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Morphological and Phytochemical Diversity among *Hypericum* Species of the Mediterranean Basin

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ABSTRACT

The genus *Hypericum* L. (St. John's wort, Hypericaceae) includes more than 480 species that occur in temperature or tropical mountain regions of the world. Monographic work on the genus has resulted in the recognition and description of 36 taxonomic sections, delineated by specific combinations of morphological characteristics and biogeographic distribution. The Mediterranean Basin has been recognized as a hot spot of diversity for the genus *Hypericum*, and as such is a region in which many endemic species occur. Species belonging to sections distributed in this area of the world display considerable morphological and phytochemical diversity. Results of a cladistic analysis, based on 89 morphological characters that were considered phylogenetically informative, are given here. In addition, a brief overview of morphological characteristics and the distribution of pharmaceutically relevant secondary metabolites for species native to this region of the world are presented.

Keywords: cladistics, hyperforin, Hypericaceae, hypericin, secondary metabolite chemistry, Turkey

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INTRODUCTION

The Mediterranean Basin has been recognized as a hot spot for *Hypericum*, with more than 150 of the currently recognized 470 species occurring in this region. Monographic work on the genus by Dr. N. K. B. Robson (1977 onwards) has provided detailed morphological descriptions for the majority of these species, which have been classified into 36 taxonomic sections. A general overview of botanical characteristics of *Hypericum*, with a special emphasis on *H. perforatum* (Common St. John's wort) due to its use as a medicinal plant, was published in 2003 (Robson 2003).

Species of *Hypericum* distributed in the Mediterranean Basin (here treated as the lands bordering the Mediterranean Sea), particularly the country of Turkey, and the adjacent regions of Macaronesia and the northeastern African highlands (particularly Socotra), display considerable morphological and phytochemical diversity and numerous endemic species have been described from this region of the world (Robson 1967). Representatives of 22 (61.1%) of the taxonomic sections are found in the Mediterranean Basin, of which 15 include fewer than 10 species and 7 are monotypic (represented by a single species) (**Table 1**). Detailed morphological information for each species, as well as species authorships and synonyms, can be found in the respective monograph chapters (see citations in **Table 1**).

The remainder of this publication presents the results of a recent cladistic analysis including *Hypericum* species occurring in the Mediterranean Basin and describes the morphological characteristics and the distribution of pharmaceutically relevant secondary metabolites among these species.

MATERIALS AND METHODS

Due to the current availability of powerful computing equipment with high-speed processors, a numerical Parsimony analysis using the program PAUP* v4.0b10 (Swofford 2002) was recently performed (Nürk and Blattner, submitted). This analysis used 89 morphological characters that were identified, considered to be phylogenetically informative and coded for all described species of *Hypericum* (Robson 1981 onwards; Nürk and Blattner, submitted). For the purposes of the current work, this cladistic analysis was repeated on a subsample of the data, focussing on species distributed within the Mediterranean Basin and those which had been identified in the earlier study to be closely allied. Maximum Parsimony settings similar to those described in Nürk and Blattner (2010) were utilized for the current analysis. The Parsimony

Received: 26 February, 2010. Accepted: 21 April, 2010.

Invited Review

Table 1 *Hypericum* occurring in the Mediterranean Basin, Macronesia and parts of the Northeastern African Highlands.

Section number	Taxonomic section	Species[A]	Type species	Distribution within the range
2	Psorophytum[C]	1	*H. balearicum* L.	Balearic Islands
3	Ascyreia[C]	1/42	*H. calycinum* L.	Turkey and S Bulgaria
5	Androsaemum[C]	2/4	*H. androsaemum* L.	Mediterranean region, N Arabian Peninsula
6	Inodora[C]	1	*H. xylosteifolium* (Spach) N. Robson	SE Pontic region (Turkey, Georgia)
8	Bupleuroides[D]	1	*H. bupleuroides* Griseb. in Wiegm.	SE Pontic region (Turkey, Georgia)
9	Hypericum (series Hypericum)[E]	5/12	*H. perforatum* L.	Throughout Mediterranean region
10	Olympia[F]	4	*H. olympicum* L.	S Balkan Peninsula, S/W Turkey; Syria
11	Campylopus[F]	1	*H. cerastoides* (Spach) N. Robson	NE Aegean region
12	Organifolia[F]	13	*H. organifolium* Willd.	SE Pontic region (Turkey, Georgia, Syria)
13	Drosocarpium[F]	11	*H. barbatum* Jacq.	Throughout Mediterranean region
14	Oligostema[F]	6	*H. humifusum* L.	W Europe, NW Africa
15/16	Crossophyllum[F]	4	*H. orientale* L.	S Bulgaria, W Turkey, Greece, Georgia
17	Hirtella[G]	28/30	*H. hirtellum* (Spach) Boiss.	Turkey, Greece, S France, S Spain, Morocco
18	Taeniocarpium[G]	28	*H. linarioides* Bosse.	Throughout Mediterranean region
19	Coridium[G]	5/6	*H. coris* L.	Throughout Mediterranean region
21	Webbia[B]	1	*H. canariense* L.	Madeira
22	Arthrophyllum[B]	5	*H. rupestre* Jaub. & Spach.	S Turkey, Syria
23	Triadenioides[B]	5	*H. pallens* Banks & Solander	Socotra, S Turkey, Syria
24	Heterophylla[B]	1	*H. heterophyllum* Vent.	Turkey (Anatolia)
25	Adenotrias[B]	3	*H. russeggeri* Fenzl.	Morocco to the N Arabian Peninsula
27	Adenosepalum[B]	24	*H. montanum* L.	Throughout Mediterranean region
28	Elodes[B]	1	*H. elodes* L.	Southern continental Europe, east to Italy

[A] Species number in this region of the world / Total species number in the taxonomic section
[B] Robson 1996; [C] Robson 1985; [D] Robson 2001; [E] Robson 2002; [F] Robson 2010a; [G] Robson 2010b

analysis followed a two-step heuristic search approach modified from Blattner (2004) with multistate taxa interpretation depending on "uncertainty" versus "polymorphism" designation. Statistical support of the clade branches was tested with 100,000 bootstrap re-samples using the 'fast and stepwise' procedure of PAUP* (Felsenstein 1985). In this type of parsimony analysis, no prior assumptions about character evolution are made (i.e. all character states are unordered) and all characters contribute in the same way (i.e. are equally weighted). The only assumption made was in the designation of a representative of *Cratoxylum* as the ultimate outgroup.

RESULTS

The results of the cladistic analysis identified four main groups within the genus (**Fig. 1**):

- A basal grade containing species belonging to the Old World sections **6a** and **25** (for section numbers, see **Table 1**). Closely associated with this grade (i.e. in basal positions in the genus or of the groups described below) are sections **6**, **21-23** and potentially **24**. The identification of these sections (representing 17 species in total) as basal is in agreement with preliminary molecular analyses of the internal transcribed spacer (ITS) region of the nuclear ribosomal DNA repeat (Mark Carine and Nicolai Nürk, pers. comm.). Species of this grade are characterized by a deciduous shrubby habit, the occurrence of (only) pale glands on the leaves, and the possession of deciduous stamens and petals (i.e. falling after flowering).
- A primarily Neotropical clade including 139 species from sections **29** and **30** (referred to here as the "Brathys" *sensu lato* group), which share the highest number of morphological congruencies (including the possession of exclusively pale glands) with the eastern Mediterranean section **24**.
- A clade containing 94 species of Old World (sections **1-5**), New World (section **20**), and circumboreally-distributed (section **7**) representatives, referred to here as the "Myriandra-Ascyreia" group. All species in this clade, with the exception of those in section **1**, lack dark (i.e. potentially naphthodianthrone-containing) glands.
- A crown-group (hypothetically most derived) containing more than 45% of the diversity of *Hypericum* referred to here as the "Euhypericum" group. These 207 species belong to 18 recognized taxonomic sections, most of which are native to the Old World. The presence of dark glands (in one organ or more) is a synapomorphic trait with both morphological and phytochemical importance, for these species.

