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SHORT COMMUNICATION

Phenolics diversity among wild populations of *Salvia multicaulis*: as a precious source for antimicrobial and antioxidant applications

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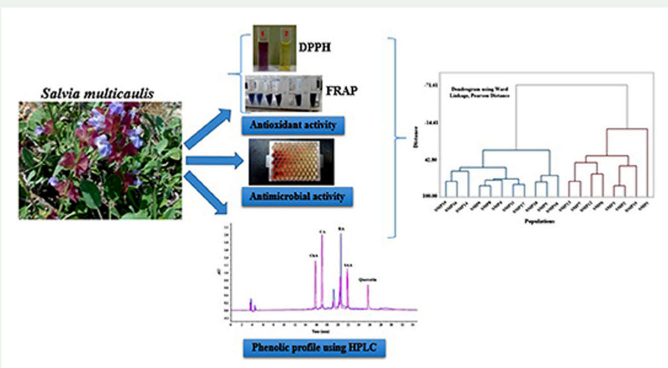
ABSTRACT

The genus *Salvia* L. belongs to the Lamiaceae family including several known species rich in natural compounds that are extensively used in pharmaceutical, food, and cosmetic industries. *Salvia multicaulis* populations contain a broad diversity of flavonoids and phenolic acids. The present study aimed to explore biological and pharmacological effects including antimicrobial and antioxidant activities of nineteen *S. multicaulis* populations (*SMPs*) grown in Iran for the first time. High content of rosmarinic acid (RA) in *SMP12* (Gazan) (5.65 ± 0.33 mg/g DW) caused high antimicrobial activity against two bacteria (*Staphylococcus aureus*, *Escherichia coli*) and the fungus *Candida albicans*, while methanolic extract of *SMP1* (Taleghan) showed high antioxidant activity due to high content of salvianolic acid A (SAA) and quercetin (0.53 ± 0.04 and 0.49 ± 0.12 mg/g DW, respectively). Altogether these results can be considered for further commercial exploitations to meet the demands of the food and pharmaceutical industries.



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1. Introduction

For centuries, many territories have used medicinal and aromatic plants (MAPs) to treat an extensive range of diseases (Cowan 1999). Secondary metabolites (SMs), produced by MAPs, are widely used in the pharmaceutical industry for their range of biological activities and significant structural diversity (Ernst 2005). Polyphenols are considered well-known SMs recognized as natural antioxidants. These bioactive compounds can be divided based on their chemical structures into two groups: flavonoids and non-flavonoids (Manach et al. 2004). Phenolic SMs, especially flavonoids and tannins, are known to have antibacterial properties and to suppress several microbial virulence factors (Daglia 2012). The evaluation of different populations and the survey in detail of the phytochemical variations associated with biological activities is necessary for commercializing wild MAPs. The discovery and production of industrial pharmaceutical products from plants are closely related to the phytochemical evaluation of the plant populations. Finding the best population as plant material for domestication and breeding is considered as one of the most important step for commercializing medicinal plants. Recently, the *Salvia* genus has attracted great interests owing to the findings related to some valuable bioactive compounds in different plant organs. *Salvia* is regarded as an important genus in the Lamiaceae family including almost 1000 species with a wide geographic distribution around the world, along with 58 species grow in Iran of which 17 are endemic (Rechinger 1982).

Salvia multicaulis Vahl (Lamiaceae) is an endemic species that is widespread in the Middle East region and disseminated in North, West, southwest, northeast and central parts of Iran. *S. multicaulis* contains phytochemicals such as diterpenoids, norditerpenoids, triterpenoids, salvimultine, flavonoids, and phenolic acids ((Ulubelen and Topcu 2000). So far, twenty-two flavonoid compounds (Flavones, flavanones, flavonols, isoflavones, dihydroflavonols, chalcones) were identified in *S. multicaulis* (Kharazian 2013; Kharazian 2014). Also, Rowshan and Najafian (2020) reported that rosmarinic acid is the most abundant polyphenol compound in *S. multicaulis* and followed by catechin, vanillin, chlorogenic acid, quercetin, and p-coumaric acid. Recently, the cytotoxicity of the plant methanolic extract has been reported against cancer cell lines (Abdollahi-Ghehi et al. 2019). The present study aimed to evaluate the extracts from 19 *S. multicaulis* populations (*SMPs*) in Iran for the first time (Figure S1), analyzing the presence phenolic acids including salvianolic acid A (SAA), rosmarinic acid (RA), chlorogenic acid (ChA), and caffeic acid (CA), as well as quercetin and evaluating the antioxidant and *in vitro* antimicrobial activity.

