EFFECT OF VARIOUS EXTRACTS OF *Momordica dioica* PULP ON CLONIDINE AND HALOPERIDOL-INDUCED CATALEPSY IN MICE

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Summary

The present study sought to determine, in more detail, the effects of various extracts of *Momordica dioica* pulp for anti-cataleptic activity as the plant is having antiasthamatic activity. The cataleptic response of mice to various extracts of *Momordica dioica* measured using a bar test, was enhanced by subcutaneous pretreatment with Clonidine (1 mg/kg). Methanol extract and Aqueous extract (50 mg/kg, i.p.) of the plant more significantly inhibited clonidine-induced catalepsy as compare to petroleum ether and ethyl acetate but not any one extract among these inhibited haloperidol-induced catalepsy. Thus the antihistaminic activity of *Momordica dioica* may be due to polar constituents.

**Key words:** *Momordica dioica*, cataleptic activity, antiasthamatic, clonidine, haloperidol.
**Introduction**

*Momordica dioica* climbing creeper plant fruits and leaves are traditionally used as medicinal agent of asthma, leprosy, bronchitis, fever, tridosha.\(^1\) Catalepsy is a condition in which the animal maintains imposed posture for long time before regaining normal posture. Catalepsy is a sign of extrapyramidal effect of drugs that inhibit dopaminergic transmission or increase histamine release in brain. Clonidine, a\(\alpha_2\)-adrenoceptor agonist, induces dose dependent catalepsy in mice, which is inhibited by histamine H\(_1\) receptor antagonists but not by H\(_2\) receptor antagonist.\(^2\) They also showed that pretreatment with L-histidine, a precursor of histamine potentiated clonidine-induced catalepsy in dose dependent manner. Muley et al., (1979) showed that intracerebroventricular injection of histamine in conscious mice induced catalepsy, which was inhibited by H\(_1\) receptor antagonist but not by H\(_2\) receptor antagonist.\(^3\) It is known that clonidine releases histamine from mast cells.\(^4\) Schwartz (1997) identified histamine containing mast cells in brain.\(^5\) Clonidine-induced release of histamine from mast cells is inhibited by \(\alpha_2\)–adrenoceptor blocker, prazocine.\(^6\) Neuroleptic agent also induced catalepsy, but by different mechanism. Neuroleptics inhibit dopamine D\(_2\) receptors in the substantia nigra.\(^7,8\) Therefore it was our objective to study the effect various extracts *Momordica dioica* pulp on clonidine-induced catalepsy, as it is used traditionally in cough, asthma and inflammation.\(^9\)
Since catalepsy is a common extrapyramidal side effect of neuroleptic agents and the effect of the plant on haloperidol-induced catalepsy is not known, we also studied their effect on haloperidol-induced catalepsy in mice.

**Material and Methods**

**Plant Material**

Pulp of *Momordica dioica* were collected from Therla, Ta. Patoda, Beed district of Maharashtra in September 2009 and authenticated by P.G. Diwakar, Botanical Survey of India, Pune, where a sample specimen (voucher number: RAMAM1) No. BSI/WRC/Tech/2009/593 has been deposited.

**Extraction**

Dried and coarsely powdered pulp of *Momordica dioica* was subjected to successive solvent extraction in Soxhlet extractor using petroleum ether, ethyl acetate, and methanol as solvent and the marc left was refluxed with water. All the extracts were vacuum dried to produce Pet. ether (1.5%), Ethyl acetate (2.6%), Methanol (18%) and Aqueous (4.67%) extracts respectively.
Animals

Male albino mice (Swiss strain) weighing 25-28 g were housed under standard laboratory conditions, five in each group. The animal had free access to food and water. The ethical committee of the institute approved the protocol of the study.

Drugs and Chemicals

The following drugs and chemicals were used. Drugs: Clonidine (Neon Lab. Ltd., India), Haloperidol (Sun pharma, India), Pheniramine maleate (Unimark Remedies Ltd., India) purchased from commercial source. Chemicals: petroleum ether (60-80°C) (RFCL Ltd, India), ethyl acetate (RFCL Ltd, India), methanol (MERCK Ltd, India), and DMSO (Research Lab Industries, India).

Assessment of Anti-cataleptic Activity

Bar test was used to study the effect of various extracts on clonidine-induced catalepsy. Clonidine (1 mg/kg, s.c.) was injected to mice (n = 5) pretreated 30 min before with vehicle (5 ml/kg, i.p.), petroleum ether, ethyl acetate, methanol, and aqueous extracts of *Momordica dioica* (50 mg/kg, i.p., each) or standard drug pheniramine maleate (10 mg/kg, i.p.). The dosages were selected based on preliminary studies (data not shown). The forepaws of mice were placed on horizontal bar (1 cm in diameter, 3 cm above the table) and the time required to remove the paws from bar was noted for each animal and the durations of catalepsy
was measured at 30, 60, 90, 120, 150 and 180 min. The standard bar test was used to determine the intensity of catalepsy (e.g. Hoffman & Donovan, 1995). Both forelegs of a mouse were placed on a horizontal bar. The latency from paw placement until the rest complete removal of one paw from the support was measured (maximal test duration, 180 s) and termed here as descent latency. If the mice did not assume the position on the bar after three attempts, it received a descent latency of 0 s.