DISCUSSION

Phylogenetic inference within *Hypericum*

The phylogenetic analysis revealed four main groups within *Hypericum* (**Fig. 1**). The arrangement of sections into these four groups and, therefore, relationships between the sections appear different to those presented in Robson (2003). However, the grouping of species into the taxonomic sections in the phylogenetic analysis is highly congruent to the classification; more than 90% of the species are placed in the phylogeny according to the sectional classification delineated by Robson (1981 onwards). In the phylogenetic tree (**Fig. 1**), some sections are revealed in more than one clade (i.e. appear polyphyletic). The phylogenetic analysis, therefore, indicates that the sections as currently described do not appear to reflect the evolutionary history of the species group. A third data set that would provide independent support for the presently accepted classification of natural relationships among *Hypericum* species or the results of the cladistic analysis, respectively, is not yet available. These hypotheses based on morphological information, however, are currently being tested by several research groups in Europe and North America using molecular tools. A final analysis of all available evidence awaits the completion of these studies.

One main difference between the sectional relationships presented in Robson (2003) and those described by the phylogenetic analysis is the position of the basal section. Robson (1981, 1985) hypothesized the Afrotropic section **1** (*Campylosporus*), containing species of *Hypericum* displaying morphological features that were considered the most "primitive," to be the most basal. In the phylogenetic analysis (**Fig. 1**), however, certain endemic sections distributed in the Mediterranean Basin and parts of the adjacent regions of Macaronesia (Canary Islands, Madeira and the Azores) and the northeastern African highlands (particularly Socotra) appear in basal positions. The latter finding is in agreement with preliminary molecular analyses (Mark Carine and Santiago Madriñán, unpublished data). Furthermore, the ag-

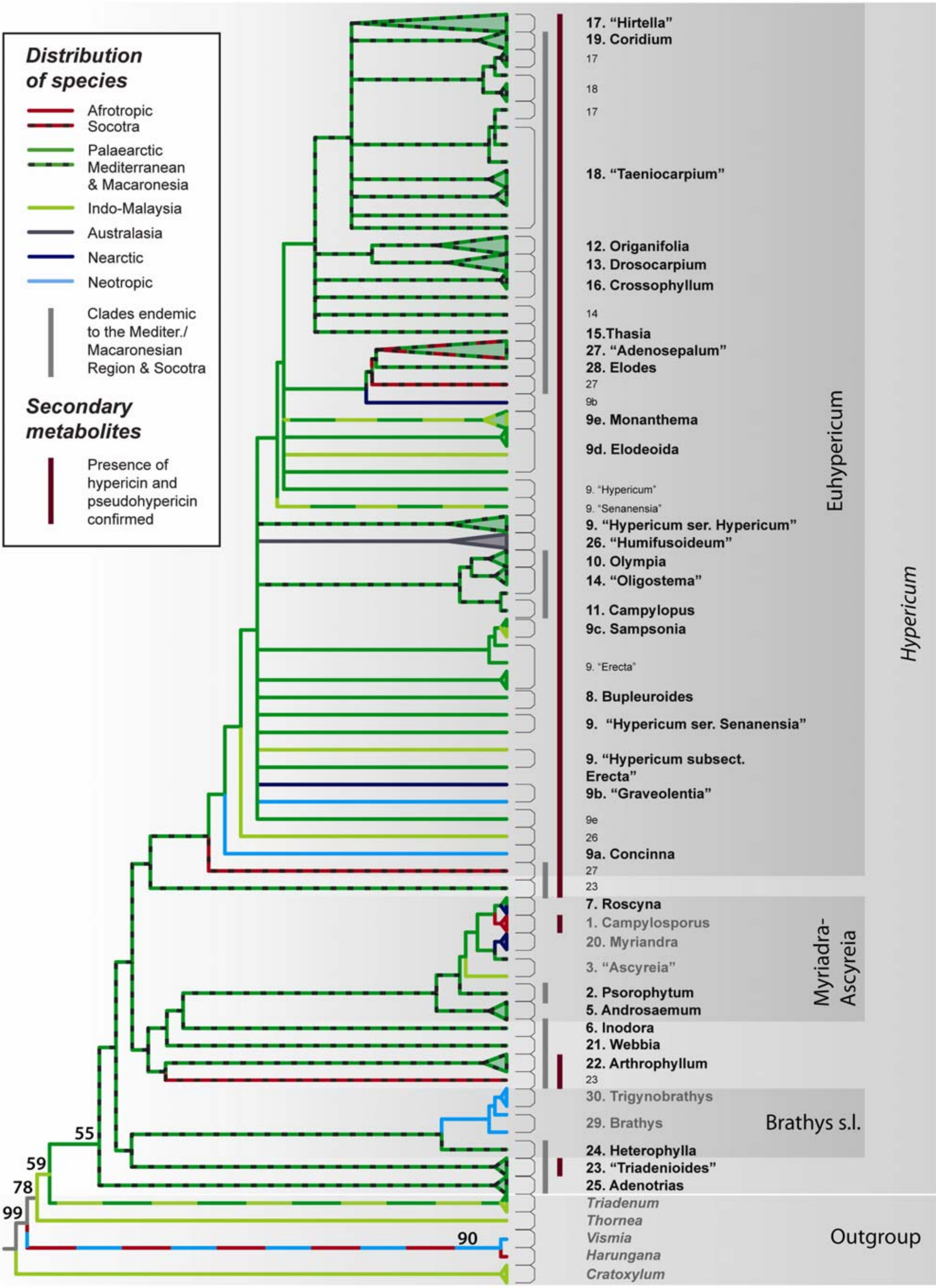

Fig. 1 Results of the cladistic analysis of morphological characters using Maximum Parsimony. In the condensed schematic strict consensus tree, phylogenetic relationships among sections of *Hypericum* are shown with an emphasis upon Mediterranean representatives. Distribution of species are marked by colors and their occurrence in the Mediterranean by black dots, respectively. The occurrence of naphthodianthrones is given (see figure legend). Square brackets and section names mark the position of sections within the tree. Section names in quotation marks appear as polyphyletic in the tree. Repeated small section numbers mark the position of parts of the polyphyletic sections. Section and genus names highlighted in grey letters are represented by one or two species only; section names in black are represented by all described species, and the size of clade branches appearing as triangles indicate the number of species within a clade (when more than two species belonging to a single section emerged in a polytomic relationship, branches in the tree were reduced to two). Numbers along branches indicate bootstrap support values. Rooting of the tree followed the results presented in Wurdack and Davis (2009).

gregation of the majority of the Palaearctic species into "Euhypericum" is reflective of previous classifications of *Hypericum* (Keller 1925). The distribution of various endemic species in the Mediterranean and the adjacent regions mentioned above, as well as the basal position in the phylogenetic tree of several of these sections, suggest that an alternative perspective on the evolution and biogeography of the genus can be considered, with a focus on the Mediterranean Basin as a possible center of origin for the genus (Nürk and Blattner, 2010).

