Phytochemistry of *Commiphora erythraea*: A Review

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Commiphora erythraea (Burseraceae) resin derives from the bark injury of the plant, a small tree native to the Arabian Peninsula. The resin is commonly known as myrrh and it is traditionally used to protect livestock from ticks and to treat diseases related to inflammation. The resin is constituted by a volatile and a non-volatile fraction. The volatile fraction is a source of furanosesquiterpenoids among which furanodienone showed to be the most promising pharmacological active compound. The composition and pharmacological activities of the extracts and the isolated compounds have been reviewed.

1. Introduction

Plant resins are lipid-soluble mixtures constituted by secondary metabolites, mostly belonging to the class of terpenoids and phenolics. They are produced by specialized tissues such as canals, pockets, cavities, trichomes and epidermal cells and are generally formed by a volatile fraction (essential oil) and a non-volatile one. The volatile fraction usually consists of mono- and/or sesquiterpenes or their oxygenated derivatives, while the non-volatile is mostly formed by di- and triterpenes and their derivatives. The ratio between volatile and non-volatile fractions influences the consistency of the resin (fluidity and viscosity). The loss of the volatile fraction determines the hardening of the resin that becomes sticky and is called "gum". Chemically, true gums are constituted by polysaccharides and produced in different tissues. Some genera (e.g. *Commiphora*) produce both exudates, and during the plant development, the wall of the secretory tissues is removed and gums and resins are mixed, giving rise to oleogum-resins [1]. Amber is fossilized resin [1].

Burseraceae, a family of flowering shrubs or trees in the order of Sapindales, is characterized by the production of resins and it is commonly called "torchwood family" due to the fact that the wood burns well for the high resin content. The family comprises 18 genera and approximately 540 species of plants distributed in tropical and subtropical regions and divided into three tribes: Bursereae, Canarieae and Protieae [2]. Among Bursereae, *Bursera*, *Commiphora* and *Boswellia* are particularly important genera for their valuable resins and oleogum resins (copal, myrrh and frankincense, respectively) that are produced in the schizogenous canals present in phloem and are released after bark damage [2].

The genus *Commiphora* comprises approximately 190 species of small trees and large shrubs, native particularly to Arabia, Somalia, eastern Ethiopia and Kenya [2]. *Commiphora* is characterized by pinnately compound leaves, a bark that often exfoliates in thin sheets, succulent stems, subdioecious flowers. Fruits are drupes usually with a 2-loculary ovary [3].

Myrrh has been used since ancient time for different purposes. In ancient Egypt it was used for embalming the bodies of Pharaohs, Jews used to give "wine mingled with myrrh" to those who were condemned to death by crucifixion to produce insensibility, and myrrh was one of the gifts brought by the wise men to infant Jesus. For its fragrant smell, myrrh has been used in the past, and it is still used, for the production of perfumes. Furthermore, several medical uses have been reported [4]. Myrrh resin is formed by water-soluble gum, alcohol-soluble resin and essential oil [5].

Today, the commercial source of myrrh is *C. myrrha* (Nees) Engl., but *C. erythraea* (Ehrenb.) Engl. was the source in ancient and classical times [4].

C. erythraea is a small tree growing in the Arabian Peninsula, particularly in Ethiopia, where the resin is called "agarsu" and is used to protect livestock from ticks [6] and for different medical purposes such as antimalarial, to prevent colds and fever, to enhance wound healing [7].

Commiphora essential oils are characterized by high amounts of sesquiterpenes and sesquiterpenoids, particularly furanosesquiterpenes and furanosesquiterpenoids that are the responsible of the resin's aromatic fragrance [8, 9].

2. Chemistry

The first literature report about *C. erythraea* dates back to '40's, when the commercial essential oil of *C. erythraea* var. *glabrescens*, known as "opopanax", was studied by several authors [10-15]. The term opopanax created several identification problems. As a matter of fact, this term has been used for the oil of *Opopanax chironium* (Apiaceae) and different species of *Commiphora* (eg. *C. kataf*, *C. guidottii*) [16-18]. Today it has been stated that the commercial opopanax is derived from *C. guidottii* [14, 18].

