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Psychopharmacological effects of *Morinda lucida BENTH* leaf aqueous extract in *Balb/C* mice in a model of LPS-induced neuroinflammation.

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Abstract

Background*:* The cost and irreversibility of Alzheimer's disease make its management difficult. To find alternative and rational solutions, our communities resort to the use of medicinal plants "*Morinda lucida BENTH*" *(M.l BENTH).* In the Republic of Congo, there are no studies highlighting the effects of *Morinda lucida BENTH* on the central nervous system.

Objective*:* to research the effects of the aqueous extract of *Morinda lucida BENTH* leaves on the behavior and memory of *Balb/C* mice. Methods: The extraction of fresh leaves of *Morinda lucida BENTH* was done by maceration. We carried out an experimental study in *Balb/C* mice. They were treated per os orally with different concentrations of this extract (200 mg/kg and 400 mg/kg) "group D and E" then intraperitoneally with LPS while distilled water 10 ml/kg "group A" was used as negative control, distilled water associated with LPS "group B" and Donepezil 5 mg/kg "group C" as positive controls.

Results*:* Analysis of the effects of *M.l BENTH* on the behavior of *Balb/C* mice showed that the aqueous extract of *M.L BENTH* leaves at doses of 200 and 400 mg/Kg did not influence ($p>0.05$) the behavior of *Balb/C* mice compared to controls in the open field test; however, in the cross maze test, the aqueous extract of *M.l BENTH* leaves at a dose of 200 mg/Kg significantly reduced NEPC : number of entries in the central part (*$p<0.01$), NEBO : number of entries in the open arms (*$p<0.02$), NEBF: number of entries in the closed arms (***$p<0.007$); moreover, at a dose of 400 mg/Kg this difference was recorded only for NEPC : (*$p<0.05$) compared to controls. The evaluation of the effects of *M.l BENTH* on memory showed a significance of the aqueous extract of *M.l BENTH* leaves at the dose of 200mg/Kg for the TEOF: time to explore familiar objects (*$p<0.02$), compared to the controls in the object recognition test. A significant difference was also observed between the aqueous extract of *M.l BENTH* leaves at the dose of 200mg/Kg (*$p<0.02$), Donepezil 5mg/Kg (Aricept*) at the dose of 5mg/kg (*$p<0.03$) for the NECC : *number of entries in the target quadrant* in the Morris test.

Conclusion: The aqueous extract of *M.l BENTH* leaves would have beneficial effects on behavior and memory. It is therefore possible that at a certain dose (200mg/Kg), *M.l BENTH* has anxiolytic properties, confirming its use in traditional medicine.

Keywords: *Morinda lucida;* Leaf aqueous extract; Memory; Behavior; *Balb/C.* mouse

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1. Introduction

In sub-Saharan Africa, the prevalence of specific dementias in people aged over 60 years is 6.38%. An estimated 2.13 million people were living with dementia in sub-Saharan Africa in 2015. This number will reach 3.48 million by 2030 and 7.62 million by 2050, with larger increases in Central and Eastern Africa. These increases compared to the World Alzheimer Report 2015 estimates are thought to be related to population aging and a slightly higher estimated prevalence. Total dementias in sub-Saharan Africa are estimated to cost US$6.2 billion in 2015; and the distribution of these costs between the three major categories (direct medical costs, social costs and informal care costs) remains preserved, with two levels at three-quarters of the total costs attributed to informal care.[6]

Among these dementias, Alzheimer's disease is mentioned, which is an irreversible and slowly spreading neurodegenerative disease. These clinical signs appear several years after the onset of pathophysiological abnormalities. It affects more than 35 million people worldwide; and it is estimated that 110 million people will be affected by 2050.[29] The management of AD is a huge global challenge because there is still no definitive treatment for AD. However, there are palliative treatments that can temporarily delay the progression of symptoms. These treatments would be more effective if the disease were diagnosed early.[24] Among the drugs, there are cholinesterase inhibitors, namely Donepezil, Galantamine and Rivastigmine, which allow a significant improvement in cognitive functioning. At the glutatergic system level, Memantine used for advanced stages of AD, acts as an antagonist of the NMDA receptor.[22]

