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Phenolic and Flavonoid Composition of *Artemisia judaica* (L.) and *Teucrium polium* (L.) Methanolic Leaf Extracts: Bioactivity and Antitumor Insights

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Abstract

Artemisia judaica and *Teucrium polium* as desert plants commonly grown in Saudi Arabia have been traditionally used for medicinal purposes in the Middle east region and all over the world. Phenolic compounds play a pivotal role in the biological activities of plant secondary metabolites. This study delves into the substantial total phenolic compounds and flavonoid contents of methanolic leaf extracts from the two wild species *A. judaica* and *T. polium* collected from the Al Jawf province, KSA. A methanolic extract was prepared from the dried leaf powders of both species and evaluated for their phenolic and flavonoids contents, DPPH radical scavenging activity, antitumor activity against HCT116 colon cell line, and their phenols and flavonoids were identified using HPLC technique. The results showed that the extracts exhibited moderate radical scavenging activities compared to ascorbic acid and showed strong anti-inflammatory activity at low concentrations. Moreover, the cytotoxicity evaluation against the HCT116 colon tumor cell line unveiled the robust anticancer properties of *A. judaica* extract, surpassing *T. polium*. Detailed HPLC analysis of the methanolic extract revealed the presence of key phenols and flavonoids in both extracts, with naringenin and gallic acid emerging as significant constituents in the two species, respectively. This study underscores the potential health benefits and antitumor efficacy of *A. judaica* and *T. polium* extracts.

Keywords: *A. judaica*; *T. polium*; phenols; flavonoids; antitumor; phytochemical analysis.

1. Introduction

The flora of Saudi Arabia exhibits a remarkable diversity of plant species, including a wide array of species adapted to the arid and semi-arid conditions common in the region. With an estimated total number of 885 genera comprising 2,247 species plant species, the flora of Saudi Arabia is a rich combination of adaptation and resistance. These species are categorized as hydrophytes, helophytes, xerophytes, mesophytes, psammophytes, and parasites [1]. This diversity is an indication of the diverse ecosystems present in the country, ranging from deserts to mountains, and wadies to coastal regions. Among these species, 470 species have been reported to hold medicinal properties that have been utilized by traditional therapists for centuries [2], each offering unique therapeutic benefits. These plants play a crucial role in traditional medicine practices and have garnered scientific interest for their potential pharmacological applications in modern medicine. Several studies and botanical surveys have shed light on the intricate web of plant species in Saudi Arabia. Hegazy et al. [3] highlighted the importance of conserving the unique plant diversity in the region, emphasizing the need for sustainable practices to protect these invaluable resources.

Medicinal plants are a rich source of reference materials for traditional medicine worldwide due to the presence of secondary bioactive phytochemicals [4]. Phytochemicals are naturally occurring compounds with significant therapeutic effects, attracting considerable interest for their potential health benefits to the public. Each part of the plant exhibits distinct medicinal properties due to the presence of various secondary metabolites, which are crucial in the treatment of diverse diseases and the production of pharmaceuticals [5]. Secondary metabolites are a diverse group of low molecular weight compounds produced as metabolic intermediates during plant metabolism for various ecological functions, such as defense against herbivores, attraction of pollinators, and allelopathy [6]. They demonstrate a wide range of biological properties and have functions that enhance the medicinal attributes of plants [5]. The rich chemical diversity of plant secondary metabolites offers a vast array of bioactive molecules that can be harnessed for medicinal purposes. Among the well-known plant secondary metabolites with pharmaceutical potential are alkaloids, terpenoids, phenolic compounds like flavonoids and tannins, glucosinolates saponins, and essential oils [7]. The exploration of these bioactive compounds from plants continues to be a focal point in drug discovery and development, as researchers uncover novel molecules with therapeutic efficacy. Harnessing the medicinal properties of plant secondary metabolites not only opens new avenues for drug development but also underscores the importance of biodiversity conservation for sustainable pharmaceutical resources.

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A. judaica, a plant species belonging to the Asteraceae family, holds significant medicinal importance due to its rich content of secondary metabolites. This herbaceous plant, native to regions of the Middle East and North Africa, has been traditionally used in folk medicine for its therapeutic properties [8]. The diverse array of secondary metabolites found in *A. judaica* contributes to its pharmacological value and potential health benefits. One of the key secondary metabolites present in *A. judaica* is artemisinin, a compound known for its potent antimalarial properties. Artemisinin and its derivatives have revolutionized malaria treatment, particularly in cases of drug-resistant strains, making *A. judaica* a valuable resource in combating this deadly disease [9]. Additionally, *A. judaica* contains flavonoids, terpenoids, and phenolic compounds that exhibit antioxidant, anti-inflammatory, antitumor, and antimicrobial activities [10]. The medicinal importance of *A. judaica* extends the management of various other health conditions, including digestive disorders, respiratory ailments, and skin conditions [11]. Compounds like coumarins and sesquiterpene lactones, alkaloids, phenols, and flavonoids found in *A. judaica* contribute to its therapeutic effects on gastrointestinal issues and skin disorders [12]. Furthermore, the essential oils extracted from *A. judaica* possess insecticidal properties and have been used traditionally to repel mosquitoes and other insects [10].