The first report on certified *C. erythraea* resin's steam distilled essential oil (SD) composition, determined by GC-MS and NMR spectroscopy, revealed the presence of monoterpenes (6.1%), monoterpenoids (0.4%), sesquiterpenes (36.6%) and sesquiterpenoids (53.7%), particularly furanosesquiterpenoids (50%) [19] (Table 1, Figure 1). α-Thujene and α-pinene were the most abundant among monoterpenes and monoterpenoids,, and α-copaene, aromadendrene and germacrene D amon sesquiterpenes. GS-MS analysis has allowed to distinguish *C. erythraea* from *C. kataf*: two species that are often mistaken for each other.
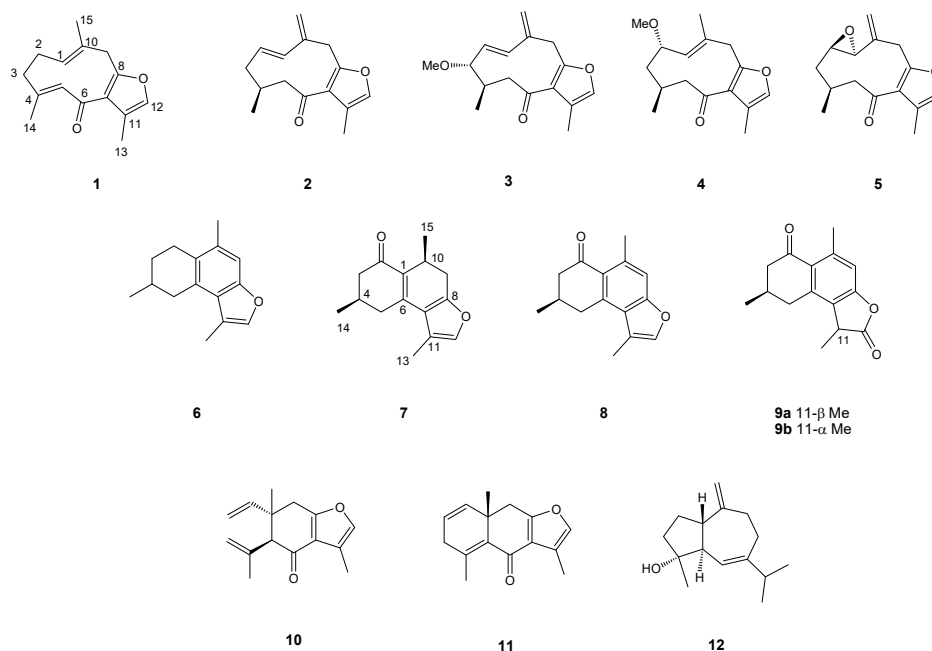
Figure 1: Isolated sesquiterpenoids from *Commiphora erythraea* resin.

The resin's volatile fraction composition is highly dependent on the extraction method [20]. Fraternale and coll. compared steam distilled essential oil (D) to hydrodistilled essential oil (HD) and they note that the latter is characterized by a higher amount of monoterpenes (22% *vs* 5.55%) and sesquiterpenes (53.7% *vs* 39%). On the other hand, it seems that hydrodistillation is not the elective preparative method to extract furanosesquiterpenoids (17.9% *vs* 44.5%) (Table 1) [20].

Extraction of the resin by solvents (*n*-hexane and supercritical CO_2) allows a better recovery of furanosesquiterpenoids, but no monoterpenes or monoterpenoids were present in the extracts, this is probably due to evaporation of such very volatile compounds together with the solvent (Table 1) [20].

