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ORIGINAL RESEARCH

Myrtus communis Leaf Extract Modulates IL-1α and VEGF Gene Expressions in HaCaT Cells: Probable Implications for Its Beneficial Effects in Hair Loss and Wound Healing

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Background and Objective: *Myrtus communis* L. (*M. communis*) is an aromatic evergreen perennial plant, which is native to Mediterranean region and West Asia, has been used in numerous diseases including some disorders of skin in traditional medicine. This study investigates the modulatory effects of *M. communis* leaf extract on IL-1α and VEGF gene expressions in human keratinocytes (HaCaT cells), considering the beneficial outcomes of this plant in hair loss and wound healing.

Methods: After preparing the *M. communis* leaf extract, implementing the phytochemical analysis and determining the non-cytotoxic concentration, we incubated HaCaT cells with the extract. RNA isolations were made from both incubated and unincubated cell groups. Gene expressions were performed by real time RT-qPCR analysis.

Results: In phytochemical analysis, *M. communis* leaf extract was found to contain 1255 ppm total phenolic substance. Results of gene expression analyses were defined as Target/Control Fold Change, and the extract yielded statistically significant downregulation of IL-1α ($p = 0.0014$) and upregulation of VEGF ($p = 0.0021$) in the incubated HaCaT cells, compared to unincubated control cells.

Conclusion: These preliminary results, which show *M. communis* leaf extract can modulate the gene expressions of IL-1α and VEGF, may partially be related with the healing effects of this plant for both non-cicatricial hair loss and chronic cutaneous wounds, reported in traditional medicine. Further, in-vitro and in-vivo experiments are needed to understand the mechanisms of the healing effects of *M. communis*.

Keywords: *Myrtus communis*, IL-1α, VEGF, hair loss, wound healing

Introduction

Myrtus communis L. (*M. communis*), myrtle, is an aromatic evergreen perennial shrub which pertains to family Myrtaceae. It is native to Southern Europe, North Africa and West Asia.[1] In folk medicine, its berries, sprigs, and leaves have been used for treating diseases of digestive, neurologic, cardiovascular, pulmonary, locomotor, urinary and integumentary systems, probably owing to its antimicrobial, antiinflammatory and antioxidant properties.[2–4] The biological properties displayed by different parts of *M. communis* may depend upon to final products such as essential oils containing terpenes, terpenoids, phenylpropanoids or varied extracts containing polyphenolic compounds such as phenolic acids, tannins, and flavonoids.[2,5] Factors which can influence the chemical profile like the type of extraction, solvents, utilised plant parts, maturation stage of plant and antioxidant activity of various *M. communis* extracts were studied previously.[2] It was revealed that leaf extracts comprised considerably greater quantities of total phenolic

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compounds than the berry extracts.[5] In addition, it was shown a significant positive correlation between the quantities of total phenols and antiinflammatory or antioxidant features of *M. communis* extracts.[2,6]

In the field of dermatology, the therapeutic use of *M. communis* generally focused on hair loss control and wound healing.[1,3,4,7–10] In an ethnobotanical study performed in Morocco, the leaves of *M. communis* were reported to be used for softening, brightening and inducing growth of the hair.[8] In a study performed on rabbits, the combination of *Rosmarinus officinalis* and *M. communis* extracts significantly enhanced hair growth in androgenetic alopecia (AGA) and it had also a comparable efficacy with minoxidil.[9] It was reported a significant boost in revascularization and a considerable increase in fibroblast quantities in the rats which received the methanolic extract of *M. communis*, compared to silver sulphadiazin group on second-degree burn wounds. In a clinical study performed on the patients with oral aphtous ulcers, significant reductions in ulcer size, pain severity, erythema and exudation levels were recorded in the group of patients who had been treated with oral paste prepared from *M. communis* leaves.[3] *M. communis* aqueous extract-containing gel was reported to have wound healing potential in streptozotocin-induced diabetic rats.[11]

Considering the literature data, especially for the healing effects of *M. communis* on hair loss and cutaneous wounds, we hypothesized that this plant would reduce pro-inflammatory- and increase pro-repair-gene expressions in the skin. Therefore, we incubated a human keratinocyte cell line (HaCaT cells) with *M. communis* leaf extract, in order to determine the gene expression levels of interleukin-1α (IL-1α), a pro-inflammatory mediator, and vascular endothelial growth factor (VEGF), a pro-repair mediator, which were previously reported as having negative and positive impacts, respectively, both on hair growth and wound healing.

