Chemical Compositions and Anticancer Potential of Essential Oil from Greenhouse-cultivated *Ocimum basilicum* Leaves

T. A. ABURJAI*, K. MANSI[1], HANAN AZZAM[2], DANA A. ALQUDAH[3], W. ALSHAER[3]* AND M. ABUIRJEI[4]

School of Pharmacy, [1]Faculty of Science, Al Al-Bayt University, Mafraq, [2]Hamdi Mango Center for Scientific Research, [3]Cell Therapy Center, The University of Jordan, Amman-Jordan, [4]Faculty of Pharmacy, Jordan University of Science and Technology, Irbid-Jordan

Aburajai *et al.*: Chemical Compositions and Anticancer Potential of Essential Oil from Leaves of *Ocimum basilicum*

In the current study, the compositions of the essential oil obtained from leaves of *Ocimum basilicum* 'Cinnamon' grown in Jordan in a greenhouse was analysed. The antitumor activity of the essential oil was examined against three different cancer cell lines including MDA-MB-231, MCF7 and U-87 MG. The hydrodistillation method was used to extract the essential oil from *Ocimum basilicum* and the chemical components were analyzed and identified using gas chromatography-mass spectroscopy. The dry weight yield of essential oil was 0.50 % (w/w). Thirty-one components representing 97.80 % of the essential oil were identified. The main chemical components revealed the presence of linalool, eugenol, eucalyptol, hinesol, trans-α-bergamotene and γ-cadinene as the major constituents. In conclusion, the essential oil extracted from greenhouse cultivated *Ocimum basilicum* European chemotype showed potent antitumor activity.

Key words: Basil, *Ocimum basilicum*, essential oils, greenhouse cultivation, antitumor, cancer

Basil (*Ocimum basilicum L.*) is a culinary herb of the family Lamiaceae and considered as one of the most aromatic plants grow widely at different places around the world, especially in Asia, North America, and Europe[1,2]. Basil is used for many applications in the pharmaceutical and food industry[3]. Traditionally, sweet basil has been used as a medicinal plant in the treatment of kidney malfunction, worms, cough, diarrhea and headache[1,4-8]. Moreover, basil contains a group of phenolic compounds that impart a good antioxidant effect[5,9-11]. *O. basilicum* is a popular culinary herb and a source of essential oils extracted from leaves and flowering tops that are used in flavoring foods, dental and oral products and fragrances[4].

Essential oil of basil primarily consists of monoterpenes, sesquiterpenes and phenylpropanoids with oxygenated derivatives[1,3,12,13]. There are important differences among basil species including the variation in the

***Address for correspondence**
E-mail: aburjai@ju.edu.jo

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chemical compositions and the essential oil content and components. In addition to the species, such variation may be linked to the growing and cultivation environment that varies among different locations[1,14]. There are two main types of basil oil commonly used in the market, the reunion type which is mostly composed estragole (80 %) and (ii) the European type usually obtained from France, Italy, Egypt, and South Africa, which is mostly composed of linalool (35-50 %) and estragole (15-25 %)[15].

Cancer is a heterogeneous group of diseases characterized by the uncontrolled growth of cells that escape from body defenses and many times from the conventional antitumor drugs. Cancer is a leading cause of morbidity and mortality worldwide. In 2018, 18.1 million new cancer cases were diagnosed and 9.6 million cancer-related deaths were reported[16,17]. The development of new therapeutics and therapeutic systems is a continuous battle for successful and effective cancer treatment. Tumor cells are heterogeneous and can develop intrinsic or acquired multidrug resistance mechanisms including increased drug efflux, drug inactivation, drug target alteration, increased DNA damage repair, epigenetics, cell death inhibition and epithelial-mesenchymal transition[18,19]. Plants are considered a rich source of natural compounds that can be used for the discovery of anticancer agents. Around 50 % of conventional anticancer chemotherapeutics are originated from plants. One important example is paclitaxel which is widely used for the treatment of different types of cancers, including breast, ovarian and pancreatic cancer[20-22]. Essential oils are aromatic secondary metabolites of plants that possess wide range bioactivities with pharmacological interests including anticancer activity[23,24]. Consequently, adding more therapeutic options for cancer prevention.

