PHARMACIA

Pharmacia 70(4): 1067–1081
DOI 10.3897/pharmacia.70.e110748

Review Article

The most promising Southeastern European *Tanacetum* species: a review of chemical composition and biological studies

Reneta Gevrenova[1], Vessela Balabanova[1], Dimitrina Zheleva-Dimitrova[1], Georgi Momekov[2]

1 *Department of Pharmacognosy, Faculty of Pharmacy, Medical University-Sofia, Sofia, Bulgaria*
2 *Department of Pharmacology, Pharmacotherapy and Toxicology, Faculty of Pharmacy, Medical University-Sofia, Sofia, Bulgaria*

Corresponding author: Dimitrina Zheleva-Dimitrova (dzheleva@pharmfac.mu-sofia.bg)

Received 8 August 2023 ♦ **Accepted** 8 September 2023 ♦ **Published** 11 October 2023

Citation: Gevrenova R, Balabanova V, Zheleva-Dimitrova D, Momekov G (2023) The most promising Southeastern European *Tanacetum* species: a review of chemical composition and biological studies. Pharmacia 70(4): 1067–1081. https://doi.org/10.3897/pharmacia.70.e110748

Abstract

Several species of the genus *Tanacetum* L. (Asteraceae) spread in the Southestern Europe are traditionally used as medicinal and aromatic plants, including *T. vulgare*, *T. parthenium*, *T. macrophyllum*, *T. balsamita*, *T. poteriifolium*. The review is focused on the phytochemical and pharmacological studies of these taxa. Major chemical constituents are acylquinic acids, sesquiterpenes, sesquiterpene lactones, methoxylated flavonoids. An in-depth depiction of more than 100 secondary metabolites was achieved in *Tanacetum* species by liquid chromatography-high resolution mass spectrometry. The ethnopharmacological studies indicate that species possess antioxidant, enzyme inhibitory and cytotoxic activity along with antimicrobial and antiviral effects. Reports revealed anti-inflamatory and neuromodulatory activity involved in the pharmacological approach in counteracting migraine attacks. Multivariate data analysis allowed the identification of the most discriminant metabolites and bioactivities in the herbal drugs. This review emphasizes *T. vulgare*, *T. macrophyllum*, *T. balsamita* and *T. parthenium* as potential raw material for health-promoting application in pharmaceutical area.

Keywords

Tanacetum, Southeastern European *Tanacetum* species, chemical composition, biological activity

Introduction

Tanacetum L. is one of the largest genera in Asteraceae family including more than 152 species spread in Europe, temperate parts of Asia, West Africa and North America, cultivated in South Africa, South America, Australia and New Zealand (Bremer 1994). The classification of Asteraceae has been the subject of several publications and monographs in the recent years. Funk et al. (2009) published the systematics, evolution and biogeography of the family.

The studied *Tanacetum* species (*T. achilleifolium* (Bieb.) Schultz Bip., *T. argenteum* (Lam.) Willd., *T. balsamita* L., *T. cilicium* (Boiss.) Grierson, *T. corymbosum* (L.) Sch. Bip., *T. macrophyllum* (Waldst. & Kit.) Sch.Bip., *T. millefolium* (L.) Tzvelev, *T. parthenium* (L.) Schultz Bip., *T. poteriifolium* (Ledeb.) Grierson, *T. praeteritum* (Horwood) Heywood, *T. vulgare* L.) are distributed in the Southeastern European regions including Balkan Peninsula, Romania, and Turkey (www.worldfloraonline.org).

Typically, the species of genus *Tanacetum* contain specific glandular structures – glandular hairs (Simmonds et al. 2002). Their essential oil is characterized by various terpenes (oxidized monoterpenes such as 1,8-cineole (**173**), camphor (**172**), borneol (**178**), thujones (**185** and

186)), but sesquiterpene lactones are with the greatest importance for the chemophenetics (Venditti et al. 2018).

Abad et al. (1995), Gören et al. (2002) and Khatib et al. (2023) summarized data on the phytochemical composition of the genus *Tanacetum*, concluding that sesquiterpenes, sesquiterpene lactones (STLs) and ceramides are with main chemotaxonomic significance. As highlighted in the recent review article, the beneficial effects of *Tanacetum* species have been demonstrated in a number of experimental models with evidences strongly suggesting that the herbal drugs are versatile treatment for inflammation, hyperglycemia, liver injury, and oxidative stress (Khatib et al. 2023). Significant advance has been made in the understanding the biochemical mechanisms underlying sesquiterpenes lactons - mediated cytotoxicity towards cancer cell lines, antimicrobial and antiviral activity of *Tanacetum* essential oils/extracts, and neuromodulatory effects of *T. parthenium*.

The selected *Tanacetum* species provide a rich source of acylquinic acids and methoxylated flavonoids, thus, the unique nature of their health promoting benefit, including oxidative stress prevention and inhibition of key enzymes in the metabolite syndrome has been associated with the naturally high levels of chlorogenic and dicaffeoylquinic acids. The aim of the study is to review and update the phytochemical composition and pharmacological properties emphasizing Southeastern European *Tanacetum* species.

Phytochemical composition of the species of genus *Tanacetum*

An overview on the main classes of secondary metabolites and their distribution in the discussed *Tanacetum* species is depicted in Table 1.

Phenolic acids and flavonoids

Ak et al. (2021) performed a study of hexane, hydroethanolic and aqueous extract from *T. vulgare* aerial parts, stems and flowering heads. They reported the highest total phenolic content (TPC) and total flavonoid content (TFC) in both *T. vulgare* hydroethanolic extracts from stems and aerial parts (up to 93 mg GAE (gallic acid equivalent)/g dry extract and 53 mg RE (rutin equivalent)/g). TFC up 82 mg RE /g was determined in the methanol-aqueous extract from *T. macrophyllum* flowering heads (Gevrenova et al. 2020). Extraction methods highly impact the TPC and TFC yielding up to 65.05 mg GAE/g (TPC) by accelerated solvent extraction and 55.40 mg RE/g (TFC) by maceration in the ethanolic extracts from *T. parthenium* (Zengin et al. 2020). TPC varied in large ranges – the lowest levels were reported for *T. vulgare* (26.37 mg GAE/g), *T. corymbosum* (5.90 mg GAE/g) and *T. macrophyllum* (0.64 mg GAE/g), while it reached up to 221 mg GAE/g in *T. vulgare* roots (Devrnja et al. 2017; Ivanescu et al. 2018).

In a comparative analysis of TPC in different agrorefinery products from the residue after the hydrodistillation of the essential oil from *T. vulgare* aerial parts (aqueous extract, acetone balsam and acetone extract), the highest content was found in the aqueous extract (142.30 mg GAE/g dry extract) (Baranauskiene et al. 2014).

Williams et al. (1999a, 1999b) investigated epicuticular (surface) and vacuolar flavonoids in 7 species of genus *Tanacetum*. The lipophilic compounds consisted mainly of 6-hydroxykaempferol-3,6,4'-trimethylether (**89**) and quercetagetin-3,6,3'-trimethylether (**91**), together with 11 other surface flavonoids (Table 1). The methyl ethers of scutellarein (**125, 126**) and 6-hydroxyluteolin (**124**) are characteristic of species with corymb inflorescences of flowering heads. Vacuolar flavonoid glycosides are represented by apigenin 7-*O*-glucoside (**98**) and luteolin 7-*O*-glucoside (**109**), 6-hydroxyluteolin 7-glucoside (**119**) occurs in *T. vulgare* and *T. pseudoachillea*; chrysoeriol 7-glucuronide (**118**) – in *T. parthenium*, *T. macrophyllum* and *T. corymbosum*. Highly methoxylated flavonoids such as eupatilin (**127**), eupatorin (**127**), casticin (**130**) have been proven in the recent studies (Devrnja et al. 2017; Ivanescu et al. 2018). Methoxylated derivatives of quercetagetin (**90–94**), 6-hydroxykaempferol (**88** and **89**), scutellarein (**125** and **126**) and 6-hydroxyluteolin (**124**) have been identified in *T. macrophyllum* flowering heads and leaves (Williams et al. 1999a). *T. macrophyllum* aerial parts were especially rich in the glucosides and glucuronides of apigenin (**98**, **99**, **102**, and **115**) and kaempferol (**79** and **81**)(Venditti et al. 2018).

HPLC-DAD analysis of the major compounds in ethanol-aqueous extracts of *T. vulgare* and *T. balsamita* showed 1.37 g/100 g extract and 0.93 g/100 g chlorogenic acid (**23**), and 3.33 g/100 g and 2.78 g/100 g chicoric acid (**69**), respectively (Baczek et al. 2017). The total content of the determined phenolic acids (caffeic (**16**), ferulic (**20**), chlorogenic (**23**), rosmarinic (**68**) and chicoric acids (**69**)) was over 4 g/100 g extract in both species. The highest content of apigenin 7-*O*-glucoside (**98**) (1.10 g/100 g extract) was determined in *T. vulgare*, and of chrysoeriol (**100**) (0.63 g/100 g) in *T. balsamita*.

Mono- and dicaffeoylquinic acids, flavone and flavonol glucosides and glucuronides were identified/annotated in methanolic, hydroalcoholic and aqueous extracts of *T. vulgare* by UPLC/ESI-QTOF-MS, LC-DAD/ESI-TOF-MS and HPLC-MS (Baranauskiene et al. 2014; Devrnja et al. 2017; Ivanescu et al. 2018) (Table 1). Among the methoxylated flavonoids, wide spread in Asteraceae family, the greatest diversity was found in *T. macrophyllum*: eupatilin (**127**) (144.09 μg/g), hispidulin (**125**) (55.83 μg/g), eupatorin (**128**) (1.48 μg/g), and acacetin (**103**), jaceosidine (**129**) and casticin(**130**) were below 1 μg/g (Ivanescu et al. 2018). Zengin et al. (2020) determined chlorogenic acid (**23**) up to 487 mg/kg, quercetin (**72**) – up to 377 mg/kg and *p*-hydroxyphenylacetic acid (**6**) – up to 280 mg/kg in the *T. parthenium* ethanolic extract obtained by accelerated solvent extraction.

Recently, a hyphenated platform liquid chromatography - high resolution mass spectrometry (LC-HRMS) for annotation and dereplication of acylquinic acids (AQAs), 6-methoxylated flavonoids and sesquiterpene lactones in selected *Tanacetum* speies was developed (Gevrenova et al. 2020, 2023; Ak et al. 2021). Secondary metabolites were an-

notated/identified in methanol-aqueous extracts from the flowering heads, leaves and roots of *Tanacetum macrophyllum*, *T. vulgare* and *T. balsamita*. They were profiled and characterized by reverse phase chromatography coupled with hybrid quadrupole-Orbitrap HRMS. The annotation/dereplication was based on the diagnostic fragment ions for each subclass of the compounds. An in-depth depiction of more than 100 secondary metabolites was achieved.

Overall, *mono*AQA, *di*AQA and *tri*AQA (**23–67**) were evidenced in the assayed *Tanacetum* species (Table 1). Among them, caffeoyl-, feruloyl- and coumaroylquinic acids, dicaffeoylquinic, feruloyl-caffeolylquinic, *p*-coumaroyl-caffeoylquinic, hydroxydihydrocaffeoyl (HC)-caffeolylquinic and dehydrocaffeoyl (DC)-caffeoylquinic acids were annotated together with tricaffeoylquinic acids and dicaffeoylquinic acid-hexosides. A variety of methoxylated derivatives of scutellarein (**125** and **126**), quercetagetin (**91–94**) and 6-hydroxyluteolin (**124**) was dereplicated.

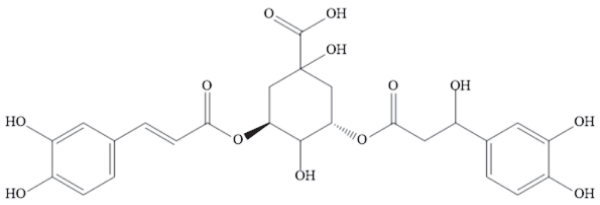
For the first time, an exceptional variation of AQAs in *T. macrophyllum* was reported (Gevrenova et al. 2020). Multivariate data analysis (PCA and hierarchical clustering analysis) allowed for the identification of markers able to discriminate the aerial parts and flowering heads from the roots (Gevrenova et al. 2020). Among them, methoxylated flavonoids patuletin (**92**), eupatorin (**128**), quercetagetin trimethyl ether (**94**) and STLs artekalin (**243**) (eudesmanolide) and artemisiifolin (**238**) (germacranolide) were dereplicated. In addition, flowering heads are discernable by 4-*p*-coumaroyl-5-caffeoylquinic acid (**54**) and 4-caffeoyl-5-*p*-coumaroylquinic acid (**42**) (Fig. 1).

