Indexed / Listed in

Publication
The journal is published six times in a year in the months of February, April, June, August, October and December.

Copyright and Photo-copying
No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy without permission in writing from the Chief Editor.

Correspondence
Enquiries should be addressed to the Chief Editor.

Disclaimer
The Chief Editor disclaims any responsibility for statements made and opinions expressed by authors or claims made by the advertisers.

Disputes
Readers, contributors, members and advertisers may approach the President, IPS, in case of disputes with the IJP.

The journal is printed on acid free paper

IPS Members
The issues are supplied for Rs. 5.00 to members in India. Members residing overseas can get the issues on payment of US$ 25/annum towards airmail charges.

Missing Issues
Claims for missing issues should be sent within 2 months of issue date.

Published by
Medknow Publications
A-109, Kanara Business Centre, Off Link Road, Ghatkopar (E), Mumbai - 400075, India. Phone: 91-22-6649 1818/1816, Fax: 91-22-6649 1817, Web: www.medknow.com

Websites
www.ijp-online.com
www.journalonweb.com/ijp
www.bioline.org.br/ph

Indian Journal of Pharmacology, The Chambers, 3rd floor, Sarkhej - Gandhinagar Highway, Bodakdev, Ahmedabad - 380054, India. Tel: 079-26853419, 26840348, 26840427 • Fax: 079 - 26853415 • Website: www.ijp-online.com • E-mail: ijp@ijp-online.com
CONTENTS

Editorial

Irrational combinations: No consideration for patient safety: Shiv Prakash 217

Review Article

Bioequivalence: Issues and perspectives: Shubha Rani 218

Research Papers

Isolation, characterization and study of enhancing effects on nasal absorption of insulin in rat of the total saponin from Acanthophyllum squarrosum: S.A. Sajadi Tabassi, H. Hosseinzadeh, M. Ramezani, E. Moghimipour, S.A. Mohajeri 226

Pharmacological and biochemical evidence for the antidepressant effect of the herbal preparation Trans-01: Md. Shalam, S.M. Shantakumar, M. Laxmi Narasu 231

Effects of dexamethasone and betamethasone as COX-2 gene expression inhibitors on rigidity in a rat model of Parkinson’s disease: Mehdi Shafiee Ardestani, Hassan Mehrab, Nourallah Sadeghzadeh 235

Activity of aqueous ethanol extract of Euphorbia prostrata ait on Shigella dysenteriae type 1-induced diarrhea in rats: Kamgang Rene, Gonsu Kamga Hortense, Wafo Pascal, Mbungni N: Jean Alexis, Pouokam Ervice Vidal, Fokam Tagne Michel Archange, Fonkoua Marie Christine 240

Antidiarrheal and antimicrobial activities of Stachytarpheta jamaicensis leaves: S. Sasidharan, L. Yoga Latha, Z. Zuraini, S. Suryani, S. Sangetha, L. Shirley 245

Research Letters

Positive inotropic and chronotropic effect of aloe gel on isolated rat heart: Pradeep Kumar, Manish Goyal, Sunita Tewari 249

Synergistic effect of cefixime and cloxacillin combination against common bacterial pathogens causing community acquired pneumonia: Astha Agarwal, N. Jain, A. Jain 251

In vitro cytotoxic and human recombinant caspase inhibitory effect of Annona reticulata leaves: Susanta Kumar Mondal, Nirup Bikash Mondal, Upal Kanti Mazumder 253

Correspondence

Counterfeit and substandard drugs: The need for an effective and stringent regulatory control in India and other developing countries: A. Sukhlecha 255

Letter to the Editor

Postgraduate education in medical pharmacology: A student’s viewpoint: Varun Gupta 256

