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Extraction and characterization of essential oil of *Lavandula dentata* L.: Evaluation of its cytotoxicity and anticonvulsant activities on an epileptic model

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Abstract
The Labiatae (Lamiaceae, Mentaceae) plant family, includes many shrubs and herbs as well as trees and vines, is economically significant. In the present study, aerial portions of *Lavandula dentata* L. (1753) were collected throughout the vegetative phase and stored in the herbarium for identification, authentication, and description. The analysis was carried out utilizing gas chromatography-mass spectrometry. The quantitative data were evaluated using peak area normalization without correction factors. Moreover, in vitro, cytotoxicity assay was examined, and anticonvulsant activity was tested in vivo using an epileptic rat model. The sulforhodamine B cell cytotoxicity assay was performed in vitro to assess cellular viability or cytotoxicity produced by the ethanolic extract and oil of *L. dentata* against HepG2 and Vero cells. In addition, seizure intensity scores and behavioral assessments were evaluaed and revealed that both essential oil and *L. dentata* extract reduced seizures, decreased distance and latency time in open field experiment, increased both grooming, rearing, and frequency of ambulation. Thus, the ethanolic extract or essential oil of *L. dentata* influences various behavioral domains and reduces depression-like symptoms in rats by inhibiting convulsion and seizure activity.

Keywords: *Lavandula dentata* L – GC-MC – Cytotoxicity- Epilepsy- Seizure and Behavioral

1. Introduction

Natural products are common and gaining popularity, and the use of plant extract, essential oil(EO), and fixed oil in industrial applications is increasing. Phytochemicals have been a crucial source of drugs since ancient times. Phytochemicals play a significant role in developing new synthetic and manufactured drugs in various medical fields. Currently, natural products are the main components of approximately 50% of useful drugs. When compared to conventional medicine, these medications typically exhibit greater medicinal value and lower adverse effects. [1]. Flavonoids may have a moderating function in treating neurodegenerative illnesses, which can affect cellular oxidative processes in the central nervous system [2]. Correspondingly, Lamiaceae is considered an attractive plant family with a lot of shrubs and herbs, and seldom trees. The species of this family enjoy vital economic and horticulture

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importance [3]. Globally, from two-hundred forty to three hundred genera 7200–7500 species make up the mint family[4]. Due to their fragrant properties and ease of cultivation, several Lamiaceae members are farmed in the desert of North Africa and the cooling region of Asia and Europe[5, 6]. Thousands of floral species in this family are commonly used in landscapes and butterfly gardens [5]. Essential oil (EO) is released by the glandular hairs on the aerial vegetative and reproductive organs in most family members [7]. *Lavandula* is a genus native to the Mediterranean region and can treat digestive disorders and kidney diseases [8]. Members of the genus produce large amounts of phytochemicals [9]. *Lavandula dentata* is one of five lavender species that grow naturally in Saudi Arabia; the species is thought to represent the origin of the genus. The species are distributed in the mountains of Abaha, Asir, and Al-Taif regions as herbaceous wild plants.

Certainly, some antiepileptic drugs have been recognized by Shannon and Love [10] as potentially causing cognitive impairment in healthy individuals, besides sharing in the cognitive abnormalities seen in patients with epilepsy disorder. Therefore, the current investigation's aim is the extraction, isolation, and description of *L. dentata* L., and the evaluation of its cytotoxicity and anticonvulsant activity.

2. Materials and Methods:

2.1. Lavandula dentata L. Taif, Saudi Arabia:

2.1.1. Collection of the plant:

The stem and leaves of *Lavandula dentata* L were obtained during the vegetative stage from Taif region, Saudi Arabia, in May 2018. A voucher specimen was deposited in the herbarium, where it was identified, authenticated, and described with the aid of Agricultural Research Centre, Dokki, Cairo, Egypt; as follows: The general climate of Taif region, Saudi Arabia is Upland region, which distinguished by rainy weather. It is characterized by a cooling temperature in winter (10-12°C) and worm weather in summer (21-28°C). Above sea level at 1,879 m Taif is located on the Hejaz Mountains slopes, that considered a vital portion of the Sarawat Mountains[11].

2.1.2. Morphological Identification & Classification:

The systematic position of *Lavandula dentata* L. (1753) in A. Engler system [12], whereas, the latter is a phylogenetic system of plant classification, adopted in the Egyptian Flora books, and major herbaria in Egypt [13-15].

2.2. Extraction and characterization of *Lavandula dentata* L:

About 250 gm of the whole dried plant material was coarsely milled and extracted with 70% ethanol extraction bath at room temperature till exhaustion (3 times). The pooled ethanol extract were evaporated under vacuum at 45 ^{0}C till evaporation of the organic solvent, part of the remaining aqueous part was frozen, and dried to produce 47g of greenish residue, and will be used as an ethanolic extract treatment group.

2.2.1. Essential oil extraction using GC/MS Assay:

Another 1 Kg of dried plant parts were ground into tiny bits and hydrodistilated for three hours using a Clevenger-style equipment in order to isolate the essential oil. In a nutshell, the plant was submerged in water and brought to a boil before the essential oil and water vapor evaporated and were eventually collected in a condenser. After being separated, the distillate was dried on anhydrous sodium sulfate. The extracted oil was kept cold until gas chromatography/mass spectrometry (GC/MS) analysis. The yield of essential oil was analysed by GC-MS analysis using Shimadzu GCMS-QP2010 (Tokyo, Japan) at Ain Shams University, Faculty of Pharmacy in Cairo, Egypt,

and record mass spectra. Briefly, the temperature was preserved at 45°C for 2 minutes in the starting column, then the temperature was raised to three hundred °C for an average of 5°C per minute and preserved for 5 minutes. An injector temperature was 250°C whereas the helium flow reached 1.41 ml/min. For registering all mass spectra some conditions must be performed such as 70 ev voltage of ionization, 200°C', and current emission filament with 60 mA and ion source. Then the split mode of injections was carried out on a dilated sample (1% v/v; split ratio: 1:15). For identifying the chemical composition of the component we compared their retention indices concerning alkanes (C8–C20) and mass spectra with authentic standards from the NIST/EPA/MSDC Mass Spectral Database. The base of the quantitative data without the correction of the unused factors was peak area normalization [16-18].

2.2.2. Estimation of Total Phenolic and Flavonoids

Regarding the gallic acid standards for total phenolic compounds [19]. Briefly, gallic acid is a solution of methanol (1 mg/ml) was prepared. After that, we prepared 7 serial dile Cons (1000, 800, 600, 400, 200, 100 & 50 µg/ml). On the other hand, rutin standards for total flavonoids are performed [20]. We prepared the sample in 3mg/ml of methanol. The seven typical samples and six duplicates of a specimen were piped in the grid's holes for the estimate of total phenolics and gallic acid standards. The measurements were taken at 630 nm. Furthermore, six replicates of the seven typical samples and one specimen were piped in the grid's holes for the estimate of total flavonoids and rutin, and the measurements were made at 420 nm.

Tests for cytotoxicity and cultivating cells (*in vitro*):

Cell line for carcinoma of the liver (HepG2) was provided by Nawah Scientific Inc. in Mokatam, Cairo, Egypt. 10% inactivated fetal bovine serum as well as 100 mg/mL streptomycin was added by Dulbecco's Modified Eagle's Medium (DMEM) and also supplemented 100 units/mL penicillin for maintaining the cellular structure at 37 °C in a humidified 5% (v/v) CO_2 surroundings. Considerably, the viability of cells and toxicity of cells caused by drugs can be investigated by the Sulforhodamine B (SRB) cell cytotoxicity test. This technique makes use of the bright-pink aminoxanthene dye SRB, that responsible for protein binding stoichiometrically in a slightly acidic atmosphere and can be taken out in basic surroundings. Therefore, the quantity of bound dye can be utilized as a measurement for cell mass as a standard and its value could be calculated at wavelength 565 nm for measurement proliferation of cells [21, 22]. Shortly, the cellular viability could be determined by the SRB technique: 96-grid's hole was treated in complete habitat for all day with aliquots of hundred microlitre cell suspension of green monkey kidney (Vero, 5x103 cells) or hepatocellular carcinoma (HepG2; 5x103 cells) cell lines. Another addition of standard equal one- hundred microlitre with serial dilutions of *Lavanduladentata* L. ethanolic extract or its essential oil (0.01, 0.1, 1.0, 10 &100 ug/ml) was added to the cells for treatment. After the cells were exposed to the extract for seventy-two hours, the fixation occurred by the addition of one-hundred- fifty microlitre of ten percent of the solution of TCA to the cultural medium for 60 minutes at a temperature of four °C. The next step is washing with distilled water 5 times to remove the excess of the TCA. By adding seventy microlitres of SRB (0.4% w/v) the next step was incubation for 10 minutes at normal temperature. After three 1% CH_3COOH washes, the plates were dried for 12 hours. When we added one-handred-fifty microlitre of TRIS (10mM), the SRB protein-bound dissolved and also the registration of wavelength was at 540nm a BMG LABTECH®-FLUO star Omega microplate reader (Ortenberg, Germany).

