Thieme

A Review of the Traditional Uses, Phytochemistry and Biological Activities of the Genus *Santolina*

Authors
Rosa Tundis, Monica Rosa Loizzo

Affiliation
Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende (CS), Italy

Key words
Santolina, Asteraceae, ethnobotany, phytochemicals, biological activities

received November 15, 2017
revised February 5, 2018
accepted February 16, 2018

Bibliography
DOI https://doi.org/10.1055/a-0585-6153
Published online March 8, 2018 | Planta Med 2018; 84: 627–637 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 0032-0943

Correspondence
Prof. Rosa Tundis
Department of Pharmacy, Health and Nutritional Sciences, University of Calabria
Via P. Bucci – Edificio polifunzionale, 87036 Rende (CS), Italy
Phone: + 39 98 44 93 246, Fax: + 39 98 44 93 10 774
rosa.tundis@unical.it

ABSTRACT

The genus *Santolina* is a taxonomically complex group of plant species widely distributed in the Mediterranean flora and used in traditional medicine since ancient times for their biological properties, including antimicrobial, anti-inflammatory, antispasmodic, digestive, and analgesic activities. Phytochemical investigations of *Santolina* species have revealed the presence of terpenoids as the main bioactive constituents of the genus. Coumarins and flavonoids were also identified. This review deals, for the first time, with information on the traditional uses, chemical profile, and biological properties of plants of the genus *Santolina* in order to provide input for future research prospects.

ABBREVIATIONS

GPT	glutamate pyruvate transaminase
HD	hydrodistillation
HSV-1	herpes simplex type 1
HSV-2	herpes simplex type 2
MIC	minimum inhibitory concentration
MPLC	medium-pressure liquid chromatography
NF-κB	nuclear factor-kappa B
PLA1	phospholipase A1
PLA2	phospholipase A2
SFE	supercritical fluid extraction

Introduction

The *Santolina* genus (family Asteraceae, tribe Anthemideae) comprises species widely distributed in the Mediterranean area. The Plant List includes 103 scientific plant names of species of this genus. However, of these, only 20 are accepted species names (*Santolina africana* Jord. & Fourr., *Santolina benthamiana* Jord. & Fourr., *Santolina canescens* Lag., *Santolina chamaecyparissus* L., *Santolina corsica* Jord. & Fourr., *Santolina decumbens* Mill., *Santolina elegans* Boiss. ex DC., *Santolina etrusca* (Lacaita) Marchi & D'Amato, *Santolina insularis* (Gennari ex Fiori) Arrigoni, *Santolina magonica* Romo, *Santolina melidensis* Rodr.Oubiña & S.Ortiz, *Santolina neapolitana* Jord. & Fourr., *Santolina oblongifolia* Boiss., *Santolina pectinata* Lag., *Santolina pinnata* Viv., *Santolina rosmarinifolia* L., *Santolina semidentata* Hoffmanns. & Link, *Santolina tincloria* "Molina", *Santolina villosa* Mill., and *Santolina virens* Mill.). It is a taxonomically complex genus consisting of plant species whose classification has been revised several times.

S. chamaecyparissus L., *S. pectinata* Lag., and *Santolina viridis* W. are the most widespread [1]. With increasing interest in bioactive secondary metabolites from *Santolina* spp., several studies related to the investigation of the phytochemical composition and biological properties of species from this genus have been carried out. In recent decades, phytochemical studies have discovered the presence of terpenoids, particularly eudesmane and germacrane sesquiterpenoids, chrysanthemane monoterpenoids [2, 3], dammarane-type triterpenes [4], flavonoids [5, 6], and coumarins

▶ **Table 1** Ethnomedicinal uses of *Santolina* species.

Santolina species	Local name	Traditional uses	Part used	Country	Ref.
S. chamaecyparissus	lavender cotton, gray santolina	antispasmodic, digestive, analgesic, anti-inflammatory, antiseptic, stimulant, and antimicrobial; to treat dermatitis	inflorescence	Mediterranean area, India	[11–14]
S. chamaecyparissus subsp. *squarrosa*	manzanilla, manzanilla de monte, manzanilla basta, manzanilla de burro	to treat ophthalmological problems, headache, belly pain, stomach problems, and as digestive and depurative	inflorescence	Spain	[15, 16]
S. corsica	crespolina di Corsica	intestinal vermifuge, parasite repellent	inflorescence	Italy	[19, 20]
S. etrusca	canfora	antiparasitic	aerial parts	Italy	[21]
S. insularis	crespolina maggiore, santolina, crespolina sarda	vermifuge and to repel insects	inflorescence	Italy	[19]
S. insularis	crespolina insulare	sedative, febrifuge, and antitussive	leaves	Italy	[18]
S. neapolitana	green santolina, crespolina napoletana	cough suppressant	aerial parts	Italy	[17]
S. oblongifolia	manzanilla de Gredos	anti-inflammatory and digestive	inflorescence	Spain	[7]
S. rosmarinifolia	green lavender cotton	antipyretic, antihypertensive, hepatoprotective, and anti-inflammatory	flower heads	Spain	[22, 26]

[6, 7] in plant species of this genus. The literature data revealed that *Santolina* species show various biological activities, including antibacterial, antifungal, antiviral, anti-inflammatory, cytotoxic, and hepatoprotective effects [2, 5, 8–11].

The aim of this review is to provide a complete overview of existing knowledge on the traditional uses, chemical constituents, and biological properties of plant species from the *Santolina* genus.

The available information on this genus was collected from scientific databases up until November 2017. The following electronic databases were used: PubMed, SciFinder, Science Direct, Scopus, Web of Science, Wiley, ACS, Springer, and Google Scholar. The search terms used for this review included *Santolina, Santolina chamaecyparissus, Santolina insularis, Santolina corsica, Santolina oblongifolia, Santolina canescens, Santolina neapolitana, Santolina pinnata, Santolina pectinata, Santolina rosmarinifolia, Santolina etrusca, Santolina semidentata, Santolina tincloria, Santolina villosa, Santolina virens*, phytochemical composition, essential oils, sesquiterpenes, phenols, flavonoids, coumarins, traditional uses, activity, pharmacology, and toxicity. No limitations were set for languages. "The Plant List" (www.theplantlist.org) was used to validate the scientific names of the *Santolina* species. Seventy-five potentially relevant records were found, from which seven were excluded after screening the titles or abstracts.

From the available literature, two species, namely, *S. chamaecyparissus* and *S. insularis*, have been the most investigated. *S. corsica, S. oblongifolia, S. canescens, S. rosmarinifolia*, and *S. etrusca* have also been phytochemically and biologically studied. *S. pectinata* and *S. semidentata* were investigated for the chemical composition of their essential oil, but no biological studies were described.

Critical evaluation of biological studies in terms of their relation to the chemical profile is highlighted. Available information on these species allows us to provide the scientific basis for future research studies and to explore their potential therapeutic use.

Traditional Uses

For a long time, several plant species have been used for medicinal purposes. Among *Santolina* species, *S. chamaecyparissus, S. etrusca, S. insularis, S. neapolitana*, and *S. oblongifolia* have been reported in traditional medicine. A summary of their traditional use is presented in ▶ **Table 1**. *S. chamaecyparissus* has been inserted in the Ayurvedic system of medicine in India for the treatment of liver diseases. Moreover, the yellow inflorescences of *S. chamaecyparissus* are widely used in Mediterranean traditional medicine for their analgesic, anti-inflammatory, antispasmodic, antiseptic, and antimicrobial properties [11, 12]. Moreover, this plant, commonly called "lavender cotton" or "gray santolina", is employed for the treatment of numerous kinds of dermatitis, as a stimulant, and as a stomachic [13, 14]. In the traditional medicine of Spain, *S. chamaecyparissus* subsp. *squarrosa* was used as a substitute for *Artemisia granatensis*, "manzanilla real", for the treatment of ophthalmological problems, headache, belly pain, stomach problems, and as a digestive and depurative [15, 16]. This species is locally named "manzanilla de monte", "manzanilla basta", and "manzanilla de burro" [16].

Savo et al. [17] reported the use of *S. neapolitana* (= *S. pinnata* subsp. *neapolitana*) against cough in the Amalfi Coast (Campania, Southern Italy). A decoction of the leaves of *S. insularis*, known in Italy as "crespolina maggiore", has been used as a sedative, febrifuge, and antitussive [18]. The whole plant was used as an intestinal vermifuge against horse strongyloidiasis and as a parasite repellent [19, 20]. Another *Santolina* species used in Italy as an intestinal vermifuge and parasite repellent is *S. corsica* [19, 20]. *S. etrusca* ("canfora") is known in Italy for its traditional uses. This is an endemic species growing in the gravel beds of rivers, clayey, and arid hills, and is found exclusively in Central Italy, particularly in Northern Latium, Tuscany, and Umbria. Its antiparasitic activity has been reported [21]. In the traditional medicine of Spain, *S. oblongifolia*, known as "manzanilla de Gredos", is used as a digestive

▶ **Table 2** The main volatiles of the essential oils from *Santolina* species.