In all the oils and extracts, furanodienone [1(10),4-furanogermacradien-6-one] (**1**) [21] resulted the most abundant compound along with 1,10(15)-furanogermacra-dien-6-one (**2**) [22], 3-methoxy-furanogermacra-1E,10(15)-dien-6-one (**3**) [23, 24], 2-methoxy-furanogermacra-1(10)E-en-6-one (**4**) [23, 24], 1,2-epoxy-furanogermacr-10(15)-en-6-one (**5**) [24], dihydropyrocurzerenone (**6**) [25], agarsenone (**7**) [26], myrrhone (**8**) [27], curzerenone (**10**) [28], furanoeudesma-1,4-dien-6-one (**11**) [29] and alismol (**12**) [30]. Agarsenone (**7**) showed to be unstable in chlorinated solvents, giving rise in short time, to mirrhone (**8**), and, by autoxidation [31], to agarsenolides (**9a** and **b**) [26] (Figure 1).

Table 1: Composition of essential oils and extracts from *C. erythraea* resin.[a]

Class of Compounds	SD[b]	D[c]	HD[d]	H[e]	SFE1[f]	SFE2[g]
Monoterpenes	6.10	5.55	22.0	=	=	=
Monoterpenoids	0.40	0.32	0.98	=	=	=
Sesquiterpenes	36.60	38.97	53.74	23.80	13.57	15.41
Sesquiterpene alcohols	2.50	5.50	2.80	3.67	0.87	0.39
Sesquiterpene ketones	0.90	1.26	0.37	=	3.62	3.01
Furanosesquiterpenoids	50.30	44.45	17.86	64.95	74.54	67.08

[a] Percentage obtained by FID peak area normalization. [b] SD: Steam distilled oil [19]. [c] D: Steam distilled oil [20]. [d] HD: Hydrodistilled oil [20]. [e] H: Hexane extract [20]. [f] SFE1: Supercritical CO_2 extract (20MPa, 20 °C, 1h) [20]. [g] SFE2: Supercritical CO_2 extract (100MPa, 40 °C, 1h) [20].

In view of their pharmacological activities, the absolute configuration of the main resin components was undertaken by means of computational analysis of chiroptical properties (optical rotatory dispersion, electronic circular dichroism, vibrational circular dichroism) [32]. All the tested furanogermacrane compounds (**2-5**) and furanocadinane ones (**7-9**) showed the same spatial arrangement at the methyl-substituted carbon C-4 suggesting a common biosynthetic pathway.

3. Pharmacological Activity

Commiphora erythraea is traditionally used to treat several diseases. For example, its bark, sap and gum are used for the treatment of foetal membrane retention, against worm infestations [7] and the traditional use of the resin to protect livestock from ticks [7] has been confirmed by Maradufu and coll. who tested the resin's hexane extract against the brown ear tick, *Rhipicephalus appendiculatus* [6, 33]. Zorloni in his work, reported also the use of the resin as anti-inflammatory to treat eye problems [7].

The antiradical, antioxidant and anti-inflammatory activity of the resin's hexane extract fractions and isolated compounds have been proved. Fraternale and coll. compared the antiradical activity of essential oils and hexane extract. They found that, in an *in vitro* antiradical test (DPPH, 1,1-diphenyl-2-picrylhydrazil) the hexane extract showed the lowest EC_{50} [34] (Table 2) [20]. Following a bioassay-guided separation of the compounds, the active hexane extract was partitioned by column chromatography (SiO_2) using hexane, methylene chloride (CH_2Cl_2) and CH_2Cl_2-ethyl acetate (EtOAc) 19:1, obtaining three fractions: H-1, H-2 and H-3, respectively. GC-MS analysis of these three fractions showed that fraction H-1 was constituted by monoterpenes and sesquiterpenes, fraction H-2 by furanodienone (**1**) (40.2%), curzerenone (**10**) (7.11%), furanogermacradienone (**2**) (36%) and dihydropyrocurzerenone (**6**). Fraction H-3 showed the presence of alismol (**12**) (4.6%), α- and β-eudesmol (0.35 and 0.58%, respectively) 3-methoxy-furanogermacradienone (**3**) (36%). 2-methoxyfuranogermacradienone (**4**) (35%) and myrrhone (**8**) (6%). Fraction H-3 showed to be the most active (Table 2), and the major isolated components (**3**, **4**, and **8**) were tested separately. Myrrhone (**8**) demonstrated to be the compound with the highest free radical scavenging activity [20].