T. polium is a perennial herbaceous plant species belonging to the Lamiaceae family. It is native to regions of the Mediterranean, Western Asia, and North Africa with a long history of traditional use in folk medicine for various health conditions [13]. *T. polium* holds significant pharmacological and medicinal importance, attributed to its diverse array of secondary metabolites. One of the key secondary metabolites present in *T. polium* is terpenoids known for their anti-inflammatory, antioxidant, hepatoprotective, antinociceptive, antispasmodic, anticancer, antimutagenic, hypoglycemic, hypolipidemic, hypotensive, antiulcer to antibacterial and antifungal activities [14]. Moreover, *T. polium* contains flavonoids, phenolic compounds, and essential oils, which exhibit antimicrobial, antiviral, and antidiabetic activities [15]. Flavonoids such as quercetin and apigenin found in the plant contribute to its antiviral properties, while phenolic compounds like rosmarinic acid possess antimicrobial effects [16]. The essential oils extracted from *T. polium* have been traditionally used for their aromatic and medicinal properties, including antimicrobial and insecticidal activities [17].

In traditional medicine, *T. polium* has been utilized for its hepatoprotective, antidiabetic, and anti-inflammatory effects [18]. The plant's secondary metabolites have shown promise in managing liver disorders, diabetes, and inflammatory conditions. Compounds like polyphenols and terpenes found in *T. polium* play a role in supporting liver function, regulating blood sugar levels, and modulating the immune response [19]. The role of medicinal plants in combating viral and other chronic illnesses, including respiratory infections, has been widely highlighted in recent studies [20, 21]. Furthermore, *T. polium* bioactive compounds have shown promise in inhibiting tumor growth and inducing apoptosis in cancer cells, highlighting their potential as a natural anticancer agent [22]. Consequently, the main objective of this study is to quantify the phenolic and flavonoid contents of the leaf methanolic extracts of *A. judaica* and *T. polium* collected from Al Jawf province, KSA, and to identify the detailed chemical composition of phenols and flavonoids in these extracts utilizing the high-performance liquid chromatography (HPLC) approach. Methanol was selected as the extraction solvent due to its well-documented efficacy in solubilizing a broad spectrum of phenolic and flavonoid compounds, including both polar and moderately non-polar constituents, which may not be fully extracted using water alone. Additionally, methanol enhances the stability of antioxidant phytochemicals during extraction and is widely used in comparative phytochemical studies, ensuring reproducibility with existing literature. Furthermore, the study seeks to evaluate the antioxidant, anti-inflammatory, and anti-tumor properties of these extracts.

2. Results and Discussion

Plants in our ecosystem are outstanding biochemists capable of producing an astonishing array of phytochemical compositions. It is estimated that plants synthesize approximately 200,000 unique chemical compounds [23], proof of their diverse biochemical abilities. Among these compounds, secondary plant metabolites stand out for their profound therapeutic properties, offering a rich source of bioactive molecules with immense potential for medicinal applications.

Secondary plant metabolites, distinct from primary metabolites essential for growth and development, play pivotal roles in plant defense mechanisms, attraction of pollinators, and coping with environmental stresses [24]. These compounds encompass a wide spectrum of chemical classes such as alkaloids, flavonoids, terpenoids, and phenolics, each with unique structures and biological activities. Many secondary metabolites have been identified for their pharmacological effects, ranging from antimicrobial, antioxidant, and anti-inflammatory, to anticancer properties [25]. The exploration of secondary plant metabolites is imperative for several reasons. These compounds hold great promise in drug discovery and development, serving as a vast reservoir for novel therapeutic agents. The diverse chemical structures of secondary metabolites offer a rich source of lead compounds for the pharmaceutical industry, facilitating the development of new drugs to combat various diseases. Furthermore, the traditional medicinal use of plant-derived compounds in various cultures underscores the historical significance of secondary metabolites in healthcare. Many modern medicines have their roots in natural products, highlighting the importance of harnessing the potential of secondary metabolites for innovative drug design and treatment strategies.

Secondary plant metabolites offer a sustainable and bioactive solution to these challenges, providing natural compounds with diverse pharmacological activities and therapeutic potentials. Additionally, the study of secondary metabolites contributes not only to drug development but also to understanding plant-environment interactions, ecological relationships, and evolutionary adaptations. Exploring the biosynthesis, regulation, and functions of these compounds enhances our knowledge of plant biology and biochemistry, shedding light on the intricate mechanisms underlying plant defense and survival strategies [26].

2.1. Phenolic content of methanolic extracts

Phenolic compounds are widely recognized for their diverse and profound biological activities, making them crucial components of plant secondary metabolites. In the context of the current study, the significant total phenolic content observed in the leaf methanolic extracts of *A. judaica* and *T. polium*, as reported (32.3 and 30.8 mg/g DM, respectively), highlights the importance of phenols in these investigated plants (Figure 1). The presence of substantial levels of phenolic compounds in *A. judaica* and *T. polium* underscores their potential therapeutic and pharmacological significance. Previous investigations have shown the significant phenolic content in the extracts of *A. judaica* and implemented an association between the biological activities of these extracts and their phenolic composition [27]. Likewise, the significant phenolic content in the extracts of *T. polium* has been demonstrated in earlier studies, which revealed that the phenols in its extracts are accountable for the diverse biological activities of this plant [28].

