



## Research Paper

# Reporting effectiveness of an extract of three traditional Cretan herbs on upper respiratory tract infection: Results from a double-blind randomized controlled trial



G. Duijker<sup>a,1</sup>, A. Bertias<sup>a,1</sup>, E.K. Symvoulakis<sup>a,1</sup>, J. Moschandreas<sup>b</sup>, N. Malliaraki<sup>c</sup>, S.P. Derdas<sup>d</sup>, G.K. Tsikalas<sup>g</sup>, H.E. Katerinopoulos<sup>g</sup>, S.A. Pirintzos<sup>e,h</sup>, G. Sourvinos<sup>d</sup>, E. Castanas<sup>f</sup>, C. Lionis<sup>a,\*</sup>

<sup>a</sup> Clinic of Social and Family Medicine, School of Medicine, University of Crete, PO Box 2208, Heraklion 71003, Greece

<sup>b</sup> Department of Social Medicine, School of Medicine, University of Crete, Heraklion, Greece

<sup>c</sup> Department of Clinical Chemistry-Biochemistry, School of Medicine, University of Crete, and University Hospital, Heraklion, Greece

<sup>d</sup> Laboratory of Clinical Virology, School of Medicine, University of Crete, Heraklion, Greece

<sup>e</sup> Department of Biology, School of Sciences and Technology, University of Crete, Heraklion, Greece

<sup>f</sup> Laboratory of Experimental Endocrinology, School of Medicine, University of Crete, Heraklion, Greece

<sup>g</sup> Department of Chemistry, School of Sciences and Technology, University of Crete, Heraklion, Greece

<sup>h</sup> Botanical Garden, University of Crete, Rethymnon, Greece

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## ABSTRACT

**Ethnopharmacological relevance:** Observations from the island of Crete, Greece suggest that infusions of traditional Cretan aromatic plants, well known for their ethnopharmacological use in Eastern Mediterranean region and Near East, could be effective in the prevention and treatment of upper respiratory tract infections, including viral-induced infections. The aim of this study was to report the effectiveness of an essential-oil extract of three Cretan aromatic plants in the treatment of cases with an upper respiratory tract infection.

**Materials and methods:** A double blind randomized controlled trial was implemented between October 2013 and February 2014. An essential-oil extract of Cretan aromatic plants in olive oil (total volume of 15 ml of essential oil per litre of olive oil) was administered as 0.5 ml soft gel capsules, twice a day, for 7 days. Placebo treatment was 0.5 ml olive oil in soft gel capsules. Eligible patients were those presenting for clinical examination in the selected setting with signs and symptoms of upper respiratory tract infection that had begun within the previous 24 hours. Real-Time Polymerase Chain Reaction (PCR) was used for the detection of respiratory viruses. The primary outcome was the severity and duration of symptoms of upper respiratory tract infection, assessed using the Wisconsin Upper Respiratory System Survey (WURSS-21) questionnaire. A secondary outcome of interest was the change in C-reactive protein (CRP) status.

**Results:** One hundred and five patients completed the study: 51 in the placebo group, and 54 in the intervention (treated) group. Baseline characteristics were similar in the two groups. No statistically significant differences were found in symptom duration or severity between the two groups, although small and clinically favorable effects were observed. When the analysis was restricted to subjects with a laboratory-documented viral infection, the percentage of patients with cessation of symptoms after 6 days of treatment was 91% in the intervention group and 70% in the control group ( $p=0.089$ ). At baseline, one third of the patients in each group had elevated CRP levels. At follow-up, the respective proportions were 0% in the intervention group and 15% in the placebo group ( $p=0.121$ ). The data were also in a favorable direction when 50% and 80% symptom reduction points were considered for specific virus types.

**Abbreviations:** ml, Milliliter; PCR, Polymerase Chain Reaction; CRP, C-reactive protein; WURSS, Wisconsin Upper Respiratory Symptom Survey; AUC, area under the curve; RCT, randomized controlled trial; GP, General Practitioner; RBC, red blood cells; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; ASAT, SGOT, serum glutamic oxaloacetic transaminase; ALP, alkaline phosphatase; PLT, thrombocytes; ALAT, SGPT, serum glutamic pyruvic transaminase; hRSV, human respiratory syncytial virus; hMpV, human metapneumovirus; hPiv, human parainfluenza virus; hCov, human coronavirus; hRv, human rhinovirus; BMI, body mass index; ln, natural logarithm

\* Corresponding author. Tel.: +30 2810394621/30 2810394671.

