RESEARCH ARTICLE

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The Anticancer Effects of *Salvia palaestina* Essential Oil Grown in Iraq

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Abstract

Objective: This preliminary in vitro study aimed to isolate the essential oil of *Salvia palaestina* and evaluate its cytotoxic activity against SKG-T4 and A2780 cancer cell lines. **Methods:** The aerial parts of the plant were air dried, ground, and subjected to hydrodistillation using a Clevenger type apparatus for 3 hours. The obtained oil was dried over anhydrous sodium sulfate and stored at +4°C in the dark until use. GC/MS analysis was performed to identify the major phytochemical constituents. Cytotoxicity was assessed using a colorimetric MTT assay on esophageal SKG-T4 and ovarian A2780 cancer cell lines, with normal human fibroblasts (NHF) serving as the control. Cells were treated with serial concentrations of S. palaestina essential oil (100, 50, 25, 12.5, 6.25, 3.12 µl/ml) for 72 hours. Data were analyzed using GraphPad Prism software (version 8). **Result:** Treatment with the essential oil resulted in decreased cell viability in a concentration dependent manner. At 100µl/ml, cytotoxicity reached 62.8% in SKG-T4 cells and 52.3% in A2780 cells. The IC_{50} values were 57.9µl/ml for SKG-T4 and 72.9µl/ml for A2780 cells, indicating notable anti cancer potential. The essential oil was slightly more potent in SKG-T4 cells and exhibited considerably lower cytotoxicity toward NHF cells, where 100µl/ml caused 27.2% cytotoxicity, with an IC_{50} of 492.1µl/ml. The safety index ($SI = IC_{50(non\ cancer)} / IC_{50(cancer)}$) was 8.5 for SKG-T4 and 6.8 for A2780, demonstrating greater selectivity toward cancer cells. Microscopic examination revealed morphological features of apoptosis, including cell shrinkage, membrane blebbing, and apoptotic body formation. GC/MS analysis showed limonene as the major constituent (73.05%), along with other phytochemicals with known anti cancer properties. **Conclusion:** The essential oil of *Salvia palaestina* demonstrates promising anti cancer activity, characterized by concentration dependent cytotoxicity and a favorable safety index, supporting its potential as a selective anticancer agent.

Keywords: anticancer- esophageal- ovarian- SKG-T4- A2780- essential oil- *salvia palaestina*- cytotoxicity

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Introduction

Cancer is one of the most significant life threatening conditions worldwide and is characterized by uncontrolled cell proliferation accompanied by invasion and metastasis [1, 2]. Its development can result from genetic abnormalities [3], biological causes such as infections [4], particularly viral agents [2], as well as exposure to physical and chemical carcinogens. Lifestyle and dietary factors also contribute substantially to cancer risk [5].

Therapeutic options for cancer are continuously evolving and include surgery, chemotherapy, radiotherapy, immunotherapy, and hormone therapy. Chemotherapy remains one of the most effective treatment modalities, especially in cases of metastatic disease [6]. However, the emergence of drug resistance in cancer cells represents a major limitation, underscoring the need for the discovery and development of new anticancer agents through ongoing research [7, 8].

Nature is a rich source of anticancer compounds. Approximately half of all anticancer drugs are of natural origin, with nearly half of these derived directly from plants [9]. For example, vinblastine and vincristine, both obtained from Vinca species, exert their anticancer activity by inhibiting cell proliferation [10]. Essential oils, in particular, have attracted attention due to their documented anticancer activities, as reported in numerous studies [11, 12]. These oils contain various bioactive phytochemicals known for their cytotoxic properties. Their mechanisms of action include induction of apoptosis through both intrinsic (mitochondria dependent) and extrinsic (death receptor mediated) pathways, along with additional anticancer processes. Moreover, essential oils have demonstrated synergistic effects when combined with chemotherapeutic agents, enhancing efficacy while reducing adverse effects [9].

The genus Salvia is especially rich in essential oils. Belonging to the family Lamiaceae, Salvia species are

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distributed across Central and South America, Central Asia, the Mediterranean region, and parts of East Asia [13]. Commonly known as "sage," Salvia species are regarded as some of the most important aromatic plants globally and are well recognized for their medicinal properties. *Salvia palaestina*, a member of this genus, is native to Mediterranean and Middle Eastern regions, particularly Palestine, Turkey, Syria, Lebanon, Iraq, Iran, and northern Egypt. It has been investigated for various pharmacological activities [14]. The aim of this study was to investigate the anticancer potential of *Salvia palaestina* essential oil using the MTT assay.