Plant species	Country	Main compounds	Reference
S. africana	Algeria	acenaphtane, calarene, ocimene	[48]
S. africana	Algeria	β-pinene, 1,8-cineol, myrcene, curcumene, spathulenol	[49]
S. canescens	Spain	santolindiacetylene, camphor, myrcene	[51]
S. canescens	Spain	camphor, 1,8-cineole, β-pinene, myrcene, sabinene, ar-curcumene	[45]
S. chamaecyparissus	France	artemisia ketone, myrcene	[33]
S. chamaecyparissus	Turkey	artemisia ketone, camphor, β-phellandrene, α-bisabolol	[34]
S. chamaecyparissus	Tunisia	1,8-cineole, β-eudesmol, terpinene-4-ol, γ-cadinene	[35]
S. chamaecyparissus	India	artemisia ketone, 1,8-cineole, myrcene, germacrene d	[36]
S. chamaecyparissus	Syria	artemisia ketone, α-amorphene, β-phellandrene, β-myrcene	[37]
S. chamaecyparissus	Algeria	camphor, cubenol, *p*-cymene, sabinene	[38]
S. chamaecyparissus	Italy	artemisia ketone, β-phellandrene, myrcene, sabinene	[39]
S. chamaecyparissus	Spain	1,8-cineole, camphor, borneol, terpinen-4-ol, terpinolene	[40]
S. corsica	Italy	camphor, borneol, aromadendrene, muurolene	[20]
S. corsica	Italy	artemisia ketone, β-phellandrene, myrcene, santolinatriene	[41]
S. corsica	Italy	myrcene, santolinatriene, β-phellandrene, β-pinene, isolyratol	[8]
S. etrusca	Italy	1,8-cineole, β-pinene, myrcene, sabinene, *trans*-pinocarveol	[48]
S. insularis	Italy	3,3,6-trimethyl-1,5-heptadien-4-one, 10-h-cyclopropyl-1,1,7-trimethyl-4-methylen-decahydro azulene, cineole, camphene	[20]
S. insularis	Italy	myrcene, β-phellandrene, *trans*-β-terpineol, ar-curcumene	[42]
S. insularis	Italy	artemisia ketone, *cis*-chrysanthemol, myrcene, β-phellandrene	[43]
S. ligustica	Italy	myrcene, 1,8-cineole, terpinen-4-ol, sabinene	[47]
S. neapolitana	Italy	γ-muurolene, α-pinene, borneol	[46]
S. pectinata	Spain	β-eudesmol, nerolidol, spathulenol, α-cadinol, γ-eudesmol,	[45]
S. rosmarinifolia	Romania	β-eudesmol, 1,8-cineole, camphor, borneol, ar-curcumene	[52]
S. rosmarinifolia subsp. *rosmarinifolia*	Spain	β-phellandrene, β-pinene, limonene, myrcene	[53]
S. semidentata	Spain	β-eudesmol, nerolidol, spathulenol, α-cadinol, τ-cadinol	[45]

sedative and tonic, and for the treatment of rheumatism and menstrual disorders [7]. This species is known for its mild flavor and sweetness, and for its beneficial effects on the digestive tract [7].

S. rosmarinifolia, known as "green lavender cotton", is a dwarf perennial shrub mainly distributed in the Iberian Peninsula and South France. *S. rosmarinifolia* flower heads (fresh or dried) are used in traditional preparations for their antihypertensive, anti-inflammatory, antipyretic, and hepatoprotective properties [22].

Phytochemicals

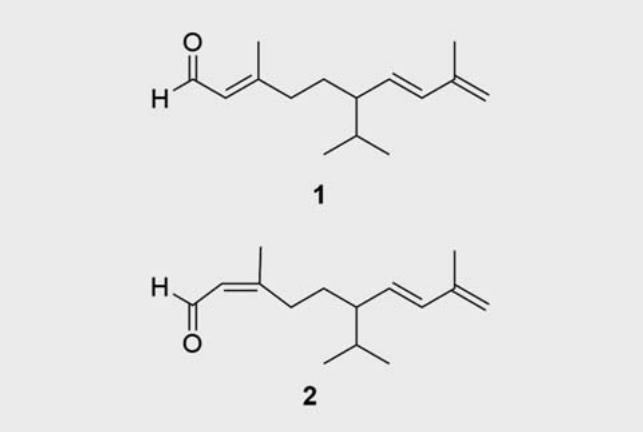
Phytochemical investigations on *Santolina* species revealed the presence of several classes of constituents. Eudesmane-type sesquiterpenes [23–27], germacrane-type sesquiterpenes [2, 23–26], dammarane-type triterpenes [4], acetylene heterocycles [4, 28, 29], spiroketalenol ether-type acetylenes [4, 24, 27–29], flavonoids [5, 6], and coumarins [6, 7, 27] have been identified as common secondary metabolites from the genus. Several *Santolina* species have been studied for their essential oil composition. *S. chamaecyparissus* is one of the most investigated *Santolina* species. A different chemical composition, depending on its origin, was evidenced by several researchers (▶ **Table 2**) [1, 30–35]. The HD of the flower heads of *S. chamaecyparissus* from Tunisia has allowed for obtaining an oil rich in 1,8-cineole (12.94%), β-eudesmol (10.49%), terpinene-4-ol (6.97%), γ-cadinene (6.55%), spathulenol (5.80%), camphor (5.27%), germacrene D (5.03%), and myrtenol (4.26%) [35]. The oil of *S. chamaecyparissus* obtained by HD of the air-dried aerial parts collected in Turkey is characterized mainly by monoterpenes (81% of the total oil) [34]. Oxygenated monoterpenes predominated over the monoterpenes hydrocarbons. The main constituents are artemisia ketone (38.1%), camphor (11.7%), β-phellandrene (9.2%), α-bisalolol (6.6%), and myrcene (4.3%). Artemisia ketone is also the dominant constituent of the essential oil of *S. chamaecyparissus* from India [36]. Other abundant compounds are 1,8-cineole (15.6%), myrcene (14.2%), germacrene D (8.8%), sabinene (4.5%), and terpinin-4-ol (2.9%). Artemisia ketone (15.65%) together with α-amorphene (12.11%), β-phellandrene (10.63%), β-myrcene (7.42%), and nootkatone (6.97%) were identified as the main compounds of the oil from Syria [37]. The composition of this oil greatly differed from the oil of *S. chamaecyparissus* collected in Algeria [38]. In

fact, Djeddi et al. [38] showed camphor (31.1%), cubenol (17.0%), *p*-cymene (8.3%), and sabinene (4.0%) as the most abundant constituents. Instead, as in the oil from India, the essential oil of *S. chamaecyparissus* collected in France [33] and in Italy [39] showed artemisia ketone as the dominant constituent. Monoterpene hydrocarbons (29.5%) and oxygenated monoterpenes (36.81%) are the main classes of the essential oil of *S. chamaecyparissus* from Italy [39], in which, besides artemisia ketone (28.24%), the other abundant constituents are *β*-phellandrene (12.78%), myrcene (8.02%), and sabinene (7.65%).

Grosso et al. [40] compared the essential oil of *S. chamaecyparissus* (Spain) obtained by SFE with the essential oil obtained by HD, and found 1,8-cineole to be the most abundant component (7–48% and 25–30% for SFE and HD, respectively), followed by camphor (8–14 and 7–9% for SFE and HD, respectively), borneol (2–11 and 7–8% for SFE and HD, respectively), terpinen-4-ol (1–4 and 6–7% for SFE and HD, respectively), and terpinolene (1–7 and 1–4% for SFE and HD, respectively). In previous studies, some *S. chamaecyparissus* subspecies from Spain were described to contain 1,8-cineole (2–18%), artemisia ketone (0.1–28%), camphor (trace-43%), borneol (1–28%), copaenol (trace-15%), *allo*-aromadendrene (19%), and cubenol (1–17%) as major constituents [12, 30]. Three works reported the chemical profile of the essential oil from *S. corsica*, a perennial shrub growing in the rocky places of Corsica (France) and Sardinia (Italy). The essential oil of *S. corsica* collected in Corsica was dominated by monoterpene hydrocarbons. Artemisia ketone (20.0%), *β*-phellandrene (14.4%), myrcene (11.7%), santolinatriene (8.2%), 1,8-cineole (4.4%), and *β*-pinene (4.3%) were identified as the main compounds [41].

Except for artemisia ketone, found with a percentage of 0.1%, myrcene (34.6%), santolinatriene (13.5%), and *β*-phellandrene (11.7%) were found to be the most abundant compounds in the Corsican essential oil in a study by Liu et al. [8]. Otherwise, the essential oil from *S. corsica* collected in Sardinia (Italy) showed camphor (18.5%), artemisia ketone (12.97%), borneol (7.41%), aromadendrene (5.55%), and muurolene (4.63%) as the main constituents [20]. 3,3,6-Trimethyl-1,5-heptadien-4-one (21.18%), 10-H-cyclopropyl-1,1,7-trimethyl-4-methylendecahydro azulene (12.7%) cineole (9.01%), camphene (8.47%), bornyl acetate (6.35%), and borneol (4.23%) were the main constituents of the essential oil of *S. insularis* collected in Sardinia (Italy) [20]. A different composition with myrcene (14.8–17%), *β*-phellandrene (8–9%), ar-curcumene (6–10%), and *trans*-*β*-terpineol (5–6%) as the main constituents was reported by Cherchi et al. [42] for the essential oils obtained from the aerial parts of *S. insularis* collected in the same Italian region (Sardinia).

More recently, Gnavi et al. [43] studied four *S. insularis* samples from Sardinia (Italy). Artemisia ketone, *cis*-chrysanthemol, myrcene, *β*-phellandrene, *β*-pinene, and santolinatriene were identified as the most abundant constituents. However, different percentages of these main compounds were reported. This work showed remarkable chemical variation in the terpenoid profile and a consistent genomic difference in the 5S-rRNA spacer regions that led to identifying four chemotypes of *S. insularis* grouped into two ecotypes. The analysis of these data showed a high variability in the composition and content of monotepenes and sesquiterpenes of *S. insularis* essential oils from the same geographical area. Two isomeric irregular sesquiterpenes, 3,9-dimethyl-6-isopropyl-2(*E*),7(*E*),9-decatrienal (**1**) and 3,9-dimethyl-6-isopropyl-2(*Z*),7(*E*),9-decatrienal (**2**), were isolated from the essential oil obtained by HD from the leaves of *S. corsica* (France) (▶ **Fig. 1** and **Table 3**) [44]. The oil was subjected to flash column chromatography on silica gel, affording a nonpolar and a polar fraction. The polar fraction was purified by column chromatography on silica gel using pentane with increasing amounts of diethyl oxide as the eluent. Compounds **1** and **2** were isolated from subfractions using pentane/diethyl ether (95/5) as the eluent. Their structure was elucidated by using 1D and 2D NMR spectroscopy. The essential oil of *S. pectinata* contained *β*-eudesmol, nerolidol, spathulenol, *α*-cadinol, *γ*-eudesmol, and elemol as the major constituents [45]. The essential oil of *S. semidentata*, an endemic species of Spain, was characterized by the presence of *β*-eudesmol, nerolidol, spathulenol, *α*-cadinol, *τ*-cadinol, *γ*-eudesmol, and elemol as the major components [45].