2.3. Seizure and Behavioral assays (*in Vivo*):

2.3.1. Experimental animals:

Animals were purchased from National Research Centre, Eldoki, Giza, Egypt a total of 40 mature male Dawley rats, weighing between 150 - 180 g, were acquired. They were kept in separate metabolic cages with a 12-hour light/dark cycle in a regulated environment (23± 1°C; humidity, 55± 5%). Dietary requirements were freely available. The Beni-Suef University animal research ethics committee authorized all methods, which were carried out following the rules for the care and use of laboratory animals. The committee's permission number was BSU/FS/2021/021/138.

2.3.2. Chemical component :

The supplier of pilocarpine hydrochloride (PILO) (99%) was Acros Organics in New Jersey, USA. In addition, Nanjing Chemical Reagent Co., Ltd. (Nanjing, China) was the supplier of diazepam, chloral hydrate, and methylscopolamine. Sanofi Aventis CO., Depakine Chrono® 500mg.

2.3.3. Induction of Epilepsy (*in vivo*):

The method of Turski*et al.* [23]& Abdel-Reheim*et al.*[24]was used to experimentally induce epilepsy. Before receiving an intraperitoneal dose of pilocarpine hydrochloride (300mg/ Kg.B.wt), the rats under investigation take a 30-minute of 1 mg/kg methylscopolamine to infused intraperitoneally. The behavior of the animal was then examined for signs of seizure activity using a set of standards. These requirements for modeling success include the following: indications of an epileptic seizure (sluggishness, salivation, tremors, convulsions, etc.). After receiving pilocarpine hydrochloride, the experimental rats exhibited these behaviors for 120 minutes, but rats in the control group behaved as usual. The rats were diagnosed with seizure episodes when they consistently displayed seizure activity in a general way without exhibiting the activity of control rats during each phase. The rats exhibited seizures for a duration of one hour, with attacks happening every two to five minutes. Diazepam (4 mg/kg, i.p.) was injected every 20 minutes to stop the activity of seizures at the time of need. The identical approach was used for the normal rats, with the exception that pilocarpine was replaced with an injection of phosphate-buffered saline (PBS, pH 7.4; 0.2 ml/rat), and diazepam was given one hour later.

2.3.4. Animal grouping:

In general, the current experiment included 40 mature male Dawley rats, weighing between 150 - 180 g. They were split up into the following five groups (8 rats/group):

(1) **Control group (C):** received routine food, unrestricted access to clean water, and oral ingasterically intubed at periods equivalent to the other groups (PBSS, pH 7.4; 0.2 ml/rat).

(2) **The epileptic control** group (EP): received an i.p. injection of pilocarpine hydrochloride (300 mg/kg bw), then fed orally via gastric intubation with PBSS (pH 7.4; 0.2 ml/rat) by intra- abdominal injection at durations that were consistent with those of the other groups.

(3) **The Depakine®-treated epileptic group:** received an i.p. injection of pilocarpine hydrochloride (300 mg/kg bw) as had been mentioned. After that, rats were given 500 mg/kg bw. of Depakine® dissolved in PBS (pH 7.4; 0.2 ml/rat) then fed orally via gastric intubation for equal periods at the same time as other groups.

Depakine treatment was carried out two times a week for successive four weeks.

(4) **Pure essential oil of *L. dentata*-treated epileptic group:** received an i.p. injection of pilocarpine hydrochloride (300 mg/kg bw), and it was subsequently fed orally with 100 µg of *L. dentata* oil per kg of body weight of rats, suspended in PBSS (pH 7.4; 0.2 ml/rat). By oral ingasterically intubation method for equal periods at the same

time as other groups, oil administration was carried out every day for successive four weeks.

(5) ***L. dentata*** **ethanolic extract-treated epileptic group:** received an i.p. injection of pilocarpine hydrochloride with a dose of 300 mg/kg, then fed an oral gastric intubation dose containing 300 mg/ kg. bw. of dissolved *L. dentata* in PBSS (pH 7.4; 0.2 ml/rat). By oral ingasterically intubation method for equal periods at the same time as other groups, feeding was carried out every day for successive four weeks.

2.3.5. Assessment of Seizure and Behavior Alterations:

The scale modification of values registered for the various stages [25] was used to evaluate the seizure intensity value in the following phases: **phase(0):**no response; **phase(I):** (twitching of the eye, ear, and face); **phase(II):** axial convulsive waves through the body); **phase(III):** myoclonic and axial convulsive waves through the body; **phase(IV):** generalized colic convulsions that turn over into the side position); **phase(V):** generalized convulsions with tonic extension episode and status epileptic) and phase **VI:** mortality.

Every behavioral examination, such as the forced swimming (FS), hot plate (HP), and open-field test (OFT), was conducted at two different times six hours after the lights were turned on or off, or at 3:00 p.m. and 03:00 a.m., successively. The animals were placed into the isolated chamber at least thirty minutes prior to every examination to conduct the behavioral experiments there. Rats that displayed unexpected recurrent seizures (SRSs) one hour prior to the commencement of the examinations were not allowed to continue with the experiment. Rats with disorders of OF, FS, and HP were observed also their behavior was noted.

2.3.5.1. Open-field test (OFT):

The Open Face Test (OFT) is a behavioral assessment that has been confirmed. It is an effective way to evaluate exploration and motor skills as well as anxiety levels in stressful or frightening settings, but it is not a model of anxiety disorders [26]. The gray polystyrene Plexiglas box was the open-field apparatus. It was separated into two zones: the inner square (center) and the outside square (periphery), which each rat would discover to be equal squares. For the rat, the central area was unpleasant. An entry into the corresponding zone was determined by the rat placing all four paws there. The following were the standard measures that were computed: The first four factors are latency time, followed by grooming count, rearing count, and ambulation frequency. After being put in the middle of the box, each rat was given five minutes to investigate. To remove unfavourable smell we washed with 0.1% acetic acid solution after each test.

2.3.5.2. Hot Plate (HP):

The hot plate test is an accepted model utilized to assess a compound's antinociceptive (acute pain model) performance concerning short thermally sensory perception]27[.In a nutshell, the apparatus was made up of an electrically warmed platform and an exposed Plexiglas tube that served as the animals' confinement. A temperature range of 56.0 ± 0.1 °C was chosen. A stopwatch was used to time how long it took for the rats to hop off, shake their hind paws, or lick their front or rear paws after they were placed on the warming surface. To ascertain whether the medication had a therapeutic impact, the time it took to respond to sucking was accepted as a pain response time.

2.3.5.3. Forced Despair Swim (FDS) Test:

A standard forced despair swimming (FDS) test was used to assess despair-like behavior [28, 29]. This test is useful for assessing depression-like performance as well as for antidepressant drug screening. Almost all antidepressants that are currently on the market can be acutely administered to reverse the increase in immobility time required for this test. The test was conducted in an obvious, transparent tube. It was filled with 24 °C tap water until it was 30 cm from the bottom. Rat water was

substituted for rat water in the device. On the first day, there were two swimming experiments, lasting 15 minutes each and 5 minutes on the second. The rat was dried and heated for ten minutes using an electric heater following each test. Two experienced experimenters who were not informed of the treatment conditions observed behavior on the second day (test). Excessive immobility, in which the rat only moves to maintain his snout above water to avoid drowning, is a sign of a depressive mood in animals. The rat was immobile for a set amount of time when it either stayed still or moved only as much as was required to maintain its head above water, and was measured in terms of seconds.

2.4. Statistical Analysis:

The method of Tukey-Kramer was utilized for post-Hoc analysis of the data for comparison of different sections with one another. There were findings in the form of mean ± SD. The statistical significance interval is defined for all the data in the form of $P < 0.05$. We use (the SPSS) version 20 program to analyze all of the data (IBM Corp., 2011).