It appears based on the literature search, no studies were reported in which the composition of the essential oil of *O. basilicum* grown in Jordan was investigated. Therefore, this study was taken up to carry out a detailed chemical investigation of the essential oil composition of the chemotypes of *O. basilicum* grown in Jordan. Moreover, this study aimed to investigate the anticancer activity of essential oil of *O. basilicum* grown in a greenhouse.

Seeds of *O. basilicum* 'cinnamon' were collected from a mother plant grown in the botanical garden of Faculty of Agriculture, The University of Jordan (UJ)-Amman, seeded and transplanted for cultivation under controlled greenhouse conditions; 25° and 40-60 % relative humidity with conventional cultivation practices of irrigation and fertilization (20-20-20-TE). Basil leaves were collected when the height of the plant reached 20-25 cm. Plant material was taxonomically identified by direct comparison with an authenticated sample at the herbarium of the Faculty of Science, Department of Biology, the University of Jordan. A voucher specimen of plant material was deposited at the School of Pharmacy, JU (GH-B-18, for greenhouse). N-hexane (GC grade) was purchased from Tedia (USA), A hydrocarbon mixture of n-alkanes (C8-C20) was purchased from Fluka (Switzerland).

Plant material (500 g) was collected as mentioned above and dried at room temperature in a shaded and ventilated area. Dried plant material (100 g) was hydrodistilled for 3 h using the Clevenger apparatus (JSGW, India). The obtained essential oil was separated, dried over anhydrous sodium sulfate (Analar, England) and stored in a sealed vial in the refrigerator. The yield of oil was calculated as percent weight by weight (w/w %) of the dry plant material.

A 5 µl aliquot of oil samples diluted with 1 ml of GC-grade n-hexane and then 1 µl samples of the diluted oil were injected into the GC-MS systems for analysis. From the diluted oil sample prepared above, 1 µl aliquot was injected using an automated injector into the GC-MS system for analysis using a variant chrompack CP-3800 GC/MS/MS-200 (Satum, Netherlands) equipped with split-splitless injector and DB-5 capillary column (5 % diphenyl 95 % dimethyl polysiloxane, 30 m×0.25 mm ID, 0.25 µm film thickness). The injector temperature was set at 250° with a split ratio of 1:30. A linear temperature program was used to separate the different oil components. The column temperature was held constant at 60° for 1 min. The temperature was then increased to 250°, at a rate of 3°/min and then was held constant at 250° for 2 min, with a total runtime of about 66 min. The flow rate of the carrier gas (helium) was 1 ml/min. Each sample was analyzed twice. The mass detector was set to scan ions between 40-400 *m/z* using full scan mode and electron impact (El, 70 eV). A hydrocarbon mixture of n-alkanes (C8-C20) was analyzed separately by GC-MS using the same column (DB-5) and under the same chromatographic conditions. Linear retention index (Arithmetic-Kovats index) was calculated for each component (each peak) separated by GC-MS using the value of its retention time and the retention times of the reference n-alkanes applying Van Den Dool Eqn.[25]. The constituents of the essential

oils were identified using their recorded mass spectra and the built-in computerized matching with WILEY, NIST and ADAMS libraries, and by comparing their calculated arithmetic indices with reported values in the literature[26]. Identification of linalool, eugenol, and eucalyptol was further confirmed by co-chromatography with authentic standards (Sigma-Aldrich) under the same chromatographic conditions mentioned above.

GC-FID analysis was also carried out to obtain qualitative complementary results to those obtained by GC-MS as well as to obtain quantitative measures of the identified compounds. GC-FID was carried out on a ThermoQuest gas chromatograph coupled to an FID detector equipped with a split-splitless injector (split ratio 1:30) and HP-5 capillary column (Crosslinked 5 % PH ME Silicone, 30 m×0.32 mm×0.25 µm film thickness). One microlitre aliquots were autoinjected into the GC-FID system and analyzed using the same linear temperature program applied in the GC-MS analysis above. The carrier gas was nitrogen (N_2 99.99 %) and the flow rate was 1 ml/min. Each sample was analyzed triplicate. Essential oil constituents were identified by calculating the linear retention index of each constituent relative to (C8-C20) n-alkanes mixture (which was analyzed separately by GC-FID using the same column) and applying Van Den Dool Eqn.[25]. To identify the constituents, the calculated arithmetic indices were then compared with reported values in the literature[26]. Constituents quantification was achieved by dividing the peak area of each constituent by the total peak area of all oil constituents and multiplying the result by 100.

