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ARTEETHER: A POTENT PLANT GROWTH INHIBITOR FROM *ARTEMISIA ANNUA*

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Key Word Index—*Artemisia annua*; Asteraceae; artemisinin; arteether; growth inhibitor; allelopathy; herbicide.

Abstract—Arteether, a derivative of artemisinin from *Artemisia annua*, was examined for its effect on the seedling growth of the dicotyledons *Artemisia annua*, *Lactuca sativa* (Asteraceae), *Raphanus sativus* (Brassicaceae), *Portulaca oleracea* (Portulacaceae) and *Amaranthus blitum* (Amaranthaceae), and the monocotyledons *Secale cereale*, *Hordeum vulgare* (Poaceae). The effect of arteether was compared with that of other compounds and derivatives of *A. annua* such as artemisinic acid, arteannuin B and artemisinin. Arteether was found to be the most effective growth inhibitor among the tested compounds. Its inhibitory effect on root was more pronounced than on the shoot. Artemisinin, the precursor for synthesis of arteether, showed equivalent or lower activity than arteether in most of the test plants. Artemisinin was more toxic to monocotyledons than dicotyledons, whereas arteether was observed to be highly toxic to dicotyledonous weeds.

INTRODUCTION

Allelopathic plants release certain chemicals in their immediate environment, which inhibit or stimulate nearby growing plants. A variety of allelochemicals have been identified, including the phenolic acids, coumarins, terpenoids, flavonoids, alkaloids, glycosides, and glucosinolates [1, 2]. The allelochemicals are considered as resources for developing herbicides, plant growth stimulators and pharmaceuticals.

Artemisia annua (Asteraceae) is the source of artemisinin, a sesquiterpene lactone having antimalarial and phytotoxic activities [3]. As a phytotoxic agent, artemisinin is known to inhibit seed germination and seedling growth of several mono and dicotyledonous plants, both cultivated and weeds. Several compounds related to artemisinin, including artemisinic acid, arteannuin B, deoxyartemisinin, artesunic acid and sodium artelinate have also been shown to be phytotoxic to differing extents [3–5].

Arteether, obtained by the etherification of dihydroartemisinin a reduction product of artemisinin [6], has been found to be far more active against malarial parasites than artemisinin. In this study the phytotoxicity of arteether has been compared with that of artemisinin and related compounds.

RESULTS AND DISCUSSION

The pure compounds (Fig. 1) artemisinin, artemisinic acid and arteannuin B were isolated from *A. annua* plants and arteether was semi-synthetically prepared from artemisinin for this investigation [6–8]. To conduct phytotoxicity tests, the compounds were used at 200, 100, 10, 1 and 0.1 ppm concentrations. The tests were conducted against the seeds of two monocotyledonous plants, *Hordeum vulgare* and *Secale cereale* and five dicotyledonous plants, *Amaranthus blitum*, *Artemisia annua*, *Lactuca sativa*, *Portulaca oleracea* and *Raphanus sativus*. The concentrations of artemisinin and related compounds that produced 50% root/shoot growth plots, were estimated and are shown in Table 1.

Among the compounds examined, arteether was found to be most toxic. The compounds could be arranged in the following order of phytotoxicity:

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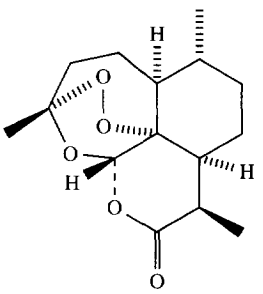
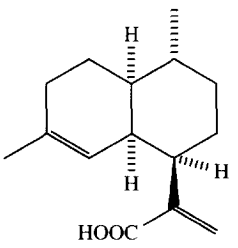


ARTEMISININ



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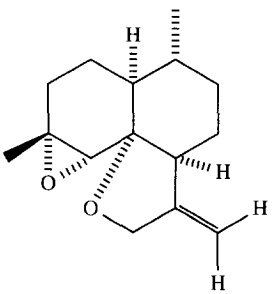
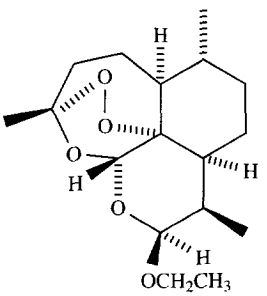