Book Review

The copies of the journal to members of the association are sent by ordinary post. The editorial board, association or publisher will not be responsible for non-receipt of copies. If any of the members wish to receive the copies by registered post or courier, kindly contact the journal’s / publisher’s office. If a copy returns due to incomplete, incorrect or changed address of a member on two consecutive occasions, the names of such members will be deleted from the mailing list of the journal. Providing complete, correct and up-to-date address is the responsibility of the members. Copies are sent to subscribers and members directly from the publisher’s address; it is illegal to acquire copies from any other source. If a copy is received for personal use as a member of the association/society, one cannot resale or give-away the copy for commercial or library use.
Depression is considered as an affective disorder characterized primarily by change of mood. The prevalence of major depression in the general population is estimated at 5%. At present, 121 million people are estimated to suffer from depression. An estimated 5.8% of men and 9.5% of women experience a depressive episode in their lifetime. Suicide remains one of the most common outcomes of depression, with depressive illness being responsible for 60% of the death toll.[1-3]

Despite the advent of new molecules in the pharmacotherapy of depression, it is unfortunate that this disorder goes undiagnosed and untreated. Although the currently prescribed molecules provide some improvement in the clinical condition of the patient, it is at the cost of having to bear the burden of their adverse effects.[2,4,5] In addition, it is difficult to predict which patient will respond to any given treatment. It is reported that only two out of three patients respond to any given treatment and, of these, one would probably have responded to placebo alone.[2,9]

On the other hand, drugs obtained from natural sources are perceived to have the least risk and low side-effect profiles, while having the ability to cure psychiatric disorders in much the same way as their synthetic counterparts. Ayurveda, the ancient traditional system of medicine, mentions a number of single and compound drug formulations of plant origin that are used for the treatment of psychiatric disorders.[14,17] In Ayurveda, compound formulations are generally used in therapy, based on the premise that such a combination would provide a synergistic therapeutic effect and help to minimize the adverse effects of the major drugs.[15,18] Trans-01 is one such herbal formulation; it has the following composition: Valeriana wallichii (45%), Convolvulus microphyllus (30%), Plumbago zeylanica (7.5%), Boswellia serrata (15%) and Acorus calamus (3.5%).

We have previously reported Trans-01 as having anxiolytic activity,[9] but there is no pharmacological evidence to demonstrate an antidepressant effect. It has been found that many anxiolytics could produce a sedative or depressive effect at high doses[10] and it is reasonable to suppose that lowering the dose may result in an antidepressant or stimulant effect. There are reports to show that some of the ingredients of this formulation, e.g., Convolvulus microphyllus, have been used as a ‘nerve tonic’ for the improvement of memory.[10-12] Valerian wallichii has specific CNS, anxiolytic and sedative activities.[13]

The aim of the present study was to evaluate Trans-01 for its possible antidepressant effect, using various animal paradigms of depression.

Materials and Methods

Animals

The experiments were performed on Wistar albino rats (180-250 gm) and Swiss albino mice (25-35 gm) of either sex procured from Venkateshwara Enterprises, Bangalore,
India. The animals were group housed in colony cages at an ambient temperature of 25 ± 1°C and 45-55% relative humidity, with a 12 h/12 h light-dark cycle and access to food and water ad libitum. Food was restricted during experiments. The experiments were carried between 0900 to 1400 h and animals were acclimatized for one week before the start of experimentation. The experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC) of V.L. College of Pharmacy, Raichur, India and were in accordance with the guidelines of the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA).

Drugs and chemicals
The investigational drug, Trans-01, was a gift sample from Shrushti Herbal Pharma Ltd, India. Venlafaxine and imipramine were gifted by Ranbaxy, Gurgaon. Corticosterone was purchased from Sigma Chemicals, USA. All the other chemicals used in the study were of analytical grade.

Experimental design

**Grouping and drug treatment:** Animals were divided into eight groups, each consisting of 6-8 animals, as follows:

- **Group 1:** Control vehicle 10 ml/kg b.w, p.o.
- **Group 2:** Venlafaxine HCl 8 mg/kg b.w, i.p.
- **Group 3:** Venlafaxine HCl 32 mg/kg b.w, i.p.
- **Group 4:** Imipramine HCl 32 mg/kg b.w, i.p.
- **Group 5:** Trans-01 25 mg/kg b.w, p.o.
- **Group 6:** Trans-01 50 mg/kg b.w, p.o.
- **Group 7:** Trans-01 75 mg/kg b.w, p.o.
- **Group 8:** Trans-01 100 mg/kg b.w, p.o.

