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Antioxidant and anti-inflammatory activity of phenolic extracts Of *Genista ferox* (*Fabaceae*)

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Abstract: Phenolic extracts of aerial parts of *Genista ferox* have been characterized and evaluated for their pharmacological properties which are still not reported. The total phenol and flavonoid contents in the extracts were estimated spectrophotometrically *via* the Folin-Ciocalteu and aluminium chloride methods, respectively. Leaves and pods extracts showed the highest contents of total phenols and total flavonoids. The same extracts exhibited also the highest antioxidant capacity (IC_{50} of 105.37µg/mL and 113.98µg/mL, respectively) assessed by the in-vitro DPPH radical scavenging method. Leave and stem extracts were explored for their possible anti-inflammatory activity assayed by carrageenan-induced paw edema model. Both extracts (at 400mg/kg) showed edema inhibitory effect, which was found to be close to that of Dichlofenac reference. However, the leave extract produced the highest significant ($p<0.001$) anti-inflammatory activity when compared with the control. A preliminary characterisation of these phenolic extracts were carried out by high performance liquid chromatography (HPLC) coupled with diode-array detector (DAD), in order to determine the relevance of identified compounds in the pharmacological properties of the plant.

Keywords: Antioxidant, anti-inflammatory, *Genista ferox*, phenolics, HPLC-DAD.

INTRODUCTION

Genista L. (*Fabaceae*) is a large genus of shrubs mainly centred in the Mediterranean region that is related to the European, North African and West Asian regions. In Algeria, the genus is represented by 25 species, among which 11 species are endemics (Quezel and Santa, 1963). Some of these plants have traditionally been used for the treatment of gastrointestinal disorders and to control hyperglycemia.

Previous studies on the phytoconstituents of the genus *Genista* reported the presence of various bioactive molecules, notably predominant flavonoids (Pistelli *et al.* 1998) which are potentially bioactive molecules (Harborne and Williams, 2000); alkaloids (Küçükboyacı *et al*. 2012); and recently saponins (Boutaghane *et al.,* 2013). Many of *Genista* species have proved several biological properties, ulcero protective (Rainova *et al.,* 1988), hepatoprotective (Baali *et al*., 2016) anti-diabetic (Rauter *et al*. 2009) and anti-inflammatory capacity (Boubekri *et al.,* 2014). This last have been, at least partially, attributed to antioxidant properties of their natural products, mainly phenolic compounds. Current researches have proved the effectiveness of phenolic extracts from different *Genista* species as antioxidant agents, using numerous tests (Orhan *et al.,* 2011; Bouchouka *et al.,* 2014; Baali *et al.,* 2016; Hanganu *et al.*, 2016).

In this paper, as a continuation of our research on algerian medicinal species with potential bioactivities (Boubekri *et al.,* 2014; Chebbab *et al.,* 2014; Ait-kaci Aourahoun *et al.,* 2015; Baali *et al.,* 2016), we report on an endemic *Genista* species, *G. ferox*, data on its phytochemistry and pharmacological activity are very scarce. In fact, only one studie on its alkaloids (Faugeras and Rene, 1966) and flavonoids (Mekkiou, 2005) have been published to date. The objective of this current study was to characterize and evaluate antioxidant and anti-inflammatory activity of phenolic extracts of *Genista ferox*.

MATERIALS AND METHODS

Plant material and extraction procedure

Genista **ferox** samples were collected locally from Boumerdes (NE of Algeria) in April 2012. Authentication of the species was made by Dr. Errol Véla from Montpelier University (France). The whole plant was air dried at room temperature in shade and the different parts (leaves, stems, flowers and pods including seeds) were separately isolated and reduced to fine powder using a laboratory blender. The powdered materials (10g of each leaves and stems 5g of flowers and 2g of pods) were separately sonicated for 1h with 2 cycles in hour, in 80ml, 50ml, 100 ml and 20ml EtOH-H_2O (80:20), respectively.

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Ultrasonic extraction was conducted on Band elin ultrasonic bath (35 kHz, 150 W). The alcohol was completely removed by rotary evaporator and further removal of water was performed by freeze-dry procedure.