Materials and Methods

Plant collection

The aerial parts of *Salvia palaestina* were collected from Kalopazyan Mountain near Sulaymaniya City during the flowering season in March 2024. Taxonomic identification of the plant was confirmed by Prof. Dr. Sukiena Saeed, Department of Biology, College of Science, University of Baghdad.

Essential Oil Extraction

The aerial parts were air dried, ground, and subjected to water distillation using a Clevenger type apparatus for 3 hours. The obtained essential oil was dried over anhydrous sodium sulfate, then stored in sealed vials at +4 °C in the dark until analysis and biological testing.

Gas Chromatography-Mass Spectrometry (GC−MS)

GC–MS is widely used for the analysis of essential oil composition. For analysis, 0.1 µl of the essential oil was dissolved in 3 ml of 99.99% methanol. GC–MS was performed using an Agilent Technologies 7820A gas chromatograph coupled to an Agilent Technologies 5977E MSD mass spectrometer under the following conditions:

- Analytical column: Agilent HP 5ms Ultra Inert (30 m × 250 µm i.d. × 0.25 µm film thickness)
- Injection volume: 1 µl
- Injection mode: Splitless
- Carrier gas: Helium (99.99%)
- Inlet pressure: 11.933 psi
- GC inlet temperature: 250 °C
- Transfer line (aux heater) temperature: 310 °C
- Ionization type: Electron ionization (EI) at 70 eV
- Ion source temperature: 230 °C
- Quadrupole temperature: 150 °C
- Mass scan range: m/z 25–1000

Oven temperature program:

- Ramp 1: 60 °C, hold for 3 min
- Ramp 2: 60 °C → 180 °C at 7 °C/min
- Ramp 3: 180 °C → 300 °C
- Ramp 4: 300 °C at 8 °C/min, hold for 5 min

Total run time: 36 min.

Identification of the essential oil constituents was performed by comparing the obtained mass spectra with those in computer based libraries and by matching retention indices with published literature data [15].

Cell Culture

The following cell lines were used in this study

• *SKGT 4 (Esophageal carcinoma cell line)*

Established from a primary tumor in 1989 from an 89 year old Caucasian male who presented with dysphagia secondary to a well differentiated adenocarcinoma arising in the Barrett's epithelium of the distal esophagus [16].

• *A2780 (Ovarian carcinoma cell line)*

Derived from an endometrioid adenocarcinoma of the ovary obtained from an untreated patient. The line was deposited with the European Collection of Authenticated Cell Cultures (ECACC) by Dr. T. H. Ward from the Cell Culture Unit, Patterson Laboratories, Christie Hospital, Manchester [17].

• *Normal Human Fibroblasts (NHF)*

Derived from adipose tissue from healthy human donors.

All cell lines were cultured in Minimum Essential Medium (MEM; US Biological, USA) supplemented with 10% (v/v) fetal bovine serum (FBS; Capricorn Scientific, Germany), 100 IU/ml penicillin, and 100 µg/ml streptomycin (Capricorn Scientific, Germany). Cultures were maintained in a humidified incubator at 37 °C with 5% CO_2. Cells in the exponential growth phase were used for all experiments [16].

Cytotoxicity Assay

Cytotoxicity was evaluated using the MTT [3 (4,5 dimethylthiazol 2 yl) 2,5 diphenyltetrazolium bromide] colorimetric assay, which measures the ability of viable cells to reduce the yellow MTT reagent to insoluble purple formazan crystals through mitochondrial dehydrogenase activity.

Cells were seeded at a density of 10,000 cells per well in 96 well microplates (NEST Biotech, China) and incubated at 37 °C for 72 hours to achieve monolayer confluence. The essential oil was sterilized using a syringe microfilter (NEST Biotech, China). Cells were then treated with serial concentrations of *Salvia palaestina* essential oil (100, 50, 25, 12.5, 6.25, and 3.12 µl/ml) diluted in culture medium containing 0.01% DMSO.

After 72 hours of incubation, 28 µl of 2 mg/ml MTT solution (Elabscience, China) was added to each well, followed by a 3 hour incubation period at 37 °C. Subsequently, 100 µl of DMSO was added to each well to solubilize the formazan crystals, and plates were incubated for 15 minutes. The optical density (OD) was measured at 492 nm using a microplate reader.