Materials and Methods

Plant Material and Preparation of the Extract

The leaves of *M. communis* were collected in İzmir, Western Turkey, in June and identifed in our laboratory, based on a reference book for flora of Turkey[12] and a stereo microscope by botanist Berrin Akyıldırım, PhD. Microwave dried (500 W, 5 min.) leaves of the plant were used for extraction. Forty grams of fine-cut leaves were extracted with 500 mL distilled water using a Soxhlet extractor at the boiling point of the solvent, completing two full cycles. The extract was filtered through a 0.45 µm filter into a glass vial. Aqueous extraction was preferred for the experiment because both it reflects the traditional use and it is more convenient for the preparation of probable topical products.

Phytochemical Analysis

The analytical procedure performed via HPLC was adapted from the literature[13] with slight changes. The system was Shimadzu (Japan), UFCL prominence with a SPD-M20A PDA detector and the column was GL Sciences, ODS-3250 mm × 3 mm × 3 µm octadecylsilyl silica gel. System conditions were as follows: Mobile Phase A: Water (1:1000) - phosphoric acid; Mobile Phase B: Acetonitrile; Flow, 0.5 mL × min^{-1}; Injection Volume, 20 µL; Column Temperature, 25°C.

HaCaT Cell Line

The cell line was supplied by Cell Lines Service (Germany). Cells were grown in our laboratory and stored under appropriate conditions.

Chemicals and Reagents

High-glucose Dulbecco's Modified Eagles Medium (DMEM), Fetal Bovine Serum (FBS), and Tri-Reagent were supplied by Sigma Aldrich (USA). dNTP set, Taq polymerase, and reverse transciptase were supplied by Fermantas (Lithuania). Fast Start DNA Green Master Mix and XTT Reagent were supplied by Roche Diagnostics (Switzerland). Primers were ordered from Integrated DNA Technologies (USA). Tryple-Express was supplied by Life Technologies (USA).

Primers

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was selected as the reference gene. Primer sequences (5'-3') for the GAPDH, IL-1α and VEGF genes are shown in Table 1.

Cell Culture Conditions

HaCaT keratinocyte cells were grown in DMEM containing high glucose, 10% heat-inactivated FBS, and 1% gentamicin. The cells were incubated at 37°C in a humidified atmosphere of 5% CO_2.

Passaging

Cells were passaged at 3–4 day intervals. First, the medium in the plate was discarded and the cells were washed with 3–4 mL of phosphate buffered saline. Cells were lifted using 500 µL of Tryple-Express for 100 mm plates and 250 µL for 60 mm plates. The cells were incubated for 5 min. and examined under an inverted microscope to ensure the cells had been lifted. About 3–4 mL of DMEM was added. The cell lysate was transferred to a 15 mL sterile flask and centrifuged at 300 × g for 5 min. The supernatant was discarded, and the pellet was either dissolved in serum-containing medium or in Tri-Reagent for RNA isolation.