▶ **Fig. 1** Chemical structures of isolated compounds **1** and **2** from *S. corsica*.

The essential oil of *S. neapolitana* obtained by HD from aerial parts collected in Italy with a yield of 0.30% (v/w) was characterized by 41 constituents [46]. *γ*-Muurolene (31.9%), *α*-pinene (15.5%), and borneol (9.4%) were the most abundant compounds. Myrcene (12.0%), 1,8-cineole (11.1%), terpinen-4-ol (9.9%), and sabinene (6.7%) were the main constituents of the essential oil of *Santolina ligustica* aerial parts [47]. *S. ligustica* is an endemic *Santolina* species that grows in Eastern Liguria (Italy), generally on ophiolitic substrates. Other compounds found in good amounts were myrtenol (4.7%), *γ*-terpinolene (4.3%), *β*-pinene (4.2%), and bisabolol (3.1%).

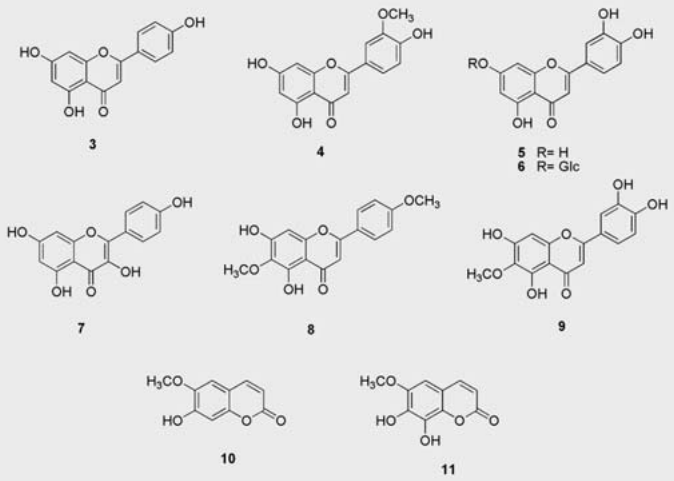
Flamini and Cioni [48] evaluated the seasonal variation of the components of the essential oil of inflorescences and fertile and sterile branches of another *Santolina* species from Italy, *S. etrusca*. The obtained results showed that the extraction yields generally increased from November to June, while decreasing in the months of August and September. Taking into account the variability of the oil during the whole year, the most abundant compounds belong to the class of monoterpene hydrocarbons, mainly, *β*-pinene, myrcene, and sabinene, and to the class of oxygenated monoterpenes, mainly 1,8-cineole. Twenty-six compounds characterized

▶ **Table 3** Isolated compounds from *Santolina* species.

	Compound name	Plant	Molecular formula, molecular weight
1	3,9-dimethyl-6-isopropyl-2(*E*),7(*E*),9-decatrienal	*S. insularis*	$C_{15}H_{24}O$, 220.36
2	3,9-dimethyl-6-isopropyl-2(*Z*),7(*E*),9-decatrienal	*S. insularis*	$C_{15}H_{24}O$, 220.36
3	apigenin	*S. oblongifolia*, *S. pinnata*	$C_{15}H_{10}O_5$, 270.24
4	chrysoeriol	*S. pinnata*	$C_{16}H_{12}O_6$, 300.26
5	luteolin	*S. oblongifolia*, *S. pinnata*	$C_{15}H_{10}O_6$, 286.24
6	luteolin-7-glucoside	*S. pinnata*	$C_{21}H_{20}O_{11}$, 448.38
7	kaempferol	*S. pinnata*	$C_{15}H_{10}O_6$, 286.24
8	pectolinarigenin	*S. pinnata*	$C_{23}H_{24}O_{11}$, 476.43
9	nepetin	*S. pinnata*	$C_{16}H_{12}O_7$, 316.26
10	scopoletin	*S. oblongifolia*, *S. pinnata*	$C_{10}H_8O_4$, 192.17
11	fraxetin	*S. pinnata*	$C_{10}H_8O_5$, 208.17
12	1*α*,10*β*-epoxy-7*α*H-germacr-4(15)-ene-2*β*,5*α*,6*β*-triol	*S. pinnata* subsp. *neapolitana*	$C_{15}H_{26}O_4$, 270.36
13	4*β*,5*α*-epoxy-7*α*H-germacr-1(10)*E*-ene-2*β*,6*β*-diol	*S. pinnata* subsp. *neapolitana*	$C_{15}H_{26}O_3$, 254.37
14	4*β*,5*α*-epoxy-7*α*H-germacr-1(10)*E*-ene-2*β*,6*β*-diol 2-acetate	*S. pinnata* subsp. *neapolitana*	$C_{17}H_{28}O_4$, 296.40
15	7*α*H-germacra-1(10)*E*,4(15)-diene-2*β*,5*α*,6*β*-triol	*S. pinnata* subsp. *neapolitana*	$C_{15}H_{26}O_3$, 254.37
16	7*α*H-germacra-1(10)*E*,4(15)-diene-2*β*,5*α*,6*β*-triol 2-acetate	*S. pinnata* subsp. *neapolitana*	$C_{17}H_{28}O_4$, 296.40
17	(1*R*,2*R*,5*R*,6*R*,7*S*,10*S*)-eudesma-4(15)-en-1,2,6-triol	*S. insularis*	$C_{15}H_{26}O_3$, 254.37
18	(1*R*,2*S*,6*R*,7*S*,10*S*)-1,2,6-trihydroxyeudesma-4-en-3-one	*S. insularis*	$C_{15}H_{24}O_4$, 268.17
19	(1*R*,2*R*,7*S*,10*S*)-eudesma-3,5-dien-1,2-diol	*S. insularis*	$C_{15}H_{24}O_2$, 236.18
20	(2*R*,3*R*,4*R*)-5-chrysanthemen-1,4-diol	*S. insularis*	$C_{10}H_{18}O_2$, 170.25
21	elegansidiol	*S. elegans*	$C_{15}H_{26}O_2$, 238.37
22	(4*E*,9*Z*)-6*β*-acetoxy-7*α*H-germacra-4,9-diene-l*α*,2*β*-diol	*S. chamaecyparissus* subsp. *squarrosa*	$C_{17}H_{28}O_4$, 296.40
23	(*E*)-6*β*-acetoxy-7*α*Hgermacra-4,10(14)-diene-l*α*,2*β*-diol	*S. chamaecyparissus* subsp. *squarrosa*	$C_{17}H_{28}O_4$, 296.40
24	(*E*)-6*β*-acetoxy-7*α*H-germacra-l(10),4-diene-2*β*-ol	*S. chamaecyparissus* subsp. *squarrosa*	$C_{17}H_{28}O_3$, 280.40
25	6*β*-acetoxy-5*β*H,7*α*H,10*β*Me-eudesm-4(15)-ene-1*α*,2*β*-diol	*S. chamaecyparissus* subsp. *squarrosa*	$C_{17}H_{28}O_4$, 296.40
26	(*E*)-7*α*H-germacra-1(10),4(15)-diene-5*α*,6*β*-diol	*S. rosmarinifolia* subsp. *canescens*	$C_{15}H_{26}O_2$, 238.37
27	4*β*,5*α*-epoxy-7*α*H-germacr-10(14)-ene-1*β*,6*β*-diol	*S. rosmarinifolia* subsp. *canescens*	$C_{15}H_{26}O_3$, 254.37
28	(*E*)-6*α*,11-dihydroxy-7*α*H-germacra-4,10(14)-dien-1-one	*S. rosmarinifolia* subsp. *canescens*	$C_{15}H_{24}O_3$, 252.35
29	(*E*)-7*α*H-germacra-4,10(14)-diene-1*α*,6*α*,11-triol	*S. rosmarinifolia* subsp. *canescens*	$C_{15}H_{26}O_3$, 254.37
30	(*E*)-7*α*H-germacra-4,10(14)-diene-1*β*,6*α*,11-triol	*S. rosmarinifolia* subsp. *canescens*	$C_{15}H_{26}O_3$, 254.37
31	(*E*)-7*α*H-germacra-4,10(14)-diene-1*α*,6*β*-diol	*S. rosmarinifolia* subsp. *canescens*	$C_{15}H_{26}O_2$, 238.37
32	(1*E*,4*E*)-7*α*H-germacra-1(10),4-dien-6*β*-ol	*S. rosmarinifolia* subsp. *canescens*	$C_{15}H_{26}O$, 222.37
33	shiromool	*S. rosmarinifolia* subsp. *canescens*	$C_{15}H_{26}O_2$, 238.19
34	(2*R*,5*R*,6*R*,7*S*)-germacra-1(10)*E*,4(15)-dien-5-hydroperoxy-2,6-diol	*S. insularis*	$C_{15}H_{26}O_4$, 270.36
35	(2*R*,5*R*,6*R*,7*S*)-germacra-1(10)*E*,4(15)-dien-5-hydroperoxy-2,6-diol-2-acetate	*S. insularis*	$C_{17}H_{28}O_5$, 312.40
36	(1*R*,2*R*,4*S*,5*S*,6*R*,7*S*)-4,5-epoxygermacra-9*Z*-en-1,2,6-triol	*S. insularis*	$C_{15}H_{26}O_4$, 270.36
37	(3*R*,6*R*,7*S*)-3,6-dihydroxygermacra-4(5)*E*,10(14)-dien-1-one	*S. insularis*	$C_{15}H_{24}O_3$, 252.35

the essential oil obtained by the flowers of *S. africana* collected in Algeria. The oil showed monoterpene hydrocarbons (27.56%) as the main class of constituents, followed by sesquiterpenes hydrocarbons (26.89%). The main compounds were acenaphtane (25.23%), calarene (21.54%), and ocimene 17.44% [49]. Instead, Zaiter et al. [50], analyzing the essential oil of *S. africana* within the same country of origin (such as Algeria), reported *β*-pinene (12.78%), 1,8-cineol (10.02%), myrcene (6.94%), curcumene (7.96%), spathulenol (5.96%), and *β*-eudesmol (14.58%) as the main components.

