80	Calocedrin	*Pterocarpus santalinus*	TNF-α	73
81	Methylcubebin	*Lychnophora ericoides*	Analgesic activity	74

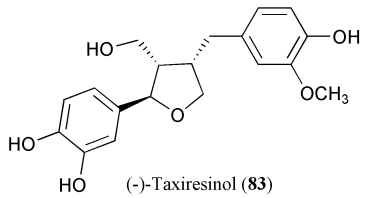
4 Antimicrobial plant lignans

Many efforts have been made to discover new antimicrobial compounds from various kinds of sources such as micro-organisms, animals, and plants.[75] The increasing prevalence of multi-drug resistant strains of microbes and the recent appearance of strains with reduced susceptibility to antibiotics raises the specter of untreatable microbial infections and adds urgency to the search for new infection-fighting strategies. Clinically, antimicrobial therapy is going through a crisis due to the rapid development of resistance to existing antimicrobial agents. Plants produce many secondary metabolites with antimicrobial activity. Reliance upon a few classes of antimicrobial agents for most of our products of medical value risks the development of resistance among pathogens. To meet such challenges, researchers are trying to find out new and potential antibacterial and antifungal plant secondary metabolites.

The lignan (+)-1-hydroxy-2,6-bis-*epi*-pinoresinol **82** is a constituent of *Valeriana laxiflora*, which has anti-mycobacterium tuberculosis potential and exhibited a minimum inhibitory concentration (MIC) of 127 μg mL^{-1} with an IC_{50} value of 91.0 μg mL^{-1}, resulting a selectivity index (SI) of 0.72 under experimental conditions used.[76] Erdemoglu *et al.* have reported that **83** and **65** possess antifungal activity.[77]



(+)-1-Hydroxy-2,6-bis-*epi*-pinoresinol (**82**)

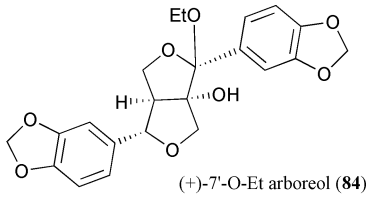


(-)-Taxiresinol (**83**)

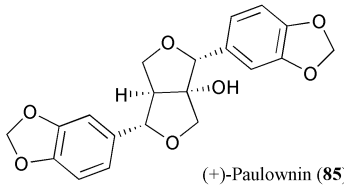
The four lignans **84–87** were evaluated for their antifungal potential in a sensitive bioassay system for antifungal activity against basidiomycetes.[78] After comparison of antifungal activity of different structures, it was concluded that the piperonyl nucleus contributed to the activity of these lignans. Of the four lignans isolated, **87** appeared to be an important antifungal constituent, since it was present in quantity in the heartwood of *Gmelina arborea*.[78]

The first report on the *in vitro* fungicidal and antiprotozoal effects of **88** was published in 2003, when it was isolated as the major component of *Phyllanthus piscatorum.* It inhibited the growth of the pathogenic fungi *Aspergillus fumigatus*, *Aspergillus flavus*, and *Candida albicans*, but was not effective against other tested pathogens *Cryptococcus neoformans* and *Blastoschizomyces capitatus*. Justicidin B **89** also exhibited strong activity against the trypomastigote form of *Trypanosoma brucei rhodesiense* and moderate activity against *Trypanosoma cruzi*. In a test against *Plasmodium falciparum*, **88** showed only weak activity.[79]

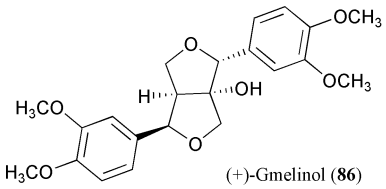
Methicillin-resistant *Staphylococcus aureus* (MRSA) is resistant to all β-lactams, penicillins, cephalosporins, carbapenem, and penems, because of its *mecA* gene, which produces an additional penicillin-binding protein, called PBP2′ (or 2a), whichhas a low affinity for β-lactam antibiotics.[80] Since there is no such gene in methicillin-sensitive *Staphylococcus aureus* (MSSA), these strains are sensitive to β-lactams. Phenylnaphthalene type lignans **89–91** from *Vitex rotundifolia* were found to afford antimicrobial activity against MRSA.[81]



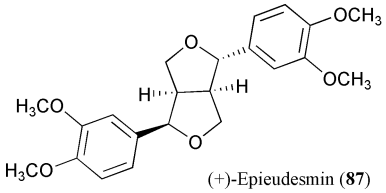
(+)-7'-O-Et arboreol (**84**)



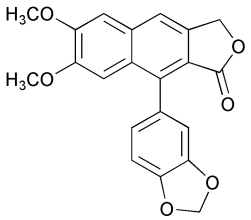
(+)-Paulownin (**85**)



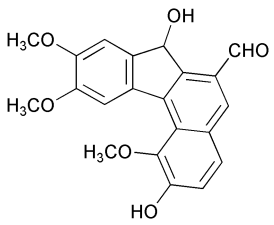
(+)-Gmelinol (**86**)



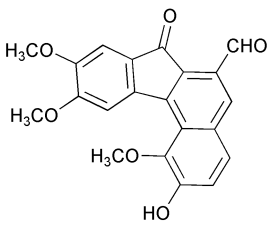
(+)-Epieudesmin (**87**)



