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Review

Tanacetum balsamita L.: Botany, Traditional Uses, Phytochemical Profiling, and Biological Activities

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Abstract: *Tanacetum balsamita* is a perennial medicinal plant belonging to the Asteraceae family. The species bears a long history as a valuable traditional drug in different cultures, while it is an essential component in the traditional cuisine of several countries. In this context, our literature review aims at providing a comprehensive overview of *T. balsamita*, covering its traditional uses, phytochemistry, biological activities, and toxicity from 1983 to 2024. Methods: Various databases were used to collect the information, including Scopus, Science Direct, Google Scholar, PubMed, and Web of Science. Results and conclusions: Although many of its traditional uses have gradually faded into obscurity over the centuries, recent decades have rekindled the interest in this species. Recent ethnobotanical surveys have reported the use of this species against various health-related conditions, while current pharmacological studies have corroborated several health benefits of the species, such as antioxidant, antidiabetic, anti-hyperpigmentation, anticancer, and antimicrobial activities. The validated properties are mainly attributed to the presence of multiple phytoconstituents belonging to flavonoids, phenolic acids, terpenes, and fatty acids, which could also indicate potential uses for *T. balsamita* in the food industry as a natural preservative and flavoring agent of food products.

Keywords: costmary; phytochemistry; traditional uses; toxicity; biological properties

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1. Introduction

Recently, there has been a growing interest in discovering new bioactive compounds (naturally occurring compounds with health-promoting effects) from plants, driven by their potential health benefits. With the vast number of species in the plant kingdom, there are still many plants that have yet to be explored, making them a promising source for novel bioactive compounds. Medicinal plants, in particular, have sparked a great deal of interest due to their potential role in the pharmaceutical, cosmetic, and food industries [1–3]. Among these, *Tanacetum balsamita* stands out as a noteworthy example, with its multifaceted potential spanning various fields of research and industry.

Commonly known as costmary or balsamita major, this yellow-flowered perennial species belongs to the Asteraceae family and is widely distributed across Asia and Europe [4,5]. The species bears a long history as a valuable medicinal plant in the traditional folk system of various cultures, with several health properties that have been documented through the ages. Although it is indigenous to western Asia, it was already well-known in ancient times by Greeks and Romans, and it has been intermittently mentioned over the

past centuries. For example, it was cited in medieval times by Walahfrid Strabo (808–849) in his *Liber de Cultura Hortorum* [6].

T. balsamita was at one time utilized as a beer flavoring, but during the 15th century, the extensive use of hop (*Humulus lupulus* L.) for the same purpose made its use redundant. However, it remained in botanical gardens, where it was exploited for its flavor and as an insecticide [6]. In 1614, the pleasant properties and delightful aroma of costmary inspired the creation of a fragrant aqueous concoction, wherein costmary stood as the principal constituent, complemented by Ceylon cinnamon, mint, and rosemary [6]. This concoction was diluted with water and used as a remedy for cough and cold and was also widely recognized for its soothing and relaxing effects, hence its name of "Anti-hysteric Water". Likewise, it has been mentioned in the Holy Bible as bitter grass, which is why it is also called "Bible leaf" [5,6]. Furthermore, costmary was employed to mask undesirable household odors and imbue closets with a pleasant fragrance. However, contemporary synthetic aromatic compounds and methods for preserving clothing rendered this specific use obsolete [7].

Recent ethnobotanical studies have highlighted the use of this species in various folk medicinal practices and traditional cuisines across southeastern and south-central Europe. For instance, the leaves of costmary have long been valued for their anti-inflammatory properties and their role as a digestive aid, diuretic, and carminative. They have also been used to treat colds, headaches, abdominal pain, and sunburn [6,8]. Numerous phytochemical studies on the extracts and essential oils of *T. balsamita* have highlighted the occurrence of numerous bioactive secondary metabolites belonging to flavonoids and their derivatives, phenolic acids, monoterpenes, sesquiterpenes, diterpenes, fatty acids, and aliphatic hydrocarbons [8–11]. Likewise, many of its claimed empirical uses have been validated through in vivo and in vitro studies, including antioxidant, antimicrobial, insecticidal, anxiolytic and antidepressant, analgesic, anti-inflammatory, and anticancer properties [12–16]. Moreover, extracts and essential oils have shown promise in improving the oxidative stability and shelf life of perishable foods due to their potent antimicrobial and antioxidant properties, which effectively quench singlet oxygen, prevent lipid peroxidation, and suppress the growth of foodborne pathogens [17,18].

To the best of our knowledge, the previous research mainly focused on the phytochemistry and biological activities of the *Tanacetum* genus [16]. Therefore, the present work aims at critically exploring the current state of knowledge regarding the ethnopharmacological uses, phytochemistry, and pharmacological properties of various extracts derived from different parts of the plant. Furthermore, we highlight the potential of *T. balsamita* in food preservation, safety, and aquaculture efficiency, focusing on its antimicrobial and antioxidant attributes.

2. Survey Methodology

The present study reviews the literature reports referring to traditional uses, phytochemistry, biological activities, and toxicity of *T. balsamita* from 1983 to 2024, using various databases (Science Direct, Scopus, Google Scholar, PubMed, Web of Science, SciFinder, Wiley, Springer, etc.). After the initial search, we screened 76 identified papers for eligibility for inclusion in the review. Only peer-reviewed papers written in English and focusing on botanical aspects, ethnopharmacology, phytochemistry, and biological activities were included. To ensure accuracy, we cross-referenced the scientific nomenclature of the species, along with its synonyms, using the online database (http://www.worldfloraonline.org, 2024), and used them as search keywords.

3. Botanical Aspects and Geographical Distribution

T. balsamita is an aromatic rhizomatous perennial herb with oval serrated leaves belonging to the Asteraceae family. The plant has an upright growth and can reach as high as six feet tall under favorable conditions, while it gives off a mild balsamic scent. Stems are erect, and either simple or ramified. Leaves are basal and cauline, petiolate (proximally), sessile, or subsessile above; blades are simple, 0.9–10 cm long, 0.6–5 cm wide, and usually elliptic to oblong. Flowers are yellow, discoid, and hermaphrodite or bisexual. The roots are fibrous, short, thin, and ramified. During summer, the little yellow button-shaped blooms arise in clusters [7,14,19]. Costmary is an invasive and easy-to-grow plant. It thrives in fully sunny locations with well-drained soil and a pH of 5–7.6, where it can develop complete flower heads (reminiscent of the flowers of the common daisy) (Figure 1). By contrast, less sunny areas are recommended to produce vegetative parts such as leaves. It is worth mentioning that flowering will be reduced if the plant is grown under shadow. Rhizome cuttings or sowing of seeds are used for multiplication purposes [14]. *T. balsamita* thrives in well-drained soils, including light (sandy), medium (loamy), and heavy (clay) soils, with a preference for mildly acidic, neutral, or mildly alkaline pH levels. It requires minimal soil nutrients and moisture. The plant can grow in semi-shade (light woodland) or full sun, favoring dry to moist conditions for optimal growth. It can withstand a variety of environmental abiotic stresses, including high temperatures, salinity, and soils contaminated with heavy metals, making it a potential medicinal plant for removing various pollutants from contaminated land, such as pesticides, metals, explosives, and polyaromatic hydrocarbons [20].



