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Review

The Medicinal Moroccan Plant *Cladanthus arabicus* as a Prominent Source of Sesquiterpenes Cladantholide and Sintenin

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Abstract: The yellow-flowering plant *Cladanthus arabicus* (L.) Cass., commonly called Arabian *Cladanthus* or palm springs daisy, is typical of the West Mediterranean region and is particularly abundant in Morocco. The plant is used in traditional Moroccan medicine for the treatment of diabetes and other ailments. Over the past 20 years, this abundant wild plant has been neglected from a phytochemical viewpoint. For the first time, the present review provides a survey of the pharmacological properties reported from extracts of *C. arabicus* and from essential oils derived from the aerial parts, mainly antimicrobial, antioxidant, and anti-inflammatory properties. The main bioactive natural products are discussed, with a focus on two rare sesquiterpenes of major interest, which are abundant in the stems and leaves: the 6,12-guaianolide cladantholide and the germacranolide sintenin. These sesquiterpene lactones and their analogues are presented to highlight their properties, extraction or total synthesis, and their therapeutic benefits. They both represent convenient biosourced precursors for the synthesis of derivatives. Sintenin may be used as a starting material for the design of hemi-synthetic germacradienolide-type costunolide or parthenolide derivatives. The 6,12-guaianolide scaffold of cladantholide offers opportunities to design novel arglabin derivatives. The therapeutic potential of the neglected and under-utilized plant *Cladanthus arabicus* and its original phytochemicals shall be explored further.

Keywords: cladantholide; *Cladanthus*; *Cladanthus arabicus*; germacranolide; guaianolide; sesquiterpene; sintenin

1. Introduction

Cladanthus is a small *genus* of twelve species with an accepted name, which are all native of the Mediterranean region and southwestern Europe (www.worldfloraonline.org accessed on 9 November 2023). They are characteristic of the sunflower family. Five species are found in Morocco: *Cladanthus mixtus* (L.) Chevall, *Cladanthus arabicus* (L.) Cass, *Cladanthus scariosus* (Ball) Oberpr. and Vogt, *Cladanthus eriolepis* (Maire) Oberpr. and Vogt, and *Cladanthus flahaultii* (Emb). Oberpr. and Vogt. With feathery leaves and a daisy-like appearance with gold or white flowers, in general, these Mediterranean plants do not go unnoticed in fields and gardens. The prevalent species in Morocco are *C. scariosus* which is endemic in the High Atlas area [1,2] and the flavonoid-rich species *C. mixtus* in other areas [3]. The latter *Cladanthus* species is a prominent source of polyphenols and flavonoids, such as the glycosyl-flavone acetylisospinosin, which has recently been identified together with many other flavonoids [4,5]. Here we have centered our analysis on the less-studied species *Cladanthus arabicus* (L.) Cass., 1817 (hereafter designated *C. arabicus*) which is well distributed in Morocco, notably in the anti-Atlas region and presents interesting phytochemical properties.

C. arabicus (Figure 1) displays feathery leaves and a daisy-like appearance with gold flowers. It is commonly called Arabian *Cladanthus* or criss-cross, golden of Araby, golden crown, palm springs daisy, or Moroccan sunshine, as well as wild Moroccan chamomile although this later trivial name is more often associated with the species *C. mixtus* [6]. *C. arabicus* (L.) Cass. is the commonly used name and the accepted botanical name. There are several synonyms, such as *C. maroccanus* Gand. and *Anthemis arabica* L., but they are rarely used in the scientific literature.

Figure 1. The plant *Cladanthus arabicus* (L.) Cass., also called (synonyms): *Anthemis arabica* L.; *Anthemis prolifera* Pers.; *Anthemis sessilis* Salisb.; *Chamaemelum cladanthus* E.H.L.Krause; *Chamaemelum proliferum* Moench; *Cladanthus ifniensis* Caball.; *Cladanthus maroccanus* Gand.; *Cladanthus proliferus* DC. (**a**,**b**) Spring pastures of the *C. arabicus*. (**c**,**d**) Flowers. (**e**) Distribution map for *C. arabicus*.

As a perennial herb, *C. arabicus* represents an attractive flowering plant, native to the Ibero–Maghreb region (Algeria, Libya, Morocco, Sicily, Spain, and Tunisia). It is a hardy or half-hardy and annual and can self-seed in light, sandy soils. The plant, very branched and up to 80 cm high, grows well on ordinary, drained soil in full sun. It behaves as a bushy and spreading plant forming a colored mound of pleasantly scented feathery foliage. All summer, it provides a profusion of large, fragrant, golden-yellow flowers. The main flower on each stem is followed by further flowers on stems arising directly under the main one (Figure 1). The ferny foliage gives rise to many golden discs, and generally each new stem radiates from the edge of the faded flower. The plant is not considered edible but the flowers can be used to garnish dishes. In Morocco, the flowers (called Tâfs (or Tafsse) in the Arabic language, and Aourzid in the vernacular Amazigh language) are used by the Messiwa people to decorate dishes and are consumed [7,8]. The plant is eaten by wild herbivores, notably by Moroccan dorcas gazelle in west-central Morocco [9] and by camels but with a risk of toxicity in this later case [10].