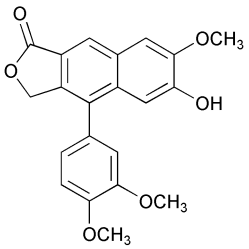
Justicidin B (**88**)



Vitrofolal C (**89**)



Vitrofolal D (**90**)



Detetrahydroconidendrin (**91**)

5 Antioxidative plant lignans

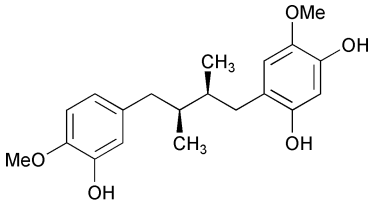
Free radicals promote beneficial oxidation that produces energy and kills bacterial invaders. In excess, however, they produce harmful oxidation that can damage cell membranes and cell contents, which may contribute to aging. Antioxidants help

Table 3 Summary of the lignans possessing antimicrobial activities

Compound	Name	Plant source	Target	Ref.
65	(−)-3-Demethylisolariciresinol	*Taxus baccata*	Antifungal activities	77
82	(+)-1-Hydroxy-2,6-bis-*epi*-pinoresinol	*Valeriana laxiflora*	Mycobacterium tuberculosis	76
83	(−)-Taxiresinol	*Taxus baccata*	Antifungal activities	77
84	(+)-7′-*O*-ethylarboreal	Heartwood of *Gmelina arborea*	Antifungal activities	78
85	(+)-Paulownin	Heartwood of *Gmelina arborea*	Antifungal activities	78
86	(+)-Gmelinol	Heartwood of *Gmelina arborea*	Antifungal activities	78
87	(+)-Epieudesmin	Heartwood of *Gmelina arborea*	Antifungal activities	78
88	Justicidin B	*Phyllanthus piscatorum*	*Aspergillus fumigatus*, *Aspergillus flavus*, *Candida albicans*, *Trypanosoma brucei rhodesiense*, *Trypanosoma cruzi*, *Plasmodium falciparum*	79
89	Vitrofolal C	*Vitex rotundifolia*	8 strains of *Staphylococcus aureus*	80
90	Vitrofolal D	*Vitex rotundifolia*	*Staphylococcus aureus*	80
91	Detetrahydroconidendrin	*Vitex rotundifolia*	*Staphylococcus aureus*	80

prevent oxidation – the common pathway for cancer, aging, and a variety of diseases – and may help increase immune function, and possibly decrease risk of infection and cancer. It is known that people who eat adequate amounts of fruits and vegetables high in antioxidants have a lower incidence of cardiovascular disease, certain cancers, and cataracts. Fruits and vegetables are rich in antioxidants, but it is not known which dietary factors are responsible for the beneficial effects. Each plant contains hundreds of phytochemicals (plant chemicals) whose presence is dictated by hereditary factors. Only well-designed long-term research can determine whether any of these chemicals, taken in a pill, would be useful for preventing any disease. The scientific community has begun to unveil some of the mysteries surrounding this topic, and the media has begun whetting our appetite for knowledge. Scientists are making efforts to find potent non-toxic plant chemicals that may help to cure illnesses.

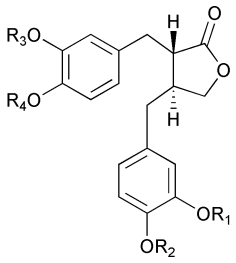
The lignan **92** was isolated from the EtOAc extracts of the underground parts of *Saururus chinensis*. It exhibited low-density lipoprotein (LDL)-antioxidative activity in various assay systems and DPPH radical scavenging activity.[82]



2'-Hydroxydihydroguaiaretic acid (**92**)

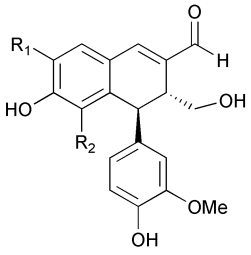
The antioxidative function of sesamin **15** on exercise-induced lipid peroxidation was studied.[83] The effects were observed in both animal and human subjects using strenuous physical exercise as a trigger for oxidative stress in the body. Experiments on both animal and humans demonstrated that **15** could scavenge free radicals and enhance lipid peroxide metabolism, resulting in a strong protective effect against exercise-induced lipid peroxidation. In addition to its independent antioxidative capacity, **15** showed the potential to work synergistically with vitamin E against lipid peroxidation.[83] Min *et al.* isolated **76** and **93–95** from the EtOAc-soluble fraction of the stem bark of *Styrax japonica*, and investigated their antioxidative properties.[84] An *in vitro* assay for antioxidative activity against DPPH radicals was performed, which revealed **76** and **93–95** to exhibit weak radical-scavenging activity.

The antioxidative activity of **96–101** was evaluated using linoleic acid as the substrate by the ferric thiocyanate method.[85]

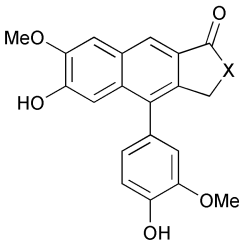


	R_1	R_2	R_3	R_4
Styraxlignolide C (**93**)	CH_3	Glc	H	CH_3
Styraxlignolide D (**94**)	CH_3	Glc	CH_3	H
Styraxlignolide E (**95**)	CH_3	H	CH_3	Glc

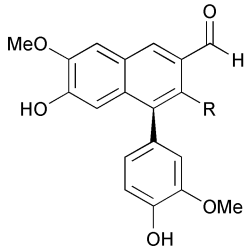
Compounds **96–101** showed stronger antioxidative activity than that of α-tocopherol, and **97–99** and **101** were more potent antioxidants than BHA. The scavenging effect of **96–101** on the stable radical DPPH was also examined. Compounds **96–101** exhibited stronger activity than that of L-cysteine, and **98**, **100** and **101** showed activities similar to α-tocopherol.