**Effect on Haloperidol-Induced Catalepsy**

The same Bar test was used using haloperidol. Haloperidol (1 mg/kg, i.p.) was injected to mice (n = 5) pretreated 30 min before with vehicle (5 ml/kg, i.p.), petroleum ether, ethyl acetate, methanol or aqueous extracts of *Momordica dioica* (50 mg/kg, i.p., each). The durations of catalepsy was measured at 30, 60, 90, 120, 150 and 180 min.

**Statistical Analysis**

The data is presented as mean ± SEM. The data was analyzed by one-way ANOVA followed by Dunnet's test. P< 0.01 and P<0.05 was considered significant.
Results

Clonidine Induced Catalepsy

All the extracts petroleum ether, ethyl acetate, methanol and aqueous (P<0.05) extracts showed significant inhibition in catalepsy (Table No. 1). But among them methanol and aqueous extracts shows more significant inhibition in catalepsy. Results were comparable with control drug clonidine.

Haloperidol-Induced Catalepsy

None of the extracts inhibited haloperidol-induced catalepsy (Table No. 2). Results were comparable with control drug haloperidol.

Discussion

Several drugs are known to induce catalepsy in animals. The neuroleptic agents induce catalepsy by inhibiting dopamine D₂ receptors in the substantia nigra. Chopra and Dandiya (1975) have studied the relative role of acetylcholine and histamine in perphenazine-induced catalepsy and suggested that anticholinergic activity of antidepressant might be due to an increase in dopamine content in brain or their ability to inhibit release of acetylcholine.
Table No. 1: Effect of various extracts of *M. dioica* on clonidine-induced catalepsy in mice

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Group/Extract</th>
<th>Duration of catalepsy (sec) Mean ± SEM at</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30min</td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td>18.6± 0.871</td>
</tr>
<tr>
<td>2</td>
<td>Standard</td>
<td>16± 0.316</td>
</tr>
<tr>
<td>3</td>
<td>Petroleum ether</td>
<td>11.8± 3.338</td>
</tr>
<tr>
<td>4</td>
<td>Ethyl acetate</td>
<td>20.4± 2.358</td>
</tr>
<tr>
<td>5</td>
<td>Methanol</td>
<td>24.8± 6.492</td>
</tr>
<tr>
<td>6</td>
<td>Aqueous</td>
<td>63± 9.13**</td>
</tr>
</tbody>
</table>

Data are expressed as Mean ± S.E.M, n = 5 in each group, Statistical analysis done by one way ANOVA followed by Dunnett’s test. **p<0.01, compared to control group.
Table No. 2: Effect of various extracts of *M. dioica* on haloperidol-induced catalepsy in mice

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Group/Extract</th>
<th>Duration of catalepsy (sec) Mean ± SEM at</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30min</td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td>31.75±</td>
</tr>
<tr>
<td>2</td>
<td>Standard</td>
<td>21.25±</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.284</td>
</tr>
<tr>
<td>3</td>
<td>Petroleum ether</td>
<td>47.25±</td>
</tr>
<tr>
<td>4</td>
<td>Ethyl acetate</td>
<td>44.5±</td>
</tr>
<tr>
<td>5</td>
<td>Methanol</td>
<td>67.5±</td>
</tr>
<tr>
<td>6</td>
<td>Aqueous</td>
<td>124±</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.327</td>
</tr>
</tbody>
</table>

Data are expressed as Mean ± S.E.M, n = 5 in each group, Statistical analysis done by one way ANOVA followed by Dunnett’s test, compared to control group.
They also showed that different stages of catalepsy to be directly correlated with brain histamine content. Uvnas (1969) studied the mast cell degranulation and its correlation with the release of histamine after administration of mast cell degranulating agent (Compound 48/80). Lakdawala et al., (1980) have shown that clonidine releases histamine from mast cells in a similar manner to a selective liberator like compound 48/80. Haloperidol, a typical neuroleptic produces catalepsy in rodents and extrapyramidal side effects in human.

Haloperidol-induced catalepsy is one of the animal models for testing the extrapyramidal side effects of antipsychotic drugs. Haloperidol, (a non-selective D₂ dopamine antagonist) induced catalepsy is primarily due to blockade of dopamine receptors in the straiatum. The agents increasing dopamine transmission inhibits neuroleptic-induced catalepsy. The straiatum and nucleus accumbens have been implicated as the major brain structures involved in antipsychotic induce catalepsy, which appears due to the blockade of dopamine neurotransmission.

Typical neuroleptic-induced catalepsy has been linked to a blockade of postsynaptic striatal dopamine D₁ and D₂ receptors. Despite this evidence, dysfunction of several other neurotransmitters such as acetylcholine, GABA and serotonin, have also been implicated. In addition to dysfunction of various neurotransmitters in catalepsy, many clinical and preclinical studies have suggested the involvement of reactive oxygen species in haloperidol induced toxicity.
The observation of this study indicated that the plant *Momordica dioica* pulp having antihistaminic activity inhibited clonidine-induced catalepsy and not inhibited haloperidol-induced catalepsy. From the present study we can conclude that the cataleptic effect of clonidine in the mouse is mediated by histamine release from mast cells and the clonidine-induced catalepsy was inhibited by aqueous and ethyl acetate extract of *Momordica dioica* pulp. The effect of these extracts on clonidine-induced catalepsy is probably due to their mast cell stabilizing property and the plants do not have activity on dopaminergic transmission. Aqueous extract of *Momordica dioica* pulp showed most potent inhibition of clonidine-induced catalepsy so it can be concluded that polar constituents may be responsible for its antihistaminic activity.

References