However, of the four (04) drugs currently available indicated in the treatment of AD "donepezil (Aricept®), galantamine (Reminyl® and Reminyl® LP), rivastigmine (Exelon® and Exelon® patch) and memantine (Ebixa®)", none has demonstrated superiority over the others. In addition, three categories of drugs are used for memory disorders: (1) antipsychotics “Risperidone and Aripiprazole”, which have a fairly limited efficacy in terms of symptom reduction and duration of efficacy; (2) antidepressants, “Citalopram and Sertraline”, of which Cirrito and al., 2011[12], had observed a significant decrease in the number of amyloid plaques in a transgenic mouse model with Citalopram; as well as a lower rate of accumulation of Aβ peptide than in patients with AD, which would explain that the serotonergic system would modulate the biological pathways allowing the elimination of Aβ peptide; (3) anticonvulsants “Carbamazepine”, which could be effective in treating the agitation and aggressiveness observed in patients.[4] New treatments currently under study (immunotherapies, secretase inhibitors, tau aggregation inhibitors and GSK3β inhibitors) would mainly target the Aβ peptide, the tau protein or the enzymes and proteins associated with them.

Currently, none of the available and recommended treatments act on the progression of the disease. Many initially promising molecules have failed in clinical trials in recent years. [9] After the discouraging trials of the last 10 years, new molecules in advanced phase development (phase III) have recently revived hope for a possible effective treatment. This is solanezumab, a monoclonal antibody present in the soluble form of the amyloid peptide, responsible for the formation of plaques. In phase III trials, this molecule did not demonstrate its efficacy on cognitive functioning or activities of daily living [31] ; in addition, in the pivotal trials on bapineuzumab and solanezumab, the absence of a therapeutic target should be noted. [32 ; 21] The absence of real long-term beneficial therapy is directing some communities in the sub-region towards rational solutions such as medicinal plants, such as *Morinda lucida BENTH*. [19] Due to its widespread use in traditional medicine, many studies have highlighted the therapeutic effects of certain parts of this plant: antimicrobial properties [15], antidiabetic and antioxidant [2 ; 34], antiparasitic, antipyretic. [14 ; 28] Recent studies on *Morinda lucida BENTH* have revealed the presence of alkaloids, flavonoids, etc. [1]

These secondary metabolites known for their antibacterial, antiviral, antiparasitic, antifungal, anti-inflammatory and other actions suggest that *Morinda lucida BENTH* could have possible effects on neuroinflammation. [33 ; 8] Despite this wide range of therapeutic properties possessed by this plant, no scientific data are available to date comparing the effects of *Morinda lucida BENTH* leaves and Donepezil on the central nervous system. In this study, we will investigate the comparative effects of *Morinda lucida BENTH* leaves on the behavior and memory of *Balb/C* mice.

2. Material and methods

2.1. Plant material and preparation of the aqueous extract

Fresh leaves of *Morinda lucida BENTH*, collected in the city of Makoua (Cuvette department), identified and registered at the Center for the Study of Plant Resources (C.E.R.VE.) under number N°: 8.014. They were reduced to powder using the electronic grinder; 50g of powder obtained were macerated in 500ml of distilled water under magnetic stirring for 48 hours. The macerate obtained was filtered using carded cotton and then concentrated to a quarter (1/4) of its initial

volume at 65°C in an oven. The pure extract obtained was transferred to a sterile plastic container; hermetically sealed and stored in the refrigerator at 4°C for psychopharmacological analyses. [27]

2.1.1. Animal material

Male and female *Balb/C* mice weighing 16–28 g (aged 7–10 weeks), divided into 5 batches of 5 animals each (total of 25 animals) were kept. They came from the animal facility of the Faculty of Health Sciences. All these animals were kept in their natural habitat and subjected to a 12/12h light/dark cycle, with free access to water and food.

