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In vitro antioxidant, antibiofilm, anticholinesterase andanti-tyrosinase activities of *Senecio hoggariensis* hydro- methanolic extract

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Abstract

This study was carried out to identify the phenolic profile of hydro-methanolic extract from an endemic Algerian species *Senecio hoggariensis* and to investigate their health properties in particular with respect to antioxidant, anticholinesterase, anti-tyrosinase, antimicrobial and antibiofilm activities. Using high-performance liquid chromatography (HPLC-DAD) techniques, nine compounds were identified: chlorogenic acid, curcumin, 4-hydroxylresorkinol, rutin, elagic acid, protocatechic acid, 4-hydroxy benzaldehid, pyrocatechol and 4-oh-benzoic acid. Antioxidant properties were determined using:DPPH$^{\bullet}$ (2,2′-diphenyl-1-picrylhydrazyl radical), ABTS$^{\bullet+}$ (2, 2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid radical cation)), β-carotene linolic acid,CUPRAC (cupric reducing antioxidant capacity) and metal chelating assays. The extract showed mild activity compared to standards. The ability of the extract to inhibit enzymes: acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and tyrosinase was investigated. The studied extract showed relatively moderate tyrosinase inhibitory activity. Also, it inhibited the development of all tested microorganisms; the highest antibiofilm activity was 51.08 % against *Candida albicans* ATCC 10239 biofilm production at 10 mg/ml concentration. The findings indicate that *S.hoggariensis* may be an alternative source of content in the fight against bacterial infections.

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Introduction

Oxidative stress is mainly marked by the lack of imbalance in the development and degradation of reactive oxygen and nitrogen species (Fujii *et al*., 2011).It is distinguished as significant in the induction and spread of many late ailments such as irritation, cataracts, tumors, autoimmune and neurodegenerative disorders (Pham-Huy *et al*., 2008). The quest for newer natural antioxidants, mainly of plant origin, has been accelerating ever since (Dehpour *et al*., 2009). Antioxidant components are extensively found in many medicinal plants, vegetables, and fruits, particularly phenolic compounds, which, when consumed, have been proved to prevent the destructive/degenerative effects caused by oxidative stress (Vinson *et al*., 2001). However, it was claimed that oxidative stress plays a role in the pathogenesis of Alzheimer's disease (AD) and other neurodegenerative disorders. The risk of AD can be diminished by large and quotidian consumption of antioxidants. It can also be delayed by the inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes (Senol *et al*., 2001). Many reports assert that anticholinesterase and anti-tyrosinase are related to the antioxidant activity (Brahmi *et al*., 2015). Thus, our research investigates the antioxidant activity, as well as the anticholinesterase and anti-tyrosinase activities.

Besides having antioxidant capacity, the phenolic compounds can also inhibit the growth of microbes depending on their concentration (Pinho *et al*., 2014; Martins *et al*., 2015). Bacterial resistance and severity of infections are contributed by bacterial biofilm, which consists of polysaccharides and certain proteins that help protect the bacterial colonies from pressure, environmental stress, host immune system, and antibiotics (Rana *et al*., 2020). Inhibition of biofilm formation is thought to be the main drug target for treating a wide variety of infections. These drugs' pharmacological production is now being widely studied (Namasivayam*et al*., 2013).

In the Asteraceae family, *Senecio* (Senecioneae) is the most voluminous and complex genus (Tidjani *et al*., 2013). It contains more than 1500 globally distributed species, which are charted to include many triterpenoids, alkaloids, phenolic compounds and volatile oils (Yang *et al*., 2011). Some of the classes showed considerable biological activities (antioxidant, antimicrobial activities besides antidiabetic, cytotoxic properties, antifeedant and toxic effects)(Loizzo *et al*., 2004).*Senecio hoggariensis* is an endemic species in the Sahara Mountains in Algeria, Niger, Chad and Egypt (Lebrun *et al*., 1981). Only one literature search for identifying flavonoids of *S.hoggariensis* growing in Egypt (Ragaa *et al*., 1981). The present work aimed to identify, for the first time, the phenolic compounds of the crude extract of *S.hoggariensis* and to investigate their biological properties, mainly focusing on their antioxidant, anticholinesterase, anti-tyrosinase, antimicrobial and antibiofilm activity.

