Reviews

Antiviral Activity of Lignans

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Lignans are found in the roots, stems, bark, fruit and seeds of many plant species and are derived from dimerization of phenylpropanoid units at the central carbons of their side chains (see Scheme 1).[1] Dimers with linkages other than this type are known as neolignans. Further cyclization can lead to cyclolignans, such as aryltetrahydronaphthalenes (aryltetralins) (**1**), arylnaphthalenes (**2**), or dibenzocyclooctadienes (**3**).[1]

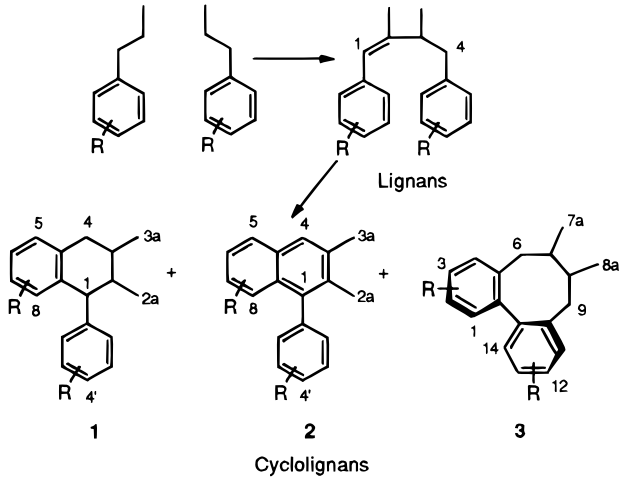
Of all the known natural plant lignans, which number in the hundreds, the best known is podophyllotoxin (**4**). This toxic lignan is the principle active component of American mandrake or mayapple (*Podophyllum peltatum* of the family Berberidaceae). An alcoholic extract of this plant (podophyllin) was first cited in 1942 as a topical treatment for venereal warts (*Condyloma acuminatum*), an ailment caused by a papilloma virus.[2] This would appear to be one of the first reported examples of the antiviral activity of a lignan natural product.

In 1978, May and Willuhn surveyed the antiviral activity of many plant extracts on four virus types (herpes-, influenza-, vaccinia-, and poliovirus). It was noted that the most active extracts were rich in tannins, and presumably lignans,[3] although the components of the extracts were not identified. The extract of *P. peltatum* was active against all but the poliovirus.[3]

Markkanen et al. published a detailed study in 1981 of the antiviral effects of 21 different lignans, including many podophyllotoxin derivatives, on Herpes simplex virus type 1 (HSV-1) in primary amnion cells.[4] Many of these compounds showed strong antiviral activity and an excellent therapeutic index (calculated from the minimum inhibitory concentration and the maximum tolerated concentration). The structures and activities are given in Table 1. In the same paper,[4] it was mentioned that deoxypodophyllotoxin (**7**) was active against HSV-2 and that it blocked the uptake of thymidine by primary amnion cells at concentrations as low as 2.5 nM.

In 1982, Bedows and Hatfield studied the effect of four of the podophyllin lignans on both HSV-1 (a DNA virus) and the measles virus (an RNA virus) infecting green monkey kidney (Vero) cells.[5] They determined the effect of a 1 μM concentration of the lignans on both cell morphology and on the ability of cells to produce infectious viral progeny. The latter was done by estimating the amount of infectious virus in the medium of infected cells that had been treated, using an ensuing plaque assay. Podophyllotoxin (**4**), picropodophyllotoxin (**10**), α-peltatin (**5**), β-peltatin (**8**), and deoxypodophyllotoxin (**7**) were studied. All of the lignans caused the cells to assume a spherical shape in the absence of virus, and the effect was strongest for podophyllotoxin, although greater than 85% of the cells remained viable. All of the lignans reduced infectivity for both viruses; ca. 90−100% for podophyllotoxin (**4**), ca.78−85% for β-peltatin (**8**) and deoxypodophyllotoxin (**7**), ca. 52−69% for α-peltatin (**5**), and ca. 16−58% for picropodophyllotoxin (**10**). These results largely paralleled those of Markkanen et al.,[4] except for α-peltatin (**5**), which was found to be more active in the earlier of the two studies. Bedows and Hatfield speculated that the antiviral effect of podophyllotoxin was due to disruption of cellular microtubules.[5] It had been previously shown that the cytotoxic effect of podophyllotoxin (**4**) was due to its ability to bind tubulin, a subunit of microtubules.

