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The essential oil of Algerian *Ammodaucus leucotrichus* Coss. & Dur. and its effect on the cholinesterase and monoamine oxidase activities

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This study aims at performing a chemical analysis of the essential oil (EO) of *Ammodaucus leucotrichus* Coss. & Dur. and investigating the anticholinesterase and anti-monoamine oxidase activities.

The EO of the *A. leucotrichus* aerial part was analyzed by Gas Chromatography Mass Spectrometry (GC-MS). The inhibitory potency against Acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE) were evaluated *in vitro* using modified Ellman's method. Monoamine oxidase activity was measured using the spectrophotometric method described by Weissbach.

The chemical analysis of EO showed that the main constituents were perillaldehyde (by about 58.3%) and limonene (by about 23.33%). Further, the essential oil extracted from *A. leucotrichus* exhibited a promising anti-butyrylcholinesterase activity with an IC₅₀ of about 95.2 µg/mL, where the perillaldehyde and limonene IC₅₀ corresponded to 42.7 µg/mL and 66.7 µg/mL, respectively. The anti-acetylcholinesterase activity was observed only with limonene with IC₅₀ = 51.6 µg/mL. The highest monoamine oxidase inhibitor activity was observed by essential oil followed by perillaldehyde. The oil demonstrated IC₅₀ values for monoamine oxidase-B (MAO-B) of 40.5 µg/mL and 98.9 µg/mL for perillaldehyde. While, IC₅₀ values for monoamine oxidase-A (MAO-A) were 112.5 µg/mL and 159.1 µg/mL for EO and perillaldehyde, respectively. No inhibitory activity against monoamine oxidase has been reported with limonene.

A. leucotrichus C. & D. essential oil may represent an alternative source useful as a moderate anticholinesterase agent, particularly against butyrylcholinesterase and monoamine oxidase.

1. Introduction

The Alzheimer's disease (AD) is a pathology that affects > 46.8 million people, the most common neurodegenerative disease for an estimated worldwide cost of US\$818 billion ([51]).

On the other hand, the Parkinson disease (PD) is the second age related neurodegenerative disease with an estimation of seven to 10 million people living with it. In spite of their description in the early 20th century and recent advancements in the understanding of possible

mechanisms relating to their etiology, these neurological disorders remain orphan of effective treatments.

Monoamine oxidases (MAOs) and cholinesterase (ChE) are enzymatic systems that are known to play a pivotal role in the cause of these neurologic disorders. MAO-A and B are ubiquitous mitochondrial enzymes present in the outer mitochondrial membrane in various tissues such as nerve terminals, gut and liver. They catalyze the oxidative deamination of neurotransmitters, physiologic or food ingested amines. MAO dependent oxidative stress is recognized as a pejorative factor in

Abbreviations: AD, Alzheimer's disease; AChE, Acetylcholinesterase; ATCh, Acetylthiocholine; BuchE, Butyrylcholinesterase; ChE, Cholinesterase; DMSO, Diméthylsulfoxyde; DTNB, Dithiobisnitrobenzoate; EO, Essential oil; MAOs, Monoamine oxidase; PD, Parkinson disease; US-FDA, US Food and Drug Administration

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the occurrence of neurological disorders such as depression, Parkinson (AD) or Alzheimer (AD) diseases ([15], [11]). There are two isoforms of MAOs differing by their substrate inhibitor specificity. The MAO-A which metabolizes aliphatic amines (serotonin, noradrenalin), and is selectively inhibited by clorgyline, while the MAO-B oxidizes preferably benzyl or phenyl amines and is selectively inhibited by selegiline. However, despite their potentiality, the clinical use of these inhibitors has been limited by the side effects associated with their prescription [15].

One of the factors known in the etiology of AD is the availability of acetylcholine into the neuronal synaptic compartment that is essential for maintaining the cognitive functions and the most consistent biochemical evidenced change in AD [16]. In this way, acetylcholinesterase (AChE) inhibitors are widely used for the symptomatic treatment of this pathology and other dementias such as myasthenia gravis. Butyrylcholinesterase is the other form of cholinesterase enzyme widely expressed in humans beings, differing by its substrate specificity but both are able to catalyze the degradation of acetylcholine neurotransmitter [10]. It was evidenced that in the AD brain, the AChE activity is maintained or repressed while the BuChE activity tends to increase [33]. This last finding raises the interest in the discovery of the molecules that inhibit AChE and BuChE as well as selective BuChE inhibitors.