ARTEANNUIN–B



ARTEETHER

Fig. 1. Structures of artemisinin and its related compounds.

arteether > artemisinin > arteannuin B > artemisinic acid. Generally the toxic effect was greater on roots than shoots. A differential toxicity effect between mono and dicotyledonous plants was observed with artemisinin, while both mono- and dicotyledonous plants were generally sensitive to the toxicity of arteether. Among all the plants tested, *R. sativus* proved to be least sensitive to arteether and other artemisinin related compounds. The dicotyledonous plants *P. oleracea* and *Lactuca sativa* were relatively more sensitive to arteether. However, artemisinin was not very toxic to these plants. Interestingly, *A. annua* seedlings tolerated all the artemisinin related compounds except arteether. *A. annua* seedlings were as sensitive to arteether as the seedlings of *A. blitum*.

The above results revealed that although arteether is more phytotoxic than artemisinin, its action is not as selective as that of artemisinin. This study also supports the view that the endoperoxide moiety of arteether and artemisinin [4] may be responsible for the inhibitory effect on the seedlings.

EXPERIMENTAL

Plant material. Artemisia annua was collected from CIMAP research farm, Lucknow, India; a voucher specimen (no-2832 dated March 8, 1992) is deposited in the herbarium of the Institute.

Extraction and isolation. Dried 50 kg aerial portion of *A. annua* were processed in the pilot plant of our Institute. Plant material was extracted with *n*-hexane, and concd under red. pres. and the concentrate (4.0 kg) was defatted and subjected to CC over silica gel, eluting with hexane, 5% EtOAc–hexane, 10% EtOAc–hexane and 15% EtOAc–hexane. The 5, 10 and 15% frs were rich in artemisinic acid, artemisinin and arteannuin B, respectively. All these frs on crystallization afforded pure crystalline compounds, which were characterized by mp, mmp, IR, NMR and MS. Artether was prepd from artemisinin, see ref. [6].

Bioassay. The compounds were dissolved in spectral grade Me_2CO, the sols of the desired concns were obtained by dilution with distilled H_2O. For an assay, 20 seeds were placed on Whatman filter paper (moistened with 5 ml of test solution in a 9 cm diameter petri dish). The test soln in dish contained the test chemicals in 20 μl or less Me_2CO. All control treatments also contained 20 μl of Me_2CO. The petri dishes were incubated for 9 days in a germinator, maintained at 25° with 90% humidity and 4 hr light/day. At the end of incubation, the observations were recorded on the seedlings in terms of shoot and root lengths. The tests were replicated $\times 3$.

Table 1. The concentrations of sesquiterpene lactones that caused 50% inhibition of growth in the germinating seedlings of different mono and dicotyledons

Compound	Plant species on which the test is performed	Concentration (ppm) at which the treated seedlings were 50% in size of those of the control on 9th day in terms of the shoot length	root length
Artemisinic acid	A	>200, ND	>200, ND
	B	>200, ND	130
	C	190	140
	D	>200, ND	120
	E	50	10
	F	195	60
	G	150	130
Arteannuin B	A	80	60
	B	90	50
	C	165	90
	D	>200, ND	130
	E	140	20
	F	130	80
	G	170	170
Artemisinin	A	8	0.9
	B	12	0.6
	C	>200, ND	70
	D	130	130
	E	50	10
	F	80	90
	G	30	120
Arteether	A	8	0.8
	B	9	0.9
	C	5	6
	D	100	80
	E	1	1
	F	9	7
	G	1	0.1

A, *Secale cereale*; B, *Hordeum vulgare*; C, *Artemisia annua*; D, *Raphanus sativus*; E, *Portulaca oleracea*; F, *Amaranthus blitum*; G, *Lactuca sativa*; ND, not determined.

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