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Bioactive ellagitannins from *Cunonia macrophylla*, an endemic Cunoniaceae from New Caledonia

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Abstract

Chemical study of *Cunonia macrophylla*, a New Caledonian Cunoniaceae, based on bioactive effects of a crude methanol extract of the leaves, detected bioactive tannins for the first time in this plant family. These ellagitannins have been identified as ellagic acid-4-*O*-β-D-xylopyranoside (**6**), mallorepanin (**3**), mallotinic acid (**1**) along with corilagin (**2**), chebulagic acid (**4**), ellagic acid (**5**) and gallic acid (**7**) and have been shown to possess antimicrobial activity and to inhibit xanthine oxidase. Antimicrobial effects on bacterial human pathogens (*Staphylococcus aureus*, *Corynebacterium accolans*) and on a plant pathogen (*Erwinia carotovora*) as well as on a human pathogenic yeast (*Candida albicans*) were investigated. Activity is reported here for the first time for compounds **1**, **3**, **4** and **6**. The inhibitory effects of all molecules against xanthine oxidase in relation to their structure was evaluated and compared. Compound **6** presented the best activity and seems to be of considerable interest for further studies.

Keywords: *Cunonia macrophylla*; Cunoniaceae; Antimicrobial activities; Xanthine oxidase inhibitors; Ellagitannins

1. Introduction

The Cunoniaceae family, in the order Oxalidales, consists of 26 genera with more than 300 species and is essentially found in the southern hemisphere (Bradford and Barnes, 2001). In New Caledonia, the family comprises 6 genera, *Acsmithia*, *Codia*, *Cunonia*, *Geissois*, *Pancheria*, *Weinmannia*, represented by more than 80 species, all of which are endemic (Guillaumin, 1948). Few New Caledonian species have been studied for pharmaceutical properties, and the literature on the Cunoniaceae family is poor, in this subject (Luis Diego Gomez, 1995; Bosisio et al., 2000), particularly in relation to their chemistry (Bate-Smith, 1977; Wollenweber et al., 2000). However, some members of the Cunoniaceae are well known to have medicinal properties and are used to cure various diseases (Luis Diego Gomez, 1995; Cambie and Ash, 1931; Rageau, 1957).

Our screening of 50 species of Cunoniaceae from New Caledonia for antimicrobial properties (Fogliani et al., 2002a) and for inhibitors of xanthine oxidase and scavengers of superoxide anions (Fogliani et al., 2002b) have revealed bioactive potential of some species. *Cunonia macrophylla* Brongniart & Gris in particular showed a capacity to inhibit bacteria as well as fungi. This species belongs to a genus of 25 species (Hoogland

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et al., 1997), 24 from New Caledonia and 1 from South Africa, *Cunonia capensis*, which is morphologically somewhat similar to *C. macrophylla* (Bradford, 1998).

Microbial infections cause significant health problems throughout the world and thus research into new antimicrobial agents from unstudied species of plants is a necessary strategy in the struggle against these infections. Other kind of infection which is interesting to fight again is the Gram-negative phytopathogenic bacteria *Erwinia carotovora* implicated in plant pathogenesis, such as soft rot in vegetables which leads to economic losses in agriculture world-wide (Wegener, 2002). The separation, isolation and identification of bioactive compounds were performed on extracts from leaves of *C. macrophylla*. As far we are aware no previous data have been reported on the phytochemistry of this species.

In addition, we essayed the identified molecules for their potentialities to inhibit xanthine oxydase as it converts hypoxanthine to xanthine and finally to uric acid, the accumulation of which causes hyperuricacidemia associated with gout (Noro et al., 1983). It is also responsible for oxidative damage to living tissues under conditions such as allergies, inflammation, diabetes, emphysema, heart ischemia-reperfusion, aging, atherosclerosis, etc. (Crastes de Poulet et al., 1994). Thus, inhibitors of XOD are expected to be therapeutically useful for the treatment of these pathologies (Goodman and Gilman's, 1990).

2. Results and discussion

2.1. Bioactivity guided separation

Since previous studies on crude methanolic extract of *C. macrophylla* leaves showed antibiotic activities (Fogliani et al., 2002a), we decided to extract leaves using a Soxhlet apparatus with three solvents (dichloromethane, ethyl acetate, methanol) to separate bioactive molecules. The results clearly showed that activities were concentrated in the methanolic extract (89.4 g) (Fig. 1). When 50 g of this methanolic extract was suspended in water and partitioned into fractions of different polarity, activities were concentrated largely in the butanolic extract which represented at least 42.8% of the methanolic extract (Fig. 1).