Cytotoxicity (%) was calculated using the following equation:

Cytotoxicity % = (OD Control – OD sample)/OD Control × 100

where $OD_{(Control)}$ represents the mean optical density of untreated wells and $OD_{(Sample)}$ represents the optical density of wells treated with essential oil [18].

Statistical Analysis

Data represent the mean of three independent replicates used to calculate the percentage inhibition of cell proliferation at each concentration. Dose–response curves were constructed, and IC_{50} values were determined as the concentration of essential oil (EO) that reduced cell viability by 50% relative to the untreated control [19]. Statistical analysis was performed using Tukey's ANOVA multiple comparison test in GraphPad Prism version 8.

Results

Cytotoxic Activity

Treatment with *Salvia palaestina* essential oil resulted in a significant, concentration dependent decrease in cell viability in both cancer cell lines ($p < 0.0001$). At the highest concentration tested (100 µl/ml), cytotoxicity reached 62.8% in SKGT 4 cells and 52.3% in A2780 cells.

The IC_{50} values for the essential oil were 57.9 µl/ml for SKGT 4 cells and 72.9 µl/ml for A2780 cells, indicating slightly higher potency against esophageal carcinoma cells. In contrast, normal human fibroblasts (NHF) exhibited much lower sensitivity, showing only 27.2% cytotoxicity at 100 µl/ml and an IC_{50} of 492.1 µl/ml. (Figures 1–3)

The safety index (SI = IC_{50} of non cancerous cells / IC_{50} of cancer cells) [20] was calculated as 8.5 for SKGT 4 cells and 6.8 for A2780 cells, demonstrating preferential cytotoxicity toward cancer cells.

Morphological assessment under an inverted microscope revealed characteristic features of apoptosis, including cell shrinkage, membrane blebbing, and the formation of apoptotic bodies (Figure 4).

GC/MS

GC MS profiling of *Salvia palaestina* essential oil identified monoterpene hydrocarbons as the predominant chemical class, with limonene as the major constituent (73.05%). Additional phytochemical components are listed in Table 1, and the chromatogram is presented in Figure 5.

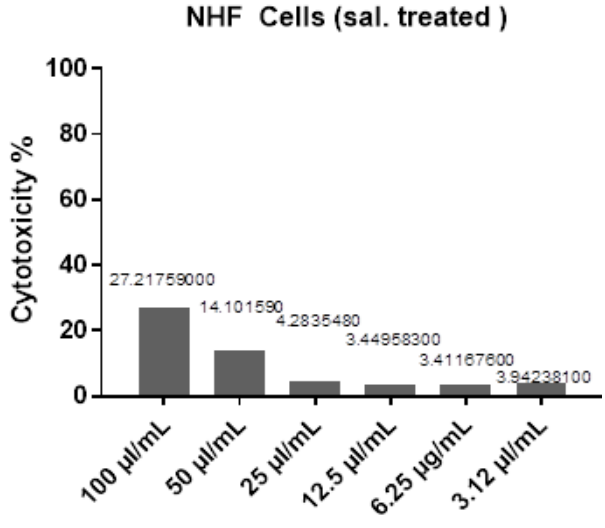

Figure 1. Percentage of Cytotoxicity (Cell Proliferation Inhibition) in Each Studied Concentration of Salvia *Palaestina* essential Oil in Normal Human Fibroblast (NHF) Cells.

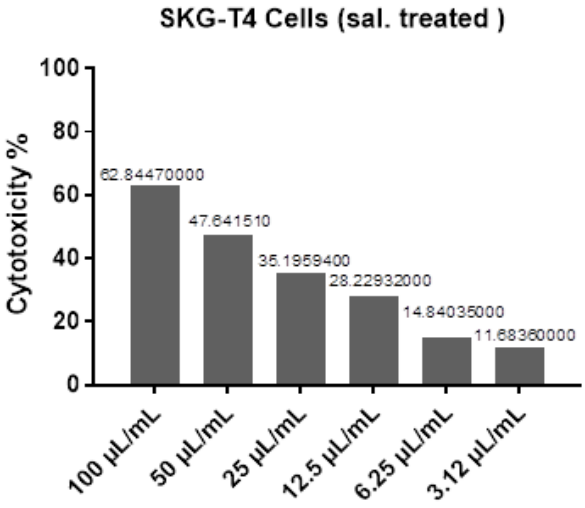

Figure 2. Percentage of Cytotoxicity (Cell Proliferation Inhibition) in Each Studied Concentration of *Salvia Palaestina* Essential Oil in SKG-T4 Cells

