

## The relevance of *Asteraceae* family plants in most of the neuropsychiatric disorders treatment

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### Abstract

Many of the traditional medicinal plants belong to one of the largest plant families: the *Asteraceae* family. These plants are widely used in alternative medicine due to their effects on the nervous system, being studied both on cellular and animal models. In this way, medicinal plants are preferred in drug therapy research due to the wide population interest. The *Asteraceae* plants phytochemical composition is mainly consisted in cholinergic, dopaminergic or serotonergic molecules which are involved in the pathophysiology of the neuropsychiatric disorders such as Alzheimer's disease, Parkinson's disease, schizophrenia, autism, anxiety or depression. Therefore, this review aims to comprise all the available information regarding the neurological activity of *Asteraceae* family plants in order to find further correlations between different components in order to explain their neuropsychiatric potential use.

**Keywords:** *Asteraceae*, Neuropsychiatry, animal models, Alzheimer, Parkinson, autism.

### Introduction

The *Asteraceae* family is one of the largest plant families with more than one thousand genres and twenty thousand species [1]. Many plants of this family are used in traditional medicine [2]. Some bio-guided research on plants of this family led to the development of drugs used in modern medicine. This was silymarin's case which is extracted from *Silybum marianum* (*Asteraceae*) and used in modern medicine for hepatic intoxication [3]. In this same way, galantamine (an alkaloid) was isolated from *Galanthus woronowii* (*Amaryllidaceae*). Galantamine, a cholinesterase inhibitor (acetylcholinesterase and butyrylcholinesterases) is used in the symptomatic treatment of Alzheimer's disease [4]. Indeed Alzheimer's disease (AD), as well as other human neuropsychiatric diseases (Parkinson's disease - PD, schizophrenia, autism, depression and anxiety), is a disease whose treatment is still a challenge for the world's scientists. In this way, researchers were able to translate these diseases in animal models in order to find explanations and remedies for these neurological dysfunctions [5]. Thus, it is known that AD is linked to a disruption of the cholinergic system while the PD and schizophrenia are pathologies related to dopaminergic system [6,7].

Since ancient times, plants have been the used in traditional medicine systems such as Ayurvedic, Chinese and African traditional medicines. The interest of modern medicine for medicinal plants significantly increased due to the recently found

enormous therapeutic potential of these plants [8]. Thus, many plants of the *Asteraceae* family are used for symptomatic relief of several neuropsychiatric disorders [9].

More than that, animal and cellular modeling experiments were performed to present scientific proof for their properties [10,11]. Correlations between traditional use and scientific research on *Asteraceae* family plants for treatments of neuropsychiatric disorders such as AD, PD, schizophrenia, autism, depression and anxiety are necessary for neuropsychiatric potential molecules discovery. In this way, this review aims to assemble traditional and scientific knowledge of *Asteraceae* family plants on neuropsychiatric disorders therapy.

### Methodology

References have been surveyed through the bibliographic search engines PubMed, ScienceDirect, Scopus, and Google Scholar. The bibliographic survey covered the period 1941 – 2015. The keywords used were: "*Asteraceae* Neuropsychiatric disorder"; "*Asteraceae* Alzheimer"; "*Asteraceae* Parkinson"; "*Asteraceae* Anxiety"; "*Asteraceae* Autism" and "*Asteraceae* Depression". This methodology allowed us to collect data (70 references).



## Traditional Uses of *Asteraceae* In Neuropsychiatry

The knowledge that the plants have medicinal properties dates back in the traditional medicine systems [8]. Also, biometrically studies showed that medicinal plants use in psychiatry is well established [12]. More than that, the plants use in neurology and psychiatry increases. *Asteraceae* family not being outdone, enough number of this family's plants has neuropsychiatric properties [10]. Thus, Philander [13] conducted an ethnobotanical survey in Western Cape of South Africa. He recorded 181 species of medicinal plants including 13 *Asteraceae* many of which (*Artemisia absinthium* L., *Artemisia afra* Jacq.ex Willd., *Centaurea benedicta* (L.) L., *Helichrysum cymosum* (L.) D. Do sybsp., *Trichogyne repens*, *Veronia oligocephala* (DC.) are used for the treatment of stomach ulcers, cough, lung and vascular problems. However, the author reveals that *Trichogyne repens* (L.) Anderb. was used to heal neurological disorders. Also, Picard [14] presented his research on discovering new neurobiological active compounds to a Canadian conference. By performing an ethnobotanical survey in the Amazon region, he identified 29 species of *Asteraceae* plants, but only 7 that could be used in the neurological diseases treatment. Also, the author strongly suggested discrimination between the use in mental disorders treatment and neurological disorders treatment.