When the butanolic extract was fractionnated in to 10 subfractions using a silica chromatography column, the best activities were found in subfraction 2 (mixture in equal volume of fraction 2.1–2.5), 3 and 4.1 being used for further studies.

Semi-preparative chromatography (HPLC) of these different subfractions as described in Section 3 yielded seven tannins.

2.2. Identified tannins isolated from Cunonia macrophylla leaves

The seven tannins isolated were identified (Fig. 2) as gallic acid (**7**) (Foo, 1993) and six ellagitannins: mallotinic acid (**1**) (Lee et al., 1990; Lin et al., 1990), corilagin (**2**) (Lee et al., 1990; Nawwar et al., 1994), mallorepanin (**3**) (Lin et al., 1990), chebulagic acid (**4**) (Tanaka et al., 1996), ellagic acid (**5**) (Nawwar et al., 1994; Li et al., 1999) and ellagic acid-4-*O*-β-D-xylopyranoside (**6**) (Tanaka et al., 1998) by comparison with the ^{1}H and ^{13}C NMR spectra cited in the literature. Some other chemical and physical characteristics of these compounds were established (Table 2).

Cunoniaceae family is recognised as rich in tannins, since in some species more than 30% of the dry weight of leaves is composed of tannins (Bate-Smith, 1977).

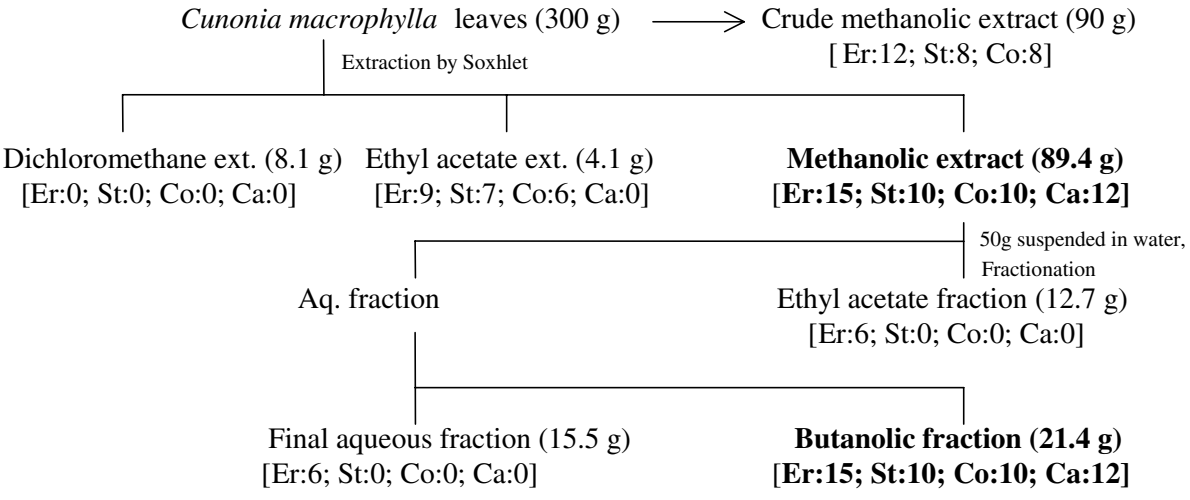

Fig. 1. Antimicrobial activities detected during step 1: (weight); [inhibition zone diameter (mm) for 500 μg of extract on *E. carotovora* (Er), *S. aureus* (St), *C. accolans* (Co), *C. albicans* (Ca)].