Since a decade, a new emerging strategy aims at bringing comfort to people suffering from neurological diseases by using of multitarget directed ligands that would be able to target and inhibit both monoamine oxidases and cholinesterase's enzymes ([17, 25, 38, 47, 49]). Plants were used for centuries for the treatment of human and animal illnesses and are the source of most common drugs. Numerous articles report about the MAOs [3, 42, 44] or ChEs [6, 22, 27] inhibitory capability of crude or purified plant extracts. Moreover, some herbal complementary preparations mainly described in the Ayurvedic or traditional Chinese medicines have been used for centuries as a treatment for neurological disorders and have demonstrated their potential both on models [20, 21, 52] and clinical studies [8, 24, 26, 31, 34, 35, 43, 50]. Previous study published a dual inhibitory effect on MAOs and AChE of *Huperzia* extract [3], but to our best knowledge, there are few articles reporting on a such dual inhibitory effect of natural preparations.

It has been demonstrated that plants belonging to the Lamiaceae, Polygalaceae, and Apiaceae families are capable of exerting effects on the central nervous system[2]. *Ammodaucus leucotrichus* C.& D., medicinal plant, belonging to the Apiaceae family, is an endemic plant and comprises one species in Algeria[37]. The local name of this plant is "Akaman" (Tamahaq) and "Oumdraiga"[29]. Its geographical distribution is in the maritime sands in the Saharan and sub-Saharan countries of North Africa; Morocco, Algeria and Tunisia, extending to Egypt and tropical Africa[5].

A. leucotrichus C.& D. is used by the Algerian Saharan population, with different preparations to treat stomach diseases, fever, vomits, allergies, and is also emmenagogue, abortive and aphrodisiac[29]. In Morocco, it is used in the treatment of cardiac diseases[23]. Several studies have shown that the *A. leucotrichus* plant is very rich in essential oil[13, 18].

In this paper we describe the preparation, chemical characterization, Monoamine oxidases and cholinesterases inhibitory potentials of an essential oil prepared from the whole plant *Ammodaucus leucotrichus* C.& D. collected in the southern Algeria.

2. Materials and methods

2.1. Chemicals and reagents

All reagents were purchased from Sigma Aldrich.

2.2. Plant material and sample preparation

The *A. leucotrichus* C.& D. aerial parts harvest was performed in April 2014 in Ghardaia, Algeria. The plant was identified by Dr. A.M.Chahma (Faculty of Sciences, University of Ouargla, Algeria). The samples were washed with a tap water then distilled water to remove any adhering soil and dust. *A. leucotrichus* parts were dried for 5 days at room temperature in a ventilated darkroom to protect the active compounds from light oxidation.

2.3. Essential oil extraction

The Clevenger-type apparatus was used for the hydrodistillation according to the method recommended by the European Pharmacopoeia [36]. The aerial parts of *A. leucotrichus* were subjected to hydrodistillation for four hours and the essential oil was recovered directly without any solvent and stored at 4 °C. The essential oil had a blue color, and the yield was 1.3% (volume/dry-weight).

2.4. GC-MS of essential oil

The analysis are carried out on a Focus GC (Thermo, country for all material and method), equipped with a BR5-MS (5% phenyl methyl siloxane) column 30 m × 0.25 mm i.d., film thickness 0.25µm (Bruker).

The spectrometer coupled to the chromatographic chain was a DSQII (Thermo) equipped with an EI source at 70 eV. The mass spectrum was recorded between 40 and 500 Da (m/z equivalent unit). The injections were performed in split mode 1/100.

The temperature of the column was programmed from 70 °C to 300 °C with 10 °C/min steps. The injector temperature was programmed at 200 °C. Therefore, the Helium gas was used as a carrier at a linear velocity 1.2 mL/min. The injected volume was 1 µL.

2.5. Components identification

The compounds identification was achieved by comparison of their recorded mass spectra with those of a computer library (NIST2008 v2.0/Xcalibur data system) provided by the instrument software.

2.6. Enzymatic activities

For all enzymatic assays, stock samples were dissolved in DMSO at 100 mg/mL. ChE and MAO activities were tested in the presence of 1 to 1000 µg/mL of each sample solution in a constant DMSO concentration. All measurements were made in triplicate and performed at 30 °C. When possible, the IC₅₀ values were calculated using the GNUPLOT package online (www.ic50.tk, www.gnuplot.info).

