The Medicinal Moroccan Plant *Cladanthus arabicus*

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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.

Keywords: cladantholide ; Cladanthus ; Cladanthus arabicus ; germacranolide

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].

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].

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][23][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].

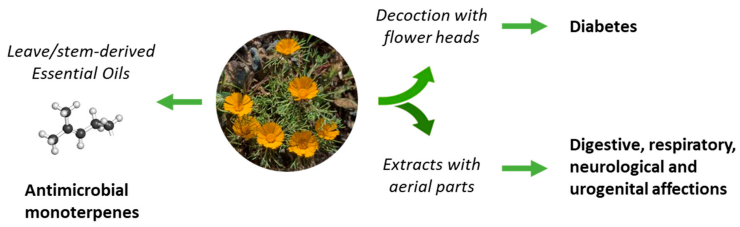

Figure 2. The uses of *C. arabicus* in traditional medicine. Decoctions prepared from flowers heads are used to treat diabetes and total extracts are used to combat a variety of diseases. Essential oils from the leaves and stems provide remedies to treat microbial infections.

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 content (**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**).

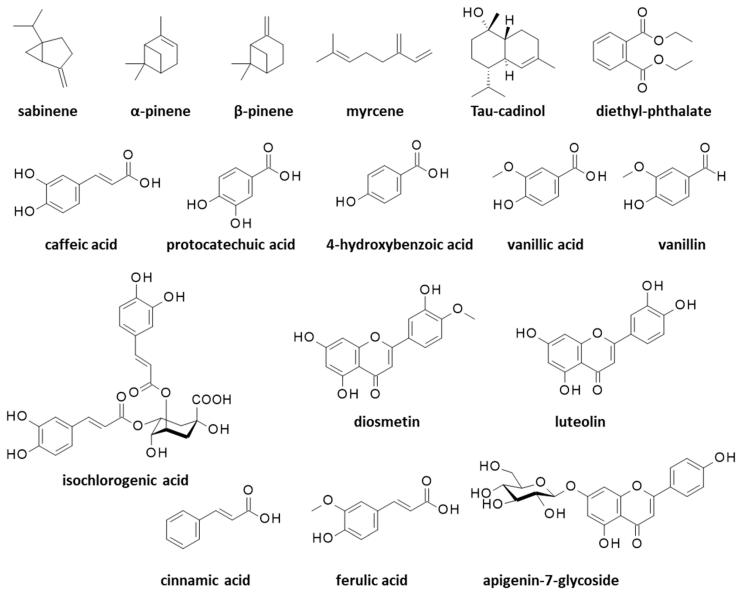

Figure 3. Structures of various natural products identified from essential oils or alcoholic extracts of *Cladanthus arabicus*.

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 hydro-methanolic 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].

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