The objectives of the study, presented here as a narrative literature survey, are to underline the ethnobotanical usages of the plant *C. arabicus* in Morocco, the pharmacological effects reported with plant extracts, and to identify the main active phytoconstituents and their mechanism of actions. For that, an extensive analysis of the scientific information was performed via the analysis of all general databases (essentially, Pubmed Central, Scopus, and Google Scholar) and specific databases from publishers (such as Oxford University Press, SAGE journals, ScienceDirect, Springer, Thieme, Wiley, and others) covering the literature (mostly in English, or occasionally French languages) from 1970 to October 2023. The search was conducted using keywords such as *Cladanthus*, phytochemicals, and sesquiterpenes. More than 160 articles were analyzed. A phytochemical analysis of

C. arabicus is reported, pointing out the unique presence of the two rare sesquiterpenes cladantholide and sintenin. This is the first and unique review on the little-known species *C. arabicus*. commonly found in semi-arid Mediterranean landscapes and in Morocco in particular.

2. Use of *C. arabicus* in Traditional Medicine

Ensuring a sustainable supply of affordable medicines for the world's fast-growing population (which now surpass 8 billion people) is a major challenge in today's economy. The challenges are even broader for people with low resources living in rural areas. There is a major need to improve access to and the affordability of health care in rural communities [11,12]. The World Health Organization (WHO) has estimated that about 80% of the world's population use traditional medicine or rely on plant-based therapy for their primary care needs [13]. Plants have long been used as traditional remedies to help fight human diseases and remain largely used today to combat parasitic and virus infections, cardiovascular, mental, and inflammatory diseases, cancers, and many other pathologies [14,15]. Moreover, the demand for health-promoting products is increasing [16]. Plants still represent a large untapped source of structurally novel compounds that might serve as a lead in the development of novel drugs [17]. Many medicines of plant origin with analgesic and anti-nociceptive activity have been used for a long time without any major adverse effects [18,19]. Similarly, traditional herbal medicines and natural plant products contribute considerably to the treatment of cancers [20,21]. The bioprospection of medicinal plants remains a valid approach to identify new molecules which could be active against cancer and inflammatory diseases [22–24].

The use of *C. arabicus* in traditional medicine is not largely documented, with only sparse citations in scientific reviews. The plant is known in Morocco for the treatment of diabetes [25]. Apparently, an infusion prepared from the flower heads of the plant, drunk twice a day, could be useful to combat type 2 diabetes [26,27] (Figure 2). *C. arabicus* can be used alone or combined with other plants, such as *Rubia peregrina*, *Corrigiola telephiifolia*, or *Ridolfia segetum*, to prepare an antidiabetic decoction [28]. There are other reports primarily citing the use of the species *C. mixtus* (L.) Chevall [29] and *C. scariosus* (*Ball*) Oberpr. and Vogt [30], but not *C. arabicus*, for the treatment of diabetes. Other anti-diabetic Moroccan Asteraceae are cited also [31,32] and could be combined with *C. arabicus*. Beyond diabetes, the uses of *C. arabicus* for the treatment of digestive disorders, neurological troubles, and respiratory and urogenital affections have been mentioned, without much detail [33]. Apparently, the plant is "good for stomach and anemia" but robust experimental evidence to support these claims is lacking [7].
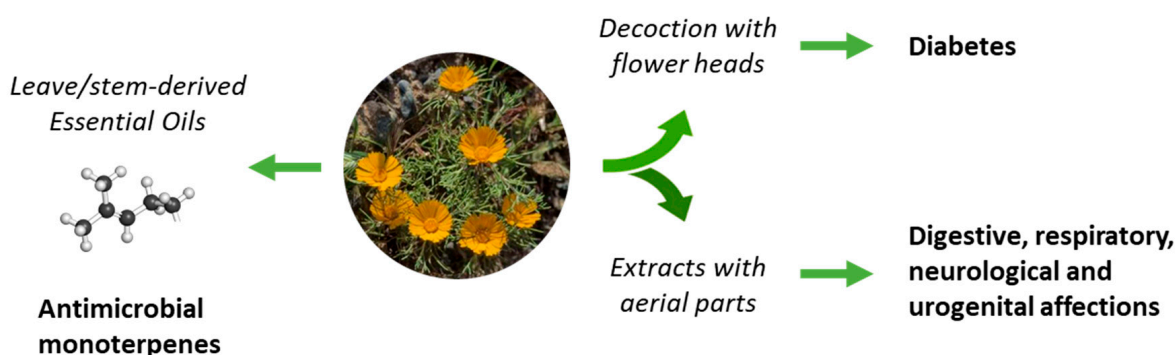

Figure 2. The uses of *C. arabicus* in traditional medicine. Decoctions prepared from flowers heads are used to treat diabetes and total extracts are used to combat a variety of diseases. Essential oils from the leaves and stems provide remedies to treat microbial infections.