Vitedoin (**96**), R_1 = H, R_2 = OCH_3
α-Conidendrinaldehyde (**98**), R_1 = OCH_3, R_2 = H

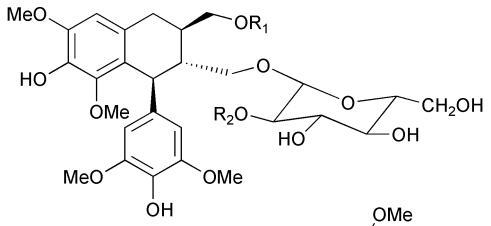


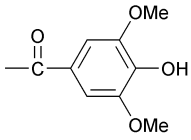
Vitedoamine A (**97**), X = NH
α-Conidendrin (**99**), X = O

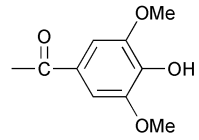


Vitrofolal E (**100**), R = H
Vitrofolal F (**101**), R = OH

The lignan constituents **51** and **15** from *Acanthopanax divaricatus* var. *albeofructus* showed antioxidative activities by the DPPH method and the TBARS assay on human plasma low-density lipoprotein (LDL); **15** exhibited the most potent antioxidative activity in Cu^{2+}-induced LDL oxidation.[86] From the stem of *Strychnos vanprukii*, three lignan glucosides **102–104**



Vanprukoside (**102**) R_1 =  R_2 = H



Strychnoside (**103**) $R_1 = R_2$ =

(+)-Lyoniresinol-3α-O-β-glucopyranoside (**104**), $R_1 = R_2$ = H

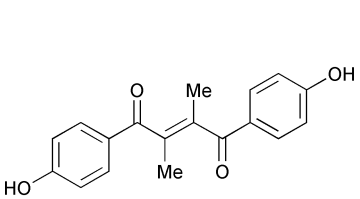
were isolated, which exhibited stronger radical scavenging activity against DPPH than ascorbic acid.[87]

Lignans **105–110** were isolated from *Larrea tridentata*. Among them, the epoxylignans possessing a tetrahydrofuran moiety (**107–110**) showed strong antioxidative activity by the DCFH method without cytotoxicity.[88] The number and position of the hydroxy- and methoxy-substituents on the phenyl moieties may contribute to the antioxidative effect in epoxylignans. On the contrary, epoxylignans with a dihydrofuran ring, for example **111**, did not show antioxidant activity, suggesting that both the tetrahydrofuran and phenyl moieties are important for activity. In addition, the destabilization effect of the benzylic carbonyl group on oxygen and carbon radicals at the aromatic ring was established to be detrimental to the antioxidative activity of compounds **105** and **106**, and its precursor **33** also showed potent antioxidative activity.[88]

Compounds **112–115** showed antioxidant properties in Trolox-equivalent antioxidant activity (TEAC) and chemiluminescence (CL) assays.[89] The aglycones **114** and **115** displayed powerful antioxidant activity. Two lignan glucosides, **116** and **117** from the antioxidative ethanol extract of prunes (*Prunus domestica*), showed effective antioxidant potentials on the basis of oxygen radical absorbance capacity (ORAC).[90]

Yoshinobu *et al.* reported **15** to exhibit an antioxidative effect on lipid and alcohol metabolism in the rat liver.[91] It was suggested that **15** was absorbed *via* the portal vein and metabolized to mono- or di-catechol metabolites by drug-metabolizing enzymes in the liver cells. Both metabolites exhibited antioxidative activity in the liver, and were finally conjugated with glucuronic acid and excreted in the bile. In another experiment, **15** and **118** elevated α-tocopherol concentration and decreased thiobarbituric acid-reactive substance (TBARS) concentration in the blood plasma and liver of rats.[91] The effects of dietary **15** and **118** on lipid peroxidation in plasma and tissues were studied. Both compounds showed a decreased lipid peroxidation by elevating α-tocopherol concentrations in rats fed docosahexaenoic acid (DHA).[91] Nakano *et al.* studied the effects of **15** on aortic oxidative stress and endothelial dysfunction in deoxycorticosterone acetate (DOCA)-hypertensive rats.[92] The results obtained suggested that the feeding of **15** inhibits the enhancement of aortic superoxide anion radical ($O^{2-\bullet}$) production in DOCA-hypertensive rats, and this effect may contribute to the antihypertensive effect of **15**.

