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SHORT COMMUNICATION

Antidepressant potential of *Mesembryanthemum cordifolium* roots assisted by metabolomic analysis and virtual screening

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ABSTRACT

Depression is a common mental disturbance that can be categorized as mild, moderate or severe. Mesemberine alkaloids, the main recognized phytoconstituents of some plants belonging to family Mesembryanthemaceae, are well-known as serotonin reuptake inhibitors. Therefore, the objective of this study is to evaluate the antidepressant activity of the alkaloidal fraction of *Mesembryanthemum cordifolium* L.f. (*Aptenia cordifolia*) roots, family Mesembryanthemaceae using forced swimming test, assisted by metabolomic analysis and *in silico* ligand-based and structure-based screening. Results showed that the alkaloidal fraction displayed an antidepressant activity superior to imipramine hydrochloride, a standard antidepressant agent. Nine alkaloids were annotated from the metabolomic analysis. Interestingly, among the dereplicated constituents, mesembrane (**5**) displayed strong binding affinity to SERT protein, which is slightly higher than the antidepressant drug venlafaxine. In conclusion, the alkaloidal fraction of the *M. cordifolium* (*A. cordifolia*) root exhibits an antidepressant activity which can be attributed in part to mesembrane (**5**).

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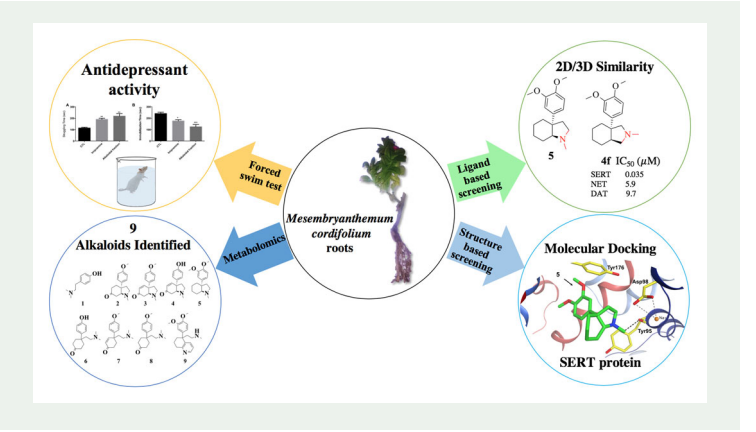


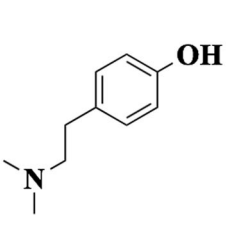
1. Introduction

Decreased brain levels of monoamines like serotonin are thought to be the main cause of depressive disorders (Rani K et al. 2014). Several plant extracts have been used for the management of the neurological health issues, particularly those belonging to family Mesembryanthemaceae (Aizoaceae) owing to its content of mesembrine alkaloids which are pharmacologically characterized as serotonin reuptake inhibitors (Terburg et al. 2013; Carpenter et al. 2016; Krstenansky 2017). Accordingly, the aim of this study was to evaluate the antidepressant activity of the alkaloidal fraction of the roots of *Mesembryanthemum cordifolium* L.f (syn:*Aptenia cordifolia* L.f) family Mesembryanthemaceae by using forced swimming test (FST), assisted by HR-LC-ESI-MS analysis and *in silico* ligand-based and structure-based screening.

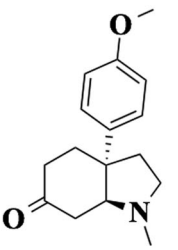
2. Results and discussion

The metabolomic profiling (Figure S1) of the alkaloidal fraction of *M. cordifolium* (*A. cordifolia*) revealed the presence of nine alkaloids (**1–9**) (Figure 1). Interestingly, six of the identified alkaloids were annotated, herein, for the first time from genus *Mesembryanthemum* including sceletenone (**4**), mesembrane (**5**), dihydro-joubertiamine (**6**), O-methyl-joubertiamine (**7**), O-methyl dihydrojoubertiamine (**8**), and touruosamine (**9**); in addition to three previously identified alkaloids namely, hordenine (**1**), 4,5-dihydro-4′-O-methylsceletenone (**2**), and 4′-O-methylsceletenone (**3**).

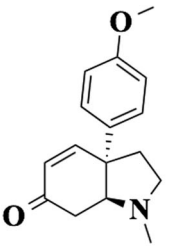
The antidepressant effects of *M. cordifolium* (*A. cordifolia*) alkaloidal fraction (100 mg/kg) and imipramine hydrochloride® (15 mg/kg) were studied by using the FST (Figure S2). The alkaloidal fraction produced a significant reduction ($p < 0.001$) in the immobility period as well as an elevation of the struggling time ($p < 0.01$) when compared to the control animals receiving only the vehicle. The alkaloidal extract exhibited a higher but not significantly different activity compared to imipramine hydrochloride® ($p < 0.001$) (Figure S3). An open field test was performed to test the exploratory behavior of the animals treated with the extract to exclude non-specific CNS stimulant



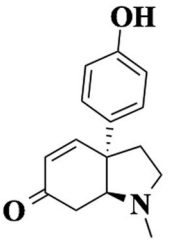
Hordenine (1)
Chemical Formula: $C_{10}H_{15}NO$
Exact Mass: 165.1154