Discussion

Many currently used anticancer drugs present significant challenges, including high toxicity, prohibitive costs, and the development of drug resistance [11]. Plants, however, represent a continually rich source of novel anticancer compounds. In recent years, there has been a surge in scientific interest in exploring plants, and particularly their essential oils (EOs), as sources for anticancer agents [9]. This focus is driven by the higher concentration of active compounds typically found in EOs compared to other plant parts or extracts, alongside

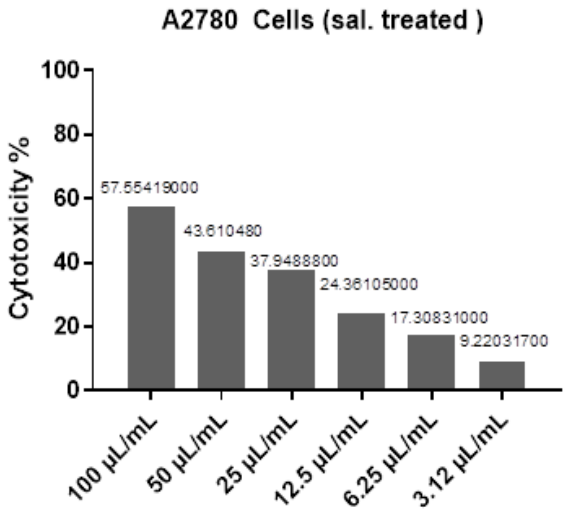

Figure 3. Percentage of Cytotoxicity (Cell Proliferation Inhibition) in each Studied Concentration of *Salvia Palaestina* Essential Oil in A2780 Cells.

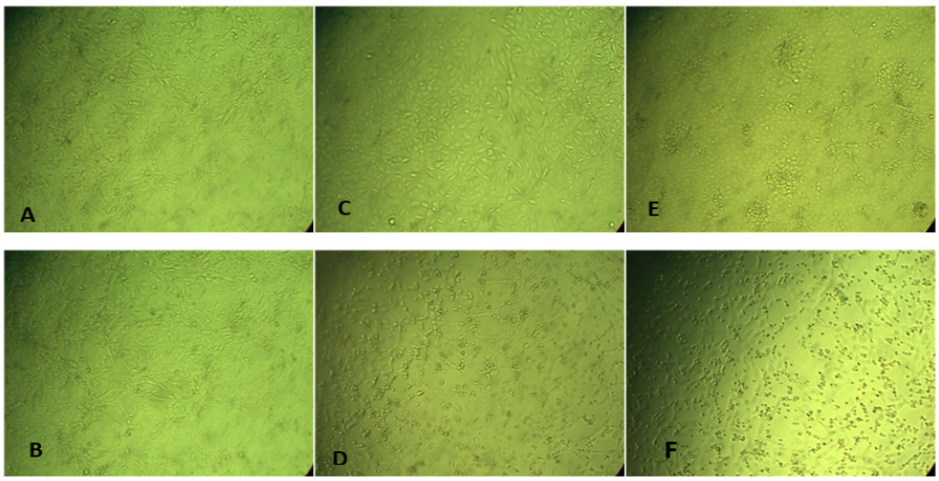

Figure 4. Morphology of Cells; control (untreated) and after treatment with Salvia palaestina essential oil for 72 hrs. (A) NHF control . (B) NHF cell treated. (C) SKG-T4 control, (D) SKG-T4 treated, (E) A2780 cells control, (F) A2780 cells treated