U-87 MG (glioblastoma cell line), MCF7 (ER+ breast cancer) and MDA-MB-231 (triple negative breast cancer cell line), were obtained from American Type Culture Collection (ATCC®; USA). U-87 MG was cultured in Eagle's minimum essential medium (EMEM, ATCC®, USA), containing 1 mM L-glutamine, 100 U/ml penicillin-streptomycin and 10 % fetal bovine serum (Gibco, USA). MCF7 was maintained in Roswell Park Memorial Institute 1640 medium (RPMI; Euroclone, UK) supplemented with 1 mM L-glutamine, 100 U/ml penicillin-streptomycin and 10 % fetal bovine serum. MDA-MB-231 was cultured in minimum essential medium (MEM, Euroclone, UK) supplemented with 1 mM L-glutamine, 100 U/ml penicillin-streptomycin and 10 % fetal bovine serum. Cells were grown at 37° in 5 % CO_2 atmosphere.

U-87 MG, MCF7 and MDA-MB-231 were seeded in 96-well plates at 7000 cells/well in 0.1 ml in complete EMEM, RPMI and MEM consequently. After 24 h, cells were treated and incubated with different concentrations of basil extract for 72 h at 37°. Afterward, the old media was aspirated and 100 µl of fresh medium and 15 µl of MTT reagent was added to each well and incubated for 4 h to allow the formation of formazan crystals. After removing all media from the wells, 50 µl of dimethyl sulfoxide (DMSO) was added to each well and mixed carefully. The absorbance values were measured using a microplate reader (GloMax®-Multi+ Detection System) at 570 nm to determine relative viabilities. Finally, data were analyzed by GraphPad Prism 6.

The results obtained revealed the presence of 31 components of the essential oil of *O. basilicum* based on GC-MS analysis (fig. 1). The identified compounds are listed in Table 1 in elution order from the DB-5

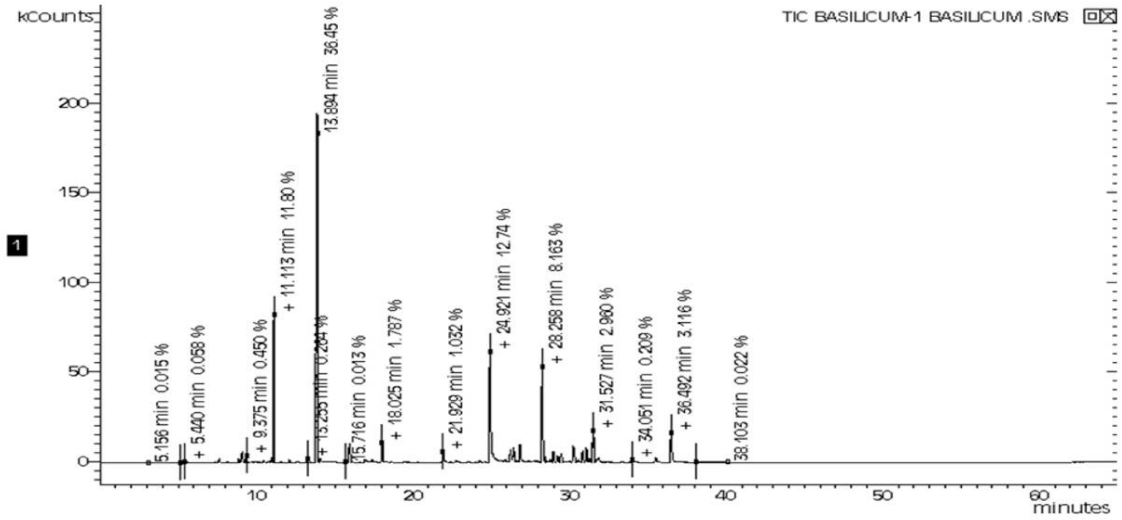

Fig. 1: GC-MS chromatographic profile of essential oil components of *O. basilicum* 'Cinnamon'