3. Pharmacological Activities of *C. arabicus* Extracts

Essential oils (EO) extracted from the aerial parts of *C. arabicus* have revealed the marked antimicrobial activities associated with a rich monoterpenic compounds con-

tent (Figure 2). In particular, an essential oil derived from the plant stems and leaves showed antibacterial activities against the opportunistic human pathogen *Bacillus cereus* and *Enterococcus faecalis* which is at the origin of nosocomial infections, but it showed no effect against the hard-to-treat pathogen *Pseudomonas aeruginosa*. This leaf/stem-derived EO principally contained the monoterpenes sabinene (13%), α-pinene (8%), β-pinene (12%), myrcene (7%), and many other volatile terpenes in smaller proportions (36 monoterpenes were identified) (Figure 3).
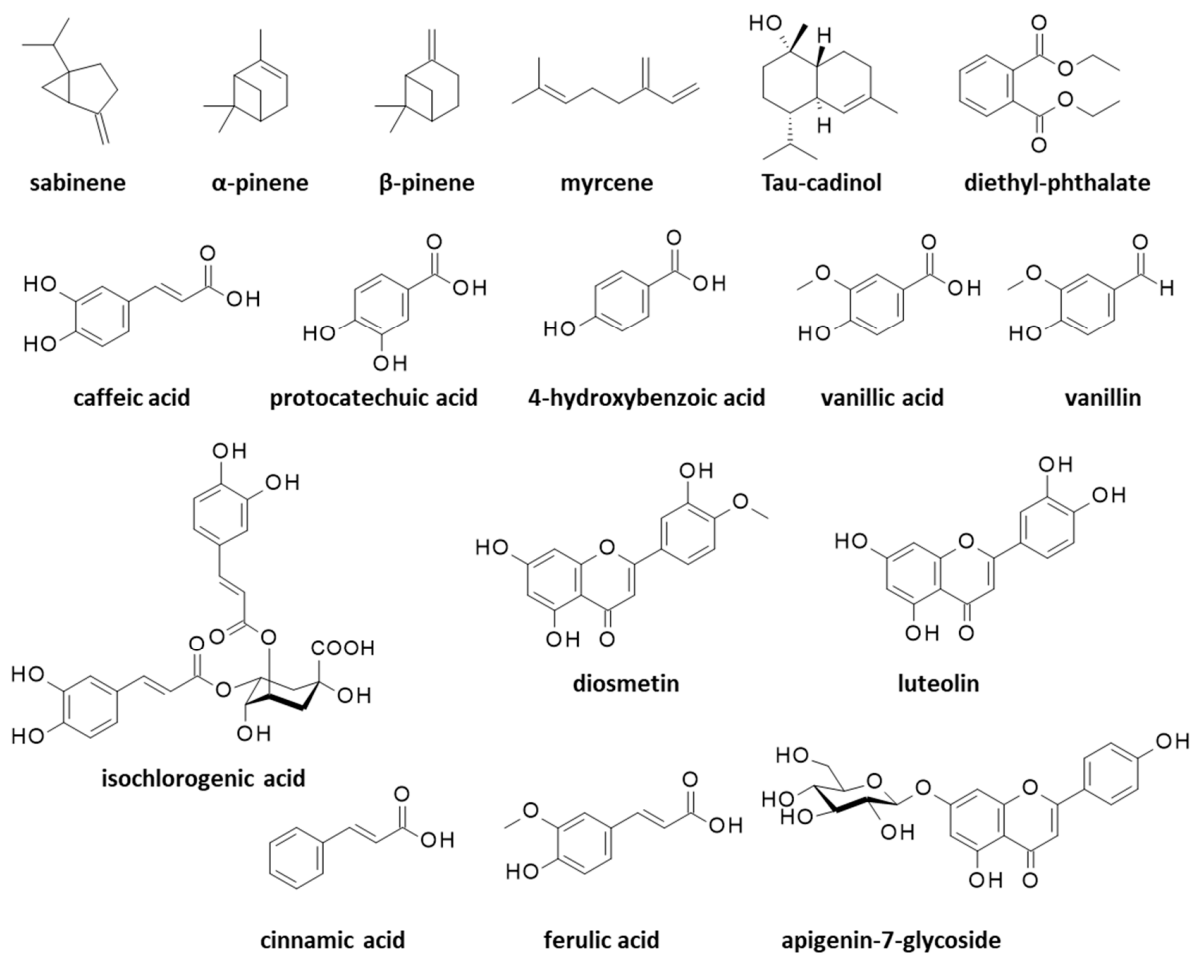

Figure 3. Structures of various natural products identified from essential oils or alcoholic extracts of *Cladanthus arabicus*.

