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ARTICLE INFO

Article history
Received 19/08/2013
Available online
30/09/2013

Keywords
Schizophrenia,
Amphetamine (AMP),
Omega-3-fatty acid (OMG),
Total cholesterol (TC),
Low density lipoprotein (LDL), Antioxidant,
Risperidone (RISP)

ABSTRACT

Schizophrenia, a disabling psychological disorder, is manifested by multifold pathophysiology. Abnormal membrane phospholipid metabolism related to abnormal essential polyunsaturated fatty acid (EPUFA) metabolism has also reported in recent studies. Antipsychotic drugs are effective in symptom control in up to two-thirds of patients, but in at least one-third of patients the response is poor often accompanied by side effects. Omega-3-fatty acids (OMG) are known to reverse lipid peroxidation. The objective of the study was to evaluate the synergistic activity of OMG in combination with reduced dose (1.5 mg/kg) risperidone (RISP) in ameliorating symptoms in rat model. Male Wistar rats were injected with Amphetamine (5 mg/kg) to induce schizophrenic-like symptoms. Following induction, the rats were administered intraperitoneal risperidone (3mg/kg), oral omega-3-fatty acids (EPA:DHA, 180:120) and combination of risperidone (1.5mg/kg) and Omega-3-fatty acids (EPA:DHA, 180:120) over 21 days. Two behavior models - motor coordination (Rota rod test) and catalepsy (catalepsy test) - were used to evaluate the schizophrenic behavior of the animals. Lipid profiles and schizophrenic symptoms were evaluated on Days 7 and 21, while antioxidant levels and dopamine levels in the rat brain were measured on Day 21 using spectrofluorimeter. On Day 21, brain dopamine decreased significantly in AMP+RISP and AMP+RISP+ OMG (p<0.01 for both) compared to AMP group, while no significant change was observed in AMP+OMG group. Latency time increased significantly from baseline to Day 21 in AMP+RISP group, AMP+OMG group and AMP+RISP+OMG group compared to AMP (p<0.01). The total cholesterol and LDL-C levels decreased significantly from baseline to Day 21 in AMP+OMG and AMP+RISP+OMG groups (p<0.05 for both) compared to AMP. Our findings suggest that in schizophrenic rats, Omega-3-fatty acids co-administered with the reduced dose of risperidone provide beneficial effect to improve the diseased state. A lower dose seems to avoid side effects caused by long-term treatment with high dose of risperidone.

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Please cite this article in press as Pandya Bhaumik et al. Evaluation of synergistic effects of risperidone and omega-3 fatty acids (EPA: eicosapentaenoic acid and DHA: docosahexaenoic acid) in schizophrenia-induced rats. Indo American Journal of Pharm Research.2013:3(9).
INTRODUCTION
Schizophrenia is a devastating illness which usually strikes adolescents and young adults. It is characterized by an admixture of positive, negative, cognitive, mood, and motor symptoms whose severity varies across patients and through the course of the illness [1]. There is increasing evidence that free oxidative stress mediated neuronal injury is involved in the pathogenesis of schizophrenia. Lower levels of omega-6 EPUFA, arachidonic acid (AA) [2] or omega-3 EPUFAs, docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) [3] or both omega-6 and omega-3 EPUFA [4] have been found in cell membranes from chronic medicated schizophrenic patients and from first-episode psychotic patients. Use of antioxidant supplementation in order to prevent neuronal membrane damage may be an important strategy in the treatment of schizophrenia [5]. EPA and DHA are the members of polyunsaturated fatty acids (PUFA). Fatty acids of the omega-6 and omega-3 series, although indispensable, cannot be synthesized by the body and hence are "essential" in the diet. Almost 30 – 40% of patients may exhibit an inadequate or poor response to conventional (typical) antipsychotic agents [5-7]. Risperidone is a benzisoxazole derivative. Its greatest affinity is for serotonin 5-HT2, histamine H1, α1-adrenergic, and dopamine D2 sites. It has been shown to be superior to typical antipsychotics in numerous clinical studies [8]. However, treatments with both typical as well as atypical antipsychotics have serious side effects that lead to a significant loss of quality of life.