Figure 1. Representative photos of *T. balsamita* at different growth stages; Florence, Italy. Adapted from Khatib et al., 2023 [16], with permission from Frontiers; published under license, Copyright© 2023.

The species originates from Asia, Asia Minor, and Australia but has since established itself in numerous parts of southern Europe, where it finds application in traditional medicine. Following the exploration and colonization of the New World, it was brought to America by early settlers, and now it grows abundantly, mainly as a roadside weed, in Eastern and Middle Eastern states. Currently, it thrives as a naturally occurring plant throughout the Mediterranean basin, encompassing countries like Spain, Italy, Germany, England, Turkey, and Romania. The importance of the species acquired over the years has been due to its interesting versatility and adaptability [7,21]. Hence, the high adaptability of *T. balsamita* to diverse environments, resilience to abiotic stresses, and ability to thrive in various soil types underscore its value as a versatile medicinal plant and a promising candidate for sustainable agricultural practices.

4. Ethnobotanical Uses of *T. balsamita*

The literature research uncovered about 12 ethnobotanical studies dealing with the traditional uses of *T. balsamita*, primarily conducted in Italy, Turkey, Iran, and Spain, where the plant is most abundant. While these studies revealed a wealth of medicinal applications, we noticed that some crucial details were lacking, including preparation methods (e.g., concentrated tea, extraction in oils, and so on), dosages, administration routes, herbarium specimen, and specific plant parts used (e.g., leaves, flowers, roots, etc.). The absence of these essential elements could hinder subsequent pharmacological and toxicological investigations aimed at validating the traditional claims. Indeed, these limitations may compromise efforts to isolate active compounds, assess the safety of their pharmacological effects, and determine their therapeutic potential.

We also noticed that one significant limitation in these ethnopharmacological reports consists of using imprecise terminology to describe the treated ailment, such as stomach ache, belly ache, and cardiovascular disorders. These terms lack precision and specificity, failing to furnish accurate information about the underlying diseases. Therefore, further rigorous studies are mandatory to comprehensively document traditional uses. These investigations should prioritize attention to these crucial elements, as they are pivotal in ensuring the precision of ethnobotanical research, which in turn may serve as a foundational guide for subsequent toxicological and pharmacological studies.

Although many of its empirical uses have gradually faded over the past decades, several ethnobotanical studies have rekindled interest in the medicinal uses of different parts of *T. balsamita*, such as leaves, aerial parts, stems, and the whole plant, against various pathological health conditions, as well as its role as an essential component in the traditional cuisine of several countries. For instance, in central Italy, the leaves with their distinctive bitter and minty-lemony flavor continue to be employed for enhancing the taste of various dishes, including salads, vegetable pies, liqueurs, omelets, cheese and eggs, and garlic cloves, while they are also used in the filling of *tortelli*, particularly on Easter Day [22,23]. However, information about the nutritional profile of the plant (e.g., mineral composition, vitamins, fat, and carbohydrate content) is still lacking and should constitute the subject of future studies.

In southern Italy, the leaves of *T. balsamita*, locally known as *pianta del té*, are used to make an infusion that is believed to be effective against bile insufficiency, cholecystitis, and nervous dyspepsia [23]. This ethnomedicinal preparation is also renowned for its antispasmodic, anti-insomnia, and sedative properties [24,25]. Additionally, the macerated water extract of *T. balsamita* and *Santolina etrusca* has been traditionally used on St. John's Eve to make fragrant water, which serves the dual purpose of perfuming and softening the skin [26]. Traditional uses suggest also that the seeds are effective in combating intestinal parasites. Furthermore, the crushed plant material can be utilized in wraps

to help strengthen the stomach. For skin irritation, a bath infused with boiling leaf water is known to be highly effective [27].

In northern Istria, during the celebration on June 21st, indigenous communities believed that the vapors generated from the combustion of *T. balsamita* leaves, combined with rose petals and wormwood, have remarkable therapeutic properties when inhaled [28]. According to tradition, the optimal day for harvesting this plant is June 24th, commonly known as St. John's Day. For this reason, this medicinal plant is often referred to as "St. John's herb". This tradition likely aligns with the observation that this period typically corresponds to the peak balsamic phase of costmary, characterized by its profoundly aromatic flavor [8].

In Turkey, this plant has been associated with various vernacular names, including *marsuvanotu*, *papatya*, *gıyakeçk*, *kılıçotu*, and *bozboz*. In terms of its medicinal uses, antidiabetic effects can be achieved by consuming two teacups of leaf infusion three times daily for three consecutive weeks [29]. Moreover, the decoctions of leaves and stems can be applied topically for deep wound healing, as a rheumatism ointment, and as an antipyretic and menstrual regulator [30].

Moreover, an ethnobotanical investigation conducted in the Hutsuls region showed that the indigenous population of this area administrated alcohol-infused flower buds and leaves externally to address heart diseases and suppurating wounds. Additionally, the people of this region employed freshly harvested aerial parts steeped in hot water to alleviate persistent wounds and furuncles [31].

In Argentinian pharmacopoeia, this plant is called *boldo*, *menta romana*, and *menta San Pedro*; indigenous people used it for its claimed health benefits against hepatic and gastrointestinal disorders [32,33]. However, there are no available data regarding the used plant parts and the techniques used to prepare these remedies. In Iranian folk medicine, the leaves and flower heads of costmary have been used in the form of decoction, infusion, and floral water as a hepatoprotective agent, sedative, general tonic, antiallergic, flatulent, and cardiotonic [14].

In Serbia, the tea from its leaves was used to treat terrible migraines and ailments during menopause [34,35]. Moreover, the infusion prepared from the whole plant has been used to deal with gallbladder diseases, headaches, and abscesses [36,37].

To summarize, *T. balsamita* is a multifaceted plant with diverse culinary and traditional therapeutic uses. Ethnobotanical studies reveal its applications in treating digestive, hepatic, dermatological, and psychological ailments, alongside its use as sedative and antispasmodic remedies. It is also valued in Italian cuisine for its distinctive flavor, enhancing dishes like salads, omelets, and traditional Easter *tortelli.*

5. Phytochemical Composition of *T. balsamita*

5.1. Essential Oils

T. balsamita contains a significant amount of essential oils (EOs) in its various parts, including its stems, leaves, and flowers. The traditional method of extracting these EOs is through hydrodistillation, which involves the use of a Clevenger-type apparatus. To identify and quantify the chemical constituents of these EOs, analytical methods such as GC–MS, GC–FID, and NMR have been employed (Table 1). These analyses have revealed a diverse range of chemical compounds, including monoterpene hydrocarbons(**1–13**), oxygenated monoterpenes(**14–66**), sesquiterpene hydrocarbons(**67–84**), oxygenated sesquiterpenes (**85–100**), fatty acid esters(**103–106**), and aliphatic hydrocarbons (**113–116**) (Figure S1, Supplementary Materials).

Table 1. Chemical composition of *T. balsamita* essential oils.

