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Phytochemical Composition, Cytotoxic Effects, and Anti-Inflammatory Capacity of Ethanol Extracts from *Erodium* Species: *E. Glaucophyllum*, *E. Hirtum* and *E. Guttatum*

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Abstract

Erodium species, native to the southern Mediterranean region, were revered as medicinal herbs celebrated for their numerous health. Polyphenols play a vital role in scavenging free radicals, and numerous health benefits. This study focuses on *E. glaucophyllum*, *E. hirtum*, and *E. guttatum*, aiming to analyze their phytochemical composition, cytotoxic effects, and anti-inflammatory capacity. Total polyphenols, total flavonoids, and condensed tannins content varied significantly among the species and plant parts, with *E. glaucophyllum* displaying the highest concentrations with 178 ± 4.6 µg GAE/g DR, 80 ± 5 µg RE/g DR, and 40.8 ± 2 µg CE/g DR, respectively. Cytotoxicity assessments revealed dose-dependent effects, indicating generally favorable safety profiles at lower concentrations. *E. glaucophyllum* exhibited significant cytotoxicity at higher concentrations, emphasizing concentration-dependent effects. The anti-inflammatory potential was evaluated by assessing NO production in murine macrophages, demonstrating dose-dependent reductions for all extracts. *E. glaucophyllum* exhibited pronounced anti-inflammatory effects, outperforming the reference drug (Vitamin C) at equivalent concentrations. These results position *E. glaucophyllum* as a promising source of bioactive compounds with notable antioxidant and anti-inflammatory effects, warranting further exploration in natural medicine and drug development.

Keywords: Medicinal plants; Natural product; Phytochemical composition; Cytotoxic effects; Anti-inflammatory capacity

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Introduction

In recent years, there has been a growing interest in exploring the therapeutic potential of natural products, particularly plant-derived compounds, due to their bioactive metabolites and minimal side effects compared to synthetic pharmaceuticals. Among the vast array of plant species, the *Erodium* genus, a member of the *Geraniaceae* family, has gained attention for its traditional medicinal uses and pharmacological potential. *E. glaucophyllum*, *E. hirtum*, and *E. guttatum*, three members of this genus, have been traditionally employed in folk medicine to treat various ailments [1,2].

Cancer and inflammatory disorders present substantial challenges to global public health, demanding the continuous search for novel therapeutic agents. Natural products, especially those sourced from plants, have long served as an invaluable reservoir of biologically active compounds with promising therapeutic effects [3]. *Erodium* species, commonly known as "storksbill" or "filaree" are distributed in various regions and have been used in traditional medicine to manage condition like skin infections, gastrointestinal disorders, and respiratory ailments [4]. These traditional uses have piqued scientific interest and prompted investigations into the pharmacological potential of *Erodium* species, particularly their leaves, which harbor diverse phytochemicals known for their medicinal attributes [2,4,5]. Moreover, the trio of plants, *E. glaucophyllum*, *E. hirtum*, and *E. guttatum*, serve as reservoirs of secondary metabolites like phenolics, prized for their natural antioxidant properties, and known primarily for their therapeutic effects, including antioxidant and antibacterial properties [5,2]. Numerous studies have indicated that bioactive metabolites exhibit variation not only between different species but also among different organs of the same plant [6]. In addition, previous study reported that the leaves extract from the three plants exhibited the high content of bioactive metabolites improving their biological activities [2].

Cytotoxicity, the capacity of a compound to induce cell damage in targeted cancer cells, is a preliminary test in the development of potential anticancer agents [7]. Several plant-derived compounds have exhibited promising cytotoxic activities against cancer cells, offering hope for new therapeutic strategies [8]. Similarly, inflammation is a complex physiological response that plays a central role in various diseases, including rheumatoid arthritis, inflammatory bowel disease, and atherosclerosis [8]. Natural products with anti-inflammatory properties have been sought after for their potential to mitigate inflammation and related pathologies [9,10]. The findings from this research may shed light on the therapeutic applications of *E. glaucophyllum*, *E. hirtum*, and *E. guttatum* leaf extracts, potentially paving the way for novel drug development and providing new insights into natural product-based treatments for cancer and inflammatory disorders.

Given the traditional uses of *Erodium* species and the potential of their bioactive compounds, the objective of this study is to enhance scientific comprehension of their cytotoxic and anti-inflammatory activities of the leaf's extracts from the three plants *E. glaucophyllum*, *E. hirtum* and *E. guttatum* using the resazurin test, fluorescence cell viability against RAW 264.7 macrophages, and *in vitro* anti-inflammatory effects of the different extracts by determination the percentage inhibition of Nitrogen Monoxide (NO).