An EO prepared under identical conditions from the plant's flowers revealed a much poorer monoterpenes content, essentially only sabinene (23%) and β-pinene (32%) [34]. The composition of the essential oil can vary significantly from one study to another, depending on the process, the plant origin and its growth, or the collecting season. For example, an EO made from *C. arabicus'* aerial parts was found to contain up to 60 terpenic compounds, principally sabinene (31%), β-pinene (17%), myrcene (12%) and α-pinene (5%). In this case, the EO was characterized for its strong antioxidant activity (IC$_{50}$ = 55.4 μg/mL in a DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay) and its antimicrobial effects, notably against *Micrococcus luteus* bacterium and the pathogenic fungus *Candida albicans* (MIC = 0.187 mg/mL in both cases) [35]. In a subsequent study, the same authors further tested this EO against other microbes and found activities against *Escherichia coli* (strain ATCC 25922), *Klebsiella pneumoniae* (strain S12b/16), and *Enterobacter cloacae* (strain S5/16), but at significantly higher doses than were measured for reference antibiotics such as amoxicillin and neomycin. Interestingly, the EO showed a synergistic activity with amoxicillin against *Proteus mirabilis* (strain S32/16),

a Gram-negative bacterium that is frequently implicated in urinary tract infections [36]. The potent antibacterial activity of *C. arabicus* EO and its strong interaction with amoxicillin warrant further investigation. Apparently, the terpene content of *C. arabicus* EO is quite variable from one preparation to another. Recently, Mziouid and coworkers [37] reported the antioxidant activity of an EO from *C. arabicus* which contained α-pinene (5.7%) and β-pinene (23.6%), but also a large proportion of tau-cadinol (9.5%) (Figure 3), a sesquiterpene commonly found in EOs but not mentioned in the aforementioned preparations using *C. arabicus*. T-cadinol is known to be an anti-trypanosomal agent which is able to induce a mitochondrial impairment in *Trypanosoma cruzi* parasites responsible for the Chagas disease [38]. The *C. arabicus* EO also contained diethyl phthalate (DEP, 7.9%) which is an unwanted estrogenic endocrine-disrupting chemical (Figure 3). In this case, the EO exhibited a modest antioxidant activity (IC_{50} = 1.33 mg/mL in the DPPH assay) [37]. A well-established, robust process is needed to prepare an EO in a reproducible manner with a constant, stable composition, which is free from toxic chemicals (following the recommendations of the European Pharmacopoeia, for example).

The antioxidant activity is more pronounced when a total plant extract is used instead of an EO. For example, the antioxidant IC_{50} value dropped from 1.33 mg/mL to 0.23 mg/mL when a methanolic extract was used in place of the EO from *C. arabicus*, due to the high phenolic content of the extract [37]. A phytochemical analysis of an alcoholic extract of the aerial parts of *C. arabicus* has revealed the presence of two major components, caffeic acid (4.9 mg/kg) and protocatechuic acid (4.7 mg/kg), followed with other polyphenols such as ferulic acid (1.8 mg/kg), 4-hydroxybenzoic acid (1.5 mg/kg), vanillin, and vanillic acid (both 1.6 mg/kg), plus a series of minor components including flavonoids which are sometimes glycosylated (diosmetin, luteolin, apigenin-7-glucoside) (Figure 3). The high polyphenols content, notably caffeic acid, suggests a possible use of the plant in combatting adverse hematologic events such as thrombocytopenia [39]. Caffeic acid is a strong antioxidant and an anti-inflammatory agent with cardioprotective and hepatoprotective effects. This common natural product is considered to be beneficial in limiting the progression of diabetes mellitus and its associated complications [40]. Protocatechuic acid is also a chemoprotective agent which is notably able to protect cardiomyocytes from oxidative damages [41]. These two polyphenols are commonly found in fruits, vegetables, grains, and herbal medicine; thus, they are definitely not specific to *C. arabicus*. Nevertheless, these compounds are important. Polyphenols from Mediterranean plants have benefits in the prevention and treatment of various diseases, notably skin diseases such as atopic dermatitis, psoriasis, and chronic urticaria [42].