Compounds	Plant Parts	Country	References
Monoterpene hydrocarbons			
α-Pinene (**1**) *β-Pinene* (**2**)	AP, L, WP	Spain, Italy, Iran	[9,15,38,39]
Sabinene (**3**)	AP, WP	Spain, Italy, Iran	[9,14,15,39,40]
β-Myrcene (**4**)	AP, L, F, S	Iran	[38,41]
Limonene (**5**)	AP, L	Turkey, Iran	[15,38,42]
(E)-β-Ocimene (**6**)	AP, L, F, S	Turkey, Iran	[9,41]
Terpinolene (**7**)	L, F, S	Iran	[41]
Camphene (**8**)	AP, L, WP	Spain, Italy, Iran	[9,15,39,40]
p-Cymene (**9**)	AP, L, WP	Spain, Italy, Turkey, Iran	[9,15,39,40]
γ-Terpinene (**10**)	AP, WP	Spain, Italy, Iran	[9,15,39,40]
Verbenene (**11**)	AP	Iran	[15]
α-p-Dimethylstyrene (**12**)	AP	Turkey	[9]
α-Phellandrene (**13**)	AP, L	Spain	[39]
Oxygenated monoterpenes			
1,8-Cineole (**14**)	AP, L	Turkey, Iran	[9,14,38,39]
Dehydro-1,8-cineole (**15**)	AP	Iran	[38]
1,4-cineole (**16**)	WP	Italy	[9]
α-Thujone (**17**)	AP, WP	Italy, Turkey, Iran	[9,14,15]
β-Thujone (**18**)	AP, WP	Italy, Turkey, Iran	[9,10,15,40]
Camphor (**19**)	AP, L, F, S	Iran	[38,41]
Carvone (**20**)	AP, F	Turkey, Iran	[10,38,40]
cis-Dihydrocarvone (**21**)	F, AP	Turkey, Iran	[10,15]
α-Terpineol (**22**)	AP	Iran	[40]
trans-Carvone oxide (**23**)	AP, L, F, S	Iran	[38,41]
trans-Carvyl acetate (**24**)	AP	Iran	[38]
cis-Carvyl acetate (**25**)	AP	Iran	[38]
cis-Sabinene hydrate (**26**)	L, F, S	Iran	[41]
trans-Pinocarveol (**27**)	AP, WP	Iran	[15,40]
Pinocarvone (**28**)	AP, L, F, S	Turkey, Iran	[10,40,41]
Verbenone (**29**)	AP	Iran	[40]
Terpinen-4-ol (**30**)	L, F, S, WP	Italy, Turkey, Iran	[9,10,14]
Borneol (**31**)	AP	Italy, Turkey, Iran	[10,40]
Isoborneol (**32**)	AP	Iran	[15]
Bornyl acetate (**33**)	AP, L, F, S	Turkey, Iran	[9,41]
Carvacrol (**34**)	L, AP, WP	Italy, Turkey, Iran	[10,41]
trans-Pinocarvyl acetate (**35**)	F, S	Iran	[41]
trans-p-Mentha-2,8-dienol (**36**)	AP	Iran	[15,40]
trans-p-Menth-2-en-7-ol (**37**)	WP	Italy	[9]
cis-p-Mentha-1,8-dien-2-ol (**38**) *p-Mentha-1,5-dien-8-ol* (**39**) *3,9-Epoxy-p-mentha-1,8-diene* (**40**) *Chrysanthenyl acetate* (**41**) *cis-Carveol* (**42**)	AP	Iran	[40]
trans-p-Mentha-1(7),8-dien-2-ol (**43**)	F	Iran	[14]
cis-p-Mentha-2,8-dienol (**44**)	AP	Iran	[14,40]
ρ-Mentha-2,8-diene-1-ol (**45**) *4-Terpineol* (**46**)	AP	Iran	[15]
cis-Verbenol (**47**)	AP	Turkey, Iran	[10,40]
trans-Verbenol (**48**)	F, AP	Turkey, Iran	[10,14]
cis-Piperitol (**49**)	F	Iran	[14]
trans-Carveol (**50**)	AP, F	Iran	[14,15]
Eucalyptol (**51**) *Linalool* (**52**) *cis-p-Menth-2-en-1-ol* (**53**) *Pulegone* (**54**) *Carvenone* (**55**) *Carvotanacetone* (**56**)	WP	Italy	[9]

Table 1. *Cont.*

Compounds	Plant Parts	Country	References
Piperitone (**57**) *Myrtenol* (**58**) *Ascaridole* (**59**) *Fenchol* (**60**) *Menthone* (**61**) *Isomenthone* (**62**) *Myrtanol* (**63**) *Pulegone* (**64**) *Verbenone* (**65**)	WP	Italy	[9]
	AP, L	Spain	[39]
Thymol (**66**)	AP, WP	Italy, Turkey	[9,10]
Sesquiterpene hydrocarbons			
β-Caryophyllene (**67**) *(Z)-γ-Bisabolene* (**68**)	AP	Iran	[38]
Germacrene D (**69**)	AP	Turkey, Iran	[10,38,40]
β-bisabolene (**70**)	AP	Iran	[38,40]
γ-Cadinene (**71**)	AP	Turkey, Iran	[40]
δ-cadinene (**72**) *α-Copaene* (**73**) *γ-Selinene* (**74**)	AP	Turkey	[10]
β-Gurjunene (**75**) *α-Cedrene* (**76**) *Longipinene* (**77**) *Aromadendrene* (**78**) *Cadalene* (**79**)	F	Iran	[14]
Calacorene (**80**) *β-Selinene* (**81**) *γ-Gurjunene* (**82**) *β-Cubebene* (**83**) *β-Farnesene* (**84**)	AP, L	Spain	[39]
Oxygenated sesquiterpenes			
Cubebol (**85**) *T-Muurolol* (**86**) *(Z)-nerolidol* (**87**)	AP	Turkey, Iran	[10,38]
β-copaen-4α-ol (**88**) *1,10-Di-epcubenol* (**89**)	AP	Iran	[38]
Spathulenol (**90**)	A.P, WP	Italy, Turkey	[9,10]
β-eudesmol (**91**)	L, AP, WP	Spain, Italy	[9,39]
Acorenone B (**92**)	WP	Italy	[9]
Caryophyllene oxide (**93**) *Gleenol* (**94**) *Cubenol* (**95**) *Germacrene D-4-ol* (**96**) *Viridiflorol* (**97**) *Selin-11-en-4α-ol* (**98**) *T-Cadinol* (**99**)	AP	Turkey	[10]
Cedrol (**100**)	AP, L	Spain	[39]
Diterpene hydrocarbons			
Neophytadiene (**101**)	WP	Italy	[9]
Oxygenated diterpenes			
Phytol (**102**)	A.P	Turkey	[10]
Fatty acid esters			
Isobutyrate (**103**) *2-Methylbutyl-2-methyl-butyrate* (**104**) *2-Methylbutyl isovalerate* (**105**)	WP	Italy	[9]
Isoamylisovalerate (**106**)	AP	Turkey	[10]

Table 1. *Cont.*

Compounds	Plant Parts	Country	References
	Fatty acids		
Hexadecanoic acid (**107**)	AP	Turkey	[10]
	Aldehydes		
Nonanal (**108**)	WP, AP	Italy, Turkey	[9,10]
Decanal (**109**)	AP	Turkey	[10]
Benzaldehyde (**110**)			
	Ketones		
Phytone (**111**)	WP	Italy	[9]
Sabina ketone (**112**)			
	Alkanes		
Pentacosane (**113**)	AP	Turkey	[10]
Heptacosane (**114**)			
Nonacosane (**115**)			
9-Hexacosene (**116**)			
	Alcohols		
Hexadecanol (**117**)	AP	Turkey	[10]

Abbreviations: AP, aerial parts; L, leaves; F, flowers; S, stems; WP, whole plant.

