Xanthine oxidase inhibitory activity of the methanolic extracts of selected Jordanian medicinal plants

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ABSTRACT

Background: The search for novel xanthine oxidase (XO) inhibitors with a higher therapeutic activity and fewer side effects are desired not only to treat gout but also to combat various other diseases associated with the XO activity. At present, the potential of developing successful natural products for the management of XO-related diseases is still largely unexplored. In the present study, we have screened the methanolic extracts of various Jordanian medicinal plants for their XO inhibitory activities using an optimized protocol. **Materials and Methods:** The methanolic extracts of 23 medicinal plants, belonging to 12 families, were tested *in vitro*, at 200 μg/ml concentrations, for their XO inhibitory potential. The dose-dependent inhibition profiles of the most active plants were further evaluated by estimating the IC_{50} values of their corresponding extracts. **Results:** Six plants were found most active (% inhibition more than 39%). These plants are *Salvia spinosa* L. (IC_{50} = 53.7 μg/ml), *Anthemis palestina* Boiss. (168.0 μg/ml), *Chrysanthemum coronarium* L. (199.5 μg/ml), *Achillea biebersteinii* Afansiev (360.0 μg/ml), *Rosmarinus officinalis* L. (650.0 μg/ml), and *Ginkgo biloba* L. (595.8 μg/ml). Moreover, four more plants, namely *Lavandula angustifolia* Mill. (28.7% inhibition), *Helianthemum ledifolium* (L.) Mill. (28.4%), *Majorana syriaca* (L.) Kostel. (25.1%), and *Mentha spicata* L. (22.5%) showed a XO inhibitory activity in the range of 22–30%. **Conclusion:** The study showed that many of the tested plant species are potential sources of natural XO inhibitors that can be developed, upon further investigation, into successful herbal drugs for treatment of gout and other XO-related disorders.

Key words: Gout, Jordanian medicinal plant extracts, *Salvia spinosa*, xanthine oxidase

INTRODUCTION

Free radicals are extremely reactive and generally highly unstable chemical species.[1] They have been regarded as the fundamental cause of different diseases, including aging, coronary heart disease, inflammation, stroke, Parkinson's disease, diabetes mellitus, rheumatism, liver disorders, renal failure, cancer, and possibly Alzheimer's disease.[2-4] In addition to exogenous sources of free radicals, such as ionizing radiation, tobacco smoke, pesticides, pollutants, and some medications, free radicals are produced continuously in all cells, as metabolic by-products, by a number of intracellular systems: small cytoplasmic molecules, cytoplasmic proteins, membrane enzymes, peroxisomes, mitochondrial electron transport systems, and microsomic electron transport systems.[1]

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Xanthine oxidase (XO) serves as an important biological source of oxygen-derived free radicals that contribute to the oxidative damage of living tissues.[5] XO is involved in the medical condition known as gout, which is characterized by hyperuricemia that leads to uric acid deposition in the joints resulting in painful inflammation. Hyperuricemia, which is present in 5–30% of the general population, seems to be increasing worldwide and is considered an important risk factor in serious disorders, e.g. renal failure.[6-8] Uricosuric drugs which increase the urinary excretion of uric acid, or XO inhibitors which block the terminal step in uric acid biosynthesis, can lower the plasma uric acid concentration, and are generally employed for the treatment of gout.[9,10] Allopurinol is the only clinically used XO inhibitor in the treatment of gout.[11,12] However, this drug suffers from many side effects such as hepatitis, nephropathy,

and allergic reactions.[13] Thus, the search for novel XO inhibitors with a higher therapeutic activity and fewer side effects are desired not only to treat gout but also to combat various other diseases associated with the XO activity.

The use of botanical materials is gaining renewed interest as the potential source of new drugs or lead compounds in the search for new medicaments for the treatment of different diseases.[14] Natural products prepared from traditional medicinal plants and microbial sources have always presented an exciting opportunity for the development of new therapeutic agents. Newman and Cragg have showed that 61% of the 877 small-molecule new chemical entities introduced as drugs worldwide during 1981–2006 can be traced to or were inspired by natural products.[15]

Natural products provide a vast pool of XO inhibitors that can possibly be developed into clinical products.[16,17] At present, the potential of developing successful natural products for the management of XO-related diseases is still largely unexplored. The screening and optimization of safe and effective XO inhibitors would provide an excellent strategy in combating XO-related diseases. The Hashemite Kingdom of Jordan acts as a flora bridge between the continents of Asia, Africa, and Europe, and it resides at the junction of four phytogeographical areas, the Mediterranean, the Irano-Turanean, the Saharo-Arabian, and the Tropical or Sudanian. These crossroads of climatic and botanic regions endow the country with a rich variety of plant life.[18] A total of 485 species of medicinal plants, belonging to 99 families have been identified as natural flora of Jordan.[19]

In the current study, we have used an optimized protocol to screen the methanolic extracts of various medicinal plants, collected from several areas of Jordan, for their XO inhibitory activities. A total of 23 medicinal plants belonging to 12 families, regardless of their claimed ethnopharmacological and/or food uses, were tested using a simple, fast, efficient, and reliable spectrophotometeric method, in an attempt to find a new herbal-derived material with potential XO inhibitory activities.