Recently, the dopamine hypothesis and omega-3 fatty acids (EPA= eicosapentaenoic acid, DHA= docosahexaenoic acid) hypothesis have been suggested to represent different aspects of the same pathology of schizophrenia and the brain concentration of certain omega-3 fatty acids are decreased [9]. It is important to develop alternative or adjunctive treatment strategies that may augment the antipsychotic actions and reduce the side effects [10]. Hence, the present study was designed to evaluate the effect of the anti-psychotic agent, risperidone along with the adjuvant therapy of omega-3-fatty acids on schizophrenia induced rat model.

MATERIALS AND METHODS
Chemicals required
Dopamine (Sigma Aldrich, USA), Risperidone (Aurobindo pharma, Hyderabad), omega-3-fatty acid (EPA: DHA) 120:180 mg soft gelatin capsule (Mexapa Merck), Amphetamine (Neo lab, Bangalore). All the other chemicals used were of analytical grade.

Animals:
Adult male Wistar rats weighing 180-200 grams, bred in animal house of Al-Ameen College of Pharmacy, Bangalore, were used. The animals were housed in groups of five in clean polypropylene cages. The lids were made of strong steel mesh, and were designed to contain feed hopper and accommodation to hold drinking water bottles. Room temperature was +25°C, humidity was 45-55% with a light period of 12 h (06.00 to 18.00) with access to food and water. Animals were acclimatized to laboratory conditions before the test. The experiment protocol was approved by Institutional Animals Ethics Committee (AACP/IAEC/Nov-2009/2010, Date- 23/11/2009) and conducted according to CPCSEA guidelines, Govt. of India.

Induction of experimental schizophrenia:
Amphetamine (AMP) (5mg/kg) was dissolved in saline (pH 7.2) and administered intraperitoneally. The dose of amphetamine given was standardized by experimentation. After 10 to 30 minutes of administration the desired behavioral changes were noticed in the animals. The blood was drawn on 7th and 21st day to evaluate parameters like lipid profile, lipid peroxidation, antioxidant levels and dopamine levels by spectrofluorimetry.

Experimental protocol for biochemical estimations and behavioral studies:
The male Albino Wistar rats (180-200g) were divided into 5 groups of 10 each. Group one: Served as control and received saline (0.9% w/v NaCl, i.p) for 21 days. Group two: Received amphetamine (5mg/kg, i.p) for 21 days. Group three: Received amphetamine (5mg/kg i.p) and risperidone (3mg/kg, i.p) for 21 days. Group four: Received amphetamine (5mg/kg i.p) and ω-3-fatty acids (EPA: DHA) (180:120) mg/day, p.o for 21 days. Group five: Received amphetamine (5mg/kg, i.p), risperidone (3mg/kg, i.p) and ω-3-fatty acids (EPA: DHA) (180:120) mg/day, p.o for 21 days.

Biochemical estimations:
Collection of serum:
The rats were subjected to a 12 hour fast. Under mild anesthesia, the blood samples were collected via retro orbital route in eppendorff’s tubes and were allowed to clot for half an hour. The sample was centrifuged using a cold centrifuge at 8000 rpm for 10 minutes to get serum.
Estimation of Lipid parameters in serum:
The serum collected was used for estimation of serum cholesterol, HDL, LDL, triglyceride estimaint. Triglycerides were estimated by analytical kit by Span Diagnostics [11], Cholesterol by Chod-Pod / Phosphotungstate Method [12], high density lipoprotein (HDL) and low density lipoprotein (LDL) concentrations were determined by methods reported earlier [13, 14]. The values are expressed in terms of mg/dL.

Preparation of Tissue Homogenate and estimation of Antioxidant enzyme levels in rat brain:
The whole brain dissected out, blotted dry and immediately weighed. The brain regions cerebral cortex (Ct), hippocampus (Hc) and striatum (St) were subsequently dissected from the intact brain carefully on ice plate (4 ± 2 °C). A 10% brain homogenate was prepared with ice-cold phosphate buffered saline (0.1 M, pH 7.4) using Teflon-glass homogenizer. The homogenate was centrifuged at 10,000 rpm at - 4 C for 15 min and the pellet discarded. The supernatant obtained was used for the quantification of antioxidant levels like Superoxide dismutase (SOD) [15], Catalase (CAT) [16], Lipid peroxidation (LPO) [17], reduced glutathione (GSH) [18], and were determined as per the earlier reported methods.