Data from earlier studies showed that regardless of the geographical origin, extracted parts, and the phenological stage of plants at harvest, two main oxygenated monoterpene chemotypes were prevailing in almost all EO extracts, namely carvone (**20**) and α-thujone (**17**), with quantities ranging from 39.8 to 56.66% and 0.1 to 21.3%, respectively [5,10,14,42]. However, it should be noted that significant qualitative and quantitative differences might be noticed in the EO chemical profiles, especially for the chemical constituents that are detected at amounts <5% of total detected compounds. These differences in the chemical profiles of EOs might be credited to the chemotype (genetic variation), geographical distribution, climatic conditions, allogamy (cross-fertilization), soil conditions, seasonal variations, and harvesting stage [9]. For example, in Iranian samples, carvone (**20**) (52.01%), α-thujone (**17**) (11.04%), and the sesquiterpene hydrocarbon (E)-β-farnesene (**84**) (3.91%) were identified as the major constituents among the 31 isolated compounds from the essential oil of flower heads [14].

Similarly, Sharif et al. reported that carvone (**20**) (39.8%), α-thujone (**17**) (11.9%), and β-bisabolene (**70**) (5%) were the predominant components in the essential oil of aerial parts of *T. balsamita* grown in Iran [14]. Likewise, Hassanpouraghdam et al. (2008) used GC–MS to analyze and quantify the chemical composition of EOs of air-dried aerial parts of *T. balsamita* grown in a hydroponic production system. They found that carvone (**20**) (42.53%), α-thujone (**17**) (21.3%), and β-bisabolene (**70**) (10.56%) were the most abundant components in the EO extract [42]. Similarly, in Italian samples, carvone (**20**) (43.54%), α-thujone (**17**) (15.61%), and β-bisabolene (**70**) (4.53%) were the major chemical constituents identified in the leaf EOs of *T. balsamita* [9]. On the other hand, in Turkish samples, the EOs of *T. balsamita* aerial parts were rich in oxygenated monoterpenes (76.3%), with carvone (**20**) (52.4%) and α-thujone (**17**) (11.7%) as the major chemical constituents, accompanied by the sesquiterpene hydrocarbon germacrene-D (**69**), which accounted for up to 3.3% of the identified compounds [10]. In this study, the distribution of carvone (**20**) enantiomers in the EOs has also been investigated. (R)-(−)-carvone was the enantiomeric form that existed in a substantial amount, consisting as high as 98.8% of total carvone found in the EO, whereas (S)-(+)-carvone was only detected in traces [10].

The previous findings are not aligned with those of Bączeket al. [9], who identified *β*-thujone (**18**) (84.43%) and *α*-thujone (**17**) (4.68%) as the dominant chemical constituents of *T. balsamita* whole-plant EOs, whereas carvone (**20**) was only present in trace amounts (0.03%) (Figure S1, Supplementary Materials) [9]. Likewise, Pérez-Alonso et al. [36] reported that carvone (**20**) (49.9–56.66%) and *β*-thujone (**18**) (10.61–13.61%) were the major components of aerial-part EOs after the flowering stage, whereas *α*-thujone (**17**) was detected in small quantities (0.04–0.13%). These significant differences might be ascribed to differences in growing conditions, as well as to genotypic differences and harvesting stage [39]. In any case, in vitro and in vivo studies have demonstrated that carvone (**20**) possesses pronounced health benefits, including antidiabetic, anticancer, anti-inflammatory, antibacterial, and anxiolytic properties. It has also been proven to be effective against multiple fungi strains such as *Candida* spp., *Penicillium* spp., *Aspergillus* spp., and *Trichophyton* spp., among others [43]. All these findings support the extensive utilization of costmary oil in folk medicine as an insect repellent and natural anxiolytic agent, and for reducing negative feelings such as anger, hysteria, and fear. Likewise, these components are likely responsible for the pleasant minty scent emitted by the plant. Due to their ubiquitous distribution throughout the plant organs, they could be used as chemotaxonomic markers of the species.

5.2. Phenolic Acids

Despite promising evidence indicating the richness of this plant species in polyphenolic compounds, primarily phenolic acids, only a few phytochemical studies have been conducted over the past decades to isolate and identify phenolic compounds from plant extracts. Eleven phenolic acids have been successfully detected and identified in *T. balsamita*, predominantly from the leaves, aerial parts, and whole plant, using high-performance liquid chromatography (HPLC) equipment (Table 2). Phenolic acids found in *T. balsamita* are categorized into hydroxybenzoic and hydroxycinnamic acid derivatives. So far, hydroxybenzoic acid derivatives are represented by three chemical components, namely 2,5-dihydroxybenzoic acid (gentisic acid) (**118**), salicylic acid (**119**), and 4-hydroxybenzoic acid (**120**) (Figure S2, Supplementary Materials) [44].

Table 2. Phenolic acids found in *T. balsamita* extracts.

Phenolic Acids	Plant Parts	Extract	Identification Method	Quantification	References
Hydroxybenzoic acid derivatives					
Gentisic acid (**118**)	AP	70% EtOH	HPLC–MS	<0.2 µg/g	[11]
Salicylic acid (**119**) 4-Hydroxybenzoic acid (**120**)	AP	EtOH	HPLC	0.057 µg/mL 2662.21 µg/mL	[44]
Hydroxycinnamic acid derivatives					
Caffeic acid (**121**)	WP	EtOH/W (40:60 *v*/*v*)	HPLC	49.14 ± 6.72 mg/100 g	[9]
Chlorogenic acid (**122**)	WP	EtOH/W (40:60 *v*/*v*)	HPLC	1368.4 ± 112.03 mg/100 g	[9]
	L	MeOH		24.32 ± 1.14 mg/g	[13]
3,5-*O*-Dicaffeoylquinic acid (Isochlorogenic acid) (**123**)	L	MeOH	HPLC–DAD	9.21 ± 0.15 mg/g	[13]
	AP	MeOH/W/HOAc (79:20:1)	HPLC–UV	0.93 mg/g	[8]
Rosmarinic acid (**124**)	WP	EtOH/W (40:60 *v*/*v*)	HPLC	50.36 ± 4.85 mg/100 g	[9]
Chicoric acid (**125**)	WP	EtOH/W(40:60 *v*/*v*)	HPLC	3333.9 ± 156.34 mg/100 g	
p-Coumaric acid (**126**)	AP	70% EtOH	HPLC–MS	9.83 ± 0.17 µg/g	[11]
Ferulic acid (**127**)	AP	70% EtOH	HPLC–MS	6.58 ± 0.42 µg/g	
Cinnamic acid (**128**)	AP	EtOH	HPLC	4.712 µg/mL	[44]

Abbreviations: WP, whole plant; AP, aerial part; L, leaves; MeOH, methanolic extract; EtOH, ethanolic extract; W, aqueous extract; HOAc, acetic acid.

