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Effects of *Cleome arabica* Ethanolic Extract on Wistar Rat Behavior, Biochemical Parameters and ACTH Hormone

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Herbal extracts have been used since ancient times for the treatment of various diseases, and contain phytochemical compounds that have many therapeutic effects. The purpose of this study is to explore the neurobiological effects of *Cleome arabica* in the wistar rat. *C. arabica*ethanolic extract was administered orally at 0.20µg/ml based on weight for 7 consecutive days. Various behavioral tests were performed on rats after administration. The results show that the plant acts on the urea and creatinine levels in rats, hypoglycemia was recorded in the treated animals, a decrease in cholesterol levels which shows the effect of this plant. Different behavioral tests (Elvated pluse maze, open field and forced swimming Test) show that this extract had a significant impact on the anxiety levels in rodents. This extract has, also, a significant influence on the biochemical parameters (glycemia, cholesterol, triglycerides, urea, creatinine) and on the ACTH hormone (AdrenoCorticoTropic Hormone)

Keywords: Ethanolic extract, *Cleome arabica*, Wistar Rat, biochemical parameters.

INTRODUCTION

The use of medicinal plants has received much attention around the world as an alternative to conventional drugs, in part due to the perceived therapeutic efficacy and low side-effect profile of natural plant-derived products (Aluko, 2016) and the demand for these remedies has recently increased (Mhuji et al. 2016).

Plants have served as the primary source of human medicine, and have continued to provide humanity with new and original therapeutic remedies to the present day (Leduc, 2006). Today, some underdeveloped countries use traditional treatments to meet their health and primary care needs (Farnsworth et al. 1985). The plants role in folk medicine has been attributed to the phytochemicals present, which are nutritive or nonnutritive plant chemicals with preventive or curative properties against diseases (Adesuyi et al. 2012; Lata and Dubey,2010).

Plants produce a wide range of secondary metabolites such as phenolic compounds, alkaloids, vitamins, terpenoids, and other secondary metabolites with proven antioxidant activity (Kaur and Kapoor, 2002; Wojdylo et al.2007).

The *Cleome* genus contains 250 species of which only 7 are used in traditional medicine (Wollenweber and Dorr, 1992). Many species of *Cleome* genus have been studied for their

medicinal properties, and some have been evaluated for their activating (Selloum et al.1995; Nagaya et al.1997; Fushiya et al.1999; Bouriche et al.2003; Simoes et al.2006; Sharma et al.2010) and analgesic (Singh and West, 1991; Paraimaladevi et al.2003; Bose et al.2007) properties. *Cleome* species have a long history of medicinal uses such as rubefacients and in the scabies treatment, inflammation and rheumatic fever (Boulos, 2000). They are also used in the various disorders treatment such as fever, diarrhea, inflammation, bronchitis, liver disease, malaria and skin diseases (Nishant and Vinod, 2009; Jane and patil, 2012). The leaves and stems were decocted for the diabetes treatment by the Bedouins of South Sinai (El-Askary, 2005) and were famous as an anti-hyperglycemic agent (Abedel-kawy et al. 2008; Abedel Motaal et al. 2011).

It is a northern species growing in the Maghreb and Saharan regions, common in the Hodna (M'sila) and some regions of the Algerian Sahara: *Cleome arabica*(Ozenda, 1991; Beniston, 1984). It is locally called "Netten" and "Netteina" (Baba Aissa, 2000), like other species, it's rich in flavonoids (Touil et al. 1998; Bouriche et al. 2003; Wollenweber& Dorr, 1992). *C. arabica L*. [*Capparidaceae]* is common specie well acclimatized in the desert areas. The leaves are described as having hallucinogenic effects and as a sedative for abdominal and rheumatic pain (Boulos, 1983; Ahmad et al. 1990; Tsichritzis et al. 1993; Baba Aissa, 2011).

The present study of *C. arabica,* focuses on the evaluation of the ethanolic extract effects on anxiety behavior, biochemical parameters and ACTH hormone in Wistar rats.

MATERIALS AND METHODS

Animal

We used the adult rats "*Rattusrattus*" of the Wistar strain, from the Pasteur Institute of Algiers (Algeria), to carry out the various experiments. The rats were raised in plastic cages lined with sawdust and fitted with steel lids and water-filled bottles. The rats were fed with sticks of corn, barley, milk and vitamin supplements. These animals have been acclimatised to the laboratory conditions (temperature 25±2°C and humidity 70-80% and photoperiod 12:12h).

