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Chemical and *In Vitro* Anti-inflammatory Assessment of *Echinops erinaceus*

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ABSTRACT

Echinops erinaceus Kit Tan is a wild plant growing in the middle regions of Saudi Arabia. From the available literature, nothing has been reported on its chemical analysis or biological activity. In this study, various extracts of *Echinops erinaceus* were estimated for their total phenolics, and flavonoids contents. The extracts were also evaluated for their *in vitro* antioxidant activity using DPPH, FRAP, and ABTS assays. Furthermore, the enzyme inhibitory activity against cyclooxygenases and 15-lipoxygenase was performed. The results showed that the polar and semi-polar extracts demonstrated considerable *in vitro* anti-inflammatory and antioxidant activities.

Keywords: *Echinops erinaceus*, Asteraceae, Antioxidant, Cyclooxygenase, Lipoxygenase.

Introduction

Family Asteraceae, the Aster family, occupies the highest rank in the plant kingdom due to its great majority and global distribution. [1] It comprises about 1400 genera and more than 25000 species of herbaceous plants, shrubs, and trees, and is classified into three subfamilies and 17 tribes. [1, 2] Genus *Echinops* L., is one of the global thistle-like herbs that belong to the family Asteraceae, it contains over 130 species. [3, 4] *Echinops* species were classified only on the basis of morphological characteristics and taxonomically is still unclear. [5] On the phytogeography bases, 120 species of *Echinops* genus were found in the northern, and tropical Africa, Europe, Central Asia, and Mediterranean region, [6] as annuals, biennials, and perennials, [7] and recently another species was found in India.[3] In folk medicine, many species of the genus *Echinops* were used as antitumor, bitter stomachic, insecticides, and against skin diseases. [1] Medicinally, the genus *Echinops* is one of the most useful genera from the family Asteraceae. Their extracts showed hepatoprotective, antioxidant, fungicidal, antiulcer, anti-inflammatory, and antiphlogistic activities, based on their content of bioactive compounds. [8] The drugs derived from the members of genus *Echinops* are used for myopathy, peripheral damage asthenic state, and stimulant nervous-muscle fibers under radiation. [9, 10] They contain many phytochemical groups, such as alkaloids, carbohydrates, lignans, phenolic compounds, sesquiterpenes, sterols, terpenoids, thiophenes, and volatile oils. [11] *Echinops erinaceus* Kit Tan is one of the wild species of the genus *Echinops* that is endemic to Eastern Arabian regions found mainly in *Ru'us Al Jabal* which is located to the north of Hajar Mountain in Oman, [12] and in districted regions in Saudi Arabia, Taif-Jeddah road, and Yemen (Aden Protectorate, a plain near *Husnel Ah Mah*, Sandy Desert) . It is worth noting that there are no chemical or biological studies reported on *E. erinaceus*.

Therefore, the various extracts of the aerial parts of *E. erinaceus* were phytochemically investigated and biologically evaluated for their antioxidant and anti-inflammatory activities. The antioxidant activity was evaluated using DPPH, FRAP, and ABTS assays. Meanwhile, the anti-inflammatory activity was investigated by evaluating their *in vitro* inhibitory effects on Cycoloxogenase-1, Cycoloxygenase-2, and 15-lipooxygenase enzymes (COX-1, COX-2, and 15-LOX).

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Materials and Methods

Plant material

Fresh aerial parts of the plant were collected from regions south of Riyadh, (Saudi Arabia) during the flowering stage (March 2018). It was identified by Mr. Mohamed Abdel Fattah, a taxonomist at the botanical garden, Department of Botany and Microbiology, College of Science, King Saud University. A voucher specimen (23.6.19.1-5) was deposited at the herbarium of the Pharmacognosy Department, Faculty of Pharmacy, Cairo University. The plant material was shade-dried, powdered, and kept for further investigation.

Preparation of the plant extracts

The powdered material (4 kg) was extracted by maceration with methanol (5 X 10 L) at room temperature. The combined methanol extracts were filtered and evaporated to dryness at 50 ºC to give 650 g of soft extract. The crude methanolic extract was fractionated successively with solvents viz. *n*-hexane (Hex), chloroform ($CHCl_3$), and ethyl acetate (EtOAc), to give 150 g, 50 g, and 60 g, respectively, in addition to 390 g of remaining aqueous extract (RAq).