Gentisic acid (**118**) has been identified in 70% ethanolic extract of the aerial parts of the subspecies *Chrysanthemum balsamita* var. *tanacetoides* by HPLC analysis; its es-

timated quantity was less than 2 µg/g [11]. Previous in vivo and in vitro studies showed that gentisic acid (**118**) (GA) possesses pronounced health benefits, including neuroprotective, hepatoprotective, nephroprotective, antioxidant, antigenotoxic, anti-inflammatory, cardioprotective, and skin-lightening properties [45]. Moreover, salicylic acid (**119**) and 4-hydroxybenzoic acid (**120**) have been isolated and characterized in ethanolic extracts of the aerial parts of the subspecies *T. balsamita* subsp. *Balsamitoides* [44]. On the other hand, hydroxycinnamic acid derivatives seem to be the most abundant polyphenols subclass in *T. balsamita* extracts; they have mainly been detected in the leaves and aerial parts of the plant [9,11,13]. These compounds can be found either in free forms, such as ferulic acid (**127**) and caffeic acid (**121**), or as depsides, such as rosmarinic acid (**124**), chlorogenic acid (**122**), and chicoric acid (**125**) [9]. Chicoric acid (**125**), also known as dicaffeoyltartaric acid, is the most abundant hydroxycinnamic acid in the plant's extracts. It has been detected in the ethanol/water (40:60 *v*/*v*) extract; its content was approximately 3333.9 ± 156.34 mg/100 g [9]. Rosmarinic acid (**124**), a caffeic acid derivative with promising health benefits, has been isolated from the ethanol/water (40:60 *v*/*v*) extract of the whole plant [9]. Chlorogenic acid (**122**) and 3,5-*O*-dicaffeoylquinic acid (**123**) have been isolated from methanolic extracts of leaves. The concentration of chlorogenic acid (**122**) (24.32 ±1.14 mg/g) appeared to be approximately 2.5 times higher than that of 3,5-*O*-dicaffeoylquinic acid (**123**) (9.21 ± 0.15 mg/g) [13]. The highest content of these two compounds has been noticed during the late growth and early growth stages of the plant, respectively [13]. On the other hand, phenolic acids are found practically in all plant-derived food products and constitute a large part of the human diet. After their rapid absorption by the stomach or the small intestine, they are metabolized to glucuronide and sulfate conjugates. Then, as conjugated forms, they circulate in human plasma, exhibiting high bioavailability and exerting several bioactivities, including antineoplastic, bacteriostatic, and antioxidant properties [46–48]. All these properties may explain the extensive use of costmary in folk medicine as a natural antidiabetic, antimicrobial, and anti-inflammatory agent, among others.

5.3. Flavonoids

In addition to phenolic acids, flavonoids are another important class of phenolic compounds found in *T. balsamita* extracts. A total of 22 flavonoids have been isolated and identified, predominantly from leaves, aerial parts, petals, and the whole plant, using high-performance liquid chromatography (HPLC) and gas chromatography–mass spectrometry (GC–MS) equipment (Table 3).

Table 3. Flavonoids found in *T. balsamita* extracts.

Flavonoids	Plant Parts	Extract	Quantification	References
Flavonols				
Quercetin (**129**)	AP	70% EtOH	26.51 ± 0.50 µg/g	[11]
Quercitrin (**130**)			42.91 ± 0.09 µg/g	
Isoquercitrin (**131**)			780.81 ± 8.20 µg/g	
Rutin (**132**)			8042.62 ± 11.38 µg/g	
Kaempferol (**133**)			30.69 ± 1.52 µg/g	
5,7,3′,4′-Tetrahydroxy-3,8-dimethoxyflavonol (**134**)	AP	MeOH/W/HOAc (79:20:1)	0.17 mg/g	[8]
Flavones				
5,7,4′-Trihydroxy-3′,8-dimethoxyflavone (**135**)	AP	MeOH/W/HOAc (79:20:1)	0.24 mg/g	[8,9,49]
Apigenin 7-*O*-glucoside (**136**)	WP	EtOH/W (40:60 *v*/*v*)	1099.3 ± 98.97 mg/100 g	
Apigenin 7-*O*-glucuronide (**137**)	L	80% MeOH	NS	
Luteolin 7-*O*-glucoside (**138**)	WP	EtOH/W (40:60 *v*/*v*)	727.5 ± 45.67 mg/100 g	[9]
Luteolin 3′-methyl ether (**139**)			472.4 ± 36.59 mg/100 g	

Table 3. *Cont.*

Flavonoids	Plant Parts	Extract	Quantification	References
Luteolin 7-*O*-*β*-D-glucopyranoside (**140**) Kaempferol 7-*O*-*α*-L-rhamnopyranoside (**141**) Luteolin 7-*O*-glucuronide (**142**) Scutellarein 6-methyl ether (**143**)	P	EO	3.3% of the EO 2.1% of the EO	[44]
6-Hydroxyluteolin 6-methyl ether (**144**) 6-Hydroxyluteolin 6,3′-dimethyl ether (**145**) 6-Hydroxyluteolin 6,7,4′-trimethyl ether (**146**) Acacetin (**147**)	L	80% MeOH	NS	[49]
Diosmetin (**148**) Diosmetin-7-glucoside (**149**)	AP	40% EtOH	NS	[50]
Myricetin (**150**)	AP	EtOH	1.812 µg/mL	[44]
Chrysoeriol 7-glucuronide (**151**)	L	80% MeOH	NS	[49]

Abbreviations: P, petals; AP, aerial parts; WP, whole plant; L, leaves; EO, essential oil; NS, not specified.

These flavonoids are grouped into flavonols (**129**–**134**) and flavones (**135**–**150**), with flavones being the most prominent subclass of flavonoids in the plant extracts [8,11,49]. Regarding flavonols, six compounds have been isolated and identified from the aerial parts of the plant. Five of these chemical components (**129**–**133**) have been detected in the methanolic extracts of aerial parts, whereas 5,7,3′,4′-tetrahydroxy-3,8-dimethoxyflavonol (**134**) was obtained from aerial parts' methanol/water/acetic acid (79:20:1) extract (Table 3). Rutin (**132**) seems to be the most abundant flavonol glycoside in the plant extracts; its content can be as high as 8042.62 ± 11.38 µg/g (Figure S3, Supplementary Materials) [11]. Due to its nontoxic chemical nature, this compound and its nanoformulation can find several biomedical applications, including antimicrobial, anti-allergic, anti-inflammatory, anticancer, anti-arthritic, antidiabetic, and wound healing properties [51].

To date, 12 flavones have been extracted and identified from aerial parts (e.g., leaves and petals) and whole plant extracts [9,49]. The aglycone flavone apigenin, bearing glucose and gluconic acid (**136**, **137**) (a glucose derivative) as the sugar moiety, is the predominant flavone in the plant extracts. It has been found in the leaves and the whole plant extracts; its content was estimated at 1099.3 ± 98.97 mg/100 g in the whole-plant ethanol–water extract (40:60 *v*/*v*) [9,49]. Key findings from earlier studies reported the potency of this chemical component in managing several health conditions, including diabetes, cancer, insomnia, depression, amnesia, and Alzheimer's disease [52].