2. Results and discussion

2.1. HPLC determination of phenolic compounds

Four phenolic acids (phenyl-propanoid) and one flavonoid (Figure S2; Table S1) were identified by reverse-phase HPLC in the extracts of 19 *SMPs* including ChA, RA, CA, SAA, and quercetin. Interestingly, RA was the major phenolic acid in all the populations while quercetin flavonoid was the minor compound, which was not even detectable in several populations. The methanolic extract of *SMP1* showed high content of

SAA and quercetin (0.53 ± 0.04 and 0.49 ± 0.12 mg/g DW, respectively) while high content of RA obtained from *SMP7*, *SMP12*, and *SMP13* (5.13 ± 0.35, 5.65 ± 0.33, 4.87 ± 0.59 mg/g DW, respectively). Roby et al. (2013) reported that the predominant phenolic compounds of *Salvia officinalis* L. are ferulic acid, RA, and apigenin, respectively. In another study, Askun et al. (2009) indicated that the most prominent phenolic compounds detected via HPLC analyses were related to RA, rutin, and catechin in *Salvia tomentosa* and CA in *Salvia fruticosa*. The different results obtained by HPLC analysis in different species can be related to genetic diversity, the different growth conditions, the extraction method, and the type of solvent used. The 19 *SMPs* demonstrated various amounts of phenolic compounds.

2.2. Antioxidant activity

Antioxidant activity of the extracts of *SMPs* was estimated through two assays: DPPH and FRAP (Table S2). Based on the results obtained in this paper, antioxidant activity was statistically different among *SMPs* ($p < 0.01$) (Table S2). The highest antioxidant activity in *SMPs* extracts was estimated in *SMP1* by DPPH and FRAP assay (93.02% and 521.66 ± 36.58 μmol acid ascorbic/g DW, respectively). In the present study, the antioxidant activity of *SMPs* extracts can be related to polyphenol content. Izabela et al. (2018) indicated that there are the positive correlations between antioxidant activity and phenolic compounds concentrations in *S. sclarea*. Although there is not necessarily a positive correlation between phenolic and non-phenolic compounds with antioxidant activity (Elfalleh et al. 2019), it can be concluded that the phenolic components could remarkably contribute to the antioxidant activity of the MAPs (Ghasemi Pirbalouti et al. 2014).

2.3. Antimicrobial activity

Antimicrobial activity of plant extracts was tested using the microdilution method with one strain of a Gram-positive bacteria (*Staphylococcus aureus*), a strain of a Gram-negative bacteria (*Escherichia coli*), and a pathogenic fungus (*Candida albicans*) (Table S2). The MIC values obtained from antimicrobial tests ranged from 0.5 to 32 mg/mL for *E. coli*, 0.125 to 8 mg/mL for *S. aureus* and 4 to 64 mg/mL for *C. albicans*. The results showed that the bacterial strain *S. aureus* was the most sensitive to *SMP8* and *SMP12* extracts, with a MIC value of 0.125 mg/mL. The lowest resistance of *E. coli* (MIC value of 0.5 mg/ml) was against *SMP12* extract. Furthermore, the fungus *C. albicans* was the most sensitive to *SMP12*, *SMP14* and *SMP18* extracts, with the MIC value of 4 mg/mL. Many studies performed on the antimicrobial activity of the *Salvia* genus in Iran are related to the essential oils (Jassbi et al. 2012). In the present study, it is possible that a correlation exists between the phenolic content and the antimicrobial activity of the methanolic extracts of *SMPs*. The high content of RA for *SMP7*, *SMP12*, and *SMP13* caused high antimicrobial activity (Table S2). Phenolic acids are non-flavonoid polyphenolic compounds (Chandrasekara and Shahidi 2010), with known antimicrobial activity against some potential respiratory pathogens including *P. aeruginosa*, *S. aureus*, *Moraxella catarrhalis,* and *Enterococcus faecalis* as well as Gram-negative bacteria are more susceptible than Gram-positive strains (Coppo and Marchese 2014). Conversely, in the present study, Gram-positive bacteria (*S. aureus*) indicated a higher sensitivity to methanolic extracts than Gram-negative bacteria (*E. Coli*).

The data related to phenolic contents and antioxidant activity were used to perform a cluster analysis of the 19 *SMPs* (Figure S3). The populations were divided into two main groups. Based on the results, *SMP1*, *SMP2*, *SMP3*, *SMP6*, *SMP7*, *SMP12*, *SMP13*, and *SMP15* were arranged in one group with the highest antioxidant activity and the highest phenolic content that result in the highest antimicrobial activity.

3. Conclusions

In the present study, the antioxidant and antimicrobial activity, and individual phenolic contents in methanolic extracts from 19 *SMPs* were analyzed. Broad variations were revealed in the antioxidant and antimicrobial activity as well as in phenolic contents. *SMP1* from Taleghan-Alborz had the strongest antioxidant activity while *SMP12* from Gazan-Kordestan had the strongest antimicrobial activity. Regarding phenolic indices, antioxidant and antimicrobial activity, *SMP1* and *SMP12* were the best candidate populations for domestication and crop improvement. Probably, different geographical regions and various abiotic factors can explain the different amounts of SMs detected in plant populations. Overall, the obtained results suggest that the methanolic extracts of *SMPs*, especially *SMP1* and *SMP12* are regarded as useful sources for the food and pharmaceutical industry. In addition, concerning terpenoids, future studies can focus on improving medicinal properties.

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Disclosure statement

The authors declared that no conflict of interest between authors.

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