column, along with the percent composition of each component, its KI and class. The major constituents of the essential oil of *O. basilicum* were linalool (36 ±2.6 %), eugenol (14.2±3.4 %), eucalyptol (11.4±2.2), trans-α-bergamotene (9.0±0.9 %), hinesol (3.2±0.1 %), and γ-cadinene (3.1±0.1 %) summarized in fig. 2A.

The chemical components of sweet basil have been described in several reports. For example, Kruger *et al.* reported the major components of 270 sweet basil accessions[27]. The major constituents were found to be linalool, methyl chavicol, citral, 1,8-cineole, camphor, thymol, methyl cinnamate, eugenol, methyl eugenol, methyl isoeugenol and elemicin[27]. Moreover, Marotti *et al*. have reported the major oil constituents of different basil chemotypes such as in the Italian basil type linalool and methyl chavicol, in the tropical basil chemotype, methyl cinnamate and in the basil chemotype grown in North Africa, Russia, Eastern Europe and parts of Asia was eugenol[28].

The major components of the essential oil can be classified into 5 major classes including oxygenated monoterpenes (51.7±4.8), sesquiterpene hydrocarbons (23±1.4), phenolic compounds (16.3±3.3), oxygenated sesquiterpenes (2.6±1.1) and monoterpene hydrocarbons (3.2±0.1). These major components represent 97.1 % of the essential oil (fig. 2B).

After analyzing the major components and chemical classes of the *O. basilicum* essential oil, an attempt was made to investigate the anticancer effect against known common and invasive cancers. For this purpose, 3 cancer cell lines were chosen for representing two types of cancers, including a triple negative breast cancer cell line (MDA-MB-231), ER+ breast cancer (MCF7), and the glioblastoma (U-87 MG). The cells were treated