Santolindiacetylene (28.5%), camphor (12.5%), myrcene (5.6%), and *β*-phellandrene (5.4%) were the main constituents identified in the essential oil of *S. canescens* from Spain, obtained by HD [51]. Other compounds found in a good amount were *allo*-



▶ **Fig. 2** Chemical structures of flavonoids **3**–**9** and coumaris **10**–**11** from *S. pinnata*.

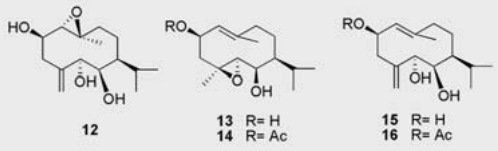
aromadendrene (4.4%), β-caryophyllene (4.1%), borneol (4.0%), α-terpineol (3.5%), and germacrene D (3.0%). A previous study reported camphor as the main constituent of the essential oil of *S. canescens*, followed by 1,8-cineole, β-pinene, myrcene, sabinene, ar-curcumene, and β-eudesmol [45].

A total of 41 compounds were identified in the essential oil from the flower heads of *S. rosmarinifolia* from Romania, which were rich in oxygenated monoterpenes and oxygenated sesquiterpenes. β-Eudesmol (13.5%), 1,8-cineole (12.9%), camphor (8.0%), borneol (5.1%), ar-curcumene (4.8%), terpinen-4-ol (4.5%), and spathulenol (4.4%) were the main constituents [52]. In an evaluation of the seasonal variation of the essential oil from the aerial parts of *S. rosmarinifolia* subsp. *rosmarinifolia* collected in Spain, β-phellandrene (14.4–27.6%), β-pinene (17.0–26.5%), limonene (2.7–5.2%), and myrcene (0.3–15.3%) were identified as the main constituents [53]. Moreover, it was found that the oil concentration showed a positive correlation with precipitation and a negative correlation with temperature. Specifically, the monoterpenes 1,8-cineole, limonene, and β-phellandrene correlated negatively with temperature, while capillene showed a positive correlation with precipitation. The other compounds did not show any manifest trend.

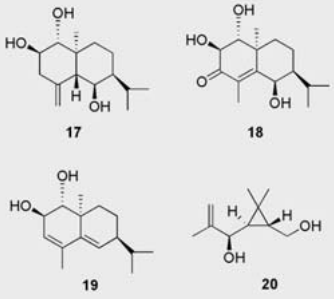
The aerial parts of *S. pinnata* collected in Tuscany (Italy) were characterized by the presence of seven flavonoids, namely, apigenin (**3**), chrysoeriol (**4**), luteolin (**5**), luteolin-7-glucoside (**6**), kaempferol (**7**), pectolinarigenin (**8**), and nepetin (**9**), and two coumarins, namely, scopoletin (**10**) and fraxetin (**11**) (▶ **Table 3** and **Fig. 2**) [6]. One new [1α,10β-epoxy-7αH-germacr-4(15)-ene-2β5α,6β-triol) (**12**)] and four known germacrane derivatives [4β,5α-epoxy-7αH-ger-macr-1(10)*E*-ene-2β,6β-diol (**13**), its 2-acetate **14**, 7αHgermacra-1(10)*E*,4(15)-diene-2β,5α,6β-triol (**15**), and its 2-acetate **16**] were isolated from the aerial parts of *S. pinnata* subsp. *neapolitana* (▶ **Fig. 3**) [54]. Compounds **13**–**16** have also been previously isolated from *S. chamaecyparissus* [25].

Three eudesmane sesquiterpenoids, (1*R*,2*R*,5*R*,6*R*,7*S*,10*S*)-eudesma-4(15)-en-1,2,6-triol (**17**), (1*R*,2*S*,6*R*,7*S*,10*S*)-1,2,6-trihydroxyeudesma-4-en-3-one (**18**), and (1*R*,2*R*,7*S*,10*S*)-eudesma-3,5-dien-1,2-diol (**19**), and the *trans*-chrysanthemyl monoterpenoid (2*R*,3*R*,4*R*)-5-chrysanthemen-1,4-diol (**20**) have been isolated from the acetone extract of the defatted aerial parts of *S. insularis* from Italy (▶ **Fig. 4**) [3]. Specifically, the acetone extract was subjected to MPLC, affording two fractions that were further purified by HPLC.

A new monocyclic sesquiterpenic alcohol, elegansidiol (**21**), was isolated from the hexane extract of *S. elegans* (▶ **Fig. 5**) [55].

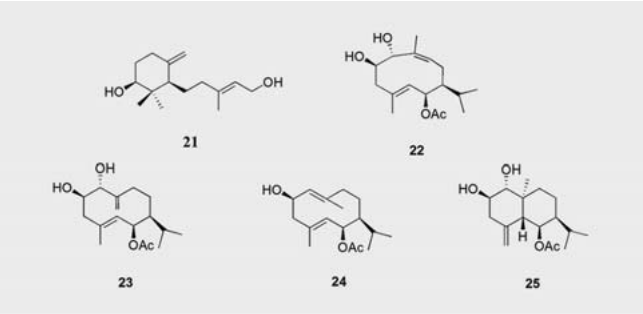


▶ **Fig. 3** Chemical structures of compounds **12**–**16**.

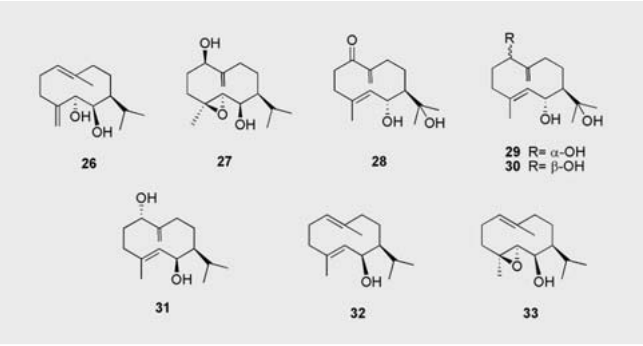


▶ **Fig. 4** Chemical structures of eudesmane sesquiterpenes **17**–**20** from *S. insularis*.

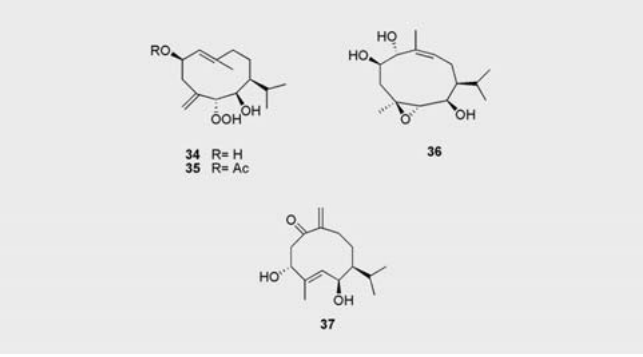
From the aerial parts of *S. chamaecyparissus* subsp. *squarrosa*, collected in Sierra Nevada (Granada, Spain), four new sesquiterpenes, (4*E*,9*Z*)-6*β*-acetoxy-7*α*H-germacra-4,9-diene-l*α*,2*β*-diol (**22**), (*E*)-6*β*-acetoxy-7*α*Hgermacra-4,10(14)-diene-l*α*,2*β*-diol (**23**), (*E*)-6*β*-acetoxy-7*α*H-germacra-l(10),4-diene-2*β*-ol (**24**), and 6*β*-acetoxy-5*β*H,7*α*H,10*β*Me-eudesm-4(15)-ene-1*α*,2*β*-diol (**25**) (▶ **Fig. 5**), were isolated [23]. The air-dried aerial parts of *S. chamaecyparissus* subsp. *squarrosa* were subjected to maceration by using *t*-butylmethyl ether as the solvent. A portion was defatted by precipitation in methanol at a low temperature. The defatted extract was subjected to column chromatography by using the mixture hexane-*t*-butylmethyl ether-EtOAc of increasing polarity as the eluent. New sesquiterpenes with a germacrane skeleton were isolated from the aerial parts of *S. rosmarinifolia* subsp. *canescens* [24]. The air-dried and powdered aerial parts of *S. rosmarinifolia* subsp. *canescens*, collected in Sierra Nevada (Granada, Spain), were extracted by the Soxhlet apparatus with hexane as the solvent. After removal of the solvent, the obtained residue was dissolved in chloroform. This mixture was added to methanol at 50 °C, allowed to cool to room temperature, then further cooled at − 10 °C for 24 h, yielding an insoluble fraction that was purified by column chromatography. The six main fractions collected were subjected to repeated separations by silica gel chromatography. The isolated compounds were (*E*)-7*α*H-germacra-1(10),4(15)-diene-5*α*,6*β*-diol (**26**), 4*β*,5*α*-epoxy-7*α*H-germacr-10(14)-ene-1*β*,6*β*-diol (**27**), (*E*)-6*α*,11-dihydroxy-7*α*H-germacra-4,10(14)-dien-1-one (**28**), (*E*)-7*α*H-germacra-4,10(14)-diene-1*α*,6*α*,11-triol (**29**), (*E*)-7*α*H-germacra-4,10(14)-diene-1*β*,6*α*,11-triol (**30**), (*E*)-7*α*H-germacra-4,10(14)-diene-1*α*,6*β*-diol (**31**), (1*E*,4*E*)-7*α*H-germacra-1(10),4-dien-6*β*-ol (**32**), and shiromool (**33**) (▶ **Fig. 6**). The aerial parts of *S. insularis* collected in Italy were sequentially extracted with *n*-hexane and acetone. The acetone extract was subjected to MPLC to afford, after purification by HPLC, 11 germacrane sesquiterpenes, four of which are new [2]. The new compounds are (2*R*,5*R*,6*R*,7*S*)-germacra-1(10)*E*,4(15)-dien-5-hydroperoxy-2,6-diol (**34**), (2*R*,5*R*,6*R*,7*S*)-germacra-1(10)*E*,4(15)-dien-5-hydroperoxy-2,6-diol-2-acetate (**35**), (1*R*,2*R*,4*S*,5*S*,6*R*,7*S*)-4,5-epoxygermacra-9*Z*-en-1,2,6-triol (**36**), and (3*R*,6*R*,7*S*)-3,6-dihydroxygermacra-4(5)*E*,10(14)-dien-1-one (**37**) (▶ **Fig. 7**).