Material and Methods

Plant material and extraction

Leaves from various medicinal plants, namely *E. glaucophyllum*, *E. hirtum*, and *E. guttatum*, were gathered from different regions of Gafsa (Figure 1), Tunisia. After washing, the collected leaves were dried in the shade and then powdered. Subsequently, 50 g of the powder was immersed in 500 mL of a water-ethanol solution (80%, v/v). Ultrasound treatment was applied at a frequency of 40 kHz for 1 h, followed by centrifugation at 3,000 g for 15 min to obtain the extract. The extract was then filtered through Whatman No. 1 filter paper to remove any particulates. The residue underwent further extraction, filtration, and concentration through freeze-drying. The resulting extracts were stored at -20°C until analysis.

Total phenolic content

The determination of total phenolic content followed the Folin-Ciocalteu method as outlined by Tlili et al. [6]. In brief, 0.125 mL of each extract was mixed with 0.5 mL of Folin-Ciocalteu reagent and 1.25 mL of Na_2CO_3 (7% w/v). After incubating the tubes in the dark for 90 min, the absorbance of each sample was measured at 765 nm. The total polyphenol content was calculated and expressed as µg Gallic acid equivalents per ml of fermented beverage (mg GAE/g).

Total flavonoid content

The total flavonoid content was determined following the method described by Tlili et al. [6] and conducted in triplicate. Total flavonoids were expressed in mg of Quercetin equivalent per ml of plant extracts (mg QE/g), estimated using a Quercetin standard curve (concentration range: 100-750 µg/mL).

Condensed tannin contents

The assessment of condensed tannin contents followed the method outlined by Tlili et al. [6] and was conducted in triplicate. Condensed tannin levels were expressed as mg catechin equivalent per g of plants extracts (mg CE/g), determined through a catechin calibration curve (100-750 µg/ml).

Cellular culture

The murine macrophage cell line RAW 264.7 (obtained from the American Type Culture Collection) was cultured in RPMI 1640 medium (from Dominique Dutscher, with L-Glutamine), supplemented with 10% Fetal Bovine Serum (FBS) (sourced from Dominique Dutscher, originating from South America), and antibiotics (penicillin 100 U/mL and streptomycin 100 µg/mL). Cell culture was maintained at 37°C in a humidified atmosphere containing 5% CO_2. Prior to each experiment, RAW cells in the exponential growth phase were seeded into 24-well plates at a density of 2 × 105 cells/well and allowed to adhere by incubating for 24 h.

Evaluation of the cytotoxicity of the extracts

To establish a range of non-toxic concentrations, the cytotoxicity of the extracts was assessed using the Resazurin test developed by Mosmann [11]. Briefly, RAW 264.7 macrophages previously seeded in 24-well plates were treated for 24 h with various increasing concentrations of each extract. Following removal of the supernatant, 1 mL of a 2% resazurin solution in PBS (Dulbecco's Phosphate Buffered Saline, from Dominique Dutscher) was added to each well. After 60-min incubation, fluorescence was measured, and cell viability was calculated relative to untreated cells using the following equation:

% inhibition = [Fluorescence (sample) × 100] / Fluorescence (control)

Anti-inflammatory activity test (Griess nitrite assay)

In inflammation, Nitrogen Monoxide (NO) plays a pivotal role among molecular elements. Our study aimed to assess the impact of extracts on the nitrite level released by RAW 264.7 cells. Macrophages adhered to 24-well plates were treated with three increasing concentrations of each extract (12.5 µg/mL, 25 µg/mL, and 50 µg/mL). After a 1 h pretreatment, cells were stimulated with LPS (1 µg/mL) and incubated for 24 h at 37°C. Supernatant was collected, and NO

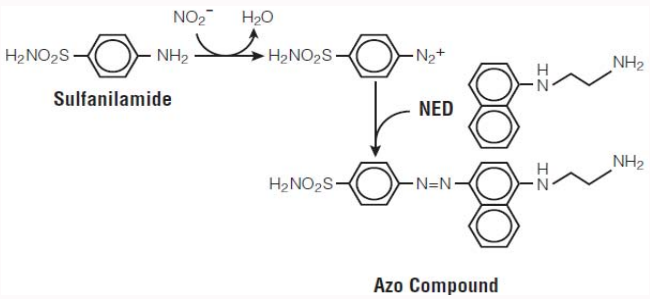

Figure 1: Griess reaction.