Scheme 1



MacRae and Towers reviewed the antiviral activity of lignans in 1984[6] and, like Bedows and Hatfield,[5] concluded that the antiviral effects of lignans were related to inhibition of microtubule formation, pointing out that other tubulin binders such as colchicine also have antiviral effects. The idea that functional cytoplasmic microtubules are a necessary prerequisite to viral infection, and that tubulin-binding drugs may inhibit viral infection by disrupting the cellular cytoskeleton, has more recently been explored.[7]

In1989, MacRae et al. surveyed the effect (plaque reduction assay) of 18 lignans against murine cytomegalovirus (MCMV, a herpes DNA virus) and Sindbis virus (an RNA virus), both grown in mouse 3T3-L1 cells.[8] The results for the four most active lignans are given in Table 2. They

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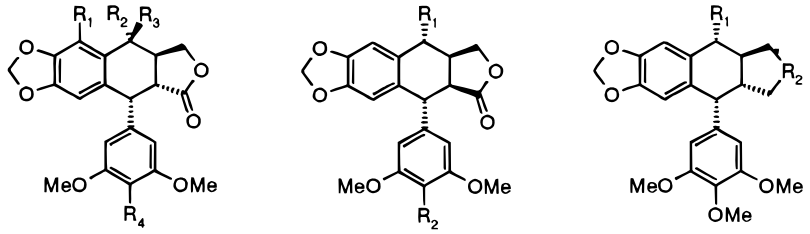
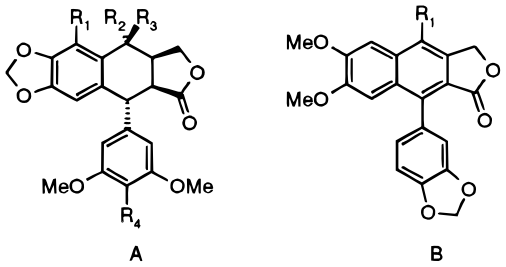
Table 1. Activity of Lignans against HSV-1 in Primary Amnion Cells



		compound		min IC[a]	MTC[b] (μM)	TI[c]
4	A	podophyllotoxin	R_1, R_3 = H; R_2 = OH; R_4 = OMe	24 nM	140	6000
5	A	α-peltatin	R_1, R_4 = OH; R_2, R_3 = H	50 nM	200	4000
6	C	anhydropodophyllol	R_1 = OH; R_2 = O	250 nM	>200	800
7	A	deoxypodophyllotoxin	R_1, R_2, R_3 = H; R_4 = OMe	38 nM	>25	667
8	A	*β*-peltatin	R_1 = OH; R_2, R_3 = H; R_4 = OMe	360 nM	120	333
9	A	4′-demethylpodophyllotoxin	R_1, R_3 = H; R_2, R_4 = OH	500 nM	>125	250
10	B	picropodophyllotoxin	R_1 = OH; R_2 = OMe	1.9 μM	140	75
11	A	epipodophyllotoxin	R_1, R_2 = H; R_3 = OH; R_4 = OMe	1.6 μM	24	15
12	A	*β*-peltatin-*β*-D-glucoside	R_1 = *β*-D-glucoside; R_2, R_3 = H; R_4 = OMe	17 μM	52	3
13	C	deoxypodophyllotoxin cyclic sulfide	R_1 = H; R_2 = S	12 μM	37	3
14	C	deoxypodophyllotoxin cyclopentanone	R_1 = H; R_2 = CO	49 μM	122	2.5
15	A	etoposide	R_1 = R_2 = H; R_3 = 4,6-*O*-ethylidene-*β*-D-glucoside; R_4 = OH	85 μM	100	1.2
16	A	4′-demethylepipodophyllotoxin	R_1, R_2 = H; R_3, R_4 = OH	13 μM	13	1

[a] Min IC is the lowest concentration that completely inhibits the pathogenic effect of HSV-1. [b] MTC is the highest concentration not to cause morphological changes on microscopic examination. [c] TI is the therapeutic index calculated from MTC/min IC.