Estimation of total phenolics content

The total phenolics content was determined by Folli-Cicalteu's assay (Luis *et al*., 2009). Gallic acid was used as standard compound. Phenolic contents of samples are expressed in mg as Gallic acid equivalent (GAE/g of dry extract) based on the calibration curve (y=0.015x- 0.0323; R^2=0.0996).

Determination of total flavonoids content

The total flavonoids content was estimated according to Kiendrebeogo *et al.* (2005), using standard Quercetine for the calibration curve (y=0.024x-0.015; R^2=0.997). Flavonoid contents were expressed as mg Quercetine equivalent (QE/g dry extract).

Antioxidant activity

Thin layer chromatography-DPPH scavenging assay

The screening of antioxidant potential of all hydro-ethanolic extracts was assayed according to Merian *et al.* (2014), with slight modifications. The extracts were chromatographied using TLC silica gel 60 F254 plates (10 x 10), using system solvent Ethyl acetate-Methanol-Water (100:13, 5:10, v/v/v).The DPPH test was performed directly on plates by spraying a 0.008% methanolic solution of DPPH to reveal the yellow zones with antioxidant activities.

DPPH scavenging assay

The antioxidant activity of leave, stem, flower and fruit extracts and standard ascorbic acid was evaluated by the radical scavenging assay method using DPPH (2,2diphenyl1picrylhydrazyl) free radical (Thakral *et al*., 2010). Radical scavenging activity is determined as the inhibition percentage (I%) computed as follows:

$$I\% = [(A_c - A_e)/A_c] \times 100$$

Where A_c is the absorbance of the blank sample and A_e is the absorbance of the tested sample.

Inhibition percentages were plotted against sample concentrations and IC_{50} value (concentration of extract or standard required for 50% inhibition) were determined. All measurements were performed in triplicate.

HPLC-DAD analysis

The HPLC analysis was done on Agilent HPLC system model 1100 equipped with four pumps and Shimadzu SPD-20 AV-UV/Vis detector. 10µl samples of each extract previously dissolved in Me OH was injected. Reversed phase Hypersil BDS C_{18} column (250 mm x 4.6 mm, 5µm) was used for chromatographic separation performed at room temperature. The elution phase consisted of acetonitrile (Solvent A) and 2% acetic acid in water (Solvent B), with gradient elution as described by Noumi, *et al.* (2011): 15% A/85% B; 0 to 12 min, 40%A/60% B 12 to 14 min, 60% A/ 40% B 14 to 18 min, 80% A/ 20% B 18 to 20 min, 90% A/10% B 20 to 24 min, 100% A 24 to 28 min. The flow rate of the mobile phase was kept at 0.5ml/min. Diode-array UV detection was performed at 280 nm for the monophenolic Gallic acid and 365 nm for the flavonoid Quercetin.

Identification and quantification of phenolic compounds

Phenolic Gallic acid and flavonoid Quercetine were initially identified by direct comparison of their retention times with those of standards. For the quantitative analysis, calibration curves were obtained by plotting the peak areas versus the tested concentrations range (0.25-100µg/mL) of each standard: Gallic acid (y=47.8394x-2.9396; R^2=0.99968); Quercetine (y=41.2466x-7.5414; R^2=0.99868). The results were expressed in µg per g of dry extract.

In vivo Anti-Inflammatory activity

Animals

Adulte male mice *Mus musculus,* weighting 20-25g, were randomly divided into 6 experimental groups consisted of 6 mice each. The animals were housed under standard conditions, fed with Amrut brand pelleted standard diet with water *ad libitum.* The animals were deprived of food and water overnight to ensure uniform hydratation. Institutional permission was obtained from Pharmaco-toxicology Laboratory Head (Research and Development Center, Algiers), and approval guide (MO.C.LP.002) for the care and the use of laboratory animals was followed.

Carrageenan-induced paw edema

The screening of anti-inflammatory activity of leave and stem extracts was assayed by carrageenan-induced mouse paw edema according to Levy (1969). The extracts LE and SE diluted in sterile water and reference drug Diclofenac were orally administered (0, 5ml) in doses 200mg/kg, 400mg/kg and 75mg/kg, respectively. The control animals received 0.5ml sterile distilled water. Following 30 min latency phase, edema was induced by subplantar injection of 25µl of carrageenan-saline solution (1% w/v) into the left hind paws of animals. Right paws served as the control (non-inflammed paws). The animals were sacrificed 4 hours after carrageenan injection and the right and the left paws were incised with a scalped at the tibiotarsal articulation for weighting, using an analytical balance. The edema percentage (E %) was calculated by the following equation:

$$E\% = [(L - R)/L] \times 100$$

Where L is the weight of the left paw and R is the weight of the right one of each mouse.