production was estimated through a colorimetric assay employing the GRIESS reagent. This assay, based on a diazotization reaction initially described by Griess et al. [12], involves the formation of a diazonium salt with sulfanilic acid by nitrites in an acidic medium, followed by coupling with an amine to produce an azo dye that absorbs at 540 nm (Figure 1). Briefly, 100 µL of cell supernatant was incubated with 100 µL of Griess's reagent (0.8% sulfanilamide, 0.75% N-naphthyl ethylene diamine in 0.5 N HCl) at room temperature for 15 min. Absorbance at 540 nm was measured using the Varioskan Flash plate reader (Thermo Scientific), and nitrite presence was quantified from a standard curve of $NaNO_2$. Percentage inhibition was calculated relative to a control treated with LPS only, without extract. Each test was conducted three times in triplicate.

Statistical analysis

Results are presented as mean ± standard error of the mean. Intergroup variation among different groups was assessed using one-way Analysis of Variance (ANOVA) followed by Tukey's HSD Post-Hoc tests for multiple comparisons, with statistical significance set at $p<0.05$.

Results and Discussion

Total phenolics, total flavonoids and condensed tannins content

Recognized as crucial players in the scavenging of free radicals, polyphenols not only enhance the functional properties of fruits and vegetables but also confer numerous health benefits. Recent attention has been directed toward identifying plant parts and specific species with optimal polyphenol levels, emphasizing their significance in promoting human health and well-being. The results presented in Table 1 demonstrate significant variations in the total phenolics, total flavonoids, and condensed tannins content extracted from different parts of *E. glaucophyllum*, *E. hirtum*, and *E. guttatum* (Table 1). Specifically, the leaf extract of *E. glaucophyllum* exhibited the highest levels of polyphenols, flavonoids, and tannins contents (178 ± 4.6 µg GAE/g DR, 80 ± 5 µg RE/g DR, and 40.8 ± 2 µg CE/g DR, respectively) compared to the extracts from other plant species.

The leaf extracts of *E. glaucophyllum* exhibited the highest level of flavonoid content (80 ± 5 µg RE/g DR) compared to those of *E. hirtum* and *E. guttatum* (52 ± 2.5 µg RE/g DR and 62 ± 3 µg RE/g DR, respectively). These findings underscore distinct variations in the phytochemical composition among the leaf extracts of *Erodium glaucophyllum*, *Erodium hirtum*, and *Erodium guttatum*. Notably, *E. glaucophyllum* emerges as a standout contender, boasting the highest concentrations of total phenolics, flavonoids, and tannins among the three species. The elevated total phenolic content in *E. glaucophyllum* signifies a robust antioxidant potential, suggesting its capacity to combat oxidative stress. Furthermore, the abundance of flavonoids, known for their anti-inflammatory properties, underscores the potential of *E. glaucophyllum* in mitigating inflammatory processes. The higher tannin content observed in *E. glaucophyllum* implies possible antimicrobial effects and astringent properties. While *E. hirtum* and *E. guttatum* also exhibit noteworthy phytochemical profiles, the supremacy of *E. glaucophyllum* in multiple categories implies its promising role as a source of bioactive compounds. These findings lay a foundation for further exploration into the specific mechanisms and potential therapeutic applications of these phytochemicals, positioning *E. glaucophyllum* as a promising candidate for future studies in the realms of natural medicine and drug development.

Table 1: Total phenolic content, total flavonoids, and condensed tannins of ethanol extracts from *Erodium glaucophyllum*, *Erodium hirtum*, and *Erodium guttatum*.

	E. glaucophyllum	*E. hirtum*	*E. guttatum*
Total phenolic content*	178 ± 4.6	152 ± 3	162 ± 2
Flavonoid's content**	80 ± 5	52 ± 2.5	62 ± 3
Tannin contents***	40.8 ± 2	34 ± 2	38 ± 2

Results are expressed as mean of 3 experiments ± SD
* µg GAE/g DR: µg gallic acid equivalents per g dry residue
** µg RE/g DR: µg of rutin equivalent per gram dry residue
*** µg CE/g DR: µg catechin equivalent per gram dry residue

Cytotoxic effects

Cell viability was evaluated by MTT assay. The cytotoxic effects of the different extracts on macrophage cell lines (RAW 264.7) are presented in Figure 2. The results provided appears to represent cell viability percentages for different concentrations of extracts from *Erodium glaucophyllum*, *Erodium hirtum*, *Erodium guttatum*, and a reference drug (Vitamin C).