Table 2. Activity of Lignans against Sindbis and MCMV Virus



		compound		concentration (nM)	% inhibition sindbis	% inhibition MCMV
4	A	podophyllotoxin	R_1, R_3 = H; R_2 = OH; R_4 = OMe	241	3	74
5	A	α-peltatin	R_1, R_4 = OH; R_2, R_3 = H	250	6	85
17	B	justicidin B	R_1 = H	274	74	14
18	B	diphyllin	R_1 = OH	263	18	11

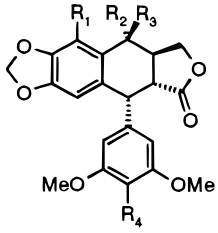
also attempted to determine which stage of infection was most sensitive to lignan action. Studies with podophyllotoxin (**4**) and α-peltatin (**5**) showed that antiviral effects against Sindbis virus were observed only if the drug were administered at the same time as the virus (pretreating the virus or posttreating infected cells had little or no effect). This would seem to indicate that the antiviral effect is related to inhibition of attachment or penetration of the virus. On the other hand, activity against MCMV was found for treatments concurrent with or postinfection. In the case of MCMV, it was concluded that the lignan must interfere irreversibly with some critical factor in the viral replication cycle. It should be noted that pretreating either virus with the lignans had little or no effect on later viability of the virus, indicating that there was no direct activity against the virus itself.[8]

In a book chapter entitled "Plants as a Source of Potential Antiviral Agents", C.-T. Che briefly reviewed (one page) the antiviral effects of lignans in 1991.[9] After reviewing some of the more general references, he concluded that antiviral properties of lignans were related to tubulin binding and that therapeutic use would be limited due to the cytotoxicity of the active compounds.

In three papers (1993 and 1994), San Feliciano et al. reported on the antiviral effects of several lignans. Plaque reduction assays were conducted against HSV-1 and vesicular stomatitis virus (VSV) infecting monkey kidney fibroblasts (CV-1) and hamster kidney fibroblasts (BHK), respectively.[10] The results for the most active compounds are given in Table 3. A few conclusions were drawn from the data obtained. In general, tetrahydro- and dihydronaphthalenic lignans were more active than their naphthalenic counterparts (data not shown). In addition, the lactonic lignans appeared to be more active than nonlactonic lignans, and *trans*-lactone compounds (e.g., podophyllotoxin) were more active than the corresponding *cis*-lactones (e.g., picropodophyllotoxin). There was a rough correlation between antineoplastic and antiviral effects, suggesting a similar mechanism of action for the compounds tested.[10]

With the onset of acquired immune deficiency syndrome (AIDS) and the characterization of the human immunode-

Table 3. Activity of Lignans against HSV-1 and VSV in CV-1 and BHK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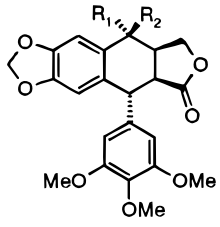
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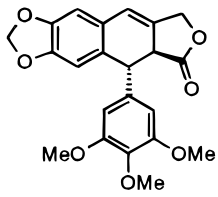
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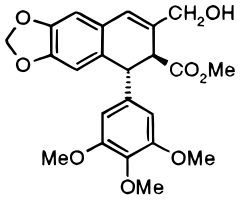
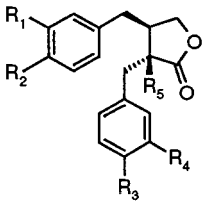

D

		compound		IC_{50} (HSV)[a] (μM)	IC_{50} (VSV)[b] (μM)
4	A	podophyllotoxin	R_1, R_3 = H; R_2 = OH; R_4 = OMe	0.05	0.1
7	A	deoxypodophyllotoxin	R_1, R_2, R_3 = H; R_4 = OMe	0.025	<0.025
9	A	4′-demethylpodophyllotoxin	R_1, R_3 = H; R_2 = OH; R_4 = OH	0.10	0.25
19	A	epipodophyllotoxin acetate	R_1, R_2 = H; R_3 = OAc; R_4 = OMe	0.44	0.22
20	A	β-peltatin A methyl ether	R_1 = OMe; R_2, R_3 = H; R_4 = OMe	0.023	0.023
21	B	deoxypicropodophyllotoxin	R_1, R_2 = H	2.0	2.0
22	A	4-*O*-methylpodophyllotoxin	R_1, R_3 = H; R_2 = OMe; R_4 = OMe	0.46	0.93
23	A	4-*O*-methylepipodophyllotoxin	R_1, R_2 = H; R_3 = OMe; R_4 = OMe	0.9	0.9
24	B	4-*O*-methylpicropodophyllotoxin	R_1 = H; R_2 = OMe	0.9	2.3
25	C	α-apopicropodophyllotoxin		0.25	0.25
26	D	methyl α-apopicropodophyllate		0.46	0.46