2.6.1. Determination of cholinesterase inhibition assay

The cholinesterase (ChE) activities were assayed following a colorimetric protocol adapted from Ellman et al. [14]. ChEs efficiently catalyze the hydrolysis of acetylthiocholine (ATCh), the sulfur analog of the natural substrate of these enzymes. Upon hydrolysis, this substrate analog produces acetate ion and thiocholine. Thiocholine, in the presence of the highly reactive dithiobisnitrobenzoate (DTNB) ion, generates a yellow color, which can be quantitatively monitored by spectrophotometric absorption at 412 nm. A typical 200 µL inhibition assay volume contained phosphate buffered saline solution (pH 7.4), DTNB (1.5 mM), test sample in DMSO (1% v/v final). Both acetylcholinesterase from *Electrophorus electricus* (Type V-S, lyophilized powder, 744 U/mg solid, 1272 U/mg protein) and butyrylcholinesterase from equine serum (lyophilized powder, ≥ 900 units/mg protein) were dissolved in PBS pH 7.4 and used at 25 mU/mL for the assay. After 10 min of pre-incubation, the substrate acetylthiocholine iodide (1.5 mM) was added to start the reaction. During 1 h of incubation, 96-Well microtiter multiplates were read on a PherastarFS

(BMG Labtech) detection system at a wavelength of 405 nm. Donepezil was used as reference ChE inhibitor. In this assay, we did not exclude the possibility of false-positive inhibition results, previously described for high concentration (> 100 µg/mL) of amine or aldehyde compounds [39, 40]. Nevertheless, the lack of inhibition observed for the essential oil versus the AChE strongly minimized this possibility.

2.6.2. Determination of monoamine oxidase inhibition assay

MAO source was prepared by homogenizing rat liver in 2 volumes of cold 50 mM phosphate buffer pH 7.4, containing 0.125 M sucrose. The mitochondrial fraction containing the bulk of MAO activity was obtained after two centrifugations: firstly at 4000g for 5 min to remove cellular debris and secondly at 17000 g for 15 min to spin down mitochondria.

The monoamine oxidase (MAO-A + B) activity was measured in one step, monitoring the conversion of kynuramine to 4-hydroxyquinoline by recording spectral absorbance changes according to Weissbach and colleagues (1960). A typical 200 µL inhibition assay volume contained reaction buffer (PBS, 0.05% NP40), test sample in DMSO (1.5% v/v), mitochondria suspension containing MAOs activities (2.5%). After 10 min of pre-incubation, the substrate kynuramine (0.45 mM) was added to initiate the reaction. The 96-Well microtiter multiplates were incubated and read for at least 1 h on a PherastarFS (BMG Labtech) detection system. In order to increase the sensitivity of the method, enzymatic activities were evaluated by taking into account the sum of the amplitude of absorbance decrease at 357 nm (disappearance of kynuramine) and the amplitude of absorbance increase at 316 nm (appearance of 4-hydroxyquinoline). Clorgyline and deprenyl were used as a reference to MAO-A and B inhibitors respectively. In order to achieve specific measurements of the MAO-A and MAO-B activities, we have combined the use of both selective inhibitors with a non-selective substrate (kynuramine) in order to distinguish between MAO subtypes. Clorgyline and deprenyl concentrations were chosen to cause minimal non-selective inhibition of MAO-B and MAO-A, respectively (usually 1000 nM and 500 nM final).

For all enzymatic activities studied, the percentage of residual activity (% Residual activity) is given as follows:

$$\% \text{Residual activity} = 100 (A_{\text{sample}}/A_{\text{control}})$$

Where A_{control} is the absorbance of the control reaction containing all reagents except the tested sample, and A_{sample} is the absorbance of the tested compounds.

3. Results and discussion

The essential oil obtained by hydrodistillation from the aerial parts of *A. leucotrichus* was blue-coloured and the yield of the extraction was about 1.3% (volume/dry weight).

GC/MS results showed that the essential oil contains essentially monoterpenes identified as perillaldehyde (58.3%), limonene (23.33%) and α -pinene (5.74%). Accordingly, β -pinene (2.26%), perillalcohol (1.86%), 3-carene (1.86%), 3-thujanone (0.7%), camphene (0.59%), myrcene (0.51%), α -copaen-11-ol (0.34%), globulol (0.34%), α -cardinol (0.22%), caryophyllene (0.16%) and cuminaldehyde (0.15%) were also identified but in less noticeable amounts (Table 1). Our results are in good agreement with the previous studies that have reported perillaldehyde and limonene as principal components of plants essential oil [13, 28, 30, 48]. The quantitative difference could be attributed to the harvest time, the origin of the plant, climatic, seasonal factors and period of the vegetative cycle.