Morphological characters and variation among *Hypericum* species distributed in the Mediterranean Basin, Macaronesia and parts of the northeastern African highlands

Details on morphological characterstics have been obtained when not otherwise stated from the individual monograph chapters for each section (see **Table 1**). Chemical structures of selected secondary metabolites are provided in **Fig. 1** of Crockett and Robson (2011).

1. Habit

Hypericum species occurring in this region of the world have a predominantly herbaceous habit. A shrubby habit (often described as "dwarf") is present in the sections described as basal and in scattered positions within the "Euhypericum" group (all species of sections **12** and **19** with the exception of the perennial herbaceous species, *H. asperuloides*; and occasionally in sections **18**, **26** and **27**).

2. Indumentum

Many members of sections **11-12**, **17-18** and **27** have hairs on the stem and leaves that are short and distinct, which may be described by many terms from scabrid to hirsute depending on their length. *Hypericum repens* (section **14**) has a glabrous stem, but an undulate or finely papillose lower-leaf epidermal surface. A limited number of species belonging to section **27**, as well as *H. elodes* (section **28**), have long fine, often wavy, hairs (Robson 1981). In the phylogenetic tree the puberulous species from section **27** and **28** group together on a clade, suggesting a common evolution for this type of hairs. Evolution of hairs within *Hypericum* in general appears more complex, and sertainly took place several times independently.

3. Glands

Two distinct types of glands have been identified in *Hypericum*, the so-called "dark" and "pale" glands. The first type is characterized by clusters of specialized cells with a black to reddish coloration indicative of their naphthodianthrone content (i.e. hypericin and/or pseudohypericin) (Ciccarelli *et al*. 2001a; Mathis and Ourisson 1963). The second type of gland ("pale" glands), clear to amber in color, is actually a schizogenous intercellular space lined by flattened cells that secrete essential oil components and phloroglucinol derivates, such as hyperforin (Ciccarelli *et al*. 2001b; Adam *et al*. 2002).

The distribution of the two gland types among these *Hypericum* species is complex. Sections **6**, **6a**, **21** and **25**, which in the cladistic analysis appear in a basal positions nearest the nearest outgroup (*Triadenum*), possess predominantly pale glands, with the exception of section **6**, which has dark glands only on the petal margins. Sections **22-23**, also appearing in basal positions, have dark glands on the stem, sepals and petals in the first case, and on leaves, sepals, petals and fruits in the second. Members of the "Brathys *s.l.*" and "Myriandra-Ascyreia" groups possess only pale glands, with the exception of section **1**, which has dark glands on the leaves, sepals and petals. Members of "Euhypericum" all possess dark glands, at least in the leaves, sepals and petals (generally in addition to the occurrence of pale glands).

4. Stem

Insertion of leaves in *Hypericum* is generally opposite-decussate with raised lines of tissue, varying from minor ridges to wing-like structures, along the internodes. Depending on the species and in some cases the age of the plant, 2, 4 or 6 ridges may be observed, or the stem may appear terete. Both pale and dark glands may be present along the stems, although eglandular representatives occur throughout the genus. Among species occurring in this region of the world, eglandular stems are characteristic for sections described as basal by Nürk and Blattner (2010) with the exception of sections **21**, and **24-25** (possessing pale glands), as well as for members of the "Myriandra-Ascyreia" group (excepting section **2**, which has pale glands). The presence of dark (and absence of pale) glands on stems is, outside of section **22**, confined to the "Euhypericum" group. Black glands on the stems are characteristic for all species of section **9** (series **1**), in which they are confined to the stem lines, and section **12** as well as for several species of section **9b**, in which they are dispersed over the stem surface. Amber glands on stems are present in several species of section **17** and in *H. vesiculosum* of section **13**, while red glands have been observed for some species of section **18**.

5. Leaves

Leaf characteristics for these species of *Hypericum* span the range of morphological diversity displayed by the genus as a whole. The leaves are estipulate and may be either sessile or have a short petiole. They may be persistent or deciduous, and if the latter, generally dehisce at or above a basal leaf articulation. The laminar venation is diverse, as is the shape of the leaves, which varies from oval to linear ("ericoid"). Leaf length is typically shorter than that of the internodes, however, a tendency towards elongation of the internodes can be observed in the "Euhypericum" group and for some New World species. Pale and/or dark glands are variously distributed within or at the leaf margin, or on the main laminar surface.

6. Sepals

The 4-5 sepals, which may be equal or unequal in size and shape, can either fold over one another in an overlapping fashion (quincuncial) or be opposite and decussate. Near the base, sepal tissue can be fused, and the free margins may display a variety of elaborations such as protruding marginal glands, (gland-dotted) teeth, or fine hairs. A slightly non-entire sepal margin has been developed only in some sections described as basal (**Fig. 1**), as well as in several sections of the "Euhypericum" group. Fully united sepal bases occur in sections **21** and **22** (closely grouping taxa in the phylogenetic analysis), and in sections of the "Euhypericum" group (with the exception of 5 species from the "Myriandra-Ascyreia" group, having slightly united sepals). Pale glands are present in nearly all sections on sepals at least on the lamina, with the exception of section **22**, which has only dark glands on the sepals. In sections **1** and **23**, dark glands are present on sepals only on the margin, but are distributed variously on the margin and lamina of the sepals in all sections of the "Euhypericum" group.

7. Petals

As with the sepals, petals can be unequal or equal, their overall shape approaches asymmetry in all species except those belonging to sections **25** and **28**. Their color usually ranges from pale lemon to golden yellow, although one species native to this region is exceptional in having white to pinkish petals (*H. albiflorum* of section **12**). Very occasionally, certain plants and populations of *H. hirsutum* (section **18**) can have flowers of such pale yellow that they appear cream-colored with a greenish tinge. Some other species have petals that are tinged with red (particularly on the outer surface, visible when the flower is in bud) or even fully suffused with red (as in *H. capitatum* var. *capitatum*, section **17**), and marginal elaborations occur (glands, fine teeth or cilia). Due to the interruption of the outer petal margin by the end of the midrib (Robson 1970), a so-called "apiculus" is observed in sections **6a** and **21-23** from the basal grade, in the "Brathys *s.l.*" group, the "*Myriandra-Ascyreia"* group and in sections **10**, **11**, **26** and **28** as well as some species of **27** within "*Euhypericum."* The distribution of this character across the phylogenetic tree suggests that it has evolved multiple times. The petals are generally persistent, but in many members of the "Myriandra-Ascyreia" group (excepting section **7** and four species of section **1**), two species of section **25** and three species of section **19**, they are deciduous.

Nearly all species of *Hypericum* have glands on the petals, at least at the lamina. Among species native to this region of the world, *H. xylosteifolium* (section **6**) has dark red glands on the petal margin, although the presence of naphthodianthrones in this species has not yet been confirmed. Otherwise, the occurrence of dark glands on petals is confined to the members of the "Euhypericum" group, and sections **22-23** (except *H. nanum* in section **22**, which lacks petal glands). Other sections described as basal or belonging to the "Brathys *s.l.*" or "Myriandra-Ascyreia" groups (**Fig. 1**) have eglandular petal margins.

