Anxiolytic, anti-depressant and metabolic effect of *Salvia* spp. essential oil on a rat model of schizophrenia

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ABSTRACT

An essential oil is a concentrated, hydrophobic liquid of volatile aromatic (odoriferous) compounds of a plant. Plants from *Salvia* genus are rich in essential oils that have an activity on the nervous system. The aim of this study was to evaluate the effect of essential oil from *Salvia* genus plants on the rat model of schizophrenia. L-methionine was used to create the animal model of schizophrenia. Schizophrenic animals were exposed to *Salvia* essential oil for 21 days. Elevated plus maze and forced swim test were used for the anxiolytic and anti-depressant effects of the *Salvia* spp. essential oil. Our results show that *Salvia* spp. essential oil significantly reduced the depression and decreases slightly the anxiety level created by L-methionine in rats. These medicinal plants could be used to delay the onset of schizophrenia and treat people with this disorder by reducing their anxiety and depression.

KEY WORDS:

Schizophrenia; *Salvia* spp.; anxiolytic; antidepressive.

INTRODUCTION

Schizophrenia, like other neuropsychiatric disorders, does not have well defined causes currently. The causes that contribute to this pathology installation involve from environmental to genetics by passing by chemistry (psychotropic drugs and receptors). This psychotic disorder is most often characterized by an altered sensory process (hallucination) and cognitive dysfunction (1, 2).

Hypotheses suggest a neuromodulator disorder in dopaminergic system also at other systems such as serotonergic, glutamatergic and GABA-ergic which are indexed to be responsible to the symptom observe in schizophrenia disorder (3, 4, 5). The real causes still not being well elucidated, the treatment of schizophrenia remains limited to its symptoms and not to the definitive cure. In this regard, researchers continue to make increasing use of medicinal plants, which contain an inexhaustible source of bioactive molecules (6). Traditionally, many plants from *Salvia* spp. genus have used for their neuropsychotropic properties such as *Salvia libanotica* (Boiss. et Gaill), *Salvia lavendulaefolia* Vahl, *Salvia divinorum* (Epling, Játiva-M), *Salvia multicaulis* Vahl, *Salvia cyanescens* Boiss and Bal (7, 8, 9). The aim of this study was to evaluate the effect of essential oil from *Salvia* genus plants on the rat model of schizophrenia.

MATERIALS AND METHODS

Plant material and essential oil extraction
Salvia spp. aerial parts were collected and dried away from sunlight, pulverized and weighed.

Essential oils of the dried powder of *Salvia* spp. were extracted by hydro-distillation with water vapor according to the method described by the 7th edition of European

Pharmacopoeia. The volume of the essential oil was measured and ranked for 100 g dry plant material.

Animals

Thirty female and male Wistar rats weighing respectively 238.40 ± 18.70 g and 310 ± 48.60 g at the start of the experiment were used. The animals were housed in a temperature and light-controlled room (22 °C, a 12 h cycle starting at 08:00 h) and were fed and allowed to drink water ad libitum. All behavioral evaluations were performed between 9 h and 16 h, respecting the current legislation for animal studies and indications of the local comities.

Chemicals

To carry out our research, we used methionine purchased from Sigma Aldrich.

Experimental design

Male rats were divided into four (4) groups (n=6) for the experiment performed: (1) control group (0.9% NaCl), (2) methionine 500 mg/kg treated group, (3) methionine 500 mg/ kg + *Salvia* spp. volatile oil 1% group and (4) methionine 500 mg/ kg +*Salvia* spp. volatile oil 3% treated group. Inhalation method was used 60 min per day during 21 successive days for *Salvia* spp. volatile oil treated groups. These rats were treated for a week with L-methionine (750 mg/kg body weight twice daily) intraperitoneally.

Experiments training

Behavior in the elevated plus-maze (EPM) is also utilized to assess exploration, anxiety, and motor behavior. The EPM consisted of four arms, 49 cm long and 10 cm wide, elevated 50 cm above the ground. Two arms were enclosed by walls 30 cm high and the other two arms were exposed. 1h after *Salvia* spp. essential oil exposition, rats were placed at the juncture of the open and closed arms

and the amount of time spent on the open arms was recorded during a 5 min test, as previously described (10). After each assay, the maze was carefully cleaned with a wet tissue. The time spent on the open arms is an index of anxiety.