3.1. Cholinesterase inhibition

The low level of acetylcholine in the brain is one of the causing factors of Alzheimer's disease, a progressive neuro-degenerative disorder associated with memory impairment and cognitive deficit.

Table 1

Chemical composition of the *A. leucotrichus* aerial parts oil.

Number	Components	Retention time	Percentage
1	α -pinene	4.44	5.74
2	β -pinene	5.02	2.26
3	Camphene	4.62	0.59
4	Myrcene	5.18	0.51
5	3-Carene	5.53	1.69
6	D-Limonene	5.86	23.33
7	3-Thujanone	6.78	0.7
8	Cumin aldehyde	8.71	0.15
9	Perillaldehyde	9.34	58.3
10	Perillalcohol	9.62	1.86
11	Acetic acid, (2 isopropenylcyclopentylidene)-, methyl ester	10.87	1.68
12	Caryophyllene	11.48	0.16
13	α -copaen-11-ol	12.83	0.34
14	Isolongifolan-8-ol	13.12	0.22
15	Globulol	13.49	0.34
16	α -cardinol	14.13	0.27
	Total		97.25

Currently, a therapeutic approach is followed according to the cholinergic hypothesis to treat Alzheimer's disease. This approach is based on the inhibition of cholinesterase enzymes (ChE) which catalyze acetylcholine hydrolysis to increase its level in the brain and thus improve the cholinergic functions in AD patients [19]. As shown in Table 2, the anticholinesterase activity of the *A. leucotrichus* and the individual main compounds of the essential oil were compared to Donepezil, used as a standard drug against Alzheimer's disease.

Essential oil and perillaldehyde have not exhibited an activity against the acetylcholinesterase. In contrast, limonene induced high acetylcholinesterase inhibitory activity with an IC_{50} of about 51.6 µg/mL. Essential oil showed also an interesting activity against BuChE (IC_{50} = 95.21 µg/mL). This oil appeared to be effective compared to inhibition results of Donepezil, a compound approved by the US Food and Drug Administration (US- FDA) for the treatment of moderate to severe Alzheimer's disease [45]. The most promising BuChE activity was observed with perillaldehyde (IC_{50} = 42.77 µg/mL), followed by limonene (IC_{50} = 66.7 µg/mL). Similar results were obtained in *E. globulus* showing satisfactory inhibitory activity against AChE with IC_{50} of 0, 1298 mg/ml [1]. This study is also focused on pure limonene showing a moderate activity against AChE and the IC_{50} value was about 0.5863 mg/mL. On the other hand, for the *C. limon* plant, despite the strong presence of limonene in its essential oil, the AChE inhibitory activity was lower with IC_{50} about 0.8499 mg/mL.

In another study, the ethanol extract from the fruits of *Pimpinella anisoides* (Apiaceae) has an interesting activity against both enzyme (AChE and BuChE) and the limonene, one of the major compounds has the lowest activity with the IC_{50} of 225.9 and 456.2 µg/mL for AChE and BuChE respectively [32]. Our results are better with a low value of IC_{50} for AChE and BuChE (51.6 and 66.7 µg/mL respectively). It should be noted that limonene has been reported as inactive by some authors [12].

For anti-butyrylcholinesterase activity, all samples have a high inhibitory activity and the lowest value of IC_{50} was obtained with perillaldehyde followed by limonene and essential oil. Anti-butyrylcholinesterase of the essential oil can be attributed to the strong presence of perillaldehyde and limonene (53.3% and 23.33% respectively). To our knowledge, no previous study reported butyrylcholinesterase inhibitory activity of essential oil of *A. leucotrichus* and perillaldehyde. [7] showed that the essential oil of *Rhanterium suaveolens* Desf rich in perillaldehyde is inactive against the two enzymes (AChE and BuChE) while the methanolic extract has a moderate inhibitory activity against AChE and a good butyrylcholinesterase inhibitory. Although, both major essential oil compounds have exhibited

Table 2

IC50 values for the inhibition of acetylcholinesterase (AChE), butyrylcholinesterase (BuChE) and the two Monoamine-oxidases isoforms (MAO-A and MAO-B) activities exhibited by *Ammodaucus leucotrichus* Coss. & Dur essential oil, reference chemical compounds.