Estimation of dopamine level in rat brain by spectrofluorimetry:
Preparation of tissue extract
On the day of experiment rats were sacrificed, whole brain was dissected out and the sub cortical region (including the striatum) was separated, weighed and homogenized in 3 ml HCl Butanol in a cool environment. The sample was then centrifuged for 10 min at 2000 rpm. 0.8 ml of supernatant phase was removed and added to an eppendorf reagent tube containing 2 ml of heptane and 0.25 ml 0.1 M HCl. After 10 min, shake the tube and centrifuged under same conditions to separate two phases. Upper organic phase was discarded and the aqueous phase was used for dopamine assay.

Dopamine assay [19]
The assay represents a miniaturization of the trihydroxy indole method. To 0.02ml of the HCl phase, 0.005 ml 0.4 ml HCl and 0.01ml EDTA/ Sodium Acetate buffer (pH 6.9) were added, followed by 0.01 ml iodine solution for oxidation. The reaction was stopped after 2 min by the addition of 0.1ml sodium thiosulphate in 5 M Sodium hydroxide. 10 M Acetic acid was added 1.5 min later. The solution was then heated to 1000C for 6 min. When the samples again reached the room temperature, excitation and emission spectra were read (330 to 375 nm) in a spectrofluorimeter. The tissue value (fluorescence of tissue extract minus fluorescence of tissue blank) was compared with an internal reagent standard (fluorescence of internal reagent standard minus fluorescence of internal reagent blank). Tissue blanks for the assay were prepared by adding the reagents of the oxidation step in reversed order (sodium thiosulphate before iodine). Internal reagent standards were obtained by adding 0.005 ml bidistilled water and 0.1 ml HCl: Butanol to 20 ng of dopamine standard.

Behavioral models:
The symptoms of schizophrenia are multitudinous in number. We chose to evaluate two important AMP induced schizophrenic symptoms in rats, motor coordination and catalepsy, by Rota rod test and bar test (catalepsy test) respectively. Total treatment period was 21 days and the behavioral parameters were measured on 7th and 21th day. Five groups of 10 rats each were divided. The AMP group (Group II), was used for comparison with other groups, i.e., Control group (Group I), AMP + RISP (Group III), AMP + OMG (Group IV), AMP + RISP + OMG (Group V). Behavioral variations were observed and recorded using Nikon D90 camera in a controlled environment to prevent variations.

Rota rod test [20]
In brief, in a training session, the rats were placed on the rod that was set to 25 rpm and the latency time that each rat was able to remain on the rota-rod was recorded. The rats were subjected to three training trials at 3- to 4-h intervals on two separate days for acclimatization purposes. In the test session, the rats were placed on the rota-rod and the latency time was recorded for 120 seconds. Rats were injected with the different drugs in their home cage and latency time was measured 90 min after administering the antipsychotic injection.

Bar Test [21]
Briefly, rat forepaws were gently placed over a horizontal bar, fixed at a height of 10 cm above the working surface. The length of time during which the animal retained this position was recorded using a camera, the time elapsing from the placement of the rat until the removal of one of its forepaws was measured. Rats were removed from the bar if their latency on the bar test exceeded 300 seconds. Results were expressed as latency time spend on bar in seconds. Considering that stress and novelty may affect the
results by reducing the rat latency on bar test, the longest latency time of three consecutive trials was recorded and considered more reliable in determining the rat acceptance of abnormal posture. Rats were injected with the different drugs in their home cage, where they were maintained until the three consecutive trials on bar test. Latency time was measured 90 min after administering the antipsychotic injection.

Statistical analyses
All values are expressed as mean ±SEM. Data were analyzed by non-parametric ANOVA followed by Dunnett’s multiple comparison tests, and other data were evaluated using Graph Pad PRISM software. A p-value<0.05 was considered significantly different.

RESULTS:
All the groups comprising 10 rats of either sex were subjected to models such as Open field test, Rota rod test, Bar test (catalepsy test). Total treatment period was 21 days and the behavioral parameters were measured on 7th and 21st days. The AMP group (Group II), was used for comparison with other groups, i.e., Control group (Group I), AMP + RIS (Group III), AMP + OMG (Group IV), AMP + RIS + OMG (Group V)

Lipid profile:
On Day 7, there was no significant difference in the cholesterol level among the treatment groups (mean ranged from 86.00 to 90.6). On Day 21, cholesterol level reduced significantly in the AMP + OMG and AMP + RISP + OMG groups (80.20 ± 3.15) (p<0.05) and (81.10 ± 3.10) (p<0.05), respectively, when compared to the AMP group (93.20 ± 3.10) group (Table 1).