Preliminary qualitative phytochemical screening

The crude methanolic extract and its fractions of *E. erinaceus* were subjected to preliminary phytochemical screening.[13]

Quantitative phytochemical analysis

The crude methanol extract as well as its different fractions were subjected to quantitative phytochemical analysis for their content of total tannins (TTC), [14] total phenolic (TPC), [15] and total flavonoids (TFC).[15]

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Determination of total tannins content
The different extracts (10 mg) were dissolved in dist. H_2O (4.0 mL), divided into two portions, and to each portion conc. HCl (4.0 mL) and dist. H_2O (1.0 mL) were added. The first portions, were heated at 100 ºC for 30 min. Meanwhile, 0.5 mL ethanol was added to the second portions at room temperature. Subsequently, the absorbances in both cases were recorded at three different wavelengths (470 nm, 520 nm, and 570 nm) using a Shimadzu UV1800 Spectrophotometer. The total tannin content (TTC in g L^{-1}) was calculated according to the previously reported protocol.[14]

Determination of total phenolic and total flavonoids contents
The total phenolic content (TPC) was assessed by Folin-Ciocalteu reagent, using gallic acid as a standard (Sigma-Aldrich Co., St Louis, MO, USA). [15] The total flavonoids content (TFC) was estimated by $AlCl_3$ colorimetric method, [15] using quercetin as a standard (Sigma-Aldrich Co., St Louis, MO, USA). The results were expressed as mg of gallic acid per gram of extract (mg GA/g ext.) for TPC and for TFC as mg quercetin per gram of extract.

Determination of in vitro antioxidant activity
DPPH radical scavenging assay
The antioxidant activity of the extracts was measured by assessing their DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical-scavenging activity using the ascorbic acid as a reference as a previously described. [16] The percentage of inhibition (PI) of the DPPH radical was calculated according to the formula:

Percentage of inhibition (PI %) = $[(A_C - A_T)/ A_C] * 100$

Where A_C = Absorbance of the control at t = 0 min and A_T = absorbance of the sample + DPPH at t = 16 min. [16] Finally, the IC_{50} was graphically expressed by plotting PI vs. concentration.[16]

ABTS radical cation decolorization assay
The ABTS radical scavenging assay was performed according to the method reported by Canabady-Rochelle et al. [17] Butylated hydroxytoluene (BHT) was used as a standard antioxidant. The percent free radical scavenging activity was calculated according to the following formula:

% Free radical scavenging activity = $[(A_N - A_S)/ A_N] * 100$

Where A_N is the final absorbance of negative control, and A_S is the final absorbance of the sample. The IC_{50} values were graphically obtained by plotting the percentage inhibition of ABTS vs. concentration. [17]

Ferric ions (Fe^{3+}) reducing antioxidant power (FRAP) assay
The various extracts of *E. erinaceus* were evaluated using ferric reducing antioxidant power (FRAP) according to the method reported by Canabady-Rochelle et al. [17] BHT was used as a reference standard. The reducing capability percentage (%) was calculated as follows. [17]
Reducing capability (%) = $1 - [(A_0 - A_S)/ A_0] * 100$
Where A_0: absorbance of the control solution. A_S: sample absorbance.

Determination of in vitro anti-inflammatory activity
In vitro cyclooxygenases inhibitory assay
The inhibitory activity (IC_{50}) of cyclooxygenases (COX-1 and COX-2) of the crude *E. erinaceus* methanol extract and its fractions was assessed by colorimetric enzyme immunoassay (EIA) screening kit (Cayman Chemicals Inc, Ann Arbor, MI, USA), using celecoxib as a positive control [18] according to manufacturer instructions.

