In Vitro Biological Activity of Ethanolic Extract of Maramiyah (*Salvia Libanotica*) and Its Combination with Essential Oil

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ABSTRACT

Introduction: *Salvia libanotica* (sage) is one of most famous and traditional herbs popular throughout the Arab world. Extracts of *S. libanotica* are found to be useful as traditional medicine. The current study aimed to further explore the phyto-constituents of the plant and its biological activity. Methodology The present study investigated the phytochemical constituent of sage and its synergism with essential oils using classical method. Biological activity was evaluated as immunomodulatory activity, anti-bacterial, cytotoxic and anti-cancer activity in vitro. **Results**: One hundred gram of ethanolic crude extract was prepared from sage leaves using classical method; its combination with essential oil was prepared as 1:1 ratio. Phytochemical studies demonstrated positive results for tannins, flavonoids and triterpenes/sterols. Immunomodulatory activity revealed that ethanolic extract is effectively inhibiting the free radicals generated during inflammation. Mild antibacterial activity was found against all gram negative bacteria in ethanolic extract but not with essential oils. Whereas, gram positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* were significantly ($p<0.05$) inhibited by ethanolic extract as well as synergistic combination of olive oil and balsam oil. Our results demonstrated that ethanolic extract with balsam oil possess significant activity ($p<0.005$) against *Bacillus subtilis* up to 80% inhibition. Furthermore. For anticancer potential on HeLa cells, combination of ethanolic extract with balsam oil was able to show mild activity 44% cell growth inhibition. However, ethanolic extract of sage was found to be toxic to fibroblast cells with IC_{50} value of 11.5+0.7. **Conclusion.** Results suggested that ethanolic extracts of most famous herb sage usually consume as tea is toxic to normal cells system as tested on fibroblast, conversely its synergistic effect with olive oil and balsam oil reduces the toxicity. Inhibition of free radical by ethanolic extract may be because of its toxic effect. Extract also showed limited anticancer activity against HeLa cells in presence of balsam oil. Hence, sage could be a leading plant against gram positive pathogen when combined with essential oils with reduced toxicity, however ethanolic extract of sage is potentially cytotoxic.

Key Words: *Respiratory burst, inflammation, anti-cancer, anti-bacterial*

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INTRODUCTION

Medicinal plants have been utilized since thousands of years ago for curing different diseases of human beings and animals and are still in use by a great percentage of world population for being well. A number of researchers are trying to analyze the traditional medicines for their useful effects and the results are promising [1, 2]. More than 50% of all the present drugs in clinical applications are of natural origin, many of which have the potential to control cancer cells [3]. Medicinal plants have immunomodulatory and antioxidant features, causing anticancer activities. They are known to possess versatile immunomodulatory activity by inducing both non-specific and specific immunity [4]. The antioxidants may prevent and treat cancer and other illnesses by protecting the cells from damage caused by free radicals. Many plant-derived products exhibit potent antitumor activity against various rodent and human cancer cell lines [5].

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Salvia libanotica (also named *S. fruiticosa* and *S. triloba*) of the "Lamiaceae" family is an aromatic medicinal plant commonly known as East Mediterranean sage or Lebanese sage [6]. In Lebanon, Syria and Jordan, the plant is commercially available and widely utilized by the elderly and folk medicine practitioners [7] The genus *Salvia* L. (Lamiaceae) includes about 900 species, spread all over the world, some of which with great economic value since they are utilized as spices and flavoring agents by perfumery and cosmetic industries [8, 9]. *Salvia* spp. has also been utilized for a long time in folk medicine as medication against fever, rheumatism, perspiration, sexual debility, and in the treatment of chronic bronchitis, as well as mental and nervous diseases [10]. The most famous species are common sage (*Salvia officinalis* L.), trilobed sage (*Salvia fruticose* Mill.), and Spanish sage (*Salvia lavandulifolia* Vahl) [11]. Sage, is a perennial, evergreen subshrub, with woody stems, grayish leaves, and blue to purplish flowers. It is native to the Mediterranean region, being currently grown in various countries [11, 12]. Sage is one of the oldest medicinal plants, and the etymology of the Latin name suggests its healing features, with *Salvia* deriving from the Latin verb salvare = to save or to cure. Sage is largely utilized as a savory food flavoring either as dried leaves or essential oil [13]. Sage leaves and its essential oil have carminative, antispasmodic, antiseptic, astringent, and antihidrotic features [11]. The predominant medicinally valuable metabolites are monoterpenes (e.g., - and - thujone, 1,8-cineole, camphor), diterpenes (e.g., carnosic acid) triterpenes (oleanoic and ursolic acids), and phenolic compounds like rosmarinic acid [14–16]. Essential oil of sage and their preparations are externally applied for inflammations and infections of the mucous membranes of throat and mouth (stomatitis, gingivitis, and pharyngitis). Internally, the essential oil is used for dyspeptic symptoms and excessive perspiration [11]. Although the biological activity of *S. officinalis* is well established, but little is known about the biological and therapeutic potential of *S. libanotica*, so in this context we have selected this herb knowing the fact that it is widely used as green tea among all Saudi Arabian peoples. Therefore, we must explore its in vitro therapeutic effectiveness