MATERIALS AND METHODS

Plant materials

Plant materials, of the selected species (n = 23), were collected from different geographical places of Jordan, during the flowering periods of these plants. The collected plants were identified taxonomically by Dr. Khaled Tawaha (Faculty of Pharmacy, Jordan University), and voucher specimens were deposited at the Herbarium Museum of the Faculty of Pharmacy, Jordan University of Science and Technology. The plant materials were cleaned of residual soil, air-dried at room temperature, ground to a fine powder using a laboratory mill, and finally passed through a 24-mesh sieve to generate a homogeneous powder. The powder materials were stored in a dark place, at room temperature (22–23°C), until extraction.

Plant extraction

Methanolic extractions were conducted using a 250-mg sample of each ground plant material, of the used parts [Table 1], in 10 ml methanol (80%), at 37°C for 3 h, in a shaking water bath. After cooling, the extract was centrifuged at 1500 *g* for 10 min, and the supernatant was recovered. The solvent was evaporated under vacuum at 40°C using a rotary evaporator. The solid residues were collected and stored in a dry condition until analysis.[20]

XO assay

The XO inhibitory activity was measured as previously reported.[16,17,21-23] The substrate and the enzyme solutions were prepared immediately before use. The reaction mixture contained an 80 mM sodium pyrophosphate buffer (pH = 8.5), 0.120 mM xanthine, and 0.1 unit of XO. The absorption at 295 nm, indicating the formation of uric acid at 25°C, was monitored and the initial rate was calculated. The methanolic dried extract, initially dissolved and diluted in the buffer, was incorporated in the enzyme assay to assess its inhibitory activity at a final concentration of 200 μg/ml. Moreover, for the plants whose extracts showed enzymatic inhibition more than 35%, the IC_{50} evaluation was also performed. In this case, five different concentrations of the dried extract (18.8, 37.5, 75, 150, and 300 μg/ml) were used to determine the concentration that inhibits 50% of the XO enzyme activity (IC_{50} value). All assays were run in triplicate; thus, inhibition percentages are the mean of three observations. A negative control (blank; 0% XO inhibition activity) was prepared containing the assay mixture without the extract. Allopurinol was used as a positive control in the assay mixture. The XO inhibitory activity was expressed as the percentage inhibition of XO in the above-mentioned assay mixture system, calculated as follows:[21-23]

$$\text{Percentage of inhibition} = (1 - \frac{\text{test inclination}}{\text{blank inclination}}) \times 100,$$

where test inclination is the linear change in the absorbance per minute of the test material, and blank inclination is the linear change in the absorbance per minute of the blank.

RESULTS AND DISCUSSION

In this study, the methanolic extracts of 23 different plants belonging to 12 different families were investigated as potential XO inhibitors. The selected plants and their XO inhibition assay results are summarized in Table 1. The degree of XO inhibition was evaluated for the extracts

Table 1: Xanthine oxidase inhibitory activities of the methanolic extracts of 24 medicinal plants collected from different locations in Jordan