In all the experiments, the animals were administered a single dose prior to performing the experiment. However, in the FSS paradigm, treatment was continued for 15 days and was then followed by the test.

In all the studies, the drugs were administered 1 h prior to the initiation of the experiment, except in the case of standard drugs, which were given half an hour before the experiment.

The experimental drug, Trans-01 and venlafaxine and imipramine (reference standard drugs) were suspended in distilled water for administration.

**Acute toxicity test**

Acute toxicity of the preparation was determined using female albino mice. The animals were fasted for 3 h prior to the experiment according to the recommended procedure (OECD guideline No. 425). As per the guidelines, the animals were observed for 48 h for any mortality following oral administration of the different doses of the preparation.

**Locomotor activity**

Naïve pretreated mice were placed in the digital photoactometer (INCO, Ambala, India), which consists of a cage which is 30 cm long and 30 cm deep with a wire mesh at the bottom. A continuous beam of light from about six lights was made to fall on corresponding photoelectric cells; the photoelectric cell got activated when an animal crossed the beam of light and thereby cuts off the rays of light falling on it. These cutoffs were counted for a period of 10 min and the figure was taken as a measure of the locomotor activity of the animal.
Statistical analysis

Results are represented as mean ± SEM. Data was analyzed using a statistical package (InStat software, San Diego, California, USA). Comparisons between various groups were made using a one-way analysis of variance (ANOVA) followed by Tukey’s multiple comparison test. P < 0.05 was considered as statistically significant.

Results

Effect of Trans-01 on acute toxicity test in mice

Animals were observed for mortality for 48 h. No mortality was observed and the preparation was found to be safe up to a dose of 5000 mg/kg b.w.

Locomotor activity in mice

Trans-01 75 mg/kg and 100 mg/kg and venlafaxine 32 mg/kg increased locomotor activity (P < 0.01 and P < 0.05, respectively), suggesting a psychostimulant effect. No sedative effects were observed at any of the doses tested. In comparison, with imipramine HCl (32 mg/kg) there was significant decrease in effects were observed at any of the doses tested. In comparison, with imipramine HCl (32 mg/kg) there was significant decrease in locomotor activity, suggesting a sedative effect Table 1.

Effect of Trans-01 on immobility time in TST in mice

The behavioral score of immobility in control, standard drugs and Trans-01 treated groups are shown in Table 2. Single dose administration of Trans-01 with different dose range in mice showed a dose-dependent decrease in immobility time as compared to control (P < 0.001) and the effect was qualitatively comparable to that of standard antidepressant drugs. However, Trans-01 at 25 mg/kg did not show any significant effect.

Effect of Trans-01 on immobility time in FST in rats

Single dose administration of Trans-01 showed a dose-dependent decrease in immobility time (P < 0.001) as compared to the vehicle treated group.

Effect of Trans-01 on plasma corticosterone in rats

The effect of swim stress, venlafaxine HCl and Trans-01 treatment on the plasma levels of corticosterone in rats is shown in Figure 1. Stress significantly increased the corticosterone levels when compared to normal controls. Trans-01, at all the doses, decreased the stress-induced corticosterone levels significantly (P < 0.001), the effect being comparable to that of standard drugs.

Discussion

Major mood disorders are the most common mental illnesses, with a lifetime risk of 10% in the general population. As many as 10-15% of individuals with this disorder and up to 25% of those with bipolar disorder, display suicidal behavior during their lifetime.

In the present study, the formulated polyherbal ayurvedic preparation Trans-01, consisting of five Indian medicinal plants, was evaluated for antidepressant activity.