Cleome arabica(Capparidaceae):

C. arabica is an herbaceous plant, annual, glandular, viscous, fetid, of grayish green general aspect. It is also a therapeutic and anti-bacterial plant (Ladhari et al. 2013). This species effect has also been proven against different orders insects (Ozenda, 1991; Doumandji-Mitiche and Doumandji, 1993; N'Guessan et al. 2009; Koïta et al. 2012). For the present study, the plant was collected in the Bousaada region (M'sila, Algeria) (33°48′24″ north latitude, 2°52′56″ east longitude).

Preparation of the *C. arabica*ethanolic extract:

Ethanolic maceration follows the Bouharb's et al. protocol (2014). This one consists in macerating 400g of plant powder for 24 hours in one liter of ethanol solvent at (99.8%) at room temperature and in the shade. After filtration, the solution obtained was evaporated in the shade and with the help of a magnetic stirrer to drive out the solvent (Keita et al. 1998) using a hot plate at a 50°C temperature until a paste was obtained, which was kept at 4°C until its use. On each bottle are noted the preparation date, extraction type and concentration. The plant was identified by PrRebbasKhellaf, Department of Biology, Faculty of Science and University of M'sila (Algeria).

Treatments:

Forty rats were separated into two groups, a control group (20 individuals: 10 males and 10 females) and a treatment group (20 individuals: 10 males and 10 females). Who will undergo the intoxication, by gavage, of 1ml of *C. arabica*(0.20µg/l) for 7 successives days?

Rat's Behaviors in different anxiety-provoking situations:

We tested the different rats groups using experimental devices recognized by the scientific society whose most used are the plus maze (EPM) (Rodgers and Dalvi, 1997; VanGaalen and Steckler, 2000; Karl et al. 2003; Elizalde et al. 2008), the open field (OP) (Crawley, 1999; Palanza, 2001; Karl et al. 2003; Prut and Belzung, 2003; Elizalde et al., 2008) and the forced swimming test or Porsolt test (FST) (Porsolt et al. 1977; Karl et al. 2003; Elizalde et al. 2008).

Effect on certain biochemical parameters:

Blood is collected from control adults and *C. arabica*'s adults. The separated plasma is frozen and stored immediately at (-20°C). ACTH plasmas were measured by radioimmunoassay (Raff et al. 2004). We also performed a blood glucose, cholesterol, triglyceride, urea and creatinine.

Data Analysis:

The various study data were analyzed by descriptive and comparative methods (variances analysis) on XLStat 2009 software**.**

RESULTSAND DISCUSSION

Rats' behaviors in different anxiety-provoking situations:

Plus maze test:

The elevated plus maze represents one of the most widely used animal models for screening for anxiolytics and anxiogens (Lister, 1987; Corbett et al. 1991). Administration of *C.arabica*ethanolic extract produced a significant reduction in the number of open arm entries in females treated with *C. arabica*ethanolic extract 3.00±0.40 entries (Tab.1) compared to controls 5.50±0.64 entries (Tab.1) as well as a highly significant reduction in the time spent in the open arm in the treated females 3.57±0.42 seconds (Tab.1) compared to the controls 117.80±1.73 seconds (Tab.1) showing that the ethanolic extract of *C.arabica* is anxiogenic.

The animal avoids the exposed open areas of the labyrinth and prefers the closed wall. The anxiogenic properties validate the central nervous system depressive properties of the plant. The anxiogenic effect of the plant resembles that of certain plants such as *Cryptolepsissanguinolenta*, *Cissuscornifolia, Careyaanboree, C. arabica* (Ansah et al. 2008; Kumar et al. 2008; Musa et al. 2008; Bekheckhche et al. 2018: Boublata et al. 2020). Anxiolytic compounds reduce animals' natural aversion to open arms and promote exploration of this aversion in the Elevated Labyrinth Plus test. On the other hand, forced or voluntary passage of the animal through the closed arms of the EPM is associated with hormonal and behavioral changes indicating increased anxiety (Hogg, 1996; Santos et al. 2012). Montgomery (1955) reported that rodents systematically spend more time in closed arms when placed in mazes with open and closed arms. We found that administration of *C.arabica*ethanolic extract caused a highly significant increase in the time spent in closed arms in treated females 296.96±0.38 seconds (Tab.1) compared to controls 175.77±2.29 seconds (Tab.1). These results are the same observed in rats treated with *C. arabica*aquoues extract (Boublata et al. 2020).