3. Results and Discussion:

The plant material was collected, and its systematic position as *L. dentata* L. was identified using A. Engler system [12], for phylogenetic plant classification. This system is adopted in Egyptian flora books and major herbaria in Egypt [13-15] and is as follows: **Division**: Angiospermae; **Class**: Dictoyldoneae; **Subclass**: Sypetalae; **Order**: Tubiflorae (Solanales); **Suborder**: Boraginineae; **Family**: Labiatae (Lamiaceae, Mentaceae); **Subfamily**: Lavanduloideae; **Genus**: *Lavandula* and **Species**: *Lavandula dentata L.*

Gas chromatography–mass spectrometry data from total EO components identified approximately 95.73% of the constituents (Table 1). The oil contained various monoterpenes, including oxygenated monoterpenes (81.94%), monoterpene ketones (58.29%), monoterpene aldehydes (49.5%), monoterpene esters (31.93%), monoterpene ethers (7.85%), and monoterpene hydrocarbons (4.59%). Other constituents included phenols (52.1%) and diterpenes (2.9%). Aromatic hydrocarbons were poorly represented (1.2%). Moreover, the unknown content of *L. dentata* extract was 0.752 ± 0.049 at an absorbance of 630 nm (Table 2). Substitution in the linear regression equation suggested a phenolic content of 261.04 ± 16.03 µg/ml. Therefore, the total phenol (gallic acid equivalents) was 87.01± 5.3 mg/g extract (Table 4).

Estimation of total flavonoids (Table 4) showed unknown content in *L. dentata* extract of 0.263 ± 0.019 at an absorbance of 420 nm. Total flavonoid content by linear regression was 74.77 ± 6.35 µg/ml; therefore, average total flavonoid content (rutin equivalents) was 24.92 ± 2.1 g. Per 100 g of extract, the total polyphenolic content was proportional to gram weight equivalents of gallic acid (%). Constituent of phenol accounted for a relative fifteen percent of *L. dentata* extract [8]. They accounted for the characteristics of the biology of the extract of hydroalcoholic in inflammation of the experimental rat [30]. Disparities could be caused by qualitative and quantitative differences in polyphenol content.

EO of *L. dentata* contained many groups of chemicals (Tables 1–2). Forty-eight components were registered, which represented 96.15% of the sample. Correspondingly, the profile of the floral family, oxygenated monoterpenes (81.94%) were the most prevalent, then came hydrocarbons monoterpene (4.59%), sesquiterpenes (3.62%), aromatic hydrocarbons (1.20%), monoterpene ethers (1.05%), monoterpene esters (1.02%), monoterpene ketones (0.88%), phenols (0.72%), monoterpene aldehydes (0.71%), and diterpenes (0.42%). The main compound was (1S-(4beta, 1Alpha & 2alpha)) 2-cyclohexane diol(46.09%), -1-isopropenyl-4-methyl-1, followed by menthone

(18.69%), fenchol (9.42%), borneol (3.35%), renal (1.72%), cis-dihydro-occidental (1.49%), linalool (1.4%), p-Cymene (1.04%), and trans-linalool oxide (1.03%). Six compounds were identified each accounting for 3.65%. The 33 remaining volatile organic compounds accounted for 8.27% of the oil.

Previous reports stated the construction of the Essential oil (EO) based on multiple causes like geographical location, genetic variability, biotic and abiotic stresses, plant age, phonological stage and chemotype, time of harvest [31], and methods of drying and extracting oil [32]; hence, there are differences in constituent composition. Thus, the constituent contents observed in the present study differ from those described in some previous reports mainly in constituents such as monoterpene hydrocarbon content (4.59%), which was greater in other studies: 17.89% in *L. multifida* from Tunisia [33], 17.60% in aerial parts of *L. dentata*[34], 15.64% in *L. dentata* from Mexico [35], and 14.80% in *L. dentata* inflorescence [34].

In contrast, higher levels of monoterpene hydrocarbons have been reported in other studies: 0.23% in *L. dentata* from Palestine[36], 0.25% in *L. dentata* [33], and2.44% in *L. stoechas*[33]. Aromatic hydrocarbons in the present *L. dentata* oil accounted for 1.20% (Taif, SA) of the total content, which was less than 1.77% in *L. multifida* from Tunisia [33] and more than 0.04% in *L. dentata* [33], 0.06% of *L. stoechas*[33], and0.5% in the aerial parts and inflorescence of *L. dentata* [34].

Table (1): Comparison between chemical compositions of the essential oil (%) of *Lavandula spss.*

Chemical Compound/ Family	*L. dentate* ***(Taif, SA) Present***	*L.dentata*(Tunisia) [33]	*L.stoechas* (Tunisia) [33]	*L.multifida* (Tunisia) [33]	*L. dentata* (Palestine) [36]	*L. dentata* (Mexico) [35]	*L.dentata*(inflorescence) [34]	*L. dentata* (aerial part) [34]
Monterpene Hydrocarbons	4.59	0.25	2.44	17.89	0.23	15.64	14.80	17.60
Aromatic Hydrocarbons	1.20	0.04	0.06	1.77	0.00	0.00	0.50	0.50
Oxygenated Monoterpene	81.94	81.94	81.94	81.94	81.94	81.94	81.94	81.94
Phenols	52.10	52.10	52.10	52.10	52.10	52.10	52.10	52.10
Monoterpene Esters	31.93	31.93	31.93	31.93	31.93	31.93	31.93	31.93
Monoterpene ketones	58.29	58.29	58.29	58.29	58.29	58.29	58.29	58.29
Monoterpene Aldehydes	49.50	49.50	49.50	49.50	49.50	49.50	49.50	49.50
Monoterpene ethers	7.85	7.85	7.85	7.85	7.85	7.85	7.85	7.85
Diterpenes	2.90	2.90	2.90	2.90	2.90	2.90	2.90	2.90
Total Identified	**95.73**	**89.66**	**100.00**	**99.98**	**99.19**	**93.96**	**98.90**	**99.20**

L. dentata in the present study showed the highest content of oxygenated monoterpene (81.94%), which was more than 58.29% and 52.10% in *L.multifida* and *L. dentata* from Tunisia, respectively [33],49.50% in *L. dentata* [36], 31.93% in *L. stoechas*[33], 7.85% in *L. dentata* from Mexico [35], and 3.40% and 2.90% in *L. dentata* aerial parts and inflorescence, respectively [34]. The present phenolic compounds accounted for 0.72% of the total content, which was less than 1.33% and 0.82% for *L. multifida* and *L. dentata* from Tunisia, respectively [33] and higher than 0.01% in *L. dentata*[36] and 0.03% in *L. stoechas*[33]. *L. dentata* from Mexico [35] and *L. dentata* inflorescence and aerial parts [34] exhibited no phenolic compounds.

Monoterpene esters in the present study of *L. dentata* (Taif, SA) were poorly represented at 1.02%, which was less than 64.45% in *L. stoechas*[33], 44.20% in *L. dentata* [36], and 28.83% and 10.56% in *L. dentata* and *L. multifida* from Tunisia, respectively [33]. In contrast, *L. dentata* from Mexico [35] and inflorescence and aerial parts of *L. dentata*[34] contained no monoterpene esters. Monoterpene ketones were also poorly represented in *L. dentata* (Taif, SA) at 0.88%, which was more than *L. stoechas* (0.14%) and *L. multifida* (0.60%) from Tunisia [33] but less than 1.88% in *L. dentata* [35], 1.90% in *L. dentata*[36], 2.34% in *L. dentata* [33], and 30.40% and 30.8% in *L. dentata* aerial parts and inflorescence, respectively [34].

Monoterpene aldehydes made up 0.71% of *L. dentata* (Taif, SA) oil, a value greater than *L. stoechas* and *L. dentata* from Tunisia (0.06% and 0.11%, respectively) [33]. Further, this value was less than that in *L. multifida* (1.77%; [33]. *L. dentata* from Palestine [36], *L. dentata* from Mexico [35], and *L. dentata* inflorescence and aerial parts [34] produced no monoterpene aldehydes. Monoterpene ethers (1.05%) of *L. dentata* (Taif, SA) exceeded the content in *L. stoechas* (0.10%) and *L. dentata* (0.54%)from Tunisia [33] but was less than 1.40% in *L. dentata*[36], 1.46% in *L. multifida*[33], and 40.40% and 46.30% in *L. dentata* aerial parts and inflorescence, respectively [34]. The highest level of esters was 68.59% for *L. dentata* from Mexico[35].