[a] IC_{50} (HSV) is the concentration required to inhibit 50% of plaque formation in monkey kidney fibroblast cells. [b] IC_{50} (VSV) is the concentration required to inhibit 50% of plaque formation in hamster kidney fibroblast cells.

ficiency virus (HIV), several papers on the effects of lignans on this virus have appeared.[11−14,16−23,27] The first paper, appearing in 1990, revealed that arctigenin (**27**) and trachelogenin (**28**), at 0.27 and 0.52 μM, respectively, reduced HIV viral protein production by 60−70% and inhibited viral reverse transcriptase activity by 69 and 57%, respectively.[11] The compounds were also found to inhibit

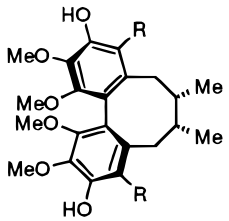


27 (-)-Arctigenin R_1,R_2,R_4 = OMe; R_3 = OH; R_5 = H
28 (-)-Trachelogenin R_1,R_2,R_4 = OMe; R_3 = OH; R_5 = OH
29 R_1,R_2,R_3,R_4 = OH; R_5 = H
30 R_1,R_2,R_3 = OH; R_4 = OMe; R_5 = H
31 R_1,R_2 = OMe; R_3,R_4 = OH; R_5 = H
32 R_1,R_2 = OMe; R_3,R_4,R_5 = H
33 R_1,R_2 = OMe; R_3 = OH; R_4,R_5 = H
34 R_1,R_2 = OMe; R_4 = OH; R_3,R_5 = H

topoisomerase II activity. In a second paper, the compounds were compared to known tubulin binders and topoisomerase II inhibitors. It was concluded that the in vivo activity of arctigenin, **27**, and trachelogenin, **28**, was related to inhibition of viral integrase and not to tubulin binding or toposiomerase inhibition.[12] The compounds were unsuitable candidates for drug therapy because of their cytotoxicities.

Eich et al. reinvestigated the action of arctigenin (**27**) and trachelogenin (**28**) on HIV-1 in 1996 and again found them to be in vivo inhibitors of HIV-1 integrase as well as being topoisomerase II inhibitors.[13] They assembled/prepared a large set of dibenzylbutyrolactone and aryltetralin lignans and tested them for inhibition of HIV-1 integrase activity in vitro. Surprisingly, they found that arctigenin (**27**) and trachelogenin (**28**) showed no in vitro inhibition of integrase and concluded that the in vivo activity was due to metabolites of these compounds. From their extensive screening, they found that only the three dibenzylbutyrolactones **29**−**31** were active against HIV-1 integrase in vitro. Notably, all of these three compounds contain at least one catechol (*o*-dihydroxyphenyl) ring in their structure. Yang et al. also synthesized several optically pure dibenzylbutyrolactones[14,15] and studied their activity against HIV-1 replication in acutely infected H9 cells.[14] EC_{50}'s of the compounds **32**−**34**, as well as (−)-arctigenin (**27**) and 3′-*O*-demethylactigenin (**31**), ranged from 0.42 to 6.7 μM with therapeutic indices less than 9.0.

In 1995, Fujihashi et al. published on lignan anti-HIV activity that was related to inhibition of reverse transcriptase (RT).[16] Gomisin J (**35**) and its derivatives were tested and found to have ED_{50}'s in the range of 0.1−0.5 μM. By determining cross-resistance in HIV mutant