Table 1. Phytochemicals Detected by GC/MS of *salvia palaestina* Essential Oil

Pk#	RT	Area%	Compound	CAS#
1	4.496	73.05	Limonene	000138-86-3
2	5.681	3.69	Camphene	000079-92-5
3	6.512	1.65	(+)-2-Bornanone	000464-49-3
4	7.187	0.41	Terpinen-4-ol	000562-74-3
5	7.447	6.23	alpha. -Terpineol	000098-55-5
6	8.313	0.42	3-Carene	013466-78-9
7	8.979	0.42	Bicyclo[4.3.0] nonane, 3-methylene-	1000152-00-6
8	11.472	0.55	Caryophyllene	000087-44-5
9	13.904	1.24	2-Carene	000554-61-0
10	14.449	1.47	Bicyclo[2.2.1] heptane, 7,7-dimethyl	000471-84-1
10	14.449	1.47	3-Carene	013466-78-9
11	19.123	0.77	Oxalic acid, allyl pentadecyl ester	1000309-24-3
12	20.395	0.52	Cyclopentane undecanoic acid	006053-49-2
12	20.395	0.52	E-11-Tetradecenoic acid	1000130-96-2
13	21.616	1.03	9,12-Octadecadienoic acid (Z,Z)-,	000112-63-0
14	22.377	3.65	9,12-Octadecadienoic acid (Z,Z)-	000060-33-3
15	23.122	0.98	2-Tetradecanol	004706-81-4
16	25.346	0.46	2-Tridecanol	001653-31-2
17	27.441	0.75	Hexadecane, 2,6,10,14-tetramethyl-	000638-36-8
18	34.235	1.35	(. +/-.)-. alpha. -Tocopherol acetate	007695-91-2

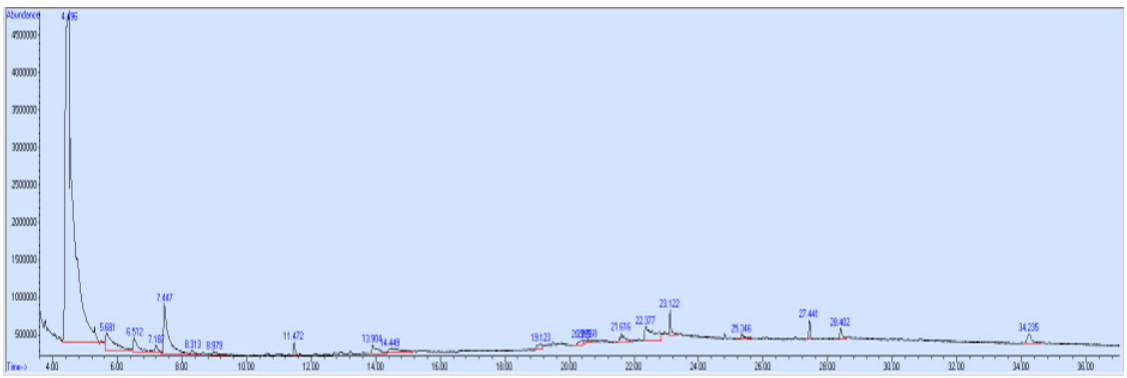

Figure 5. GC-MS Chromatogram of *salvia palaestina* essential Oil

a unique profile of constituents [12, 21]. This study aimed to investigate the anticancer activity of the essential oil extracted from *Salvia palaestina* cultivated in Iraq.

The MTT assay is a standard method for evaluating the potential toxic effects of a compound on cell lines by assessing cell viability across a range of concentrations. Viable cells metabolize the yellow MTT reagent into purple formazan crystals. Following solubilization, the concentration of formazan, which is directly proportional to the number of viable cells, is measured spectrophotometrically, typically at 570 nm. The half-maximal inhibitory concentration (IC_{50}), representing the compound concentration required to reduce cell viability by 50%, is estimated from the resulting dose–response curve [19].

Our findings demonstrate that the essential oil of *Salvia palaestina* exhibits significant and concentration-dependent cytotoxic activity against the SKG-T4 and A2780 cancer cell lines. The calculated IC_{50} values of 57.9 µl/mL for SKG-T4 and 72.9 µl/mL for A2780 indicate potent inhibition of cancer cell proliferation. According to the National Cancer Institute (NCI) guidelines, crude extracts with IC_{50} values below 20 µg/mL are considered to possess strong cytotoxic activity, those between 21–200 µg/mL are moderately cytotoxic, and values between 201–500 µg/mL indicate weak activity [22]. Our results fall within the moderate categories, suggesting potential for development.

Crucially, the essential oil displayed markedly lower cytotoxicity towards normal human fibroblasts (NHF), with an IC_{50} of 492.1 µl/mL. This resulted in favorable selectivity indices (SI) of 8.5 for SKG-T4 and 6.8 for A2780. Such selectivity, indicating a higher toxicity towards cancer cells compared to normal cells, is highly desirable for therapeutic applications as it expands the therapeutic window.