MATERIALS AND METHODS

Plant material and Extraction

Sage (*Salvia libanotica*), an aromatic herb native to the lands surrounding the Mediterranean Sea, was obtained in purified form from Jordan, dried and blended as powdered leaves. *Salvia libanotica* (500 g) was subjected to percolation with 10-fold ethanol 70%. The combined alcoholic extracts were concentrated under reduced pressure at a temperature of 40ºC till dryness to yield 70 g of total extract. The concentrated ethanol extract was mixed with 0.5 L of deionized water and partitioned several times with n-hexane, chloroform, ethyl acetate and n-butanol, then concentrated under reduced pressure at 40ºC to give 20g, 16g, 8g and 18g, respectively using classical method. Phytochemical Studies Phytochemical studies were carried out on all fractions by reported method. The tests were performed to find out the presence of Alkaloids (Mayer's Test, Wagner's Test and Dragendorff's Test), Carbohydrates/Glycosides (Molisch Test, Fehling Test), Tannins (FeCl3 Test), Saponins (Froth Test), Flavonoids (Sodium Hydroxide Test), Triterpenoids (Acetic anhydride Test) and Anthraquinones (Borntragers Test). All chemicals used were of analytical grade [17].

Immunomodulating activity

Luminol-enhanced chemiluminescence assay was performed, [18] various concentrations of extracts of ethanol (A), synergism with olive oil (B), and synergism with balsam oil (C) (50, 150 and 250 µg/mL) were incubated at 37 ºC for 15 minutes in the thermostat chamber of luminometer with whole blood in another set of experiment. After incubation intracellular reactive oxygen detecting probe luminol working solution (7 x 10^{-5} M), and serum opsonized zymosan (SOZ) was added into each well except blank wells (containing only $HBSS^{++}$). The oxidative burst ROS production was monitored with the luminometer for 50 minutes in the repeated scan mode. The level of the ROS was recorded as total integral readings as relatively light units (RLU).

Determination of Cytotoxicity and anti-cancer activity

Hela cells and 3T3 mouse fibroblast cells were maintained at sub-confluence in DMEM medium supplemented with 10% FBS, 1% Pen/Strep (penicillin, streptomycin), and 1% glutamine. Cell lines were maintained in a humidified incubator at 37 ºC with 5% CO_2. The cytotoxic and anti-cancer activity test was done using MTT assay as describe previously [19]. To find cytotoxic effects 3T3 (6×10^4) cells were plated in a 96-well flat bottom plates for 24 hours to allow the cells attachment. The media were replaced, various concentration of the test compounds (50, 5, 0.5 µg/mL) were added into the wells and the plates were further incubated for 48 hours. The medium was again removed by flipping the plate. MTT solution (200 µL) was added to the wells and the plates were incubated for 4 hours at 37ºC. The solutions were aspirated from each well and the cells were mixed with 100 µL of DMSO for 15 minutes on a rocker to dissolve the formazan crystals. The absorbance was measured at 570 nm by microplate Spectra Max 340 (Molecular Devices, CA, USA) and the IC_{50} values were calculated. The anticancer activity of the test compound was determined by using the same method

as above. The cells were replaced with Hela cervical cancer cell line at concentration of $5x10^5$ cells/mL. Cyclohexamide was used, as a positive control to induce cellular toxicity.