PCA and discriminant analyses allowed for the identification of the most discriminant secondary metabolites and bioactivities in *T. vulgare* flowering heads, stems and aerial parts in terms of extraction solvents (Ak et al. 2021). Among the compounds are jaceosidin (**129**), kaempferol 3-*O*-glucoside (**78**), luteolin 7-*O*-glucoside (**109**), naringenin *O*-hexuronide (**151**), caffeic acid *O*-hexoside, caffeoyl-hexose (**21**), thujone (**185** and **186**), and caryophyllen/bisabolene (**194**).

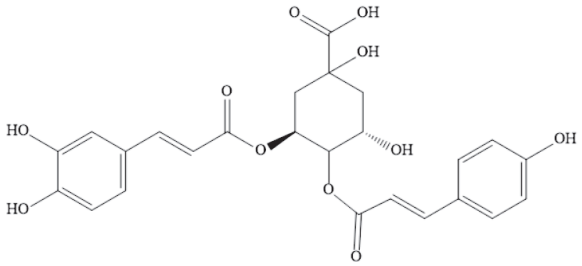
Essential oil. Chemotypes in *Tanacetum* species

The main feature of genus *Tanacetum* and the species of tribe Anthemideae is the production of a specific "non-standard" group of monoterpenes, the result of the so-called "middle-to-tail" coupling of the terpene precursors isopentenyl pyrophosphate and dimethylallyl pyrophosphate (in contrast to the typical "head-to-tail" condensation) (Abad et al. 1995). A major precursor in this group is chrysanthemic acid. Opening the ring of this compound in various ways leads to the formation of artemisia ketone (**189**), artemisia alcohol (**190**), etc. Abad et al. (1995) divided *Tanacetum* species into two main groups according to essential oil (EO) composition: "monoterpene group (*T. vulgare*, *T. parthenium*, *T. boarale*)" and "sesquiterpene group" (species from Central and Southeast Europe: *T. macrophyllum*, *T. cilicium*, *T. corymbosum*, *T. millefolium*).

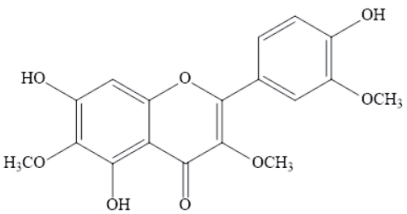
The bitter taste of the aerial parts of *Tanacetum* species is due to sesquiterpenes (farnesene (**196**), germacrene D (**198**), etc.). The EO composition of *Tanacetum* species and its biological activity is summarized by Kumar and Tyagi (2013). Over 200 compounds have been identified. The main characteristic is the chemovariability in the species and subspecies taxonomic category. The main components are camphor (**172**), bornyl acetate (**180**), α-phellandrene (**181**), chrysanthenyl acetate (**187**), *α*-terpinene (**163**), *p*-cymene (**165**), terpinen-4-ol (**177**), α-terpineol (**176**), caryophyllene oxide (**208**), *α*- and *β*-thujone (**185** and **186**), *α*-pinene (**158**), camphene (**160**), *β*-caryophyllene (**194**), carvacrol (**184**) etc. (Table 1) (Kumar and Tyagi 2013).



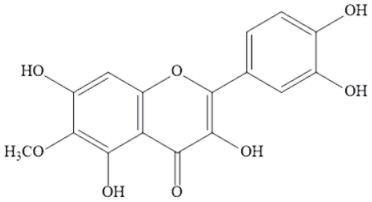
3-hydroxydihydrocaffeoyl-5-caffeolylquinic acid (3-HC-5-CQA) (**33**)



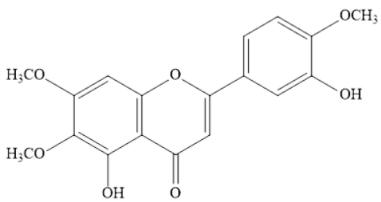
4-*p*-coumaroyl-5-caffeoylquinic acid (4-*p*-Co-5-CQA) (**54**)



quercetagetin-3,6,3'-trimethyl ether (**91**)



patuletin (**92**)



eupatorin (**128**)

Figure 1. Structure of some acylquinic acids and flavonoids in *Tanacetum* species.

Table 1. Major classes of secondary metabolites and compounds in genus *Tanacetum*.

Compounds	*Tanacetum* Species	References
Phenolic compounds and derivatives		
Hydroxybenzoic acids*:** protocatechuic (**1**), gentisic (**2**), vanillic (**3**), syringic (**4**), *p*-hydroxybenzoic (**5**), *p*-hydroxyphenylacetic acid (**6**) and their hexosides, salicylic acid (**7**), dihydroxyphenylacetic acid-pentosylhexooside (**8**) ***Sugar esters: vanillyl-hexose (**9**)	*T. parthenium*, *Chrysanthemum balsamita* var. *balsamita*, var. *tanacetoides*, *T. macrophyllum*, *T. vulgare*, *T. balsamita*, *T. balsamita*	Zengin et al. 2020; Benedecetal.2016;Vendittietal.2018; Gevrenova et al. 2020, 2022; Ak et al. 2021
4-*O*-β-D-glucopyranosyl-vanillic acid (**10**)	*T. macrophyllum*	Venditti et al. 2018
caffeoyl-syringic acid (**11**), caffeic acid-*O*-(hydroxybutanoyl)-hexoside (**12**), gentisic acid-*O*-(caffeoyl)-hexoside (**13**)	*T. macrophyllum*	Gevrenova et al. 2020
vanillic acid -4-*O*-(6-*O*)-caffeoyl)-hexoside (**14**)	*T. vulgare*, *T. macrophyllum*	Gevrenova et al. 2020; Ak et al. 2021
caffeic acid-O-(salicyl)-hexoside (**15**)	*T. vulgare*	
Hydroxycinnamic acids and derivatives		
caffeic (**16**), *o*-, *m*-, *p*-coumaric (**17, 18, 19**), ferulic acid (**20**) and their hexosides ***Sugar esters***: caffeoyl-hexose (**21**), caffeoylgluconic acid (**22**)	*T. parthenium*, *T. vulgare*, *Chrysanthemum balsamita* var, *balsamita*, var. *tanacetoides*, *T. macrophyllum*, *T. vulgare*, *T. balsamita*	Zengin et al. 2020; Benedec et al. 2016; Baszek et al. 2016; Baranauskiene et al. 2014; Gevrenova et al. 2020, 2022; Ak et al. 2021
Caffeoylquinic (CQA), feruloylquinic (FQA), p-coumarylquinic (p-CoQA)acids		
chlorogenic (5-CQA) (**23**), neochlorogenic (3-CQA) (**24**), 1-CQA (**25**), 4-CQA (**26**), 3,4-*di*CQA (**27**), 3,5-*di*CQA (**28**), 4,5-*di*CQA (**29**), 5-FQA (**30**), 4-FQA (**31**), 5-*p*-CoQA (**32**), 3-HC-5-CQA (**33**), 1-C-3HCQA (**34**), 3-DC-5-CQA (**35**), 3-F-5-CQA (**36**), 4-F-5-CQA (**37**), 4-C-5-FQA (**38**), 3-F-4-CQA (**39**), 3-*p*-Co-5-CQA (**40**), 1-*p*-Co-5-CQA (**41**), 4-C-5-*p*-CoQA (**42**), 3,4,5-*tri*CQA (**43**)	*T. parthenium*, *T. macrophyllum*, *Chrysanthemum balsamita* var. *balsamita*, var. *tanacetoides*, *T. vulgare*, *T. balsamita*, *T. macrophyllum*	Zengin et al. 2020; Benedec et al. 2016; Venditti et al. 2018; Baranauskiene et al. 2014; Baszek et al. 2016; Devrnja et al. 2017; Gevrenova et al. 2020, 2022; Ak et al. 2021
1-FQA (**44**), 1-*p*-CoQA (**45**), 1,5-*di*CQA (**46**), 3-HC-4-CQA (**47**), 4-HC-5-CQA (**48**), 3-C-4-DCQA (**49**), 1-C-3-DCQA (**50**), 1-C-5-DCQA (**51**), 3-*p*-Co-4-CQA (**52**), 3-C-4-*p*-CoQA (**53**), 4-*p*-Co-5-CQA (**54**), 3-F-4-CQA (**55**), 1-C-5-FQA (**56**), 3-C-5-FQA (**57**), 1-C-3-FQA (**58**), 1,3,5-*tri*CQA (**59**), 1,3,4- *tri*CQA (**60**)	*T. macrophyllum*	Gevrenova et al. 2020
3-*p*-CoQA (**61**), 3-*p*-CoQA (**62**), 3-C-5-HCQA (**63**), 1-C-3-HCQA (**64**), 4-DC-5-CQA (**65**), 3-C-5-*p*-CoQA (**66**)	*T. vulgare*, *T. macrophyllum*	Gevrenova et al. 2020; Ak et al. 2021
3-DC-5-CQA (**67**)	*T. vulgare*	Ak et al. 2021
rosmarinic (**68**), cichoric acid (**69**)	*T. vulgare*, *T. balsamita*	Baszek et al. 2016
quinic acid (**70**)	*T. vulgare*, *T. macrophyllum*, *T. balsamita*	Baranauskiene et al. 2014; Venditti et al. 2018
shikimic acid (**71**)	*T. vulgare*, *T. balsamita*	Ak et al. 2021; Gevrenova et al. 2023
Flavonoids		
Flavonols – quercetin (Qu) (**72**), Qu 3-*O*-galactoside (**73**), Qu 3-*O*-glucoside (**74**), Qu 3-*O*-rhamnoside (**75**), rutin (**76**), kaempferol (Km) (**77**), Km 3-*O*-glucoside (**78**), isorhamnetin 3-*O*-glucoside (**79**),	*T. parthenium*, *T. vulgare*, *T. balsamita*, *T. macrophyllum*	Zengin et l. 2020; Devrnja et al. 2017; Baszek et al. 2016; Venditti te al. 2018
Km-3-*O*-glucuronide (**80**)	*T. macrophyllum*	
Qu 3-glucuronide (**81**), gossypetin 8-*O*-glucoside (**82**) Km 7-*O*-rutinoside (**83**)	*T. vulgare*, *T. balsamita*	Devrnja et al. 2017; Gevrenova et al. 2023
isorhamnetin *O*-hexuronide (**84**)	*T. balsamita*, *T. vulgare*, *T. macrophyllum*	Gevrenova et al. 2020; Ak et al. 2021
isorhamnetin *O*-pentoside (**85**)	*T. balsamita*	
Qu-7-*O*-hexuronide (**86**), Qu-*O*-acetylhexoside (**87**)	*T. vulgare*, *T. macrophyllum*	
6-methoxylated flavonols		
6-hydroxykaempferol-3,6-dimethyl ether (**88**)	*T. parthenium*	Williams et al. 1999a, 1999b
6-hydroxykaempferol-3,6,4'-trmethyl ether (**89**)	*T. parthenium*, *T. macrophyllum*	Williams et al. 1999a, 1999b
quercetagetin-3,6-dimethyl ether (axillarin) (**90**)	*T. vulgare*, *T. parthenium*, *T. balsamita*	Baranauskiene et al. 2014; Williams et al. 1999a, 1999b
quercetagetin-3,6,3'-trimethyl ether (**91**)	*T. vulgare*, *T. parthenium*, *T. macrophyllum*, *T. cilicium*	Williams et al. 1999a, 1999b
quercetin 6-methyl ether (patuletin) (**92**)	*T. balsamita*, *T. macrophyllum*, *T. vulgare*	Gevrenova et al. 2020, 2022; Ak et al. 2021
quercetagetin-6,3'-dimethyl ether (spinacetin) (**93**)	*T. balsamita*	Gevrenova et al. 2023
quercetagetin-3, 6,3'(4')-trimethyl ether (**94**) 6-methoxykaempferol (**95**)	*T. vulgare*, *T. macrophyllum*, *T. balsamita*	Gevrenova et al. 2020, 2022; Ak et al. 2021