Trans-01 was found to be safe, as no mortality was observed following treatment with doses as high as 5000 mg/kg. The increase in ambulatory behavior indicates a stimulant effect and Trans-01 has shown stimulant activity in a dose-dependent manner in the photoactometer.[13] This prompted us to study it further, using other paradigms of depression like TST and FST.

Table 1

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Activity counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>193.6 ± 13.27</td>
</tr>
<tr>
<td>Venlafaxine HCl 08 mg</td>
<td>201 ± 15.98</td>
</tr>
<tr>
<td>Venlafaxine HCl 32 mg</td>
<td>288 ± 14.10*</td>
</tr>
<tr>
<td>Imipramine 32 mg</td>
<td>96.25 ± 19.30*</td>
</tr>
<tr>
<td>Trans-01 25 mg/kg</td>
<td>357.1 ± 25.05***</td>
</tr>
<tr>
<td>Trans-01 50 mg/kg</td>
<td>320.25 ± 27.32*</td>
</tr>
<tr>
<td>Trans-01 100 mg/kg</td>
<td>289.8 ± 13.45*</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM obtained from 6-8 animals. ns: statistically nonsignificant; *P < 0.05; ***P < 0.001 vs normal control.

Table 2

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Immobility time (in seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FST</td>
</tr>
<tr>
<td>Control</td>
<td>198.2 ± 12.73</td>
</tr>
<tr>
<td>Venlafaxine HCl 8 mg</td>
<td>158.2 ± 10.48**</td>
</tr>
<tr>
<td>Venlafaxine HCl 32 mg</td>
<td>98.2 ± 11.24***</td>
</tr>
<tr>
<td>Imipramine 32 mg</td>
<td>125.5 ± 11.55***</td>
</tr>
<tr>
<td>Trans-01 25 mg/kg</td>
<td>157.3 ± 7.89**</td>
</tr>
<tr>
<td>Trans-01 50 mg/kg</td>
<td>128.8 ± 10.46***</td>
</tr>
<tr>
<td>Trans-01 75 mg/kg</td>
<td>120.32 ± 5.76***</td>
</tr>
<tr>
<td>Trans-01 100 mg/kg</td>
<td>98.8 ± 14.46***</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM obtained from 10 animals.

FST - Forced swimming test, TST - Tail suspension test, ns: statistically nonsignificant; *P < 0.05; ***P < 0.001 vs normal control.
The immobility exhibited by test animals in these models is indicative of a behavioral despair which reflects a depressive state. Trans-01 significantly reduced the immobility time in these paradigms, following a single dose treatment. Thus, it was proven to be a potential antidepressant.

The various types of stressors induce hormonal alterations in experimental animals which are reminiscent of those observed in depressed patients. FSS in rats was used as a stressor to induce alterations in the hypothalamic-pituitary-adrenal axis (HPA). In depression, increased release of corticotropin-releasing factor (CRF) and cortisol are observed. In our study, swim stress for 25 min caused an increase in corticosterone levels when compared to the unstressed rats, which was in conformity with the earlier reports, thus validating the procedure used.

Treatment with Trans-01 for 15 days effectively prevented the abnormal rise in corticosterone in a dose-dependent manner. The results obtained with the drug clearly demonstrate its antidepressant property.

The mechanism of the antidepressant effect of Trans-01 may thus be partly due to its action on the HPA axis. However, GABA receptors are reported to be altered in stress and involvement of the GABAAergic system cannot be ruled out, especially so since the anxiolytic effect of Trans-01 has been shown to be mediated by its action on GABA receptors. Further studies are needed to elucidate the same by observing its effect on neurotransmitter levels in brain; such studies are underway in our lab.

In conclusion, the polyherbal formulation Trans-01 showed promise as an antidepressant and can be a potential candidate for managing depression.

Acknowledgement

We are grateful to Dr. Shubha Hegde, Managing Director, Shrushti Herbal pharma, Bangalore, for supplying the investigational drug and financial assistance. We are also thankful to the Management, AME’s society for providing the facilities for the research work.

References