Table (2): Comparison between individual chemical compositions of the essential oil (%) of *Lavandula spss.*

Compound	*L. dentate (Taif, SA) Present*	*L.dentata*(Tunisia) [33]	*L. stoechas* (Tunisia) [33]	*L.multifida* (Tunisia) [33]	*L. dentata* (Palestine) [36]	*L. dentata* (Mexico) [35]	*L.dentata*(inflorescence) [34]	*L. dentata* (aerial part) [34]
Monterpene Hydrocarbons								
Tricyclene	0.04	0.02	0.67	0.11	N.D.	N.D.	N.D.	N.D.
α-Thujene	N.D.	0.02	0.08	3.83	N.D.	N.D.	N.D.	N.D.
α-Pinene	0.50	0.06	0.96	0.45	0.10	2.87	3.70	3.70
Camphene	0.92	0.01	0.33	10.06	N.D.	N.D.	1.30	1.20
Sabinene	N.D.	0.01	0.02	0.95	0.10	N.D.	0.70	0.80
Santolina triene	N.D.	N.D.	N.D.	N.D.	0.02	N.D.	N.D.	N.D.
Beta-Phellandrene	0.11	N.D.	N.D.	N.D.	0.01	N.D.	N.D.	N.D.
β-Pinene	0.73	0.01	0.32	0.34	N.D.	11.53	5.30	6.10
Limonene	0.04	0.08	0.03	0.10	N.D.	N.D.	3.20	5.20
D-Limonene	2.25	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Citronelol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.30	0.30
Terpinolene	N.D.	0.04	0.03	2.05		1.24	N.D.	N.D.
Total	4.59	0.25	2.44	17.89	0.23	15.64	14.50	17.30
Aromatic Hydrocarbons								
p-Cymene	1.04	0.04	0.06	1.77	N.D.	N.D.	0.50	0.50
o-cymene	0.16	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Total	1.20	0.04	0.06	1.77	0.00	0.00	0.50	0.50
Oxygenated Monoterpene								
1-Octen-3-ol	0.02	0.13	0.02	0.25	N.D.	N.D.	N.D.	N.D.
Myrtenal	1.72	0.48	0.46	0.80	0.40	0.55	0.60	1.10
Linalool	1.40	47.30	20.25	50.05	40.80	1.63	0.30	0.30
β-Thujone	0.21	0.02	8.97	0.14	N.D.	N.D.	N.D.	N.D.
(1S-(1Alpha,2alpha,4beta))-1-isopropenyl-4-methyl-1,2-cyclohexanedi	46.09	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

Compound	*L. dentate (Taif, SA) Present*	*L.dentata*(Tunisia) [33]	*L. stoechas* (Tunisia) [33]	*L.multifida* (Tunisia) [33]	*L. dentata* (Palestine) [36]	*L. dentata* (Mexico) [35]	*L.dentata*(inflorescence) [34]	*L. dentata* (aerial part) [34]
ol								
Borneol	3.35	0.07	0.07	0.21	0.50	N.D.	N.D.	N.D.
Plinol C	N.D.	N.D.	N.D.	N.D.	2.60	N.D.	N.D.	N.D.
Lavandulol	N.D.	0.02	0.23	1.29	N.D.	N.D.	N.D.	N.D.
3-Octanol	N.D.	N.D.	N.D.	N.D.	0.10	N.D.	N.D.	N.D.
Menthone	18.69	0.04	0.02	0.37	N.D.	N.D.	N.D.	N.D.
Terpinene-4-ol	0.04	0.82	0.09	0.24	0.80	0.57	N.D.	N.D.
α-Terpineol	0.55	0.67	0.97	0.26	4.30	1.11	0.40	0.50
Myrtenol	0.03	0.12	0.02	0.27	N.D.	1.01	0.90	0.80
δ-Terpineol	N.D.	1.47	0.03	1.64	N.D.	1.83	N.D.	N.D.
trans-Pinocarveol	0.09	N.D.	N.D.	N.D.	N.D.	1.15	0.70	0.70
Nerol	N.D.	0.04	0.53	2.01	N.D.	N.D.	N.D.	N.D.
Geraniol	N.D.	0.02	0.25	0.25	N.D.	N.D.	N.D.	N.D.
Fenchol	9.42	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Dehydrolinalool	0.33	tr	tr	N.D.	N.D.	N.D.	N.D.	N.D.
(E)-Isoeugenol	N.D.	tr	tr	0.27	N.D.	N.D.	N.D.	N.D.
Total	81.94	52.10	31.93	58.29	49.50	7.85	2.90	3.40
Phenols								
Thymol	0.10	0.79	0.01	0.20	N.D.	N.D.	N.D.	N.D.
Carvacrol	0.62	0.03	0.02	1.13	0.01	N.D.	N.D.	N.D.
Total	0.72	0.82	0.03	1.33	0.01	0.00	0.00	0.00
Monterpene Esters								
bornyl formate	0.15	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Fenchyl acetate	0.78	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Linalyl acetate	N.D.	28.65	64.30	7.30	42.10	N.D.	N.D.	N.D.
Hexyl ethanoate	N.D.	lptol	N.D.	N.D.	0.40	N.D.	N.D.	N.D.
Lavandulyl acetate	N.D.	0.14	0.02	0.12	0.40	N.D.	N.D.	N.D.
P-Menth-8-en-1-olacetate	N.D.	N.D.	N.D.	N.D.	1.30	N.D.	N.D.	N.D.
Methyl citronellate	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.30	0.30
Bornyl acetate	0.08	0.02	0.08	3.03	N.D.	N.D.	N.D.	N.D.
α-Terpenyl acetate	0.01	0.02	0.05	0.11	N.D.	N.D.	N.D.	N.D.
Total	1.02	28.83	64.45	10.56	44.20	0.00	0.30	0.30
Monoterpene ketones								
Fenchone	N.D.	tr	0.03	0.20	0.10	N.D.	15.80	13.40
Verbenone	0.41	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Camphor	0.15	2.32	0.04	0.30	1.80	1.03	15.00	17.00
Carvone	0.32	0.02	0.07	0.10	N.D.	0.85	N.D.	N.D.
3-octanone	N.D.	0.90	0.02	0.24	N.D.	N.D.	N.D.	N.D.
Total	0.88	3.24	0.16	0.60	1.90	1.88	30.80	30.40
Monoterpene Aldehydes								
Neral	N.D.	0.03	0.03	1.61	N.D.	N.D.	N.D.	N.D.
cumenal	0.13	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
a-Campholenal	0.58	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Geranial	N.D.	0.08	0.03	0.16	N.D.	N.D.	N.D.	N.D.
Total	0.71	0.11	0.06	1.77	0.00	0.00	0.00	0.00
Monoterpene ethers								
1,8-Cineole	N.D.	0.44	0.04	0.19	1.40	68.59	46.30	40.40
cis-Linalool oxide	0.02	0.02	0.05	1.23	N.D.	N.D.	N.D.	N.D.

Compound	*L. dentate (Taif, SA) Present*	*L.dentata*(Tunisia) [33]	*L. stoechas* (Tunisia) [33]	*L.multifida* (Tunisia) [33]	*L. dentata* (Palestine) [36]	*L. dentata* (Mexico) [35]	*L.dentata*(inflorescence) [34]	*L. dentata* (aerial part) [34]
trans-Linalool oxide	1.03	0.08	0.01	0.04	N.D.	N.D.	N.D.	N.D.
Total	1.05	0.54	0.10	1.46	1.40	68.59	46.30	40.40
Diterpenes								
Andrographolide	**0.42**	**N.D.**	**N.D.**	**N.D.**	**N.D.**	**N.D.**	**N.D.**	**N.D.**
Sesquiterpenes								
β-Caryophellene	N.D.	0.14	0.09	2.13	1.90	N.D.	0.30	0.70
α-bisabolene	0.03	N.D.	N.D.	N.D.	N.D.	N.D.	0.30	0.70
β-selinene	0.59	N.D.	N.D.	N.D.	N.D.	N.D.	0.90	1.00
α-selinene	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.60	1.20
β-Farnesene	N.D.	N.D.	nr	0.13	N.D.	N.D.	N.D.	N.D.
γ-Gurjunene	0.01	0.04	0.18	0.32	N.D.	N.D.	N.D.	N.D.
Germacrene-D	N.D.	0.11	0.02	0.84	N.D.	N.D.	0.90	2.40
2-Carene	N.D.	N.D.	N.D.	N.D.	0.02	N.D.	N.D.	N.D.
1,3,8-p-Menthatriene	N.D.	N.D.	N.D.	N.D.	0.03	N.D.	N.D.	N.D.
Bicyclogermacrene	N.D.	3.40	0.02	0.14	N.D.	N.D.	N.D.	N.D.
Cuparene	0.02	tr	0.02	0.54	N.D.	N.D.	N.D.	N.D.
γ-Cadinene	N.D.	0.13	0.03	0.20	N.D.	N.D.	N.D.	N.D.
ὸ-Cadinene	N.D.	0.02	0.02	0.43	N.D.	N.D.	N.D.	N.D.
Nootkatene	0.53	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
cis-dihydro-Occidentalol	1.49	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Curcumene	0.03	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
8-Isopropenyl-1,3,3,7tetramethyl-bicyclo[5.1.0]oct-5-en-2-one	0.31	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Cadalene	0.24	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Sesquisabinene hydrate	0.14	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
alpha-alaskene	0.21	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Elemol	N.D.	0.04	0.02	0.14	N.D.	N.D.	N.D.	N.D.
Caryophyllene oxide	0.02	0.26	N.D.	0.10	N.D.	N.D.	0.60	0.90
T-Cadinol	N.D.	0.04	0.08	0.41	N.D.	N.D.	N.D.	N.D.
α-Eudesmol	N.D.	0.34	0.26	0.35	N.D.	N.D.	N.D.	N.D.
Cadinol	N.D.	0.08	0.03	0.43	N.D.	N.D.	N.D.	N.D.
epi-α-Cadinol	N.D.	0.03	0.02	0.15	N.D.	N.D.	N.D.	N.D.
Total	3.62	4.63	0.79	6.31	1.95	0.00	3.60	6.90
Total Identified	**95.73**	**89.66**	**100.00**	**99.98**	**99.19**	**93.96**	**98.90**	**99.20**