The *Asteraceae* plants mentioned by Picard for neuropsychiatric traditional use were similar to those Jäger & al. [15] listed in their study, almost 10 years earlier. Also, almost 80% of them were found in the traditional medicine used by the locals.

## *Asteraceae* Plants Used in Neuropsychiatric Diseases

Before modern medicine, in Chinese traditional medicine and in European herbal medicine, plants were used in order to cure or alleviate neuropsychiatric distress. The traditional use of these plants was passed through generation as a heritage, until now when it consists in a wide database for scientific research in neuropsychiatry [16]. Based on these traditional uses, scientific research managed to find even more medicinal plants properties for neurological diseases treatment.

Thus, the group of Sayyah & al. [9] evaluated the effects of *Silybum marianum* (L.) Gaertn. on 18 patients with obsessive-compulsive disorder (OCD), a common neuropsychiatric condition. This pathology is due to a dysfunction in brain frontal-subcortical circuit with high hyperactivity, cognitive flexibility, motor inhibition deficit, and depression [17,18]. Their study lasted for 8 weeks comparing patients who received extract doses to a control group (17 patients treated with fluoxetine, usually used for OCD treatment). Experiments were carried out according to procedures described by A.P.A. [19]; Goodman & al. [20]; Kaplan&Saddock [21]; and Ramezani & al. [22]. Their results showed no significant differences between capsules of *Silybum marianum* and fluoxetine. The group

concluded that this extract could reduce obsessive and compulsive symptoms.

Also, Saidi & Mofidi [23] report that *Xanthium strumarium* (*Asteraceae*) 7 days decoction gave hepatotoxic convulsions and loss of consciousness to a woman in Iran. This report indicates that this plant contains chemical compounds (glycoside carboxy atractyloside) which could exhibit neurological effects.

In other studies, it has been shown that the *Asteraceae* plants phytochemical components have the ability to pass the blood-brain barrier. These molecules could exhibit beneficial psychiatric effects [9], which could be used in depression, AD, PD, schizophrenia, and autism treatment, but also that could exhibit dangerous adverse neurological effects [24]. Therefore, toxicological studies are imperative before considering a new neuropsychiatric active plant.

## *Asteraceae* Plants in Animal Models of Neuropsychiatric Disorders

In order to find valuable explanations and therapies for neuropsychiatric diseases, various animal models that exhibit specific neuropsychiatric symptomatology were developed [5]. In this way, researchers tested plant extracts on these animals to isolate neuropsychiatric potential molecules [14].

Thus, Taiwe & al. [25] group assessed antipsychotic and sedative activities of *Crassocephalum bauchiense* (Hutch.) Milne-Redh leaves aqueous extract on rodents (mice). For this study, six tests have been used. The primary observation was made by testing mice which received different doses of extract by gavage for the changes in the rectal temperature per time intervals [26,24].

The novel induced rearing behavior was performed by individually placing in transparent cages after injection by gavage with various doses of extract, alkaloid fraction or chlorpromazine (1 mg/kg, intraperitoneal). The number of rearing of mice is evaluated in 30 min [27,28].

Extracts effect on fighting and stereotyped behaviors induced by apomorphine was performed according to the method described by Kenneth& Kenneth [29]. Chlorpromazine (1 mg/kg, intraperitoneal) was used as a positive control and the test duration was 5 minutes. The catalepsy test was performed according to the method described by Sanberg & al. [30]. The test was performed 30 and 60 minutes after extract and controls administration and lasted for 5 minutes.

Sleep induction test with sodium pentobarbital was conducted by the method described by Gonzalez-Trujano & al. [31]. Extracts (oral administration) and the positive control (diazepam, 3 mg/kg, intraperitoneal) were administered one hour before sodium pentobarbital injection (42 mg/kg, intraperitoneal). The antihypnotic activity was evaluated by sleep interval and righting reflex.

The mice GABA brain concentrations were evaluated by Lowe & al. [32] method which uses a fluorescence emission technique (a

fluorescent complex formed between ninhydrin and GABA, in alkaline medium, is measured at 377/451 nm) [33].

For primary observation test, significant differences were observed, as compared to the control, including induced hypothermia due to alkaloid fractions doses, successfully corrected after 24 hours. In the spontaneous rearing test, the alkaloid fraction produced a systematic inhibition of this behavior. As for the chlorpromazine positive control, rearing behavior inhibition was nearly 65%. The apomorphine-induced stereotyped behavior of mice was corrected by *Crassocephalum bauchiense* aqueous extract and alkaloids fractions, as high as 65.63%. Just as the catalepsy-inducing chlorpromazine, only the aqueous extracts of the plant induced catalepsy in 30 to 60 minutes.

