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Antipsychotic and sedative effects of the leaf extract of *Crassocephalum bauchiense* (Hutch.) Milne-Redh (Asteraceae) in rodents

Germain Sotoing Taïwe [a,b,c,*], Elisabeth Ngo Bum [d], Emmanuel Talla [e], Amadou Dawe [f], Fleur Clarisse Okomolo Moto [d,g], Gwladys Temkou Ngoupaye [d,h], Neteydji Sidiki [d], Bernard Dabole [e,i], Paul Désiré Djomeni Dzeufiet [b], Théophile Dimo [b], Michel De Waard [c,j]

[a] Department of Zoology and Animal Physiology, Faculty of Science, University of Buea, P.O. Box 63 Buea, Cameroon
[b] Department of Animal Biology and Physiology, Faculty of Science, University of Yaoundé I, P.O. Box 812, Yaoundé, Cameroon
[c] Institut National de la Santé et de la Recherche Médicale, Unité 836, Laboratoire Canaux Calciques, Fonctions et Pathologies, Grenoble Institut de Neurosciences, Université Joseph Fourier, Chemin Fortuné Ferrini, Site santé de la Tronche, P.O. Box 170, 38042 Cedex 9, Grenoble, France
[d] Department of Biological Sciences, Faculty of Science, University of Ngaoundéré, P.O. Box 454, Ngaoundéré, Cameroon
[e] Department of Chemistry, Faculty of Science, University of Ngaoundéré, P.O. Box 454, Ngaoundéré, Cameroon
[f] Higher Teachers' Training College, University of Maroua, P.O. Box 55, Maroua, Cameroon
[g] Higher Teachers' Training College, University of Yaoundé I, P.O. Box 47, Yaoundé, Cameroon
[h] Department of Animal Biology, Faculty of Science, University of Dschang, P.O. Box 67, Dschang, Cameroon
[i] Department of Organic Chemistry, Faculty of Science, University of Yaoundé I, P.O. Box 812, Yaoundé, Cameroon
[j] Smartox Biotechnologies, Floralis, Biopolis, 5 Avenue du Grand Sablon, 38700 La Tronche, France

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ABSTRACT

Ethnopharmacological relevance: *Crassocephalum bauchiense* (Hutch.) Milne-Redh (Asteraceae) has been used as a medicine for the treatment of epilepsy, insomnia, dementia and psychotic disorders in Cameroonian traditional medicine.

Aim of the study: This study was designed to examine whether the aqueous extract and the alkaloid fraction prepared from the leaves of *Crassocephalum bauchiense* possess antipsychotic and sedative properties in rodents.

Materials and methods: The rectal temperature of mice was recorded with a probe thermometer at a constant depth. Novelty-induced rearing behavior is used to evaluate a central excitatory locomotor behavior in mice. The antipsychotic effects of the extracts were assessed using the apomorphine animal model of psychosis. The catalepsy test was tested based on the ability of the leaves extracts of *Crassocephalum bauchiense* to alter the duration of akinesia by placing the naive mice with both forelegs over a horizontal bar. The extracts of *Crassocephalum bauchiense* effects were evaluated on sodium pentobarbital-induced sleeping time. In addition, gamma-aminobutyric acid concentrations in the brain treated mice were also estimated.

Results: The aqueous extract and the alkaloid fraction from *Crassocephalum bauchiense* caused dose-dependent inhibition of novelty-induced rearing behavior, decreased the apomorphine-induced stereotypy and fighting, and had significant fall of the body temperature. The aqueous extract prolonged the sodium pentobarbital sleeping time. This prolongation was not reversed by bicuculline, a light-sensitive competitive antagonist of $GABA_A$ receptors complex. However, the effect of the aqueous extract on sodium pentobarbital-induced sleeping time was blocked by *N*-methyl-β-carboline-3-carboxamide, a partial inverse agonist of the benzodiazepine site in the $GABA_A$ receptor complex and flumazenil, a specific antagonist of the benzodiazepine site in the GABAA receptor complex. In biochemical experiments, the concentration of the inhibitory amino acid, gamma-aminobutyric acid, was significantly increased in the brain of animals treated with the aqueous extract of *Crassocephalum bauchiense* and sodium valproate.