The current *L. dentata* (Taif, SA) oil was the only extract that showed diterpene content (0.42%) (Table 3). Moreover, the sesquiterpene content of the present *L. dentata* (Taif, SA) oil (3.62%) exceeded the 0.79% content in *L. stoechas*[33], 1.95% in *L. dentata*[36], and 3.60% in *L. dentata* inflorescence[34]. However, the content was greater in *L. dentata* at 4.63% [33], *L. multifida* at 6.31% [33], and aerial parts of *L. dentata* at 6.90% [34]. *L. dentata* from Mexico [35] had no

sesquiterpene content. Among the more important and effective compounds (Table 3),linalool (1.42%) is a monoterpene in the EO of coriander. The N-methyl-D-aspartate (NMDA) receptor is considered a vital competitive antagonist that displays antitumor and anticardiotoxic activity.

PPARα ligand is the compound that is responsible for the reduction of plasma triglyceride rate and modulates the hepatic determination of the genes working on or off and the quantification of the entire metabolites in the plasma [37, 38]. Further, linalool may act as a nonsteroidal anti- inflammatory agent (Chu and Kemper 2005) and display neuroprotective properties associated with the inhibition of NMDA glutamate receptors[36]. Moreover, borneol, which accounted for 3.35% of the present oil content, at this time is a naturally occurring bicyclic monoterpene that has analgesic and anesthetic properties in conventional Chinese medication. Borneol has an EC_{50} of 248 μM and increases GABA receptor activation. Borneol makes direct stimulation to GABAA receptors with high doses (>1.5 mM), resulting in maximal response of GABA (84%). This feature revealed a weakening action of the agonist. At α1β2γ2L GABAA receptors, borneol generates a positive modulation of Cl conductance dose that is stimulated by low-dose GABA [39] (Table 3). Moreover, thymol (a monoterpene phenol) *L. dentata* (0.1%) is primarily found in EO-represented plant isolation related to a family of Lamiaceae. Thymol has antioxidant, anti-inflammatory, antibacterial, and antifungal properties [40]. Despite an IC50 of 1.32 mM, β-pinene, a significant turpentine component found in *L. dentata* (0.7%), inhibits the spread of the viral bronchitis virus [41, 42]. The activities of the antimicrobial and bactericidal are possessed by β-Pinene [43].Andrographolide represents about 0.42% of the EO.Andrographolide is a bicyclic diterpenoid lactone produced by *Andrographispaniculate*. This small antagonist for NF-κB activation covalently modifies cysteine 62 of p50. Andrographolide can reduce the stimulation of NF-κBg during the activation of endothelial cells. This role inhibits leukocyte adherence mediated by the cell adhesion molecule E-selectin by reducing its expression. The molecule does not affect IκBα degradation or p50 and p65 nuclear translocation [45]. Despite the NFκB pathway being regulated negatively in the stimulation of RAW 264.7 cells in LPS, the Alpha-cyperone (0.03% in the present study) shows anti- inflammatory activity by reduction of IL-6 and COX-2 [46]. The deficiency of Rac1, COX, Cdc42-2, IL-6, & Nck-2 significantly impacts Alpha-cyproterone and, thereby reduces inflammation. This property could be extremely useful in treating cellular inflammation that occurs in the disease of Alzheimer's. *In vitro* Sulforhodamine B (SRB) cell cytotoxicity assay of both ethanolic extract and the essential oil of *Lavandula dentata (Taif, Saudi Arabia)* against the hepatocellular carcinoma (*HepG2*) cell line (Fig. 1). and against Green monkey kidney (*Vero*) cell line (Fig. 2) showed that The standard curve for the sulforhodamineB cytotoxicity assay was plotted (Fig.2) and supported an IC_{50} of *L. dentata L. e*xtract, or its oil, as >100 μg with R% (NA). *L. dentata* is widely used for itsanticonvulsant and antidepressant [47], sedative [48], and antioxidant properties [49]. A positive impact on teaching and memory appeared by the plant [50]. When taken orally, EO formulations have calming and anxiolytic effects that happen more quickly than with first-choice anxiety medications like benzodiazepines and serotonin reuptake inhibitors[51]. Oral preparations of the EO show anxiolytic and calming effects with a faster onset than first-choice anxiety treatments, such as serotonin reuptake inhibitors and benzodiazepines [52].

Table (3): Review for different biological functions of the most common active constituents of *Lavandula dentata (Taif, Saudi Arabia)*

Compound	%	Biological Functions	References
α-Pinene	0.5	α-Pinene is a monoterpene enhances sleeping, binds directly to GABAA-benzodiazepine (BZD) receptors, and acts as a partial modulator at the BZD binding site	[44]
β-Pinene	0.73	β-Pinene consider as vital component of turpentine, which has antimicrobial and antiviral activities, whereas it can inhibit infectious bronchitis virus (IBV) with an IC_{50} of 1.32 mM.	[41, 42]
D-Limonene	2.27	A monoterpene found in many pine-needle oils and in turpentine. (-)-Limonene can induce a mild bronchoconstrictive effect	[57]
linalool	1.42	Linalool is a natural monoterpene component in essential olis of coriander. Linalool acts as a competitive antagonist of Nmethyl d-aspartate (NMDA) receptor, with anti-tumor, and anti-cardiotoxicity activity. Linalool is a PPARα ligand reducing plasma TG levels and rewires the hepatic transcriptome and plasma metabolome.	[37, 38]
borneol	3.35	Borneol represents a natural bicyclic monoterpene used for analgesia and anesthesia in traditional Chinese medicine. Also, it enhances GABA receptor activity with an EC_{50} of 248 μM. At high concentrations (>1.5 mM). It activates GABAA receptors producing 84% of the maximal GABA response indicative of a weak partial agonist action. Borneol produces dose-dependent positive modulation of the Cl^- conductance generated by extremely low dose GABA at α1β2γ2L GABAA receptors.	[39]
Caryophyllene oxide	0.02	Caryophyllene oxide, isolated from *Annona squamosa L.* bark. It poses analgesic and anti-inflammatory activity.	[58]
α-Terpinene[	0.16	α-Terpinene (Terpilene) is natural monoterpene of the essential oils in various foods and aromatic plants such as *Mentha piperita*. α-Terpinene acts against *Trypanosoma evansi* . It also a potential treatment for trypanosomosis. In addition, it poses antioxidant and antifungal activities.	[59-62]
Andrographolide	0.42	The plant andrographis (*Andrographis paniculate*) is a key producer of Andrographolide. Andrographolide (Andro) suppresses NF-κB activation by modifying reduced cysteine 62 of p50, the expression of cell adhesion molecule E-selectin, and E-selectin-mediated leukocyte adhesion.	[45]
Cedrol	0.05	Cedrol represents a bioactive sesquiterpene, a potent competitive inhibitor of cytochrome P-450 (CYP) enzymes. Cedrol is found in cedar essential oil and possess anti-septic, anti-inflammatory, anti-spasmodic, tonic, astringent, diuretic, sedative, insecticidal, and anti-fungalproperties.	[63, 64]
Isolongifolene, 4,5,9,10-dehydro-	0.04	A tricyclic sesquiterpene isolated from *Murrayakoenigii*. Isolongifolene reduces induced oxidative stress, mitochondrial dysfunction, and apoptosis through the regulation of P13K/AKT/GSK-3β signaling pathways. Isolongifolene has antioxidant, anti-inflammatory, anticancer and neuroprotective activities.[65]	[65]
alpha-Cyperone	0.03	alpha-Cyperone associates with the downregulation of COX-2, IL-6, Nck-2, Cdc42 and Rac1, which reduce inflammation., It may be a potential treatment of inflammatory diseases such as AD. alpha-Cyperone has anti-inflammatory activity. It is correlated with the down-regulation of COX-2 and IL-6 by down regulation of the NFκB pathway in LPS-stimulated RAW 264.7 cells.	[46]
β-Bisabolene	0.03	β-Bisabolene is a sesquiterpene isolated from opoponax (*Commiphoraguidotti*). β-Bisabolene, has anti-cancer activities, can be used for the study of breast cancer.	[66]
β-Elemene	0.01	β-Elemene is isolated from natural plant *Curcuma wenyujin* with an antitumor activity. β-Elemene may induce cell apoptosis.	[67]
Thymol	0.1	Thymol represents the major monoterpene phenol of essential oils isolated from plants belonging to the Lamiaceae family, and other plants such as those belonging to the Verbenaceae, Scrophulariaceae, Ranunculaceae and Apiaceae families. Thymol poses antioxidant, anti-inflammatory, antibacterial and antifungal activities.	[40]
Carvacrol	0.12	Carvacrol represents a monoterpenoid phenol isolated from Lamiaceae family plants, with antioxidant, anti-inflammatory and anticancer properties. Carvacrol arrests cell cycle in G0/G1, downregulates Notch-1, and Jagged-1, and induces apoptosis.	[55, 68]
Bornyl acetate	0.08	Bornyl acetate is a major odorants of fresh ginger juice, as it exhibits one of the highest FD factors. Bornyl acetate has a pivotal sensory roles in the	[69]