2.2. Psychopharmacological activities and treatment

2.2.1. Open field test

It was initially described by Hall (1932) [17] , in order to assess the emotional reactions of the rodent, the test consisted of placing the animal in one of the four pieces of a 60 x 60 cm wooden square (head turned towards the corner of the device) and observing its behavior while assessing its exploratory capacity in a stressful context for 10 minutes per 5-minute phase.[19] Five (5) groups of five (5) *Balb/C* mice per group were formed and treated for 7 days orally then by LPS for groups (B, C, D, E) for 3 days by IP (intraperitoneal injection) as follows: group A, treated with distilled water 10ml/kg; group B, treated with distilled water then by LPS; group C, treated with Donepezil 5 mg/kg then by LPS; group D, treated with aqueous extract of *M.l BENTH* leaves 200mg/kg then with LPS; and group E, treated with aqueous extract of *M.l BENTH* leaves 400mg/kg then with LPS. One hour (1h) after the administration of the different products, each naive animal was placed in the experimental device; and using a Canon 3.6v camera, the number of entries in the central and peripheral part, the total number of tiles crossed were evaluated.

2.2.2. Cross Maze Test

It consisted of knowing the type of anxious behavior developed by the rodents, placed in a maze composed of two open arms and two closed arms (50 cm x 10 cm x 40 cm) connected by a central platform (10 cm × 10 cm) and located 50cm above the ground.[18] Five (5) groups of five (5) *Balb/C* mice per group were formed and treated for 7 days orally then by LPS for groups (B, C, D, E) for 3 days by IP (intraperitoneal injection) as follows: group A, treated with distilled water 10ml/kg; group B, treated with distilled water then by LPS; group C, treated with Donépezil 5 mg/kg then by LPS; group D, treated with aqueous extract of *M.l BENTH* leaves 200mg/kg then by LPS; and group E, treated with aqueous extract of *M.l BENTH* leaves 400mg/kg then by LPS. One hour (1h) after administration of the different products, each naive animal was placed in the center of the device facing an open arm; and using a Canon 3.6v camera the time spent in the different parts of the device, the number of entries into the closed arms and into the open arms.

2.2.3. Object Recognition Test

This test was used to assess the declarative memory of rodents; by evaluating their ability to recognize a novel object compared to a familiar object in a known environment. Five (5) groups of five (5) *Balb/C* mice per group were formed and treated for 7 days orally then with LPS for groups (B, C, D, E) for 3 days by IP (intraperitoneal injection) as follows: group A, treated with distilled water 10ml/kg; group B, treated with distilled water then with LPS; group C, treated with Donepezil 5 mg/kg then with LPS; group D, treated with aqueous extract of *M.l BENTH* leaves 200mg/kg then with LPS; and group E, treated with aqueous extract of *M.l BENTH* leaves 400mg/kg then with LPS. One hour (1h) after the administration of the different products, each animal was placed in the experimental device (40x40cm) containing two identical objects; to explore it freely for 10 minutes. After 2 minutes of retention, the animal was placed back in the experimental device for 5 minutes to explore the objects again, one of which had been replaced. [11] Using a 3.6v Canon camera, the exploration time of the objects (familiar and new), the exploration index and the discrimination ratio were evaluated.