Compounds	*Tanacetum* Species	References
Flavones – luteolin (Lu) (**96**), apigenin (Api) (**97**), Api 7-*O*-glucoside (**98**), Api 7-*O*-glucuronide (**99**), chrysieriol (**100**) Api 7-*O*-glucosylglucuronide (**101**) Api 7-*O*-diglucuronide (**102**) Api-4'-methyl ether (acacetin) (**103**) diosmetin 7-*O*-glucuronide (**104**)	*T. parthenium*, *T. vulgare*, *T. macrophyllum*, *T. cilicium*, *T. balsamita*, *T. parthenium*, *T. parthenium*, *T. cilicium*, *T. vulgare*, *T. macrophyllum*, *T. vulgare*, *T. macrophyllum*, *T. vulgare*	Williams et al. 1999a, 1999b; Zengin et al. 2020; Baranauskiene et al. 2014; Devrnja et al. 2017; Venditti et al. 2018
scutellarein (**105**), baicalein 7-glucuronide (**106**)	*T. vulgare*	Devrnja et al. 2017
saponarin (**107**), Lu 7-*O*-glucuronide (**108**), Lu 7-*O*-glucoside (**109**), Lu 7-*O*-rutinoside (**110**), Api 7-*O*-rutinoside (**111**)	*T. vulgare*, *T. parthenium*, *T. vulgare*, *T. macrophyllum*, *T. cilicium*, *T. balsamita*, *T. balsamita*	Devrnja et al. 2017; Williams et al. 1999a, 1999b; Gevrenova et al. 2023
Lu *O*-hexuronide (**112**), Lu *O*-hexuronosyl-*O*-hexoside (**113**), Lu *O*-pentosylhexoside (**114**), Api *O*-hexuronide (**115**), Api *O*-pentosylhexoside (**116**), chrysoeriol *O*-pentosylhexoside (**117**), chrysoeriol *O*-hexuronide (**118**)	*T. balsamita*, *T. vulgare*, *T. macrophyllum*	Gevrenova et al. 2020, 2022; Ak et al. 2021
6-hydroxyluteolin *O*-hexoside (**119**), Lu 7-*O*-gentiobioside (**120**), Lu 7-*O*-neohesperidoside (**121**), Lu *O*-acetylhexoside (**122**), Lu *O*-caffeoylhexoside (**123**)	*T. vulgare*	Ak et al. 2021
6-methoxilated flavones		
Lu-6-methyl ether (nepetin) (**124**)	*T. vulgare*, *T. balsamita*, *T. macrophyllum*	Williams et al. 1999a, 1999b; Devrnja et al. 2017; Baranauskiene et al. 2014; Ivanescu et al. 2018
scutelarein-6-methyl ether (hispidulin) (**125**)	*T. vulgare*, *T. macrophyllum*, *T. corymbosum*, *T. balsamita*	Williams et al. 1999a, 1999b; Devrnja et al. 2017; Baranauskiene et al. 2014; Ivanescu et al. 2018; Venditti et al. 2018
scutelarein-6, 4'-dimethyl ether (**126**)	*T. vulgare*, *T. macrophyllum*, *T. cilicium*	
3,7-dihydroxy-6,3',4'-trimethoxyflavone (eupatilin)/santin (**127**)	*T. vulgare*, *T. macrophyllum*, *T. balsamita*	Gevrenova et al. 2020, 2022; Ak et al. 2021
5, 3'-dihydroxy-6,7,4'-trimethoxyflavone (eupatorin) (**128**)	*T. corymbosum*, *T. macrophyllum*, *T. balsamita*	
5,7,4'-trihydroxy-6,3'-dimethoxyflavon (jaceosidin) (**129**)	*T. corymbosum*, *T. macrophyllum*, *T. balsamita*, *T. vulgare*	
3'-hydroxy-3,6,7,4'-tetramethoxyflavone (casticin) (**130**) 5, 4'-dihydroxy-6,7-dimethoxyflavone (cirsimaritin) (**131**)	*T. vulgare*, *T. macrophyllum*, *T. corymbosum*, *T. macrophyllum*, *T. vulgare*, *T. balsamita*	
5,3',4'-trihydroxy-6,7-dimethoxyflavone (cirsiliol) (**132**)	*T. balsamita*	
jaceosidin *O*-hexuronide (**133**)	*T. vulgare*	
C-glycosides - naringenin 6,8-di*C*-hexoside (**134**), homoorientin (**135**), apigenin 6,8-di*C*-hexoside (**136**)	*T. balsamita*, *T. balsamita*, *T. vulgare*	Gevrenova et al. 2023
nepetin *O*-pentosylhexoside (**137**), axillarin *O*-pentosylhexoside (**138**), hispidulin-*O*-pentosylhexoside (**139**), jaceosidin *O*-hexuronide (**140**), jaceosidin *O*-hexoside (**141**), eupatilin *O*-hexoside (**142**)	*T. balsamita*	Gevrenova et al. 2023
hispidulin *O*-hexuronide (**143**)	*T. vulgare*, *T. macrophyllum*	
nepetin *O*-hexoside (**144**)	*T. balsamita*, *T. macrophyllum*, *T. vulgare*	
nepetin O-hexuronide (**145**)	*T. vulgare*	
Flavanones – hesperetin (**146**), erioddictyol (**147**), naringenin (**148**), methoxyeriodictyol *O*-hexuronide (**149**), eriodictyol *O*-hexuronide (**150**), naringenin *O*-hexuronide (**151**), hesperetin *O*-rutinoside (**152**), hesperetin *O*-hexuronide (**153**)	T. *parthenium*, *T. vulgare*, *T. vulgare*	Zengin et l. 2020; Ak et al. 2021
Sterols		
β-sitosterol (**154**), stigmasterol (**155**), campesterol (**156**), ergosterol (**157**)	*T. vulgare*, *T. macrophyllum*, *T. corymbosum*	Ivanescu et al. 2018
Monoterpenes		
α-pinene (**158**), *β*-pinene (**159**), camphene (**160**), sabinene (**161**), myrcene (**162**), *α*-terpinene (**163**), limonene (**164**), *p*-cymene (**165**), terpinolene (**166**), *cis*-sabinene hydrate (**167**), *trans*-sabinene hydrate (**168**), pinocarvone (**169**), β-cyclocitral (**170**), linalool (**171**), camphor (**172**), 1,8-cineol (eucalyptol) (**173**), carvone (**174**), *trans*-pinocarvone (**175**), *α*-terpineol (**176**), *δ*-terpineol (**177**), borneol (**178**), isobornyl acetate (**179**), bornyl acetate (**180**), α-phellandrene (**181**), chrysanthenol (**182**), thymol (**183**), carvacrol (**184**), *α*-thujone (**185**), *β*-thujone (**186**)	*T. macrophyllum*, *T. vulgare*, *T. balsamita*	Demirci and Baser 2007; Radulovic et al. 2010; Venditti et al. 2018
trans-chrysanthenyl acetate (**187**), *γ*-terpinene (**188**), artemisia ketone (**189**), artemisia alcohol (**190**), Z (E)-dihydrocarvone (**191**)	*T. vulgare*	Baszek et al. 2016; Devrnja et al. 2017

Compounds	*Tanacetum* Species	References
Sesquiterpenes		
α-copaene (**192**), β-copaene (**193**), β-caryophyllene (**194**), β-bisabolene (**195**) ,β-farnesene (**196**), α-humulene (**197**), germacrene D (**198**), α-muurolene (**199**), γ-muurolene (**200**), bicyclogermacrene (**201**), δ –cadinene (**202**), γ-cadinene (**203**), zingiberene (**204**), farnesol (**205**), spathulenol (**206**), cubebol (**207**), caryophyllene oxid (**208**), 10-epi-γ-eudesmol (**209**), β-sesquiphellandrene (**210**), α-amorphene (**211**), cyclosativene (**212**), sesquilavandulol (**213**), γ-eudesmol (**214**), α-bisabolol (**215**), copaborneol (**216**),	*T. macrophyllum*, *T. vulgare*, *T. balsamita*	Demirci and Baser 2007; Radulovic et al. 2010; Polatoğlu al. 2013; Venditti et al. 2018
longiverbenone (**217**)	*T. vulgare*	
Sesquiterpene lactones		
Guaianolides		
canin (**218**), artecanin (**219**), secotanapartholide A (**220**), B (**221**), 8α-hydroxyachillin (**222**), macrotanacin (**223**), tanaphillin (**224**)	*T. macrophyllum*, *T. parthenium*	Todorova and Evstatieva 2001;
tanapartin-β-peroxide (**225**), 3,4-β-epoxy-8-deoxicumambrin (**226**), 8-deoxycumambrin (**227**), achillin (**228**), 4α, 10α-dihydroxy-1,5H-guaia-2,11(13)dien-12,6α-olide (**229**), 10β-hydroxycichopumelide (**230**)	*T. parthenium*	
Germacranolides		
9β-propionyloxycostunolide (**231**), 9β-butyryloxycostunolide (**232**), 1α, 10β-epoxyhaageanolide (**233**), 9β-propionyloxy- (**234**), 9β-isobutyryloxy- (**235**) and 9β-(2-methyl)-butyryloxy-1α, 10β-epoxyhaageanolide (**236**)	*T. balsamita*	De Almeida et al. 2016; Todorova and Evstatieva 2001
hanphyllin (**237**), artemisiifolin (**238**)	*T. macrophyllum*	
parthenolide (**239**)	*T. parthenium*	De Almeida et al. 2016
tatridin A (**240**), B(**241**)	*T. vulgare*	Todorova and Evstatieva 2001
hydroxypelenolide (**242**)	*T. parthenium*	
Eudesmanolides		
artecalin (**243**)	*T. macrophyllum*	
reynosin (**244**), armefolin (**245**), 1β-hydroxyarbusculin A (**246**)	*T. vulgare*, *T. parthenium*	
santamarin (**247**)	*T. parthenium*	
vulgarin, 4-epi-vulgarin (**248**),	*T. achilleifolium*, *T. millefolium*	
11,13-dihydro-santamarin (**249**)	*T. vulgare*, *T. achilleifolium*, *T. millefolium*	
1β,4α,6α-trihydroxy-11(13)-eudesman-12,8-olide (**250**), 1β,4α-dihydroxy-6α-tigloyloxy-11(13)-eudesmen-12,8-olide (**251**)	*T. corymbosum*	
tanacetin (**252**), 1-epi-ludovicin C (**253**), 3α-hydroxyreynosin (**254**), 3-epi-armefolin (**255**)	*T. vulgare*	
ludovicin A (**256**), B (**257**)	*T. vulgare* ssp. *siculum*, *T. praeteritum*	Rosselli et al. 2012; Gören 1995
douglanin (**258**)	*T. vulgare* ssp. *siculum*, *T. praeteritum*, *T. argenteum* subsp. *canum*	Rosselli et al. 2012; Gören and Tahtasakal 1997
1α-hydroxy-1-deoxoarglanine (**259**)	*T. vulgare* ssp. *siculum*, *T. praeteritum*	Rosselli et al. 2012; Gören 1995
11,13-dehydrosantonin (**260**)	*T. vulgare* ssp. *siculum*	Rosselli et al. 2012

About 30 chemotypes have been reported for *T. vulgare* depending on the composition of the essential oil and their main components, as well as for *T. balsamita* - 4 (Baczek et al. 2017; Devrnja et al. 2017). The most common chemotypes are β-thujone (**186**), α-thujone (**185**), camphor (**172**), trans-chrysanthenyl acetate (**187**), eucalyptol (**173**), and artemisia ketone (**189**). Less common are the chemotypes α-pinene (**158**), sabinene (**161**), dihydrocarvone (**191**), chrysanthenol (**182**) (Rohloff et al. 2004). In Europe, the most common hemotypes are thujone (**185** and **186**), camphor (**172**), chrysantenyl acetate (**187**), and artemisia ketone (**189**). Regarding *T. balsamita*, 4 main chemotypes have been described in the literature survey – carvone (**174**), camphor (**172**), camphor (**172**)+thujone (**185** and **186**), carvone (**174**)+thujone (**185** and **186**) (Baczek et al. 2017). Trans-chrysanthenol (**182**), β-thujone (**186**), bornyl acetate (**180**) and pinocarvone (**175**) types have also been described.