Material and methods

Plant collection and identification

Plant material was collected from El-Hoggar Mountains (South-West Algeria) in April 2017. It was identified by Dr. Youcef Halice (technical Research Centre for Arid Areas). Their voucher specimen was deposited at Larbi Ben Mhidi University, Laboratory of Biomolecules and Plant Breeding, Oum El Bouaghi, Algeria, under the herbarium number ZA67.

Extract preparation procedure

At room temperature,air-dried and powdered aerial parts (100 g) were macerated with an 80/20 mixture of methanol/water. A residue was obtained after filtration and evaporation of the solvent at a low temperature (< 50°) and low pressure.

Analysis of phenolic compounds

The analysis of the hydro-methanolic extract and 27 phenolic standards were carried out using a Shimadzu reverse-phasehigh-performance liquid chromatography (RP-HPLC-DAD) (Shimadzu Cooperation, Japan) system that consistsof a Shimadzu model LC-20AT solvent delivery unit and a Shimadzu model SPD-M20A diode array detection system. They were controlled by LC-solution software

(CBM-20A System Controller Shimadzu). The column temperature was set at 35 ^{0}C. The chromatographic separation was performed on an Inertsil ODS-3 (4µm, 4.0 mm × 150 mm) column and Inertsil ODS-3 guard column, mobile phases were aqueous acetic acid 0.1% (A) and methanol (B). Gradient elution from 2% to 100% was performed as previously shown by Barros *et al.*(2009) and Tel-Çayan *et al.*(2015). The stock solution of this sample was prepared in methanol at 8 mg/ml and filtered with an Agilent 0.45 µm filter.

The injected volume was 20 µL. Detection was carried out adiode array detector (DAD) using 254 nm wavelength. The detectedphenolics were characterized by a comparison of their retention times and results were expressed as micrograms per gram of dry weight.

Antioxidant activity

The total antioxidant activity of the studied extract was determined usingthe β carotene-linoleic acid test system as previously reported in the literatureby Miller(1971) methods witha slightly modified version (Sabudak*et al.*, 2009).The assay described byBlois (1958) withminor modificationÖztürk*et al.*(2014)was used to assess the DPPH$^{\bullet}$ (2,2′-diphenyl-1-picrylhydrazyl radical)radical scavenging activity. The spectrophotometric analysis of ABTS$^{\bullet+}$(2, 2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid radical cation)scavenging activity was performed in accordance using Re *et al.*(1999)process. Reducing powers were determined according to Apak. *et al.*(2004) methods with a slight modification. Metal chelating activity on ferrous ions was determined as per the method reported by (Decker and Welch, 1990) slightly modified (Sabudak*et al.*, 2009).

Enzyme inhibitory activity

Anticholinesterase and anti-tyrosinase activities were measured using Ellman *et al.* (1961) with slight modifications (Öztürk *et al.*, 2014) and Khatib*et al.* (2005) methods, respectively.

Determination of antimicrobial (MIC) and anti-biofilm activity

As recommended by the Clinical and Laboratory Standards Institute (CLSI) (2006) and by a microtitre broth dilution method, the extract's minimal inhibitory concentration (MIC) on five tested microorganisms: *Escherichia coli* (*E. coli* ATCC 25922), *Pseudomonas aeruginosa* (*P. aeruginosa* ATCC27853), *Staphylococcus aureus* (*S. aureus* ATCC 25923), *Enterococcus faecalis* (*E. faecalis* ATCC 29212) *and Candida albicans* (*C. albicans* ATCC 10239)was determined. The biofilm effect was determined using a microplate biofilm assay (Merritt *et al.*, 2005).

Statistical analysis

Results are reported as means value±SD of three measurements; Data were analyzed by one-way ANOVA followed by Tukey's multiple comparisions test using GraphPad Prism software (version 8.0.1); p values < 0.05 were regarded as significant.

Results

Phenolic profiles of S.hoggariensis hydro-methanolic extract

Nine phenolic compounds were identified and quantified as figured in Table (1).

Table 1. HPLC-DAD analysis from *S. hoggariensis* hydro-methanolic extract.