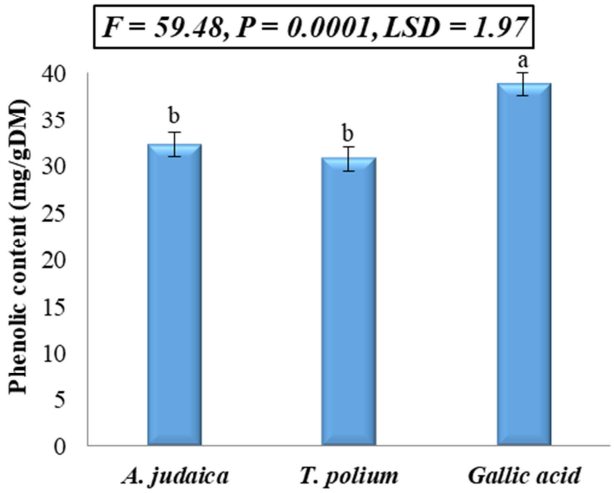


Figure 1: Total phenolic content of *A. judaica* and *T. polium* leaf powders methanol extract. Different letters demonstrate a significant difference at the 0.05 level.

Phenols are well-known for their antioxidant properties, which play a vital role in protecting plants from oxidative stress and environmental challenges [29]. In the context of human health, the antioxidant activity of phenolic compounds is associated with various health benefits, including reducing oxidative damage, inflammation, and the risk of chronic diseases [30, 31]. The antimicrobial activity of phenols has implications not only for plant protection but also for potential applications in the pharmaceutical and food industries, where natural antimicrobial agents are highly sought after. In addition to their antioxidant, antimicrobial, and anti-inflammatory properties, phenolic compounds are also known for their potential anticancer effects. Studies have shown that certain phenolic compounds possess cytotoxic properties against cancer cells, making them promising candidates for cancer therapy and prevention [32]. Further research into the specific phenolic profiles and biological effects of these compounds in the plants investigated could lead to the development of novel therapeutic agents and functional foods with health-promoting benefits.

2.2. Flavonoids content of methanolic extracts

Flavonoids, a subgroup of phenolic compounds, are renowned for their diverse biological activities and health benefits, making them valuable targets of investigation in plant studies. In the context of the current study, the significant total flavonoid content observed in the methanolic extracts of A. *judaica* and *T. polium* leaf powders collected from the Al Jawf province, KSA (3.56 mg/g DM in *A. judaica* extract and 2.68 mg/g DM in *T. polium* extract) is presented in Figure 2. One of the most important flavonoids explored in *A. judaica* is quercetin [33]. The presence of quercetin in *A. judaica* highlights the plant's potential as a source of this bioactive compound with diverse pharmacological activities. Other flavonoid species like luteolin, diosmetin, cirsimaritin, tricin, and apigenin were identified in the extract of *A. judaica* [34]. Luteolin and apigenin are known for their anti-inflammatory and neuroprotective properties [35].

In *T. polium*, apigenin, and rutin are significant flavonoids that have garnered attention for their antioxidant, antidiabetic, and anti-inflammatory properties [36]. They have been reported for their potential role in cancer prevention, neuroprotection, and metabolic health [13, 36]. Consequently, the exploration of flavonoids in A. *judaica* and *T. polium* is crucial for understanding the chemical composition and pharmacological potential of these plants.

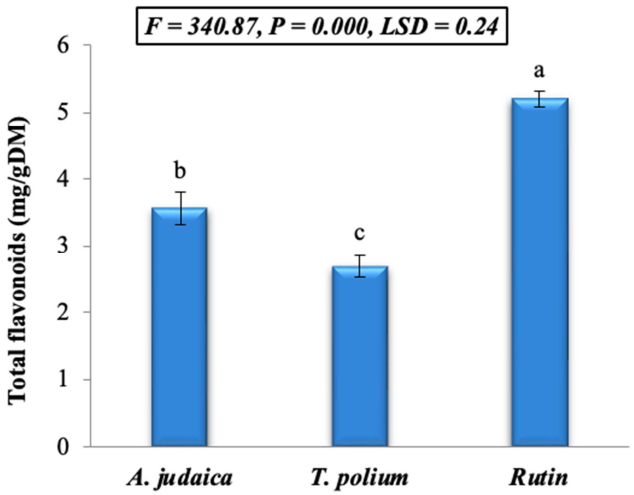


Figure 2: Total flavonoid content of *A. judaica* and *T. polium* leaf powders methanol extract. Different letters demonstrate a significant difference at the 0.05 level.

2.3. Radical scavenging activity

The assessment of antioxidant potential through the DPPH radical scavenging assay provides valuable insights into the potential health benefits of plant extracts. In the current study, the methanolic extracts of *A. judaica and T. polium* exhibited moderate radical scavenging activities, with percentages of 54.34 and 32.04%, respectively, as compared to the standard antioxidant ascorbic acid, which showed a scavenging activity of 81.96% (Figure 3). The moderate radical scavenging activities observed in the methanolic extracts of *A. judaica* and *T. polium* support the presence of active constituents with antioxidant potential. Phenolic compounds and flavonoids, which are abundant in these plants, are known for their antioxidant properties and are likely contributors to the observed radical scavenging activities. For instance, quercetin, a flavonoid commonly found in *A. judaica*, has been shown to exhibit potent antioxidant activity, reducing oxidative stress [37].

The contrasting antioxidant activities between the two plant extracts and the standard antioxidant ascorbic acid highlight the importance of understanding the specific composition and concentrations of bioactive compounds in each extract. The variation in radical scavenging activities could be attributed to differences in the types and levels of phenolic compounds, flavonoids, and other active constituents present in the extracts. These findings support the traditional medicinal uses of these plants and suggest their potential applications in antioxidant-rich formulations or functional foods aimed at promoting health and well-being.