Open Field Test:

The open field test provides information on anxiety-related behavior characterized by rodents' natural aversion to an open, lighted area (Choleris et al. 2001). The animals are therefore afraid of the center and spend more time in the protective corners and in an immobility state, which we found in our results that male rats treated with the *C.arabica* ethanolic extract showed a significant decrease ($p \leq 0.05$) in the time spended in the device center (Tab.2) and in immobility times in treated females (Tab.2). These results are similar to those of Harquin et al. (2014) when they used *Tapinanthusdodoneifolius*m ethanolic extract to observe that decreasing in distance travelled in central zone could be due to a locomotion alteration. The decrease in locomotor activity of treated rats provides more evidence of its depressive activity Harquin et al (2014). The time and number decreases in recoveries are emotional activity parameters, were also significantly affected by treatment with *C.arabica*ethanolic extract for both sexes. In other seminal research by Sana et al (2014), administration of *Cleome brachycarpa*ethanolic extract once daily, induced a significant decrease in locomotor activity and has CNS depressant effects. Previous studies show that locomotor activity is controlled by peripheral signals from the spinal cord and the cerebral zone, which plays a role in controlling cerebellar movement and posture (Bekhakheche et al.2018; Boublata et al. .2020).

Forced swim test:

In the forced swimming test, animals are forced to swim in a very confined space 'where there is no means of escape. They quickly develop a state of desperation characterized by poor motivation to escape as shown by the increase in immobility periods. In this experiment, the immobility displayed by rodents when subjected to unavoidable stress such as forced swimming is thought to reflect a desperation state or lowered mood, which would be reflective of depressive disorders in humans. This behavioral test is sensitive to serotonergic compounds, such as the selective serotonin reuptake inhibitor, fluoxetine (Beppeet al.2014).The administration of *C.arabica*ethanolic extract caused a highly significant increase in the immobility time of treated male and female compared to the controls groups (Tab.3).

Table 1: *C. arabica* effect on the behavior of rats (in Elvated plus maze)

N=10	Time spent in closed arms	Time spent in open arms	Number of closed arms	Number of open arms
♂C	235.60±0.40	58.00±0.64	5.75±0.47	2.50±0.64
♂*C.a*	195.26±37.10	61.87±1.35	4.25±0.25	2.75±0.75
t_{obs}	*1.08*	*-2.57*	*2.77*	*-2.25*
P	*0.33*	*0.04**	*0.03**	*0.80*
♀C	175.77±2.29	117.80±1.73	6.50±0.28	5.50±0.64
♀*C.a*	296.96±0.38	3.57±0.42	5.75±0.75	3.00±0.40
t_{obs}	*-44.30*	*74.28*	*0.93*	*3.27*
P	*<0.0001***	*<0.0001***	*0.38*	*0.01**

[C: Control; C.a: C. arabica] [* significant*; ** highly significant; *** very highly significant]

Table 2: *C. arabica* effect on the behavior of rats (in open filed)

N=10	Time spent in the central area	Time spent in the peripheral area	Time spent in the corners	Number of adjustments	Time of immobility
♂C	1.43±0.36	298.86±0.45	201.03±31.20	22.50±4.53	119.06±13.95
♂C.a	0.51±0.11	299.55±0.13	259.38±18.23	11.66±1.97	188.88±35.15
t_{obs}	2.32	-1.44	-1.61	2.18	-1.84
p	0.04*	0.18	0.13	0.05	0.09
♀C	0.58±0.11	139.93±23.61	230.43±22.58	15.50±1.38	139.93±23.61
♀C.a	0.60±0.32	204.50±12.18	258.38±12.60	8.83±1.70	204.50±12.18
t_{obs}	-0.04	-2.43	-1.08	3.03	-2.43
p	0.96	0.03*	0.30	0.01*	0.03*