▶ **Fig. 5** Chemical structures of compounds **21**–**25**.



▶ **Fig. 6** Chemical structures of sesquiterpenes with a germacrane skeleton (**26**–**33**) isolated from *S. rosmarinifolia* subsp. *canescens*.



▶ **Fig. 7** Chemical structures of germacrane sesquiterpenes **34**–**36** isolated from *S. insularis*.

Biological Properties

Several *Santolina* species have been studied for their biological properties. The antimicrobial, antifungal, antiviral, and anti-inflammatory activities were mainly investigated. However, most of the literature data concern *in vitro* studies (▶ **Table 4**). Few studies are performed by using *in vivo* models.

Antibacterial and antifungal

In the last years, the search for new antibiotics has accelerated. There are two main reasons. Nearly every antibiotic used today is based on a discovery of more than 30 years ago. At the same time, multidrug-resistant bacteria have been observed with increasing frequency over the past several decades. Many plants have been used for their antimicrobial properties due to their constituents, including phenolic compounds and essential oils. The essential oil of several *Santolina* species was subjected to investigations against different gram-positive bacteria, gram-negative bacteria, and fungi. The essential oil of *S. corsica* was tested *in vitro* for its antimicrobial properties by using the agar diffusion method against two gram-positive bacteria (*Staphylococcus aureus* and *Listeria innocua*) and four gram-negative bacteria (*Campylobacter jejuni*, *Enterobacter aerogenes*, *Escherichia coli*, and *Pseudomonas aeruginosa*) [8]. The essential oil inhibited the growth of *S. aureus* (14.7 mm) and, especially, the growth of *C. jejuni* (39 mm). A moderate antimicrobial activity was found against *L. innocua*

▶ **Table 4** Investigated bioactivities of *Santolina* species.

Activity	Species	Test/bacteria/fungi/yeast/cell line	Sample	Ref.
Anti-inflammatory	*S. chamaecyparissus*	PLA2-induced mouse paw edema	methanol extract	[11]
	S. chamaecyparissus	carrageenan paw edema in rats	chloroform extract	[59]
	S. chamaecyparissus	inhibition of PLA1	methanol extract	[60]
	S. insularis	croton oil-induced dermatitis in mouse ears	methanol extract	[5]
	S. oblongifolia	adjuvant carrageenan-induced inflammation, ACII, model using Wistar male rats	hexane, dichloromethane, ethyl acetate, and methanol extracts	[61]
	S. oblongifolia	ionophore-stimulated mouse peritoneal macrophages	hexane, dichloromethane, ethyl acetate, and methanol extracts	[62]
	S. viscosa	NF-κB, IL-6, IL-8, TNF-α, PGE2	petroleum ether, ethyl acetate, and methanol extracts	[64]
Antimicrobial	*S. africana*	*A. flavus, A. niger, B. subtilis, C. albicans, E. coli, E. faecalis, K. pneumonia, P. aeruginosa, P. vulgaris, S. aureus, S. epidermidis*	essential oil	[49]
	S. chamaecyparissus	*B. bronchiseptica, C. albicans, E. coli, K. pneumonia, M. luteus, P. aeruginosa, E. faecalis, S. aureus, S. cerevisiae, S. epidermis*	essential oil	[38]
	S. chamaecyparissus	*A. fumigatus, C. albicans, C. freundii, E. floccosum, E. coli, E. faecalis, M. canis, S. aureus, S. brevicaulis, S. dimidiatum, P. aeruginosa, P. mirabilis, T. rubrum*	essential oil	[35]
	S. chamaecyparissus	*C. albicans*	essential oil	[9]
	S. corsica	*C. jejuni, E. aerogenes, E. coli, L. innocua, P. aeruginosa, S. aureus*	essential oil	[8, 56]
	S. etrusca	*S. ferax*	aqueous and methanol extracts	[57]
	S. rosmarinifolia	*B. cereus, C. albicans, E. coli, S. aureus, S. lutea*	essential oil	[51]
Antiviral	*S. insularis*	HSV-1 and HSV-2	essential oil	[10]
	S. insularis	HSV-1	liposome-incorporated essential oil	[58]
Cytotoxic	*S. chamaecyparissus*	MCF-7, HCT116, A549, HepG2 human tumor cell lines	essential oil	[65]
Hepatoprotective	*S. canescens*	carbon tetrachloride-induced hepatotoxicity in Wistar rats model	essential oil	[66]

(9.5 mm), while the growth of *E. aerogenes*, *E. coli*, and *P. aeruginosa* was not inhibited. In order to identify the compounds responsible for this activity, fractions were tested. An interesting antimicrobial activity of a lyratol-rich fraction (84%) was observed against *C. jejuni* (90 mm) and *S. aureus* (19 mm), suggesting that lyratol could be the main responsive of the antimicrobial properties of *S. corsica*.

A bactericidal action was recognized for *S. corsica* essential oil, which rapidly inhibited the cell viability of *S. aureus* (MIC of 5 mg/mL) [56]. After treatment with the MIC value and 8 times the MIC value of *S. corsica* essential oil, no lytic effect was observed. The cell wall and the cytoplasmic membrane are involved in the activity of *S. corsica* essential oil. In fact, invaginations of the plasmic membrane with thickenings of the cell wall and aggregations of the cytoplasmic contents were detected in *S. aureus* treated with the *S. corsica* essential oil at the MIC value.

A study reported on the antimicrobial activity of the essential oil *S. rosmarinifolia* flower heads [51]. The essential oil showed good activity against the gram-positive bacteria *Bacillus cereus, S. aureus*, and *Sarcina lutea*, and a minor activity against the fungus *Candida albicans* and the gram-negative *E. coli*. The strongest activity was reported against *S. aureus* with MIC and MBC values of 0.3 and 0.6 µL/mL, respectively. The antimicrobial effects of *S. chamaecyparissus* essential oil were studied in different works. The oil of *S. chamaecyparissus* from Algeria was tested by the agar disc diffusion method against the gram-negative bacteria *Bordetella bronchiseptica, E. coli, Klebsiella pneumonia*, and *P. aeruginosa*, the gram-positive bacteria *Enterococcus faecalis, Micrococcus luteus, S. aureus*, and *Staphylococcus epidermis*, the fungus *C. albicans*, and the yeast *Saccharomyces cerevisiae* [38]. The essential oil strongly inhibited the growth of *C. albicans* and *K. pneumonia*. Interesting results were also obtained with the essential oil of *S. chamaecyparissus* collected in Tunisia [35]. This essential oil

was investigated against seven strains of fungi (three dermatophytes, *Epidermophyton floccosum, Microsporum canis*, and *Trichophyton rubrum*; one opportunist pathogenic yeast, *C. albicans*; and three hyphamycetes, *Aspergillus fumigatus, Scopulariopsis brevicaulis*, and *Scytalidium dimidiatum*), two gram-positive bacteria (*E. faecalis* and *S. aureus*), and four-gram negative bacteria (*E. coli, P. aeruginosa, Proteus mirabilis*, and *Citrobacter freundii*) [35]. Except for *C. albicans*, the inhibition of the fungi growth rate varied in the range of 73.0–89.25% in the presence of 500 µg/mL *S. chamaecyparissus* essential oil. *E. floccosum* was the most sensitive to the flower head essential oil (89.25%). The MIC values varied in the range from 500 to 1000 µg/mL. Generally, *S. chamaecyparissus* oil showed antibacterial activity against all bacterial strains with MIC values in the range of 0.625–10 µg/mL. In the agar diffusion method, the gram-positive bacterium *E. faecalis* (inhibition zone of 26 mm) was the most susceptible microorganism to the action of the flower head essential oil. *S. chamaecyparissus* essential oil from India showed potent antifungal activity against *C. albicans*, with MICs from 62.5 to 125 µg/mL of broth [9]. Clotrimazole was used as a positive control. The drug showed an MIC value of 3.125–6.25 µg/mL. When the mixture of *S. chamaecyparissus* oil and clotrimazole at the D4 dilution (31.25 and 3.125 µg/mL for the essential oil and clotrimazole, respectively) was tested, the MIC was effective in controlling *C. albicans*. The *S. chamaecyparissus* oil was also effective *in vivo* in controlling experimental vaginal candidiasis. This activity was comparable to that of clotrimazole. The essential oil of *S. africana* demonstrated activity against several microorganisms (standard strains *Bacillus subtilis, E. faecalis, E. coli, P. aereginosa, Proteus vulgaris, S. aureus*, and *S. epidermidis*, clinical strain *K. pneumonia*, and fungi *Aspergillus flavus, Aspergillus niger*, and *C. albicans*), with an inhibition zone medium diameter in a concentration-dependent manner [49]. The inhibitory activity was in the range of 7.0–20.15 mm. The highest inhibition zone was found for *B. subtilis* at 8×10^3 µg/mL. Saprolegniosis is a very common mycosis of animals that live in fresh and mesohaline water. The aqueous and methanol extracts of *S. etrusca* aerial parts were studied for their potential antimicrobial properties against *Saprolegnia ferax* [57]. The most active extract was the aqueous extract that exhibited an MIC value of 2%. The methanol extract showed an MIC of 1%.

Overall, studies on *Santolina* species as antimicrobial agents are of interest. Some of the essential oils obtained by *Santolina* species showed comparable activity to widely used drugs such as clotrimazole. For this reason, an urgent need of animal and human studies to determine their effectiveness in whole-organism systems, with particular reference to their potential toxicity, are required in order to clarify if these phytochemicals could be used in therapy or in lead compounds for the development of more efficacy and a safe antimicrobial product. Moreover, in addition to tests and classic bacteriostatic and bactericidal activities, it is also important to investigate extracts and pure compounds against alternative bacterial targets, such as host-directed targets, pathogenesis, and virulence.