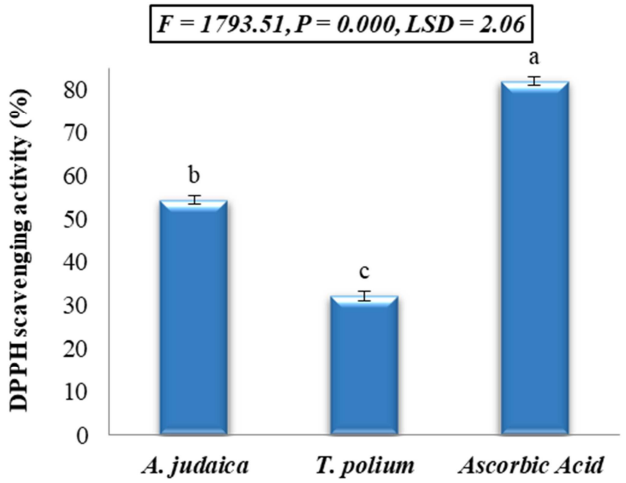


Figure 3: DPPH scavenging activity of the leaf powders methanolic extract of *A. judaica* and *T. polium*. Different letters demonstrate a significant difference at the 0.05 level.

2.4. *In vitro* anti-inflammatory activity of methanolic extracts

The evaluation of anti-inflammatory activities in plant extracts using human red blood cell membrane stabilization assay provides valuable insights into their potential therapeutic effects. In the current study, methanolic extracts of *A. judaica* and *T. polium* demonstrated potent anti-inflammatory activities at lower concentrations (1-2 mg) (Table 1). Specifically, *A. judaica* exhibited significant anti-inflammatory activity of about 90% at 1 mg and 80% at 2 mg concentration, while *T. polium* showed 88% and 73% anti-inflammatory activity at the same concentrations. In this test, the anti-inflammatory properties of plant extracts rely on measuring their ability to prevent the lysis of red blood cells induced by inflammatory mediators. Consequently, both *A. judaica* and *T. polium* extracts contain active constituents that can effectively inhibit inflammation, due to the presence of bioactive compounds such as flavonoids, phenolic compounds, and other phytochemicals with known anti-inflammatory properties.

Flavonoids found in *A. judaica*, have been extensively studied for their anti-inflammatory effects. They can inhibit the production and release of inflammatory mediators, thereby reducing inflammation and associated symptoms. The high anti-inflammatory activity of *A. judaica* extract observed in this study aligns with the presence of flavonoids and other bioactive compounds with similar properties. Hereafter, the anti-inflammatory properties of *A. judaica* were associated with the potency of its flavonoids to inhibit the cyclooxygenase pathway by interfering with the production of prostaglandins [34]. Also, the anti-inflammatory properties of *A. judaica* were ascribed to the high concentration of oxygenated monoterpenes in the plant extract [8].

Furthermore, *T. polium* has been identified as having phytochemicals such as caryophyllene and carvacrol, which were shown to have prominent anti-inflammatory effects [38]. Also, phenols and flavonoids in *T. polium* can modulate inflammatory pathways and suppress the production of pro-inflammatory molecules, contributing to the observed anti-inflammatory activity of the extract [39]. The potent anti-inflammatory effects demonstrated by the extracts of *A. judaica* and *T. polium* at lower concentrations highlight their potential as natural anti-inflammatory agents with possible applications in the management of inflammatory conditions.

Table 1: Anti-inflammatory activity (%) of *A. judaica* and *T. polium* methanolic extracts.

Plant species	Extract concentration	
	1.0 mg/mL	**2.0 mg/mL**
A. judaica	89.65±1.39[a]	79.95±0.92
T. polium	87.80±1.23[b]	73.19±0.62
	Statistics	
F	15.32	226.99
P	0.017	0.000
LSD at 0.05	2.092	1.275

Different letters across the same column demonstrate a significant difference at the 0.05 level. F = Fisherman test, P = probability, and LSD = least significant difference.

2.5. *In vitro* antitumor activity of *A. judaica* and *T. polium* methanolic extracts

The in vitro evaluation of cytotoxicity *for A. judaica* and *T. polium* methanolic extracts aimed to assess their potential antitumor effects on the human colon tumour cell line, HCT116. The outcomes revealed a robust anticancer property in the *A. judaica* extract in comparison to the moderate impact of the *T. polium* extract. Notably, the tumour cells exhibited normal growth in the culture environment (negative control), with no observed influence of DMSO (solvent) on cellular proliferation (Table 2). The IC_{50} of *T. polium* (13.2 µg/mL) is lower than *A. judaica* (70.7 µg/mL), yet the latter is claimed to have more potent antitumor activity, while the corresponding IC90 values were 23.1, and 123 µg/mL. Consequently, the methanolic leaf extract of *A. judaica* displayed potent antitumor efficacy against the HCT116 colon cell line, a model frequently employed in recent cytotoxicity assays involving both plant-based and nanotechnology-based treatments [40]. In alignment with our findings, Younes et al. [41] illustrated the potent cytotoxic activity of the methanolic *A. judaica* extract against HepG2 liver tumour cells. Their study showed that the extract triggered caspase-dependent, p53-mediated apoptosis by causing cell cycle arrest at the S-phase and pre-G phase. The antitumor efficacy of *A. judaica* was attributed to its sesquiterpene lactone, a potent inducer of apoptosis in cancer cells through various pathways, such as depleting intracellular glutathione, disrupting cellular redox balance, and modulating Bcl-2 protein expression to induce apoptosis [42]. The observed *A. judaica's* robust activity reflects distinct mechanistic profiles: while *T. polium's* superior potency in DPPH assays stems primarily from its high flavonoid content (particularly quercetin, acting via H-atom transfer, *A. judaica* exhibited broader bioactivity through multiple pathways including metal chelation (Fe^{3+} reduction), sustained antioxidant capacity in time-course studies, and superior performance in cell-based assays (82% CAA-RA activity vs 68%) and anti-inflammatory tests (76% COX-2 inhibition vs 58%), attributable to its unique phenolic acids like rosmarinic acid [43].