The antioxidant activity of *C. erythraea* resin oil and extracts was evaluated by the inhibition of 5-lipoxygenase (5-LOX) mediated lipid peroxidation and by reduction of lipopolysaccharide (LPS)-mediated NO production in BV-2 microglial cell.

Table 2: Antiradical, antioxidant and anti-inflammatory activity of *C. erythraea* oils, extracts, fractions and isolated compounds.

	Sample	DPPH EC_{50} [a,b]	LOX inhibition IC_{50} [a]	Oedema reduction % (dose)
Oils and extracts	HD[c]	9.08±0.66	15.12±0.52[e]	
	D[c]	14.29±2.09	14.258±1.56[e]	
	SF1[c]	11.04±0.99	17.89±1.09[e]	
	SF2[c]	8.515±0.59	23.76±4.86[e]	
	H[c]	4.16±0.17	0.74±0.04[e]	84 (1000 μg)
Fractions	H-1[d]	169.55±10.75	56.85±8.36[e]	12 (10 μg)[g]
	H-2[d]	12.87±1.75	1.36±0.20[e]	7 (73 μg)[g]
	H-3[d]	3.49±0.30	0.76±0.06[e]	90 (708 μg)[g]
Pure compounds	1		0.09±0.01[f]	
	2		0.09±0.03[f]	
	3	4.29±0.33	3.38±0.08[f]	30 (0.3 μmol)[g]
	4	2.56±0.14	3.26±0.06[f]	26 (0.3 μmol)[g]
	8	1.08±0.08		32 (0.3 μmol)[g]
Controls	Ascorbic acid	0.11±0.07	18.63±1.31[e] 105.78±1.31[f]	
	BHT	0.09±0.007	3.86±0.85[e] 17.52±0.85[f]	
	Trolox	0.01±0.001		
	Caffeic acid		5.76±0.48[e] 31.99±0.48[f]	
	Indomethacin			58 (0.3 μmol)

[a] The values are the average of three determinations (±standard deviation);
[b] EC_{50}: mg/mL; [c] For the abbreviations see Table 1; [d] H-1: obtained by elution with hexane, H-2: obtained by elution with CH_2Cl_2, H-3: obtained by elution with CH_2Cl_2-EtOAc 19:1; [e] IC_{50}: μg/mL; [f] IC_{50}: μM; [g] Dose equivalent to 1000 μg of the parent extract

Bioassay-guided isolation of antioxidant compounds from *C. erythraea* resin, led to the isolation of **1** and **2** as the most active ones (Table 2) [35]. Docking experiments using Induced Fit Docking (IFD) procedure have been performed in order to gain some insights on the binding mode of both isomers *S* and *R* of compound **2** at 5-LOX binding site.The anti-inflammatory activity of compounds **1-4** was also tested in an *in vitro* model of LPS-induced neuroinflammation. The 10-fold increase of NO generation in BV-2 microglial cells after the LPS treatment, was reduced by treatment with tested compounds.. The most active compound resulted furanodienone **1** [20]. The neuroprotective activity of furanodienone was confirmed in a *in vivo* model. As a matter of fact, in LPS i.p.-injected mice, compound **1** effectively reduced liver and brain TNFα and IL-1β expression showing that it can counteract degenerative neuroinflammation [36].