The anti-inflammatory activity was expressed as percentage of the edema inhibition (EI) in treated mice compared to the control mice, using the formula:

$$EI\ \% = [(C - T)/C] \times 100$$

Where C is edema percentage of the control group and T is edema percentage test group.

STATISTICAL ANALYSIS

Statistical analysis was performed using Student's t-test to determine significant differences between the control and the treated groups, using SPSS (version 9) statistical software. The data are represented as mean ± SEM. Significant differences were considered at $p \leq 0.05$.

RESULTS

Determination of total phenols and flavonoids

The aerial parts of *G. ferox* were extracted by ultrasound assisted extraction process. The average percentage yields of hydro-ethanolic extracts were found to be: 15.15% (stems), 23.15% (leaves), 24.75% (pods) and 32.2% (flowers).

The total phenolic contents (TPC) expressed as mg GAE/g dry extract and total flavonoid contents determined as mg QE/g dry extract are presented in table 1.

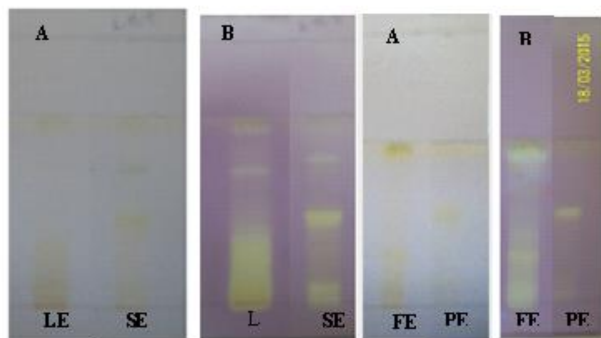

Fig. 1: TLC chromatograms of leave extract (LE), stem extract (SE), flower extract (FE) and pod extract (PE); before (A) and after (B) spraying of methanolic DPPH solution.

The highest amounts of phenolics were determined for leave extract LE (177mg GAE/g) and pod extract PE (165.33 mg GAE/g) which were also more richer in flavonoids (164.13mg QE/g and 120.05mg QE/g, respectively) than other samples, whereas the lowest contents in these compounds were recorded in flower extract FE.

Screening and evaluation of DPPH scavenging activity of phenolic extracts

Before DPPH scavenging assay, TLC-DPPH test was performed to screen our extracts for antioxidant compounds. Observation of the plates revealed several yellow bands before and after spraying of methanolic DPPH solution, with important yellow spot at Rf=0 observed notably in leave extract (fig. 1). This indicates the contribution of flavonoids and other probably phenolic compounds in the reduction of DPPH radical.

All investigated extracts showed moderate to weak antioxidant activity than that of the positive standard ascorbic acid (IC_{50} 16.16µg/ml). LE and PE were more potent than those FE and SE, with IC_{50} 105.37µg/ml and 113.98µg/ml, respectively. The scavenging effect of the samples on the DPPH radical decreased by increasing of IC_{50} values according to the following order: ascorbic acid > LE > PE > FE > SE.

Qualitative and quantitative HPLC-DAD analysis

Two phenolic compounds, flavonoid Quercetine and phenolic acid Gallic acid, were selected to allow justification of biological activities of leave and stem extracts. Quantification of Quercetin and Gallic acid, were made by measuring their absorbance in extracts at 365 nm for Quercetin and at 280 nm for Gallic acid. Both extracts showed very similar chromatographic fingerprint at both 280nm and 365nm. However, identified compounds were in largely different concentrations (tab. 2). Gallic acid was 2 fold higher in SE than in leave one (355.45µg/g extract *versus* 167.5µg/g extract), whereas Quercetine content in LE was 7 fold higher than in SE (14.60 µg/g extract *versus* 2.34µg/g extract).