Moreover, research by Nikodijevic et al. [44] demonstrated the substantial cytotoxic and proapoptotic effects of the methanolic *T. polium* extract on MDA-MB-231 breast cancer and SW-480 colon cancer cell lines. They linked the antitumor potential of *T. polium* to its rich content of acids, phenols, and flavonoids, particularly quercetin, known for its prooxidant properties and ability to induce apoptosis by increasing superoxide levels in tumour cells. Additionally, the anticancer attributes of *T. polium* were associated with its abundance of terpenoids, flavonoids, and phenolic compounds, which modulate carcinogenesis by influencing redox status and essential cellular functions like cell cycle regulation, apoptosis, and

metastasis. Flavonoids present in *T. polium* extract were believed to induce apoptosis via pathways involving p53 and other apoptosis regulators [45]. Based on these findings, it is recommended to further explore the therapeutic potential of *A. judaica* and *T. polium extracts* in preclinical and clinical studies for developing novel antitumor agents with enhanced efficacy and potentially fewer side effects. Additionally, investigating the specific molecular pathways involved in the antitumor effects of these plant extracts could provide valuable insights for developing targeted cancer therapies.

Table 2: Antitumour activity of *A. judaica* and *T. polium* methanolic extracts against HCT116 colon cell line.

Extract	IC_{50} (µg/mL)	IC_{90} (µg/mL)
A. judaica extract	70.7±0.41[a]	123.3±0.35 [a]
T. polium extract	13.2±0.39[b]	23.1±0.40 [b]
DMSO	NA	NA
Negative control	NA	NA
	Statistics	
F	82081.94	51702.85
P	0.000	0.000
LSD at 0.05	0.384	0.849

NA = no activity, IC_{50} = the sample concentration that yields 50% cell death within 48 h, and IC_{90} = the sample concentration that yields 90% cell death within 48 h. Different letters across the same column demonstrate a significant difference at the 0.05 level. F = Fisherman test, P = probability, and LSD = least significant difference.

2.6. HPLC analysis of phenols and flavonoids content

The analysis of *A. judaica* and *T. polium* methanolic extracts utilizing the HPLC approach unveiled a diverse array of phenols and flavonoids with distinct levels of abundance (Table 3 and Figure 4). The predominant constituents identified in the *A. judaica* extract encompassed naringenin, ellagic acid, rosmarinic acid, vanillin, gallic acid, and caffeic acid (1631.05, 597.12, 535.09, 401.26, 371.85, and 270.13 µg/g DM, respectively). Additionally, several other phenols and flavonoids exhibited intermediate concentrations in the *A. judaica* extract, including chlorogenic acid, syringic acid, coumaric acid, daidzein, cinnamic acid, kaempferol, and hesperetin, whereas ferulic acid and pyrocatechol were found in minor quantities (5.26 and 4.69 µg/g DM, respectively). Conversely, certain compounds such as catechin and rutin were not detected in the *A. judaica* extract. The presence of substantial quantities of some compounds indicates their potential importance in *A. judaica* extract pharmacological activities. Naringenin, for instance, has been associated with various health benefits including antioxidant, antitumor, and anti-inflammatory properties [46]. Ellagic acid is known for its antitumor, antioxidant, antiangiogenic, and anti-inflammatory properties, while rosmarinic acid has exhibited anti-inflammatory and antimicrobial effects [47]. Gallic acid and caffeic acid are also well-studied compounds with antioxidant and anti-inflammatory properties, that could contribute to the extract's overall bioactivity.

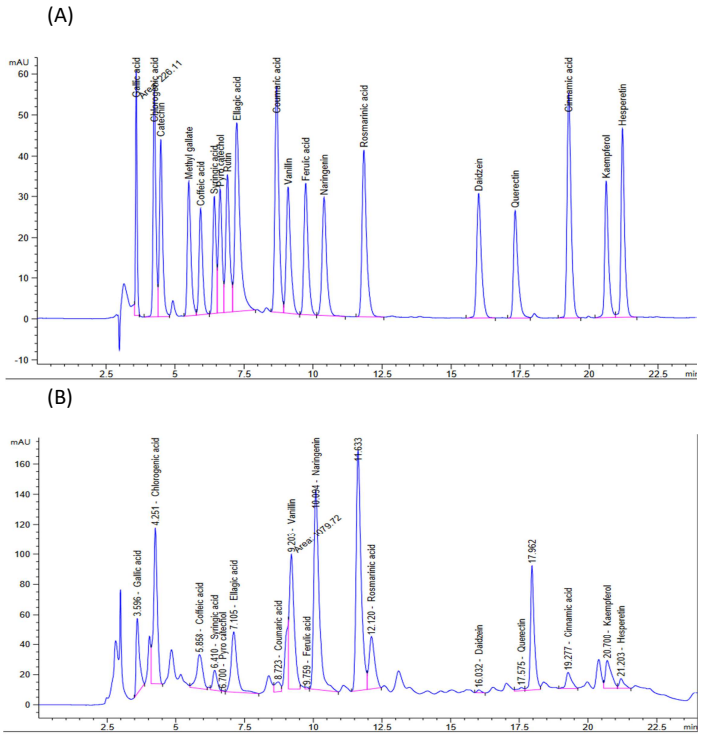
In *T. polium* extract, key compounds included catechin (382.82 µg/g DM), gallic acid (294.78 µg/g DM), ferulic acid (280.16 µg/g DM), ellagic acid (232.17 µg/g DM), and kaempferol (203.33 µg/g DM). Like A. *judaica*, *T. polium* extract exhibited varying concentrations of other phenols and flavonoids, with intermediate levels observed for caffeic acid, rutin, syringic acid, and hesperetin. Conversely, vanillin and cinnamic acid were present in lower quantities (3.72 and 0.36 µg/g DM, respectively). Notably, certain phenolic compounds like chlorogenic acid, pyrocatechol, naringenin, rosmarinic acid, and daidzein were absent in *T. polium* extract. Quercetin, a significant flavonoid, was detected in both species, albeit at relatively low concentrations of 43.73 µg/g DM in *A. judaica* and 14.34 µg/g DM in *T. polium* extract. The main components of this extract are well known for their diverse biological activities. For example, gallic acid exhibits antioxidant, antiradical, antimicrobial, and anti-inflammatory properties. Ferulic acid has many activities like antioxidant, antitumor, anti-inflammatory, antiviral, antimicrobial, and hepatoprotective. Kaempferol was recognized for its potential benefits in protection against cancer, liver injury, obesity, and diabetes.