2.2.4. Morris Pool

This test was designed by Morris in 1984 [25] to evaluate the referential memory and working memory of rodents placed in an aversive situation (pool immersed in a platform). The Morris pool is a circular enclosure of 120 cm in diameter and 25 cm in height, half filled with water at 23 ° C, submerged with a plastic platform invisible to the animal (cylinder of 10 cm in diameter) under the surface of the water at 0.5 cm. The experiment lasts 5 days, the first consists of an adaptation phase to a new environment. The following 3 days consist of the acquisition phase with 3 trials for each mouse, separated by a delay of 5 minutes each. However, the latency time to find the plate is limited to 60 seconds and the mouse is allowed to stay there for 30 seconds, if the mouse does not find the platform during the 60 seconds of the test, it will be guided to the platform. Twenty-four (24) hours after the last day of learning, the platform was removed for a one-minute retention test.[3] Five (5) groups of five (5) *Balb/C* mice per group were formed and treated for 7 days

orally and then with LPS for groups (B, C, D, E) for 3 days by IP (intraperitoneal injection) as follows: group A, treated with distilled water 10ml/kg; group B, treated with distilled water then with LPS; group C, treated with Donepezil 5 mg/kg then with LPS; group D, treated with aqueous extract of *M.l BENTH* leaves 200mg/kg then with LPS; and group E, treated with aqueous extract of *M.l BENTH* leaves 400mg/kg then with LPS. One hour (1h) after administration of the different products, each animal was subjected to forced swimming for 1 minute; and using a Canon 3.6v camera, the latency to find the platform, the number of entries into the target quadrant and the time spent in the target quadrant were evaluated.

2.3. Statistical analysis

The results are expressed as mean ± SEM. The significance level was $P < 0.05$; and it was calculated by Student's T test in IBM SPSS Statisticts 23 software.

3. Results

In Table 1, the administration of *M.l BENTH* leaf aqueous extract at doses of 200 and 400 mg/kg; Donepezil (Aricept*) 5 mg/kg did not significantly influence ($p>0.05$) the behavior of *Balb/C* mice compared with the control.

In the cross maze test, *M.L BENTH* leaf aqueous extract at a dose of 200 mg/kg significantly reduced NEPC (*$p<0.01$), NEBO (*$p<0.02$), NEBF (***$p<0.007$); However, at the dose of 400 mg/kg this difference is mentioned only for NEPC (*$p<0.05$) compared to controls. No significant differences were observed for TPPC ($p>0.05$), TPBO ($p>0.05$) and TPBF ($p>0.05$) compared to controls (Table 2).

Table 1 Effect of aqueous extract of *M.l BENTH* in the open field test in *Balb/C* mice (n = 5)

Parameters	Water Dist.10ml/Kg	LPS + Water Dist.10ml/Kg	LPS+Donépezil 5mg/kg	LPS + *M.l BENTH* 200mg/Kg	LPS + *M.l BENTH* 400mg/Kg
NCT	350.60±32.67	210.00±55.57	337.00±40.57	321.40±41.53	186.20±59.04
NEPC	6.00±1.58	8.00±2.91	16.80±4.85	6.20±1.46	3.40±1.91
NEPP	7.00±1.58	8.00±2.91	16.80±4.78	6.20±1.46	3.40±1.91

Dist.: Distilled, *M.l : Morinda lucida*, NCT: number of tiles crossed; NEPC: number of entries in the central part; NEPP: number of entries in the peripheral part.

Table 2 Effect of aqueous extract of *M.l BENTH* in the crossed maze test in *Balb/C* mice (n = 5)

Parameters	Water Dist.10ml/Kg	LPS + Water Dist.10ml/Kg	LPS+Donépezil 5mg/kg	LPS + *M.l BENTH* 200mg/Kg	LPS + *M.l BENTH* 400mg/Kg
NEPC	5.20±1.74	11.60±3.07	14.20±5.75	25.00±6.07*	21.00±5.54*
NEBO	2.60±0.67	1.40±0.40	4.20±1.82	7.60±1.88*	5.80±1.46
NEBF	3.80±1.39	10.20±3.07	10.80±4.07	18.20±4.21**	14.80±4.16
TPPC	23.20±9.90	42.40±15.11	31.40±19.01	51.00±10.13	45.00±16.08
TPBO	108.80±49.24	19.00±6.81	76.60±22.60	103.40±12.89	68.60±15.11
TPBF	468.00±44.23	538.60±21.66	491.80±39.04	445.60±22.12	485.00±27.56

NEPC: number of entries in the central part; NEBO: number of entries in the open arms; NEBF: number of entries in the closed arms; TPPC: time spent in the central part; TPBO time spent in the open arms TPBF: time spent in the closed arms.