Cell Proliferation Assay and Cytotoxicity Analysis

The toxicity of plant extract at the cellular level was investigated using the XTT Cell Proliferation Assay. Cells were lifted from the plate surface according to the passaging protocol and solubilized in DMEM containing the appropriate amount of serum and antibiotics. Cell concentration was determined by counting cells using a Thomas hemacytometer under an inverted microscope. Cytotoxicity analysis is based on the principle that metabolically active cells can convert the yellow tetrazolium salt XTT into orange formazan crystals. Formazan crystals are water-soluble, and their intensity at a specific wavelength can be measured spectrophotometrically. In this case, the dye absorbance will be proportional to the number of metabolically active cells. For cytotoxicity analysis, 10,000 cells were seeded into wells using a 96-well plate on the first day. These were treated for 24 hours at 37°C, 5% CO_2. On the second day, the medium was decanted and fresh medium was added, and plant extracts prepared at different concentrations (100%, 3%, 1%, 0.5%, 0%) were added to the wells. The wells were treated for 72 hours at 37°C, 5% CO_2. At the end of the 72-hour treatment period, XTT solution and activator were added to a final concentration of 0.3 mg/mL. The wells were treated for 4 hours at 37°C, 5% CO_2, and then readings were taken at 450 nm using a Biorad-iMax microplate reader (Bio-Rad, USA). The study was conducted in triplicate. Compared to the control group, the live cell ratios at the abovementioned concentrations were calculated and accordingly the appropriate extract dose for incubation was determined. The concentration of extract was chosen at the value which corresponded to nearest 80% cell proliferation ratio. Otherwise, to take that ratio higher or lower would make the experiment to be performed with a very low or toxic concentration, respectively, which might be inappropriate for the outcomes.

Table 1 Primers (5' - 3') of the Genes Studied

Primers	Forward Primer	Reverse Primer
GAPDH*	ATGGGTGTGAACCATGAGAA	GTGCTAAGCAGTTGGTGGTG
IL-1α	ACCAGTGCTGCTGAAGGAGAT	GTGCCGTGAGTTTCCCAGAA
VEGF	ATGCGGATCAAACCTCACCA	CCACAGGGACGGGATTTCTTG

Note: **GAPDH is the reference gene.*

Total RNA Isolation

The cells were incubated with extracts at appropriate concentrations in the medium for three days. The cells were then lifted from the surface using Tryple-Express and a passaging protocol was applied. The cell pellet was homogenized in 1.5 mL of Tri-Reagent. Following incubation, 300 µL of chloroform was added and shaken for 15 seconds. Phase separation was observed, and centrifuged at 12,000 × g, 4°C, for 15 min. After centrifugation, the clear supernatant was transferred to an RNAse-free tube, and 500 µL of cold isopropanol was added and incubated for 10 min. at room temperature. The pellet was then centrifuged at 12,000 × g, 4°C, for 10 min. After discarding the supernatant, the pellet was washed with 1.5 mL of cold 75% EtOH and then left at room temperature to evaporate the ethanol. It was dissolved in an appropriate amount of sterile, RNAse-free water. It was incubated in a block heater at 55°C for 10 min. It was stored at −20°C. The quantity and purity of the isolated total RNA were measured using a Biospec-nano instrument (Shimadzu, Japan) and determined by the spectrophotometric wavelength values of 260 nm and 280 nm. A pure RNA should have an A260/280 value between 1.8 and 2.0.

Reverse Transcription (RT)

For complementary DNA (cDNA) synthesis, 1 µg of RNA and 2 µL of primer (10 mM) were added to an RNAse-free Eppendorf tube and the final volume was made up to 13 µL with RNAse-free dH_2O. The tube was incubated at 65°C for 5 min. The tube was then placed on ice, and 4 µL of RT Buffer (5X), 2 µL of dNTP-mix (10 mM), and 1 µL of Moloney-Murine Leukemia Virus Reverse Transcriptase (Fermentas, Lithuania) were added. The tube was incubated for 60 min. at 42°C and for 10 min. at 72°C in the thermal cycler. The final product was stored at −20°C.