8. Stamen fascicles

The stamens, ranging in number from 5 to more than 200, are arranged in bundles termed fascicles. These may be free from one another or fused in a variety of combinations (mostly in a combination 2+1+1, which results in 3 visible fascicles), and that are usually persistent. Deciduous stamen fascicles have been described for most sections of the "Myriandra-Ascyreia" group for some species of section **19**. A single gland (pale amber to reddish-black, depending on the species) is found on the anther connective. Black anther glands are confined to species in sections **12-14**, **15** (section *Thasia*, which in Robson 2010a is submerged within section **16**), **23**, **26** (rarely) and **27**, all in the "Euhypericum" group.

9. Styles and placentae

The ovary in *Hypericum* is generally (2-) 3-5-merous, with a corresponding number of styles (which may be variously free or sometimes united), and most species of *Hypericum* occurring in the Mediterranean have 3 styles (with the exceptions of sections **1-3**). The styles are mostly free (except in some members of section **3**), although in sections **8** and **23-25** they are basally appressed and are more or less fully appressed in section **1**. Placentation is predominantly axile (ovules generally many to ∞, but can be reduced to a few, especially in section **23**).

10. Fruit

The fruiting capsule is generally dry and dehisces from the apex. Elongate or punctate glands that are present on the outer capsular surface are termed generally as "vittae" when they are narrow to linear in form and specifically as "vesicles" when short and broad (as in sections **9**, **12-13**, **18** and **23**). In color, these glands are usually pale amber, although reddish-black vesicles have been observed on some species of section **13**, but the contents of these vesicles have only rarely been studied. One such study (Gronquist *et al*. 2001) resulted in the isolation of phloroglucinol and other terpenoid derivatives from particular species of sections **3** and **20**, which may indicate a biosynthetic congruence between these glands and those present on the leaves and stems.

11. Seeds

Seed characters for species of *Hypericum* occurring in the Mediterranean Basin and adjacent regions follow the general trends within the genus. They are typically small (0.3-1.5 mm long), cylindric to ellipsoid, and may be narrowly winged. A general evolutionary trend from cylindrical to carinate and/or narrowly winged seeds could be inferred from the cladistic analysis. Successful germination of certain species of *Hypericum* native to this part of the world has been achieved using *in vitro* culture conditions on Murashige and Skoog plant growth medium (Ayan and Çirak 2006; Çirak *et al.* 2007; Oluk and Orhan 2009; Karacaş *et al.* 2009) or in Petri dishes, pre-treated with either a mild acid or gibberelic acid (Çirak 2007), however, further studies with additional species (particularly endemic species) are needed.

12. Basic chromosome number

Basic numbers (n) within the genus have been proposed to form a descending series from 12 – 7. Counts of $n = 9$ and 10 are most frequently reported for species with a shrubby habit, while $n = 7$ and 8 is most frequent for herbs (Robson and Adams 1968; Robson 1981; da Cruz *et al*. 1990). Among Mediterranean *Hypericum* species, only those belonging to sections **1-3** display a basic chromosome number of $n = 12$. Most species that have been studied are diploid, but both tetraploids and hexaploids have been reported from sections **3** and **9**, and tetraploids from sections **21, 27** and possibly **28**. Interestingly, an ascending series of chromosomal base numbers from $n =$ 10-12(14) has been reported for species belonging to section **17**.

Phytochemical characters and variation

Within plants, secondary metabolites are biosynthesized via the acetate, shikimate, mevalonate and deoxyxylulose phosphate pathways. Fatty acids and aromatic polyketides (including simple phenols and anthraquinones) are formed via the acetate pathway, beginning with the building block of acetyl-CoA. This building block can also be utilized via the mevalonate pathway in the formation of terpenoids and steroids. Interestingly, these compound classes may alternatively be formed via the deoxyxylulose phosphate pathway, fed by two intermediates from glycolysis (Dewick 2002). Other primary metabolites from glycolysis and the pentose phosphate pathway feed into the shikimate pathway, leading to the biosynthesis of aromatic amino acids (often further involved in the production of alkaloids), benzoic and cinnamic acids, lignans, phenylpropanes and coumarins. Finally, products of the acetate and shikimate pathways can be combined enzymatically, resulting in the formation of a wide diversity of secondary metabolites, including flavonoids, stilbenes, flavonolignans and isoflavonoids.

Secondary metabolites assigned to many of these classes have been isolated and identified from species of *Hypericum* (Nahrstedt and Butterweck 1997 and citations therein; Hölzl and Petersen 2003; Avato 2005). The distribution of 9-10 compounds (so-called *biomarkers*) belonging to the classes of naphthodianthrones (hypericin and pseudohypericin), acylphloroglucinol derivatives (hyperforin), biflavones (I3, II8-biapigenin, amentoflavone) and flavonoid glycosides (rutin, hyperoside, isoquercitrin, quercitrin, quercetin) in *H. perforatum* are of particular interest from the perspective of the pharmaceutical industry (Müller 2005). **Table 3** of Crockett and Robson (2011) provides a general overview of the distribution of these compounds for sections of *Hypericum* distributed in the Mediterranean Basin with reference to selected examples of extant phytochemical literature. Interestingly, three taxonomic sections other than section *Hypericum* (**9**) with distributions within the Mediterranean Basin were identified that produce the biomarker compounds known for *H. perforatum*: sections **13** (10), **18** (9) and **27** (10). However, due to the unique morphological characteristics and distinct geographic ranges of these species as compared to the more wide-spread *H. perforatum*, purposeful adulteration or misidentification during wild collection is unlikely.

Due to the large number of papers that have been published on *Hypericum* in general (to date more than 5000), and on species occurring in this part of the world (more than 350) in particular, this article makes no attempt to review the literature exhaustively. Instead, readers are directed towards general reviews of *Hypericum* phytochemistry (Avato 2005; Hölzl and Petersen 2003; Nahrstedt and Butterweck 1997 and citations therein). Particular reports of secondary metabolite chemistry for these species, organized by taxonomic section, are presented in the following portion of the paper (see **Fig. 1** of Crockett and Robson (2011) for structures of frequently isolated compounds). Sections are discussed below by clade (see **Fig. 1**), and within each clade by sub-clade, where appropriate.

1. The basal grade

All species belonging to the basal grade and the "Brathys *s.l.*" clade (discussed below), which have been the subject of phytochemical study, have been shown to produce simple anthrones, flavonoids and flavonoid glycosides.

Section *Adenotrias* (**25**): The three species belonging to this section, forming a basal grade along with section **6a** within the genus, are found in the Mediterranean Basin in parts of North Africa, on islands in the Mediterranean Sea (e.g. Crete, Malta, Sardinia), and eastward to Syria. Only phytochemical data for *H. aegypticum* has been, to date, collected. An examination of the volatile constituents of *H. aegypticum* identified ishwarane, caryophyllene oxide and β-caryophyllene as major compounds (Crockett *et al.* 2007). Makovetska (2001) additionally isolated simple anthrones, selected flavonoids and flavonol glycosides from this species.