TABLE 1: COMPOSITION OF THE ESSENTIAL OIL OF *O. BASILICUM*

Compound name	Formula	Mol weight (g/mol)	KI* cal.	KI** lit.	% content GH (Avg±SD) 5 µl oil/1 ml hexane	Chemical class
α-Pinene	$C_{10}H_{16}$	136.24	934	932	0.28±0.02	Monoterpene hydrocarbon
Sabinene	$C_{10}H_{16}$	136.23	973	969	0.31±0.05	Monoterpene hydrocarbon
ß-Pinene	$C_{10}H_{16}$	136.24	980	974	0.88±0.21	Monoterpene hydrocarbon
Myrcene	$C_{10}H_{16}$	136.24	988	988	0.44±0.13	Monoterpene hydrocarbon
Limonene	$C_{10}H_{16}$	136.24	1030	1024	0.30±0.09	Monoterpene hydrocarbon
Eucalyptol (1,8-cineol)	$C_{10}H_{18}O$	154.25	1034	1026	11.36±2.23	Oxygenated monoterpene
Terpinolene	$C_{10}H_{16}$	136.24	1087	1086	0.26±0.05	Monoterpene hydrocarbon
Linalool	$C_{10}H_{18}O$	154.25	1101	1095	36.26±2.58	Oxygenated monoterpene
Trans-sabinenehydrate	$C_{10}H_{18}O$	154.25	1105	1098	0.47± 0.02	Monoterpene hydrocarbon
Camphor	$C_{10}H_{16}O$	152.24	1150	1141	1.61±0.09	Oxygenated monoterpene
δ-Terpineol	$C_{10}H_{18}O$	154.25	1172	1162	0.26±0.02	Oxygenated monoterpene
Terpinen-4-ol	$C_{10}H_{18}O$	154.25	1182	1174	0.24±0.00	Oxygenated monoterpene
α-Terpineol	$C_{10}H_{18}O$	154.25	1197	1186	1.91±0.07	Oxygenated monoterpene
Bornyl acetate	$C_{12}H_{20}O_2$	196.29	1286	1287	1.11±0.02	Miscellaneous
Eugenol	$C_{10}H_{12}O_2$	164.20	1355	1356	14.2±3.36	phenolic compound
ß-Elemene	$C_{15}H_{24}$	204.36	1391	1389	2.78±0.02	Sesquiterpene hydrocarbon
Methyl eugenol	$C_{11}H_{14}O_2$	178.23	1400	1403	2.1±0.00	Phenolic compound
Trans-α-bergamotene	$C_{15}H_{24}$	204.35	1434	1432	9.00±0.86	Sesquiterpene hydrocarbon
α-Guaiene	$C_{15}H_{24}$	204.36	1438	1437	0.41±0.15	Sesquiterpene hydrocarbon
Trans-ß-farnesene	$C_{15}H_{24}$	204.36	1452	1454	1.00±0.08	Sesquiterpene hydrocarbon
α-Humulene	$C_{15}H_{24}$	204.36	1458	1452	0.59±0.02	Sesquiterpene hydrocarbon
Cis-murrola-4(14),5-diene	$C_{15}H_{24}$	204.36	1464	1465	0.86±0.04	Sesquiterpene hydrocarbon
Germacrene D	$C_{15}H_{24}$	204.36	1483	1484	2.01±0.16	Sesquiterpene hydrocarbon
Cis-ß-guaiene	$C_{15}H_{24}$	204.36	1491	1492	0.29±0.01	Sesquiterpene hydrocarbon
Valencene	$C_{15}H_{24}$	204.36	1498	1496	0.99±0.04	Sesquiterpene hydrocarbon
Trans-ß-guaiene	$C_{15}H_{24}$	204.36	1504	1502	1.31±0.08	Sesquiterpene hydrocarbon
Cis-α-bisabolene	$C_{15}H_{24}$	204.35	1509	1506	0.37±0.05	Sesquiterpene hydrocarbon
γ-cadinene	$C_{15}H_{24}$	204.36	1515	1513	3.2±0.11	Sesquiterpene hydrocarbon
Trans-calamenene	$C_{15}H_{22}$	202.34	1522	1521	0.28±0.00	Sesquiterpene hydrocarbon
ß-Sesquiphellandrene	$C_{15}H_{24}$	204.35	1524	1521	0.60±0.19	Sesquiterpene hydrocarbon
Hinesol	$C_{15}H_{26}O$	222.37	1645	1640	3.17±0.07	Oxygenated sesquiterpene

KI* cal. linear (arithmetic) retention index calculated on a DB-5 equivalent column; KI** lit. Reference retention index value from literature; ND is not detected