Table (3): Review for different biological functions of the most common active constituents of *Lavandula dentata (Taif, Saudi Arabia)*			
Compound	**%**	**Biological Functions**	**References**
		aroma of fresh Japanese ginger.	
Carvone	0.32	Carvone (D Carvone) is a natural compound found in various foods and can be used in flavoring foods.	[70]
Verbenone	0.41	Verbenone is a natural terpene in tree leaves, *Suregadazanzibariensis* Verdc·. Verbenone has anti-aggregation property and interrupts the attraction of bark beetles to their aggregation pheromones.	[71, 72]
fenchylacetate	0.78	Fenchyl alcohol is a monoterpene in the essential oils isolated from Douglas fir needles, acts as a fragrance. Fenchyl alcohol inhibits the rumen microbial activity of both sheep and deer.	[73]
Isoborneol	0.04	Isoborneol is a monoterpene in the essential oils of various medicinal plants posing antioxidant and antiviral properties. Isoborneol is a potential inhibitor of herpes simplex virus type 1.	[74, 75]
Valencene	0.05	Valencene is a sesquiterpene isolated from *Cyperus rotundus*, posing antiallergic, antitumor, anti-inflammatory, and antioxidant properties. Valencene suppress the exaggerated expression of Th2 chemokines and proinflammatory chemokines through blocking of the NF-κB pathway. Valencene is used in flavoring foods and drinks	[76-78]

Table (4): Estimation of Total Phenolic and Flavonoids of *Lavandula dentata (Taif, Saudi Arabia):*

TotalPhenolic		**TotalFlavonoids**	
Gallic acid (µg/ml)	**Absorbance /630 nm**	**Rutin (µg/ml)**	**Absorbance / 420 nm**
1000	2.9552	1000	3.253
800	2.5155	600	1.943
600	1.739	400	1.368
400	1.109	200	0.7758
200	0.5218	100	0.372
100	0.2324	50	0.1537
50	0.1686	10	0.0248

Seizure Intensity Scale:

Seizure intensity measurements (Table 5) indicated that some natural products increase the latency between the uncontrolled seizures that recur and lessen the frequency of those seizures while receiving treatment. The behavior observed during pilocarpine-induced status Epileptic (SE) in rats composed of initial shaking of wet-dog, head bowing, and facial and ear shaking. These behaviors progressed to Phase II with axial rhythmic waves that were constant throughout the body. Phases III represented by involuntary twitching of the muscle (myoclonic) and IV constituted a generalized repetitive jerking movement of arms and legs (clonic convulsions) followed by the assumption of aside status, rhythmic stretch segments, and widespread convulsions together with SE (phase V).

Total distance traveled and vertical activity in control rats showed diurnal fluctuations in locomotor activity (grooming, rearings counting, frequency of standing on hind limbs, and ambulation frequency). In open-field examinations, the hyperactivity of epileptic rats was reduced to control levels through E-DK® and ethanolic extract and Essential oil (EO) of *L. dentata* ($p< 0.01$). The frequency of seizures was considerably decreased and the intervals of the latency period was prolonged in all epileptic stages, particularly phase V, which included widespread seizures and rigid extension episodes, by both ethanolic extract and oil (17.353 ± 0.167 and 16.837 ± 0.505 sec, respectively).

All treatments attenuated pilocarpine-induced anxiety mostly by reducing the spending time and distance in the central portion. Control rats exhibited less immobility time and lack of

variations during the diurnal time by applying melatonin treatment. Besides, the rat treatment with various degenerative models [53-55]. Moreover, Alvi *et al.* [55] indicated that either ethanolic extract or essential oil (EO) of *L. dentata*displayed depressing conduct during mandatory swimming exams (FSTs) [56].

Antiepileptogenic treatment with either Depakine® or *L. dentata* oil or ethanolic extract was assessed via evaluation of latency between involuntary jerking movement of muscle, interval between seizures that are tonic-clonic in general, numbers of these seizures, and severity of seizures after each subconvulsant PTZ injection during kindling [79, 80]. The present data are consistent with studies by Singh *et al.* [80], Löscher [81], who confirmed that AEDs alleviated exacerbation of seizure severity during kindling. Therefore, a possible role of crude ethanolic extract or essential oil (EO) is the modulation of changes in neurochemistry, which might be responsible for depression in epilepsy [80]. Many reports indicate a significant role of monoterpenes as agents had protective, antioxidant, and anti-inflammatory roles incarveol, a monoterpene, can decrease seizure intensity and frequency and delay seizure onset.

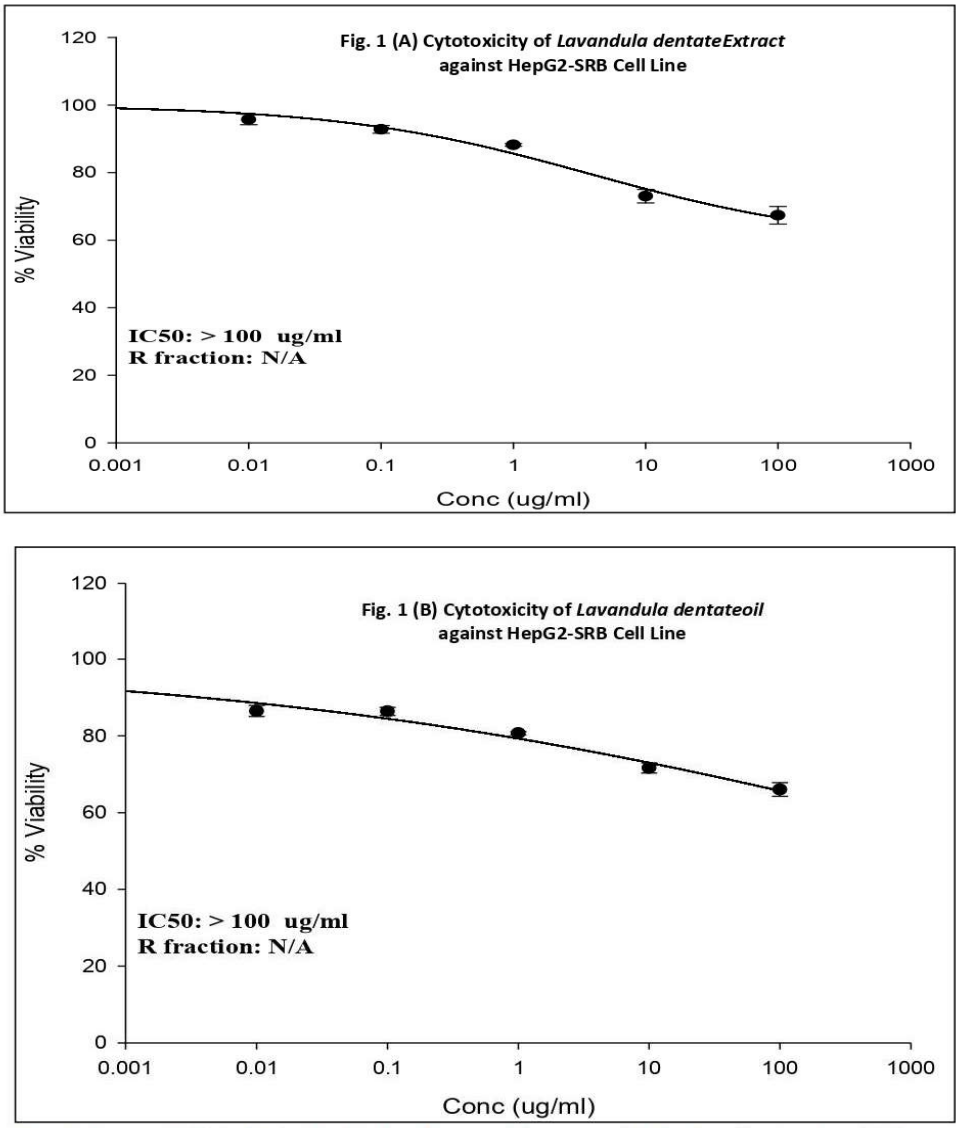

Fig. 1: *In vitro* Sulforhodamine B (SRB) cell cytotoxicity assay of [A] ethanolic extract and [B] essential oil of *Lavandula dentata (Taif, Saudi Arabia)* against Hepatocellular Carcinoma (*HepG2*) cell line.