2. The "Brathys sensu lato" clade

Section Heterophylla (**24**): This section, the only member of the "Brathys *s.l.*" clade with a distribution in this part of the world, is represented by a single species, *H. heterophylla*, whose leaves differ in form (as the name indicates) between the lower (perennating) and upper (deciduous) parts of the stem (see Robson 1996, pp. 146-147). Although the plant occurs only in its native habitat in northwestern and west-central Anatolia in Turkey, it has been brought into cultivation, in part due to its unique features. Chemically, it is poorly known, although the isolation of simple anthrones, selected flavonoids and flavonol glycosides was accomplished by Makovetska (2001).

3. Basal members to the "Brathys sensu lato" clade

Section Triadenioides (**23**): The five species of section **23** have restricted distributional ranges, with two species found from southwestern Turkey to the mountain ranges defining the Lebanon-Syria border, and three species confined to the island of Socotra (Yemen). In the phylogenetic analysis, species belonging to this section were observed grouping in both Basal Clade 1 (sister to members of "Brathys *s.l.*") and Basal Clade 2 (discussed below, sister to members of "Myriandra-Ascyreia"). Other than a report of naphthodianthrones, simple anthrones, flavonoids and flavonol glycosides in *H. pallens* (Makovetska 2001), little is known about the phytochemistry of this group. Interestingly, the three species occurring on Socotra lack dark glands, while the two species distributed in parts of Turkey, Syria and Lebanon have red to black glands present on the flowers and sometimes leaves and stems (Robson 1996). The endemic nature of these species indicates an urgent need for *ex vivo* conservation work (e.g. development of seed germination, cell culture, and other propagation protocols).

Section Arthrophyllum (**22**): The five species of section **22** are found from southwestern Turkey to the mountain ranges defining the Lebanon-Syria border, overlapping in distribution with particular species of section **23**. A single report of naphthodianthrones, simple anthrones, flavonoids and flavonol glycosides in *H. nanum* has been published (Makovetska 2001). As with section **23**, *ex vivo* conservation work (e.g. development of seed germination, cell culture, and other propagation protocols) is needed. This section is the only one from this clade, broadly including the sister "Myriandra-Ascyreia," for which naphthodianthrones have been reported.

Section Webbia (**21**): *Hypericum canariense*, the monotypic representative of section **21**, is both locally abundant in its native habitat on the Canary Islands (Macaronesia) and has become naturalized elsewhere (e.g. Hawaii, California). Simple anthrones, flavonoids and flavonol glycosides were isolated from this species by Makovetska (2001). The report of hypericin in this species by Mederos-Molina (2002) and descriptions of micropropagation techniques for enhancement of this production is a puzzling one based on morphological features (i.e. purely clear to amber glands) and because plants that are cultivated in a greenhouse or common-garden setting do not seem to produce this compound (K. Dlugosch and S. Crockett, unpublished data). The working group of C. C. Sánchez-Mateo and R. M. Rabanal in Spain has conducted several *in vivo* tests of extracts of this plant and established antidepressant activity (Sánchez-Mateo *et al.* 2002; Prado *et al.* 2002; Sánchez-Mateo *et al.* 2005), *ex vivo* work demonstrating analgesic and anti-inflammatory activity (Rabanal *et al.* 2005), and *in vitro* anti-microbial (Gram-positive) activity (Rabanal *et al.* 2002), although the active constituents have not yet been identified.

Section Inodora (**6**): The monotypic representative of this section is *H. xylosteifolium*, a species distributed in similar habitat to that of *H. calycinum* near the Black Sea borders in Turkey and Georgia. This distribution of this species lies outside the Mediterranean Basin, but a discussion of its characteristics is valuable due to its placement in the cladistic analysis. Makovetska (1999a) detected simple anthrones, flavonoids and flavonoid glycosides. Work in our laboratory on this species has preliminarily resulted in the isolation of γ-pyrone derivatives, similar to those previously isolated from *H. mysorense* (= *H. mysurense* Wallich ex Wight & Arnott) collected in Sri Lanka (S. Crockett unpublished data).

4. The "Myriandra-Ascyreia" clade

All species belonging to the "Myriandra-Ascyreia" clade, which have been the subject of phytochemical study, have been shown to produce simple anthrones, flavonoids and flavonoid glycosides. Sections **2**, **3** and **5** have additionally been shown to produce xanthones, and sections **3** and **5**, to produce acylphloroglucinol derivatives and biflavones.

Section Androsaemum (**5**): Two of the four species belonging to section **5**, namely *H. androsaemum* and *H. hircinum* L. (including 4 subspecies) are distributed within the Mediterranean Basin. The Macaronesian species of *H. grandifolium* Choisy (Canary Islands and Madeira) and *H. foliosum* Aiton (the Azores) are found on islands off the northwestern coast of Africa, the floras of which contain many northern African elements.

The first of these species, *H. androsaemum*, has been the subject of much phytochemical study, due to the ease of its cultivation and unique pinkish to purplish fleshy capsules. In fact, the natural color variation in the fresh capsules has been exploited through directed breeding and line selection, resulting in economically highly successful cultivars. Fresh stems of these plants, many of which are cultivated in South America and imported to the Netherlands for wider distribution and sale, are particularly popular in bridal bouquets. Interestingly, the pigment denoting the reddish color to the capsular tissue has not yet been studied. From various parts of the plant, caffeic acid derivatives (Seabra and Alves 1989a), flavonoid glycosides (Hargreaves 1966; Makovetska 1999b; Šmelcerović *et al.* 2008), an unusual sulfated flavonoid (Seabra and Alves 1989a), triterpenes (Hargreaves *et al.* 1968; Seabra 1988), simple anthrones (Makovetska 1999b) and xanthones (Nielsen and Arends 1979) have been isolated. Much research on cell culture of this species has been performed and, under these conditions, it has proved a good model with which to study xanthone and benzophenone biosynthesis (Schmidt and Beerhues 1997; Peters *et al.* 1998; Dias *et al.* 2000; Schmidt *et al.* 2000a, 2000b; El-Mawla *et al.* 2001; Dias 2003; Liu *et al.* 2003). Studies of the volatile constituents have revealed high levels of long-chain hydrocarbons, caryophyllene oxide and ishwarane (Guedes *et al.* 2003, 2004; Morteza-Semnani and Saeedi 2005).

Simple anthrones have also been isolated from *H. hircinum* and *H. grandifolium* (Makovetska 1999b). From *H. hircinum*, major volatile constituents include long-chain hydrocarbons (e.g. nonane) and α- and β-pinene (Bertoli *et al.* 2000). Flavonoids with antimicrobial activity (Pistelli *et al.* 2000) and inhibitory activity against monoamine oxidase A (Chimenti *et al.* 2006) have been isolated and identified. Extracts of *H. grandifolium* have been shown to possess antidepressant (Prado *et al.* 2002; Sánchez-Mateo *et al.* 2002, 2009), antibacterial (Rabanal *et al.* 2002) and wound-healing (Bonkanka *et al.* 2008) activities, but the active constituents have not yet been identified. Reports from *H. foliosum* are few, excepting that nonane, limonene, terpinolene and β-caryophyllene have been cited as major volatile constituents of the inflorescences (Santos *et al.* 1999) and that a simple acylphloroglucinol derivative with antibacterial activity has been isolated (Gibbons *et al.* 2005).