Quantitative Polymerase Chain Reaction (q-PCR)

For each reaction, 10 µL of Sybr Green, 10 mM forward and reverse primers, 25 ng of template cDNA, and an appropriate amount of RNAse-free dH_2O were added to reach a final reaction volume of 20 µL. Each sample was prepared in triplicate. Three no-template controls and four standards (1:1, 1:10, 1:100, 1:1000) were added to the reaction. Relative quantification analysis was performed using Roche LightCycler Software (Roche Diagnostics, Switzerland). Target gene expression (relative to GAPDH gene expression) in extracted and untreated cells was calculated as a fold change using the formula: Fold change = $2^{-\Delta\Delta Ct,}$ *where*

$$\Delta\Delta Ct = \left(Ct_{target} - Ct_{internal\ control}\right)_{treatment} - \left(Ct_{target} - Ct_{internal\ control}\right)_{no\ treatment}.$$

Statistical Analysis

Experiments were independently repeated at least three times before statistical analysis, which was performed using GraphPad Prism 5.0 Software. Changes in expression of various genes in the extracted cell groups, compared to the control gene and the control group, were calculated. The results were analyzed using paired *t*-test. Data are expressed as mean ± standard error of the means, together with 95% confidence interval. Statistical significance was defined as $p < 0.05$.

Results

Phytochemical Analysis

The phenolic compounds detected by high performance liquid chromatography (HPLC) analysis of *M. communis* leaf extract are listed in Table 2.

The phenolic compound analysis of *M. communis* revealed that *myricetin, gallic acid* and *malic acid* were the most notable compounds. The raw extract without any further processing contained 1255 ppm total phenolic substance.

Cell Proliferation Assay and Cytotoxicity Analysis

Considering the concentrations of the extract that cause different cytotoxicity levels, the cell proliferation ratios of treated cells were found. The concentration of extract at the value which corresponds to nearest 80% cell proliferation ratio was

Table 2 Phenolic Compounds Detected in *Myrtus communis* Leaf Extract

Phenolic Compound	Concentration (µg/mL)
Fumaric acid	10
Gallic acid	463
Caffeic acid	4
p-Coumaric acid	20
Malic acid	129
Caftaric acid	3
Chlorogenic acid	2
Quercetin	35
Myricetin	589
Total	**1255**

chosen. As the higher and lower concentrations would be incompatible and would give inaccurate results based on our experiences, the most feasible concentration was settled as 1% (w/v) for the following analysis, and therefore HaCaT cells were incubated with 1% (w/v) concentration of the extract (Figure 1).

Gene Expression Analysis

Analyses via real time reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) showed that plant extract caused statistically significant downregulation of IL-1α ($p = 0.0014$) and significant upregulation of VEGF ($p = 0.0021$) gene expressions in incubated HaCaT cells, compared to unincubated control cells. Results were defined as Target/GAPDH Fold Change. The incubation of HaCaT cells in *M. communis* leaf extract ended up with 0.45 ± 0.10 and 8.38 ± 1.04 fold changes for IL-1α and VEGF, respectively (Figure 2).