Antiviral activity

The only *Santolina* species that was investigated for its antiviral activity was *S. insularis*. In particular, the essential oil of *S. insularis* was studied against HSV-1 and HSV-2 [10]. Infections by HSV-1 and HSV-2 are among the most common viral infections in humans. When HSV-1 and HSV-2 were exposed to the *S. insularis* essential oil for 1 h at 37 °C, a concentration-dependent inhibition of plaque formation was observed. A 50% inhibition was observed at 0.88 and 0.7 µg/mL for HSV-1 and HSV-2, respectively. The inactivation of both HSV-1 and HSV-2 depends on the length of exposure to *S. insularis* essential oil. In fact, a higher inhibition was detected when HSV-1 and HSV-2 were preincubated for 2 h at the same temperature of 37 °C (50% inhibition at 0.31 and 0.26 µg/mL for HSV-1 and HSV-2, respectively). Moreover, the inactivation of HSV-1 was more efficient than HSV-2 when viruses were preincubated for 15 min before adsorption (50% inhibition at 6.39 and 7.66 µg/mL for HSV-1 and HSV-2, respectively). In attachment tests, a 50% inhibition was demonstrated in respect to the untreated controls at concentrations > 30 µg/mL for both viruses. These values were higher than those obtained with the controls of viruses preincubated (for 2 h at 4 °C) in the presence of the same concentrations of *S. insularis* oil, showing that attachment was not affected and the activity was primarily due to the direct effects on the virion. Overall, obtained results indicated that *S. insularis* essential oil is effective in inactivating HSV-1 and HSV-2. The inactivation is time and temperature independent. No differences were detected in the plaque reduction assays when cells were treated with the oil before virus adsorption.

The way in which *S. insularis* essential oil acts is unique in that no natural products are able concomitantly to inactivate the virus and inhibit cell-to-cell virus spread. Moreover, it is of interest that the IC_{50} values of *S. insularis* essential oil against both HSV-1 and HSV-2 is comparable to those reported for approved drugs for the treatment of HSV infections, such as acyclovir and ganciclovir. Further studies are necessary to investigate the effect of the essential oil in animal models infected with HSV, and to isolate phytochemicals responsible for the antiviral activity.

Successively, Valenti et al. [58] prepared, characterized, and investigated the *in vitro* antiviral activity of liposome-incorporated *S. insularis* essential oil (multilamellar and unilamellar vesicles obtained from hydrogenated soya phosphatydilcholine and cholesterol). The anti-HSV-1 properties were studied by plaque and yield reduction tests. The *S. insularis* essential oil could be incorporated in high amounts in the prepared liposomes. The essential oil inactivated HSV-1. This activity is mainly due to direct virucidal effects. The *S. insularis* oil was more active than the liposome-incorporated essential oil. The ED_{50} values were considerably lower when cells were preincubated with the oil before the adsorption of the virus. These data suggested an intracellular mechanism for the activity of the oil of *S. insularis*. Importantly, liposomal *S. insularis* essential oil was nontoxic in the range of concentrations tested in the study.

Despite the recent progress made in immunization and drug development, many infections represent a serious health problem since there are no vaccines and efficient antiviral therapies, which are often surrounded by the generation of viral mutants. Consequently, the search for new antiviral drugs is a hot topic of research. Taking into account that plants are an excellent source of phytochemicals with a broad range of bioactivity, including antiviral, the research of natural compounds with this property will be

enhanced. In this context, *S. insularis* represents a promising species that requires much attention.

Anti-inflammatory activity

Studies were carried out in order to validate the traditional uses of some *Santolina* species as anti-inflammatory agents. Some extracts of *S. chamaecyparissus* were the object of study for evaluation of their potential anti-inflammatory activity. Giner et al. [59] proved the anti-inflammatory properties of the chloroform extract of *S. chamaecyparissus* against carrageenan paw edema in rats. The anti-inflammatory activity of the methanol extract of *S. chamaecyparissus* was demonstrated in different experimental models [60]. In particular, this extract inhibited PLA1 activity *in vitro* at 1 mg/mL. No lipoxygenase inhibitory effects were found.

Sala et al. [11] reported the activity of the methanol extract of *S. chamaecyparissus* against PLA2-induced mouse paw edema. An inhibition of the edema with percentages of 55 and 60% at 30 and 60 min, respectively, was evidenced. This activity is comparable to the reference drug cyproheptadine with 65 and 66% inhibition at 30 and 60 min, respectively. After fractionation by using solvents with different polarities (hexane, dichloromethane, ethyl acetate, and butanol), only the dichloromethane extract was active against the PLA2 *in vitro* test with a percentage of inhibition of 48%. Moreover, it was shown to reduce the edema induced by 12-*O*-tetradecanoylphorbol-13-acetate and arachidonic acid in a multidose test.

Fractionation of the dichloromethane extract gave eight fractions, three of which were active with inhibition percentages against PLA2 activity ranging from 47 to 62%. From the active fractions, four purified sesquiterpenes and one flavone, spathulenol, (7*S*)-4*β*,5*α*-epoxygermacrl(10)*E*-en-2*β*,6-diol, (7*S*)-germacra-4(15)*Z*,9dien-1*α*,2*β*,5*α*,6*β*-tetraol, (7*S*)-germacra-1(10)*E*,4(15)-dien-2*β*,5*α*,6*β*-triol, and nepetin, were isolated. Only the fraction from which nepetin was isolated maintained an inhibition range of 50%, including the flavonoid with a percentage of 52%.

Hexane, dichloromethane, ethyl acetate, and methanol extracts obtained from the air-dried aerial parts of *S. oblongifolia* by means of a Soxhlet extractor were investigated for their potential anti-inflammatory activity by using the adjuvant carrageenan-induced inflammation (ACII) model using Wistar male rats [61]. Elevated serum Cu levels and decreased serum Zn levels associated with the development of arthritis in ACII immunizing Wistar rats were demonstrated.

Administration of *S. oblongifolia* extracts significantly prevented the development of ACII in Wistar rats, and they were more active than the positive control indomethacin in the chronic phase of the experiment. The most interesting extract was the ethyl acetate extract, which possesses potent activity against these parameters of chronic inflammation [62]. The flavonoids apigenin (**3**), luteolin (**5**), and quercetin were isolated from this extract and tested together with the coumarins aesculetin, herniarin, scopoletin (**10**), and scopolin [7]. The isolated coumarins showed a marked activity as inhibitors of eicosanoid release from ionophore-stimulated mouse peritoneal macrophages. A significant inhibitory activity of eicosanoid release from ionophore-stimulated mouse peritoneal macrophages was found. Scopoletin, aesculetin, scopolin, and herniarin showed IC_{50} values of 5, 11, 77, and 84 µmol, respectively. In the LTC4-release test, only aesculetin exhibited a significant effect, with an IC_{50} value of 18 µmol. Scopolin showed an inhibition rate of 55% at the highest concentration, while herniarin and scopoletin demonstrated no significant effects on LTC4 release.

Apigenin, luteolin, quercetin, herniarin, scopoletin, scopolin, and aesculetin, isolated from *S. oblongifolia*, have been investigated for their anti-inflammatory activity [63]. All phytochemicals influenced the response to thromboxane B(2) release in a dose-dependent way, and with percentages of inhibition being slightly lower than ibuprofen, used as a reference drug. Among all investigated classes of phytochemicals, flavonoids and coumarin exerted the most potent activity, probably due to their ability to inhibit arachidonic acid metabolism. Several researches evidenced that flavonoids are safe alternatives to combat several inflammatory reactions. However, recently, certain side effects related to the use of these compounds were reported [64]. Even though it is widely accepted that natural products are safe, evidence suggests that upon clinical use, these drugs are never being seen without risk. In this context, *Santolina*-derived products could represent an alternative, but only after investigation of their nontoxic character.

The aerial parts of *Santolina viscosa* collected in Spain, together with 60 other plant species, were subjected to a sequential extraction by petroleum ether, ethyl acetate, and methanol [65]. The obtained extracts were studied for their potential anti-inflammatory activity targeting NF-*κ*B and other proinflammatory mediators (IL-6, IL-8, TNF-*α*) or PGE2 in monocytes. A weak inhibitory activity was found against NF-*κ*B, while in tests against the cytokines. a number of species, including *S. viscosa*, inhibited TNF-*α* (10 µg/mL).

The methanol extract of *S. insularis* leaves was studied for its chemical profile and topical anti-inflammatory activity by using croton oil-induced dermatitis in the mouse ear [5]. Six flavonoids, namely, cirsimaritin, hispidulin, luteolin, luteolin 7-*O*-*β*-D-glucopyranoside, nepetin, and rhamnocitrin, and one new xanthone, (*E*)-3-(6-[(*E*)-3-hydroxy-3-oxo-1-propenyl]-9-oxo-9Hxanthen-2-yl)-2-propenoic acid, were isolated and tested. All compounds were able to inhibit croton oil-induced ear edema. The most active, after topical application, was luteolin (0.3 µmol/cm^2), that led to a 62% reduction of edema, while indomethacin (0.3 µmol/cm^2), used as a reference compound, led to a 59% reduction of edema. Cirsimaritin, hispidulin, nepetin, and rhamnocitrin showed lower anti-inflammatory activity compared to luteolin. Taking into account that all these flavonoids are methoxylated, the lack of one of the free hydroxyl groups determined a decrease of activity. After topical application, xanthone showed only a 20% reduction of edema.

Cytotoxic activity

Few studies reported the cytotoxic activity of *Santolina* species. The essential oil of *S. chamaecyparissus* was investigated against MCF-7, HCT116, A549, and HepG2 cancer cell lines [66]. The highest cytotoxic activity was found against HepG2 cancer cells.

Eleven germacrane sesquiterpenes were isolated from the acetone extract of the aerial parts of *S. insularis* and tested for their potential cytotoxic activity against the human colon carcinoma

cell line Caco-2 [2]. The highest activity was found for compound **36**, with an IC_{50} value of 1.1 µM. These results encourage research towards the study of the antiproliferative activity of other *Santolina* species and isolated constituents.