In *C. arabicus* extracts, the polyphenol content was rich, whereas the levels of heavy metals (Cd, As and Pb) were low, and the extract revealed a marked antibacterial activity against *Escherichia coli* strain S33/16 (MIC = 0.125 mg/mL) [43]. The same hydromethanolic extract has revealed the presence of diverse flavonoids and phenolic acids, including isochlorogenic acid and cinnamic acid (Figure 3). All together, these compounds are responsible for the marked antioxidant activity of the extract, as well as its modest inhibitory activity toward cholinesterase, acetylcholinesterase, tyrosinase, and α-glucosidase enzymes [44].

4. Phytochemical Analysis

The first phytochemical analysis of *C. arabicus* was reported 30 years ago, when Daniewski and coworkers reported the isolation of a new sesquiterpene they called cladantholide from a methanolic extract of the total dried aerial parts (without flowers) of a sample of *C. arabicus* cultivated locally [45]. The product is abundant in the plant. Over 100 mg of the newly purified product was obtained from an initial 1.46 kg of the dried plant material. Cladantholide corresponds to a three-ring system with a central seven-membered ring fused to planar a cyclo-pentenone ring on one side and a five-membered lactone ring on the other side (Figure 4). It is an isomer of cichoralexin (first isolated from chicory [*Cichorium intybus*] also known as *Carpesia* lactone [46]) and is a close analogue to the two sesquiter-

pene lactones leucodin and achillin (Figure 5) found in *Achillea* species. These two products display antihypertensive and vasorelaxant effects [47]. They also exhibit anti-inflammatory properties via the inhibition of cyclooxygenase 2 (COX-2) expression and activity. They are considered to be of potential interest in the treatment of pain and inflammation and for cardiometabolic diseases [48]. Leucodin has revealed a high anti-hypercholesterolemic potential [49,50] coupled with smooth muscle relaxant activity [47,51]. This type of 6,12-guaianolide structure (Figure 5) has been found in diverse *Achillea* species (Asteraceae) notably those used to prepare chamomile herbal tea [52].
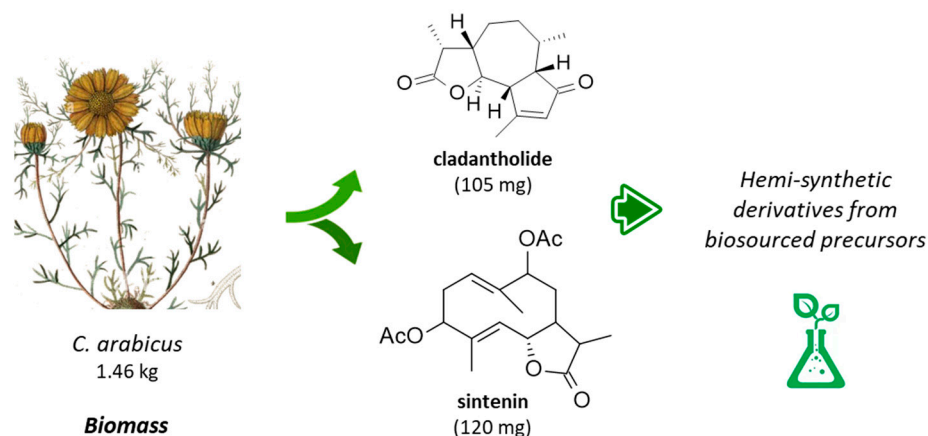

Figure 4. Structures cladantholide and sintenin isolated from the stems and leaves of *C. arabicus*.
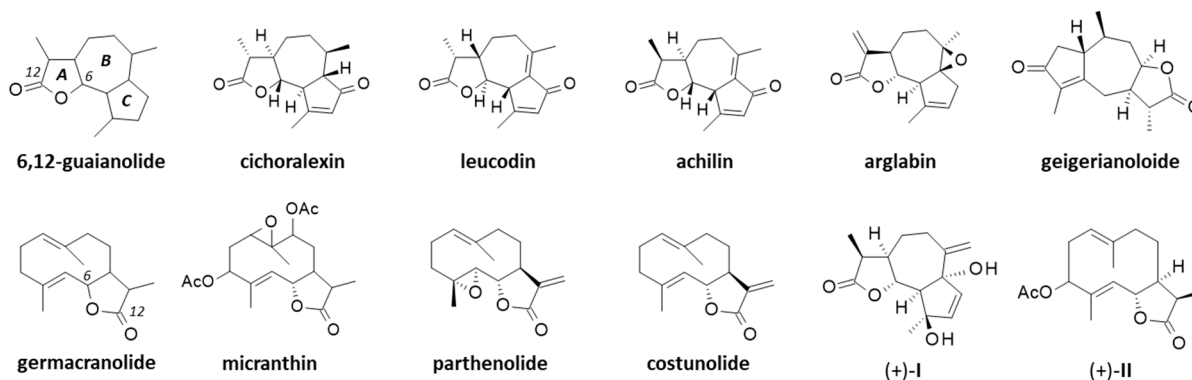

Figure 5. Structures of several guaianolides related to cladantholide and germacranolides related to sintenin.