Section Psorophytum (**2**): *Hypericum balearicum* is the only representative of this uniquely defined section, and has been the subject of a limited number of phytochemical studies. Xanthones (Alberto *et al.* 1981), flavonoids, triterpenes (Wollenweber *et al.* 1994) and simple anthrones (Makovetska 1998) have been isolated. Interestingly, the anthrones that have been identified are the presumed biogenetic precursors to naphthodianthrones (e.g. hypericin). This section is treated as basal to sections **1**, **3**, **7** and **20**, of which only section **1** produces naphthodianthrones.

Section Ascyreia (**3**): All but one species of this section are native to Asia, with species distributions ranging north and east of the Himalayas from Pakistan to China, and south and east in India, Sri Lanka, Thailand, Vietnam and western Indonesia. *Hypericum calycinum*, however, is distributed naturally in forested regions of southeastern Bulgaria and eastern Turkey (primarily in the Pontic region toward the Black Sea, but with isolated records closer to the Mediterranean Sea). This species is also widely cultivated and is naturalized in many additional countries around the world.

Phytochemical investigations of this plant have revealed the presence of interesting cytotoxic terpenoid and acylphloroglucinol derivatives (Decosterd *et al.* 1989, 1991; Gronquist *et al.* 2001) as well as hyperforin (Boubakir *et al.* 2005; Klinglauf *et al.* 2005), cinnamic acid derivatives (Seabra and Alves 1989b; Kirmizibekmez *et al.* 2009), xanthones (Konovalova 2007), and flavonoids and flavonoid glycosides. Analyses of the volatile constituents have identified α-terpineol and β-pinene as major compounds (Erken *et al.* 2002; Demirci *et al.* 2005).

5. "Euhypericum": Members of a basal polytomy within the clade

All species belonging to the "Euhypericum" basal polytomy, which have been the subject of phytochemical study, have been shown to produce simple anthrones, flavonoids, flavonoid glycosides and biflavones.

Section Hypericum (**9**): As explained in Robson (2001), section **9** has been shown to encompass seven taxa, identified respectively as subsections and, within subsection 1, series. Several species belonging to subsection 1, series 1 (see detailed account in Robson 2002) have part or all of their distributions in the Mediterranean Basin. The best-known of these species, *H. perforatum*, has been the subject of an enormous number of phytochemical and pharmaceutical studies, and readers are referred to the works of Nahrstedt and Butterweck 1997, Hölzl and Petersen (2003), Avato (2005) and Müller (2005) and citations therein for more information. Of the remaining four species, *H. maculatum* Crantz has the highest probability of being confused with *H. perforatum* during field collection. Usually, these species can be distinguished by determining whether the stem internodes are completely 4-lined or 4-winged (as with *H. maculatum*) or partially 4-lined or 2-lined (as with *H. perforatum*). Hybridization between the taxa in areas where their distributional ranges overlap resulting in either ephemeral or stable populations (e.g. the stable taxon referred to as *H. maculatum* ssp. *obtusiusculum* (Tourlet) Hayek may be the result of recent introgression with *H. perforatum*), however, creates difficulties. For this reason, reports of phytochemical constituents from wild-collected plants of *H. maculatum*, particularly in regions where the distributional range overlaps with that of *H. perforatum* (and *vice-versa*) must be treated with care.

Beyond reports of the 9-10 biomarker compounds used for phytochemical profiling of *H. perforatum*, reports of secondary metabolites isolated from *H. maculatum* are surprisingly limited. A xanthone was isolated from the roots by Arends (1969). The bioactive acylphloroglucinol hyperforin has been detected in this species and the related *H. tetrapterum* using HPLC (Šmelcerović and Spiteller 2006; Šmelcerović *et al.* 2006; Kusari *et al.* 2009). Antimicrobial activity has been cited for both the crude methanol extract (Radulović *et al.* 2007) and for the essential oil, major components of which were identified as spathulenol and globulenol (Saroğlou *et al.* 2007). A study of the volatile constituents of *H. perforatum*, *H. maculatum* and *H. tetrapterum* described their overall similarities to one another (Šmelcerović *et al.* 2007).

As with *H. maculatum*, research on *H. tetrapterum* beyond the detection and quantification of the biomarker compounds described for *H. perforatum* has been limited. Antimicrobial and antioxidant activities for the crude extract of this species, as compared to those of standard substances, have been reported by Radulović *et al.* (2007) and Cecchini *et al.* (2007). In the latter study, a promising inhibitory activity against the yeast *Candida albicans* was cited, however, as is unfortunately too often the case, the active constituents were not further isolated and identified.

Hypericum undulatum Schousb. ex Willd. occurs in the Mediterranean Basin in western and southern Spain, western Algeria and northern Morocco, and also is found in Macaronesia on Madeira and the Azores Islands. Research on this species has primarily been conducted by the research group of Rosa Seabra, resulting in the isolation of caffeic acid derivatives, xanthones, and flavonoid glycosides (Seabra and Alves 1989b, 1990), as well as the more unusual sulfonated flavonoids (Seabra *et al.* 1991). Simple anthrones and naphthodianthrones were detected, along with flavonoids and flavonoid glycosides, by Makovetska (1999c). Bioassay screening of the crude extract of this species revealed a high capacity for acetylcholinesterase inhibition and antioxidant activity (Ferreira *et al.* 2006).

A considerable number of studies have focussed on the production of naphthodianthrones in *H. triquetrifolium*, as a potential alternative source for isolation of these compounds (Alali *et al.* 2004; Ayan and Çirak 2008; Çamas *et al.* 2008), which are particularly interesting due to their high antiviral activity and low cytotoxicity (i.e. for treating

HIV-1) (Meruelo *et al.* 1988; De Clerq 2000). In addition to field studies, *in vitro* propagation and manipulation methods with a primary aim of increasing naphthodianthrone content have been conducted (Oluk and Orhan 2009; Namli *et al.* 2009; Karakaş *et al.* 2009). Related bisanthraquinone derivatives with moderate antiviral activity against the Herpes Simplex type I DNA virus have also been identified in this species (Afifi *et al.* 2001). As in other related *Hypericum* species, caffeic acid derivatives, flavonoids and flavonoid glycosides, and biflavones have been found in *H. triquetrifolium* (Couladis *et al.* 2002), some of which have displayed good antioxidant activity (Conforti *et al.* 2002; Nassar and Gamal-Eldeen 2003). The anti-inflammatory activity has been examined in a rat-model with positive results, significant due to the traditional use of extracts of this plant topically against inflammation (Ozturk *et al.* 2002). Promising antifungal and antibacterial activities of the crude extract have been shown against panels of phytopathogenic fungi (Fraternale *et al.* 2006) and gram-positive and –negative bacteria, respectively (Pistelli *et al.* 2005). In the latter study, the flavonoid quercetin and biflavone I3, II8-biapigenin were targeted as active constituents. Nonane, α- and β-pinene, α-humulene and *cis*-calamenene have been reported as major volatile constituents (Bertoli *et al.* 2003; Karim *et al.* 2007).