The existing scientific evidence may explain the extensive usage of various extracts from this plant to treat diabetes and depression, and as an anxiolytic agent. From leaves' 80% methanolic extract, five flavones have been isolated and identified, namely luteolin 7-*O*-glucuronide (**142**), scutellarein 6-methyl ether (**143**), 6-hydroxyluteolin 6-methyl ether (**144**), 6-hydroxyluteolin 6,3′-dimethyl ether (**145**), and 6-hydroxyluteolin 6,7,4′-trimethyl ether (**146**) [49]. From the EOs of petals, luteolin 7-*O*-*β*-D-glucopyranoside (**140**) and kaempferol 7-O-*α*-*L*-rhamnopyranoside (**141**) have been detected using GC–MS, whereas 5,7,4′-trihydroxy-3′,8-dimethoxyflavone (**135**) was identified from aerial parts' methanol–water–acetic acid (79:20:1) extract in amounts of 0.24 mg/g [8]. Acacetin (**147**), also known as 5,7-dihydroxy-4′-methoxyflavone, a monomethoxyflavone, diosmetin (**148**) 4′-methyl ether derivative of luteolin, as well as its glycone form diosmetin-7-glucoside (**149**) have been identified in aerial parts' 40% ethanolic extract of the plant [50].

5.4. Miscellaneous Compounds

Ascorbic acid (**152**) has been detected in the ethanolic extract of aerial parts at a concentration of 0.759 µg/mL through HPLC analysis. Abscisic acid (ABA) (**153**), a major phytohormone and sesquiterpene signaling molecule, was also found in the same extract at a concentration of 4.162 µg/mL [44]. Curcumin (**154**) has been found in substantial

amounts in the ethanolic extract of aerial parts (16.453 µg/mL) [44], while scopoletin (**155**) (Figure S4, Supplementary Materials), a naturally occurring coumarin, has been identified in the essential oil of *T. balsamita* petals [53].

6. Biological Activities

6.1. Antimicrobial Activity

The demand for eco-friendly antimicrobial agents has been increasing due to the decline in bacteria's susceptibility to conventional antibiotics. Plants have been used as folk remedies for treating infectious diseases, making them a great source for novel natural antimicrobial agents that can effectively combat various infections. Given their antimicrobial action, plant extracts could potentially be utilized as substitutes for synthetic food additives to prevent foodborne infections caused by pathogenic microorganisms [54,55]. To date, all studies on the antibacterial and antifungal activities of *T. balsamita* have been carried out in vitro, since no clinical studies have been reported so far. Moreover, the reported antimicrobial studies are often preliminary and lack essential details, with problems such as the use of non-standard bacterial strains, the lack of a positive control, and single-dose usage. Additionally, one of the major drawbacks of these preclinical studies is the use of the disc diffusion assay to evaluate the antimicrobial potency of extracts, which are mainly composed of mixtures of compounds with different polarities. As a result, these compounds may not diffuse through the aqueous agar matrix as readily as polar compounds, leading to false negative or positive results.

Despite these constraints, many attempts have been made to explore the antimicrobial effects of *T. balsamita* and support its folk application as an antimicrobial agent. These studies provide early pieces of evidence regarding the capacity of different plant-based extracts to suppress the growth of a range of bacteria and fungus strains, particularly Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus*, *Bacillus cereus*, and *Listeria monocytogenes* (Table 4).

In a preliminary study, the EO from the aerial parts showed antimicrobial properties against three bacterial strains, namely *B. subtilis* (ATCC 465), *B. pumilus* (PTCC 1274), and *S. epidermidis* (ATCC 12228). The inhibition zones were 31 $\pm$ 0.3, 34 $\pm$ 0.2, and 35 $\pm$ 0.5 mm, and minimum inhibitory concentrations (MIC) values were 1.87, 0.93, and 0.93 mg/mL, respectively, compared to the positive control ampicillin (14 $\pm$ 0.4, 19 $\pm$ 0.5, and 15 $\pm$ 0.3 mm, respectively). In contrast, the EO was found inactive against *Pseudomonas aeruginosa* (ATCC 85327) and moderately active against the fungus strain *Saccharomyces cerevisiae* (ATCC 9763) [40].

In a similar study, the EO from the aerial parts was found active against two Gram-positive and two Gram-negative bacteria strains, namely *B. subtilis* (ATCC 6633), *S. aureus* (ATCC 6538 P), *E. coli* (ATCC 25922), and *Salmonella typhimurium* (NRRLB 4420), respectively. The study found that the inhibition zone (IZ) diameters ranged from 13 to 17 mm, and highlighted the capacity of the EO extract to inhibit yeast strains, namely *Candida glabrata* (ATCC 66032) and *C. tropicalis* (ATCC 13803), with inhibition zones of 15 and 14 mm, respectively [56]. Furthermore, Bączek et al. investigated the antimicrobial potency of EOs and hydroethanolic extracts against eight strains of Gram-positive bacteria and eleven strains of Gram-negative bacteria using the method of serial microdilutions. The results showed that the costmary EO was more effective against all the tested strains compared to the hydroethanolic extract. The EOs at the concentration of 32 µL/mL exhibited excellent inhibitory effects against all the tested strains (100%), while the hydroethanolic extract at the same concentration showed moderate inhibitory effects (68%) against the tested strains. Gram-negative bacteria were generally more resistant. The authors attributed the strong antimicrobial effects to the high amounts of oxygenated monoterpenes, especially β-thujone (**18**) [9].

Karimzadeh et al. assessed the antimicrobial effectiveness of *T. balsamita* aerial-part essential oil (EO) against three major tooth-decay-causing bacteria: *Streptococcus mutans* (PTCC 1683), *S. salivarius* (PTCC 1448), and *S. sanguinis* (PTCC 1449). The disc diffusion assay was used to assess the EO at concentrations of 12.5, 25, 50, and 100 µg/mL. The findings revealed that the concentration of 12.5 µg/mL had no inhibitory impact on bacterial development, but the dose of 100 µg/mL demonstrated significant activity against *S. mutans*, *S. salivarius*, and *S. sanguinis* when compared to standard mouthwashes such as chlorhexidine and Oral B mouthwashes. The study sought to corroborate ethnobotanical claims with scientific evidence [57]. Additionally, Kubo and Kubo conducted a study to evaluate the antimicrobial properties of eight β-unsaturated aldehydes, three fatty acids, and one saturated aldehyde separated from a distillate fraction of the dried flowers of *T. balsamita* *n*-hexane extract. The study used GC–MS analysis to identify the compounds and tested their antibacterial and antifungal properties. The results showed that all the compounds had varying antibacterial properties, with (E)-2-heptenal showing significant bactericidal capacity against all the fourteen tested microorganisms. Nine of the studied compounds showed noticeable antifungal activity, especially against *Trichophyton mentagrophytes* and *Penicillium chrysogenum*, with MIC values ranging between 1.56 and 400 µg/mL [58].

Table 4. Antimicrobial activity of the EO and crude extracts of *T. balsamita*.