Cladantholide has been isolated from *C. arabicus* together with the germacranolide derivative sintenin (Figure 4), which is also a sesquiterpenoid found in diverse *Achillea* species, such as *A. clavennae*, *A. millefolium*, and others [53,54]. Sintenin is a sesquiterpene lactone initially isolated from the aerial parts of *Achillea sintenisii* Hub.-Mor. (Compositae) [55] and is also present in *A. falcata* L. [56] and *A. micrantha* Willd. [57]. But the sintenin content in *Achillea* plants is limited. For example, only 6 mg of sintenin was obtained from 1.37 kg of the dried aerial parts of *A. sintenisii* [55]. A much higher quantity can be obtained from the stems and leaves of *C. arabicus*. Recently, cladantholide has also been identified from the plant species of *Scorzonera longiana* Sümbül (an endemic species to Turkey), together with other terpenes and dihydroisocoumarin derivatives [58]. The ground-up dry underground parts (rootstock, 600 g) of *S. longiana* afforded 10.7 mg of cladantholide, which is 4-times less than the yield obtained from the dried aerial parts of *C. arabicus*. This latter fast-growing and easily accessible plant can provide a convenient source of cladantholide.

Alternatively, the product can be obtained by chemical synthesis. The total synthesis of (+)-cladantholide was reported in 1997, starting from (−)-carvone via a long and tedious procedure (16 steps, 5.0% overall yield) implicating a *cis*-fused hydroazulenic

lactone intermediate, as depicted in Figure 6 [59]. This clever chemical work based on a radical cyclization cascade has been recognized as a remarkable synthesis of a complex guaianolide [60]. This is a technical tour-de-force and still the only stereoselective synthesis described thus far to obtain (+)-cladantholide (the (−)-isomer was not obtained). In recent years, several chemical procedures have been described to produce other 6,12-guaianolides [61], but none to specifically produce cladantholide apart from the original process described 27 years ago [59].
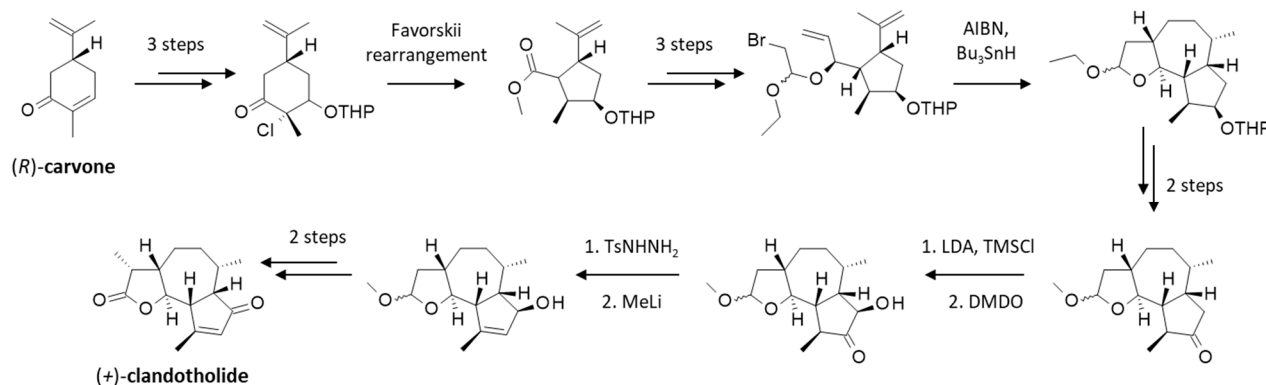

Figure 6. Total synthesis of (+)-cladantholide, as originally reported [59] and summarized [60]. Details of the 16 steps can be found in the original reports.

Sintenin is even more abundant than cladantholide in *C. arabicus* [45]. A dried sample of the plant (1.46 kg) was used to obtain 105 mg of cladantholide and 120 mg of sintenin (Figure 4). Over the past 30 years, these two compounds have rarely been reported. Sintenin and its epoxide derivative micranthin have been identified in an ethyl acetate extract of the aerial parts of the plant *Achillea biebersteinii* Afan. and the extract was well characterized for its antidiabetic and gastric antisecretory effects [62]. It is therefore plausible that sintenin contributes to the antidiabetic effect of *C. arabicus*. Sintenin is a non-cytotoxic lactone, with no effect on the proliferation of different types of cancer cells [53,54]. Sesquiterpene lactones often present marked antitumor properties, such as those isolated from the *Inula* species for example [63,64], but it is not the case for sintenin and cladantholide, both non-cytotoxic compounds. They deserve further studies as anti-inflammatory and antidiabetic agents. Interestingly, a structural analogy can be seen between cladantholide and the sesquiterpene lactone geigerianoloide isolated from the antidiabetic plant *Geigeria alata* (DC) Oliv. and Hiern. (also from the Asteraceae family) [65] (Figure 5).