The cytotoxicity results of the three extracts showed dose-dependent manner (Figure 2), and significant differences were revealed at 25, 50, and 100 µg/ml concentrations as compared to the control. Also, a significant difference was observed between 50 and 100 µg/ml. In addition, the results showed that the three extracts were significantly revealed at 25 and 50 µg/ml compared to the control. Also, the results showed that, at 25, 50 µg/ml, all extracts and the drug demonstrate high cell viability (<90%), indicating minimal cytotoxicity. At 100 µg/ml, there is a notable decrease in cell viability for all extracts and the drug. *E. glaucophyllum* exhibits the lowest viability, indicating a significant cytotoxic effect. *E. guttatum* still maintains higher viability compared to *E. hirtum*.

Overall, the results suggest concentration-dependent cytotoxic effects, with *E. glaucophyllum* showing a substantial impact on cell viability, especially at higher concentrations. The comparison with the reference drug provides a context for evaluating the efficacy of the plant extracts. Further investigations, such as determining the specific cytotoxic mechanisms and potential therapeutic applications, would contribute to a comprehensive understanding of these findings.

Anti-inflammatory capacity

The *in vitro* anti-inflammatory activity was studied using macrophage cell lines (RAW 264.7) are presented in Figure 3. The anti-inflammatory activity of ethanol plant extracts and a reference drug (Vitamin C) was determined by assessing their potential to inhibit the production of NO induced LPS in murine macrophages RAW cells.

The data illustrates a noteworthy anti-inflammatory potential in the ethanol extracts of *E. glaucophyllum*, *E. hirtum*, and *E. guttatum*. Upon exposure to Lipopolysaccharide (LPS), a substantial increase in Nitric Oxide (NO) production was evident, reflecting an induced inflammatory response. However, the ethanol extracts from all three Erodium species exhibited a dose-dependent mitigation of this inflammatory effect. At concentrations of 12.5, 25, and 50 µg/ml, the extracts consistently demonstrated a reduction in NO production. Specifically, *Erodium glaucophyllum* exhibited a prominent decrease from approximately 28.18 to 7.37, showcasing its robust anti-inflammatory impact. *Erodium hirtum* and *Erodium guttatum* also displayed notable dose-dependent responses, with declining NO concentrations across the increasing extract concentrations. The diminishing trend in NO production suggests a concentration-

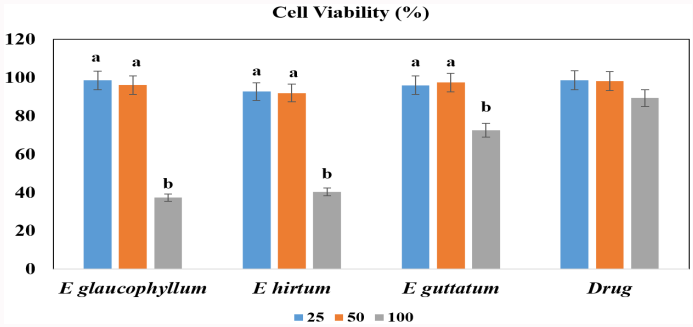

Figure 2: Cytotoxic effects of ethanolic leaves extracts from *Erodium glaucophyllum*, *Erodium hirtum* and *Erodium guttatum*.

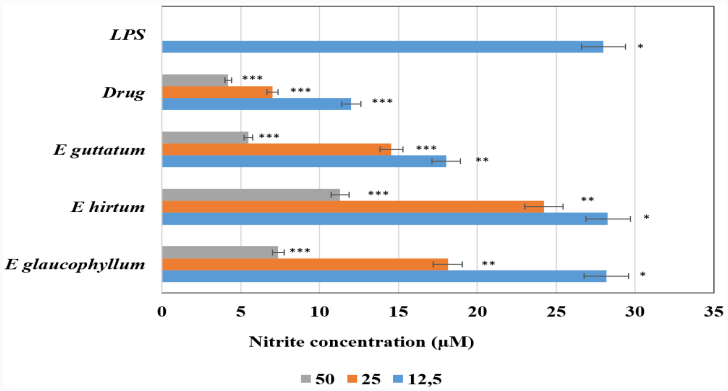

Figure 3: Effect of *Erodium glaucophyllum*, *Erodium hirtum* and *Erodium guttatumon* nitric oxide production by murine macrophages stimulated with LPS. Data are presented as mean ± standard deviation of three independent experiments. (*p)

dependent anti-inflammatory effect for all three extracts. Notably, the extracts outperformed Lipopolysaccharides (LPS) in mitigating NO production at equivalent concentrations. However, at 50 µg treatment of three ethanolic extracts did not show such a significant difference to compare with Vitamin C, which could be attributed to low NO concentrations. This underlines the potential of these *Erodium* species as anti-inflammatory agents, warranting further exploration into the specific molecular mechanisms underpinning their effects and their potential applications in therapeutic contexts.