Triglyceride levels were similar among treatment groups on Day 7. On Day 21, when AMP group (56.50 ± 3.18) was compared to AMP + OMG group and AMP + RISP + OMG group, there was significant decrease in triglyceride level (51.10 ± 2.85) (p<0.01) and (53.40 ± 3.26) (p<0.05) respectively. No significant change was noted in the AMP + RIS group (Table 1).

LDL-C level on Day 7 did not differ significantly between AMP (25.60 ± 1.70) and control (21.80 ± 1.98) groups, while a significant decrease in was noted in AMP + OMG group (19.80 ± 2.34) when compared to AMP (p<0.01). There were no significant change in AMP + RISP group and AMP + RISP + OMG group when compared to AMP group (Table 1). On Day 21, LDL level showed a significant increase in the AMP group (28.30 ± 2.34) group when compare to the control group (22.70 ± 2.18) (p<0.05), while there was a significant decrease in LDL level in AMP + OMG and AMP + RISP + OMG groups (16.80 ± 2.57; p<0.001) and (16.10 ± 2.59; p<0.001) respectively, when compared to the AMP group. However no significant change in AMP + RISP group was observed. The HDL level was comparable across treatments both on Days 7 and 21 (Table 1).

Table 1: Lipid profile on the 7th day of treatment

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>TC</th>
<th>HDL-C</th>
<th>LDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Control</td>
<td>88.70 ± 4.57</td>
<td>56.30 ± 1.91</td>
<td>21.80 ± 1.98</td>
<td>52.40 ± 2.15</td>
</tr>
<tr>
<td>II</td>
<td>AMP</td>
<td>90.30 ± 3.95</td>
<td>54.00 ± 2.86</td>
<td>25.60 ± 1.70</td>
<td>54.50 ± 3.45</td>
</tr>
<tr>
<td>III</td>
<td>AMP + RISP</td>
<td>90.60 ± 3.48</td>
<td>53.60 ± 1.61</td>
<td>26.50 ± 1.87</td>
<td>54.30 ± 3.50</td>
</tr>
<tr>
<td>IV</td>
<td>AMP + OMG</td>
<td>86.00 ± 3.15</td>
<td>55.50 ± 2.78</td>
<td>19.80 ± 2.34y</td>
<td>52.90 ± 3.10</td>
</tr>
<tr>
<td>V</td>
<td>AMP + RISP + OMG</td>
<td>87.60 ± 3.22</td>
<td>54.90 ± 2.10</td>
<td>22.50 ± 2.15</td>
<td>51.60 ± 4.30</td>
</tr>
<tr>
<td>Day 21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Control</td>
<td>89.60 ± 4.51</td>
<td>56.20 ± 2.98</td>
<td>22.70 ± 2.18</td>
<td>52.80 ± 2.90</td>
</tr>
<tr>
<td>II</td>
<td>AMP</td>
<td>93.20 ± 3.10</td>
<td>53.80 ± 1.76</td>
<td>28.30 ± 2.34a</td>
<td>56.50 ± 3.18</td>
</tr>
<tr>
<td>III</td>
<td>AMP + RISP</td>
<td>93.10 ± 3.81</td>
<td>53.90 ± 1.92</td>
<td>27.90 ± 2.25</td>
<td>56.10 ± 2.90</td>
</tr>
<tr>
<td>IV</td>
<td>AMP + OMG</td>
<td>80.20 ± 3.15x</td>
<td>53.20 ± 2.68</td>
<td>16.80 ± 2.57z</td>
<td>51.10 ± 2.85y</td>
</tr>
<tr>
<td>V</td>
<td>AMP + RISP + OMG</td>
<td>81.10 ± 3.10x</td>
<td>54.30 ± 4.12</td>
<td>16.10 ± 2.59z</td>
<td>53.40 ± 3.26x</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± SEM (n=6). Statistical Analysis: One way analysis of variance followed by Dunnett’s Multiple Comparison Test was performed on 7th day and 21st day values of each parameter.

a (p<0.05), b (p<0.01), c (p<0.001) Vs control group,
x(p<0.05), y (p<0.01), z(p<0.001) vs AMP group.