IC50	AChE	BuChE	MAO		
			MAO-A	MAO-B	MAO-A + B
Essential oil, ug/mL	>1000	95.2 ± 15.0	112.5 ± 21.3	40.5 ± 3.8	53.4 ± 4.1
Limonene, ug/mL	51.6 ± 0.7	66.7 ± 12.6	>1000	>1000	>1000
Perillaldehyde, ug/mL	>1000	42.7 ± 4.8	159.1 ± 25.9	98.9 ± 7.2	100.4 ± 9.2
Donepezil, nM	95.6 ± 12.0	8600 ± 570	NA	NA	NA
^a Acorenone B µg/mL	40.8	10.9	NA	NA	NA
^a Niphogeton dissecta EO µg/mL	>1000	11.5	NA	NA	NA
Clorgyline, nM	NA	NA	7.1 ± 1.7	NA	NA
Deprenyl, nM	NA	NA	NA	59.1 ± 2.3	NA

NA = not applicable.

^a IC50 values determined under identical conditions for Niphogeton dissecta essential oil and its major constituent. [6].

an interesting inhibitory activity and the essential oil has a lower activity. This can be explained by the antagonistic effect among the components of the oil of *A. leucotrichus* [41].

3.2. MAO inhibition

The MAOs inhibitory effect of the *A. leucotrichus* essential oil, perillaldehyde, and limonene were evaluated and the results are represented in Table 2.

In our study, EO and perillaldehyde were able to inhibit MAO-A in a dose-dependent manner (1-1000 µg/mL) with IC₅₀ values of 112.5 and 159.1 µg/mL respectively. In comparison to clorgyline as an irreversible MAO-A inhibitor, the essential oil is much less active. With respect to the effect on MAO-B, the EO and perillaldehyde exhibited a high inhibitory activity with IC₅₀ values of 40.5 and 98.9 µg/mL respectively. On the other hand, for MAO-A + B, both samples cited above showed good inhibitory effect presented with the IC₅₀ values of 53.4 and 100.4 µg/mL, respectively, and no anti-MAOs activity was observed with limonene. From the obtained values of IC₅₀, it could be predicted that the EO and perillaldehyde are better inhibitors for MAO-B than MAO-A.

The highest MAOs inhibition was observed by the essential oil. The MAO-A inhibitors inhibit the catabolism of serotonin, norepinephrine and dopamine which lead to increase the levels of these neurotransmitters in the brain. They are effective in the treatment of depressions in elderly patients [53, 55].

The essential oil and perillaldehyde have an affinity for MAO-B. This enzyme is present with a high level in people affected by Parkinson's disease due to the malfunction in the dopaminergic system [53]. MAO-B is responsible for the catabolism of neurotransmitters amines; it metabolizes a dopamine in the basal ganglia. For this, the inhibition of this enzyme in Parkinson's patients conserve dopamine in the brain, which leads to relieve symptoms of the Parkinson's disease [9, 54].

The inhibition of MAOs by the essential oils is not well documented. Some studies have shown that the Myristicin which is an essential oil compound of nutmeg was able to inhibit rodent brain MAO activity [4]. Eugenol, another constituent of EO has been proven as an inhibitor of MAO-A and B [46].

To this fact, it is very important to point out that this study is the first report on the inhibition of cholinesterase and monoamine oxidase properties of the essential oil of *A. leucotrichus* and its major compounds. According to the BuchE and MAOs results of the EO of *A. leucotrichus*, it seems that this plant may have promising applications in the treatment of the Alzheimer's disease and neurodegenerative disorders.

4. Conclusion

The results presented in this study are the first information on the

anticholinesterase and anti-monoamine oxidase activities of *A. leucotrichus* C. & D. essential oil, collected from Algeria. The essential oil, as well as its main compounds, perillaldehyde and limonene have exhibited a global cholinesterase and monoamine oxidase inhibitory activity. A selectivity towards BuChE and the MAO isoform B is evidenced. A consequence of this dual inhibition capability is that consumption of *A. leucotrichus* may protect people against the Alzheimer's disease and neurodegenerative disorders without any side effect as observed from the traditional practice. Yet, further studies, particularly *in vivo* tests, are needed to understand *A. leucotrichus* C. & D. essential oil activity in biological systems.

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Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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