Section Bupleuroides (**8**): The distributional range of *H. bupleuroides*, a *Hypericum* unusual in its possession of distinctly perfoliate leaves, overlaps with that of *H. xylosteifolium* in the Black Sea border region of Turkey and Georgia. As with the latter species, the distribution of *H. bupleuroides* is outside the Mediterranean Basin, but a discussion of its characteristics is valuable due to its placement in the cladistic analysis. Simple anthrones, flavonoids and flavonoid glycosides were identified by Makovetska (1999a). Additionally, caffeic acid derivatives, the biflavone amentoflavone and naphthodianthrones were detected using HPLC by Ayan *et al.* (2009). A study of the volatile constituents revealed β-sesquiphellandrene and β-caryophyllene as major compounds (Demirci and Başer 2006). Due to the limited distributional range, specific habitat requirements and danger of extinction of this species, an *in-vitro* plant regeneration method using vegetative tissue has been developed (Çirak *et al.* 2007a).

6. "Euhypericum": Subcluster 1

All species belonging to the "Euhypericum" subcluster 1, which have been the subject of phytochemical study, have been shown to produce flavonoids, flavonoid glycosides and naphthodianthrones.

Section Campylopus (**11**): This section is represented by a single species, *H. cerastoides*, upon which only a limited amount of work has thus far been conducted. It appears basal in the phylogenetic analysis with respect to its sister taxa in sections **10** and **14**. The few phytochemical studies include reports of flavonoid glycosides and naphthodianthrones (Makovetska 1999d; Crockett *et al.* 2005) and an analysis of volatile components by Erken *et al.* (2002). This species has been brought into cultivation and is not infrequently to be found in botanical gardens, but its restricted native distribution makes further research on micropropagation, optimal seed germination conditions and *in vitro* culture desirable.

Section Olympia (**10**): The four species belonging to section **10** are distributed in the eastern portion of the Mediterranean Basin, particularly extending on the Balkan Peninsula. *Hypericum polyphyllum* and *H. olympicum* are known due to their introduction into cultivation (Huxley *et al.* 1992), and are the only species for which phytochemical data is currently available. Naphthodianthrones, simple anthrones, flavonoids and flavonol glycosides (Makovetska 1999d; Akhtardzhiev *et al.* 1973) and biflavones (Baureithel *et al.* 1997). Primary volatile constituents of *H. olympicum* have been reported as (*E*)-anethole, β-farnesene, germacrene D and (*E*)-caryophyllene (Gudžić *et al.* 2001; Pavlović *et al.* 2006). Promising antimicrobial and antioxidant activity has been determined (Radulović *et al.* 2007) and may be in part due to the presence of as yet undescribed acylphloroglucinol derivatives (Crockett, pers. obs; Gibbons, pers. comm.).

Section Oligostema (**14**): The six species of section **14** also possess dark glands, although the presence of naphthadianthrones has only been verified thus far for *H. repens* (Makovetska 2000a) and *H. humifusum* (Umek *et al.* 1999). Phytochemical data for most of these species are still lacking, although caffeic acid derivatives, flavonoids, flavonoid glycosides and biflavones and xanthones (i.e. mangiferin) have been detected in *H. hirsutum* (Seabra and Alves 1989b; Umek *et al.* 1999). A single report on the volatile constituents of a sample this species collected in Portugal exists (Nogueira *et al.* 2008). Research related to *ex situ* conservation of *H. andjerinum*, *H. repens* and *H. kelleri* is needed due to their extremely restricted distributions and the danger of extinction due to habitat loss.

7. "Euhypericum": Subcluster 2

All species belonging to the "Euhypericum" subcluster 2, which have been the subject of phytochemical study, have been shown to produce simple anthrones, naphthodianthrones, flavonoids, flavonoid glycosides and acylphloroglucinol derivatives.

Section Elodes (**28**): Considering the somewhat inconspicuous nature of the monotypic *H. elodes*, which is found in its native habitat creeping in the moist soil of bogs, streamsides and in shallow ponds, it is somewhat surprising that phytochemical work has been conducted at all. Nevertheless, an unusual sulfated flavonol and a corresponding sulfated flavonol glycoside were isolated by Seabra and Alves (1988 and 1991). Additionally, Koch (2001) determined that naphthodianthrones, simple anthrones, flavonoids and flavonol glycosides were present. Piovan *et al.* (2004) verified the presence of hypericin and pseudohypericin in the red glands on the sepals of this species, and also found the acylphloroglucinol derivatives hyperforin and adhyperforin in sepal secretory canals.

Section Adenosepalum (**27**): Extracts of the Macronesian species *H. glandulosum* and *H. reflexum* have been tested in the same series of bioassays as those of *H. canariense* by the working group of Sánchez-Mateo and Rabanal (see section **21**), with similar findings. Bioassay-guided fractionation of an extract of *H. glandulosum* has resulted in the isolation of several acylphloroglucinol derivatives with interesting anti-mycobacterial activities (S. Crockett unpublished results), and it is tempting to speculate that these compounds may be in part responsible for the observed antidepressant, analgesic and anti-inflammatory effects, although this remains to be verified. Additionally, xanthones, xanthonolignoids and a biphenyl, as well as two unusual spiroterpenoids (hyperireflexolide A and B) have been isolated from *H. reflexum* (Cardona *et al.* 1990, 1993).

Naphthodianthrones, simple anthrones, flavonoids and flavonol glycosides were identified in *H. pubescens*, *H. reflexum*, *H. athoum*, *H. atomarium* and *H. tomentosum* by Koch (2001). Major volatile constituents for the latter species collected in Tunisia were identified as menthone and n-octane (Hosni *et al.* 2008). Similar studies with *H. delphicum* allowed the identification of caryophyllene oxide, β-caryophyllene and undcane as major constituents (Crockett *et al.* 2007), while for *H. atomarium*, the most abundant components were isocarophyllene, γ-cadinene and 2,4-diisopropenyl-1-methyl-1-vinyl-cyclohexane (Gudžić *et al.* 2004).

The detection of rather unusual terpenes is not confined to a single species in this group. Quite recently, a complex caged terpenoid derivative (sinaicinone) was isolated from the endemic species *H. sinaicum*, collected in northern Egypt (Rezanka and Sigler 2007), while the acylphloroglucinol derivative hyperforin and naphthodianthrone protopseudohypericin were identified from a sample collected in Jordan (Alali *et al.* 2009). Flavonol glycosides and both para- and ortho-coumaric acids have been identified from the flowering stems of *H. caprifolium* (Ayuga and Rebuelta 1986; Ayuga and Carretero 1987).

In contrast to other species in this section, considerable phytochemical work has been done on *H. montanum* and *H. annulatum*, resulting in the identification of flavonoids (Shatunova 1979), xanthones and xanthone-C-glucosides (Kitanov and Nedialkov 1998, 2000; Mitcheva *et al.* 2006), caffeic acid derivatives (Maleš *et al.* 2004), flavonol glycosides, biflavones and naphthodianthrones (Umek *et al.* 1999; Koch 2001; Šmelcerović *et al.* 2008). *Hypericum annulatum* is particularly interesting phytochemically, producing benzophenone and chromone derivatives, some of which have a demonstrated hepatic protective activity (Kitanov and Nedialkov 2001; Mitcheva *et al.* 2006; Zheleva-Dimitrova *et al.* 2007) and an isocoumarin with moderate anti-leukemic activity (LAMA-84 cells) (Nedialkov *et al.* 2007b). An acylphloroglucinol derivative (hyperatomarin) with antibacterial (Gram-positive) and cytotoxic activity has also been isolated from this species (published under the synonym *H. atomarium* ssp. *degenii* by Šavikin - Fodulović *et al.* 2003; as *H. annulatum* ssp. *annulatum* by Momekov *et al.* 2008).