GC-MS analysis of EM from *T. vulgare* (aerial parts, origin Serbia) showed a 93% content of oxidized monoterpenes, among which trans-chrysanthenyl acetate (**187**) (41%), trans-chrysanthenol (**182**) (12.5%), cis-thujone (**185** and **186**) (5.3%), camphor (**172**) (5%), 1,8-cineole (eucalyptol) (**173**) (3.9%) (Devrnja et al. 2017). According to the classification based on the composition of EM, this type belongs to the chrysantenyl acetate (**187**) chemotype. For Serbia, the types thujone (**185** and **186**), chrysanthenyl, chrysanthenyl acetate (**187**) and camphor (**172**) have been established. Buckwheat EM yield and composition are affected by genetic variation and/or environmental conditions, e.g., the yield of EM from 40 populations in Norway is varying between 0.35 and 1.90% (Rohloff et al. 2004).

The chrysantenyl acetate (**187**) chemotype is characterized by a good antibacterial effect (Devrnja et al. 2017).

In a comparison of EM between *T. vulgare* (Poland) and *T. balsamita* (Turkey), it was found that the differences were mainly quantitative - 96% and 83% oxidized monoterpenes, respectively (Baczek et al. 2017). *T. balsamita* EM mainly contains β-thujone (**186**) (84.4%), α-thujone (**185**) (4.7%), eucalyptol (**173**) (4.1%), while major components in *T. vulgare* EM are trans-chrysanthenyl acetate (**187**) (18.4%), (E)-dihydrocarvone (**191**) (11%) and artemisia ketone (**189**) (9.2%), *β*- and *α*-thujone (**185** and **186**) are 14.3% and 0.8%. Of the monoterpenes, *α*-pinene (**158**) and sabinene (**161**) are contained in the EM of *T. vulgare*, and only in traces in *T. balsamita*. There is also a difference in sesquiterpenes: 5.1% oxidized sesquiterpenes and 0.4% sesquiterpene hydrocarbons in *T. vulgare* and only 0.7% oxidized sesquiterpenes in *T. balsamita* (Baczek et al. 2017). Baranauskiene et al. (2014) identified EM from Lithuania as β-thujone (**186**) chemotype (86%) together with *α*-thujone (**185**) (2.5%) and sabinene (**161**) (2.5%). The composition of *T. macrophyllum* EM is presented in Table 1. Radulovic et al. (2010) found eucalyptol (**173**) (8.6%), camphor (**172**) (6.4%), *γ*-eudesmol (**214**) (6.2%) and isobornyl acetate (9.5%) in the EM from aerial parts of *T. macrophyllum*. In Turkish populations, the main components are *β*-eudesmol (**209**) (21.4%) and cis-chrysanthenol (**182**) (12%) (Demirci and Baser 2007). Polatoğlu et al. (2013) analyzed EM from flowering heads and leaves separately and identified 64.9% oxidized sesquiterpenes (*γ*-eudesmol (**209**), sesquivalandulol (**213**), and copaborneol (**216**) in the flowering heads, and 47.2% oxidized monoterpenes (eucalyptol (**173**), bornyl acetate (**180**), borneol (**178**), and *β*-thujone (**186**)) in the leaves. A different EM profile from flowering heads and leaves of *T. macrophyllum* (origin Italy) was found by Venditti et al. (2018). EM from the flowering heads is characterized by 39.4% oxidized monoterpenes and 28% oxidized sesquiterpenes; the individual components are 10-epi-*γ*-eudesmol (**204**) (12.5%), camphor (**172**) (11%), linalool (**171**) (10.8%) and eucalyptol (**173**) (8.8%). The leaves EM contains more sesquiterpene hydrocarbons (39.3%) - mainly germacrene D (**198**) (30.9%) and oxylated monoterpenes (25.4%), of which camphor (**172**) (11.1%) and eucalyptol (**173**) (5.5%). Oxidized sesquiterpenes in the leaves were fewer and included 10-epi-γ-eudesmol (**209**) (3.9%) and caryophyllene oxide (**208**) (3.4%). Significant amount of p-methyl benzyl alcohol was found in *T. macrophyllum* EM (Abad et al. 1995). Recently, the dominant compounds of *T. parthenium* EM were found to be camphor (**172**) (45.47%), trans-chrisantenyl acetate (**187**) (21.65%), camphene (160) (9.48%), and cis-isogeraniol (5.42%) (Lechkova et al. 2023), while camphor (**172**) (25.24%), trans-chrysantenyl acetate (**187**) (18.35%), cis-verbenol (10.58%), thujone (**185**) (6.06%), eucaliptol (**173**) (5.99%), and α-campholenal (5.98%) were the main compounds in *T. vulgare* (Karcheva-Bahchevanska et al. 2023).

Sesquiterpene lactones (STLs)

STLs in *Tanacetum* species distributed in Bulgaria were studied by Todorova and Evstatieva (2001) (Fig. 2) and correspond to their taxonomic position - in two sections of *Tanacetum* (*T. vulgare*, *T. achilleifolium*, *T. millefolium*) and sect. Pyrethrum (*T. corymbosum*, *T. macrophyllum*, *T. parthenium*). *T. achilleifolium* and *T. millefolium* produce only STLs of eudesmanolid type; they are the only Bulgarian species in which 11, 13 dihydroeudesmanolides were determined. Three chemotypes have been established for *T. vulgare*: with germacranolides, with eudesmanolides and without STLs (Todorova and Evstatieva 2001). Similar results were found for the species from Italy (Rosselli et al. 2012). *T. vulgare* STLs have α- methylene-γ-lactone residue (Fig. 2) (Abad et al. 1995). *T. corymbosum* contains lactones from the small group of eudesman-12,8-olides, which are not typical for the genus (Todorova and Evstatieva 2001).

T. macrophyllum and *T. parthenium* have the all three types of STLs, but mostly - guaianolides, which have a variety of *O*-containing functional groups. Among the STLs in *T. macrophyllum*, the guaianolides macrotanacin (**223**) and tanaphyllin (**224**) (found in large quantities in the species originating in Bulgaria) should be noted. A major STL in *T. parthenium* is parthenolide (**239**). Douglanin (**258**) has been isolated from *T. praeteritum*, *T. argenteum* subsp. *canum*, *T. vulgare* ssp. *siculum* (Gören 1995; Gören and Tahtasakal 1997; Rosselli et al. 2012). Ludovicin B (**257**), A (**256**) were found in *T. praeteritum* and *T. vulgare*, and 1α-hydroxy-1-deoxyarglanin (**259**)- *T. praeteritum* (Gören 1995; Rosselli et al. 2012).

Ethnopharmacological data on the genus *Tanacetum*

T. parthenium is used as an antipyretic and anti-inflammatory agent, for headaches and earaches (Ivanescu et al. 2018); the leaves are used in English folk medicine to prevent migraines (Kumar and Tyagi 2013). *T. balsamita* has a sedative, diuretic, carminative and expectorant effect (Venditti et al. 2018). *T. vulgare* is a diuretic, anthelmintic and acaricidal agent (Baczek et al. 2017; Dere and Akcin 2017; Ivanescu et al. 2018), used as an antispasmodic for stomach pains. In Morocco, *T. vulgare* is applied as an antihypertensive and diuretic agent (Lahlou et al. 2007). In Bulgaria, the leaves and flowering heads are used as an antiseptic and against dandruff (Kumar and Tyagi 2013).

In Russia, an infusion of *T. vulgare* flowering heads is used for wound healing, as an analgesic and as an appetite stimulant (Devrnja et al. 2017). In the Mediterranean region, the resistance of *T. corymbosum* flowering heads is used in parasitic intestinal diseases (worms) (Venditti et al. 2018). The leaves can be used as a spice instead of cinnamon and nutmeg; sometimes, it is used in preparing of omelets, salads, cakes and spice mixes (Baranauskiene et al. 2014). Recommended for its strong aroma, the plants are used as a repellent against flies and other insects.

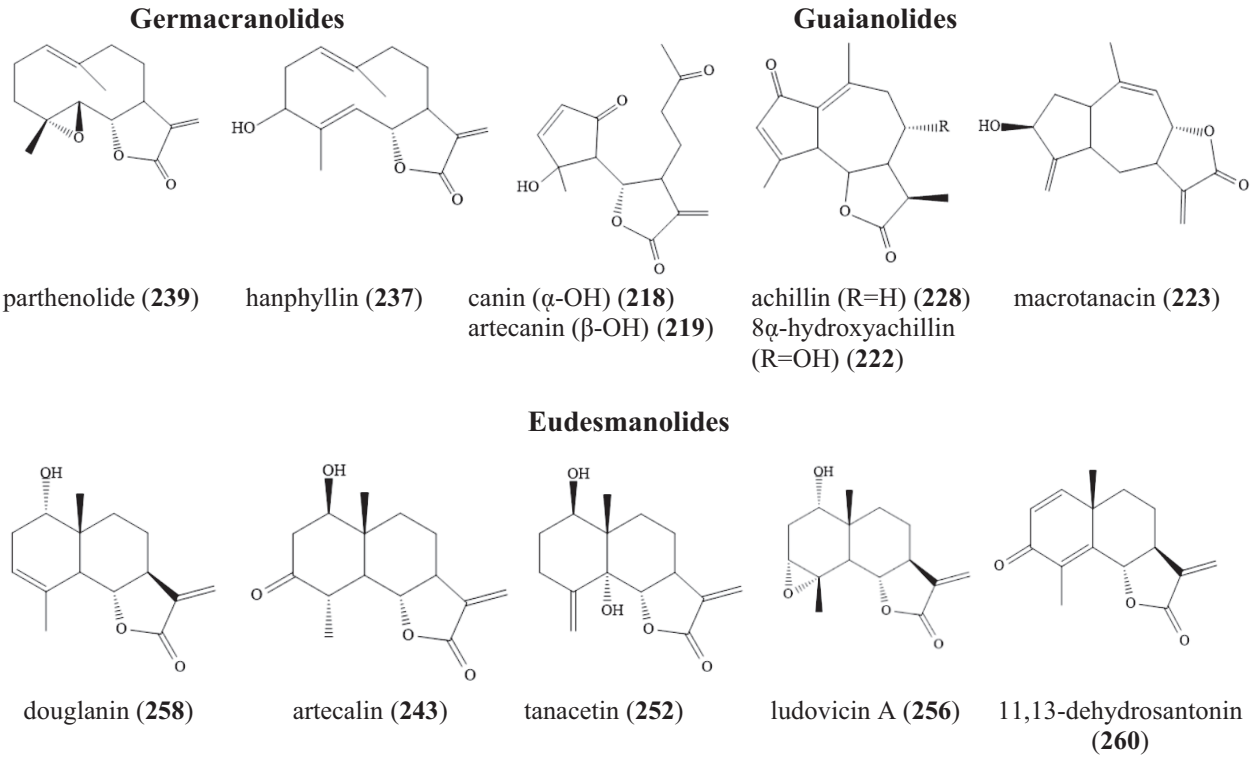


Figure 2. Structure of STLs (germacranolides, guaianolides and eudesmanolides) in species of the genus *Tanacetum*.

Phytopharmacological studies of extracts and compounds from species of the genus *Tanacetum*

The established phytopharmacological effects are mainly of crude extracts or fractions, and essential oils (EM). Comparative analyzes and conclusions are quite difficult to be made by the fact that chemotypes exist for each species, e.g., up to 30 chemotypes for *T. vulgare*. The biological activity of the plant substances is largely associated with the content of STLs, acylquinic acids and methoxylated flavones and flavonols, which are characteristic of the Asteraceae family. Kumar and Tyagi (2013) summarize data on traditional use and pharmacological studies of essential oils of *Tanacetum* species. The most important data on the phytopharmacology of the genus are systematized in Table 2.