The aqueous extracts of *Crassocephalum bauchiense* prolonged pentobarbital-induced injection sleep time in a dose-dependent manner. As against, the alkaloid fractions significantly influenced sleep duration. Finally, the authors showed that the brain GABA concentration was increased by aqueous extracts of *Crassocephalum bauchiense* and sodium valproate (positive control) administration. It is known that the drugs which increase brain GABA can reduce anxiety and can have anti-convulsive properties [34].

These authors concluded that antipsychotic and sedative activities of *Crassocephalum bauchiense* were explained by the impact of its extracts on the dopaminergic system. It was well established that a correlation between dopaminergic system and neuropsychiatric disorders such as Parkinson Diseases (PD) and schizophrenia is obvious [5]. Thus, extracts of *Crassocephalum bauchiense* could have beneficial effects in neuropsychiatric diseases treatment through the impact on the dopaminergic system.

In Czech Republic, the group of Yamamotova & al. [35] studied N-feruloylserotonins isolated from *Leuzea carthamoides* (*Asteraceae*) effects on rats' anxiety and nociception. Wistar rats were exposed to stressful swimming test for 3 minutes [36,37] and to the assessment of nociception test using plantar and tail-flick tests [38,39] in a first experience. In a second experiment, 30 minutes after injection of N-feruloylserotonins (10 mg/kg) or saline, anxiety test was performed using the elevated plus maze test in 5 minutes [40].

No statistically significant differences for plantar and tail-flick testing between N-feruloylserotonins treated rats and the control group were observed. Similarly, no statistically significant differences between test and control groups for anxiety evaluation test were observed. However, a significant negative correlation between rat's pain and anxiety was observed.

Yamamotova & al. [35] concluded that an interpretation of mechanism action of isolated N-feruloylserotonins from *Leuzea carthamoides* on the serotonergic system (modulator of pain sensation and anxiety) cannot be carried according to obtained results.

For better results in psychiatric diseases treatment, several traditional medicines used plants mixtures. Thus, the group of Azmat & al. [41] studied *Somina* (an herbal drug used in traditional

medicine in Pakistan) neuropharmacological profile on rats and mice. *Somina* consisted of five medicinal plants (*Sesamum indicum* (14%), *Prunus amygdalus* (12%), *Papaver somniferum* (10%), *Lactuca scariola* (5%)). Among these plants, only *Lactuca scariola* belongs to Asteraceae family whose seed extract was used in *Somina*. *Lactuca scariola* was also known for its use against nervousness, insomnia and depression treatments in Pakistan traditional medicine. This plant has hypnotic and sedative activities [42]. Azmat & al. [41] evaluated the anxiolytic activity by elevated plus maze test [40] and forced swim test [36]; sedative activity by open field test in 5 minutes [43]; and the hypnotic activity by sleep induction method using Sodium Pentothal [44]. Before 30 minutes of experiment, *Somina* (285mg/kg or 10g/kg) or saline were injected to rats.

The results showed that the rats which received *Somina* spent more time in the open arms of elevated plus maze with an increased mobility time. This drug presented sedative effects significantly by dose-dependent and reduced anxiety. At a dose of 285mg/kg, *Somina* significantly reduced sleep induction time caused by Sodium Pentothal. In their study, the group of Azmat concluded that this medicinal formulation had physiological and pharmacological properties. Also, its use reduced the chances of neuropsychiatric disorders.

In 2012, a second group of Azmat evaluated *Somina* effects on rat memory. For this test, rats had received 285 mg/kg dose for 29 consecutive days by gavage. After, elevated plus maze test [45] was performed followed by plasma and cerebral 5-hydroxytryptamine (5-HT) and tryptophan assay using high pressure liquid chromatography [46]. The elevated plus maze test showed that treated rats had significantly reduced latency time for males and females compared to control groups. The content of 5-HT and its main metabolite were increased and tryptophan content was decreased, but no statistically significant differences were observed, as compared to the control groups. This study concluded that *Somina* was physiologically and pharmacologically active. Also, this herbal drug improves memory functions especially in learning. Ability of *Somina* to modify serum and brain serotonin and its metabolites levels showed that this drug contains beneficial molecules that could offer at least symptomatic relief for neuropsychiatric disorders such as depression, anxiety, schizophrenia [47,48].

### *Asteraceae* Plants and their Neuropsychiatric-Related Cellular and Molecular Effects

Research on cellular and even molecular models was conducted in order to better explain the neuropsychiatric diseases phenomenon [49,50].