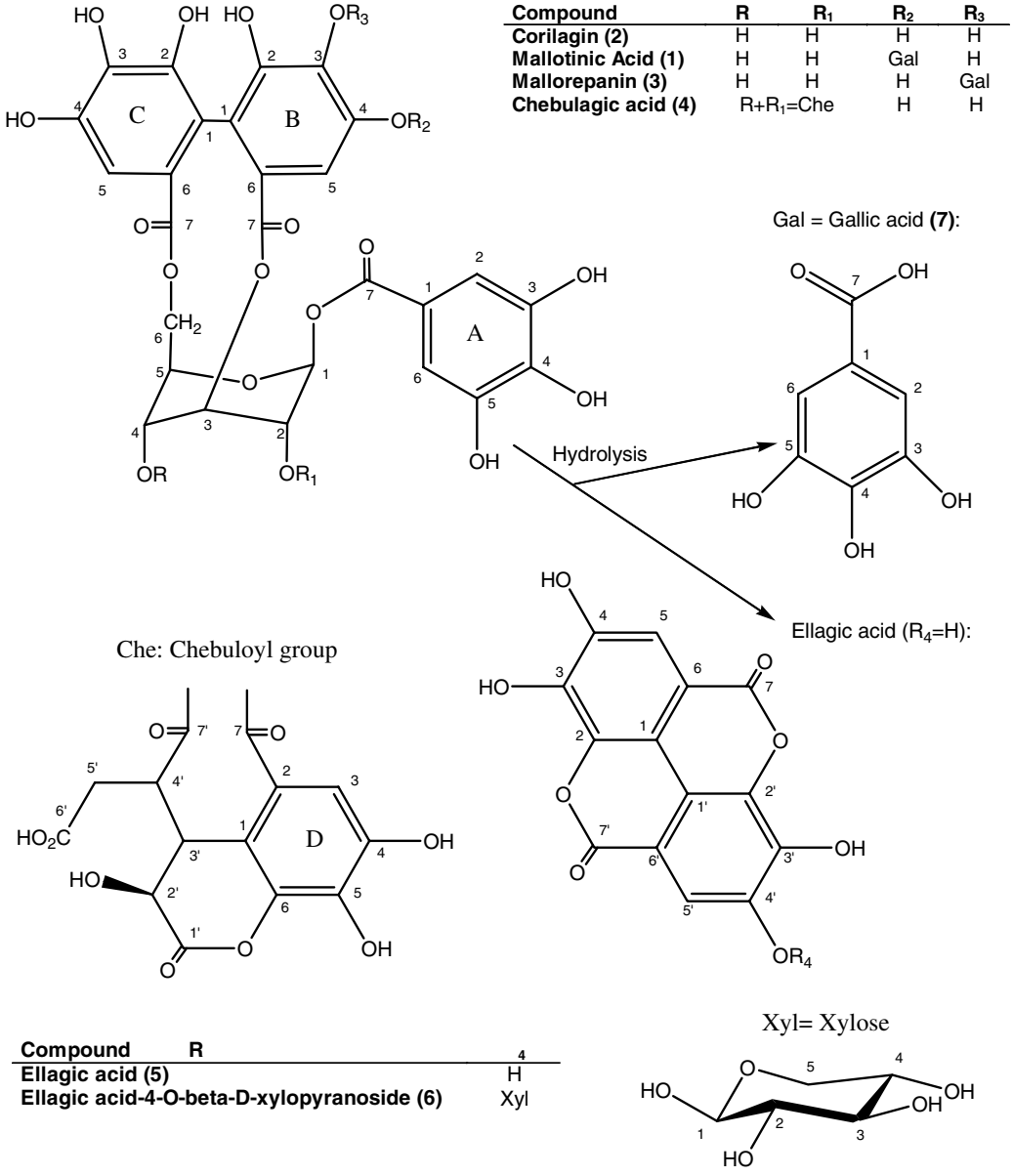

Fig. 2. Chemical structures of isolated compounds.

Previous studies have shown the presence of ellagic acid in some species of the genera *Cunonia*, *Weinmannia*, *Pancheria* and *Vesselowskya* (Bate-Smith, 1977), recently grouped into the tribe Cunonieae using chloroplast DNA sequence data and morphology (Bradford and Barnes, 2001). *C. macrophylla* has not been previously studied but seems to be close to the species *Cunonia capensis* (South Africa taxon) for which ellagic acid was detected (Bradford and Barnes, 2001). Our results confirm the occurrence of this compound in *C. macrophylla*. Moreover, we isolated five ellagitannins not previously detected in this family. All of them are known in other plant families but none belonging to the order Oxalidales, which compromises nine families including Cunoniaceae (Cronquist, 1981).