Morphological observations further corroborated these quantitative findings. Microscopic examination revealed characteristic apoptotic features in treated cancer cells, including cell shrinkage, membrane blebbing, and the formation of apoptotic bodies (Figure 4), suggesting that the observed cytotoxicity is mediated, at least in part, by programmed cell death.

Extracts of *Salvia palaestina* have been investigated for various pharmacological activities. These include antioxidant properties attributed to the presence of numerous phenolic compounds, particularly flavonoids [23]; demonstrated anti-bacterial efficacy [24]; inhibitory effects on the 15-LO enzyme, which partially supports its folkloric use in wound healing [25]; and antitumor activities [13, 26]. While previous research has explored the antimicrobial [27, 28] and antioxidant [29] properties of S. palaestina essential oil, its anticancer potential has not been previously studied.

The findings of this study align with previous research demonstrating the anticancer potential of extracts and essential oils from other Salvia species. These studies indicate that Salvia species can exert selective antiproliferative effects on various cancer types, primarily by inducing apoptosis and inhibiting invasion and metastasis pathways [30–32].

The proposed primary mechanism for the anticancer effect of *Salvia palaestina* essential oil in this study is the induction of apoptosis in cancer cells, though other mechanisms may also contribute. Several plant-derived essential oils, including those from eucalyptus, chamomile, Artemisia vulgaris (mugwort), and Verbena officinalis, have been shown to induce apoptosis in tumor cells. Furthermore, certain essential oils are known to disrupt mitochondrial membrane potential. Research suggests that essential oils can initiate both the intrinsic (mitochondria-dependent) and extrinsic (death receptor-dependent) apoptotic pathways. In addition to these pro-apoptotic effects, essential oils often display antioxidant properties and can inhibit cell proliferation [9].

The observed cytotoxic and selective properties of *Salvia palaestina* essential oil position it as a promising candidate for further anticancer drug development. However, extensive in vitro and in vivo investigations are warranted to fully elucidate its mechanism of action and comprehensively assess its safety profile.

GC/MS

The Gas Chromatography-Mass Spectrometry (GC/MS) analysis of the *Salvia palaestina* essential oil revealed a complex phytochemical profile rich in compounds with documented anticancer effects. Limonene was identified as the major constituent (73.05%), providing strong evidence for anticancer potential. Decades of research, including Phase I/II clinical trials, have demonstrated D-limonene's efficacy in triggering tumor regression in breast cancer patients and its chemopreventive activity in rodent models across various cancer types [33]. Additionally, a Phase I clinical trial by Vigushin et al. (1998) further supports its therapeutic promise [34]. Other notable constituents with robust preclinical anticancer evidence include Terpinen-4-ol [12, 35] and α-Terpineol [36]. The oil also contained Camphene, β-Caryophyllene [37], Humulene (α-Caryophyllene) [38], and Camphor ((+)-2-Bornanone) [39], among other phytochemicals with potential anticancer activities.

A significant finding of this study is the distinct chemical composition of the Iraqi S. palaestina essential oil compared to samples from other regions [25, 40]. Previous research in other areas identified sesquiterpenes, particularly β-caryophyllene and linalool, as major constituents [15, 29, 41, 42]. In contrast, the Iraqi S. palaestina essential oil analyzed here was predominantly rich in limonene (73%). This compositional difference highlights the impact of geographical origin and environmental factors on the chemotype of S. palaestina and may explain variations in observed biological activities.

Salvia palaestina is a valuable source of phytochemicals exhibiting a range of pharmacological effects, including anti-inflammatory [25], antibiotic [24, 43], and antioxidant [44] activities.

In conclusion, the essential oil of *Salvia palaestina* demonstrates significant potential as an anticancer agent. This is supported by its concentration-dependent cytotoxic effect on cancer cells, coupled with a favorable safety index, suggesting a potential therapeutic window. To

further validate these promising findings and definitively confirm its anticancer efficacy, subsequent in vivo studies are recommended.

Author Contribution Statement

Hiba Abdulmohsin: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft. Mohammed Qasim: Conceptualization, Funding Acquisition, Project Administration, Resources, Supervision, Writing – Review & Editing.

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Approval

This research did not require formal ethical approval as it did not involve human subjects or sensitive data. The study forms part of an approved PhD thesis, with committee approval documentation provided as supplementary material.

Conflict of Interest

There is no conflict of interest

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