Antioxidant activity

Fraisse et al. (2011) established a correlation between the antioxidant activity, the total dihydroxycinnamic derivatives and the total phenols in extracts of Asteraceae species, among which were *T. vulgare* and *T. parthenium*. There is a significant relationship between DPPH radical scavenging activity and TPC (R2 = 0.8904), total dihydroxycinnamic derivatives (R2 = 0.8529) and total caffeoyl derivatives (R2 = 0.7172). Thus, the antioxidant activity mainly depends on the main caffeoyl derivatives; the quantity of 3,5-dicaffeoylquinic acid (**28**) in *T. parthenium* (30.08 g/kg) was 48.92%. In a comparative study of methanolic extracts of *T. vulgare* different plant parts, TPC was found from 83.6 to 221.7 mg GAE/g dry weight, with the content decreasing in the order roots>leaves>-flowering heads>stems (Devrnja et al. 2017). In the DPPH test, the roots have the highest activity with an IC_{50} of 44 μg/ml, followed by the flowering heads – 58.3 μg/ml. The Pearson correlation coefficient between the two indicators is R=-0.8 with R2 = 0.64. In the test for reducing power, the root extract was the most active: in a concentration of 0.1 mg/ml – 0.123, 1 mg/ml – 0.903 (Trolox 0.926).

Applying the biorefinery (agrorefinery) concept, Baranauskiene et al. (2014) compared the antioxidant activity of EO and different products of the residue after hydrodistillation (water extract, acetone balsam and acetone extract). The highest TPC in the aqueous extract (142.30 mg GAE/g dry extract) is also consistent with the highest antioxidant activity in the DPPH assay (IC_{50} 1.33 mg/ml), ABTS (IC_{50} 1.40 mg /ml), FRAP (546.20 μM Trolox/g extract) and ORAC (11947.5 μM Trolox/g extract). The antioxidant potential of two varieties of *Chrysanthemum balsamita* var. *balsamita* and *Ch. balsamita* var. t*anacetoides* was established in DPPH assays (IC_{50} 59.70 and 121.13 μg/ml, respectively), SNPAC (silver nanoparticle antioxidant capacity) (71.44 and 34.25 μMGAE/g, respectively), EPR radical detection (integral intensity 228.04 and 361.50, respectively) (Benedec et al. 2016).

According to Baranauskiene et al. (2014), the antioxidant activity of the water extracts is due to acylquinic acids - mono- and dicaffeoylquinic acids; the effect of 3,5-dicaffeoylquinic acid (**28**) (Juan-Badaturuge et al. 2009) as well as that of flavonoids (Juan-Badaturuge et al. 2009; Pukalskas et al. 2010; Benedec et al. 2016) are specifically discussed.

The antioxidant potential of *Tanacetim* species is exclusively associated with the content of phenolic acids. The high antioxidant potential of *T. vulgare* is due to the high content of caffeic (**16**), rosmarinic (**68**) and ferulic (**20**) acids (Baczek et al. 2017). According to Baranauskiene et al. (2014), mono- and dicaffeylquinic acids are with the most pronounced effect as well as 3,5-dicaffeylquinic acid (**28**) and flavonoids (substituted with hydroxyl groups in ring B and C) (Juan-Badaturuge et al. 2009).

In the antioxidant assays of *T. vulgare* extracts, the hydroalcoholic aerial parts extract exhibited the strongest radical scavenging activity (up to 148 mg TE/g and 176 mg TE/g for DPPH and ABTS, respectively) and reducing power (404 and 188 mg TE/g for CUPRAC and FRAP) (Ak et al. 2021). The best metal chelating activity and total antioxidant capacity in phosphomolibdenum assay was found for the infusion stem extract (25 mg EDTAE/g) and hydroalcoholic stem extract (2.07 mg TE/g). Discriminant analysis showed that radical scavenging activity (DPPH and ABTS), reducing power (CUPRAC and FRAP), and methal-chelation ability account mostly for the extract discrimination.

Antioxidant activity of *T. parthenium* was especially pronounced in the ethanolic extracts obtained by accelerated solvent extraction in terms of radical scavenging activity (Zengin et al. 2020), and notably the reducing power in the FRAP assay (up to 330 mg TE/g). Remarkable radical scavenging activity (300 mg TE/g and 573 mg TE/g for DPPH and ABTS) and reducing power (443 mg TE/g and 277 mg TE/g for CUPRAC and FRAP) was assessed for *T. macrophyllum* roots and flowering heads, respectively (Gevrenova et al. 2020). Multivariate analysis demonstrated that radical scavenging activity (DPPH and ABTS) and reducing power mostly accounted for the high antioxidant potential of *T. macrophyllum*. Generally, ABTS hold significance for the separation of the studied *T. macrophyllum* plant parts. Concerning *T. balsamita* hydromethanolic extracts, supervised partial least square discriminant analysis (PLC-DA) revealed that radical scavenging activity and reducing power have marked impact on the pronounced antioxidant potential of flower heads (Gevrenova et al. 2023). The same trend was observed for the water extracts from *T. poteriifolium* aerial parts (Zengin et al. 2019). Overall, the smallest antioxidant activity was evaluated for *T. balsamita* in comparison with *T. vulgare*, *T. macrophyllum*, *T. poteriifolium* and *T. parthenium*.

Table 2. Protective effects of plant substances and secondary metabolites in *Tanacetum* species.

Tanacetum species	Protective effects	References
Antioxidant activity		
Methanol extracts from *T. vulgare*, *T. macrophyllum*, *T. corymbosum*	*T. vulgare* showed the highest DPPH activity (IC_{50} 242.8 μg/ml) and reducing power (IC_{50} 112.06 μg/ml)	Ivanescu et al. 2018
Methanol extracts from *T. vulgare*	In DPPH assay the highest activity showed the roots with IC_{50} 44 μg/ml following by the flowering heads – 58.3 μg/mL. Reducing power of the root extract was as follows: 0.1 mg/ ml – 0.123, 1 mg/ ml – 0.903 (Trolox 0.926).	Devrnja et al. 2017
Hexan, hydroalcoholic and aqueous extracts from *T. vulgare* flower heads, stems and aerial parts	The hydroalcoholic aerial parts extract exhibited the strongest radical scavenging activity (up to 148 mg TE/g and 176 mg TE/g for DPPH and ABTS, respectively) and reducing power (404 and 188 mg TE/g for CUPRAC and FRAP). Infusion and hydroalcoholic stem extracts showed the best metal chelating activity (25 mg EDTAE/g) and total antioxidant capacity (2.07 mg TE/g).	Ak et al. 2021
Methanol extracts from *T. vulgare* and the major compound 3,5-dicaffeoylquinic acid (3,5-*di*CQA) (**28**)	DPPH assay revealed: IC_{50} 37 μg/ml for the extract; IC_{50} 9.7 μM for 3, 5-*di*CQA and IC_{50} 8.8 μM for quercetin	Juan-Badaturuge et al. 2009
Agrorefinery products from the residuces after the hydrodistiillation of essential oil from *T. vulgare*	The highest antioxidant activity showed the water extract: DPPH (IC_{50} 1.33 mg/ml), ABTS (IC_{50} 1.40 mg/ml), FRAP (546.20 μM Trolox/g extract) and ORAC (11947.5 μM Trolox/g extract).	Baranauskiene et al. 2014
Ethanolic extract from *T. macrophyllum* aerial parts	DPPH activity (IC_{50} 32.7 μg/ml); ABTS (IC_{50} 37.2 μg/ml); FRAP (361 mgTE/g)	Venditti et al. 2018
Hydroethanolic extracts from *T. vulgare* and *T. balsamita*	*T. vulgare* extract showed the higher antioxidant activity in compareison with *T. balsamita* in DPPH assay (13.86 and 13.59 μM Trolox/g, respectively) and FRAP (585.6 and 339.1 μM Trolox/g).	Baczek et al. 2017
Hydroethanolic extracts (70%) from *Chrysanthemum balsamita* var. balsamita and *Ch. balsamita* var. *tanacetoides*	DPPH assay: IC_{50} 59.70 and 121.13 μg/ml, respectively; SNPAC (silver nanoparticle antioxidant capacity): 71.44 and 34.25 μMGAE/g , EPR radical detection: integral intensity 228.04 and 361.50	Benedec et al. 2016
Ethanolic extracts from *T. parthenium* obtained by accelerated liquid extraction (ALE), microvawe extraction, macearion, Soxhlet and sonication	The highest activity showed the extracts obtained by ALE as follows: DPPH (105.26 mg TE/g), ABTS (179.19 mg TE/g), reducing power CUPRAC (485.82 mg TE/g) and FRAP (330.92 mg TE/g). The highest metal chelating capacity and total antioxidant activity showed the extract by maceration: 23.30 mg EDTAE/g, and 2.48 mM TE/g, respectively.	Zengin et al. 2020
Ethylacetate, methanol and water extracts from *T. poteriifolium*	The highest activity showed the water extracts as follows: DPPH (238.12 mg TE/g), ABTS (282.54 mg TE/g), reducing power CUPRAC (555.03 mg TE/g) and FRAP (285.79 mg TE/g). The highest metal chelating capacity showed the ethylacetate extract (41.07 mg EDTAE/g).	Zengin et al. 2019
Methanol-aqueous extractd from flowering heads, leaves and roots of *T. balsamita*.	The flowering heads extracts showed the highest DPPH (84.54 mg TE/g), ABTS (96.35 mg TE/g), reducing power CUPRAC (151.20 mg TE/g) and FRAP (93.22 mg TE/g). The highest metal chelating capacity showed the ethylacetate extract (36.16 mg EDTAE/g).	