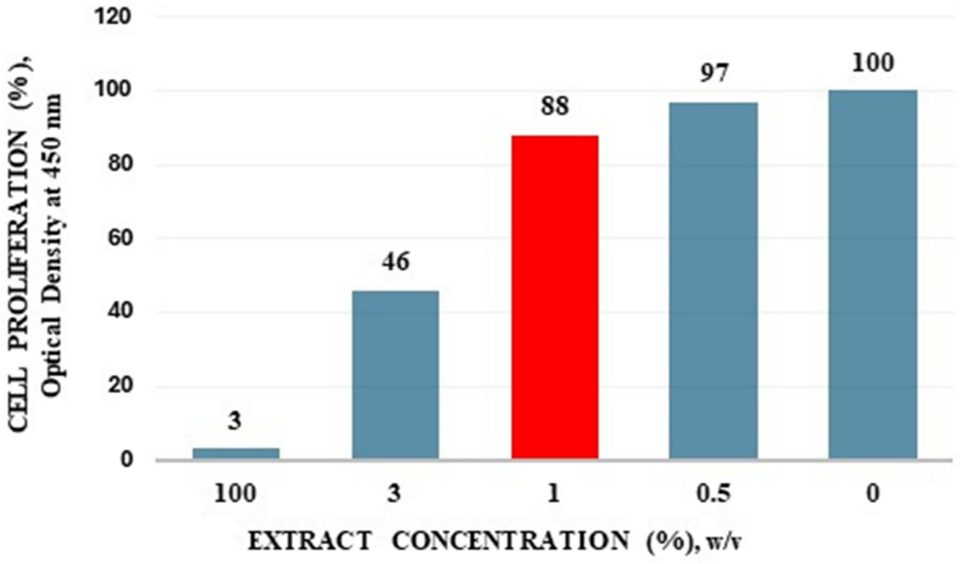

Figure 1 Cytotoxicity analysis result of *Myrtus communis* leaf extract. The red bar represents the extract concentration chosen for incubation.

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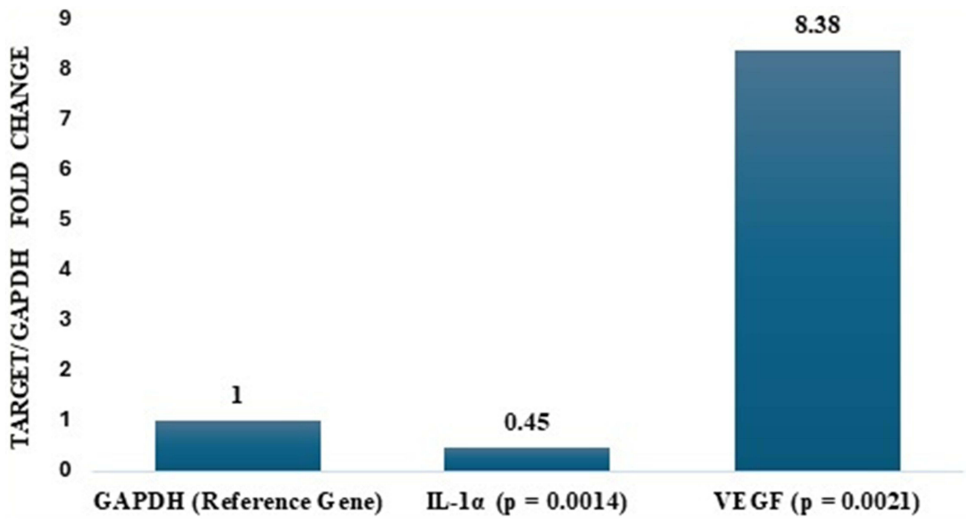

Figure 2 Gene expression levels and p values of IL-1α and VEGF in HaCaT cells incubated in *Myrtus communis* leaf extract, compared to unincubated control cells.

Discussion

IL-1α is a pro-inflammatory polypeptide mediator, and keratinocytes have the ability to both synthesizing and reacting to it, confirming that it has important functions in epidermal physiopathology.[14,15] IL-1α has antiproliferative effects in hair follicles and it is a prominent agent in the pathogenesis of AGA, telogen effluvium, and alopecia areata.[16–20] Additionally, it was shown that IL-1α was downregulated during anagen phase of hair cycle.[21,22] Besides hair growth, IL-1α has negative effects also on wound healing. Although it conducts wound healing reactions after various injuries, uncontrolled IL-1α increase can promote inflammation leading to tissue damage.[23] Treatment of burn wounds in rats reduced IL-1α in the lesions.[24] In a study comparing the fluids collected from acute and chronic wounds, IL-1α levels in the acute wound fluids were found significantly lower. But, while the chronic wounds continued to recover, IL-1α levels were shown to decrease significantly compared to their initial values. IL-1α was also found to stimulate collagenase production.[25]