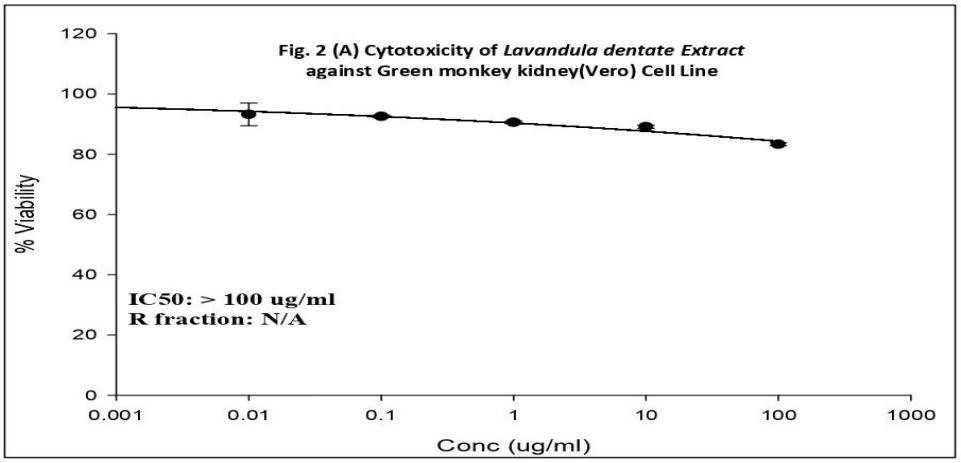

Fig. 2: *In vitro* Sulforhodamine B (SRB) cell cytotoxicity assay of [A] ethanolic extract and [B] essential oil of *Lavandula dentata (Taif, Saudi Arabia)* against Green monkey kidney (*Vero*) cell line.

Table (5): Changes in the seizure intensity was evaluated using the following modified scale of different groups: epileptic (EP), Depakine®-treated (EP_DK®), *L. dentata* oil–treated (EP_LO) and *L. dentata* extract–treated (EP_LX). Values were represented as Mean ± SD & n = 8 animals. Means within the same parameter and not sharing a common superscript symbol(s), are differ significantly at $P < 0.05$. This scale is applied for the occurrence of seizure-related behavioral changes and its severity. Each number represents latency and intervals of the seizure severity.

Phase #	Seizure Intensity Scale									
	Phase -0	Phase -I		Phase -II		Phase -III		Phase -IV		Phase -V	
Symptoms	No Response	Ear and facial twitching		Convulsive waves axially through the body		Myoclonic		Generalized clonic convulsions turn over into side position		Generalized convulsions with tonic extension episode and status epilepticus	
Groups		Latency/ min.	Intervals/ sec.	Latency/ min.	Intervals/ sec.	Latency/ min.	Intervals/ sec.	Latency/ min.	Intervals/ sec.	Latency/ min.	Intervals/ sec.
EP		1.430± 0.113^{b}	0.877± 0.669^{ab}	2.313± 0.939^{b}	0.733± 0.381^{ab}	3.047± 0.567^{b}	3.437± 2.069^{b}	6.483± 2.627^{c}	5.683± 0.791^{b}	12.167± 1.893^{c}	5.683± 0.791^{b}
Ep_DK®		3.540± 0.454^{c}	0.767± 0.436^{ab}	1.497± 0.265^{b}	0.873± 0.109^{ab}	2.370± 0.210^{b}	1.183± 0.473^{a}	3.553± 0.500^{b}	4.950± 0.925^{b}	8.503± 0.690^{b}	4.950± 0.925^{b}
EP_LO		5.197± 0.127^{e}	0.200± 0.165^{ab}	5.397± 0.123^{c}	3.460± 0.421^{c}	8.857± 0.357^{d}	0.883± 0.400^{a}	9.740± 0.639^{c}	7.613± 0.473^{c}	17.353± 0.167^{d}	7.613± 0.473^{c}
EP_LX		4.613± 0.396^{d}	1.127± 0.772^{b}	5.740± 1.083^{c}	1.650± 1.355^{b}	7.390± 0.878^{c}	2.210± 1.525^{a}	9.600± 0.656^{c}	7.237± 0.274^{c}	16.837± 0.505^{d}	7.237± 0.274^{c}
F value		183.637	2.681	43.777	12.037	160.330	3.743	32.429	78.442	175.328	78.442
P<		0.000	0.094	0.000	0.001	0.000	0.041	0.000	0.000	0.000	0.000

Healthy control Rats' overall distance traveled and vertical activity indicated typical fluctuations in their movement activity (rearing) ($p < 0.05$) in some behavioral assessments, e.g., open field tests (Table 6). The rats with epileptic disorders were less troubled than control animals, as demonstrated by a longer delay period spent in the negative center zone of the field and by decreased locomotion of frequency. This was minimized by injection of oil or *L. dentata* extract, enhancing grooming, parenting, and frequency of moving around while lowering the distance and latency's intervals in the central region. Depakine® lowers the duration of grooming even when locomotion, rearing, and excretion are not modified. The anxiety-reducing properties of valproate may be the source of this activity[82].This study evaluated behavioral effects caused by ethanolic extract and essential oil (EO) of *L. dentata* were performed to explore their role with antiepileptic drugs in *vivo*.. In earlier models of epilepsy, changed behavioral reactions were thought to represent different feelings outputs. The present model used sub convulsive pilocarpine doses to induce epileptic seizures. In earlier models of epilepsy, changed behavioral reactions were thought to represent different feelings outputs [55, 81, 83].

Generally, the open field test (Table 6) is an acceptable model to measure anxiety status in stressful or threatening situations. The epileptic (EP) group showed a long latency time to react with the open field (154.00± 13.53 sec) when compared to controls (12.00± 1.00 sec). Conversely, epilepsy-DK® exhibited a significantly ($p< 0.05$) shorter latency time (41.667± 2.887 sec) than the Epileptic group. Both essential oil (EP_LO) and extract of *L. dentata* (EP_LX) exhibited a highly significant decrease in entering the central part of the apparatus ($P<0.01$) (11.15± 0.787 and 12.77± 2.36 sec) in contrast to epilepsy group. Increased time spent in the central zone or decreased latency for entering this zone are indications of anxiolysis [84, 85]. The frequency of entries, time spent in latency, and the central square are all indicators of the behavior of exploration and fear [84]. The grooming tasks in the open area exam, involve quickly wiping the front legs toward the body or face. Epileptic animals showed a significantly decreased activity (5.667± 1.528 /3 min, $P<0.05$) relative to controls (13.00± 2.00 /3 min). Conversely, the epilepsy_DK section, which exhibited hyperactivity significantly, recording (15.33± 4.16 with $P<0.05$) was regarding to epilepsy group. Similarly, a corresponding elevation ($P<0.05$)in the movement of the forelegs towards the face and the body was recorded in EP_LO and EP_LX (17.333± 2.082 and 13.000± 1.000 /3 min, respectively) comparable to EP (5.667± 1.528 / 3 min) Table (6). Any new setting is likely to elicit grooming, which is a migration behavior. Anxiety can be reduced in difficult times by grooming oneself. Compared to grooming replies, the importance of grooming as a behavioral sign of depression has received substantially less research[86]. There were no differences seen in the research rats' latency of getting into the central zone, falling in locomotion action, or rearing. Rats that were administered extract or Essential oil (EO) of *L. dentata* displayed significantly increased grooming activity compared with Depakine® treatment ($p< 0.01$). Depakine® (valproic acid) displays anxiolytic properties [87]. Therefore, the rats with higher anxiety are distinguished by locomotion and grooming.