The antioxidative potency and the radical scavenging capacity of superoxide and peroxyl radicals were assessed for 13 hydrophilic knotwood extracts,[93] followed by the evaluation of five pure lignans for the inhibition of lipid peroxidation *in vitro*. The study revealed **25**, **30**, **38**, **62** and **119** to have a high antioxidative potency.[93] These compounds were also able to scavenge superoxide and peroxyl radicals *in vitro*. Compound **120**, an isolate of *Phyllostachys edulis*, possessed an inhibitory effect on ADP/Fe^{2+}-induced liposomal lipid peroxidation, and was about 16 times more potent than the well-known antioxidant α-tocopherol.[94] Phyllostadimer A **120** may inhibit lipid peroxidation by radical scavenging, like α-tocopherol, since **120** has four phenolic OH groups. However, the greater activity of **120** cannot be explained simply by the difference in the number of phenolic OH groups, and perhaps the unique structure of **120** may also contribute to its potent antioxidant effect.



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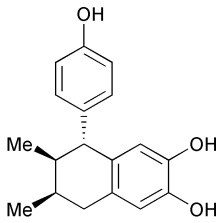

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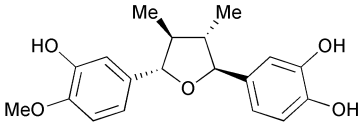

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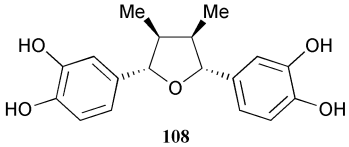

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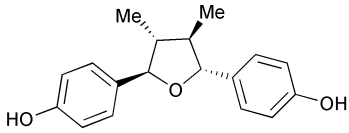
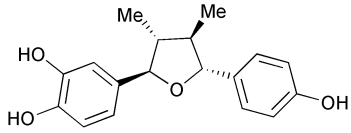
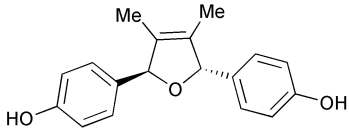


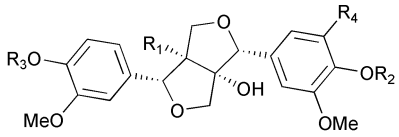
4-*epi*-larreatricin (**109**)



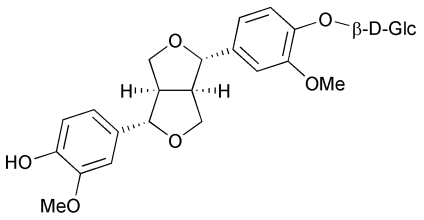
3"-hydroxy-4-*epi*-larreatricin (**110**)



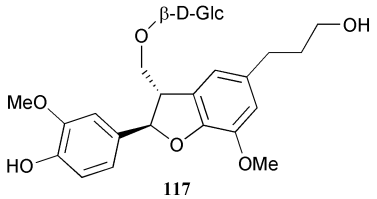
3,4-dehydrolarreatricin (**111**)



	R_1	R_2	R_3	R_4
Prinsepiol-4-O-β-D-glucoside (**112**)	OH	β-D-glucosyl	H	H
8-Hydroxypinoresinol-4'-O-β-D-glucoside (**113**)	H	H	β-D-glucosyl	H
8-Hydroxypinoresinol (**114**)	H	H	H	H
Prinsepiol (**115**)	OH	H	H	H



(+)-Pinoresinol mono-β-D-glucopyranoside (**116**)



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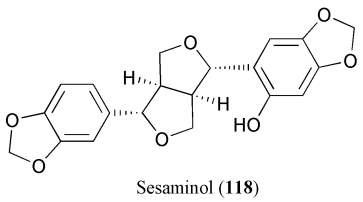
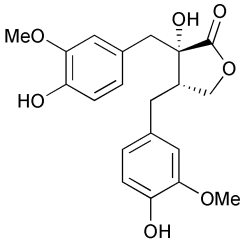
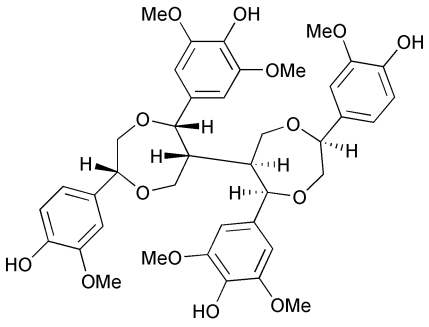


Sesaminol (**118**)

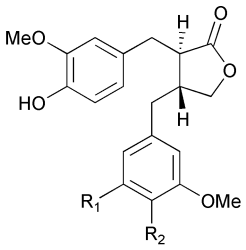


Nortrachelogenin (**119**)

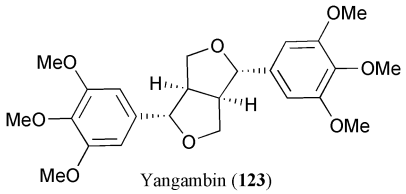


Phyllostadimer A (**120**)