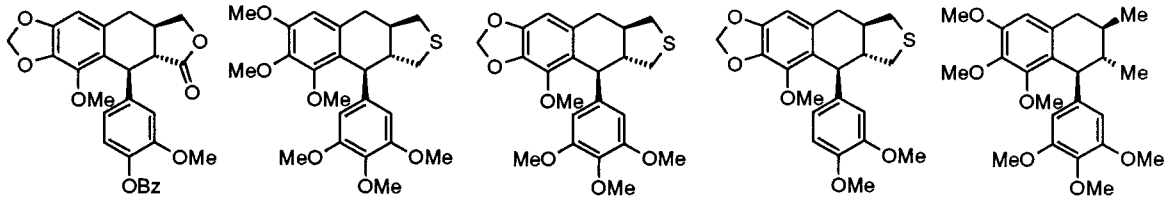


35 (-)-Gomisin J R=H
and derivatives R= Cl, Br,

strains resistant to other reverse-transcriptase inhibitors, the authors concluded that the gomisin derivatives bound to reverse transcriptase at a site close to that where nevirapine (a nonnucleoside anti-HIV compound) binds. High serum levels of gomisin derivatives were easily achievable by oral administration of the drug, and therapeutic indices, greater than 50, indicated that these drugs deserved further study.[16]

Two other papers have appeared describing the antiviral activity of dibenzocyclooctadiene lignans.[17,18] The lignans interiotherin A (**36**) and schisantherin D (**37**), whose structures are similar to gomisin J (**35**), were found to have anti-HIV activity (6.2 and 0.96 μM, respectively, with therapeutic indices of 13.2 and 50.6).[17] The IC_{50}'s (thera-

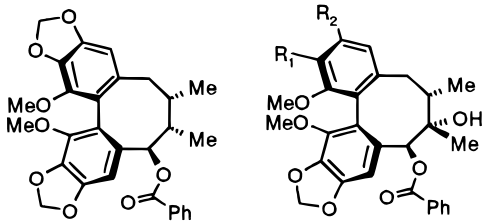
Chart 1. [a]



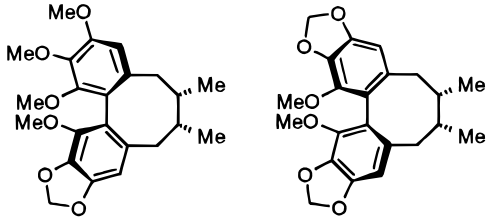
48 5.22 (>840) **49** 0.8 (58) **50** 5.1 (163) **51** 3.3 (>840) **52** 3.2 (34)

[a] Activity of compounds against HIV-1 in MT-4 cells EC_{50} (dosage to achieve 50% protection) and CD_{50} (dosage to kill 50% of cells). All concentrations are micromolar.

peutic index) of gomisin G (**38**), kadsuranin (**39**), and schisandrin C (**40**) were 0.011 μM (300), 2.0 μM (56), and 3.1 μM (33), respectively.[18] It appears that both the C-6 hydroxyl group and the C-7 benzoyloxy group in these compounds enhance activity.[17,18]

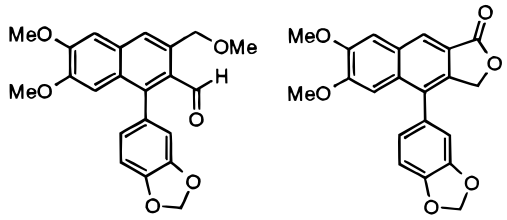


36 Interiotherin A **37** Schisantherin D (R_1,R_2=OCH_2O)
38 Gomisin G (R_1,R_2=OMe)



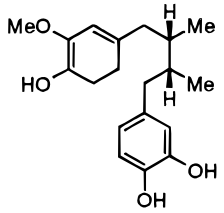
39 Kadsuranin **40** Schisandrin C

Chang et al. studied inhibition of HIV-RT by several lignans and compared their activity to inhibition of human DNA polymerase-α (HDNAP-α).[19] The two most potent lignans in their study were phyllamycin B (**41**) and retrojusticidin B (**42**) (IC_{50}'s 3.5 and 5.5 μM, respectively), and their corresponding activities against HDNAP-α were quite low (IC_{50}'s of 289 and 989 μM, respectively). Later, an attempt was made to correlate the antiviral effects to various physicochemical and structural parameters.[20]



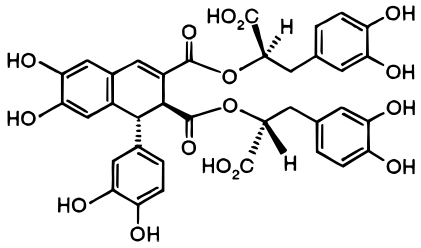
41 Phyllamycin B **42** Retrojusticidin B

The lignan mal.4 (**43**), also known as Malachi 4:5-6, isolated from *Larrea tridentata* Cov. (Zygophyllaceae), is an inhibitor of HIV basal transcription and HIV Tat-transactivated transcription, interfering with binding of the transcription factor Sp1 (a protein) to HIV DNA in the long terminal repeat region (LTR).[21,22] The exact mode of action could be either binding to the Sp1 protein itself or binding to the DNA.