E-mail addresses: [gdujker@hotmail.com](mailto:gdujker@hotmail.com) (G. Duijker), [abertias@med.uoc.gr](mailto:abertias@med.uoc.gr) (A. Bertias), [symvouman@yahoo.com](mailto:symvouman@yahoo.com) (E.K. Symvoulakis), [j.moschandreas@med.uoc.gr](mailto:j.moschandreas@med.uoc.gr) (J. Moschandreas), [nikimall@me.com](mailto:nikimall@me.com) (N. Malliaraki), [derdas@med.uoc.gr](mailto:derdas@med.uoc.gr) (S.P. Derdas), [gtsikalas@chemistry.uoc.gr](mailto:gtsikalas@chemistry.uoc.gr) (G.K. Tsikalas), [kater@chemistry.uoc.gr](mailto:kater@chemistry.uoc.gr) (H.E. Katerinopoulos), [pirintzos@biology.uoc.gr](mailto:pirintzos@biology.uoc.gr) (S.A. Pirintzos), [sourvino@med.uoc.gr](mailto:sourvino@med.uoc.gr) (G. Sourvinos), [castanas@med.uoc.gr](mailto:castanas@med.uoc.gr) (E. Castanas), [lionis@galinos.med.uoc.gr](mailto:lionis@galinos.med.uoc.gr) (C. Lionis).

<sup>1</sup> These authors contributed equally.

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**Conclusions:** Compared with placebo the essential-oil extract of three Cretan aromatic plants provided no detectable statistically significant benefit or harm in the patients with upper respiratory illness, although descriptive differences were identified in favorable direction mainly in the virus-positive population.

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## 1. Introduction

Novel H1N1, referred also as “swine flu”, as well as other viral agents involved in common cold infections, compose a public health problem, accountable for many visits to primary and secondary health care services and hospital admissions; additionally, a considerable number of deaths is likewise documented, especially in vulnerable people. These infections are easily transmitted by exposure to infected droplets expelled by coughing or sneezing that can be inhaled, or contaminated hands or surfaces. Symptoms include fever, cough, headache, muscle and joint pain, sore throat and runny nose, and sometimes vomiting and diarrhea. The new Influenza A (H1N1) appears to be as contagious as seasonal influenza, and spreads rapidly, particularly amongst young people. The severity of the disease ranges from very mild symptoms to serious illness and occasionally even death. The majority of people who contract the virus experience mild disease and recover without antiviral treatment or medical care. Additionally, more than 50% of serious hospitalized cases have underlying health conditions or impaired immune function. Antiviral drugs may reduce the symptoms and duration of illness and may also contribute to preventing severe disease and death. However, the effectiveness and cost of administered therapy remains an interesting topic for further investigation, as a recent Cochrane meta-analysis, although contested, reported a limited effect of Oseltamivir (Tamiflu<sup>®</sup>), a classical antiviral drug (Jefferson et al., 2014), mainly related to the time-limited and usual self-healing nature of the disease.

Much discussion has been dedicated to the use of herbal medicine for the common cold. A randomised controlled trial (RCT) has reported on the effects of So-cheoug-ryong-tang (Ko et al., 2004) and Yeon-gyo-pae-dok-san on the common cold (Byun et al., 2011). The use of herbs as ailments in the island of Crete has been mentioned since the Bronze Age (Arnott, 1996). Herbal medicine also has a long history in ancient Greece. Popular medical handbooks from the Byzantine era forward incorporated material rooted in ancient medicine and routinely claimed Hippocrates and Galen (among others) as sources (Clark, 2002). In current times, the antioxidant activity of herbs in rural Crete has been investigated and it has been shown that herbal extracts decrease lipid peroxidation in cultured lung cells exposed to iron or ozone (Lionis et al., 2004).