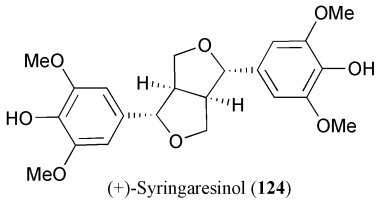
Three dibenzylbutyrolactone lignans (**34**, **121** and **122**) from the bark of *Torreya nucifera* showed significant hepatoprotective activity against CCl_4-induced injury in primary cultures of rat hepatocytes.[95] The hepatotoxic effects of CCl_4 are attributed to its metabolism by P450 to yield toxic trichloromethyl radicals that can act as free radical initiators.[96] These radicals are believed to induce injury either by interacting with the unsaturated fatty acids of cell membranes, thereby causing lipid peroxidation, or by binding covalently to important macromolecules such as proteins, lipids, and DNA.[97] The lignans **34**, **121** and **122** significantly reduced the level of GPT released from CCl_4-injured rat hepatocytes into the medium in a concentration-dependent manner. The different hepatoprotective activity of **34**, **121** and **122** may result from differences in hydrophilicity and the positions of methoxy substituents; unpaired electron delocalization might affect oxidative coupling in phenylpropanoid radicals.[98] Cui *et al.* isolated 4 furofuran lignans (**15**, **75**, **123** and **124**) from Chinese propolis. Their antioxidative activity was evaluated by measuring the inhibition of lipid peroxidation in rat liver microsomes, the compounds had IC_{50} values of 9.0–14.0 μg mL^{-1}.[99]



(-)-Traxillagenin (**121**), $R_1 = R_2 = OCH_3$
(-)-4'-Demethyltraxillagenin (**122**), $R_1 = OCH_3$, $R_2 = OH$

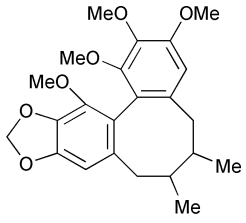


Yangambin (**123**)



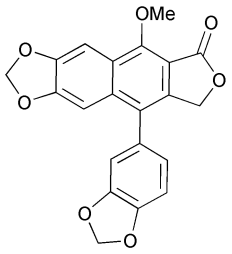
(+)-Syringaresinol (**124**)

A lignan constituent of *Schisandra chinensis*, **125**, showed its effect on hepatic mitochondrial glutathione antioxidant status in control and CCl_4-intoxicated mice.[100] Pretreatment with **125** or α-tocopherol protected against CCl_4 hepatotoxicity, with **125** being more potent.

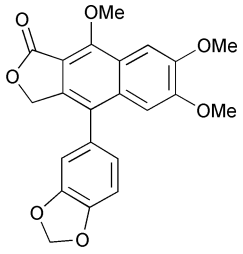


Schisandrin B (**125**)

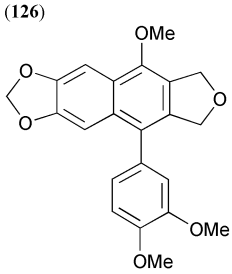
The antioxidative properties of **38** were studied *in vitro* in lipid peroxidation, superoxide and peroxyl radical scavenging, and LDL-oxidation models in comparison with the known synthetic antioxidants – Trolox (a water-soluble vitamin E derivative), butylated hydroxyanisol (BHA) and butylated hydroxytoluene (BHT).[101] On a molar basis, **38** was a more effective antioxidant than Trolox in all assays and more effective than BHT or BHA in the lipid peroxidation and superoxide scavenging tests. The plant lignans **25** and **30** and mammalian lignans **26** and **27** showed an antioxidative activity higher than that of ascorbic acid, and comparable to that of the known antioxidant **32**.[102] The mammalian lignans were far less active in the FRAP assay. The degree of hydroxylation was the major determinant of the reducing power of the dietary polyphenols. The additional methoxy group, the main structural difference between the plant and mammalian lignans, may be responsible for the different antioxidative activities observed.[102] Lignans **9**, **89**, **126**, **127** and **128** from the ethanol extract of *Justicia procumbens* exhibited *in vitro* effects on rat hepatic cytochrome P450-catalyzed oxidation.[103] Among these lignans, **127** had the strongest inhibitory effect on AHH activity, and caused a significant decrease of 7-methoxyresorufin *O*-demethylation activity, whereas other tested lignans did not show significant inhibitory potential. These compounds also decreased testosterone 6β-hydroxylation activity, while **127** had the least inhibitory effect.[103]



Neojusticin A (**126**)

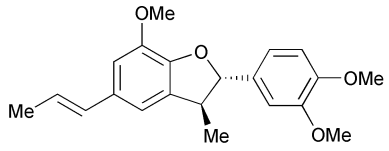


Neojusticin B (**127**)

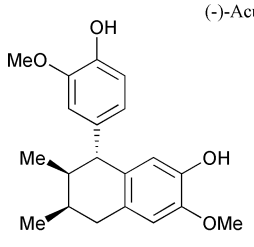


Chinensinaphthol methyl ether (**128**)

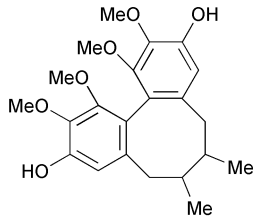
Yu *et al.* reported the potent antioxidative properties of **20**, **129** and **130** isolated from the CH_2Cl_2 fraction of the bark of *Machilus thunbergii*.[104] These compounds significantly reduced the level of glutamic pyruvic transaminase release. The three lignans tested, **20**, **129** and **130**, also ameliorated lipid peroxidation, as demonstrated by a reduction of malondialdehyde production,[104] suggesting that **129**, **130** and **20** exert diverse hepatoprotective activities, perhaps by serving as potent antioxidants. Gomisin J **131** from *Kadsura interior* exhibited good inhibitory influences on lipid peroxidation and the superoxide anion radical.[105] This extensive study revealed that **131** could inhibit the xanthine → xanthine oxidase reaction with dose-dependency in the luminol-dependent CL system. In addition, it could inhibit lipid peroxidase (LPO) induced by the hydroxyl free radical in rat liver mitochondria, and scavenge the superoxide anion radical.[105]