Extract	Microbial Strains	Methods	Key Findings	References
EO and EtOH–H_2O	*Bacillus cereus* (ATCC 11778 and 15) *B. subtilis* (ATCC 6633) *S. aureus* (ATCC 25923 and A-529) *S. epidermidis* (ATCC 12228) *Listeria monocytogenes* (17/11) *Enterobacter aerogenes* (ATCC 13048) *Escherichia coli* (ATCC 25922) *Klebsiella pneumoniae* (ATCC 13883) *Proteus mirabilis* (ATCC 35659) *S.* ser. *enteritidis* (ATCC 13076) *S.* ser. *typhimurium* (300/11) *Pseudomonas aeruginosa* (ATCC 27853)	Microdilution method	The EO at 32 µL/mL had inhibitory effects against all the tested strains (100%), while the hydroethanolic extract at the same concentration exhibited inhibitory effects towards 68%.	[9]
EO	*B. subtilis* (ATCC 6633) *S. aureus* (ATCC 6538 P) *E. coli* (ATCC 25922) *Salmonella typhimurium* (NRRLB 4420) *S. aureus* (ATCC 6538 P) *Candida globrata* (ATCC 66032) *Candida tropicalis* (ATCC 13803)	Disc diffusion method	The EO exhibited antibacterial activity against Gram-positive and Gram-negative bacteria, with inhibition zones ranging from 13 to 17 mm. The EO had antifungal activity against both penicillin-resistant strains, with inhibition zone values of 15 and 14 mm, respectively.	[56]
70% ETOH	*S. aureus* (ATCC 6538 P) *B. cereus* (ATCC 14579) *E. coli* (FV 755-0139) *P. aeruginosa* (ATCC 27853) *S. typhimurium* (ATCC 14028)	Disc diffusion method	The hydroalcoholic extract displayed moderate in vitro antibacterial potency against all Gram-positive bacteria (IZ = 8 $\pm$ 0.2 and 7 $\pm$ 0.1 mm, respectively), whereas all the tested Gram-negative bacteria were resistant.	[59]
EO	*L. monocytogenes* (NCTC 11994) *S. aureus* (ATCC 25093) *E. coli* (ATCC 8739) *S. enterica* (NCTC 6017)	Agar well diffusion method	The leaves' EO was found active against the tested strains, with the Gram-positive bacteria *L. monocytogenes* (NCTC 11994) and *S. aureus* (ATCC 25093) being the most susceptible to the EO (IZ = 30 and 20 mm, respectively).	[60]
EO	*Streptococcus mutans* (PTCC 1683)	Disc diffusion method	The EO at 100 µg/mL displayed remarkable activity against *S. mutans*, *S. salivarius*, and *S. sanguinis*, as compared to standard mouth rinses such as chlorhexidine and Oral B mouthwashes.	[57]

Furthermore, there have been several attempts to elucidate the efficacy of costmary as a sustainable source for environmentally friendly food packaging materials. In this regard, Khodayari et al. explored the potential of a poly(lactic acid) composite film infused with

2% *T. balsamita* essential oil (TBE), 1% cellulose nanocrystals composite (CNC), and 2% propolis ethanolic extract (PEE) in extending the shelf life of vacuum-packed sausages. The study aimed to develop eco-friendly food packaging materials. The composite film exhibited strong antimicrobial properties and significantly prolonged the shelf life of cooked sausages during 50 days of refrigerated storage. The film was particularly effective against Gram-positive bacteria, with *Bacillus cereus* being the most susceptible. The study also pointed to a synergistic interaction between TBE and propolis ethanolic extract, with TBE contributing to the film's flexibility [18]. Similarly, a recent study examined the vapor phase of *T. balsamita* essential oil, focusing on its impact on both Gram-positive and Gram-negative microorganisms. Results indicated that EOs derived from leaves demonstrated significant effectiveness against various pathogens, including *S. pneumoniae*, *L. monocytogenes*, and *Y. enterocolitica*, on different produce, such as apples, pears, carrots, and white radishes. This study stands out by evaluating the antimicrobial properties of EO vapor, a novel approach, and highlights the potential of EOs as eco-friendly and functional alternatives to synthetic chemicals in food preservation [18]. It also emphasizes the promising role of *T. balsamita* EO in prolonging the shelf life of fruits and vegetables through their antimicrobial properties. Further exploration of their applications and mechanisms can contribute to environmentally friendly food preservation solutions [18].

6.2. Cytotoxic Activity

The in vitro anticancer activity of the EO and carvone (**20**), the main constituent of the EO, was assessed against breast cancer (MDA-MB 468) and human melanoma (A375) cell lines using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cell proliferation assay. The results indicated that both carvone and EOs exhibited limited cytotoxicity, with IC_{50} values ranging from 3657.4 to 6038.0 µg/mL for MDA-MB 468 and 1312.1 to 2323.6 µg/mL for A375 cells. Statistical analysis revealed no significant difference ($p > 0.05$) in cytotoxicity between carvone and EOs against A375 cells, while EOs exhibited a slightly higher activity than carvone against MDA-MB 468 cells ($p > 0.05$). Subsequently, chitosan nanoparticles loaded with carvone (**20**) and *T. balsamita* EO were formulated to enhance their cytotoxic effects. Notably, chitosan nanoparticles containing *T. balsamita* EO demonstrated the highest activity against both A375 and MDA-MB 468 cell lines, with IC_{50} values of 85.3 and 240.1 µg/mL, respectively [12].

Moreover, a recent study examined the antitumor properties of *T. balsamita* EO from different plant parts, namely flowers (FEO), leaves (LEO), and stems (SEO), against breast cancer cells. The authors found that these EOs significantly reduced cell viability in a time- and dose-dependent manner, with SEO showing the strongest effect. These EOs also impacted oxidative balance by decreasing $O_2\bullet-$ levels and increasing nitric oxide (NO) production, contributing to their antitumor activity. Moreover, the EOs inhibited cell migration, making them potential chemotherapeutic agents. These findings suggest the potential of these EOs for future antitumor therapies, warranting further investigation [61].

6.3. Antioxidant Activity

Phytochemicals found in plants are crucial for maintaining good health, and therefore, a diet rich in antioxidants or antioxidant supplements generally provides beneficial health effects. A wide variety of medicinal plants, many of which have already been explored for their content of different nutrients and a range of bioactive compounds, can be used in the pharmaceutical, cosmetic, and nutritional fields [13]. The therapeutic properties of *T. balsamita* are attributed to a series of active ingredients concentrated in the leaves and flowers, including terpenes, phenolic acids, and flavonoids. Specifically, the aqueous extract is known for its anti-inflammatory, antitumor, and antioxidant properties, and

active protection against photoaging and neurodegenerative pathologies [62–64]. These properties are ascribed to the presence of a high amount of polyphenolic compounds, which can reach as high as 8% in the leaves [63].