In vitro 15-lipoxygenase inhibitory assay
In vitro 15-LOX enzyme inhibitory assay was performed according to the reported method, based on the addition of the hydroperoxy moiety to linoleate substrate. [18] The inhibitory activity was assessed by calculating the hydroperoxide production inhibition (%) at 30s for 5 min and the absorbance was measured at 234 nm (UV-Visible Spectrophotometer 2450, Shimadzu, Japan). [18]

Statistical analysis
The results were expressed as mean ± SEM. The significance of difference amongst the control and treated groups was determined by One-Way analysis of Variance (ANOVA) followed by Tukey's Kramer multiple comparisons Dunnett's post hoc. test, P value < 0.05 was statistically significant by Graphpad Prism software (San Diego, CA. USA).

Results and Discussion

Phytochemical analysis
Qualitative phytochemical analysis
Echinops erinaceus is a wild plant that is indigenous to the districted area in Saudi Arabia. Phytochemical screening of various extracts exhibited the presence of several secondary metabolites, including alkaloids, tannins, saponins, phytosterols, terpenoids, and flavonoids.

Quantitative phytochemical analysis
The total tannins, total flavonoids, and total phenolic contents were estimated for various extracts as shown in table 1. The results showed that the RAq has the highest amount of TTC (1.585 g/L^{-1}) followed by EtOAc extract (0.494 g/L^{-1}). The TFC was detected as mg quercetin equivalent per g dry weight of extract (mg QRE/g-dw ext.), while the TPC was determined as mg gallic acid equivalent per g dry weight extract (mg GAE/g-dw ext.). The TFC was estimated for MeOH, EtOAc, $CHCl_3$ and RAq extracts, as 12.09 ± 0.57, 7.05 ± 0.73, 6.74 ± 0.28, and 3.98±0.24 mg QRE/g-dw, while the values of TPC were 17.11 ± 0.95, 10.12 ± 0.84, 7.66 ± 0.56, 5.36 ± 0.18 mg GAE/g-dw, respectively. The quantitative phytochemical analysis reported high values of TFC and TPC for the MeOH extract followed by the EtOAc while the RAq showed the highest amount of TTC.

In vitro antioxidant activity
Radical scavenging potential using DPPH, FRAP and ABTS assays
The presence of flavonoids and phenolics represent the greatest percentage of the detected phytochemicals, increasing the possibility of playing an important role in the bioactivities of the tested plant. The *in vitro* antioxidant potential of the different extracts of the aerial parts of *E. erinaceus* are represented in Table 2. The EtOAc exhibited the highest DPPH radical scavenging activities with of IC_{50} 33.9 ± 2.3 µg/mL, compared to ascorbic acid (IC_{50}10.6 ± 0.8 µg/mL).
For ABTS radical scavenging activity, all studied extracts suppressed the blue-green color of the radical $ABTS^+$ in various percentages. The EtOAc showed the highest $ABTS^+$ radical scavenging activity (IC_{50} 35.5 ± 2.8 µg/mL) followed by the RAq (IC_{50} 94.4 ± 4.6 µg/mL), compared to BHT (IC_{50} 17.5 ± 0.8 µg/mL). In both assays, the *n*-hexane fraction showed the weakest antioxidant activity.
The ferric reducing antioxidant power (FRAP) of the various extracts of *E. erinaceus* is shown in Table 2.

Table 1: The results of quantitative phytochemical analysis

Type of extract	Total tannins (g L^{-1})	Total flavonoids (mg/g-dw)	Total phenolics (mg GAE/g-dw)
MeOH ext.	0.387 ± 0.015	12.09 ± 0.57	17.11 ± 0.95
Hex. ext.	0.045 ± 0.008	5.07 ± 0.31	6.25 ± 0.43
$CHCl_3$ ext.	0.024 ± 0.001	6.74 ± 0.28	7.66 ± 0.56
EtOAc ext.	0.494 ± 0.015	7.05 ± 0.73	10.12 ± 0.84
Aqueous ext.	1.585 ± 0.11	3.98 ± 0.24	5.36 ± 0.18

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Table 2: The results of *in vitro* antioxidant activity using DPPH (IC_{50}, µg/mL), ABTS (IC_{50}, µg/mL), and reducing power using FRAP (mMol Fe^{+2}/g), Values (mean ± SD) are average of triplicate measurements, level of significance: * $P < 0.05$.