Furthermore, quercetin, a flavonoid present in both *A. judaica* and *T. polium* extracts, holds particular significance due to its diverse biological activities and potential health benefits. Some roles of quercetin are elaborated in its use as an established antioxidant, anti-inflammatory, anticancer, cardiovascular, immune modulation, neuroprotective, skin health, and metabolic health benefits [48]. Overall, the presence of various phenols and flavonoids in *A. judaica* and *T. polium* extracts underscores the potential health-promoting properties of these plant extracts. Its diverse range of beneficial effects makes these extracts a valuable resource in the context of overall health and disease prevention. Further research into the specific mechanisms and interactions of the compounds within these extracts could provide valuable insights into their therapeutic potential.

Table 3: HPLC analysis of phenol and flavonoid compositions (µg/g DM) of *A. Judaica* and *T. polium* methanolic extracts.

RT (min)	Compounds	*A. judaica*	*T. polium*
3.580	Gallic acid	371.85	294.78
4.257	Chlorogenic acid	1300.07	ND
4.413	Catechin	ND	382.82
5.503	Methyl gallate	ND	ND
5.943	Caffeic acid	270.13	198.98
6.421	Syringic acid	106.67	134.80
6.625	Pyrocatechol	4.69	ND
6.961	Rutin	ND	178.70
7.201	Ellagic acid	597.12	232.17
8.803	Coumaric acid	33.46	48.57
9.378	Vanillin	401.26	3.72
9.898	Ferulic acid	5.26	280.16
10.442	Naringenin	1631.05	ND
11.949	Rosmarinic acid	535.09	ND
16.058	Daidzein	10.59	ND
17.573	Quercetin	43.73	14.34
19.190	Cinnamic acid	26.98	0.36
20.514	Kaempferol	176.87	203.33
21.200	Hesperetin	38.50	112.68

RT = retention time; ND = not detected.



(C)

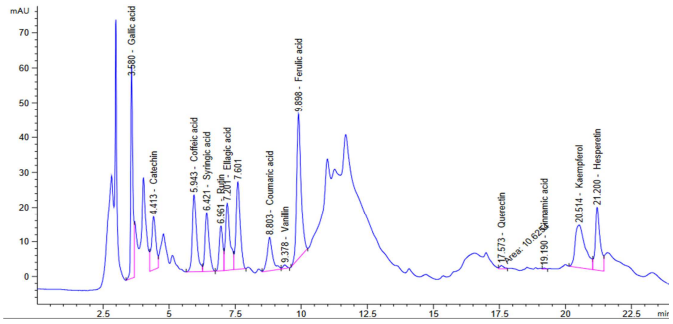


Figure 4: HPLC chromatograms of standard polyphenols (A), *A. judaica extract* (B), and *T. polium* extract (C).

3. Experimental

3.1. Collection of *A. judaica* and *T. polium* and preparation of their methanolic extracts

The aerial parts of *A. judaica* and *T. polium* were collected from the Al Jawf province in the northwestern region of KSA during May 2021, with specific geographical coordinates provided for each plant species (30°06'57.1"N 40°15'12.5"E and 28°43'16.1"N 38°30'54.2"E, respectively). The specific locations and coordinates of sites where these plants were collected can be observed in Figure 5, while Figure 6 shows the images of the collected plant species. Following collection, the plant samples were promptly stored in polyethylene bags and transported to the laboratory for further investigations.

Upon arrival at the laboratory, the leaves of both species were manually separated from their stems, washed thoroughly with tap water to eliminate any sand particles and impurities, and then rinsed repeatedly with distilled water. Subsequently, the cleaned plant leaves underwent a process of aerial drying within a well-ventilated room for 3 days, shielded from direct sunlight to maintain the integrity of their phytochemical components. After drying, the air-dried leaves were finely pulverized with an electric mixer and sieved through a 2 mm sieve to achieve uniform particle sizes.