Conclusions: The results show that the antipsychotic and sedative properties of *Crassocephalum bauchiense* are possibly mediated via the blockade of dopamine D-2 receptors and GABAergic activation,

Abbreviations: ANOVA, analysis of variance; AE, aqueous extract; AF, alkaloid fraction; BIC, bicuculine; CPZ, chlorpromazine; DZP, diazepam; FG 7142, *N*-methyl-β-carboline-3-carboxamide; GABA, gamma-aminobutyric acid; ID_{50}, dose of extract necessary to reduce the response by 50% relative to the control value; NIH, National Institutes of Health; RO 151788, flumazenil; S.E.M, standard error of the means; SV, sodium valproate

* Corresponding author at: Department of Zoology and Animal Physiology, Faculty of Science, University of Buea, P.O. Box 63, Buea, Cameroon. Tel.: +237 77 71 86 70; fax: +237 22 15 73 70.
E-mail address: taiwe_sotoing@yahoo.fr (G. Sotoing Taïwe).

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respectively. However, pharmacological and chemical studies are continuing in order to characterize the mechanism(s) responsible for these neuropharmacological actions and also to identify the active substances present in the extracts of *Crassocephalum bauchiense*.

1. Introduction

Psychosis is a chronic recurrent neuropsychiatric disorder that affects the quality of life of the sufferers and is a major public health concerns (Ehmann et al., 2004). Although the etiology of the disease is unknown, hyperdopaminergic activity is closely linked with the pathogenesis of psychosis (Harrison, 1999). Individuals with psychoses are more prone to suicide, depression, anxiety, aggression, substance abuse, cognitive impairment, victimization, poverty and increased medical problems (Mullen, 2006). Current drugs used for the disorder have failed to alter the course of the disease but only provide symptomatic relief (Baldessarini, 2001; Davis et al., 1991). Adverse events can affect every system of the body and range from the annoying photosensitivity and jaundice, for example to the disabling seizures and blindness, among others to the potentially fatal agranulocytosis and neuroleptic malignant syndrome (Arana, 2000). Moreover, the overall functional and quality of life outcomes of patients still remain poor after treatment (Mullen, 2006) and the clinical efficacy of these drugs is largely limited by adverse effects associated with their use (Ray et al., 2009). Thus, there is a critical need to search for more effective and less toxic agents for the treatment of the disease. An increasing number of herbal products have been introduced into psychiatric practice, as alternative or complementary medicines, and also there is a large number of herbal medicines whose therapeutic potential has been assessed in a variety of animal models (Zhang, 2004).

Crassocephalum bauchiense (Hutch.) Milne-Redh (Asteraceae) is a medicinal herb reputed to be of beneficial effect in the Cameroonian traditional system of medicine. It is common in the savanna woodland from Nigeria to northern and southern Cameroon, and is generally widespread in tropical Africa (Biholong; 1986; Burkill, 1985). In "Fulfuldé" language, in northern Cameroon it is known as "Hako kahdam" (Arbonnier, 2000). The leaves decoction of *Crassocephalum bauchiense* is effective in the cases of cerebral deficit, anxiety, epilepsy, cerebral malaria, behavioral disturbances in mentally retarded children (Adjanohoun et al., 1996; Biholong, 1986) and neuropathic pain (Arbonnier, 2000). Similarly, an aqueous extract of the whole plant is commonly employed in the treatment of insomnia, psychosis and other central nervous system disorders (Adjanohoun et al., 1996; Arbonnier, 2000; Biholong, 1986; Dalziel, 1937). Local people of northern and western Cameroon use the *Crassocephalum bauchiense* extract to relieve toothache and nervousness. It is also used to treat infantile convulsion, cerebral malaria, gastrointestinal infections as well as liver disorders (Arbonnier, 2000; Biholong, 1986; Mouokeu et al., 2011; Taïwe et al., 2012). According to Cameroonian traditional healers, the leaves of *Crassocephalum bauchiense* are the preferred part of the plant used for treating epilepsy, insomnia and dementia (Adjanohoun et al., 1996; Arbonnier, 2000; Biholong, 1986). This part is usually harvested, sun dried, and pulverized to obtain powder. About 100 g of the powdered material is macerated in 500 ml of water.