Concerning there was frequency of standing on hind limbs (rearing) of the open field test, Table (6) illustrated a significant hypoactivity in the epilepsy group (EP)($P<0.05$) (5.00± 2.00 /3 min) comparable to the control group (11.00± 2.65 /3 min). On the other hand, rearing of rats in EP_DK,

EP_LO, and EP_LX sections revealed higher activity (P<0.05) also registered 9.00± 1.00, 11.00± 1.00 and 13.00± 1.00, respectively, as compared with EP group. Moreover, a significant decrease in the ambulation frequency (i.e. total number of entered squares/3min)(P<0.05) in the epilepsy group (EP, 19.00± 1.00) is comparable to normal rats (33.33± 5.93). Moreover, however, the EP_DK group showed a no significant increase (25.33±3.51). While EP_LO and EP_LX animals showed significant hyperactivity and entered more squares (P<0.05), as recorded at 37.33± 4.29, and 43.33± 3.51, respectively, in contrast to the EP group.

Some antiepileptic drugs (AEDs) such as Depakine® benefit some patients with epilepsy and cause a variety of adverse consequences, such as irritation, anger, and violence. Moreover, Depakine® strongly inhibits seizure-induced neurogenesis [88].

Table (6): Assessment of behavioral tests (open field, hot plat and despair forced swim tests) between different experimental group: Control; epileptic (EP), Depakine®-treated (EP_DK®), *L. dentata* oil–treated (EP_LO) and *L. dentata* extract–treated (EP_LX). Values were represented as Mean ± SD & n = 8 animals. Means within the same parameter and not sharing a common superscript symbol(s), are differ significantly at P < 0.05.

Behavioral Test	Open Field Test				Hot Plate	Despair Swim
	Latency time (Sec.)	Grooming /3 min.	Rearing /3 min.	Ambulation Frequency /3 min.	Latency time (Sec.)	Latency time (Sec.)
Control	12.00± 1.00^{a}	13.00± 2.00^{b}	11.00± 2.65^{bc}	33.33± 5.93^{bc}	13.00± 1.00^{a}	33.33± 6.69^{a}
EP	154.00± 13.53^{c}	5.67± 1.528^{a}	5.00± 2.00^{a}	19.00± 1.00^{a}	70.00± 5.00^{c}	111.67± 10.41^{d}
Ep_DK®	41.67± 2.88^{b}	15.33± 4.163^{b}	9.00± 1.00^{b}	25.33± 3.51^{ab}	33.333± 2.89^{b}	68.33± 4.163^{c}
EP_LO	11.15± 0.78^{a}	17.33± 2.082^{b}	11.00± 1.00^{bc}	37.33± 4.29^{c}	16.67± 4.76^{a}	35.67± 3.512^{ab}
EP_LX	12.77± 2.36^{a}	13.00± 1.00^{b}	13.00± 2.00^{c}	43.33± 3.51^{c}	12.33± 2.08^{a}	46.00± 2.65^{b}
F value	286.326	10.075	8.118	5.478	146.658	83.842
P<	0.000	0.002	0.003	0.013	0.000	0.000

The present data demonstrate that grooming behavior is a response to any unfamiliar environment and helps calm anxiety caused by stress. It is a better marker for anxiety than depression because grooming represents a state of pleasure or comfort. Therefore, in conflict situations, grooming activity or, more commonly, discrete grooming fragments are observed[89].In Table (6), the test of the hot plate is a behavioral design of nociception and a mirror for analgesic impact. The present data revealed a higher obviously increased latency time to paw withdrawal latency time in reaction to thermal noxious stimulation as heat pain in epilepsy group EP (70.00± 5.00sec, P<0.001) in contrast to controls (13.00± 1.00sec).Conversely, a shorter paw withdrawal latency time was registered by the group administered with Depakine® (EP_DK) and also had a notably more sensitive response (33.33± 2.89sec, P<0.05), in comparison with the epilepsy section. There was a significantly greater feeling and a shorter paw withdrawal delay time to respond in both the EP_LO and EP_LX groups (16.67± 4.73 and 12.333± 2.082 sec, respectively, P<0.001) in contrast to epileptic animals. The pain action can be measured by the delay period of licking [90] and

for evaluation of analgesic effects. The HPT measures a complex response to a non inflammatory acute nociceptive input and is normally used for assessing central nociception [91, 92]. With the treatment of extraction or EO of *L. dentata,* the pain was reduced and passivity in HPTs was higher significantly ($p< 0.001$) which suggests analgesic potential via prostaglandin pathways. Multiple noxious-evoked patterns were described by Espejo and Mir [93] and responses of exploration and self-care in rats during HPTs. Finally, rats reacted to heat stimuli and attempted escape according to sequential behavior structures based on the first occurrence. Various behaviors were used to quantify nociceptive thresholds, e.g., hindpaw-licking and stamping latency. Such patterns are initial reactions to heat as a noxious stimulus. Moreover, valproic acid decreases the phases of inflammation and acute pain. The drug shortened the duration of licking during the stage of inflammation [94, 95].

Forcing swim (FST) test was performed on the experimental rats with epilepsy disorder (Table 6) showed distinct oscillations together with prolonged immobility (111.67± 10.41sec) ($P<0.05$) when corresponding with the behavior of rats in the control group (33.33± 6.67sec). These diurnal alterations were improved by the injection of oil and extract of *L. dentata* and significantly decreased with the Depakine®-treated group (EP_DK®), *L. dentata* oil–injected section (EP_LO), and *L. dentata* extract–treated group (EP_LX) (68.33± 4.16, 35.67± 3.512 and 46.00± 2.65 sec respectively) as compared to the EP group. When enclosed in an impenetrable container in FSTs, treated rats had an immovable expression. This mobile action was not registered in most pilocarpine-treated rats. Instead, these animals showed less time despairing as they continued to swim, trying to escape from the cylinder. The present results are consistent with those of Ilbay *et al.* [96], who reported that caffeine-treated animals explored significant immobilization delay and prolonged continuous swimming in FSTs compared with untreated controls.

Generally, the "behavioral despair" test, is known as FST, and used in clinical forms of mental disorder to assess behavior resembling depression. [97, 98]. FST causes alterations in neurochemical and endocrine release [99, 100]. Moreover, neurochemical changes coincided with endocrine and immune alterations associated with rats in FSTs. Furthermore, a stress reaction to antidepressant medication may account for the present higher latency period for animals receiving treatment in FSTs as contrasted with second-group epileptic animals. On the other hand, during forced swimming, post-pilocarpine SE mice remained motionless for a prolonged duration, suggesting a condition akin to despair (Mazarati *et al.*[101]. Similar researchers proposed that serotonergic circuit changes are not the exclusive cause of depression in SE. The pathophysiological relationship between depression and seizures is due to impairments in serotonergic conduction[102]. In contrast, Gröticke *et al.* [103] explained enhanced performance under different adverse environments of FST in SE in mice compared with controls. Epileptic animals showed significantly increased anxiety-related behavior. Moreover, motor activity was increased in FST in SE animals.

SE rats' swimming trials may be indicative of cognitive decline in a learning test that depends on the hippocampal region. Rather than hippocampal damage, this disorder could be linked to aberrant regeneration in the *dentata* gyrus in SE mice. Whereas the animals receiving treatment did not actively search for the concealed platform, the SE rats just swam within a comparatively small area of the maze or in rings around its perimeter[88].

Components of *L. dentata* that contain flavonoids or saponins have anticonvulsant effects

[104]. Additionally, monoterpenes and flavonoids have been shown to protect versus seizures caused by picrotoxin, PTZ, and NMDA [105]. Numerous therapeutic effects on the CNS, such as anticonvulsant and anxiolytic effects, have been linked to flavonoids, sterols, and terpenoids [106].Sterols and flavonoids have neuromodulatory and central inhibitory effects [107]. Ethanolic extract and Essential oil (EO) of *L. dentata* increased seizure thresholds and inhibited pilocarpine-induced convulsions. Extract and Essential oil (EO) of *L. dentata* show antiepileptic properties, likely due to some phytoconstituents that facilitate GABA transmission. Extract and Essential oil (EO) of *L. dentata* also show some motor impairment and decreased spontaneous locomotor activity at anticonvulsant doses. The impairment in muscle movement may be caused by different phytoconstituents, such as phenols, saponins, terpenoids, and flavonoids [108]. Analgesic medication concepts working through prostaglandin routes may be the source of a substantial decrease in pain following treatment [92].

In conclusion, the present study provides evidence that ethanolic extract and Essential oil (EO) of *L. dentata* modulate several behavioral domains by controlling seizures in conjunction with antiseizure medications and via shorter latency time and greater ambulation frequency. Therefore, reduced depression-like symptoms in the EP_LO and EP_LX animals might be a consequence of reduced convulsion and seizure activity.

Conflict of Interest & Disclosure Statement:

The authors have no potential conflict of interest with any groups.

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