The methanolic extract (M) of *C. erythraea* showed antiviral activity against parainfluenza virus type-3 (PIV 3) [37]. The activity was evaluated by a plaque forming units (PFU) reduction test in HEp cells (Table 3). Bioassay-guided separation of the active compounds showed that furanodienone **1** and myrrhone **8** were the most active ones.

The IC_{50} and CC_{50}, at 25 μg/mL, were defined for the two most active compounds and the SI (selectivity index, CC_{50}/IC_{50}) was calculated [38]. As it is reported in Table 3, furanodienone **1** showed to be a promising antiviral compound against PIV 3 with IC_{50} = 11.7 μg/mL and SI = 66.6 (Ribavirin used a positive control showed an IC_{50}= 5.1 and SI = 152.9).

Table 3: Anti-PIV 3 activity of extract, fractions and isolated compounds in HEp-2 cells by the plaque forming units (PFU) reduction assay.[a]

Compounds	% PFU inhibition	IC_{50} (μg/mL)[b]	CC_{50} (μg/mL)[b]	SI
M	74.5±1.82			
M1	9.7±0.34			
M2	33.4±0.86			
1	53.2±0.99	11.7±0.48	780±1.27	66.6
2	31.9±0.59			
3	7.2±1.41			
4	20.7±0.78			
8	58.1±1.50	22.3±0.67	390±175	17.5
DMSO	0.0			
Ribavirin	80.2±0.62	5.1±0.48	780±0.87	152.9

[a] Results are the mean of four determinations ±SD; [b] Results obtained at a concentration of 25 μg/mL.

In view of an increasing interest towards the use of essential oils as food preserver, the antifungal activity against *A. solani*, *F. culmorum* and *P. cryptogea* of different oils and extracts was tested (Table 4).

Table 4: Antifungal activity of *C. erythraea* oils, extracts, fractions and isolated compounds.

	Sample	Fungal growth (%)[a]		
		A. solani	*F. culmorum*	*P. cryptogea*
Oils and extracts	HD[b]	100[c]	90.3±8.3	55.5±4.6
	D[b]	100[c]	98.5±8.5	62.9±5.9
	SF1[b]	63.2±5.8	94.6±8.9	63.2±5.8
	SF2[b]	100[c]	92.2±8.7	66.6±6.0
	H[b]	100[c]	90.3±8.6	66.0±6.0
Fractions	H-1[d]	60.1±5.6	50.5±4.8	33.5±2.7
	H-2[d]	86.2±7.9	90.1±8.7	67.3±6.1
	H-3[d]	70.7±6.8	76.7±6.9	55.4±4.9
Pure compounds	**1**	80.7±7.5	82.4±7.8	76.5±7.1
	2	24.7±1.8	49.3±4.2	23.4±1.9
	3			
	4			
	8			
Controls	Nystatin (100 ppm)	100[e]	100[e]	100[e]

[a] The values are the average of three determinations (±standard deviation), Tested dose 3000 ppm; [b] For the abbreviations see Table 1; [c] fungistatic [d] H-1: obtained by elution with hexane, H-2: obtained by elution CH_2Cl_2, H-3: obtained by elution with CH_2Cl_2-EtOAc 19:1; [e] fungicidal

Among oils and extracts, the hexane extract (H) was the most active, and bioassay guided isolation identified fraction H-2 as the most active and in particular furanodienone **1**. The most sensitive strain was *F. culmorum*.

4. Conclusions

The resins of *Commiphora* species are a good source of traditional medicines for the treatment of several pathologies, such as inflammation, arthritis, obesity, microbial infection, wound, pain, fractures, tumor and gastrointestinal diseases.

The resin of *C. erythraea* is used traditionally to protect livestock from ticks and also as anti-inflammatory to treat eye problems and different works confirmed these pharmacological activities. Furthermore, recent studies showed that the extracts of the resin possess also antiviral and antifungal properties.

The pharmacological activities of the resin and extracts can be ascribed to the presence of furanosesquiterpenoids, whose absolute configuration has been determined by computational analysis of chiroptical properties.

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