(-)-Acuminatin (**129**)

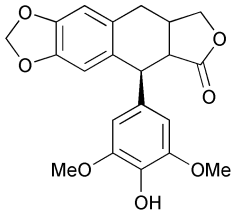


Isoguaiacin (**130**)



Gomisin J (**131**)

At a concentration of 50 μM, sauchinone (**55**) significantly reduced the release into the culture medium of glutamic pyruvic transaminase from CCl_4-damaged cultures of rat hepatocytes, which reflects its hepatoprotective properties.[106] It has been determined that glutathione, superoxide dismutase and glutathione peroxidase all play important roles in cellular defense against oxidative stress. Compound **55** appeared to protect primary cultured rat hepatocytes exposed to CCl_4 from significant drops in the levels of each of these three specific markers, respectively. It also seemed to ameliorate lipid peroxidation, as demonstrated by a reduction in the production of the oxidized lipid byproduct, malondialdehyde. These results suggest that **55** may exert hepatoprotective activity through antioxidative activity.[106] Lignans **6** and **132** exerted inhibition of lipid peroxidation in rat brain and kidney homogenates and rat erythrocyte hemolysis.[107] Compound **132** was found to be a more potent antioxidant in both lipid peroxidation and hemolysis assays, whereas **6** did not show any significant activity. Clearly, the aromatic hydroxyl group is very important for antioxidative effects of the compounds. In another study on antioxidant lignans, Filleur *et al.* reported **20**, **22** and **23** to exert an antiproliferative effect on MCF-7 cells, as well as antioxidative activity on DPPH radical.[108]



4'-Demethyldeoxypodophyllotoxin (**132**)

6 Immunosuppressive activities of plant lignans

There are few examples of clinical procedures that have moved from complete failure to outstanding success in such a short space of time. Organ transplantation therapy is one of those examples. The human HLA antigen proved such a barrier to organ grafting that prior to the late 1950's, transplantation yielded uniformly dismal and consistently fatal results. It was only through the discovery, evolution, and routine use of immunosuppressants that this barrier has finally been overcome.

A mixture of immunosuppressive therapies is typically used to prevent a recipient's body from rejecting a transplanted organ. Rejection is one of the most common causes of death in the first year after heart transplantation. Humoral rejection has been recently described in liver, kidney and heart transplant recipients by the National Institutes of Health (NIH) Consensus Conference.[109] Humoral rejection is caused by the body making antibodies that can attack the donor organ, which is similar to the way that antibodies attack other foreign objects such as viruses or other infectious agents. This form of rejection can occur immediately (hyperacute rejection), or some time after transplantation. The antibodies are either pre-formed antibodies (causing hyperacute rejection) or represent antibodies against the donor organ that developed after transplantation. In fact, many organ transplantations are now routine clinical procedures – the kidney transplant is a prime example, with 15 122 procedures performed in 2003.[110] Organ transplantation therapy is highly dependent on the success of pharmacotherapy to suppress recipient immune responses to the foreign organ; allograft rejection remains the major barrier to long-term graft survival in patients. In fact, transplant patients require life-long immunosuppressive drug therapy to prevent this rejection. Despite these significant advances, it is important to bear in mind the mechanism behind immunosuppression: immunosuppressants dampen the body's immune system. With current therapy, there are adverse side-effects that include, among others, a high incidence of opportunistic infection and transplant-related malignancies in patients. These are the unfortunate consequences of over-immunosuppression. Accordingly, a major goal of immunosuppression is to identify the optimal balance of therapy, such that there is effective prevention of allograft rejection, while drug-related adverse effects, infection, and malignancies are minimized. Because this compromise is largely unsatisfactory, there is a constant search for more effective and specific immunosuppressive agents.

Classical cytotoxic immunosuppressants act by inhibiting DNA synthesis. Others may act through activation of suppressor T-cell populations or by inhibiting the activation of helper cells. While immunosuppression has been brought about in the past primarily to prevent rejection of transplanted organs, new applications involving mediation of the effects of interleukins and other cytokines are emerging. Cytotoxic or T-cell-suppressing properties of lignans can open a new era of research to find more potent classes of immunosuppressive agents.