The total polyphenol content in ethanol extracts of leaves can vary according to the growing period and the variety. For instance, in two varieties of *Chrysanthemum balsamita* (*balsamita* and *tanacetoides*), the content was 4.40 and 2.92 g per 100 g of dry weight, respectively, whereas the total flavonoid content ranged between 2.23 and 2.19 g per 100 g of dry weight, respectively [11]. Flavonoids were able to confer a high antiradical and antioxidant activity to the leaf extracts of this plant [8,11,13,49]. In this context, Baczek et al. assessed the antioxidant activity of a hydroethanolic extract of the whole air-dried *T. balsamita* using the DPPH scavenging reaction and ferric reducing antioxidant power (FRAP) assays in vitro. The results showed that the extract had significant antioxidant activity in both assays (IC_{50} = 13.59 ± 0.21 µmolTrolox/g for DPPH and IC_{50} = 339.1 ± 17.12 µmolTrolox/g for FRAP). The authors attributed the potent antioxidant activity to the high levels of phenolic acids, especially caffeic acid (**121**), chlorogenic acid (**122**), and chicoric acid (**125**), as well as flavonoid glycosides, including luteolin 7-*O*-glucoside (**138**) and apigenin 7-*O*-glucoside (**136**) [9].

In another study, Popova et al. (2013) evaluated and compared the antioxidant potency of *T. balsamita* fresh and frozen leaves' aqueous extracts using four assays, namely ABTS, DPPH, FRAP, and CUPRAC. The findings revealed that frozen leaves' aqueous extract has slightly higher free-radical-scavenging activity than fresh leaves' aqueous extract in all the tested assays except for the DPPH method, where no differences were recorded. The authors accredited these differences to the variation in total phenolic content between fresh and frozen leaves (0.59 mg GAE/g plant weight and 0.68 mg GAE/g plant weight, respectively), which was ascribed to changes in the cellular structure [60].

Furthermore, Bonetti et al. (2021) tested the overall antioxidant and antiradical capacity of leaves' methanol:water 80:20% (*v*/*v*) extract during different phenological growth stages by employing the DPPH and ORAC assays. According to the authors, the leaves collected at early and late growth stages showed the highest antioxidant and antiradical capacities in both tests (EC_{50} = 0.04 ± 0.01 and 0.07 ± 0.02 mg/g dry weight (DW) at the early and late growth stages in the DPPH system, respectively; and EC_{50} = 1681 ± 112 and 1689 ± 175 µMTE/g DW at the early and late growth stages in the ORAC test, respectively). The authors correlated the powerful antioxidant properties of the extract with the substantial amounts of flavonoids and phenolic acids present in the leaves' extracts, including chlorogenic acid (**122**) and quercetin (**129**). These polyphenols reached their highest concentrations in the leaves during the early and late phenological growth stages, which may explain the aforementioned results [13]. Despite promising in vitro antioxidant activity demonstrated in *T. balsamita*, further in vivo studies using animal models or clinical trials are mandatory to validate its efficacy in addressing oxidative stress. Investigating its bioavailability and biological impact in living systems will enhance our understanding of its potential in managing oxidative-stress-related conditions.

6.4. Enzyme Inhibitory and Miscellaneous Properties

Savcı et al. studied the DNA protection activity of *T. balsamita* ethanolic extract at the concentrations of 25, 50, and 100 mg/mL on H_2O_2-induced pBR322 plasmid DNA damage. Results showed that the extract exerted a weak protective effect on H_2O_2- and UV-induced pBR322 plasmid DNA damage [44]. Furthermore, aerial parts' ethyl acetate extract has been found to exhibit moderate inhibitory activity towards α-glucosidase enzyme, with an IC_{50} of 0.808 mg/mL [65]. Recently, the 80% MeOH methanolic extract of *T. balsamita* roots demonstrated inhibitory effects towards α-glucosidase and α-amylase (0.71 ± 0.07 mmol acarbose/g and 0.43 ± 0.02 mmol acarbose/g, respectively). The same extract showed

cosmeceutical properties in vitro through inhibiting the tyrosinase enzyme, with an IC_{50} value of 54.65 mg kojic acid/g [66].

7. Toxic Effects

To date, there have been no published reports addressing the potential toxicity and adverse effects associated with *T. balsamita*. Nevertheless, a noteworthy effort was undertaken by Yousefzadi et al. to explore the cytotoxicity of *T. balsamita* aerial-part essential oils (EOs) in relation to monkey kidney (Vero) and human fetal skin fibroblast (HFSF) cell lines. This evaluation utilized the MTT assay, revealing a relatively weak cytotoxic impact against both cell lines, with IC_{50} values of 2500 and 1250 µg/mL, respectively [40]. While these findings suggest a favorable safety profile for the plant's essential oils, further in vivo and in vitro studies are necessary to thoroughly assess the plant's safety.

8. Conclusions and Future Perspectives

T. balsamita bears a rich history as a revered folk remedy in diverse cultures. Its prominence extends to traditional cuisines, particularly in the regions of south-central Europe. Ethnobotanical surveys have documented its multifaceted use in managing various health-related conditions, encompassing bile acid deficiency, diabetes, gallbladder diseases, headache, cholecystitis, dyspepsia, antispasmodic ailments, insomnia, and cough, as well as its carminative properties and even its use as a diuretic. Recent pharmacological investigations have substantiated many of these empirical applications, unveiling the plant's impressive array of biological activities, including antioxidant, antimicrobial, anticancer, and antinociceptive properties, along with anxiolytic effects, among others. These therapeutic attributes can be attributed to the presence of bioactive compounds, notably flavonoids and their derivatives, phenolic acids, terpenes, fatty acids, and more, concentrated in various plant parts such as leaves, aerial components, petals, and stems.

However, while local communities in regions like Turkey have long harnessed various parts of *T. balsamita*, such as its leaves, for diabetes management, in vitro and in vivo investigations into its hypoglycemic effects remain scarce. Conducting in vitro studies to assess the plant-based extracts with regard to other key enzymes involved in diabetes pathogenesis, including protein tyrosine phosphatase 1B (PTP1B) and dipeptidyl peptidase IV (DPP IV), as well as in vivo experiments in normal and diabetic animal models, would be pivotal to evaluating this species' efficacy in lowering blood glucose levels and restoring cellular sensitivity. Additionally, the plant's historical use as an anthelmintic agent for cattle in Spain merits further scrutiny. Conducting comprehensive in vivo and in vitro studies could help validate these ethnoveterinary claims and ascertain potential synergistic effects when combined with standard antibiotic drugs, such as amoxicillin and tetracycline, especially against Gram-negative and Gram-positive bacteria exhibiting multidrug resistance phenotypes (MDR), using appropriate controls and positive references, conducting experiments with various doses and sufficient replication, the inclusion of standardized microbial strains or well-identified clinical isolates, and the use of representative standard endpoints, such as IC_{50} or MICs values rather than the inhibition zones. Further studies are also needed to investigate the effects of plant extracts on the oxidative stability, shelf life, and nutritional composition of oxidizable oils.

Finally, further research focusing on the extraction and identification of bioactive compounds from additional parts of the plant, including the roots, stems, and petals, is also mandatory. This will not only deepen our understanding of the plant's full therapeutic potential but also enhance its value for applications in the food, nutraceutical, and pharmaceutical industries, contributing to the sustainable use and commercialization of *T. balsamita* in modern medicine and industry.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ddc4010010/s1, Figure S1: Volatile organic compounds (VOCs) identified in *T. balsamita* EO; Figure S2: Phenolic acids found in *T. balsamita* extracts; Figure S3: Chemical structures of the flavonoids in *T. balsamita* extracts; Figure S4: Miscellaneous compounds found in *T. balsamita* extracts.

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