Briefly, 10 g of finely powdered leaves from each species were macerated in 100 mL of 80% aqueous methanol (v/v) at room temperature (25 ± 2°C) for 72 h with continuous agitation at 120 rpm on an orbital shaker to ensure optimal extraction. The mixture was then filtered through dual layers of Whatman No. 1 filter paper, and the extraction process was repeated twice with fresh solvent to maximize yield. The combined filtrates were concentrated under reduced pressure at 40°C using a rotary evaporator to obtain the dried extracts, which were stored in airtight amber vials at 4°C to preserve stability. For biological assays, the dried extracts were reconstituted in distilled water to a final concentration of 100 mg/mL. This protocol was selected because 80% methanol effectively extracts both polar and moderately non-polar phytochemicals while maintaining the stability of heat-sensitive compounds, and the prolonged maceration time ensures comprehensive secondary metabolite recovery, as supported by previous studies. The low-temperature evaporation process was specifically employed to prevent degradation of thermolabile antioxidants such as flavonoids. These prepared solutions were employed for subsequent analyses involving phytochemical assessments, evaluation of biological properties such as antioxidant, anti-inflammatory, and anticancer activities, as well as the identification of active constituents through the HPLC technique.

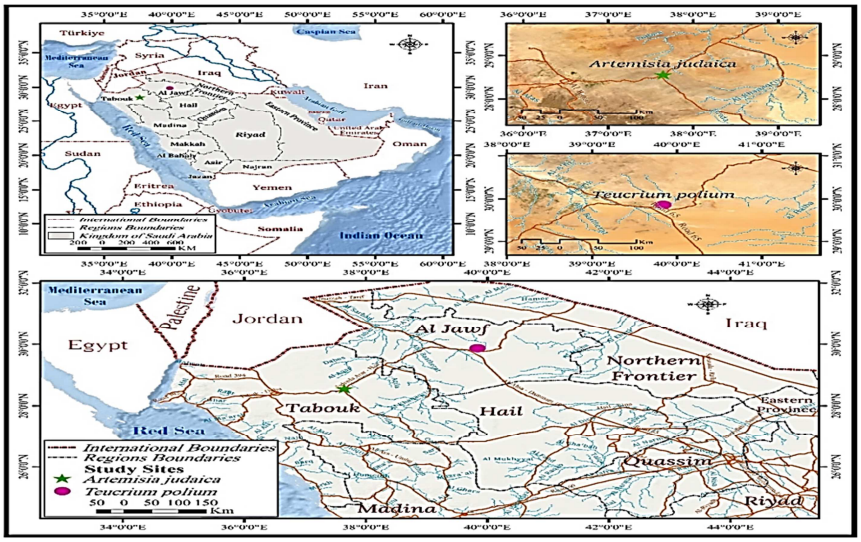


Figure 5: A satellite map of Al Jawf province, Saudi Arabia, indicating the collection sites of *A. judaica* and *T. polium*.

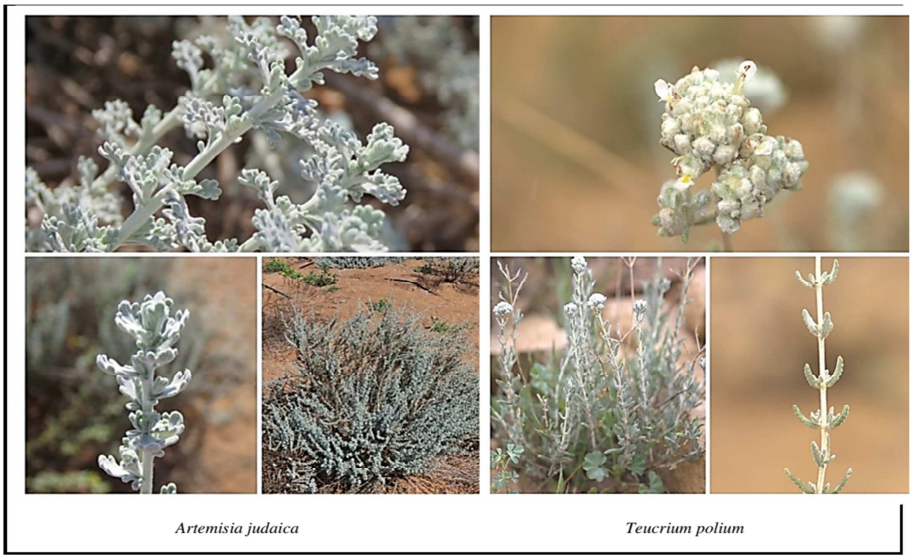


Figure 6: Photo image of *A. judaica* and *T. polium* collected from Al Jawf province, KSA during the summer season of 2021.

3.2. Quantification of total phenolic and flavonoid contents

The quantification of total phenolic content was conducted utilizing the Folin-Ciocalteu method following the procedure outlined by Shiban et al. [49]. A volume of 0.5 mL extract was mixed with 5 mL of 0.2 N Folin-Ciocalteu reagent. Subsequently, 2 mL of 15% Na_2CO_3 was added, and the reaction mixture was allowed to incubate at 50°C for 15 min. The absorbance at 760 nm was measured against a blank. The total phenolic content of the extracts was determined using standard gallic acid solutions ranging from 0.0 to 0.1 mg/mL and expressed in in the dry matter (DM) as mg gallic acid equivalents (GAE)/g DM.

The total flavonoid content of the aqueous methanolic extracts derived from the leaves of *A. judaica* and *T. polium* was determined through a colorimetric assay based on the methodology described by Brighente et al. [50]. A volume of 0.5 mL of 2% $AlCl_3$ in methanol was mixed with 0.5 mL of the methanolic plant extracts. After the incubation for 1h at room temperature, the absorbance was measured at 415 nm. Total flavonoid content was quantified using a standard curve prepared with rutin and expressed in mg g/g DM.