On the other hand, VEGF is a widely manifested pro-angiogenic factor in the integumentary system. It is synthesized by diverse cell categories, but primarily by keratinocytes.[26] Follicular keratinocytes release VEGF, which boosts perifollicular angiogenesis and causes enlargement in the sizes of follicles.[27] VEGF mainly stimulates hair growth by easing the replacement of nutritional molecules in the follicles.[28] Minoxidil was shown to increase human hair follicle vascularization by increasing the expression of VEGF in dermal papilla cells.[29] In a study performed to reveal VEGF expression in cultured human follicular cells, dermal papilla cells, fibrous sheath fibroblasts, dermal fibroblasts, and keratinocytes; all expressed VEGF in various amounts at mRNA level.[30] VEGF is also critical in wound healing and it is an indispensable factor in fibroblast migration. It accelerates tissue repair via increasing vascularization, epithelialization, and collagen deposition.[31,32] VEGF synthesis was found decreased in chronic diabetic wounds, implying that the insufficiency of this factor might be related with failure in wound repair.[26]

Regarding the abovementioned reports, it can be suggested that, while VEGF exerts positive effects on hair growth and wound healing, IL-1α has negative effects on both. Therefore, our results given as significant downregulation of IL-1α with a fold change of 0.45 and significant upregulation of VEGF with a fold change of 8.38 caused by *M. communis* leaf extract may partially explain the healing effects of this plant for both non-cicatricial hair loss and chronic cutaneous wounds, reported in traditional medicine. Lack of protein level validations may be considered as the limitation of this study. Due to the close relationship between the quantities of total phenols and antiinflammatory or antioxidant features of *M. communis* extracts;[2,6] the phenolic contents of our extract probably contributed to the relevant modulatory effects. Therefore, the main phenolic compounds; *myricetin, gallic acid* and *malic acid* can be considered as the bioactive molecules of this extract. On the other hand, it should be kept in sight that extracts, unlike pharmaceuticals, do not have sole targets and mechanisms of action.[7] The complexity of chemical composition of extracts indicates participation of varied mechanisms, or the compounds

may act in synergistic ways.[5] It is quite probable that the revealed features of *M. communis* leaf extract, as inhibition of IL-1α and induction of VEGF, together with its antiinflammatory and antioxidant effects which are proved by its phenolic contents, work synergistically against both hair loss and cutaneous ulcers. Indeed, to establish a cause-effect relationship in this manner, will be quite complicated and will need additional studies for each revealed effect and constituent separately, and then collectively to uncover probable synergistic effects. Through additional in-vitro and in-vivo studies, and by way of understanding its constituents and mechanisms of therapeutic effects further, *M. communis* may be utilized in producing supportive topical medicinal products against both non-cicatricial hair loss and chronic cutaneous wounds.

Conclusions

Given the significant positive correlation between the phenolic contents and antiinflammatory or antioxidant activities of the plant, it might be considered that the rich phenolic content of *M. communis* leaf extract supports its beneficial effects to a great extent. The significant downregulation of IL-1α and upregulation of VEGF gene expressions provide preliminary evidence that leaf extract of this plant modulates gene expressions in keratinocytes, which may partially explain the healing effects of this plant for both non-cicatricial hair loss and chronic cutaneous wounds, reported in traditional medicine.

Abbreviations

AGA, Androgenetic alopecia; DMEM, Dulbecco's Modified Eagle Medium; GAPDH, Glyceraldehyde-3-phosphate dehydrogenase; HaCaT cells, Human keratinocyte cell line; HPLC, High performance liquid chromatography; IL-1α, Interleukin-1α; *M. communis, Myrtus communis*; RT-qPCR, Reverse transcriptase quantitative polymerase chain reaction; VEGF, Vascular endothelial growth factor.

Data Sharing Statement

The original contributions presented in this study are included in this article. Further inquiries can be directed to the corresponding author.

Ethics Statement

This study did not require ethical approval as it did not involve humans or animals.

Disclosure

The authors report no conflicts of interest in this work.

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