Activity	DPPH (µg/mL)	ABTS (µg/mL)	FRAP (mMol Fe^{+2}/g)
	IC_{50} ± SD		
Total methanol ext.	203.9 ± 6.3	214.6 ± 8.7	2.13 ± 0.39
n-Hexane fr.	weak antioxidant activity		0.93 ± 0.25
Chloroform fr.	245.4 ± 13.8	116.9 ± 3.9	1.75 ± 0.41
Ethyl acetate ext.*	33.9 ± 2.3	35.5 ± 2.8	2.47 ± 0.28
Remaining aqueous fr.	294.2 ± 5.4	94.4 ± 4.6	1.48 ±0.54
BHT	-----	17.5 ± 0.8	7.59 ± 0.37
Ascorbic acid	10.6 ± 0.8	-----	2.86 ± 0.42

The method evaluates the ability of the tested extract to donate an electron to the ferric/ferricyanide complex to form a ferrous ion (blue-colored complex). Thus, the concentration of the produced ferrous ion is monitored as the potential antioxidant activity. The results are compared to BHT (7.59±0.37 mmol Fe^{+2}/g), and ascorbic acid (2.86±0.42 mmol Fe^{+2}/g). The EtOAc showed the strongest FRAP activity (2.47±0.28 mmol Fe^{+2}/g) and was comparable to ascorbic acid followed by the MeOH (2.13±0.39 mmol Fe^{+2}/g). This result is in agreement with the results of both the DPPH and ABTS assays and to the TFC and TPC.

Anti-inflammatory activity

Arachidonic acid (AA) is the most abundant polyunsaturated fatty acid bound to the cell membranes. Cyclooxygenase isozymes (COX-1, COX-2, and COX-3) and lipoxygenases (LOX-5 and 15-LOX) are responsible for metabolizing AA. In the case of COXs, AA metabolism results in the production of considerable amounts of proinflammatory mediators, including prostaglandins (PGs), prostacyclin (PGI2), thromboxanes (TXA2), and leukotrienes (LTs). Whereas for LOXs, produce the final metabolites, leukotrienes (LTs).
In humans, 5-LOX causes the allergic reaction of the airways and the other inflammatory diseases, while 15-LOX is associated with atherosclerosis. [19] Several studies have correlated the anti-inflammatory effect of plant extracts to their polyphenolic content. [19] The molecular mechanism of the anti-inflammatory effect of plant polyphenols is related to their ability to inhibit COXs and LOXs. [19, 20] The concentrations able to inhibit the enzyme activity by 50% (IC_{50}) were determined (Fig. 1, Table 3). Among the tested extracts, the RAq exhibited remarkable COX-1, COX-2, and 15-LOX enzymes inhibition with IC_{50} 0.24 ± 0.015 µg/mL, 1.06 ± 0.05 µg/mL, and 1.8 ± 0.05 µm, respectively, which attributable to its high content of tannins. [21] Nevertheless, the EtOAc and Hex extracts possessed IC_{50} values towards COX-1/COX-2 enzymes, (0.3 ± 0.015 µg/mL/1.46 ± 0.05 µg/mL, and 0.37 ± 0.015 µg/mL/1.66 ± 0.05 µg/mL, respectively) compared to celecoxib (COX-1, IC_{50} 0.33 ± 0.005 µg/mL/ COX-2, IC_{50} 1.16 ± 0.005 µg/mL). On the other hand, the EtOAc, and $CHCl_3$ extracts showed higher 15-LOX inhibition (IC_{50} 2.26 ± 0.05 µm, and 2.9 ± 0.05 µm, respectively) compared to quercetin as a positive control (IC_{50} 3.33 ± 0.005 µm). However, the Hex extract showed an IC_{50} of 3.63 ± 0.05 µm, which was comparable to quercetin. The antioxidant activity results further correlated the COXs and 15-LOX inhibitory activities to the phenolic content of the EtOAc extract and its absence in the case of the Hex extract. [13, 19, 22, 23]