Literature data suggest that mallotinic acid, mallorepanin and particularly ellagic acid-4-*O*-β-D-xylopyranoside are known only in a few families. (**1**) and (**3**) were isolated from species of Euphorbiaceae (Lin et al., 1990) and (**6**) was discovered 10 years ago in Rosaceae (Pei et al., 1991) and more recently detected in Juglandaceae (Tanaka et al., 1998) but no biological activities were investigated.

2.3. Biological activities of isolated tannins

Some of the six ellagitannins that we isolated are already well known as demonstrating biological activities. Ellagic acid, corilagin and chebulagic acid possess antimicrobial activities (Burapajada and Bunchoo, 1995)

and antiviral properties (Chen Liu et al., 1999). Our results confirm their antimicrobial activities as all of them were efficient against the microbial strains we tested (Table 1). However, antimicrobial activities have not been previously reported in the case of mallotinic acid, mallorepanin and ellagic acid-4-*O*-β-D-xylopyranoside.

Careful examination of the structures of the different compounds in relation to their activities reveals some interesting facts.

First, structures of mallorepanin and mallotinic acid are obtained by addition of a gallic acid on C_3 or C_4 respectively of the cycle B of corilagin (Fig. 2). This seems to have an impact on activity as corilagin is more effective than its substituted forms. Moreover, the form substituted on C_4 appears less active than that substituted on C_3.

Chebulagic acid structure, which is more complex than corilagin, gave approximately the same activities whatever the strain tested.

The structures of compounds **1**–**4** reveal that ellagic acid (**5**) and gallic acid (**7**) can be obtained from their hydrolysis. In the case of gallic acid, the same kind of activities are detected but with less efficiency than for compounds **1**–**4**. Ellagic acid showed different results as it was more or less active than compounds **1**–**4** depending on the pathogenic strain tested with an exception for *Staphylococcus aureus* on which it had no effect. It is interesting to note that ellagic acid, which is a dimer form of gallic acid, presents better antimicrobial activities than the latter.

Comparison of the activity of ellagic acid and ellagic acid-4-*O*-β-D-xylopyranoside, established that the addition of a xylose on C4 has a negative effect on antimicrobial activities, as no more effects were detected on *Corynebacterium accolans* and on *Candida albicans* and a lesser one on *E. carotovora*.

A study of the mode of action of these different compounds would be of interest to explain these findings.

Tannins are also recognised to possess anti-oxidative effects as well as enzyme inhibition activities (De Bruyne et al., 1999). Our previously results (Fogliani et al., 2002b) on *C. macrophylla* showed that extracts of this species have an effect on xanthine oxidase but at high concentration, and we did not determined if it was due to scavengers of superoxide anions or xanthine oxidase inhibition. We decided from this result to assay the tannins we isolated for their potential to inhibit this enzyme.

Results (Table 2) clearly showed that all the compounds isolated possess this capacity but with different efficiencies. They also confirmed results obtained by Hatano et al. (1990) for some compounds. We were able to determine low activities for mallotinic acid, mallorepanin and chebulagic acid which were not previously reported. Moreover, in case of ellagic acid-4-*O*-β-D-xylopyranoside, this new activity is also efficient with an IC_{50} estimated at 2.1 μg/ml (4.7 μM).

The structure–activity relationship reveals that the position of the galloyl group which is different between mallorepanin (**3**) and mallotinic acid (**1**), had no effect on inhibitory activity as the IC_{50} was above 100 μM for both compounds. The increase in molecular weight of our monomeric hydrolyzable tannins, corilagin (**2**), mallotinic acid (**1**) and mallorepanin (**3**), had no effect on the inhibitory activity as also revealed by Hatano et al. (1990). However, chebulagic acid (**4**), with the highest molecular weight, possessed a better activity but as we do not have more compounds to compare with we cannot clearly establish if it is due simply to its molecular weight or to the complexity of its structure, in comparison with ellagic acid and ellagic acid-4-*O*-β-D-xylopyranoside.

Among the polyphenols of low molecular weight, ellagic acid (**5**) and ellagic acid-4-*O*-β-D-xylopyranoside (**6**), both of which have two lactone groups, showed inhibitory effects stronger than gallic acid (**7**). Compound (**6**) in particular presented the best inhibitory effect of our study, twice that of (**5**), essentially due to the presence of a xylose. In our experimental conditions, XOD inhibition by 10 μM (3.4 μg/ml) of quercetin was 58.8%, while the IC_{50} for quercetin has been reported as 10 μM (Robak and Gryglewsky, 1988). In comparison, ellagic acid-4-*O*-β-D-xylopyranoside (**6**) appears to be a good inhibitor of xanthine oxidase and requires further investigation.