Previous ethnobotanical field studies have revealed the existence of an indigenous knowledge system in rural Crete and certain combinations of different aromatic plants in rural areas of Crete have been used for the prevention and cure of the common cold and influenza (Lionis et al., 1998). The biological effects and bioactivity of essential oils and as well as their antibacterial properties have been reported in the literature (Cowan, 1999; Burt, 2004; Bakkali et al., 2008; Koroch et al., 2007). Similarly, the antiviral potential of medicinal plants has been discussed as well (Jassim and Naji, 2003; Mukhtar et al., 2008). It is also exciting that even though the term “virus” is a very recent term in modern medicine (Silverstein, 2009), these rural societies, without any prior knowledge of the term and in the absence of any immunologic knowledge, were protecting the population using traditional and folk-medicine. As stated above, it was interesting to study to what extent this ethnopharmacological knowledge is evidence-based and effective in virus-induced diseases. To that effort we have also taken into account certain Cretan history and archeological elements, as well as their ethnopharmacological uses in the Eastern Mediterranean and Near East regions, suggesting a beneficial action of such a combination in upper respiratory viral infections (Dafni et al., 1984;

Honda et al., 1996; Lev and Amar, 2002; Said et al., 2002; Hanlidou et al., 2004; Lardos, 2006; Hudaib et al., 2008).

As stated above, this study reports the results of the effectiveness of an extract based on three Cretan aromatic plants in the reduction of duration and severity of symptoms of patients with upper respiratory tract infections, utilizing a standardized questionnaire, physical examination measurements and the decrease of inflammation assayed by C-reactive protein [CRP] levels.

## 2. Subjects and methods

### 2.1. Plant material identification

Plant material has been identified by one of the authors (SP) and voucher specimens of the three species have been deposited at the Herbarium TAU of the Aristotle University of Thessaloniki (UOCSP101-1, UOCSP101-2, and UOCSP101-3).

### 2.2. Preparation of essential oil extracts

Formulation of the essential oil extracts was provided by the authors and prepared by Olvos SA, according to the patents and patent applications related to the subject (WO2010GB01836 20100929; GB20090017086 20090929; EP2482831; CN102762218) of thyme or Spanish oregano (*Coridothymus capitatus* (L.) Rchb. f. synonym of *Thymbra capitata* (L.) Cav.), dictamnus or Cretan dittany (*Origanum dictamnus* L.) and sage (*Salvia fruticosa* Mill., *Salvia pomifera* L.) extracts through steam distillation. Analysis of essential oils was performed by Gas Chromatography–Mass Spectroscopy, in a GC–MS, Shimadzu, QP 5050A apparatus. GC was equipped with MDN-5 column (length 30 m, film thickness 0.25 µm, diameter 0.25 mm, max. useable temperature 325 °C) and a Quadrupole Mass Spectrometer as detector. MDN-5 column temperature was initially 50 °C for 5 min. It was then gradually increased to 150 °C at 5 °C/min and kept for 10 min, and finally increased to 280 °C at 5 °C/min and held for 20 min. The carrier gas was helium, the flow rate 0.9 mL/min. 2 µL was used as an injection volume. The sample was measured in a split mode procedure with a split ratio 1:35. Injector and detector were maintained at 230 and 250 °C, respectively. For GS–MS detection an electron ionization system was used with ionization energy at 70 eV. The chemical and percentage composition of specific constituents in each essential oil (Adams, 2007) is shown in Supplemental Tables 1–3.

Essential oils (at a dilution of 15 ml/L) in extra virgin olive oil (used as a vehicle) were formulated as 0.5 ml soft-gel capsules, for a daily dose of two capsules. This dose has been based on anthropological reports of fieldwork work studies carried on Crete (Lionis et al. 2004) and corresponds to two cups of infusion of the aforementioned aromatic plants. Placebo capsules contained only extra-virgin oil, equally formulated as 0.5 ml soft-gel capsules. GC–MS chemical and percentage composition of the formulated mixture (Adams, 2007) are shown in Supplemental Table 4.

### 2.3. Subjects and setting

Participants were recruited from October 10th, 2013 to February 10th, 2014. Eligible subjects were patients aged 18 years or older, presenting at their local Health Centre of Harakas in the prefecture of Heraklion, in rural Crete, Greece, with symptoms of upper respiratory

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