Anti-inflammatory activity

The effects of leave and stem extracts from *G. ferox* on carrageenan-induced mice paw edema, are summarized in table 3. Four hours after intraplantar injection of carrageenan, both stem and leave extracts of *G. ferox* elicited a dose dependent edema inhibition. The extracts were found to exhibit maximum reduction in paw weight at the dose 400 mg/Kg (SE 13.22%, $p<0, 01$ and LE 11. 36%, $p<0.001$). The most active extract was that of LE, with edema inhibition value of 66.42%, while SE presented EI value that was close to Diclofenac reference (60.92% and 58.41% respectively).

DISCUSSION

Phenolic compounds are mostly found in plants, and they have been reported to have a broad range of bioactivities, including antioxidant and anti-inflammatory properties.

The few reports on phenolic and flavonoid contents of *Genista* species revealed lower TPC (33.52mg GAE/g) and TFC (16.06mg QE/g) of aqueous ethanolic extract (70%) from aerial parts of *G. tinctoria* (Hanganu *et al.,* 2016). However, higher TPC and TFC were obtained from aerial parts of *G. vuralii* (212.24mg GAE/g and 203.82 mg QE/g) and *G. sandrasica* (166. 94 mg GAE/g

Table 1: Total phenols (mg/g extract as gallic acid equivalent), total flavonoids (mg/g as quercetin equivalent) and scavenging activity against DPPH radical (IC_{50} value) of *G. ferox* extracts.

Extracts	TPC (mg GAE/g)	TFC (mg QE/g)	IC_{50} (µg/ml)
LE	177 ± 2	164.13 ± 3.15	105.37 ± 0.6
SE	107.66 ± 3.92	61.52 ± 1.4	206.61 ± 2.92
FE	73.66 ± 0.88	29.52 ± 0.83	174.47 ± 1.16
PE	165.33 ± 3.17	120.05 ± 1.65	113.98 ± 1.72

TPC: Total phenolic content; TFC: total flavonoid content; LE: leave extract; SE; stem extract; FE: flower extract; PE: pod extract. Results are Means ± SEM (n=3).

Table 2: Concentration of Phenolic compounds (µg/g extract) in stem and leave extracts of *G. ferox.*

Compound	Rt (min)	LE	SE
Gallic acid	6.576	167.5	355.45
Quercetin	23.204	14.60	2.34

Rt; retention time; LE: leave extract; SE: stem extract.

Table 3: Anti-inflammatory effect of *G. ferox* extracts on carrageenan-induced pawedema in mice.

Solutions	Dose (mg/kg)	E %[a]	EI %
Control (water)	-	33.83 ±2.23	-
SE	200	20.76 ± 5.3*	38.63
	400	13.22 ± 4.58**	60.92
LE	200	27.82 ± 2.78	17.76
	400	11.36 ± 1.66***	66.42
Dichlofenac	75	14.07 ± 2.76**	58.41

E: edema; EI: edema inhibition. [a]Values are Mean ± SE (n = 6); *p<0.05, **p<0.01,*** p<0.001 compared to control.

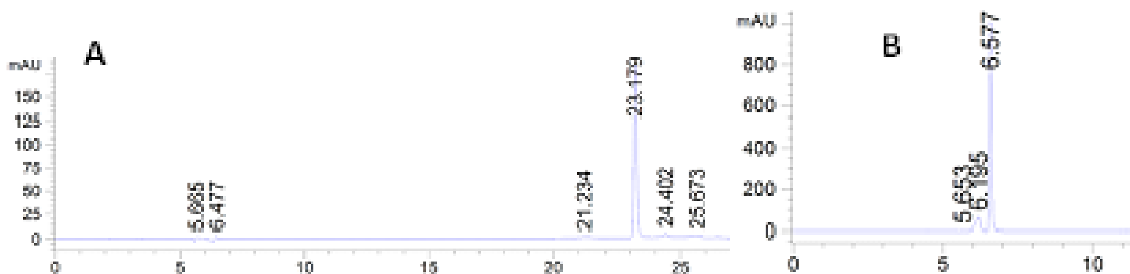

Fig. 2: HPLC-DAD chromatograms of standars Quercetin (A) at 365 nm and Gallic acid (B) at 280 nm.

and 158.06mg QE/g), extracted with methanol under ultrasonic vibrations (Orhan *et al.*, 2011).