N°	Compounds	Rt*(min)	Composition (mg/g)
1	Pyrocatechol	24.65	0.24
2	Protocatechic acid	24.68	0.10
3	4-Hydroxybenzoic acid	31.69	Tr
4	4-Hydroxy benzaldehyde	33.36	0.35
5	Chlorogenic acid	38.88	5.97
6	Rutin	47.52	1.29
7	Ellagic acid	50.00	0.50
8	Curcumin	72.89	3.39
9	4-Hydroxylresorcinol	73.06	2.85

Rt - retention time.*

Results are expressed as mg/g extract. The examined extract includes phenolic acids and flavonoids; as can be seen,chlorogenic acid (5.97 mg/g) was the most abundant compound found, followed by curcumin (3.39mg/g), 4-hydroxylresorkinol (2.85mg/g) and rutin (1.29mg/g). Some compounds like ellagic acid, protocatechuic acid, 4-hydroxy benzaldehyde, pyrocatechol, 4-hydroxybenzoic acid were also detected in small amounts.

Antioxidant activity

The antioxidant activity of *S.hoggariensis* extract was illustrated in Table 2. Compared to the standards (α-tocopherol, BHT, BHA and quercetin), The tested extract displayed moderate activity with IC_{50}=58.00 ±1.20, 63.48 ±1.59, 31.06 ± 0.93, 52.78±2.21 µg/ml in β-carotene linoleic acid, DPPH•, $ABTS^{•+}$ and metal inhibition, respectively. The properties of iron and copper ion reduction in the tested sample were expressed as $A_{0.5}$ values calculated from absorbance curves. The studied extract had the lowest $A_{0.5}$ values (84.98 ±2.51µg/ml).

The iron and copper ions were strongly reduced by BHA, BHT and quercetin, which were used as standards (Table 2).

Table 2. Antioxidant activity of *S.hoggariensis* extract by DPPH•, $ABTS^{•+}$, β-carotene linoleic acid, CUPRAC and metal chelating assays.

Extract and standards	Antioxidant activity				
	β-Carotene linoleic acid IC_{50}(µg/ml)	*DPPH* Assay IC_{50} (µg/ml)	*ATBS* Assay IC_{50}(µg/ml)	*CUPRAC* Assay $A_{0.50}$ (µg/ml)	*Metal chelating* assay IC_{50} (µg/ml)
S.hoggariensis	58.00±1.2[b]	63.48±1.59[e]	31.06±0.9[c]	84.98 ±2.51[d]	52.78±2,21[a]
α-Tocopherol	2.10 ±0.09[a]	12.26±0.07[c]	4.31±0.10[b]	10.20 ± 0.01[b]	*NT*
BHT	1.34±0.04[a]	45.37±0.47[d]	4.10±0.06[b]	3.80 ± 0.00 [a]	*NT*
BHA	1.84±0.14[a]	5.73±0.41[b]	1.81±0.10[a]	24.40±0.69 [c]	*NT*
Quercetin	1.81 ± 0.11[a]	2.07 ± 0.10[a]	1.18±0.03[a]	*NT*	250.09±0.87[b]

IC_{50}:*the means ± SEM of three parallel measurements. Analysis of variance (ANOVA) revealed significant effect (p< 0.05). Results with different superscript letters are significantlydifferent.*

$A_{0.50}$: *the means ± SEM of three parallel measurements (p< 0.05).*

NT: not tested.

Anticholinesterase and anti-tyrosinase activity

Table 3 shows the results of AChE and BChE inhibitory activities of the studied extract compared with that of Galantamine used as a standard compound. The extract was found to be inactive. Moreover, the studied extract displayed moderate tyrosinase enzyme inhibition activity (41.31±1.84 %) compared to kojik acid (79.8±0.6 %) used as standard at 100 µg/ml (Table 3).

Minimum inhibitory concentrations and antibiofilm activity

The antimicrobial profile from *S.hoggariensis* hydro-methanolic extract for each bacteria is summarized in Table 4. The extract showed a moderate antimicrobial activity on the five tested microorganisms (*S. aureus, E. faecalis, P. aeruginosa, E. coli* and *C. albicans*) and had a better effect against *C. albicans*.