It is known that Alzheimer's disease (AD) is due to a deficiency of the adrenergic system combined with the neuronal loss. Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are enzymes that breakdown acetylcholine in choline and acetyl. The

inhibition of these enzymes helps to reduce the brain decline of acetylcholine level (ADEWUSI & al. [51]). Thus, Adewusi group reviewed the medicinal plants which were potential sources of these enzymes inhibitors. They identified 123 plants for AChE inhibition and 42 plants for BChE inhibition. Among these plants, the methanol extract of the flowers of *Carthamus tinctorius* L. (*Asteraceae*) inhibited AChE at  $30.33 \pm 9.22\%$  at a concentration (0.1 mg/ml).

Two years later, Ribeiro & al. [52] group evaluated AChE of tick larvae *Rhipicephalus (Boophilus) microplus* and Wistar rats brain *in vitro* inhibitor activities of *Calea serrata* Less. (*Asteraceae*) hexan extract using the methods described by Ellman & al. [53] and Baxter & al. [54]. The results showed that at *C. serrata* extract concentrations of 3 and 6 mg/ mL, the activity of AChE of *R. microplus* and brain (3 parts) of rats was significantly reduced. But at 1.5 mg/ml of extract concentration, only activity of AChE of *R. microplus* was significantly reduced. These authors concluded that AChE inhibition is believed to be caused by the toxicity of hexane extract on *R. microplus* larvae.

Our research group from Laboratory of Biochemistry and Applied Chemistry of the University of Ouagadougou worked on acetylcholinesterase *in vitro* inhibitory potential extracts of some *Asteraceae* using Ellman & al. [53] method. The results suggested that these *Asteraceae* plants could be used in AD treatment after more advanced experiments [55-57].

Tryptophan is one of the 5-HT precursors of which deficit lead to depression due to serotonin synthesis reduction [58,59]. The degradation of tryptophan is caused by indoleamine 2,3-dioxygenase (IDO), an iso-enzyme of tryptophan 2,3-dioxygenase (TDO). The inhibition of IDO was thus of physiological and pharmacological interest [60]. Therefore, Temml group evaluated the possible interactions between arctigenin, trachelogenin and matairesinol - isolated lignans from *Carthamus tinctorius* (*Asteraceae*) - with the binding site of indoleamine 2,3-dioxygenase (IDO) using methods described by Wolber & Langer [61], Sugimoto & al. [62], Hawkins & al. [63], Accelrys Software Inc. [64], and M.O.E. [65]. Their results showed that only arctigenin and trachelogenin had an activity on indoleamine 2,3-dioxygenase binding site; inhibitions were dose-dependent ( $IC_{50} = 26.5$  mmol/L for arctigenin and  $IC_{50} = 57.4$  mmol/L for trachelogenin). Temml & al. [60] concluded that these two active lignans have a weak binding probability to the tryptophan normal enzyme (TDO) given that the similarity between IDO and TDO was 12.357%.

The use of medicinal plants in neuropsychiatric diseases involving dopaminergic receptors D1 or D2 (eg schizophrenia, Parkinson's disease) was studied by Luedtke & al. [10] who evaluated 163 medicinal plants of Bolivian, Chinese and Pakistani Pharmacopoeia aqueous and organic extracts activities on subtypes D<sub>1</sub> and D<sub>2</sub> of dopamine receptors on cell model Sf9 using methods described by Scatchard [66], Shimizu & al. [67], Luedtke & al. [68], and Luedtke & al. [69]. Among these plants, there were 17 *Asteraceae* plants. The results of these authors showed that no agonists for subtypes D<sub>1</sub> and D<sub>2</sub> receptors could be extracted; though, several extracts had inverse effects agonists D<sub>1</sub> and 5 extracts inhibited D<sub>2</sub> receptor dependent cAMP activation.

Some *Asteraceae* plants contain phenylalanine or tyrosine, which are precursor of dopamine. It is the case of *Chrysanthellum americanum* [70]. The presence of these amino acids in these *Asteraceae* could have any effect on types D<sub>1</sub> or D<sub>2</sub> receptors of dopamine.

## Conclusion

Worldwide, the neuropsychiatric disorders remain a challenge to overcome for the biomedical research. In this way, plants are an invaluable source of chemical compounds which could cure many diseases. Our review showed that *Asteraceae* family, an important family of medicinal plants, is used in the search for neuropsychiatric diseases remedies, but also in traditional and modern treatment of these disorders. These *Asteraceae* have phytochemical compounds that would have cholinergic, dopaminergic or serotonergic systems actions, which are major systems, involved in the manifestations of the neuropsychiatric disorders such as Alzheimer's disease, Parkinson's disease, schizophrenia, autism, anxiety or depression and could open new important research avenues and future scientific experiments.

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