Administration of the aqueous extract of *M.l BENTH* at the dose of 200 mg/kg showed significance for TEOF (*$p<0.02$), for TEOF (*$p<0.02$); TENO (*$p<0.02$); TEOF-NO (*$p<0.02$) in *Balb/C* mice treated with LPS + distilled water 10 ml/kg. No significant differences for TENO ($p>0.05$); TENO ($p>0.05$) and TEOF-NO ($p>0.05$) compared to Donepezil (Aricept*) 5 mg/kg and aqueous extract of *M.L BENTH* at a dose of 400 mg/kg compared to the control (Table 3).

Memory assessment by Morris test revealed a significant difference of aqueous extract of *M.l BENTH* at a dose of 200 mg/kg (*p<0.02), Donepezil (Aricept*) at a dose of 5 mg/kg (*p<0.03) for NECC; No significant differences were observed for TPPC (p>0.05), TLTPF (p>0.05) and TPCC (p>0.05) compared to controls (Table 4).

Table 3 Effect of the aqueous extract of *M.l BENTH* in the object recognition test in *Balb/C* mice (n = 5)

Parameters	Water Dist.10ml/Kg	LPS + Water Dist.10ml/Kg	LPS+Donépezil 5mg/kg	LPS + *M.l BENTH* 200mg/Kg	LPS + *M.l BENTH* 400mg/Kg
TEOF	19.80±1.80	7.00±3.70*	22.00±5.21	28.80±2.31*	15.20±3.08
TENO	6.00±0.7	1.60±1.36*	4.80±2.03	7.60±1.63	6.20±2.01
TEOF-NO	3.60±0.24	1.20±0.80*	2.60±1.16	3.80±1.24	2.00±0.63

TEOF: time to explore familiar objects; TENO: time to explore new objects; TEOF-NO: exploration time of the familiar object compared to the new object

Table 4 Effect of the aqueous extract of *M.l BENTH* in the Morris test in *Balb/C* mice (n = 5)

Parameters	Water Dist.10ml/Kg	LPS + Water Dist.10ml/Kg	LPS+Donépezil 5mg/kg	LPS + *M.l BENTH* 200mg/Kg	LPS + *M.l BENTH* 400mg/Kg
NECC	8.20±0.58	8.00±0.83	5.20±0.48*	5.20±0.96*	6.80±1.31
TLTPF	26.40±10.13	21.40±10.26	36.80±10.18	41.40±11.01	41.80±8.72
TPCC	20.00±2.58	15.80±0.73	13.60±3.47	12.00±3.31	15.00±1.64

NECC: number of entries in the target quadrant; TLTPF: latency to find the platform and TPCC: time spent in the target quadrant.

4. Discussion

Neuroinflammation contributes to the development of neurodegenerative diseases and cognitive dysfunctions. Establishing appropriate animal models is very important to study the association of neuroinflammation with cognitive disorders and neurodegenerative diseases. Studies demonstrate that LPS injection contributes to the establishment of neuroinflammation that damages the blood-brain barrier, thereby causing memory impairment and amyloid plaque synthesis. [26] Chronic LPS administration can cause memory impairment that mimics the cognitive decline observed in Alzheimer's disease. In addition, the induction of inflammation in the brain by LPS is accompanied by neuronal loss and microglia activation that stimulates the synthesis of neurotoxic factors such as inflammatory cytokines.[16 ; 30]