The scavenging DPPH radical assay is widely used to evaluate the free radical scavenging ability of natural antioxidant products. The concentration of antioxidant required to decrease the initial DPPH concentration by 50% (IC_{50}) is a parameter that allows the determination of the antioxidant effectiveness, which corresponds with a lower IC_{50} value. Comparing to other species of genus *Genista*, phenolic extracts of *G. ferox* exhibited a higher level of radical scavenging than the hydro-ethanolic extract from *G. sagittalis* with IC_{50} 304.05 µg/ml (Hanganu *et al.,* 2016) and methanolic extracts of *G. vuralii* and *G. sandrasica* which expressed IC_{50} values of 0.98 mg/mL and 1.11mg/ml, respectively (Orhan *et al.,* 2011). However, hydro-ethanolic extract from aerial parts of *G. tinctoria* was shown to cause the best scavenging activity with IC_{50} 65.45µg/ml (Hanganu *et al.,* 2016).

On another hand, it is interesting to note that despite its high contents in total phenolics and flavonoids, the stem extract showed the weakest DPPH scavenging ability (IC_{50} 206.61µg/ml). Similar results were found by Brighente *et al.* (2007); Bouchouka *et al.* (2012) and Chebbah *et al.* (2014). Therefore, considering all tested extracts of *G. ferox*, a lower correlation coefficients were found between TPC and TFC and IC_{50} (R^2 =0.71 and R^2=0.73, respectively). However, excluding the stem extract, a high linear correlations were established between TPC and TFC and DPPH scavenging activity (R^2=0.999 and R^2=0.955, respectively). This could be related to the different contents of these extracts in efficient DPPH scavenger compounds, such as identified

Gallic acid and Quercetin. In fact, the effect of these compounds on DPPH radical scavenging has already been demonstrated. Previous studies reported the values of IC_{50} 2.1 µg/mL (Brighente *et al.*, 2007) and IC_{50} 1µg/mL (Lu *et al.*, 2002) for Quercetin. For Galliq acid, the values of IC_{50} 2.6µg/mL (Brighente *et al.*, 2007) and 1.5µg/ml (Lu *et al.*, 2014) have been established. This clearly indicates that antioxidant activity of Quercetine, more concentrated in the LE, is slightly greater than that of Gallic acid.

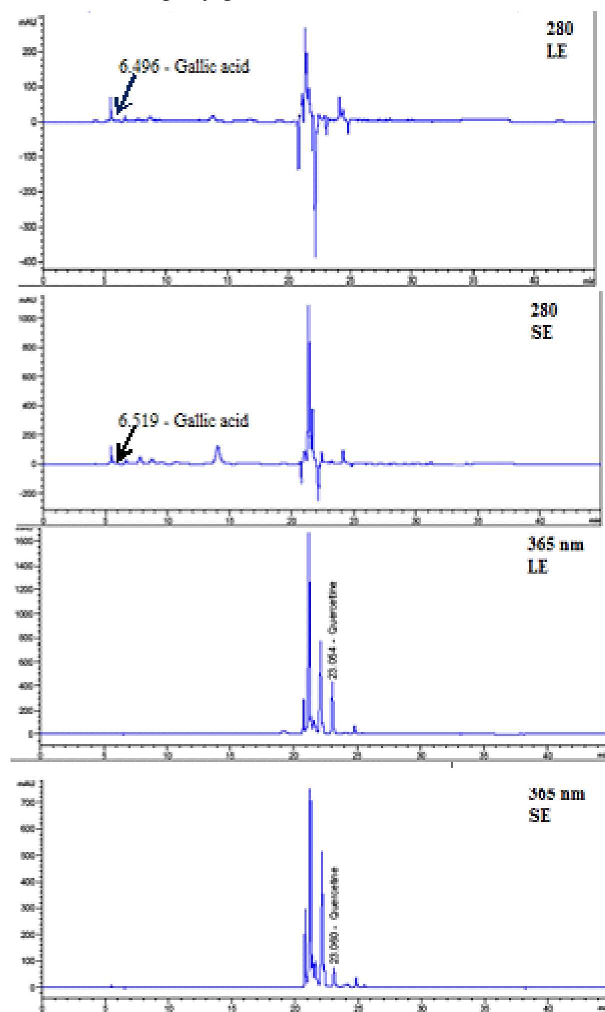

Fig. 3: HPLC chromatograms at 280 nm and 365 nm of leave extract (LE) and stem extract (SE) of *G. ferox.*