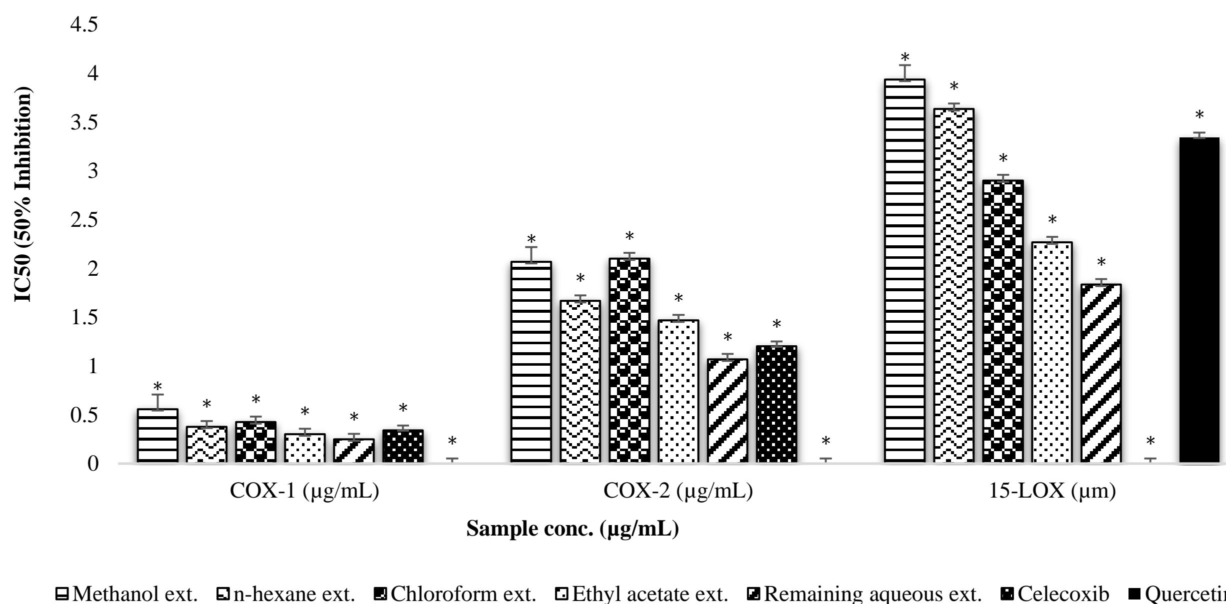

Figure 1: *In vitro* COX-1, COX-2, and 15-LOX inhibition activities of various extracts of *Echinops erinaceus,* using celecoxib for COXs and quercetin for 15-LOX as positive controls. Values (mean ± SD) are average of triplicate measurements, level of significance: * $P < 0.05$.

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Table 3: *In vitro* COX-1, COX-2, and 15-LOX inhibitory activities of various extracts of *E. erinaceus.*

Code	COX-1 $IC_{50} \pm SD$ (µg/mL)	COX-2 $IC_{50} \pm SD$ (µg/mL)	15-LOX $IC_{50} \pm SD$ (µg/mL)
Methanol ext.	0.55 ± 0.014	2.0 ± 0.014	3.9 ± 0.0129
n-Hexane fr.	0.37 ± 0.014	1.6 ± 0.008	3.6 ± 0.005
Chloroform fr.	0.42 ± 0.0129	2.1 ± 0.008	2.9 ± 0.008
Ethyl acetate fr.	0.30 ± 0.008	1.4 ± 0.011	2.2 ± 0.014
Remaining aq. fr.	0.24 ± 0.014	1.0 ± 0.008	1.8 ± 0.005
Celecoxib	0.34 ± 0.001	1.2 ± 0.0003	-----
Quercetin	-------	-----	3.34

Values (mean ± SD) are average of triplicate measurements, level of significance: * $P < 0.05$.

Conclusion

Wild plants are considered the treasure of natural healers. Plants of the genus *Echinops* L. indigenous to Saudi Arabia, are used traditionally in the treatment of various disorders. Hence, the current research aimed at the phytochemical and biological screening of the different extracts of *E. erinaceus.* Herein, the *in vitro* antioxidant and anti-inflammatory activities of the polar and semi-polar extracts of the aerial parts of this plant were evaluated for the first time. The polar fractions showed promising antioxidant and anti-inflammatory activities in COXs and LOX enzymes inhibition. However, for more safety, further studies are required to isolate and identify the active biochemical(s) responsible for these effects, and *in vivo* study will be carried out to identify the mechanism of action for the most potent extract.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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