The MIC values were determined so that antibiofilm activity could be performed at sub-MIC concentrations.

The percentage inhibition of biofilm inhibitions was 39.19 ± 0.63 (*S. aureus*), 18.36 ± 0.57 (*E. faecalis*), 34.12 ± 1.25 (*P. aeruginosa*), 46.49 ± 1.09 (*E. coli*) and 51.08 ± 1.63 (*C. albicans*), at the maximum test concentration 10 mg/ml. From the overall results, the decreasing order of susceptibility of the microorganisms' biofilm inhibition was found to be *C. albicans*, *E. coli, S. aureus, P. aeruginosa* and *E. faecalis*.

Table 3. Anticholinesterase and anti-tyrosinase activities of *S.hoggariensis*extract.

Species	Extract	AChE (%)	BChE (%)	Tyrosinase inhibitory (%)
S.hoggariensis	Hydro-methanol extract	NA	NA	41.31±1.84[b]
Standards	Galantamin	78.59±0.47	65.02±0.44	NT
	Kojik acid	NT	NT	79.8±0.6[a]

%: Inhibition of 100 µg/ml concentration of the extract.

NT: not tested.

Discussion

In the present study, the phenolic profile and pharmacogonostic activity of *Senecio hoggariensis* hydro-methanolic extract have been reported for the first time. In HPLC-DAD results, a diversified mixture of phenolic components from the phenolic acids and flavonoids was identified. It has been noted that chlorogenic acid was the main component of extract.

The appearance of chlorogenic acid in relatively high quantities in the plant kingdom and species belonging to the Apiaceae family was described mainly in literature (Upadhyay *et al.*, 2013; Generalic Mekinic *et al.*, 2016). Our results were in accordance with the study of Albayrak *et al.*(2014),who demonstrated the dominance of chlorogenic acid in all nine *Senecio* species tested (*S.mollis, S.othonnae, S.cilicius, S.inops subsp. karamanicus, S.olympicus, S.sandrasicus, S. salsuginea, S. tauricolus* and *S.viscosus*) using the same solvent in the studied extract. According to research conducted by Ajiboye *et al.*(2018) concentration of chlorogenic acid in the crude extract of *Senecio Biafra* was estimated at 2.73 ± 0.03 mg/g of extract.

Table 4. MIC values and antibiofilm inhibition activity of *S. hoggariensis*extract.

Microorganisms	Planktonic	% inhibition on biofilm formation			
	MIC(mg/ml)	MIC	MIC /2	MIC /4	MIC /8
E. coli ATCC 25922	≥10	46.49±1.09	36.08± 1.53	21.48±0.67	-
P. aeruginosa ATCC27853	≥10	34.12±1.25	10.36±1.53	-	-
S. aureus ATCC 25923	≥10	39.19±0.63	10.81 ±0.28	-	-
E. faecalis ATCC 29212	≥10	18.36±0.57	-	-	-
C. albicans ATCC 10239	10	51.08±1.63	32.85 ±1.00	23.35±0.40	-

- : No inhibition.

Antioxidant activity has been assessed in a variety of ways based on different mechanisms of action. Many assays may be used to determine the composition of extracts, which work through a variety of mechanisms, including preventing continued hydrogen abstraction, radical scavenging, reductive capacity, and chain initiation prevention(Li *et al.*, 2008).The results of this analysis showed that the absorbance values of the methanolic extract of *S.hoggarienis* increased in proportion to the concentration. The results were similar to those of Alqahtani *et al.* (2020) analysis'swho demonstrated the antioxidant capacity of the crude extract from *S.glaucus,* which displayed weak inhibition against DPPH and ABTS assays (values of 21.6 ± 3.6% and 22.3 ± 2.4% at 100 µg/ml, respectively). Furthermore, our results corroborate with those of Ajiboye *et al.*(2018), who found that the *S.biafrae* crude extract showed inhibitory abilities against all free radicals in a concentration-dependent manner, with IC_{50} in