In the present study, we stimulated neuroinflammation using needle injection of LPS; and to address this, we sought comparative effects of aqueous extract of *M.l BENTH* leaves at doses of 200 and 400mg/Kg and Donepezil (Aricept*) 5mg/kg. Indeed, Donepezil (Aricept*) is one of the cholinesterase antioxidants that significantly improves cognitive functioning in patients with Alzheimer's disease. [7] To evaluate the comparative effects of aqueous extract of *M.l BENTH* leaves at doses of 200 and 400mg/Kg and Donepezil (Aricept*) 5mg/kg on behavior and memory in our study model, we used the open field test, the crossed maze test, the Morris test and the object recognition test. In the open field test, the number of entries in the central and peripheral part, the total number of tiles crossed are variables measured to assess the exploratory capacity of animals in experimentation in a stressful context. The administration of aqueous extract of *M.l BENTH* leaves at doses of 200 and 400mg/Kg; Donepezil (Aricept*) 5mg/kg does not significantly influence (p>0.05) the behavior of *Balb/C* mice compared to the control. In contrast to the animal model of our study, M. Cachard-Chastel and al., 2007 [23] used scopolamine (1 mg kg-1 in 5 ml kg-1, s.c., 30 min before the experiment) to induce memory impairment in *C57Bl/6j* mice; and to correct these memory impairments, they used Prucalopride and donepezil. This work showed a significant difference between the different study groups.

The cross-maze test represents a model for detecting the neurobiological bases of anxiety and screening anxiolytic substances. This model is based on the work of Montgomery in 1955 who demonstrated that rodents tend to avoid the open areas of the Y-maze. The cross-maze test has several advantages over other experimental models of anxiety. [13] The number of entries and the time spent in the open arms are the parameters that reflect the anxious state. In our study, the aqueous extract of *M.l BENTH* leaves at a dose of 200 mg/Kg significantly reduced NEPC (*p<0.01), NEBO (*p<0.02), NEBF (***p<0.007); However, at the dose of 400mg/Kg this difference is only mentioned for NEPC (*p<0.05) compared to controls. No significant difference was observed for TPPC (p>0.05), TPBO (p>0.05) and TPBF (p>0.05)

compared to control groups. It is therefore possible that at this dose, the aqueous extract of *M.l BENTH* leaves has anxiolytic properties. These results are consistent with the work of Bakou N. F. and al., 2020.[5]

The object recognition test was used to assess the declarative memory of mice in experimentation. [11] In our study, the administration of the aqueous extract of *M.l BENTH* at the dose of 200mg/Kg showed a significance for TEOF (*p<0.02), for TEOF (*p<0.02); TENO (*p<0.02); TEOF-NO (*p<0.02) in *Balb/C* mice treated with LPS + Water Dist.10ml/Kg. No significant difference for TENO (p>0.05); TENO (p>0.05) and TEOF-NO (p>0.05) with Donepezil (Aricept*) 5mg/Kg and with the aqueous extract of *M.l BENTH* at the dose of 400mg/Kg compared to the control. Morris pool test was used to assess working and learning memory in mice [10] ; in our study, memory assessment by Morris test revealed a significant difference of *M.l BENTH* aqueous extract at a dose of 200mg/Kg (*p<0.02), Donepezil (Aricept*) at a dose of 5mg/kg (*p<0.03) for NECC; No significant differences were observed for TPPC (p>0.05), TLTPF (p>0.05) and TPCC (p>0.05) compared to controls. These results show that *M.l BENTH* at a dose of 200mg/Kg would have possible beneficial effects on learning memory.

5. Conclusion

In conclusion, the results obtained in our study suggest that the aqueous extract of *M.l BENTH* leaves has possible beneficial effects on behavior and memory. It is therefore possible that at certain doses (200mg/Kg), the aqueous extract of *M.l BENTH* leaves has anxiolytic properties, resulting from its wide use in traditional medicine.

Compliance with ethical standards

Authors' contribution

RDMO and LMM designed this work under the coordination of AAA. RDMO carried out the experimental studies and statistical analyses with the help of BFEK and IOCA. MORD, MLM and JBM wrote the preliminary version of the manuscript. All these authors revised this manuscript.

Disclosure of conflict of interest

We declare that we have no conflict of interest.

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