Potential Benefits of *trans*-dehydrocrotonin on the Central Nervous System

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Introduction

The 19-*nor*-clerodane *trans*-dehydrocrotonin (DCTN) is the most important biologic diterpene-type clerodane reported from *Croton cajucara* Benth. (Euphorbiaceae). This clerodane showed striking correlation with the folk traditional therapeutic use of this *Croton*, proving to possess antitumor, antiulcerogenic, hypoglycemic, hypolipidaemic, antiatherogenic, antioestrogen, antigenotoxicity, antiinflammatory and antinociceptive activities[1,2].

In this work we have undertaken some DCTN pharmacological studies on the central nervous system (CNS).

Results and Discussion

DCTN by intraperitoneally (i.p.) administration exhibited no analgesic activity at dose of 25 mg/kg on the hot-plate test. Meanwhile, at a dose of 50 or 100 mg/kg exhibited mild analgesic activity after 120 or 60 minutes. DCTN at 50 and 100 mg/kg doses inhibited abdominal writhing by 66.85 and 81.92%, respectively. DCTN at 100 mg/kg dose (i.p. administration), after 120 min., exhibited mild CNS depressant activity and no effects on the hole cross test with 25 and 50 mg/kg doses was evidenced. DCTN (100 mg/kg) exhibited negligible depressant activities, after 60 min of drug administration. This depressant effect persisted for about 60 to 120 min., after 240 min. observation period, the depressant effect was abolished.

In the open field test with 25 and 50 mg/kg doses, DCTN exhibited mild central depressant activities ($p<0.05$). Meanwhile, with a dose of 100 mg/kg (i.p. DCTN administration) exhibited mild to moderate central depressant activity. Its highest depressant activity was achieved after 120 minutes. Data collected from this dose at 30 min. ($p=0.027$), 60 min. ($p=0.001$), 120 min. ($p<0.001$) and 240 min. ($p=0.01$) are significant. Therefore, in the rotarod test at different doses (25, 50 and 100 mg/kg) DCTN had no effect.

In the pentobarbitone induced sleeping time test, the effect of this clerodane is very much ambiguous. At low dose (25 mg/kg, i.p.) DCTN exhibited mild stimulant effect. But in higher doses (50 and 100 mg/kg, i.p.) exhibited mild depressant effect on the mice. At the dose of 100 mg/kg, the depressant effects of DCTN decreased in little extent. On the forced swimming test, DCTN exhibited negligible antidepressant effect on mice.

DCTN attenuated the acetic acid, but not the hot-plate thermal stimulation. Therefore, it is probable, that this diterpene could produce its analgesic effect via peripherally (not centrally) as was previously observed by Carvalho[3], who proved that in the acute toxicity, there were no observed symptoms that justify the central nervous system action of DCTN, such as stereotypy, ataxia, and convulsion. Moreover, the LD_{50} of this DCTN was 555 mg/kg (p.o) for mice (which is 10 times higher than the ED_{50})[3]. DCTN in higher doses increased the sleep latency and in lower dose, decreased the total duration of sleeping. Those observed results may support the possible evidence that DCTN at low dose acts as an enzyme inducer increasing the hepatic metabolizing enzyme responsible for the biotransformation of barbiturate. Therefore, at higher doses DCTN may decreased the biotransformation of barbiturate in the liver by inhibiting the enzymes responsible for barbiturate metabolism, in this case DCTN acts as an enzyme inhibitor in the liver.

Conclusions

DCTN intraperitoneally exhibited mild analgesic activity on hot-plate test, but exhibited strong antinociceptive activity against acetic acid-induced abdominal writhing and the ED_{50} was calculated to be 44.88 mg/kg. At higher doses (100 mg/kg) it exhibited mild CNS depressant activities in laboratory animals. Moreover, it has negligible antidepressant activity. After taking consideration of the drug interaction, the DCTN can be used as a potent analgesic agent in case of peripheral algesia, without affecting the CNS.

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