Other properties

A study was conducted to investigate possible protective effects of the essential oil of *S. canescens* and its main constituent santolindiacetylene on carbon tetrachloride (CCl_4)-induced hepatotoxicity in an experimental Wistar rat model [67]. Determination of GPT serum levels is a useful indicator of hepatocellular damage. In fact, in the presence of damage to the cell membrane, some cytoplasmatic enzymes such as GPT are released into the bloodstream. In the employed model, a dose of carbon tetrachloride produced a rise in GPT levels and lipid peroxides in the liver. The protective effects of *S. canescens* essential oil and santolindiacetylene were demonstrated by their ability to prevent this increase. In both groups treated with the essential oil or santolindiacetylene, levels of GPT were clearly lower than in the group treated only with CCl_4. Moreover, no significant differences between the results obtained with *S. canescens* and santolindiacetylene and those obtained with silymarin (known as a hepatoprotective agent, used as a positive control) were found. The interest in the essential oils as biopesticides is growing because the long-term uses of synthetic insecticides lead to the accumulation of residues and produce adverse effects on human health and ecosystems. In this context, the biocidal properties of *S. chamaecyparissus* were investigated [68]. Specifically, the objects of the study were the nematicidal (*Meloidogyne javanica*), ixodicidal (*Hyalomma lusitanicum*), insect antifeedant (*Leptinotarsa decemlineata, Myzus persicae, Spodoptera littoralis*, and *Rhopalosiphum padi*), and phytotoxic effects (*Lolium perenne* and *Lactuca sativa*). The essential oil of *S. chamaecyparissus* demonstrated strong antifeedant effects against *R. padi* and *H. lusitanicum* while showing moderate activity against *L. decemlineata* and *S. littoralis*. Moreover, moderate phytotoxic activity against the leaf growth of *L. perenne* was found.

Conclusions and Perspectives

This review summarized the uses in traditional medicine and the main phytochemicals and biological properties of species of the genus *Santolina*.

Some *Santolina* species are traditionally used in different countries for their antispasmodic, digestive, analgesic, anti-inflammatory, antiseptic, stimulant, and antimicrobial properties. To a certain extent, some traditional uses have been scientifically validated and supported by biological studies. In particular, results obtained on the antimicrobial effects of *Santolina* species showed a good correlation with the reported traditional uses. However, according to literature information, only a few species of this genus have been extensively investigated for the evaluation of their chemical profile. Among isolated constituents, terpenes (mainly germacrane and eudesmane derivatives) are the most representative compounds. Several new sesquiterpenes have been identified in *S. insularis, S. chamaecyparissus* subsp. *squarrosa, S. pinnata* subsp. *neapolitana, S. rosmarinifolia* subsp. *canescens*, and *S. insularis*. These constituents may be considered chemotaxonomic markers of the genus. However, phytochemical investigations on more *Santolina* species are required in order to confirm the possibility to use these molecules as taxonomic markers.

Although phytochemical and biological studies on *Santolina* species have received considerable interest, some gaps are still noteworthy. Firstly, most of the studies are aimed at evaluating the nonpolar constituents of *Santolina* species and not at characterizing the polar compounds, such as flavonoids, identified in *S. insularis* and *S. pinnata*. Secondly, studies mainly focused on four *Santolina* species, *S. chamaecyparissus, S. insularis, S. corsica*, and *S. oblongifolia*. Therefore, a comprehensive investigation of other species is necessary. Thirdly, various biological activities of the extracts and pure compounds were mainly investigated by using *in vitro* tests and less were carried out by *in vivo* models. Therefore, there are few reported data focused on toxicity, side effects, and clinical efficiency. Fourthly, the few pharmacological studies are still insufficient to determine the effects and validate the uses of *Santolina* species in traditional medicine. Therefore, more detailed studies are required 1) to investigate *Santolina* species that have never been chemically and biologically studied, 2) to analyze the potential toxicity of *Santolina* extracts and/or essential oils, 3) to identify the pharmacokinetics and pharmacodynamics of bioactive compounds isolated from the most promising extracts/essential oils, and 4) to develop systems to increase the efficacy and safety of *Santolina*-derived products.

Conflict of Interest

The authors declare no conflicts of interest.

References

[1] Derbesy M, Touche J, Zokd A. The essential oil of *Santolina chamaecyparissus* L. J Essent Oil Res 1989; 1: 269–275

[2] Appendino G, Aviello G, Ballero M, Borrelli F, Fattorusso E, Petrucci F, Santelia FU, Taglialatela-Scafati O. Cytotoxic germacrane sesquiterpenes from the aerial parts of *Santolina insularis*. J Nat Prod 2005; 68: 853–857

[3] Fattorusso E, Santelia FU, Appendino G, Ballero M, Taglialatela-Scafati O. Polyoxygenated eudesmanes and *trans*-chrysanthemanes from the aerial parts of *Santolina insularis*. J Nat Prod 2004; 67: 37–41

[4] De Pascual TJ, Bellido IS, González MS, Vicente S. Tetracyclic triterpenes and nerolidol derivatives from *Santolina oblongifolia*. Phytochemistry 1985; 25: 185–190

[5] Cottiglia F, Casu L, Bonsignore L, Casu M, Floris C, Sosa S, Altinier G, Della Loggia R. Topical anti-inflammatory activity of flavonoids and a new xanthone from *Santolina insularis*. Z Naturforsch C 2005; 60: 63–66

[6] Flamini G, Ghelli GC, Pistelli L, Morelli I. Phenolic compounds from *Santolina pinnata*. Planta Med 1994; 60: 97

[7] Silván AM, Abad MJ, Bermejo P, Sollhuber M, Villar A. Antiinflammatory activity of coumarins from *Santolina oblongifolia*. J Nat Prod 1996; 59: 1183–1185

[8] Liu K, Rossi PG, Ferrari B, Berti L, Casanova J, Tomi F. Composition, irregular terpenoids, chemical variability and antibacterial activity of the essential oil from *Santolina corsica* Jordan et Fourr. Phytochemistry 2007; 68: 1698–1705

[9] Suresh B, Sriram S, Dhanaraj SA, Elango K, Chinnaswamy K. Anticandidal activity of *Santolina chamaecyparissus* volatile oil. J Ethnopharmacol 1997; 55: 151–159

[10] De Logu A, Loy G, Pellerano ML, Bonsignore L, Schivo ML. Inactivation of HSV-1 and HSV-2 and prevention of cell-to-cell virus spread by *Santolina insularis* essential oil. Antiviral Res 2000; 48: 177–185

[11] Sala A, Recio MC, Giner RM, Máñez S, Ríos JL. Anti-phospholipase A2 and anti-inflammatory activity of *Santolina chamaecyparissus*. Life Sci 2000; 66: PL35–PL40

[12] Villar A, Giner RM, Rios JL. Chemical composition of *Santolina chamaecyparissus* subsp. *squarrosa* essential oil. J Nat Prod 1986; 49: 1143–1145

[13] Giner RM, Rios JL, Villar A. Pharmacological study of *Santolina chamaecyparissus*. Phytother Res 1988; 12: 37–41

[14] Yoganarasimhan SN. Medicinal Plants of India-Tamilnadu, vol II. Bangalore: Cyber Media; 2000: 276

[15] Calvo MI, Cavero RY. Medicinal plants used for ophthalmological problems in Navarra (Spain). J Ethnopharmacol 2016; 190: 212–218

[16] Akerreta S, Cavero RY, López V, Calvo MI. Analyzing factors that influence the folk use and phytonomy of 18 medicinal plants in Navarra. J Ethnobiol Ethnomed 2007; 3: 16–34

[17] Savo V, Giulia C, Maria GP, David R. Folk phytotherapy of the Amalfi Coast (Campania, Southern Italy). J Ethnopharmacol 2011; 135: 376–392

[18] Loi MC, Poli F, Sacchetti G, Selenu MB, Ballero M. Ethnopharmacology of Ogliastra (Villagrande Strisaili, Sardinia, Italy). Fitoterapia 2004; 75: 277–295

[19] Ballero M, Fresu I. Piante officinali impiegate in fitoterapia nel territorio del Marganai (Sardegna sud-occidentale). Fitoterapia 1991; 62: 524–531

[20] Poli F, Bonsignore L, Loy G, Sacchetti G, Ballero M. Comparison between the essential oils of *Santolina insularis* (Genn. ex Fiori) Arrigoni and *Santolina corsica* Jord. et Fourr. from the island of Sardinia (Italy). J Ethnopharmacol 1997; 56: 201–208

[21] Guarrera PM, Forti G, Marignoli S. Ethnobotanical and ethnomedicinal uses of plants in the district of Acquapendente (Latium, Central Italy). J Ethnopharmacol 2005; 96: 429–444

[22] Novais MH, Santos I, Mendes S, Pinto-Gomes C. Studies on pharmaceutical ethnobotany in Arrabida Natural Park (Portugal). J Ethnopharmacol 2004; 93: 183–195

[23] Barrero AF, Alvarez-Manzaneda R, Quilez JF, Mar Herrador M. Sesquiterpenes from *Santolina chamaecyparissus* subsp. *squarrosa*. Phytochemistry 1998; 48: 807–813

[24] Barrero AF, Herrador MM, Quilez JF, Alvarez-Manzaneda R, Portal D, Gavin JA, Gravalos DG, Simmonds MS, Blaney WM. Bioactive sesquiterpenes from *Santolina rosmarinifolia* subsp. *canescens*. A conformational analysis of the germacrane ring. Phytochemistry 1999; 51: 529–541

[25] Alberto Marco J, Sanz-Cervera JF, Carda M, Lex J. Oxygenated germacranes from *Santolina chamaecyparissus*. Phytochemistry 1993; 34: 1549

[26] Sanz JF, Garcia-Sarrion A, Alberto Marco J. Germacrane derivatives from *Santolina chamaecyparissus*. Phytochemistry 1991; 30: 3339–3342

[27] Maqua MP, Vines ACG, Caballero E, Grande MC, Medarde M, Bellido IS. Components from *Santolina rosmarinifolia*, subspecies *rosmarinifolia* and *canescens*. Phytochemistry 1988; 27: 3664