Parenthetically, caution must be exercised when studying the scientific literature because a totally distinct product exists which is also called sintenin, which is a naturally occurring ester, (3-(3,4-dimethoxyphenyl)propyl 3-(3,4-dimethoxyphenyl)propanoate) with cytotoxic properties, used as a template for the synthesis of derivatives endowed with antioxidative and neuroprotective activities [66,67]. This ester sintenin has nothing to see with lactone sintenin from *C. arabicus* which is a non-cytotoxic compound.

Beyond cladantholide and sintenin, two other sesquiterpenes designated (+)-I and (+)-II (Figure 5) have been isolated from the original methanolic extract of a sample of *C. arabicus* (cultivated in Poland). The corresponding structures were presented but no specific information was reported [68]. Compound I is unknown. Compound II is an analogue of sintenin lacking one of the two acetyl groups. We could not find these two compounds in chemical databanks.

Five other products should be mentioned at this stage, the alkaloids embellicines A and B, and three polyketides named embeurekols A–C (A and B are isomers) but they originate from an endophyte fungus *Embellisia eureka* (renamed *Alternaria eureka*) not directly from *C. arabicus* [69,70] (Figure 7). This fungus grows on the surface of healthy stem tissues of *C. arabicus* in Morocco. It can be cultivated and used for the biotransformation of natural products, performing oxygenation, oxidation, and epoxidation reactions on sapogenins for

example [71–73]. Similarly, the small bicyclic molecule 3,4-dihydro-3,4,8-trihydroxy-1[2*H*]-naphthalenone (Figure 7) has been isolated from an extract of *Embellisia eureka* collected on a Moroccan sample of *C. arabicus* [74]. Trihydroxytetralones are bioactive secondary metabolites produced by diverse pathogenic fungi [75–77].
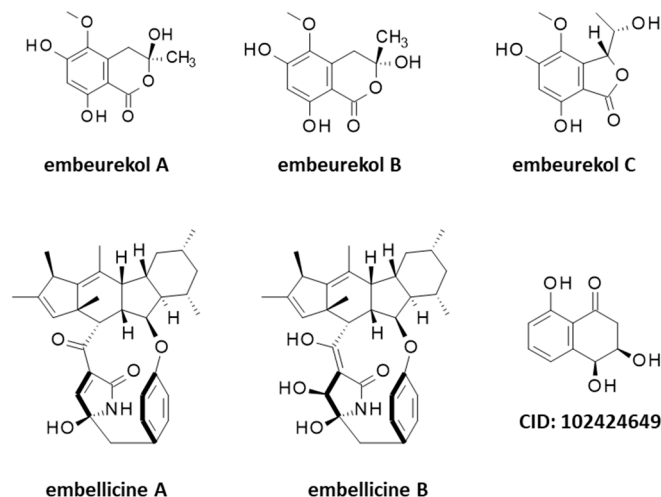

embeurekol A embeurekol B embeurekol C

embellicine A embellicine B CID: 102424649

Figure 7. Structures of several guaianolides related to cladantholide and germacranolides related to sintenin.

Most phytochemical studies of *C. arabicus* are concerned with the terpenes and alkaloids found in the plant. But, as mentioned above, diverse flavonoids have been identified in plant extracts, such as apigenin and its glycosyl derivative apigenin-7-glucoside [36,44]. Another flavonoid of medicinal interest found in *C. arabicus* is diosmetin [43] (Figure 3). This common flavonoid, found in many plants, displays anti-inflammatory, antioxidant, antimicrobial, antilipolytic, and analgesic activities [78]. Diosmetin might well contribute to the antidiabetic action of *C. arabicus* extracts because it has been shown to ameliorate glucose metabolism in diabetic mice via the regulation of the PI3K/AKT signaling pathway and a restoration of the unbalanced gut microbiota [79]. It is an inhibitor of aldose reductase ($IC_{50} = 15.7$ μM), an enzyme of the polyol pathway implicated in hyperglycemia, and a useful compound to combat type 2 diabetes mellitus [80,81].