Antioxidant enzyme levels:
AMP-treated rats showed significant decrease (7.13 ± 1.10c) (p<0.001) in levels of antioxidant enzyme SOD when compared to the
control group (17.90 ± 1.23). While AMP + OMG and AMP + RISP + OMG treated rats showed significant increase (13.3 ± 1.22; p<0.01) and (11.60 ± 1.64; p<0.05), respectively, in the SOD level when compared to AMP treated group. However, no significant change was noted in AMP + RISP treated rats (7.63 ± 1.17) (Table 3).

AMP treated rats showed significant decrease (21.00 ± 1.20) (p<0.001) in levels of antioxidant enzyme catalase when compared to the control group (30.80 ± 1.97), while AMP + OMG and AMP + RISP + OMG treated rats showed significant increase (26.80 ± 1.50; p<0.05) and (26.5 ± 1.10; p<0.05), respectively, in the catalase level when compared to AMP treated group. There was no significant change in AMP + RISP treated rats (21.4 ± 1.55) (Table 3). There was a significant increase in the MDA level in brain due to lipid peroxidation in AMP treated rats (9.50 ± 1.21) (p<0.01) as compared to control group (4.13 ± 1.15), while there were significant decrease in MDA level in AMP + OMG and AMP + RISP + OMG treated rats (5.13 ± 1.27; p<0.05) and (5.63 ± 1.07; p<0.05) respectively when compared to AMP group (9.50 ± 1.21). No significant change in AMP + RISP treated rats (10.1 ± 1.30) was seen (Table 3).

There was a significant decrease in the GSH level in AMP treated rats (13.00 ± 1.27) (p<0.01) as compared to control group (20.50 ± 1.65), while there were significant increase in GSH level in AMP + OMG and AMP + RISP + OMG treated rats (18.90 ± 1.49; p<0.05) and (17.90 ± 1.15; p<0.05), respectively, when compared to AMP group (13.00 ± 1.27). No significant change in AMP + RISP treated rats (11.90 ± 1.20) was noticed (Table 3).

Table 2: Antioxidant levels in the brain

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>SOD</th>
<th>CAT</th>
<th>LPO</th>
<th>GSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Control</td>
<td>17.90 ± 1.23</td>
<td>30.80 ± 1.97</td>
<td>4.13 ± 1.15</td>
<td>20.50 ± 1.65</td>
</tr>
<tr>
<td>II</td>
<td>AMP</td>
<td>7.13 ± 1.10c</td>
<td>21.00 ± 1.20c</td>
<td>9.50 ± 1.21b</td>
<td>13.00 ± 1.27b</td>
</tr>
<tr>
<td>III</td>
<td>AMP + RISP</td>
<td>7.63 ± 1.17</td>
<td>21.4 ± 1.55</td>
<td>10.1 ± 1.30</td>
<td>11.90 ± 1.20</td>
</tr>
<tr>
<td>IV</td>
<td>AMP + OMG</td>
<td>13.3 ± 1.22</td>
<td>26.80 ± 1.50x</td>
<td>13 ± 1.27x</td>
<td>18.90 ± 1.49</td>
</tr>
<tr>
<td>V</td>
<td>AMP + RISP + OMG</td>
<td>11.60 ± 1.64</td>
<td>26.5 ± 1.10</td>
<td>5.63 ± 1.07</td>
<td>17.90 ± 1.15</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± SEM (n=6), One way analysis of variance followed by Dunnett's Multiple Comparison Test.

Effect of drug treatment on brain dopamine level: (pg/mg tissue)

There was a significant increase in brain dopamine level in AMP treated rats (1140 ± 43.30) (p<0.001) when compared to control group (669 ± 38.40), while there was a significant decreased in brain dopamine level in AMP + RISP and AMP + RISP + OMG treated rats (919 ± 25.90) (p<0.01) and (931 ± 39.90y) (p<0.01) respectively, while there was no significant change in the AMP + OMG treated rats (1013 ± 46.20) when compared to AMP treated rats (1140 ± 43.30) (Figure 1).