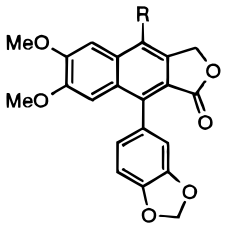
43 Malachi 4:5-6 (Mal.4)

Rabdosiin (**44**) is a caffeic acid tetramer, and the sodium and potassium salts of this compound, and one of its diastereomers, are also strong inhibitors of HIV-1 (EC_{50} of 2−5 μM with therapeutic indices of 20−30),[23] although the source of the activity may be related to the ability of this lignan to inhibit topoisomerase I and II.[24]



44 Rabdosiin

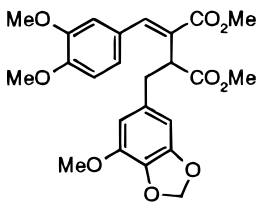
Ten lignans, isolated from *Justicia procumbens* var. *leucantha*, have shown antiviral activity against vesticular stomatitis virus (VSV) in cultured rabbit lung cell (RL-33).[25] The more active compounds, justicidin A (**45**), justicidin B (**17**), and diphyllin (**18**), had minimum inhibitory concentrations (MIC) and minimum cytotoxic concentrations of 0.33/159, 0.16/85, and 0.65/166 μM, respectively.[25] The results for justicidin B (**17**) and diphyllin (**18**) were similar to those found for inhibition of Sindbis virus and MCMV (see Table 2).



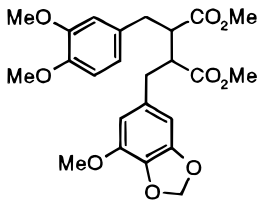
45Justicidin A (R = OMe)
17 Justicidin B (R = H)
18 Diphyllin (R = OH)

The two lignans rhinacanthin E (**46**) and rhinacanthin F (**47**) have shown inhibitory activity against influenza virus type A with EC_{50}'s of 3.8 and 2.1 μM, respectively (toxicities, TC_{50}'s, were 99 and 38 μM, respectively) but not

against the herpes virus HSV-2.[26] This would suggest that their mode of action is particular to the influenza A virus.



46 Rhinacanthin E



47 Rhinacanthin F

Hara et al. investigated the anti-HIV-1 activity of a large number of aryltetralin (aryltetrahydronaphthalene) lignan analogues, both in vivo and in vitro.[27] Activity against HIV-1 strains resistant to other transcriptase inhibitors was studied. HIV-1 strains resistant to the lignan analogues were also produced, and cross resistance to other RT inhibitors was studied. It appears that the lignan analogues bind to reverse transcriptase at the same site as many other RT inhibitors. The structures for a few of the more active compounds, **48**−**52**, from this study, with their EC_{50}'s and toxicities, are provided in Chart 1.

Conclusions. It appears that there are several modes of antiviral activity associated with lignans. These include tubulin binding, reverse transcriptase inhibition, integrase inhibition, and topoisomerase inhibition. Most notable among the tubulin binding lignans are those related to podophyllotoxin. By binding to tubulin, these lignans are able to disrupt the cellular cytoskeleton and interfere with some critical viral process. Reverse transcriptase inhibition is found for lignans of all classes, including dibenzylbutyrolactones, dibenzylbutanes, dibenzocyclooctadienes, and aryltetralins. In the case of the aryltetralins, the lignans appear to bind HIV reverse transcriptase at the same site as other nonlignan reverse transcriptase inhibitors. The association of antiviral activity with toposiomerase inhibition is less strong, although it has been suggested for etoposide (**15**) and rabdosiin (**44**).

In general, the antiviral effects of lignans are not strong, and a reviewer has pointed out that it would be unwise to attempt to reach broad conclusions, particularly from those studies reporting weak inhibition of plaque formation. There appears to be no commercial application of lignan antivirals except for podophyllotoxin (**4**), which is used topically to treat various warts caused by the human papilloma virus (HPV).

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References and Notes

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