Table 4 Summary of the lignans possessing antioxidative activities

Compound	Name	Plant source	Target	Ref.
6	Deoxypodophyllotoxin	*Scutellaria baicalenm*,	Lipid peroxidation in rat brain and kidney homogenates and rat erythrocyte hemolysis	107
9	Justicidin A	*Justicia procumbens*	Rat hepatic cytochrome P450	103
15	Sesamin	Sesame oil, Chinese propolis	Lipid peroxidation, Cu^{2+}-induced LDL oxidation, lipid and alcohol metabolism, TBARS, aortic oxidative stress and endothelial dysfunction	83, 86, 91, 92
20	*meso*-Dihydroguaiaretic acid	*Machilus thunbergii*	Hepatoprotective activity, DPPH	103, 108
22	Nectandrin-B	*Myristica argentea*	DPPH)	108
23	*erythro*-Austrobailignan-6	*Myristica argentea*	DPPH)	108
25	*seco*-isolariciresinol	Knotwood extracts	Antioxidative potency, scavenging capacity for superoxide and peroxyl radicals	93, 102
30	Matairesinol	Knotwood extracts	Antioxidative potency, scavenging capacity for superoxide and peroxyl radicals	93, 102
32	Nordihydroguaiaretic acid	*Larrea tridentata*	Antioxidative activity in DCFH	88
34	(−)-Arctigenin	*Torreya nucifera*	Hepatoprotective activity, iNOS, EC1.14.13.39	51, 95
38	Hydroxymatairesinol	Knotwood extracts	Antioxidative potency, scavenging capacity for superoxide and peroxyl radicals	93, 101
51	Savinin	*Acanthopanax divaricatus* var. *albeofructus*	Cu^{2+}-induced LDL oxidation	86
55	Sauchinone	*Saururus chinensis*	Hepatoprotective activity by lipid peroxidation	106
62	Lariciresinol	Knotwood extracts	Antioxidative potency, scavenging capacity for superoxide and peroxyl radicals	93
75	(+)-Pinoresinol	Chinese propolis	Lipid peroxidation	99
76	(−)-Pinoresinol glucoside	*Styrax japonica*	DPPH	84
88	Justicidin B	*Justicia procumbens*	Rat hepatic cytochrome P450	103
92	2′-Hydroxy dihydroguaiaretic acid	*Saururus chinensis*	(LDL)-antioxidant	82
93	Styraxlignolide C	*Styrax japonica*	DPPH	84
94	Styraxlignolide D	*Styrax japonica*	DPPH	84
95	Styraxlignolide E	*Styrax japonica*	DPPH	84
96	Vitedoin	*Vitex negund*	DPPH	85
97	Vitedoamine A	*Vitex negund*	DPPH	85
98	α-Conidendrinaldehyde	*Vitex negund*	DPPH	85
99	α-Conidendrin	*Vitex negund*	DPPH	85
100	Vitrofolal E	*Vitex negund*	DPPH	85
101	Vitrofolal F	*Vitex negund*	DPPH	85
102	Vanprukoside	*Strychnos vanprukii*	DPPH	87

Table 4 (*Contd.*)

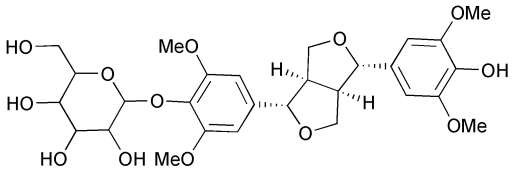
Compound	Name	Plant source	Target	Ref.
103	Strychnoside	*Strychnos vanprukii*	DPPH	87
104	(+)-Lyoniresinol-3α-*O*-β-glucopyranoside	*Strychnos vanprukii*	DPPH	87
105	[(*E*)-4,4′-Dihydroxy-7,7′-dioxolign-8(8′)-ene	*Larrea tridentata*	Antioxidative activity in DCFH	88
106	3′-Demethoxy-6-*O*-demethylisoguaicin	*Larrea tridentata*	Antioxidative activity in DCFH	88
107	(7*S*,8*S*,7′*S*,8′*S*)-3,3′,4′-Trihydroxy-4-methoxy-7,7′-epoxylignan	*Larrea tridentata*	Antioxidative activity in DCFH	88
108	*meso*-(7*S*,8*S*,7′*R*,8′*R*)-3,4,3′,4′-Tetrahydroxy-7,7′-epoxylignan[a]	*Larrea tridentata*	Antioxidative activity in DCFH	88
109	4-*epi*-Larreatricin	*Larrea tridentata*	Antioxidative activity in DCFH	88
110	3″-Hydroxy-4-*epi*-larreatricin	*Larrea tridentata*	Antioxidative activity in DCFH	88
112	Prinsepiol-4-*O*-*β*-D-glucoside	*Valeriana prionophylla*	Antioxidative properties in TEAC and CL	89
113	8-Hydroxypinoresinol-4′-*O*-β-D-glucoside	*Valeriana prionophylla*	Antioxidative properties in TEAC and CL	89
114	8-Hydroxypinoresinol	*Valeriana prionophylla*	Antioxidative properties in TEAC and CL	89
115	Prinsepiol	*Valeriana prionophylla*	Antioxidative properties in TEAC and CL	89
116	(+)-Pinoresinol mono-*β*-D-glucopyranoside	*Prunus domestica*	Antioxidant (ORAC)	90
117	3-(*β*-D-Glucopyranosyloxymethyl)-2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-(2*R*,3*S*)-dihydrobenzofuran	*Prunus domestica*	Antioxidant (ORAC)	90
119	Nortrachelogenin	Knotwood extracts	Antioxidative potency, scavenging capacity for superoxide and peroxyl radicals	93
120	Phyllostadimer A	*Phyllostachys edulis*	Liposomal lipid peroxidation	94
121	(−)-Traxillagenin	*Torreya nucifera*	Hepatoprotective activity	95, 98
122	(−)-4′-Demethyltraxillagenin	*Torreya nucifera*	Hepatoprotective activity, iNOS	51, 95, 98
123	Yangambin	Chinese propolis	Lipid peroxidation	99
124	(+)-Syringaresinol	Chinese propolis	Lipid peroxidation	99
125	Schisandrin B	*Schisandra chinensis*	Hepatic mitochondrial glutathione antioxidant	100
126	Neojusticin A	*Justicia procumbens*	Rat hepatic cytochrome P450	103
127	Neojusticin B	*Justicia procumbens*	Rat hepatic cytochrome P450	103
128	Chinensinaphthol methyl ether	*Justicia procumbens*	Rat hepatic cytochrome P450	103
129	(−)-Acuminatin	*Machilus thunbergii*	Hepatoprotective activity	104
130	(−)-Isoguaiacin	*Machilus thunbergii*	Hepatoprotective activity	104
131	Gomisin J	*Kadsura interior*	Lipid peroxidation, superoxide radical anion	105
132	4′-Demethyldeoxypodophyllotoxin	*Sinopodophyllum emodi*	Lipid peroxidation in rat brain and kidney homogenates, rat erythrocyte hemolysis	107

[a] The *R* and *S* assignments are relative.