ABTS radical scavenging ability (78.25g/ml), DPPH radical scavenging potential (92.08g/ml) and Fe^{2+} chelating ability (118.76g/ml). Mohamed *et al.*(2015) recorded low IC_{50} values in a study performed on the methyl alcohol extract of *S. glaucus* roots growing in Egypt (IC_{50}=79.57±0.74 µg/ml). Tundis *et al.* (2012) have also reported the antioxidant activity of the methanol extract of *Senecio stabianus Lacaita* by using DPPH and ABTS methods (IC_{50} values of 66.0 mg/ml and 72.3 mg/ml, respectively). Moreover, the methanol extract of *S. chrysanthemoides* demonstrated very low potency in both DPPH and ABTS free radical scavenging assays (Singh *et al.*, 2018). The presence of flavonoids and phenolics in extracts such as gallic acid, chlorogenic, caffeic acid, and rutin may reduce cellular oxidative stress(Adefegha *et al.*, 2015).

Alzheimer s disease (AD) is a neurologic disorder resulting in loss of memory. One of the ways to treat AD is to control the activity of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitors (Tel-Çayan *et al.*, 2018). In our study, the crude extract was tested for their AChE inhibitory potential by Ellman's colometric method. According to our results, the hydro methanolic extract of *S.hoggariensis* had no ability for inhibiting cholinesterase. Our results go in accordance with Kaufmann *et al.*(2016), who found that methanol extract of *Senecio scandens* showed no inhibition of AChE activity. In another study reported by Ajiboye *et al.*(2018), the crude extract of*S.biafrae* appeared to be better compared to our finding with IC_{50} of 347.22µg/ml and 378.79 µg/ml in AChE and BChE inhibitory activity, respectively.

In mammals, tyrosinase is the key enzyme responsible for enzymatic browning and melanogenesis (Maghsoudi *et al.*, 2013). Measurement of dopachrome produced in the presence of tyrosinase and L-dopa as the enzyme-substrate is used to determine the enzyme inhibitory activity of tyrosinase (Chang, 2009). There is no research on antityrosinase activities of *Senecio* species in the literature to our knowledge, so this is the first review on tyrosinase inhibitors. Previously, the tyrosinase inhibitory effects of methanol extracts from thirteen Umbelliferae plant species were investigated. Orhan *et al.*(2016) found that all methanolic extracts had low tyrosinase inhibitory activity.

A biofilm is a form of the self-produced extracellular matrix that bacteria embed in order to provide a safe environment for them to develop (Al-kafaween *et al.*, 2020). The tested extract inhibits biofilm formation by the test microorganisms in different percentages at MIC and belowMIC concentrations.

The tested extract is able to inhibit biofilm formation at MIC and belowMIC concentrations by the test microorganisms in various percentages. In a similar study byFlorian (2015),it was found that methanol extract from *Senecio calvus* showed a very low antimicrobial activity against *Pseudomonas aeruginosa* and *Escherichia coli*. However, its capacity to inhibit biofilm formation is manifest.

Extract tested has a moderate action against biofilm formation; it may hypothesize that the presence of molecules such as chlorogenic acid, curcumin and other phenolic compounds can be responsible for this activity. Some works also reported that phenolic compounds and flavonoids could act as biofilm inhibitors (Magesh *et al.*, 2013; Onsare *et al.*, 2014). Curcumin is a well-known antimicrobial agent that acts against a wide variety of Gram-negative and Gram-positive pathogens(Jaiswal *et al.*, 2018). At the molecular level, the mechanism of action has not been established exactly. However, it is thought to disrupt the bacterial cell membrane(Tyagi *et al.*, 2015; Teow *et al.*, 2016). As previously reported by Alalwan *et al.* (2017), it has the ability to inhibit the biofilm formation of*C. albicans* in a dose-dependent manner.

Conclusion

This study investigated the phenolic profile, antioxidant, anticholinesterase and tyrosinase antimicrobial and antibiofilm activities of the methanolic extract obtained from an endemic species

in the Algeria mountains *Senecio hoggariensis*. The results indicate that the hydro-methanolic extractcontains various phenolic compounds, particularly chlorogenic acid, and exhibit moderate antioxidantand tyrosinase activities. Also, the plant extract tested in this study had potential antimicrobial and antibiofilm activities against different tested bacteria; it could be used as an alternative to regulating the formation of microbial biofilms or as a model for the development of new drugs.

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