3.3. *In vitro* determination of antioxidant activity by DPPH assay

The efficacy of the prepared plant extracts in scavenging the free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) was assessed following the technique delineated by Bondet et al. [51], with minor modifications. Specifically, 0.5 mL of the test samples or the standard ascorbic acid was introduced to 3 mL of DPPH solution (0.67%) in methanol. Subsequently, the reaction mixture was allowed to incubate at room temperature within a dark environment for 30 min. The reduction in the intense violet color of DPPH was quantified by measuring the absorbance at 517 nm. The percentage of DPPH scavenging activity was calculated using the following formula:

DPPH scavenging activity (%) = $[(A\ control - A\ sample)/(A\ control)] \times 100$

Where, A control represents the control absorbance, while A sample represents the test sample absorbance.

3.4. *In vitro* anti-inflammatory activity

The *in vitro* anti-inflammatory activity of aqueous methanolic leaf extracts of *A. judaica* and *T. polium* was evaluated using the human red blood cell (HRBC) membrane stabilization method, following the protocol outlined by Vane and Botting [52]. Blood from a healthy donor was mixed with sterilized Alsever solution and centrifuged to isolate packed cells. These cells were then suspended in isosaline for testing. Samples, along with diclofenac sodium and aspirin, were mixed with phosphate buffer, hyposaline, and the HRBC suspension. After incubation and centrifugation, the haemoglobin content in the supernatant was measured at 560 nm. The percentage of haemolysis was determined using the formula:

$$\%\ Haemolysis = (OD\ of\ test\ /\ OD\ of\ control)\ x\ 100$$

The percentage of HRBC membrane stabilization was calculated as

$$\%\ Protection = 100 - (OD\ of\ test\ /\ OD\ of\ control)\ x\ 100.$$

3.5. Antitumor activity of the leaf methanolic extracts

The investigation involved assessing the cytotoxic effects of methanolic leaf extracts of *A. judaica* and *T. polium* on HCT116 (colon cell line). Cell viability was evaluated by monitoring the reduction of MTT to formazan, a mitochondrial-dependent process [53]. All experimental procedures were accurately accomplished within a sterile environment using a biosafety class II laminar flow cabinet (Baker, SG403INT, Sanford, ME, USA). Cells were cultured in DMEM-F12 medium supplemented with an antibiotic-antimycotic mixture and L-glutamine at 37 ºC under 5% CO_2.

The study involved the preparation of AH plus mixtures, which were dried and then soaked in DMEM media for two and four weeks, with the same experiment incorporating nanosilver in a 1:1:1 ratio. Following a period of cell culture (10 days), the cells were seeded in microliter plates ($10x10^3$ cells/well) and exposed to the prepared mixtures, with and without nano silver, for 48 h in a 5% CO_2 incubator (Sheldon, TC2323, Cornelius, OR, USA). Subsequently, MTT salt was added to each well and incubated before terminating the reaction with SDS solution (10%). Absorbance readings were taken at 595 nm using DOX as a positive control (100 µg/mL) using a multi-well reader (Bio-Rad Laboratories Inc., model 3350, Hercules, California, USA) [54]. Statistical analysis was performed using an independent t-test in SPSS 11 to compare samples with negative control (n=6 wells per concentration). DMSO was utilized as the solvent for plant extracts, ensuring a final cell concentration of less than 0.2%. The percentage change in cell viability was computed using the formula:

$$(Reading\ of\ extract\ /\ Reading\ of\ negative\ control)\ -\ 1)\ x\ 100$$

Additionally, a probit analysis was conducted through SPSS 11 to determine IC_{50} and IC_{90} values.

3.6. Identification of polyphenolic and flavonoid compounds

Polyphenolic and flavonoid compounds in *A. judaica* and *T. polium* methanolic extracts were identified through HPLC analysis utilizing an Agilent 1260 series system. Separation was achieved using a Zorbax Eclipse Plus C8 column (4.6 mm x 250 mm i.d., 5 µm). The mobile phase comprised water (A) and 0.05% trifluoroacetic acid in acetonitrile (B) at a flow rate of 0.9 mL/min. A linear gradient program was employed for the mobile phase: 0 min (82% A), 0–1 min (82% A), 1-11 min (75% A), 11-18 min (60% A), 18-22 min (82% A), 22-24 min (82% A). Detection was performed at 280 nm using a multi-wavelength detector, with each sample injection volume set at 5 µl. The column temperature was maintained at 40 °C during the analysis [55].

3.7. Statistical analysis

All measurements were conducted thrice, and the results were reported as the average values ± standard deviations (SD). The statistical analysis was performed using one-way analysis of variance (ANOVA) using the CoStat software package (CoHort, V. 6.311) to compare the means of the data, followed by the LSD test. Differences were considered significant at $P < 5\%$.

4. Conclusions

This study elucidates the rich phenolic and flavonoid composition of *A. judaica* and *T. polium* extracts, underscoring their significant bioactive potential. The high levels of key compounds correlate with their demonstrated antioxidant, anti-inflammatory, and antitumor properties, reinforcing their pharmacological value. These findings hold promising implications for both pharmaceutical and nutraceutical industries. For instance, the identified bioactive compounds could serve as lead molecules in drug development, particularly for designing antioxidant-rich or anti-inflammatory therapies. Additionally, the extracts' health-promoting properties make them viable candidates for incorporation into functional foods or dietary supplements aimed at chronic disease prevention. Further research should explore the synergistic interactions of these compounds and their efficacy in preclinical models to facilitate their translation into therapeutic or nutraceutical applications.

5. Conflicts of interest

There are no conflicts to declare.

6. Funding

Not applicable.

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