Antimicrobial Activity

Agar well diffusion method was utilized to investigate antimicrobial activity following reported procedure [20]. The test sample was used in concentration of 3 mg/mL and zones of inhibition were measured as mm ± standard deviation. The activity of tested samples was studied against the *Staphylococcus aureus* (AICC25923), and *Bacillus subtilis* (NCTC8236), *Pseudomonas aeruginosa* (AICC27853), *Escherichia coli* (AICC25922), and *Salmonella typhi* (ATCC-19430).

Data analysis

The results were expressed as percentage and mean ± standard deviation (S.D.); p-values less than 0.05 and 0.005 were considered statistically significant *p< 0.05 ** p< 0.005

RESULTS:

Phytochemical screening

The initial phytochemical screening of ethanolic extract fractions of sage extract revealed positive results for tannins, flavonoids and triterpenes/sterols. Alkaloid and Saponins were not found in ethanolic extract (Table 1).

Table 1. Screening of Phyto-constituents in *Salvia libanotica*

Samples	Phyto-constituents
Alkaloid	negative
Tannins	positive
Saponin	negative
Triterpenoid	positive
flavanoids	positive
Sterols	positive

Effect of *Salvia libanotica* as antibacterial agent

Anti-microbial activity of all three extracts i.e. ethanol (A), synergism with olive oil (B) and synergism with balsam oil (C) was carried out against some gram positive and gram negative bacterial strains mentioned in Table 2. All samples were found to be moderately effective p<0.05 against *Staphylococcus aureus* with percent inhibition of 60±0.8%, 62±0.5%, and 34±0.06%, respectively. *Bacillus subtilis* was inhibited with significant percentage of inhibition (57±0.2%, 66±0.2%, 80±0.6% respectively). Inhibition of gram positive bacteria suggests that the compound may have inhibitory effect on cell wall peptidoglycan. On the other hand, the gram negative bacteria remain unaffected by the compound and its combinations, because of presence of lipopolysaccharide on the outer surface that doesn't allow these fractions to enter in bacterial cell. The ethanolic extract showed mild inhibitory effect against *Salmonella typhi*, *P. aeruginosa*, *E. coli* with percentage inhibition of below 30%. Ofloxacin was used as standard drug that showed % inhibition against *S aureus*, *B subtilis P. aeruginosa*, *E. coli* and *Salmonella typhi* as 94.7%, 92.5%, 92.4%, 88%, and 94.1%, respectively.

Table 2. Antimicrobial activity of *Salvia libanotica* extracts against selected microorganisms.

	% inhibition ±SDV at 200µg/mL			
Bacterial strains	Ethanol (A)	Ethanol extract +olive oil (B)	Ethanol extract +Balsam oil (C)	Standard (Ofloxacin)
Gram +ve bacterial strains				
Staphylococcus aureus (ATCC25923)	60± 0.8*	34± 0.06	62± 0.5*	94.7± 0.5
Bacillus subtilis (NCTC8236)	57± 0.2*	66± 0.2*	80± 0.6**	92.5± 0.4
Gram -ve bacterial strains				
Pseudomonas aeruginosa (ATCC27853)	30.5± 0.1	19± 0.3	NI	92.4± 0.1
Escherichia coli (ATCC25922)	26.5± 0.1	NI	NI	88± 0.08
Salmonella typhi	33± 0.2	NI	0.6± 0.01	94.1± 0.2

NI = no inhibition
*p<0.05**p<0.005

Effect of *Salvia libanotica* on Immunomodulation

Immunomodulatory properties of crude extracts and fractions were evaluated using oxidative burst assay by chemilluminescence. The peripheral whole blood cells were activated with zymosan and incubated with compounds. The results showed mild inhibitory activity against reactive oxygen species (ROS) production using 3 concentrations (250, 50, 5 µg/mL) of ethanolic extract. The synergistic activity was not effective against immunomodulation until 250 µg/mL (Table 3).

Table 3. Immunomodulatory activity of plant extracts using chemilluminescence technique on activated whole blood phagocytes.

S. No	Sample 250µg/mL	Average IC_{50} ±SDV µg/mL
1	Ethanolic extract sage	30 ± 2.1
6	Ethanolic + olive oil (1:1)	> 250
7	Ethanolic +Balsam oil (1:1)	> 250
8	Ibuprofen	43.4±0.9

Effect of *Salvia libanotica* on cell viability and anti-cancer activity.