5. Discussion

C. arabicus is endemic to the West Mediterranean area, in particular to Morocco where the plant is abundant and underused [82]. Large fields of this wild sunflower plant can be found, notably in the Aouganz region in the High Atlas [83]. It is one of the many Moroccan medicinal plants traditionally used to treat painful digestive symptoms and to combat certain microbial infections [84]. *C. arabicus* is considered to be an antidiabetic plant, as it is the case for *C. mixtus* and many other Moroccan plants [25,29,85]. Extracts of *C. arabicus* are of interest to treat type 2 diabetes, owing to the presence of compounds like diosmetin and luteolin. This later flavonoid is well-known for its anti-inflammatory and antidiabetic properties [86,87]. But it is a common antioxidant compound found in many plants and is not specific to *C. arabicus*. Diosmetin can be readily isolated from in citrus fruits for examples [88].

Despite the natural abundance of the plant and its multiple medicinal usages, *C. arabicus* is little exploited at present. The plant is consumed by some herbivores [9,10] and by local monkeys (the Barbary macaques, also known as the Barbary ape or magot (*Macaca sylvanus*) [89]. Therefore, the plant may be used more broadly to feed animals, at least when combined with other grass species. The shoot tissue of *C. arabicus* may accumulate heavy metals, notably chromium [90]. Therefore, the potential use of the plant as a food source for animal feeding must be monitored and adapted. The wild plant is abundant, at least in some parts of Morocco. In addition, the cultivation of the plant could be developed. This

is already the case for the related species *C. mixtus* and *C. scariosus* for which procedures for seed germination and the growth of plantlets have been developed [91,92]. Similar processes could be adapted for *C. arabicus*.

One of the main reasons for interest in *C. arabicus*, at least from a phytochemical perspective, is the presence of the two rare sesquiterpenes sintenin and cladantholide, which are both relatively abundant in the plant and readily extractable. These two original products have been little studied in recent years and largely neglected in general. It is time to underline the potential uses of these molecules, if not for their pharmacological properties (largely unknown at present) but at least as starting materials for the design of other molecules. The synthesis of guaianolide sesquiterpene lactones is a current topic of interest to design novel anticancer and/or anti-inflammatory agents [93–95]. Novel guaianolide lactones capable of inhibiting the release of pro-inflammatory cytokines are regularly reported, such as the millefoliumines which inhibit the release of nitric oxide and the expression of TNF-α and IL-6 [96]. Cladantholide could be used as a model 6,12-guaianolide to modulate or to substitute the lactone A-ring, and/or to modify the cyclopentenone C-ring. It may serve as a model to access diverse analogues, as has been the cases with the prototypic 6,12-guaianolides arglabin and thapsigargin [97,98]. Arglabin (Figure 5) has recently been characterized as an anticancer inhibitor of EGFR tyrosine kinase [99,100] and a regulator of neuroinflammation [101]. Hemi-synthetic derivatives could be designed starting from cladantholide. Thapsigargin is also a leading 6,12-guaianolide from which analogues of pharmacological interest have been designed, such as the prodrug mipsagargin (G-202) which is currently in phase II clinical testing for the treatment of advanced hepatocellular carcinoma [102–104]. It is, therefore, of interest to consider cladantholide as a source compound for the design of novel 6,12-guaianolides. By the same token, sintenin could be used as a starting material for the design of germacradienolide-type derivatives. Sintenin is a diacetylated derivative of costunolide which is a potent anti-inflammatory agent and a blood–brain barrier permeable compound of interest to address certain brain diseases [105–107]. Costunolide derivatives targeting pyruvate kinase M2 (PKM2) are being designed for the treatment of ulcerative colitis [108]. Other derivatives could be designed based on the sintenin scaffold.

The presence of the sesquiterpenes cladantholide and sintenin make *C. arabicus* a plant of prime interest. Thus far, different studies have been focused in other *Cladanthus* species, notably *C. mixtus* which is abundant in the northern part of Morocco [4]. This species contains many useful bioactive products (polyphenols, flavonoids, terpenoids, sterols, etc.) and displays anticancer properties [5,109]. But its phytochemical profile is distinct from that of *C. arabicus*, which is the only species that contains cladantholide and sintenin. This plant produces an unusual amount and variety of terpenoids. The unique terpenoid composition of *C. arabicus* likely arises from the involvement of terpene synthases with different specificities, but they have not been identified thus far.

In conclusion, the plant *Cladanthus arabicus* which grows well and is abundant in Morocco has received little attention thus far, apart from its ornamental characteristics and the occasional use in traditional medicine to treat diabetes and other mild affections. The plant has been largely neglected thus far as a possible source of bioactive compounds, despite the presence in the stems and leaves of original natural products, notably the germacranolide sintenin and the 6,12-guaianolide cladantholide. These two interesting products shall be better considered as precursors for the design of bioactive derivatives. The time has come today to have a new look at this abundant but neglected plant for the identification of novel phytochemicals and the development of new remedies against human diseases.

Conflicts of Interest: Author Christian Bailly is the owner of OncoWitan, a private consulting office. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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