Tanacetum species	Protective effects	References
Enzyme inhibitory activity		
Ethanolic extract from *T. macrophyllum* aerial parts	AchE inhibitory activity with IC_{50} 0.57 mg/ml, 17.89 GALE (galantamin)/g); Galantamin (IC_{50} 10.2 mg/ml)	Venditti et al. 2018
Ethanolic extract from *T. parthenium*	α-Glucosidase inhibitory activity 1.63–1.67 mM ACAE (acarbose)/g extract and against α-amylase - 0.51–0.56 mM ACAE/g BChE inhibitory activity (4.63–5.21 mg GALAE/g); AChE inhibitory activity (2.84–3.38 mg GALAE/g)	Zengin et al. 2020
Hexane, hydroalcoholic and aqueous extracts from *T. vulgare* flowering heads, stems and aerial parts	Flower heads hydroethanolic extract showed the best AchE and BChE (1.95 and 1.79 mg GAE/g), and α-glucosidase (10.77 mg ACAE/g) inhibitory activity, while hexan extract inhibited tyrosinase (31.81 mg KAE/g) and α-amylase (0.53 mg ACAE/g).	Ak et al. 2021
Methanol-aqueous extracts from *T. macrophyllum* flowering heads, aerial parts and roots.	Aerial parts hydroethanolic extract showed the best AchE and BChE (4.46 and 2.26 mg GAE/g), α-glucosidase (1.45 mg ACAE/g) and tyrosinase (107.64 mg KAE/g) inhibitory activity, while flowering heads extract inhibited α-amylase (0.65 mg ACAE/g).	Gevrenova et al. 2020
Methanol-aqueous extractd from flowering heads, leaves and roots of *T. balsamita*.	Leaves hydroethanolic extract showed the best AchE and BChE (2.11 and 2.43 mg GAE/g), α-amylase (0.44 mg ACAE/g) and tyrosinase (54.65 mg KAE/g) inhibitory activity, while the roots extract inhibited α-glucosidase (0.71 mg ACAE/g)	Gevrenova et al. 2023
Anti-inflammatory activity		
Methoxylated flavones and flavonols from *T. parthenium* and *T. vulgare* leaves	Methoxylated flavonols inhibit the arachidonic acid metabolism by cyclooxygenase and 5-lipoxygenase pathways. 6-hydroxykaempferol 3,6-dimethyl ether and santin (6-hydroxykaempferol 3,6,4'-trimethyl ether with IC_{50} 27 and 58 μM, respectively.	Williams et al. 1999a
Acetone extracts and fractions from *T. parthenium*, *T. vulgare*, *T. niveum* and *T. ptarmiciflorum* (the content of parthenolide (**239**) was up to 2.62% (*T. niveum*)	In the model of human polymorphonuclear leukocytes IC_{50} was 0.79 and 1.32 mg dry weight leaves/mL blood for *T. parthenium* and *T. niveum*, respectively. The activity was related to the proteinkinase inhibition.	Brown et al. 1997
Commercial aqueous extract from *T. parthenium* (0.5%) parthenolide (**239**)	The extract reduced PGE2 release and IL-1β gene expression in ex-vivo mice cortex, while IL-10 and BDNF gene expressions increased. The extract could be effective in controlling the inflammatory pathways that occur during cortical-spreading depression.	Recinella et al. 2020
Neuromodulatory activity		
Hexane extracts from *T. vulgare* flowering heads, stems and aerial parts	At 10 μg/ml (non toxic concentation) they reduced MDA, TNFα and BDNF (brain-derived neurotrophic factor) gene expression and stimulated norepinephrine release in HypoE22 cells. An involvement of the hexane extracts in the modulation of the hypothalamic appetite-regulating network could be suggest.	Ak et al. 2021
Commercial aqueous extract from *T. parthenium* (0.5%) parthenolide (**239**)	The extract (10–100 μg/mL) decreased in concentration dependant manner the extracellular dopamine level and in the range 10-50 μg/mL increased the dopamine transporter (DAT) gene expression. In silico interaction between parthenolide (**239**) and DAT binding site was found.	Recinella et al. 2020
Antibacterial activity		
T. vulgare and *T. balsamita* Essential oil Alcohol-water extracts	G(+/-) bacteria: *B. cereus*, *B. subtilis*, *S. epidermidis*, *S. aureus*, *E. coli*, *Salmonella enterica* (MIC 1–32 mg/ml); *K. pneumoniae*, *Y. enterocolitica* (MIC 1–8 mg/ml). *T. balsamita* essential oil in 4 mg/ml inhibited 58% of the strains, while *T. vulgare* - 42%. G(+) bacteria (MIC 1–16 mg/ml); *K. pneumoniae*, *Y. enterocolitica* (MIC 2–4 mg/ml). *T. balsamita* extract in 4 mg/ml inhibited 47% of the strains, while *T. vulgare* - 26%.	Baczek et al. 2017
Sesquiterpene lactone parthenolide (**239**) from *T. parthenium* leaves and fruits Essential oil from stem and flowering heads of *Tanacetum argyrophyllum* var. argyrophyllum	Antibacterial activity against G (+) bacteria *Bacillus cereus* (125 μg/ml essential oil)	Kumar and Tyagi 2013; Polatoglu et al. 2010
Methanolic extracts from *T. vulgare*, *T. macrophyllum*, *T. corymbosum*	Moderate activity against G(+) bacteria: *Staphylococcus aureus*: *T. corymbosum* (MIC 3.12 mg/ml); *T. vulgare*, *T. macrophyllum* (MIC 6.25 mg/ml).	Ivanescu et al. 2018
Essential oil from *T. vulgare*	Antibacterial activity against G (+/-) bacteria *Escherichia coli*, *Enterobacter cloacae* (MIC 0.03 and 0.11 mg/ml), and *Staphylococcus aureus* (MIC 0.21 mg/ml) which possess an outer lipopolysaccharide covering, that restricts diffusion of hydrophobic compounds.	Devrnja et al. 2017
Antifungal activity		
Methanolic extracts from *T. vulgare*, *T. macrophyllum*, *T. corymbosum*	Against *Candida parapsilosis* and *Candida albicans* as follows: *T. vulgare* > *T. macrophyllum* > *T. corymbosum.*	Ivanescu et al. 2018
T. vulgare essential oil (contains mainly oxygenated monoterpenes, the major compound is *trans*-chrysanthenyl acetate (**187**))	Against pathogenic fungi *Aspergillus*, *Trichoderma* and *Penicillium*; the highest activity towards *P. funiculosum* with MIC 0.002 mg/ml (bifonazole and ketoconazol have MIC 0.2 mg/ml)	Devrnja et al. 2017
Antiviral activity		
Different polarity fractions from methanolic extracts of *T. vulgare* aerial parts and roots	Petroleum ether and ethylacetate fractions revealed the highest activity against Herpes simplex viruses HSV-1 and HSV-2 showing a good selectivity indexes and effective concentrations (EC_{50}) 69.9 and 95.7 μg/ml (HSV-1), and 61.6 and 59.4 μg/ml (HSV-1), respectively; high activity of 3,5-*di*CQA (EC_{50} 31.1 and 46.99 μg/ml). Positive control aciclovir (EC_{50} 0.94 μg/ml)	Álvarez et al. 2011
Ethylacetate extract from *T. vulgare* and STL parthenolide (**239**)	Against HSV-1 showed EC_{50} 40 μg/ml and 0.3 μg/ml, respectively. Parthenolide (**239**) inhibited the virus replication.	Onozato et al. 2009

Tanacetum species	Protective effects	References
Anthelmintic activity, agaricidal, insecticidal and repellent activity		
Crude extract and essential oil (EO) (84% *β*-thujon **186**) from *T. vulgare*	Crude extract in 50, 100, 200 µg/mL and EO (200 µg/mL) showed caused 100% mortality of all adult worms of *Schistosoma*	Godinho et al. 2014
Extract from *T. parthenium* aerial parts and parthenolide (**239**)	The extract (200 µl/ml) and parthenolide (**239**) in concentrations from 12.5 to 100 µM showed caused 100% mortality of all adult worms of *Schistosoma*	de Almeida et al. 2016
EO from *T. vulgare*	EO showed agaricidal activity against *Tetranychus urticae*	Chiasson et al. 2001
Parthenolide (**239**) from *T. argentums* ssp. *argenteum*	Parthenolide (**239**) showed agaricidal activity against *Spodoptera littoralis* worms	Kumar and Tyagi 2013
Steam distillate of fresh leaves and flowers of *T. vulgare*	Repellents to Colorado potato beetles, *Leptinotarsa decemlneata.*	Kumar and Tyagi 2013
Cytotoxic activity		
Methanolic extracts from *T. vulgare*, *T. macrophyllum*, *T. corymbosum*	In 200 µg/ml shoed cytotoxicity against a cell line HeLa as follows: 69.87% (*T. macrophyllum*). 77.68% (*T. vulgare*) and 93.71% (*T. corymbosum*), and a cell line Vero (95%–96.98%)	Ivanescu et al. 2018
Chloroform extract from *T. vulgare*	showed cytotoxicity towards cell lines HeLa (IC_{50} 47.72 µg/ml), A2780 (IC_{50} 37.53 µg/ml), MCF7(IC_{50} 27.98 µg/ml) by cell cycle arrest (phase S) and apoptosis.	Gospodinova et al. 2015
Methanolic extracts from *T. vulgare* leaves and flowering heads	showed cytotoxicity against a cell line HeLa (IC_{50} < 100 µg/ml). The activity was related to the methoxylated flavonoids nepetin, hispidulin and eupatilin.	Devrnja et al. 2017
Sesquiterpene lactones (STLs) eudesmanolide type isolated from *T. vulgare* ssp. *siculum*	Shoed cytotoxicity against a cell line A549. The main STL is douglanin with IC_{50} 15.3 µM.	Rosselli et al. 2012
EO from *T. macrophyllum* leaves (germacrene D (**198**) and 10-epi-γ-eudesmol (**209**)) Ethanolic extract from *T. macrophyllum* aerial parts (contains apigenin (**97**), apigenin 7-glucoside (**98**), chlorogenic (**23**) and 3, 5-*di*CQA (**28**))	EO showed cytotoxicity against a cell lines HCT116 and A375 with IC_{50} 8.5 and 9.17 µg/ml, respectively, and a cell line (positive control cisplatin (0.4 and 2.5 µg/ml). The extract showed cytotoxicity against A375 and HCT116 with IC_{50} 32.5 and 35.6 µg/ml	Venditti et al. 2018

HeLa- human cervical adenocarcinoma cell line; A2780- human ovarian cancer cell line; MCF7 and MDA-MB 231- breast cancer cell line; A549- human lung carcinoma cell line; A357-melanoma cell line; HCT116-colon carcinoma cell line.

Enzyme inhibitory activity

The bio-inhibitory effects of EO can be explained rather by the synergistic effects of their components. The AChE inhibitory potential of some EO terpenes of *T. macrophyllum* flowering heads and leaves was determined: 1,8-cineole (**173**) (IC_{50} = 0.67 mM), camphor (**172**) (IC_{50} > 10 mM), germacrene D (**198**) also has proven inhibitory capacity (Venditti et al. 2018).

On the other hand, the interaction between different terpenes plays an important role, in the light of synergism between monoterpenes and antagonism between monoterpenes and sesquiterpenes. EO of *T. macrophyllum* flowering heads and leaves had a lower AChE inhibitory effect (IC_{50} 15.23 and 1049 mg/ml) compared to the ethanolic extracts (IC_{50} 0.57 mg/ml). This is a 60-fold lower value than that of galantamine (positive control). In many cases, the insecticidal activity of plant extracts is due to AChE inhibitory activity.

In a comparative study of enzyme inhibitory activity of ethanol extracts of *T. parthenium* obtained with different extraction methods, activity towards α-glucosidase (1.63–1.67 mM ACAE (acarbose)/g extract) and α-amylase (0.51–0.56 mM ACAE/g) was assayed (Zengin et al. 2020). A strong inhibitory effect on glucosidase combined with a moderate one on amylase has a good effect on postprandial hyperglycemia, which is the main cause of complications such as diabetic retinopathy, neuropathy, cardiovascular problems in diabetics. The inhibitory activity on tyrosinase was from 163.67 mg KAE (kojic acid)/g extract to 183.07 mg KAE/g extract obtained by ultrasound and accelerated liquid extraction, respectively. The inhibition of cholinesterases is more pronounced on BChE (4.63–5.21 mg GALAE (galantamine)/g), and on AChE - 2.84–3.38 mg GALAE/g extract (Zengin et al. 2020). In this regard, increased activity of AChE was found in the early stages of dementia, and of BChE – in the later stage. Hierarchical clustering combined with PCA showed that ultrasound extraction was the most distinct from the other extraction methods and was associated with lower antioxidant activity in terms of DPPH, ABTS, FRAP, CUPRAC and tyrosinase inhibitory activity, but with pronounced metal-chelating ability and amylase inhibition (Zengin et al. 2020).

T. vulgare flowering heads hydroethanolic extract showed the best AChE and BChE (1.95 and 1.79 mg GAE/g, respectively), and α-glucosidase (10.77 mg ACAE/g) inhibitory activity, while hexane extract inhibited tyrosinase (31.81 mg KAE/g) and α-amylase (0.53 mg ACAE/g) (Ak et al. 2021). In this context the most pronounced AChE inhibitory potential has been found for the *T. macrophyllum* methanol-aqueous extract (up to 4.46 mg GAE/g) (Gevrenova et al. 2020). It's worth noting that the *T. balsamita* methanol-aqueous extracts exerted lipase inhibitory activity up to 8.15 mg OE (orlistat)/g (Gevrenova et al. 2023).

Anti-inflammatory activity

Methoxylated flavonoids isolated from leaves of *T. parthenium* and/or *T. vulgare* have been investigated for inhibi-

tion of cyclooxygenase and 5-lipoxygenase (Williams et al. 1999a). The *T. parthenium* flavonoids 6-hydroxykaempferol 3,6-dimethyl ether (**88**) and santin (6-hydroxykaempferol 3,6,4'-trimethyl ether) (**127**) have the same enzyme inhibitory activity profile, but santin is more active (IC_{50} 27 and 58, respectively μM). Quercetagetin 3,6,3'-trimethyl ether (**91**) was more active against cyclooxygenase (IC_{50} 22 μM). Nepetin (6-hydroxyluteolin) (**124**) and jaceosidin (6-hydroxyluteolin 6,3'-dimethyl ether) (**129**) from *T. vulgare* leaves inhibited both enzymes but were less active against cyclooxygenase (IC_{50} 61 and 89 μM, respectively) compared to the corresponding flavonols. Methoxylated flavonoids inhibit the two main pathways of arachidonic acid metabolism – the cyclooxygenase and 5-lipoxygenase pathways.

The anti-inflammatory activity of *T. parthenium*, *T. vulgare*, *T. niveum*, *T. ptarmiciflorum* was investigated in a human polymorphonuclear leukocyte model (Brown et al. 1997). In the acetone extracts of the leaves and their fractions, the germacranolide parthenolide (**239**) was found, which is associated with the anti-inflammatory effect of *T. parthenium* and *T. niveum* (1.72% and 2.62% parthenolide (**239**)); The IC_{50} was 0.79 and 1.32 mg leaf dry weight/ml blood, respectively. This activity is due to inhibition of protein kinase C.