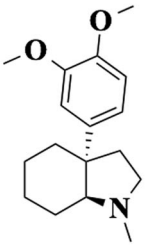
4,5-Dihydro-4'-O-methylsceletenone (2)
Chemical Formula: $C_{16}H_{21}NO_2$
Exact Mass: 259.1572



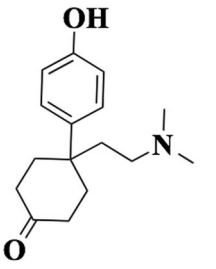
4'-O-Methylsceletenone (3)
Chemical Formula: $C_{16}H_{19}NO_2$
Exact Mass: 257.1416



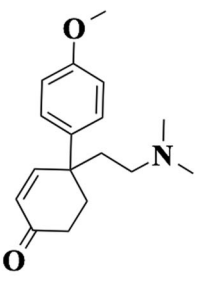
Sceletenone (4)
Chemical Formula: $C_{15}H_{17}NO_2$
Exact Mass: 243.1259



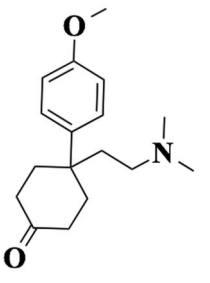
Mesembrane (5)
Chemical Formula: $C_{17}H_{25}NO_2$
Exact Mass: 275.1885



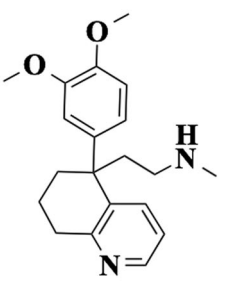
Dihydro-joubertiamine (6)
Chemical Formula: $C_{16}H_{23}NO_2$
Exact Mass: 261.1729



O-Methyl-joubertiamine (7)
Chemical Formula: $C_{17}H_{23}NO_2$
Exact Mass: 273.1729



O-Methyl-dihydro-joubertiamine (8)
Chemical Formula: $C_{17}H_{25}NO_2$
Exact Mass: 275.1885



Touruosamine (9)
Chemical Formula: $C_{20}H_{26}N_2O_2$
Exact Mass: 326.1994

Figure 1. Dereplicated metabolites of the alkaloidal fraction of *A. cordifolia* root.

effects. The test showed no significant effects of the extract on ambulation, grooming and rearing compared to vehicle treated rats.

The "SwissTargetPrediction" method was used to screen possible molecular targets for our compounds (Gfeller et al. 2013). All compounds did not show any probability higher than 90% to any molecular target except compound **5** which has high and equal probabilities (90.5%) towards norepinephrine (NET), serotonin (SERT) and dopamine (DAT) transporters. Afterwards, the "SwissSimilarity" online software was used to

analyze the structural similarity of our compounds with FDA approved drugs and bioactive ligands databases (Zoete et al. 2016). Remarkably, compound **5** showed both 2 D- and 3 D-based structural similarity with various antidepressant ligands but the most similar one was compound **4f** (Shao et al. 2011). Compounds **5** and **4f** showed 2 D and 3 D similarity score of 1.0 and 0.97, respectively (Figure S4). Therefore, we expected that compound **5** has a very high probability (>90%) to have antidepressant activity chiefly via SERT inhibition similar to compound **4f**. The FDA approved antidepressant drug; venlafaxine showed an acceptable 2 D similarity score to only three compounds, namely compound **2**, **5**, **8** (Figure S5).

A recent molecular docking study confirmed that venlafaxine exhibited antidepressant activity predominantly via highly selective inhibition of SERT (Malikowska et al. 2017). Accordingly, we conducted a molecular docking simulation for the three most similar compounds to venlafaxine (compound **2**, **5**, and **8**) on the crystal structure of SERT protein. All the docked compounds shared the same binding orientation in the active site while they showed different binding interactions with the key residues (Figure S6). These different interactions are mainly responsible for their different binding affinities and IC_{50} to SERT protein (Table S1). Interestingly, compound **5** showed strong binding affinity to SERT protein which is equivalent to that of the reference compound **4f** and slightly higher than the antidepressant drug venlafaxine.

All dereplicated compounds (**1–9**) displayed satisfactory drug-likeness and pharmacokinetic profiling with no potential toxicity (Tables S2 and S3). Moreover, all compounds have high gastrointestinal absorption and can cross the blood brain barrier (BBB) (Figure S7), which predicts that these systemically targeted molecules will affect the CNS (Daina and Zoete 2016; Daina et al. 2017). This BBB permeability prediction was confirmed by measuring the total ion chromatogram of the tested rats' brain homogenate (Figure S8), where the molecular ion peaks of the compounds **2**, **5**, **6** and **8** were detected (Figure S9).

3. Conclusion

The current study evidently revealed the significant antidepressant activity of the alkaloidal fraction of *M. cordifolium* (*A. cordifolia*) root extract, that might be attributed in part to its considerable content of mesembrane alkaloid (**5**) which is postulated to have a potent SERT inhibitory activity suggested by *in silico* virtual screening. The current results, thus, present *M. cordifolium* (*A. cordifolia*) as a folk antidepressant remedy and recommend future pharmacological and toxicological studies to precisely determine its potential use in this regard.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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