Effect of sage and its combination on cell viability was determined on 3T3 Fibroblast cells, the percentage of inhibition was determined and compared with the standard drug Cyclohexamide. The data is presented in table 4. The ethanolic extract was added at final concentration of 30µg/mL and fibroblast cell were incubated for 48 hours. The result showed significant inhibition of up to 80% of cell growth and therefore IC_{50} value was identified using 3 different concentrations 50, 5 and 0.5 µg/mL. IC_{50} value for ethanolic extract was 11.5 +0.7 that clearly demonstrated toxic potential of Maramiyah on fibroblast cells. However, the synergistic effect with essential oils reduced the toxicity to 45% by balsam oil and 15% with olive oil. These ethanolic extract appear to be more toxic when compared to the Cyclohexamide, that is inhibiting the cell growth up to 71%.

Salvia libanotica extracts and combinations were analyzed for its anti-cancer activity on Hela cervical cancer cell line. The data presented in table 4 indicated that *S. libanotica* is not able to suppress cancer cell viability significantly except in combination with balsam oil exhibited moderate anticancer activity by inhibiting the cancer cell growth with percent inhibition of 44% and results were compared with standard drug doxorubicin that is inhibiting the Hela cells by 71.3% at same concentration.

Table 4. Cytotoxic activity of plant extracts using MTT Assay on 3t3 fibroblast cells and cervical cancer cell line at final concentration of 30µg/mL

S. No	Sample 30µg/mL	Average % inhibition HeLa cervical cancer cells	Average % inhibition 3T3 fibroblast cells	IC_{50}
1	Ethanol extract sage	1.0±0.03	80±0.03	0.7+ 11.5
2	Ethanolic +Balsam oil (1:1)	44±0.6	45±0.9	NA
3	Ethanolic + olive oil (1:1)	1±0.04	15±0.08	NA
4	Doxorubicin	71.3±4.0	NA	1.2±0.2
5	Cyclohexamide	NA	71.4±0.05	0.8±0.2

NA: not applicable

DISCUSSION

The results of our investigation confirmed the rationale for the medicinal use of the *Saliva libanotica* (sage). It is used as traditional medicine as antiseptic, antiscabies, antisyphilitic, and anti-inflammatory, being frequently used against skin diseases as reported earlier [21]. Our study, based on biological effects of *S. libanotica* alone as well as its synergistic effect with olive oil and balsam oil in 1:1 ratio, aimed the assessment of the antibacterial and anti-inflammatory potential and their cytotoxicity on HeLa cancer cells and 3T3 fibroblast cells.

One hundred gram of ethanolic crude extract was prepared from sage and was subjected to phytochemical studies. Tannins, flavonoids and triterpenes/sterols present in the ethanolic extract were responsible for biological activity [22]. Mild antibacterial activity was found against all gram negative bacteria in ethanolic extract but not with essential oils. Whereas, gram positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* were significantly inhibited by ethanolic as well as synergistic combination of olive oil and balsam oil. It has been known that *Saliva* specie possess significant biological potential. The phytochemical analyses of various sage plants have reported monoterpenoids and diterpenoids with cytotoxic, antimicrobial, antiprotozoal, antioxidant, phytotoxic and insecticide effects. The other heavier terpenoids, including 3 sesterterpenes, triterpenoids and β-sitosterol have been introduced as minor bioactive compounds in the sage plants. [23]. We have observed the individual effect of sage as well as its synergism that was certainly enhanced with balsam oil against *Bacillus subtilis* up to 80%. Many previous researches suggested the growth-inhibitory and proapoptotic effects of the sage essential oils against human melanoma cell lines, A375, M14, and A2058 [24] and colon cancer [25]. However, anticancer potential of sage on HeLa cells in presence of balsam oil was able to show mild anti-cancer activity. Nevertheless, in our study sage has no effect on Hela Cancer cell line. In contrast, ethanolic extract sage was found to be toxic to fibroblast cells as reported earlier that consuming too much could have side effects which can be caused by the high content of thujone. [26]. This intriguing study revealed the toxicity potential of sage against normal cells but not against cervical cancer cells.

CONCLUSION:

Although, Sage has been consuming as herbal tea since centuries, its toxic effect cannot be undermined, specifically to normal cells system, while synergistic effect with olive oil and balsam oil could be helpful to reduce the toxicity. The observation related to immunomodulating potential of sage could be because of its toxic effect on immune cells. Extract also showed limited anticancer activity against HeLa cells in presence of balsam oil but not alone. Hence, sage could be a leading plant against the pathogen when combined with essential oils with reduced toxicity.

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