Antiviral activity

In a comparative study of the antiviral activity of different polarity fractions of methanolic extracts of *T. vulgare* aerial parts and roots, and compounds of the species on Herpes simplex viruses HSV-1 and HSV-2, it was found that the petroleum ether and ethyl acetate fractions were the most active with a good selective index (Álvarez et al. 2011). The mean effective concentrations (EC_{50}) were 69.9 and 95.7 μg/ml (HSV-1) and 61.6 and 59.4 μg/ml (HSV-1), respectively. The isolated compound with the highest activity was 3,5-dicaffeylquinic acid (**28**) (EC_{50} 31.1 and 46.99 μg/ml against HSV-1 and HSV-2, respectively). Among the other compounds, the flavonoid axillarin (**90**) showed strong activity against HSV-2 - EC50 42.7 μg/ml.

STL parthenolide (**239**) (germacran type) showed the highest cytotoxicity at 25 μg/ml and had no antiviral activity at a concentration 1.5 times lower than the cytotoxic concentration. Parthenolide (**239**) was found from 0.33% in the crude extract to 2.7% in the chloroform fraction. Antiviral activity of *T. vulgare* is mainly associated with 3,5-dicaffeylquinic acid (**28**). Ethyl acetate extract of *T. vulgare* and parthenolide (**239**) were tested for HSV-1 antiviral activity; they have an IC_{50} of 40 μg/ml and 0.3 μg/ml, respectively (Onozato et al. 2009). Parthenolide (**239**) exhibits activity on viral replication.

Cytotoxic activity

T. vulgare ssp. *siculum* chloroform extract was analyzed and 5 STLs from the group of eudesmanolides were isolated, which were tested for cytotoxicity against lung carcinoma cell lines A549 and hamster lung fibroblast-like line V79379A. IC_{50}s were 15.3–59.4 μM and 5.0–33.4 μM, respectively (Rosselli et al. 2012). The main STL douglanin (**258**) shows the highest activity. STL parthenolide (**239**) is involved in the processes of oxidative stress in prostate carcinoma cells by activating NADPH oxidase - the formation of ROS is the basis of the effects on hepatocellular carcinoma. The compound has anti-angiogenesis and anti-metastatic activity (Shields 2017). Methanol extracts of *T. vulgare* leaves and flowering heads have a cytotoxic effect on HeLa cell line - IC_{50} is below 100 μg/mL (Devrnja et al. 2017). The activity is associated with the content of methoxylated flavonoids nepetin (**124**), hispidulin (**125**) and eupatilin (**127**).

Neuromodulatory activity

Toxicological profile of *T. vulgare* extracts from different polarity was assayed in the brine shrimp (*Artemia salina*) lethality test where all of them showed a high degree of toxicity with $IC_{50} < 2$ mg/ml (Ak et al. 2021). The cytotoxic effects towards HypoE22 cells was found in the concentration range 50–100 μg/mL.

The bioinformatics analysis through the SwissTargetPrediction platform predicted interaction of flavonoids axillarin (**90**), quercetagetin -3,6,3'(4')-trimethyl ester (**94**) and hesperetin (**146**) together with quinic (**70**), chlorogenic (**23**) and dicaffeoylquinic acid (**28**), and parthenolide (**239**) with target proteins (hydrolase), electrochemical transporters and transcription factors involved in neuromodulation and neuroprotection (Ak et al. 2021).

The possible neuroprortective effects of *T. vulgare* extracts was studied on hypothalamic HypoE22 cells (Ak et al. 2021). At 10 μg/ml (non toxic concentation) hexane extracts reduced the marker of oxidative stress MDA (malonyldialdehyde) and gene expression of TNFα (pro-inflammation cytokine). It's worth noting that down regulation of the BDNF (brain-derived neurotrophic factor) gene expression was found. On the other hand, the hexane extracts exerted stimulating effects on the norepinephrine levels in HypoE22 cells. All together, the aforementioned effects suggest putative involvement of the *T. vulgare* hexane extracts in the modulation of the hypothalamic appetite-regulating network. However, the reduced BDNF gene expression could account also for potential neurotoxicity following the administration of *T. vulgare* herbal extracts.

T. parthenium (feverfew), has been traditionally employed as a phytotherapeutic remedy in the treatment of migraine (Guibot et al. 2017; Moscano et al. 2019). *T. parthenium* crude extract and STL parthenolide (**239**) inhibit serotonin and platelet aggregation relevant to migraine (Marles et al. 1992). Aqueous extract of the species has been shown to inhibit prostaglandin biogenesis and gives a very good result in migraine patients without side effects.

The dopaminergic pathways are key targets for novel pharmacological approaches in counteracting migraine attacks. In this context, anti-inflammatory and neuromodulatory effects of a commercial aqueous *T. parthenium* extract was studied in an *ex vivo* model of cortical spreading depression (CSD) in mice cortex. It reduced prostaglandin

G2 (PGE2) release and IL-1β gene expression in ex-vivo mice cortex, while up-regulation of IL-10 and BDNF gene expressions was observed. The extract could be effective in controlling the inflammatory pathways that occur during CSD. In the concentration range 10–100 μg/mL the extract decreased in concentration dependant manner the extracellular dopamine level, while between 10 and 50 μg/mL it increased the dopamine transporter (DAT) gene expression. *In silico* interaction between parthenolide (**239**) and DAT binding site was found.

Plant substances and products containing *Tanacetum* sp.

The species *T. parthenium* (L.) Schultz Bip is included in the European Pharmacopoeia. (European Pharmacopoeia 2008). A purified extract of flavonoids and phenolic acids from tansy flowering heads under the name Tanacechol is registered in Russia as a choleretic and antispasmodic agent, which is used in cholecystitis and biliary dyskinesias. SeptimebTM and Setarud (IMODTM) are plant extracts that include tansy and are used in the therapy of sepsis and HIV-positive patients, respectively (Paydary et al. 2012; Pourdast et al. 2017). In Romania, there are herbal supplements of tansy flowering heads in the form of hydroalcoholic extracts and glycerine macerates (Ivănescu et al. 2018).

The commercial EO product from tansy is a thujone type; despite its protective effects, in high concentrations thujone is toxic. The US FDA (Food and Drug Administration) restricts the use of tansy in alcoholic beverages due to the toxic effects of thujone. EMA (European Medicinal Agency) and EC (European Commission) recommend intake of thujone (**185** and **186**) in products from 3 to 7 mg/day (EMA 2012). Reception with products from the diet of the order of 1 mg on average has no special objections.

Conclusion

Several *Tanacetum* species are renowned for their ethnomedicinal use in the countries of Southeastern Europe as flavor, carminative, antidiabetic, antiviral and analgesic agents, for alleviation of migraine attask, kidney and stomach problems. Latest studies provide new insights on the *Tanacetum* species in terms of phytochemical characterization of extracts obtained by different extraction methods and solvents highlighting the efficiency of accelerated liquid extraction and hydroalcoholic and hexane extracts. With recent exponential developmet of metabolite and biological profiling, in combination with multivariate data analysis, in-depth studies on *T. vulgare*, *T. macrophyllum*, *T. balsamita*, *T. parthenium* and *T. poteriifolium* bring a more extended view on the secondary metabolites and the mode of action of the taxa. Liquid chromatography-high resolution mass spectrometry/diodarray analyses integrated with an assessment of antioxidant and enzyme inhibitory potential allowed for the identification/annotation of more than 100 secondary metabolites emphasizing exceptional variety of acylquinic acids and methoxylated flavones and flavonols in *T. macrophyllum*, *T. vulgare* and *T. balsamita* flowering heads and aerial parts along with sesquiterpenes and sesquiterpene lactones. In addition to evoking an antioxidant response, *Tanacetum* extracts/isolated compounds displayed inhibitory activity towards acetylholinesterases and enzymes involved in carbohydrate metabolism which generates further interest in the species as potential candidates for the management of neurodegenerative conditions and metabolite syndrome. Because the down-regulation of prostaglandin and dopamine release supported by the bioinformatics analysis, the inhibition of dopaminergic pathway may be therapeutic target for the treatment of migraine. It is worth noting that further *in vivo* studies are needed to evaluate health-promoting application of *Tanacetum* extracts and isolated metabolites in pharmaceutical scale.

Acknowledgments

This study is financed by the European Union-NextGenerationEU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, project No. BG-RRP-2.004-0004-C01.

References

Abad MJ, Bermejo P, Villar A (1995) An approach to the genus *Tanacetum* L. (Compositae): Phytochemical and pharmacological review. Phytotherapy Research 9: 79–92. https://doi.org/10.1002/ptr.2650090202

Ak G, Gevrenova R, Sinan KI, Zengin G, Zheleva D, Mahomoodally MF, Senkardes I, Brunetti L, Leone S, Di Simone SC, Recinella L, Chiavaroli A, Menghini L, Orlando G, Ferrante C (2021) *Tanacetum vulgare* L. (Tansy) as an effective bioresource with promising pharmacological effects from natural arsenal. Food and Chemical Toxicology 153: 112268. https://doi.org/10.1016/j.fct.2021.112268

Álvarez AL, Habtemariam S, Juan-Badaturuge M, Jackson C, Parra F (2011) *In vitro* anti HSV-1 and HSV-2 activity of *Tanacetum vulgare* extracts and isolated compounds: An approach to their mechanism of action. Phytotherapy Research 25: 263–301. https://doi.org/10.1002/ptr.3382

Baczek KB, Kosakowska O, Przybyl JL, Pióro-Jabrucka E, Costa R, Mondello L, Gniewosz M, Synowiec A, Węglarz Z (2017) Antibacterial and antioxidant activity of essential oils and extracts from costmary (*Tanacetum balsamita* L.) and tansy (*Tanacetum vulgare* L.). Industrial Crops and Products 102: 154–163. https://doi.org/10.1016/j.indcrop.2017.03.009

Baranauskiene R, Kazernaviciute R, Pukalskiene M, Mazdzieriene R, Venskutonis PR (2014) Agrorefinery of *Tanacetum vulgare* L. into valuable products and evaluation of their antioxidant properties and phytochemical composition. Industrial Crops and Products 60: 113–122. https://doi.org/10.1016/j.indcrop.2014.05.047

Benedec D, Filip L, Vlase L, Bele C, Sevastre B, Raita O, Olah N-K, Hanganu D (2016) *In vitro* study of antioxidant activity and phenolic content of *Chrysanthemum balsamita* varieties. Pakistan Journal of Pharmaceutical Sciences 29: 1359–1364.

Bremer K (1994) Asteraceae: Cladistics and Classification. Timber Press, Portland.

Brown AMG, Edwards CM, Davey MR, Power JB, Lowe KC (1997) Effects of extracts of *Tanacetum* species on human polymorphonuclear leucocyte activity *in vitro*. Phytotherapy Research 11: 479–484. https://doi.org/10.1002/(SICI)1099-1573(199711)11:7%3C479::AID-PTR129%3E3.0.CO;2-W

Chiasson H, Bélanger A, Bostanian N, Vincent C, Poliquin A (2001) Acaricidal properties of *Artemisia absinthium* and *Tanacetum vulgare* (Asteraceae) essential oils obtained by three methods of extraction. Journal of Economic Entomology 94(1): 167–171. https://doi.org/10.1603/0022-0493-94.1.167

de Almeida LMS, de Carvalho LSA, Gazolla MC, Pinto PLS, da Silva MPN, de Moraes J, da Silva Filho AA (2016) Flavonoids and sesquiterpene lactones from *Artemisia absinthium* and *Tanacetum parthenium* against *Schistosoma mansoni* Worms. Evidence-Based Complementary and Alternative Medicine 2016: 9521349. https://doi.org/10.1155/2016/9521349

Demirci B, Baser KHC (2007) The essential oil composition of *Tanacetum macrophyllum* (Waldst. et Kit.) Schultz. Bip. Journal of Essential Oil Research 19: 255–257. https://doi.org/10.1080/10412905.2007.9699272

Dere S, Akcin TA (2017) Anatomical and micromorphological properties of some *Tanacetum* L. (Asteraceae) taxa from Turkey and their systematic implications. Acta Botanica Croatica 76: 138–145. https://doi.org/10.1515/botcro-2017-0005

Devrnja N, Anđelković B, Aranđelović S, Radulović S, Soković M, Krstić-Milošević D, Ristić M, Ćalić D (2017) Comparative studies on the antimicrobial and cytotoxic activities of *Tanacetum vulgare* L. essential oil and methanol extracts. South African Journal of Botany 111: 212–221. https://doi.org/10.1016/j.sajb.2017.03.028

EMA [European Medicines Agency] (2012) Public statement on the use of herbal medicinal products containing thujone EMA/HMPC/732886.