Table 1
Antimicrobial activities dectected for each compound: inhibition zone diameter (mm) for 100 μg of compound

Compound	*E. caratovora*	*S. aureus*	*C. accolans*	*C. albicans*
(**2**) Corilagin	20	12	12	12
(**1**) Mallotinic acid	13	9	9	9
(**3**) Mallorepanin	15	10	10	10
(**4**) Chebulagic acid	19	11	10	12
(**5**) Ellagic acid	15	0	12	10
(**6**) Ellagic acid-4-*O*-β-D-xylopyranoside	12	0	0	0
(**7**) Gallic acid	13	7	7	7
Gentamycin sulfate (10 μg)	21	14	28	–
Nystatin (20 μg)	–	–	–	11

Table 2
IC_{50} values estimated for xanthine oxidase inhibitory activity of each compound with some characteristics

Compound	IC_{50} (μg/ml)	Molecular weight (g/mol)	IC_{50} (μM)	Powder color	Solubility	λ_{max} (H_2O/acetonitrile) (nm)	Melting point (°C)
(**2**) Corilagin	72.9	634	>100	Yellow	MeOH H_2O	269	211
(**1**) Mallotinic acid	>100	802	>100	Pale brown	MeOH	265	–
(**3**) Mallorepanin	>100	802	>100	Pale brown	MeOH	265	–
(**4**) Chebulagic acid	46.3	954	48	Yellow	MeOH	277	179
(**5**) Ellagic acid	2.8	302	9.3	Yellow	DMSO	254 368	–
(**6**) Ellagic acid-4-*O*-β-D-xylopyranoside	2.1	444	4.7	Pink	DMSO	254 361	–
(**7**) Gallic acid	7.1	170	41.7	–	MeOH	–	–
Quercetin (reference inhibitor; Robak and Gryglewsky, 1988)	3.4	302	10	Yellow	DMSO	–	314

In conclusion, this study on the tannins produced by *C. macrophylla*, from the family Cunoniaceae, revealed compounds of considerable interest. Biomolecules recently identified as ellagic acid-4-*O*-β-D-xylopyranoside, mallorepanin and mallotinic acid present new bioactive effects and seem to be good candidates for further experiments.

3. Experimental

3.1. General

For all isolated compounds, UV spectra were measured by using the diode array detector (DAD) G 1315A on the HPLC (HP 1100) apparatus. ^1H and ^{13}C NMR spectra were recorded on a DBX-500 Bruker apparatus.

Chemicals: dichloromethane, ethyl acetate (Fischer Chemicals), butanol (Prolabo rectapur), methanol, acetonitrile, CD_3OD, DMSO-d_6 (Prolabo Chromanorm).

3.2. Plant material

The leaves of *C. macrophylla* were collected at Mt. Koghis in New Caledonia in March 2000. The voucher specimen (Reg. No.: BF 053) was identified using Hoogland et al. (1997) by Fogliani, verified by Hopkins (Lancaster University) and Bradford (Missouri Botanical Garden) who are currently revising some genera of New Caledonian Cunoniaceae. It was deposited in the "Laboratoire de biologie et physiologie végétales appliquées, Université de la Nouvelle-Calédonie".

3.3. Extraction and isolation

Step 1: Dried leaves of *C. macrophylla* (300 g) were extracted using Soxhlet apparatus (20 cycles of 500 ml of solvent) with CH_2Cl_2. The residue was dried, extracted in the same way with EtOAc and then with MeOH. All extracts obtained were concentrated in vacuo at below 45 °C and tested for their antibiotic potential. Methanolic extract (50 g) was suspended in water (0.5 l), and partitioned with EtOAc (0.2 l × 3) and *n*-BuOH (0.2 l × 3), successively to obtain 12.7, 21.4 g, respectively and 15.5 g of aq. Fraction. Each fraction was then tested for antibiotic activities.