Figure 1: Effect of the drug treatment on brain dopamine level in AMP model

Values are expressed as Mean ± SEM (n=6), One way analysis of variance followed by Dunnett's Multiple Comparison Test

a (p<0.05), b (p<0.01), c (p<0.001) Vs control group.

x (p<0.05), y (p<0.01), z(p<0.001) vs AMP group.
Rota Rod Test
On the 7th day of treatment, in comparison with control group (116.00 ± 3.44), the latency time in the AMP group was decreased by (63.80 ± 2.09) (p<0.001), whereas in AMP + RISP and AMP + RIS + OMG group when compared to AMP group there were significant increase in the latency time (77.90 ± 3.32) (p<0.05) and (77.00 ± 3.12) (p<0.05) respectively, while no significant change in AMP + OMG group (67.70 ± 3.66) was observed. On the 21st day of treatment, in comparison with control group (117.00 ± 2.90), the latency time in the AMP group was decreased (57.20 ± 2.10) (p<0.001) whereas in AMP + RISP group, AMP + OMG group and AMP + RISP + OMG group when compared to AMP group there was a significant increase in the latency time (70.80 ± 2.61) (p<0.01), (70.80 ± 2.61) (p<0.01) and (80.10 ± 3.97) (p<0.01) respectively (Figure 2).

Values are expressed as Mean ± SEM (n=10), One way analysis of variance, Dunnett's Multiple Comparison Test
a (p<0.05), b (p<0.01), c (p<0.001) Vs control group.
x (p<0.05), y (p<0.01), z(p<0.001) vs AMP group.

Bar test (catalepsy):
On the 7th day of treatment, in comparison with control group (3.55 ± 0.12), the latency time in the AMP group was decreased by (1.10 ± 0.28) (p<0.001), whereas in AMP + RISP group when compared to AMP group there was a significant increase in the latency time (2.32 ± 0.30) (p<0.01), while there were no significant change in AMP + OMG group (1.15 ± 0.25) and AMP + RISP + OMG group (1.21 ± 0.25). On the 21st day of treatment, in comparison with control group (3.58 ± 0.25), the latency time in the AMP group decreased (1.06 ± 0.26) (p<0.001) whereas in AMP + RISP and AMP + RISP + OMG group when compared to AMP group there was significant increase (3.08 ± 0.13) (p<0.001) and (2.12 ± 0.35) (p<0.05) respectively. No significant change in AMP + OMG group (Figure 3).

Values are expressed as Mean ± SEM (n=10), One way analysis of variance, Dunnett's Multiple Comparison Test
a (p<0.05), b (p<0.01), c (p<0.001) Vs control group.
x (p<0.05), y (p<0.01), z(p<0.001) vs AMP group.
DISCUSSION:
Evidence for increased oxidative stress in chronic schizophrenic patients is primarily based on the altered levels of antioxidant enzymes like SOD, CAT, GSH and MDA. Optimum levels and proper balance among these enzymes may be critical for the prevention of cellular oxidative injury [22].

The levels of antioxidant enzymes varied. In the present study OMG co administered with reduced dose of risperidone, decreased the elevated lipid peroxidation levels and increased the levels of SOD, CAT, GSH levels and significant decrease in MDA antioxidant levels was observed followed by the treatment with OMG+RISP combination therapy in schizophrenic rats. RISP+ OMG treated rats showed significant decrease in TC and LDL level in lipid profile, while there were no significant changes in TG level and HDL level in all the groups. Previous studies indicate that high dose of RISP showed significant decrease in brain dopamine levels [23]. OMG + RISP also showed significant results similar to high dose of RISP treated rats as found in the present study.

AMP, administered in rats, induces hyperactivity. It is well known that dopaminergic mechanisms play important role in the mediation of the locomotor activity. Our observation of sedative-like (motor-suppressive) effects confirms slowed movement (bradykinesia), this can be linked to the disruption of motor cortex activity associated with risperidone blockade of D2 receptors causing reduced dopaminergic function.

CONCLUSION:
Our results indicate that OMG is beneficial as an adjuvant therapy with reduced dose of RISP in schizophrenia. Despite low dose of RISP, in its combination with OMG, beneficial effects similar to the prescribed high doses were observed. Thereby, reduced side effects caused by high doses of RISP can be expected during the treatment. Further research involving long-term studies would establish the potential of combining OMG with RISP in the treatment of schizophrenia.

AUTHORS’ STATEMENTS
Competing Interests
The authors declare no conflict of interest.

ACKNOWLEDGEMENT
The authors would like to thank Dr CN Ramchand and Anuj Kapoor for their guidance in design and conduct of this trial. We would also like to thank Dibyajyoti Mazumder for support in drafting this manuscript.

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