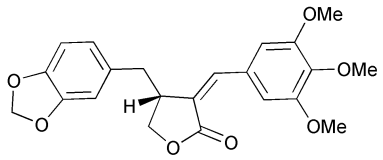
Table 5 Summary of the lignans possessing immunosuppressive activities

Compound	Name	Plant source	Target	Ref.
75	(+)-Pinoresinol	*Saussurea medusa*	Cytokines	113
133	Eleutheroside E1	*Scorzonera hispanica*	Immunomodulating properties with respect to both cellular and humoral immunity response on the experimental model of azathioprine-induced immunosuppression	111
134	Nemerosin	*Bupleurum scorzonerifolium*	CD28-costimulated activation of human peripheral T-cells	112
135	Isochaihulactone	*Bupleurum scorzonerifolium*	CD28-costimulated activation of human peripheral T-cells	112
136	Lirioresinol B	*Gnetum gnemon*, *Stellera chamaejasme*	Cytokines	113

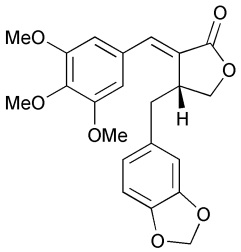
The immunomodulating effect of **133**, a lignan glucoside from cultivated cells of *Scorzonera hispanica* was studied, with respect to the cellular and humoral immune response on the experimental model of azathioprine immunosuppression.[111] It was established that **133** is capable of eliminating the azathioprine-induced decrease in the relative weight of thymus and in the response index value in the delayed hypersensitivity test. Eleutheroside E1 **133** possesses pronounced immunomodulating properties with respect to both the cellular and humoral immunity response on the experimental model of azathioprine-induced immunosuppression.[111] Nemerosin **134** and isochaihulactone **135** from *Bupleurum scorzonerifolium* were also found to possess immunosuppressive activity.[112] The effects of isolates **134** and **135** on CD28-costimulated activation of human peripheral T-cells were examined – both compounds exhibited potent inhibitory activities on CD28-costimulated T-cells, but also showed a significant cytotoxic effect on T-cells. Compounds **75** and **136** showed effect on cytokine production from LPS (or phytohemagglutinin)-stimulated human peripheral mononuclear cells.[113] The effects were compared with the reference compound (prednisolone),[114] and the results revealed that both compounds exhibited a significant inhibitory effect on all the tested cytokines.



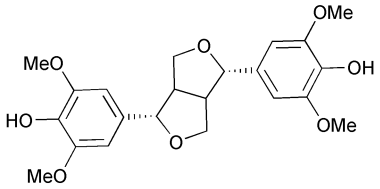
Eleutheroside E1 (**133**)



Isochaihulactone (**134**)



Nemerosin (**135**)



Lirioresinol B (**136**)

Other than these few reports, no significant work has been done on lignans in this specific area, and the results obtained from the tests with eleutheroside E1 (**133**) revealed that lignans and its synthetic derivatives can serve as potential candidates to be used as a new class of immunosuppressive agents.

7 Conclusion

In this review, 56 lignans are reported to possess antioxidative activity, and 48 have been reported to have anticancer properties. Thirty-four plant lignans were found to have anti-inflammatory activity, whereas reports of antimicrobial activity (11 lignans) and immunosuppressive activity (5 lignans) are much scarcer, indicating that more efforts are needed to explore the utility of lignans in this area of medicine.

This review covers a considerable number of plant lignans that possess anticancer potential, and many others that have anti-inflammatory and antioxidative activities. It has long been suspected that inflammation is intimately linked to carcinogenesis. Thus, agents with anti-inflammatory properties are likely to exert chemopreventive action.[115] Overexpression of COX-2 is also believed to be an early event in colon carcinogenesis, and in the development of other epithelial tumors.[116] The lignans exhibiting the inhibition of COX-2 may play a beneficial role in modulating carcinogenic processes. Antioxidants are compounds that exert their protective action either by suppressing the formation of free radicals or by scavenging free radicals.[117] A wide range of biological effects, established experimentally, may inhibit carcinogenesis. These include effects on tumor initiation, promotion and progression, cell proliferation and differentiation, as well as DNA repair, cell membrane stability and immune function. Therefore, anti-inflammatory and antioxidant lignans can be used indirectly as potential cancer chemopreventative agents.

This discussion helps to conclude that in future the lignans may be an effective means of dealing with cancer, as well as providing anti-inflammatory and antioxidant benefits. A fruitful area of future research may be in modifying natural lignans or in synthesizing new lignans with unique structural diversity and potent pharmacological activities.

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