Previous works have shown that the ethyl acetate extract from *Crassocephalum bauchiense* has antibacterial activities against all the tested microorganisms (Mouokeu et al., 2011). A single dermal dose of this extract up to 32 g/kg body weight did not produce any visible sign of toxicity (Mouokeu et al., 2011). Also, daily dermal application of the *Crassocephalum bauchiense* extract gel formulation for 28 day did not show any negative effect, instead some biochemical parameters such as alanine aminotransferase, aspartate aminotransferase, low density lipoprotein, high density lipoprotein and triglycerides were significantly affected positively (Mouokeu et al., 2011). In the course of pharmacological studies, antinociceptive property of the aqueous extract and the alkaloid fraction prepared from the leaves of *Crassocephalum bauchiense* have already been reported from our laboratory (Taïwe et al., 2012).

An extensive search of the literature reveals no reports on the psychopharmacological activity of *Crassocephalum bauchiense*. Therefore, the present work was undertaken in order to investigate whether the aqueous extract of *Crassocephalum bauchiense* and the alkaloid fraction from the leaves of *Crassocephalum bauchiense* have antipsychotic and sedative potentials and if it is able to induce behavioral modifications in rodents.

2. Materials and methods

2.1. Plant material

Fresh leaves of *Crassocephalum bauchiense* used in this study were harvested in the Mawi area of Ngaoundéré, Cameroon in July 2007. The species was authenticated and a voucher was deposited at the National Herbarium, Yaoundé (No. 7954/SRF/Cam). Authenticated leaves of *Crassocephalum bauchiense* were extracted as described elsewhere (Taïwe et al., 2012). The aqueous extract of *Crassocephalum bauchiense* (AE, 20, 40, 80 and 160 mg/kg) and the alkaloid fraction no. Fr. XVI, isolated from *Crassocephamum bauchiense* (AF, 5, 10, 20 and 40 mg/kg), were dissolved in saline 0.9% containing dimethyl sulfoxyde 2% (vehicle) and administered orally in a volume of 10 ml/kg (Taïwe et al., 2012).

2.2. Preliminary qualitative phytochemical analysis

Preliminary phytochemical properties of the aqueous extract and the alkaloid fraction of *Crassocephalum bauchiense* were tested using the following chemicals and reagents: flavonoids (NaCl and HCl), alkaloids with Mayer and Dragendoff's reagents, saponins (frothingtest), tannins ($FeCl_3$), glycosides ($NaCl_3$ and Fehling's solutions A and B), cardiac glycosides (Salkowski test), anthraquinones (Borntrager's reaction), phenols ($FeCl_3$ and $K_3Fe(CN)$) and lipids (filter paper) (Evans, 2002).

2.3. Drugs

Apomorphine, bicuculine (BIC), chlorpromazine (CPZ), flumazenil (RO 151788), *N*-methyl-β-carboline-3-carboxamide (FG 7142), sodium pentobarbital are from Sigma Chemical, USA. Diazepam (DZP) and sodium valproate (SV) are from Sanofi-Synthelabo. All other chemicals and reagents used in the brain gamma-aminobutyric acid (GABA) content estimation are from Sigma Chemical, USA. These substances were prepared in saline 0.9% containing dimethyl sulfoxyde 2% (vehicle) and administered in a volume of 10 ml/kg.

2.4. Animals

The experiments were conducted using male and female Swiss mice (24–26 g). All animals were housed in a controlled environment, with free access to food, water and were maintained on a 12 h light-dark cycle. Each animal was used only once. All experiments were