It must also be kept in mind that antioxidant compounds, depending of their structure, they could act by multiple mechanisms: free radical-scavenging, chemical reducing activity, quenching of singlet oxygen and complexing of pro-oxidant metals (Brighente *et al.*, 2007; Baali *et al.,* 2016). Thus, the stem extract could potentially act by one of those mechanisms other than by act as hydrogen donor.

Leave and stem extracts were evaluated for their eventual anti-inflammatory potential, by carrageenan-induced paw edema. This *in vivo* model of acute inflammation is widely used for screen potential natural anti-inflammatory agents. Both extracts showed significant edema inhibitory effect, with a high significant level exhibited by leave extract (66.42%, $p<0.001$).

The capacity of anti-inflammatory agents to inhibit mediators of inflammation is the basis of carrageenan-induced inflammation assay. These mediators include serotonin, histamine and bradykinin, which are responsible for the induction of inflammation in the first phase The second late phase of inflammation is mediated by cycloxygenase products, prostaglandins and lipoxygenase products prostaglandins that are released from the 3rd-4th hour (Vinegar *et al.,* 1969). According to Winter *et al.* (1962), during the second phase of carrageenan-induced edema, compounds which are anti-inflammatory agents are detected as a result of decrease of prostaglandin concentration. As shown in the table 3, there was a high significant percentage inhibition of paw edema, at 4th hour by hydroalcolic leave extract (66.42%, $P<0.001$) and stem extract (60.92%, $P<0.01$) at dose of 400 mg/kg. Therefore, it can be inferred that the extracts possibly act by inhibiting the synthesis and/or action of prostaglandin since the extracts showed a significant inhibitory activity at the late phase of the edema development.

In addition, the high contents in phenolics of leave and stem extracts could be, at least partially, responsible for their anti-inflammatory effect. In fact, the potential of these compounds to scavenge free radicals and modulate inflammatory reactions has been demonstrated (Lee *et al.*, 2007). Moreover, inhibition of cyclooxygenase and lipoxygenase has been attributed to many phenolics, such as flavonoids, in addition to their suggested ability to inhibit neutrophil degranulation which leads to diminution of the release of arachidonic acid by neutrophils and other immune cells (Robert *et al*. 2001).

The anti-inflammatory activities exhibited by both LE and SE could also be partially explained by the presence of identified compounds. Kim *et al*. (2005) provided that Gallic acid inhibits mast cell-derived inflammatory allergic reactions by blocking histamine release and pro-inflammatory cytokine expression. Quercetin have been found of to have significant anti-inflammatory activity ($P<0.05$) against carrageenan induced paw edema and cotton pellet granuloma mode in guinea pigs (Kaidama and Gacche, 2015). Another current report shown that Quercetin displayed inhibitory effects on prostaglandin E2 production in lipopolysaccharide (LPS)-stimulated macrophages (Seo *et al*., 2016). Furthermore, a recent study showed that the efficacy of Quercetin to inhibit cyclooxygenase enzymes COX-1 and COX-2 (measured by determined IC_{50} for both enzymes) was mostly higher compared to that Gallic acid (4,9-69 and 10-3,01, respectively) (El-Hawary *et al.,* 2016). That might also partly explain the high anti-inflammatory efficiency of leave extract compared to that stem one.

CONCLUSION

The present study reports the first data on the phenolic content and the pharmacological properties about *G. ferox*. Our study indicated that among all characterised phenolic extracts of aerial organs of *G. ferox*, those of leaves and pods showed highest contents of total phenols and total flavonoids. The same extracts exhibited also the highest antioxidant capacity. Evaluation of anti-inflammatory activity of leaves and stem extracts provided, at high tested dose, significant edema inhibitory effect, which was found to be close to that of Diclofenac reference. HPLC analysis indicated a higher content of leave extract in Quercetine while stem extract was found to be richer in Gallic acid.

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