Plant name[a] (Family; voucher specimen no.)	TPC (±SD)[b]	Percentage yield[c]	Percentage inhibition (±SD)[d]	IC_{50}[e]
Achillea biebersteinii Afanasiev (Asteraceae; Ac-Bi-JU)	23.3 ± 0.9	25.0	45.0 ± 0.7	360.0
Anagallis arvensis L. (Primulaceae; An-Ar-JU)	19.5 ± 0.7	30.7	1.6 ± 0.2	–
Anchusa italica Retz. (Boraginaceae; An-It-JU)	6.1 ± 0.3	10.1	13.4 ± 0.4	–
Anthemis palestina Reut. ex Boiss. (Asteraceae; An-Pa-JU)	23.2 ± 0.7	23.8	51.5 ± 1.5	168.0
Artemisia herba-alba Asso (Asteraceae; Ar-HA-JU)	34.6 ± 4.2	28.5	16.2 ± 0.3	–
Calendula arvensis L. (Asteraceae; Ca-Ar-JU)	12.3 ± 0.4	22.1	2.2 ± 0.3	–
Chrysanthemum coronarium L. (Asteraceae; Ch-Co-JU)	59.6 ± 4.1	31.9	57.3 ± 1.1	199.5
Eryngium creticum Lam. (Apiaceae; Er-Cr-JU)	13.3 ± 0.5	28.9	4.5 ± 0.3	–
Fumaria densiflora DC. (Papaveraceae; Fu-De-JU)	16.9 ± 0.3	20.9	7.3 ± 0.6	–
Ginkgo biloba L. (Ginkgoaceae; Gi-Bi-JU)	35.3 ± 1.0	59.0	39.2 ± 0.7	595.8
Glaucium aleppicum Boiss. and Hausskn. ex Boiss. (Papaveraceae; Gl-Al-JU)	20.6 ± 0.6	28.7	3.3 ± 0.3	–
Haplophyllum buxbaumii (Poir.) G.Don (Rutaceae; Ha-Bu-JU)	16.6 ± 0.3	31.5	10.4 ± 0.3	–
Helianthemum ledifolium (L.) Mill. (Cistaceae; He-Le-JU)	17.3 ± 1.0	19.9	28.4 ± 1.0	–
Hypecoum dimidiatum Delile (Papaveraceae; Hy-Di-JU)	13.9 ± 0.3	16.4	7.3 ± 0.3	–
Lavandula angustifolia Mill. (Lamiaceae; La-An-JU)	8.3 ± 0.0	29.0	28.7 ± 0.4	–
Majorana syriaca (L.) Kostel. (Lamiaceae; Ma-Sy-JU)	22.1 ± 3.2	23.0	25.1 ± 0.8	–
Mentha spicata L. (Lamiaceae; Me-Sp-JU)	39.1 ± 3.9	24.1	22.5 ± 0.9	–
Ononis natrix L. (Fabaceae; On-Na-JU)	21.1 ± 0.7	24.0	11.8 ± 0.9	–
Onosma gigantean Lam. (Boraginaceae; On-Gi-JU)	4.6 ± 0.2	11.5	–5.0 ± 0.2	–
Paronychia argentea Lam. (Illecebraceae; Pa-Ar-JU)	15.5 ± 1.0	23.9	13.0 ± 0.5	–
Reseda lutea L. (Resedaceae; Re-Lu-JU)	15.1 ± 0.3	24.1	6.6 ± 0.2	–
Rosmarinus officinalis L. (Lamiaceae; Ro-Of-JU)	39.1 ± 3.6	34.5	42.0 ± 1.2	650.0
Salvia spinosa L. (Lamiaceae; Sa-Sp-JU)	21.5 ± 0.5	20.3	71.5 ± 1.7	53.7
Allopurinol (positive control)	–	–	–	4.6

[a]Aerial parts were the part used for all plants except *C. coronarium*, where leaves and flowers were used, [b]Total phenolic content values (±SD) as obtained from references 26 and 27 (data are expressed as milligrams of gallic acid equivalents (GAE) per gram dry weight of the plant), [c]Mean percentage yield of the methanolic extract (w/w of the dry material) of three extraction replicates, [d]Percentage inhibition is the mean of three replicates (±SD) using 200 μg/ml concentration of the plant extract in each, [e]IC_{50} (μg/ml) values were measured for the most active plants (n = 6)

of all species at a concentration of 200 μg/ml. However, the IC_{50} values were determined only for those plants (n = 6) which showed an inhibitory activity of 40% or more when compared to uninhibited enzymatic reaction. These latter plants are *Salvia spinosa* L. (Lamiaceae), *Chrysanthemum coronarium* L. (Asteraceae), *Anthemis palestina* Reut. ex Boiss. (Asteraceae), *Achillea biebersteinii* Afansiev (Asteraceae), *Rosmarinus officinalis* L. (Lamiaceace), and *Ginkgo biloba* L. (Ginkgoaceae). The inhibitory profiles of three selected examples of these plants are shown in Figure 1.

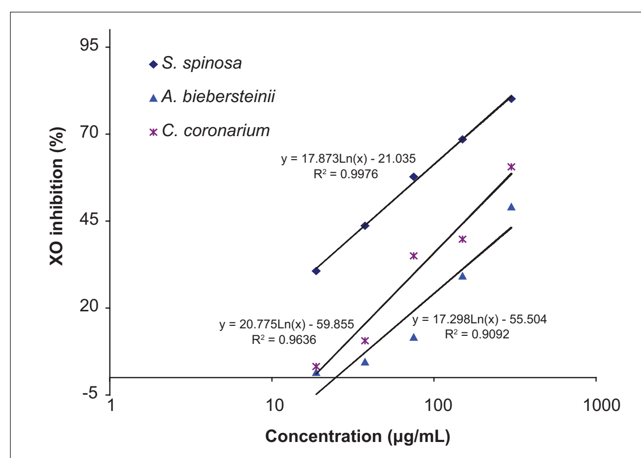

Figure 1: The inhibitory effects of different concentrations of methanolic extracts of *S. spinosa*, *C. coronarium*, and *A. biebersteinii* on the activity of xanthine oxidase