[C: Control; C.a: C. arabica] [* significant*; ** highly significant; *** very highly significant]

Table 3: *C. arabica* effect on depressive state

N=10	Swimming time	Climbing time	Time of immobility
♂C	126.33±2.03	2.27±0.07	61.70±0.61
♂C.a	123.93±1.41	2.20±0.24	121.20±0.13
t_{obs}	0.96	2.29	-111.06
p	0.33	0.77	<0.0001***
♀C	126.52±0.83	2.47±0.14	117.16±1.36
♀C.a	123.36±1.01	1.47±0.16	120.92±0.64
t_{obs}	2.42	4.56	-2.69
p	0.06	0.004**	0.04*

[C: Control; C.a: C. arabica] [* significant*; ** highly significant; *** very highly significant]

A decrease in the immobility time is indicative of an anti-stress effect, while an increase in this time compared to control group, is associated with stress effects (Yeap, 2015; Bekhakheche et al. 2018; Kanase and Shaikh, 2019). In animals, immobility is interpreted as a lack of will to survive and considered as a depression sign (Porsolt et al. 1977, Petit Demouliere et al. 2005).

***C. arabica* effect on biochemical parameters and the hormone ACTH :**

The administration of *C. arabica*ethanolic extract induced a very highly significant decrease in the urea and creatinine levels of the treated animals for both sexes compared to the control rats. These results were consistent with those of Narendhirakannan et al (2005) when a *C. arabica* extract was administered. *Cleome gynandra* extract to arthritic rats resulted in a significant reduction in urea, creatinine levels; also, a significant decrease blood glucose levels was observed in diabetic rats treated with *Cleome rutidosperma* (Oridupa et al.2020). These results are also similar to those of Helal (2002) when the administration of the aqueous and ethanoloic extract of *C. droserifolia*. The decrease in amino acid absorption may explain the low serum urea level observed in treated animals due to

depression of the deamine/ornithine cycle in the liver (Harper et al. 1993). Abd El-Baky et al, (2009), noted that *Citrulluscolocynthis* extract significantly decreases blood glucose, cholesterol and triglyceride levels. Therefore, they concluded that *C.colocynthis* exerts a hypoglycemic, lipid-lowering and antioxidant effect in normal and diabetic rats (Rai et al. 2007; Asif, 2014; Michel and Sapana, 2017; Bekhakheche et al.2018).

The hypoglycemic effect of plants and/or their products has been studied and confirmed in several studies (Herrera-Arellono et al.,2004;Jayawardena et al.2005;Jasmine and Daisy, 2007;Krouf et al. 2008 ; Taleb-Senouci et al.2009;Zennaki et al.,2009; Ludvik et al.2013Baragob et al.2014;Kumar et al.2015;Mousavi et al.2016).

Cholesterol levels also decrease after treatment with *C.arabica*. This increased cholesterol level was found to activate these cells and lead to enhanced production of reactive oxygen species (ROS) (Kamesh and Sumathi, 2012). Samout*et al* (2015) showed a significant increase in the total cholesterol, LDL-chol and triglycerides levels, and a significant de- crease in HDL-chol in the hypercholester- olemic rats compared to controls.

C. arabica induces a significant decrease in Triglycerides, Urea and Creatinine levels. In Boublata et al and Samout et al studies (2020, 2015), it was found that an increase in total plasma TG, SGOT, SGPT, LDH, PAL, urea and creatinine occurred with a decrease in HDL-cholesterol and uric acid value. Our results are similar to these studies which shows that *C.arabica* acts on urea and creatinine rate which decrease after treatment.

We recorded a significant decrease in the ACTH hormone level in males and females treated with *C.arabica*ethanolic extract, which is consistent with the results of Oliver et al (1994) when they used the *G. biloba* extract to decrease norepinephrine and adrenocorticotropic concentrations'

CONCLUSION

The *C. arabica* is a widespread and well-known species in the Algerian desert. Despite its importance in local traditional medicine and its abundance in the region, it remains economically little exploited. The present study focused on the plant effects on biochemical parameters and behavior in Wistar rats. The results obtained in this study suggest that the *C. arabica* leaves demonstrated efficacy on the cholesterol, urea and creatinine levels' observed in treated animals.
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CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

All authors contributed equally

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