Step 2: As antibiotic activity was confined to the butanolic fraction, 10 g of this was subjected to a flash chromatography on a Si gel (normasil prolabo C60, 40–60 μm, 250 g) column (∅ 8 × 24 cm) eluted successively with 500 ml of EtOAc–MeOH–H_2O in the following ratios (10:1:1), (6:1:1), (4:1:1), (3:1:1) and (2:1:0.5) to yield 10 subfractions. These 10 subfractions were obtained as follows: subfraction 1 (0.37 g, 500 ml), subfractions 2.1–2.5 (0.99, 0.61, 0.52, 0.32, 0.12 g, respectively, 5 × 100 ml), subfraction 3 (1.51 g, 500 ml), subfractions 4.1–4.2 (1.08 g, 2.11 g, 2 × 250 ml) and subfraction 5 (2.09 g, 500 ml), respectively, from each ratio.

Step 3: The dissolution of subfraction 2.1 in MeOH at room temperature was not complete. After centrifugation, each part, soluble fraction and residue were treated separately. Chromatography of subfraction 2.1 supernatant (0.87 g) on Spherisorb ODS2 column (∅ 2 × 25 cm) with a stepwise gradient elution (100 ml each) from water to 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45% and 50% acetonitrile led to the isolation of, respectively, compounds, **1** (7.1 mg), **2** (50 mg), **3** (50 mg) and **4** (5 mg). Residue of subfraction 2.1 (0.11 g) was dissolved in MeOH at ambient temperature, and recrystallised by cooling the MeOH. The same method was used three times to obtain compound **5** (31.8 mg).

Using the subfraction 3 (1.51 g), the same method was used to obtain compound **6** (91.8 mg) using the subfraction residue of the suspension in MeOH.

Suspension of subfraction 4.1 (1.08 g) in MeOH subjected to chromatography over Sephadex LH20 Pharmacia Upsala (∅ 1 × 100 cm) with MeOH as the mobile phase yielded 50 fractions (6 ml each). Subfractions 23–26 showing similar HPLC profiles were

combined and subjected to a chromatography on Spherisorb ODS2 column (∅ 2 × 25 cm) with a stepwise gradient elution (100 ml each) from water to 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45% and 50% acetonitrile to give compound **7** (26.3 mg).

All compounds were subjected to UV spectra measurement and ^{1}H, ^{13}C NMR spectra record and analysis.

3.4. Antimicrobial assays

During all steps of the work, the antimicrobial activities were determined using the disc diffusion method (Bauer et al., 1966) on strains of human pathogenic bacteria (*S. aureus*, *C. accolans*) and on a plant pathogen (*Erwinia carotovora*) as well as on a human pathogenic yeast (*C. albicans*). Petri dishes (9 cm diameter) containing 12 ml of MH agar medium were seeded with 24-h-old cultures of a selected microbial strain. Five hundred microgram (step 1), 250 μg (step 2), and 100 μg (step 3) of a selected extract or pure isolated compounds were deposited on a sterile filter paper disc (6 mm diameter) before being placed on the surface of the medium. Solvent used for suspension served as negative controls. Standard discs containing gentamycin sulfate (10 μg), an antibiotic drug with a wide spectrum, was used as a positive control on bacteria. In the case of *C. albicans*, nystatin (20 μg) was used as a control. Plates were incubated for 24 h at 37 °C for human pathogens and at 30 °C for plant pathogens. The assessment of antimicrobial activity was based on the diameter of inhibition zones formed around the discs. Four independent trials were conducted for each extract on four different plates for each strain.

3.5. XOD inhibitory activity assay

The enzyme activity was measured spectophotometrically at 295 nm following the conversion of xanthine to uric acid for 3 min as reported by Robak and Gryglewsky (1988) with the following modifications. The assay mixture contained 0.1 M K^{+}–phosphate buffer, pH 7.8, 10 μM EDTA, 0.1 mM xanthine, 0.04 units/ml XOD, with a final volume of 1 ml. This mixture was preincubated for 15 min at 25 °C with the test material before adding the substrate. The reaction was terminated by adding 100 μl of 1 N HCl and the variation of absorbance was measured against a blank prepared in the same way except that the enzyme solution was added to the assay mixture after adding HCl. XOD inhibitory activity was expressed as the percentage of inhibition calculated as $(1 - B/A) \times 100$, where A is the absorbance without the test material and B the absorbance with the test material. Molecules **1**–**6** were tested at different concentrations between 0.1 and 50 μg/ml to determine their IC_{50}. Quercetin (3.4 μg/ml) was used as a reference inhibitor. Nine independent trials were conducted for each extract.

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