European Pharmacopoeia [8th ed.] (2008) *Tanaceti parthenii* herba 01/2008:1516. European Directorate for the Quality of Medicines and Health Care (EDQM), Council of Europe Strasbourg.

Funk VA, Susanna A, Stussey TF, Bayer RJ [Eds] (2009) Systematics, evolution, and biogeography of Compositae. IAPT, Vienna.

Gevrenova R, Zheleva-Dimitrova D, Balabanova V, Voynikov Y, Sinan KI, Mahomoodally MF, Zengin G (2020) Integrated phytochemistry, bio-functional potential and multivariate analysis of *Tanacetum macrophyllum* (Waldst. & Kit.) Sch. Bip. and *Telekia speciosa* (Schreb.) Baumg. (Asteraceae). Industrial Crops and Products 155: 112817. https://doi.org/10.1016/j.indcrop.2020.112817

Gevrenova R, Zengin G, Sinan KI, Zheleva-Dimitrova D, Balabanova V, Kolmayer M, Voynikov Y, Joubert O (2023) An in-depth study of metabolite profile and biological potential of *Tanacetum balsamita* L. (costmary). Plants 12(1): 22. https://doi.org/10.3390/plants12010022

Godinho L, de Carvalho L, Barbosa CC, Dias MM, de Faria Pinto P, Crotti AEM, Pinto PLS, de Moraes J, Da Silva Filho AA (2014) Anthelmintic activity of crude extract and essential oil of *Tanacetum vulgare* (Asteraceae) against adult worms of *Schistosoma mansoni*. Scientific World Journal 2014: 460342. https://doi.org/10.1155/2014/460342

Gören N (1995) Sesquiterpene lactones from *Tanacetum praeteritum*. Phytochemistry 38: 1261–1264. https://doi.org/10.1016/0031-9422(94)00746-G

Gören N, Tahtasakal E (1997) Sesquiterpenoids from *Tanacetum argenteum* subsp. *canum* var. *canum*. Phytochemistry 45: 107–109. https://doi.org/10.1016/S0031-9422(96)00790-X

Gören N, Arda N, Caliskan Z (2002) Chemical characterization and biological activities of the genus *Tanacetum* (Compositae). Studies in Natural Products Chemistry 27: 547–658. https://doi.org/10.1016/S1572-5995(02)80044-8

Gospodinova Z, Antov G, Angelova S, Krasteva M (2014) *In vitro* antitumor potential of Bulgarian *Tanacetum vulgare* L. on human breast adenocarcinoma cells. Results in Pharma Sciences 4: 468–472.

Gospodinova Z, Bozsity N, Ocsovszki I, Orbán-Gyapai O, Krasteva M, Zupkó I (2015) Chloroformic fraction of *Tanacetum vulgare* L. induces cell cycle arrest and apoptosis in MCF7 cells. International Journal of Pharma Sciences 5: 986–990.

Guilbot A, Bangratz M, Ait Abdellah S, Lucas C (2017) A combination of coenzyme Q10, feverfew and magnesium for migraine prophylaxis: A prospective observational study. BMC Complementary Medicine and Therapies 17: 433. https://doi.org/10.1186/s12906-017-1933-7

Ivănescu B, Tuchiluș C, Corciovă A, Lungu C, Mihai CT, Gheldiu AM, Vlase L (2018) Antioxidant, antimicrobial and cytotoxic activity of *Tanacetum vulgare*, *Tanacetum corymbosum* and *Tanacetum macrophyllum* extracts. Farmacia 66: 282–288.

Juan-Badaturuge M, Habtemariam S, Jackson C, Thomas MJK (2009) Anti-oxidant principles of *Tanacetum vulgare* L. aerial parts. Natural Product Communications 4: 1561–1564. https://doi.org/10.1177/1934578X0900401121

Karcheva-Bahchevanska D, Benbassat N, Georgieva Y, Lechkova B, Ivanova S, Ivanov K, Todorova V, Peychev L, Peychev Z, Denev P (2023) A study of the chemical composition, antioxidant potential, and acute toxicity of Bulgarian *Tanacetum vulgare* L. essential oil. Molecules 28: 6155. https://doi.org/10.3390/molecules28166155

Khatib S, Sobeh M, Faraloni C, Bouissane L (2023) *Tanacetum* species: Bridging empirical knowledge, phytochemistry, nutritional value, health benefits and clinical evidence. Frontiers in Pharmacology 14: 1169629. https://doi.org/10.3389/fphar.2023.1169629

Kumar V, Tyagi D (2013) Chemical composition and biological activities of essential oils of genus *Tanacetum* - A review. Journal of Pharmacognosy and Phytochemistry 2: 155–159.

Lahlou S, Tahraoui A, Israili Z, Lyoussi B (2007) Diuretic activity of the aqueous extracts of *Carum carvi* and *Tanacetum vulgare* in normal rats. Journal of Ethnopharmacology 110: 458–463. https://doi.org/10.1016/j.jep.2006.10.005

Lechkova B, Karcheva-Bahchevanska D, Ivanov K, Todorova V, Benbassat N, Penkova N, Atanassova P, Peychev L, Hrischev P, Peychev Z, Terziev D, Ivanova S (2023) A study of the chemical composition, acute and subacute toxicity of Bulgarian *Tanacetum parthenium* essential oil. Molecules 28: 4906. https://doi.org/10.3390/molecules28134906

Marles RJ, Kaminski J, Arnason JT, Pazos-Sanou L, Heptinstall S, Fischer NH, Crompton CW, Kindack DG, Awang DV (1992) A bioassay for inhibition of serotonin release from bovine platelets. Journal of Natural Products 55: 1044–1056. https://doi.org/10.1021/np50086a003

Moscano F, Guioducci M, Maltoni L, Striano P, Ledda MG, Zoroddu F, Raucci U, Villa MP, Parisi P (2019) An observation study of fixed-dose *Tanacetum parthenium* nutraceutical preparation for pro-

phylaxis of pediatric headache. Italian Journal of Pediatrics 45: 36. https://doi.org/10.1186/s13052-019-0624-z

Onozato T, Nakamura CV, Cortez DA, Filho BPD, Ueda-Nakamura T (2009) *Tanacetum vulgare*: Antiherpes virus activity of crude extract and the purified compound parthenolide. Phytotherapy Research 23: 791–796. https://doi.org/10.1002/ptr.2638

Paydary K, Emamzadeh-Fard S, Khorram Khorshid HR, Kamali K, SeyedAlinaghi SA, Mohraz M (2012) Safety and efficacy of Setarud (IMODTM) among people living with HIV/AIDS: A review. Recent Patents on Anti-Infective Drug Discovery 7: 66–72. https://doi.org/10.2174/157489112799829756

Polatoglu K, Demirci F, Demirci B, Gören N, Can Baser KH (2010) Antimicrobial activity and essential oil composition of a new *T. argyrophyllum* (C. Koch) Tvzel var. *argyrophyllum* chemotype. Journal of Oleo Science 59: 307–313. https://doi.org/10.5650/jos.59.307

Polatoğlu K, Karakoç ÖC, Demirci F, Gören N, Can Başer KH (2013) *Sitophilus granaries* L. (Coleoptera) toxicity and biological activities of the essential oils of *Tanacetum macrophyllum* (Waldst & Kit.) Schultz Bip. Journal of Oleo Science 64: 881–893. https://doi.org/10.5650/jos.ess15078

Pourdast A, Sanaei M, Jafari S, Mohammadi M, Khalili H, Shafiee G, Ahadi Z, Rostami M, Alizad S, Heshmat R, Mohraz M (2017) Effect of SeptimebTM as a new natural extract on severe sepsis: A randomized clinical trial. Caspian Journal of Internal Medicine 8: 35–43.

Pukalskas A, Venskutonis PR, Dijkgraaf I, van Beek TA(2010) Isolation, identification and activity of natural antioxidants from costmary (*Chrysanthemum balsamita*) cultivated in Lithuania. Food Chemistry 122: 804–811. https://doi.org/10.1016/j.foodchem.2010.03.064

Radulovic NS, Blagojević PD, Skropeta D (2010) Misidentification of tansy, *Tanacetum macrophyllum*, as yarrow, *Achillea grandifolia*: a health risk or benefit? Natural Product Communications 5: 121–127. https://doi.org/10.1177/1934578X1000500129

Recinella L, Chiavaroli A, di Giacomo V, Antolini MD, Acquaviva A, Leone S, Brunetti L, Menghini L, Ak G, Zengin G, Di Simone SC, Ferrante C, Orlando G (2020) Anti-inflammatory and neuromodulatory effects induced by *Tanacetum parthenium* water extract: Results from *in silico*, *in vitro* and *ex vivo* studies. Molecules 26: 22. https://doi.org/10.3390/molecules26010022

Rohloff J, Mordal R, Dragland S (2004) Chemotypical variation of Tansy (*Tanacetum vulgare* L.) from 40 different locations in Norway. Journal of Agricultural and Food Chemistry 52: 1742–1748. https://doi.org/10.1021/jf0352430

Rosselli S, Bruno M, Raimondo F, Spadaro V, Varol M, Koparal AT, Maggio A (2012) Cytotoxic effect of eudesmanolides isolated from flowers of *Tanacetum vulgare* ssp. *siculum*. Molecules 7: 8186–8195. https://doi.org/10.3390/molecules17078186

Shields M (2017) Chemotherapeutics. In: Badal S, Delgoda R (Eds) Pharmacognosy, Fundamentals, Applications and Strategies. Academic press, 295–313. https://doi.org/10.1016/B978-0-12-802104-0.00014-7

Simmonds CB, Krishna S, Saxena PK (2002) Morphocytological characterization of feverfew, *Tanacetum parthenium* (L.) Schultz Bip. Journal of Herbs, Spices & Medicinal Plants 9: 29–45. https://doi.org/10.1300/J044v09n01_05

Todorova M, Ognyanov IV (1989) Sesquiterpene lactones in a population of *Balsamita major* cultivated in Bulgaria. Phytochemistry 28: 1115–1117. https://doi.org/10.1016/0031-9422(89)80194-3

Todorova MN, Evstatieva LN (2001) Comparative study of *Tanacetum* species growing in Bulgaria. Zeitschrift für Naturforschung C 56: 506–512. https://doi.org/10.1515/znc-2001-7-806

Venditti A, Frezza C, Sciubba F, Serafini M, Bianco A, Cianfaglione K, Lupidi G, Quassinti L, Bramucci M, Maggi F (2018) Volatile components, polar constituents and biological activity of tansy daisy (*Tanacetum macrophyllum* (Waldst. et Kit.) Schultz Bip.). Industrial Crop and Prodcts 118: 225–235. https://doi.org/10.1016/j.indcrop.2018.03.056

Williams CA, Harborne JB, Geiger H, Hoult JRS (1999a) The flavonoids of *Tanacetum parthenium* and *T. vulgare* and their anti-inflammatory properties. Phytochemistry 51: 417–423. https://doi.org/10.1016/S0031-9422(99)00021-7

Williams CA, Harborne JB, Eagles J (1999b) Variations in lipophilic and polar flavonoids in the genus *Tanacetum*. Phytochemistry 52: 1301–1306. [www.worldfloraonline.org] https://doi.org/10.1016/S0031-9422(99)00425-2

Zengin G, Sieniawska E, Senkardes I, Picot-Allain MCN, Sinan KI, Mahomoodally MF (2019) Antioxidant abilities, key enzyme inhibitory potential and phytochemical profile of *Tanacetum poteriifolium* Grierson. Industrial Crop and Products 140: 111629. https://doi.org/10.1016/j.indcrop.2019.111629

Zengin G, Cvetanović A, Gašić U, Stupar A, Bulut G, Şenkardes I, Dogan A, Sinan KI, Uysal S, Aumeeruddy-Elalfi Z (2020) Modern and traditional extraction techniques affect chemical composition and bioactivity of *Tanacetum parthenium* (L.). Sch. Bip. Industrial Crop and Products 146: 112202. https://doi.org/10.1016/j.indcrop.2020.112202