[28] Bohlmann F, Zdero C. Polyacetylenverbindungen, 152. Die Acetylenverbindungen aus *Santolina chamaecyparissus* L. Chem Ber 1968; 101: 2062

[29] Lam J, Bildsoe H, Christensen LP, Thomasen T. Chemical constituents of *Santolina chamaecyparissus*. Acta Chem Scand 1989; 43: 799–802

[30] Perez-Alonso MJ, Negueruela V. Essential oil components of *Santolina chamaecyparissus* L. Flav Fragr J 1992; 3: 37–41

[31] Giner RM, Manez S, Rios JL. Seasonal variations in the essential oil of *Santolina chamaecyparissus* L. Sci Pharm 1993; 61: 169–173

[32] Lawrence M. *Santolina* Oil. In: Lawrence BM, ed. Essential Oils, 1992–1994. Card Stream, IL USA: Allured Publ. Corp.; 1995: 57–59

[33] Vernin G. Volatile constituents of the essential oil of *Santolina chamaecyparissus* L. J Essent Oil Res 1991; 3: 49–53

[34] Demirci B, Ozek T, Baser KHC. Chemical composition of *Santolina chamaecyparissus* L. essential oil. J Essent Oil Res 2000; 12: 625–627

[35] Salah-Fatnassi KBH, Hassayoun F, Cheraif I, Khan S, Jannet HB, Hammami M, Aouni M, Harzallah-Skhiri F. Chemical composition, antibacterial and antifungal activities of flowerhead and root essential oils of *Santolina chamaecyparissus* L., growing wild in Tunisia. Saudi J Biol Sci 2017; 24: 875–882

[36] Garg SN, Gupta D, Mehta VK, Kumar S. Volatile constituents of the essential oil of *Santolina chamaecyparissus* Linn, from the Southern hills of India. J Essent Oil Res 2001; 13: 234–235

[37] Khubeiz MJ, Mansour G. *In vitro* antifungal, antimicrobial properties and chemical composition of *Santolina chamaecyparissus* essential oil in Syria. Int J Toxicol Pharmacol Res 2016; 8: 372–378

[38] Djeddi S, Djebile K, Hadjbourega G, Achour Z, Argyropoulou C, Skaltsa H. *In vitro* antimicrobial properties and chemical composition of *Santolina chamaecyparissus* essential oil from Algeria. Nat Prod Commun 2012; 7: 937–940

[39] Tognolini M, Barocelli E, Ballabeni V, Bruni R, Bianchi A, Chiavarini M, Impicciatore M. Comparative screening of plant essential oils: phenylpropanoid moiety as basic core for antiplatelet activity. Life Sci 2006; 78: 1419–1432

[40] Grosso C, Figueiredo AC, Burillo J, Mainar AM, Urieta JS, Barroso JG, Coelho JA, Palavra AM. Supercritical fluid extraction of the volatile oil from *Santolina chamaecyparissus*. J Sep Sci 2009; 32: 3215–3222

[41] Rossi PG, Panighi J, Luciani A, de Rocca Serra D, Maury J, Gonny M, Muselli A, Bolla JM, Berti L. Antibacterial action of essential oils from Corsica. J Ess Oil Res 2007; 19: 176–182

[42] Cherchi G, Deidda D, De Gioannis B, Marongiu B, Pompei R, Porcedda S. Extraction of *Santolina insularis* essential oil by supercritical carbon dioxide: influence of some process parameters and biological activity. Flavour Fragr J 2001; 16: 35–43

[43] Gnavi G, Bertea CM, Usai M, Maffei ME. Comparative characterization of *Santolina insularis* chemotypes by essential oil composition, 5S-rRNA-NTS sequencing and EcoRV RFLP-PCR. Phytochemistry 2010; 71: 930–936

[44] Ferrari B, Tomi F, Richomme P, Casanova J. Two new irregular acyclic sesquiterpenes aldehydes from *Santolina corsica* essential oil. Magn Reson Chem 2005; 43: 73–74

[45] Pérez-Alonso MJ, Velasco Negueruela A. The essential oils of four *Santolina* species. Flav Fragr J 1988; 3: 37–42

[46] Senatore F, De Feo V. Composition of the essential oil of *Santolina neapolitana* Jordan et Fourr. Flav Fragr J 1994; 9: 77–79

[47] Flamini G, Bertoli A, Taglioli V, Cioni PL, Morelli I, Spinelli G. Composition of the essential oil of *Santolina ligustica*. J Essent Oil Res 1999; 11: 6–8

[48] Flamini G, Cioni PL. Seasonal variation of the chemical constituents of the essential oil of *Santolina etrusca* from Italy. Chem Biodiv 2007; 4: 1008–1019

[49] Derouiche K, Zellagui A, Gherraf N, Bousetla A, Dehimat L, Rhouati S. Chemical composition, antimicrobial and antioxidant activities of the essential oils of *Santolina africana* flowers, endemic in Algeria. J BioSci Biotech 2013; 2: 201–206

[50] Zaiter L, Benayache F, Beghidja N, Figueredo G, Chalard P, Chalchat JC, Marchioni E, Benayache S. Essential oils of *Santolina africana* Jord. & Fourr. and *Santolina chamaecyparissus* L. J Essent Oil Bear Pl 2015; 18: 1338–1342

[51] Mateos JPC, Martínez A, Navarro MC, Utrilla MP, Jiménez J. Multiple headspace extraction of volatiles from *Santolina canescens* Lagasca during its growth cycle. J Essent Oil Res 2001; 13: 170–173

[52] Ioannou E, Poiata A, Hancianu M, Tzakou O. Chemical composition and *in vitro* antimicrobial activity of the essential oils of flower heads and leaves of *Santolina rosmarinifolia* L. from Romania. Nat Prod Res 2007; 21: 18–23

[53] Palá-Paúl J, Pérez-Alonso MJ, Velasco-Negueruela A, Palá-Paúl R, Sanz J, Conejero F. Seasonal variation in chemical constituents of *Santolina rosmarinifolia* L. subsp. *rosmarinifolia*. Biochem Syst Ecol 2001; 29: 663–672

[54] Kisiel W, Dawid-Pać R, Grabarczyk H, Nowak G. Germacrane derivatives from *Santolina pinnata* subsp. *neapolitana*. Z Naturforsch C 2003; 58: 793–796

[55] Barrero AF, Alvarez-Manzaneda EJ, Mar Herrador M, Alvarez-Manzaneda R, Quilez J, Chahboun R, Linares P, Rivas A. The first route toward oxygenated monocarbocyclic terpenoids: synthesis of elegansidiol, a new sesquiterpene from *Santolina elegans*. Tetrahedron Lett 1999; 40: 8273–8276

[56] Guinoiseau E, Luciani A, Rossi PG, Quilichini Y, Ternengo S, Bradesi P, Berti L. Cellular effects induced by *Inula graveolens* and *Santolina corsica* essential oils on *Staphylococcus aureus*. Eur J Clin Microbiol Infect Dis 2010; 29: 873–879

[57] Macchioni F, Perrucci S, Flamini G, Cioni PL, Morelli I. Antimycotic activity against *Saprolegnia ferax* of extracts of *Artemisia verlotorum* and *Santolina etrusca*. Phytother Res 1999; 13: 242–244

[58] Valenti D, De Logu A, Loy G, Sinico C, Bonsignore L, Cottiglia F, Garau D, Fadda AM. Liposome-incorporated *Santolina insularis* essential oil: preparation, characterization and *in vitro* antiviral activity. J Liposome Res 2001; 11: 73–90

[59] Giner R, Rios JL, Villar A. Pharmacological study of *Santolina chamaecyparissus*. I. Acute toxicity, antiinflammatory and antiulcer activity. Planta Med 1986; 52: 540–541

[60] Cuéllar MJ, Giner RM, Recio MC, Just MJ, Máñez S, Cerdá S, Ríos JL. Screening of antiinflammatory medicinal plants used in traditional medicine against skin diseases. Phytother Res 1998; 12: 18–23

[61] Silván AM, Abad MJ, Bermejo P, Villar A. Effect of *Santolina oblongifolia* on ACII-immunized animals. Inflammopharmacology 1997; 5: 351–361

[62] Silván AM, Abad MJ, Bermejo P, Villar A, Söllhuber M. Anti-inflammatory activity of three flavonoids from *Santolina oblongifolia*. Phytother Res 1996; 10: S65–S66

[63] Silván AM, Abad MJ, Bermejo P, Villar A. Effects of compounds extracted from *Santolina oblongifolia* on TXB(2) release in human platelets. Inflammopharmacology 1998; 6: 255–263

[64] Martinez SE, Davies NM, Reynolds JK. Toxicology and Safety of Flavonoids. In: Davies NM, Yáñez JA, eds. Flavonoid Pharmacokinetics: Methods of Analysis, preclinical and clinical Pharmacokinetics, Safety, and Toxicology. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2012: 249–267

[65] Bremner P, Rivera D, Calzado MA, Obón C, Inocencio C, Beckwith C, Fiebich BL, Muñoz E, Heinrich M. Assessing medicinal plants from South-Eastern Spain for potential anti-inflammatory effects targeting nuclear factor-Kappa B and other pro-inflammatory mediators. J Ethnopharmacol 2009; 124: 295–305

[66] Elsharkawy ER. Anticancer effect and seasonal variation in oil constituents of *Santolina chamaecyparissus*. Chem Materials Res 2014; 6: 85–91

[67] Utrilla MP, Navarro MC, Jimenez J, Montilla MP, Martin A. Santolindiacetylene, a polyacetylene derivative isolated from the essential oil of *Santolina canescens*. J Nat Prod 1995; 58: 1749–1752

[68] de Elguea-Culebras GO, Sánchez-Vioque R, Berruga MI, Herraiz-Peñalver D, González-Coloma A, Andrés MF, Santana-Méridas O. Biocidal potential and chemical composition of industrial essential oils from *Hyssopus officinalis, Lavandula x intermedia* var. *super* and *Santolina chamaecyparissus*. Chem Biodivers 2018; 15: e1700313. doi:10.1002/cbdv.201700313