Forced swimming test (FST)

The antidepressant effects of *Salvia* spp. essential oil on rats were assessed, using the method described by Cojocariu (11) with some modifications. Firstly, rats were individually placed into cylindrical recipients (diameter 30 cm, height 59 cm) containing 25 cm of water at $24 \pm 1^\circ\text{C}$ during 2 min of training. After this session, the test was performed in a 6 min swim session. 1 h before the training, the rats had been exposed to *Salvia* spp. essential oil. During the test session, the following behavioral responses were recorded: (1) immobility (time spent

floating with the minimal movements to keep the head above the water) and (2) swimming (time spent with active swimming movements).

DATA ANALYSIS

All results were expressed as mean $\pm$ standard error of the mean (S.E.M). Behavioral activities of rats were statistically analyzed with analysis of variance (one-way ANOVA). Tukey's test was used to determine level of significance of all results obtained on XLSTAT. Results were regarded as significant at $p < 0.05$.

RESULTS

Anxiolytic of *Salvia* spp. essential oil

Numbers and time spent in open arms (figure 1) showed that L-methionine increased the rats anxiety level compared to untreated rats.

Fig. 1 *Salvia* spp. essential oil effect in elevated plus maze

The values are mean $\pm$ S.E.M. (n=6 per test).

*p < 0.05 vs. control.

level of anxiety in these rats compared to untreated rats.

The rats treated with L-methionine behavior (figure 2) have also indicated an increased

Fig. 2 *Salvia* spp. essential oil effect in elevated plus maze

The values are mean $\pm$ S.E.M. (n=6 per test)

*p < 0.05 vs. Control.

Anti-depressant activity of *Salvia* spp. essential oil

By analyzing immobility times, our study showed that L-methionine creates depression in rats compared to untreated rats. However, *Salvia* spp. essential oil significantly reduced this depression.

DISCUSSION

In the literature, the anxiety disorders present in schizophrenia are Obsessive-compulsive disorder, Panic disorder, Social phobia or the Posttraumatic stress disorder. Existing treatments are conventional (clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline) and act on the symptoms. These treatments are effective in varying percentages (12, 13, 14).

In our work, indeed L-methionine has caused a schizophrenia state in the rat which is more anxious than control rats. The results of EPM and Forced swim test showed this anxiety and depression in treated rats.

L-methionine has been used to induce in our study the animal model of schizophrenia. The role of this amino acid is to inhibit the action of glutamate on its N-methyl-D-aspartate (NMDA) receptor. Thus, rats treated with L-methionine have a disorder in their glutaminergic system causing a disturbance in their intelligence.

Schizophrenia is a neuropsychiatric disorder whose causes are not well defined. However, oxidative stress, microbial diseases, and the environment have a considerable influence on the genetic predisposition to this pathology of schizophrenia.

Many medicinal plants are known to have antioxidant, antimicrobial or immune-stimulant activities (15, 16, 17). This antioxidant property would fight against the installation of atheroma plaque, which would delay the installation of neuropsychiatric disorders such as schizophrenia. The

antimicrobial properties of these plants would allow the organism to resist also against the installation of these disorders in the nervous system which schizophrenia is a part (18).

These biological properties of plants are at the core of chemical compounds that these plants possess. As far as plants from *Salvia* genus are concerned, it is their essential oils that are targeted. These essential oils from *Salvia* genus plants, in addition to have properties on the central nervous system (like *Salvia divinorum* used in divination rites) have antioxidant and antimicrobial properties (19, 20).

All these data could also have an increased metabolic significance, considering the various metabolic disorders associated with the schizophrenic pathology (21, 22, 23), as well as the way the plant extract are affecting the general and specific metabolism in various disorders (24, 25) with special focus here in this report on schizophrenia

CONCLUSIONS

Plants from *Salvia* genus belong to the *Lamiaceae* family. These plants are well known for their effects on the nervous system through their essential oils. The morbidity of this disorder affects both the sick person and his relatives. In this research, we created an animal model of schizophrenia and used *Salvia* spp. essential oil to relieve depression and anxiety. Our results showed that exposure of schizophrenic animals to *Salvia* spp. essential oil for 21 days relieved the animals' state of depression and anxiety.

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