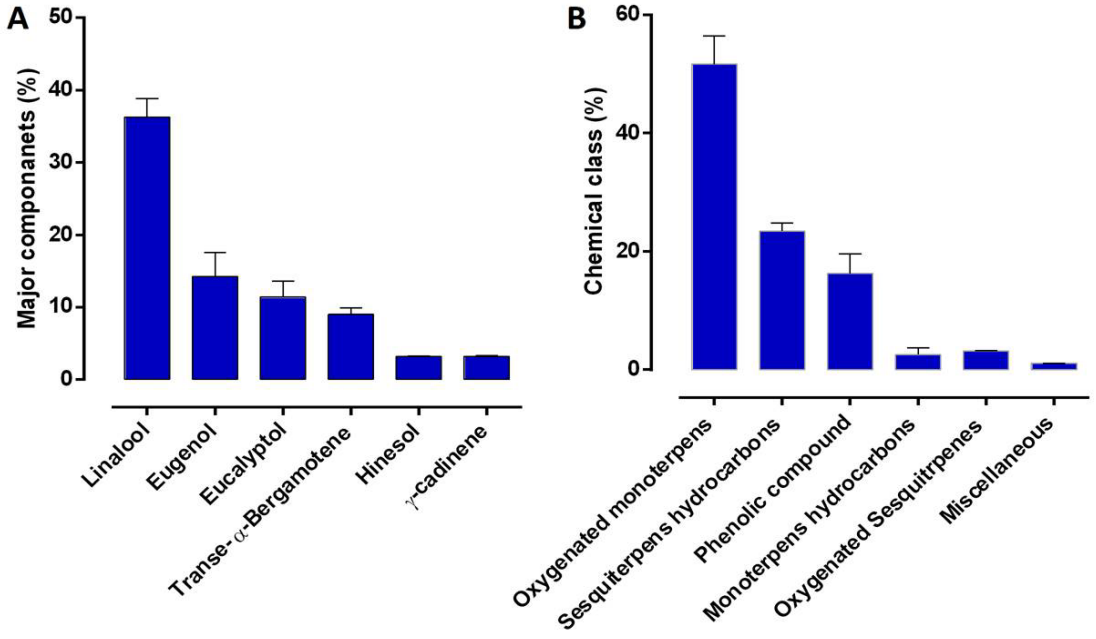

Fig. 2: Major components and class
(A) Comparison of the % contents of major components identified in the essential oil of *O. basilicum* cinnamon leaves, (B) comparison of the % contents of chemical class group identified in the essential oil of *O. basilicum* cinnamon leaves

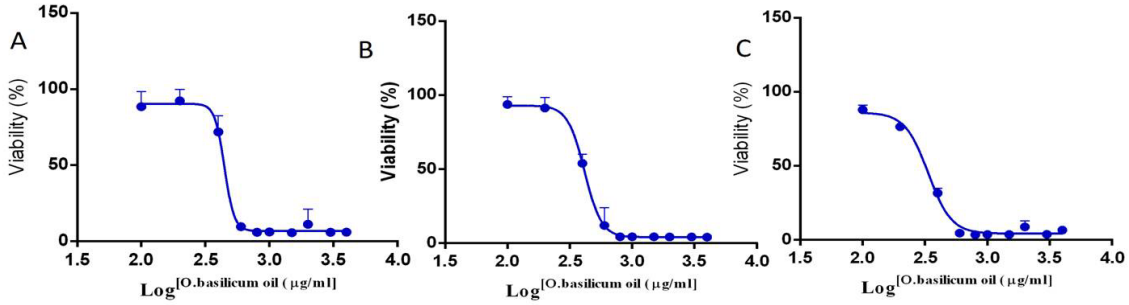

Fig. 3: Effect of *O. basilicum* essential oil on viability of cancer cell lines
Dose response curves to determine IC_{50} of *O. basilicum* essential oil on A. U-87 MG, B. MDA-MB-231 and C. MCF7 cell lines

with different concentrations of essential oil for 72 h followed by the detection of viable cells using MTT assay. The inhibitory concentrations 50 (IC_{50}) were calculated based on the percent remaining viable cells of 3 independent experiments. The IC_{50} values were 432.3±32.2 µg/ml on MDA-MB-231, 320.4±23.2 µg/ml on MCF7 and 431.2±15.3 µg/ml on U-87 MG as shown in fig. 3. These results agree with previously reported results. Linalool, eugenol and eucalyptol are the major components of *O. basilicum* essential oil, which have been shown to exhibit anticancer effect against different types of cancers such as leukemia, lymphoma, breast, colorectal, bone sarcoma, hepatic, gastric, lung and melanoma[14,29-31]. Interestingly, linalool was reported to potentiate doxorubicin on both MCF7 breast cancer and the doxorubicin-resistant MCF7/Adr cells through inducing apoptosis[32]. Different mechanisms have been described for such anticancer effects, including the induction of DNA repair, apoptosis, cell cycle arrest, detoxification and antioxidant enzymes[29-31].

To the best of our knowledge, this is the first report on the essential oil composition of *O. basilicum* grown in Jordan and its chemotype. The main essential oil components of *O. basilicum* were linalool/eugenol, suggested the linalool chemotype essential oil of *O. basilicum* European chemotype. In the literature, there is a low amount of data describing the anticancer effect of *O. basilicum* essential oil on triple-negative breast cancer cell line (MDA-MB-231), ER+ breast cancer (MCF7), and the glioblastoma (U-87 MG). The findings of this study revealed the promising anticancer effect of *O. basilicum* essential oil cultivated in Jordan.

Conflict of interest:

The authors declare no conflict of interest.

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