Discussion

Polyphenols, a prominent category of secondary metabolites in plants, encompass diverse bioactive compounds offering a broad spectrum of biological activities [13]. This group includes flavonoids, tannins, and phenolic acids; each contributing to the antioxidant potential of plants [13]. The study developed a comprehensive exploration into the properties of the different extracts, focusing on total phenolics, flavonoids, condensed tannins, cytotoxic effects, and anti-inflammatory capacity. The research contributes significantly to understanding the distinct phytochemical compositions of these *Erodium* species and their potential applications in health and medicine. Our results supported by previous workers [2]. The investigation begins by highlighting polyphenols as key secondary metabolites in plants, emphasizing their diverse biological activities. The study specifically looks at flavonoids, tannins, and phenolic acids, which contribute to the antioxidant potential of plants. Our findings are consistent with previous studies suggesting that *E. glaucophyllum* possesses elevated levels of polyphenols, flavonoids, and tannins [5]. The attention to identifying plant parts and species with optimal polyphenol levels underscores the importance of these compounds in promoting human health.

The results, as presented in Table 1, reveal significant variations in total phenolics, flavonoids, and tannins content among the extracts from the three *Erodium* species. Notably, *E. glaucophyllum* emerges as the leader in these categories, showcasing the highest concentrations. This information positions *E. glaucophyllum* as a particularly promising source of bioactive compounds.

Moving on to cytotoxic effects, the study employs the MTT assay to assess cell viability on macrophage cell lines. The results exhibit a dose-dependent cytotoxic response for all extracts, with *E. glaucophyllum* displaying significant cytotoxicity at 100 µg/ml. However, at lower concentrations (25 and 50 µg/ml), all extracts maintain high cell viability, indicating minimal cytotoxicity. This nuanced understanding of cytotoxic effects provides valuable insights into the potential safety profile of these extracts.

While inflammation serves as an essential autoimmune response to harmful stimuli, its transition from acute to chronic stages can lead to the development of inflammation-mediated disorders [14]. Oxidative stress-induced inflammation is implicated in the onset and progression of various chronic diseases [15-18]. The beneficial properties of numerous marine natural products in mitigating oxidative stress-induced inflammation are widely recognized [19]. For instance, phytoprostanes and phytofurans derived from *Gracilaria Longissima* red algae have demonstrated anti-inflammatory effects in endothelial cells [20]. The anti-inflammatory capacity is evaluated by assessing the ability of extracts to inhibit the NO production induced by LPS in murine macrophages. The findings demonstrate a notable anti-inflammatory potential for all three extracts, with *E. glaucophyllum* exhibiting the most substantial reduction in NO

production. Interestingly, the extracts outperform the reference drug (Vitamin C) at equivalent concentrations, emphasizing their efficacy in mitigating inflammation.

In summary, the study has developed a thorough analysis of the phytochemical composition, cytotoxic effects, and anti-inflammatory capacity of ethanol extracts from *Erodium* species. The results position *E. glaucophyllum* as a standout candidate for further exploration in natural medicine and drug development, given its remarkable concentrations of bioactive compounds and potent anti-inflammatory effects. This comprehensive investigation sets the stage for deeper inquiries into the specific mechanisms and therapeutic applications of these extracts.

Conclusion

In summary, the study reveals that ethanol extracts from the three medicinal plants: *E. glaucophyllum*, *E. hirtum*, and *E. guttatum* exhibit distinct phytochemical compositions. *E. glaucophyllum* emerges as a standout source, boasting the highest concentrations of total phenolics, flavonoids, and tannins, indicating robust antioxidant potential. Cytotoxicity assessments suggest generally favorable safety profiles for these extracts at lower concentrations. Notably, *E. glaucophyllum* exhibits significant cytotoxic effects at higher concentrations. In terms of anti-inflammatory capacity, all three extracts effectively mitigate LPS-induced NO production, with *E. glaucophyllum* demonstrating the most pronounced reduction and outperforming the reference drug at equivalent concentrations. These findings position *E. glaucophyllum* as a promising candidate for further exploration in natural medicine and drug development, highlighting its potential as a source of bioactive compounds with notable antioxidant and anti-inflammatory effects.

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