Interestingly, the most potent extract was prepared from *S. spinosa*, a plant with no previous reports of XO inhibitory activity. The genus is well known as a rich source of polyphenols and some of the common species, e.g., *S. officinals*, were previously reported to possess XO inhibitory effects.[24-27] A few research has been previously published about the chemical constituents and/or the biological activities of *S. spinosa*. In two studies from Jordan, a good correlation was found to exist between the antioxidant activity and the total phenolic contents of both methanolic and aqueous extracts prepared from a wild growing *S. spinosa*.[26,27] Phytochemically, hydrodistilled volatile oil of the aerial part was the most studied fraction of the plant; thymol was found as the principal component in a Jordanian species, whereas (E)-β-ocimene, β-caryophyllene,

and isopentyl isovalerate were the major compounds of an Iranian species.[28,29] Moreover, our results showed an agreement with previously reported XO inhibitory activities for extracts obtained from various plants of Lamiaceae family like *Majorana syriaca* (L.) Kostel, *Mentha spicata* L., and *Rosmarinus officinalis* L., whose activities were attributed to the presence of some phenolics, particularly flavonoids.[30,31] The reported antioxidant activities of these plants were found to be, at least in part, due to its inhibitory activity on XO.

G. biloba, cultivated in the north of Jordan, showed a significant inhibitory effect; however, this activity was previously reported and was attributed to its two isolated flavonoid glycosides based on the aglycones kaempferol (IC_{50} = 24 ppm) and quercetin (IC_{50} = 12 ppm).[32]

Of the other tested species, *C. coronarium* also showed a significant XO inhibitory activity with an IC_{50} value of 199.5 μg/ml. Although such activity was reported for some other species of *Chrysanthemum* like *C. sinense*,[33,34] this is the first report on *C. coronarium*. The same scenario was also noticed for *Artemisia herba-alba* Asso, where the XO inhibitory activity was previously reported for the species *A. vulgaris*,[33] *A. minor*,[35] *A. scoparia*,[36] *A. princeps*,[37] and *A. asiatica*.[38] It's noteworthy that much of the XO inhibitory activity of the latter plants was reported to be attributed to their phenolic, mainly flavonoid, constituents, which generally play an important role in decreasing lipid peroxidation and oxidative stress of diseased animals.

On the other hand, the present study reports for the first time the XO inhibitory activities of seven active plants, namely, *A. biebersteinii*, *A. palestina, Ononis natrix* L., *Lavandula angustifolia* Mill., *Helianthemum ledifolium* (L.) Mill., *Anchusa italica* Retz., and *Onosma giganteum* Lam. Neither these plants nor any of the other species of their genera were reported before to possess such activity. Here, for the purpose of correlating the obtained activity with the plant chemistry, we surveyed the literature about chemical constituents identified in these latter species. The intensive survey revealed no reported chemical information for three species, namely, *A. palestina, H. ledifolium*, and *O. giganteum* whereas only poly[3-(3,4-dihydroxyphenyl)glyceric acid and some alkaloids were reported from *A. italica*.[39,40] Phenolics of classes flavonoids, coumarins, simple phenols (e.g., thymol and eugenol), and their derivatives were reported to occur in various extracts and volatile oils obtained from *O. natrix*.[41-43] Volatile oil was the main fraction studied for *A. biebersteinii*; 1,8-cineole and camphor were the major oxygenated oil components reported in various studies.[44] The plant also variably contained some other constituents such as flavonoids, sesquiterpene lactones, and polyacetylenic amides.[45-47] On the other hand, *L. angustifolia* (true lavender) is a well-known aromatic plant rich in volatile oil, which is frequently reported to contain linalool and linalyl acetate as the major oil constituents.[48] The plant was also reported to contain phenolics including flavonoids and the caffeic acid derivative rosmarinic acid.[49,50]

Furthermore, in two previous studies conducted in Jordan, the methanolic and aqueous extracts of most of the plants of the present study were shown to possess significant antioxidant effects, which were correlated, as reported, to their phenolic contents (phenolic content data are shown in Table 1).[26,27] Undoubtedly, the XO inhibition, reported in the present study, would be an additional mechanism that can explain their antioxidant activities.

In conclusion, the obtained results suggest that the studied plants can form a good source of effective crude inhibitors for XO which can be used in the treatment of gout and other XO-related disorders. However, further biological investigations are needed, particularly using animal models, to verify the reported inhibitory activities under *in vivo* conditions. In future works, these active plants will be further investigated in order to isolate, identify, and evaluate the potentially phytoactive compounds responsible for the XO inhibitory activities reported in the present study.

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