8. "Euhypericum": Subcluster 3

All species belonging to the "Euhypericum" subcluster 3, which have been the subject of phytochemical study, have been shown to produce simple anthrones, naphthodianthrones, flavonoids and flavonoid glycosides. Most have been shown to produce acylphloroglucinol derivatives and xanthones.

Section Crossophyllum (including Thasia) (**15/16**): Section **15** (*Thasia*) has been merged with section **16** in the most recent taxonomic treatment (Robson 2010a). The phylogenetic analysis indicates that particular species currently assigned to section **14** may also display morphological features which would make them appropriate to include in this grouping. Some species of sections **15/16**, such as *H. adenotrichum* and *H. orientale*, have unique gland-fringed leaves and striking foliar auricles. The use of extracts of *H. adenotrichum* in Turkey in the traditional medicine as an antiseptic and to speed healing of wounds has inspired several phytochemical investigations. Doğanca and Öksüz (1989) first reported on the presence of flavonoids, flavonoid glycosides and the naphthodianthrone hypericin in a polar extract of the plant. Twenty years later, a study by Çirak *et al.* (2009) confirmed these results, additionally detecting pseudohypericin, the acylphloroglucinol hyperforin, the caffeic acid chlorogenic acid and the biflavone amentoflavone using HPLC. Ozmen *et al.* (2009) described anti-proliferative activity for the non-polar extract and determined that hyperforin, hypericin and amentoflavone were not responsible for this activity.

Simple anthrones, flavonoids, flavonol glycosides and caffeic acid derivatives have been isolated from *H. orientale* (Makovetska 2000a). In contrast to *H. adenotrichum*, apigenin-7-O-glucoside has not been detected in *H. orientale* (Çirak *et al.* 2007c, 2009). Both hypericin and pseudohypericin were initially determined as present in this species (Ayan and Çirak 2008), which data was verified by Šmelcerović *et al.* 2008. A study on the seed germination protocols has been published by Çirak (2007). A limited amount of phytochemical research has been conducted on *H. aucheri* (sometimes mistakenly spelled *H. aucherii*). Caffeic acid derivatives, flavonoids and flavonol glycosides have been isolated (Kitanov *et al.* 1979a; Kitanov 1988). 1,3,6,7-tetrahydroxyxanthone (Kitanov and Blinova 1980) and the xanthone-C-glucosides isomangiferin (Kitanov 1988) and mangiferin (Kitanov and Nedialkov 1998; Nedialkov *et al.* 1998) have also been identified. The biflavone 3, 8"-biapigenin, which has also been isolated from *H. perforatum*, was first identified in the genus from this species (Kitanov 1985, 1988).

Hypericum thasium, which differs from the preceding species in its possession of a 5-merous gynoecium (as opposed to 3-merous) and black anther gland (as opposed to amber), has been collected from specific locations in Greece, Bulgaria and Turkey. Few recent collections of the plant in its native habitat have been published and further work is needed on the population biology of this species is needed. Recently, however, the isolation of flavonoids, flavonoid glycosides, the biflavone 3, 8"-biapigenin, and four simple benzophenone derivatives with some structural similarities to compounds previously reported from *H. annulatum* (section **27**) from a sample collected from the Edirne region of Turkey was reported (Demirkiran *et al.* 2009). This observation is interesting in the light of the phylogenetic analysis, which supports a close relationship between these two sections. The Edirne region is close to the site of an earlier collection of *H. thasium* in the Strandža mountain range in southeastern Bulgaria, and gives hope that other populations of this species might be present in this region. In this study, 288 grams of dried aerial plant tissue, corresponding to an estimated 1.5-2 kg of fresh plant material, was extracted for analysis. The mature plant generally attains the height of 40 cm under ideal growing conditions, and is branching. A fresh plant with this size and character would usually provide 20-30 grams tissue (Crockett, pers. obs.) and 60-75 plants would be needed to provide this amount of material for phytochemical analysis. Having made this observation, it is to be hoped that the authors of this work are also engaged in research on *ex situ* conservation for this species. A single additional report of simple anthrones, naphthodianthrones, flavonoids and flavonoid glycosides exists (Makovetka 2000a).

Section Organifolia (**12**): Thirteen species are currently described for this section, of which some (such as *H. salsugineum*) are extremely restricted in distribution, while others (such as *H. organifolium*) are more widespread. Most are to date still poorly known, phytochemically. The presence of naphthodianthrones, simple anthrones, flavonoids and flavonol glycosides has been verified in *H. organifolium* and *H. laxiflorum* (= *H. aviculariifolium* ssp. *depilatum*) (Makovetska 1999d; Ayan and Çirak 2008; Šmelcerović *et al.* 2008). Quantitative and qualitative variability in specific biomarker compounds according to ontogenetic, morphogenetic and diurnal factors has been studied in these species (Ayan *et al.* 2006; Çirak *et al.* 2006, 2007b; Odabas *et al.* 2008). Seed germination methods for *ex situ* conservation of *H. organifolium* have recently been developed (Çirak 2007), methods which hopefully can be tested and extended to some of the species of this section with more limited distributions. The phylogenetic analysis indicates that this section is closely affiliated with section **13**.

Section Drosocarpium (**13**): The distribution of these 11 species ranges from the islands off the northwestern coast of Africa (i.e. Madiera, Canary Islands) to the Black Sea regions of Georgia and Turkey. As in the preceding section, some species (e.g. *H. perfoliatum*) are distributed throughout the range of the section, while others (e.g. *H. trichocaulon*) are highly endemic. In contrast to section **12**, however, several species of section **13** have been phytochemically investigated, at least to some degree. Dark glands on the leaves, sepals, petals and anthers of these species indicate the presence of naphthodianthrones, and this has been verified by several authors (Fornasiero *et al.* 2000; Makovetska 2000a; Çirak *et al.* 2007c; Ayan and Çirak 2008; Šmelcerović *et al.* 2008).

Simple anthrones, flavonoids, flavonol glycosides and caffeic acid derivatives have been additionally detected in *H. perfoliatum*, *H. bithynicum*, *H. montbretii*, *H. barbatum*, *H. rumeliacum* and *H. richeri* (Sakar *et al.* 1991; Makovetska 2000a; Maffi *et al.* 2001; Šmelcerović and Spiteller 2006; Çirak *et al.* 2007c; Odabas *et al.* 2008; Šmelcerović *et al.* 2008). The acylphloroglucinol derivative hyperforin, also found in *H. perforatum*, is found in *H. montbretii*, with highest levels detected in the fresh (green) fruits (Çirak and Radušienė 2007), *H. barbatum* and *H. rumeliacum* (Šmelcerović and Spiteller 2006). Another acylphloroglucinol derivative (hyperfoliatin) has been isolated from *H. perfoliatum* (Benkiki *et al.* 2003), which displayed an *in vivo* anti-depressant effect in mice, related to inhibition of monoamine uptake at synaptosomal transporters (Do Rego *et al.* 2007).

The major volatile constituents of *H. richeri* have been identified as (*Z*)-β-ocimene and n-nonane (Ferretti *et al.* 2005); for *H. barbatum*, α- and β-pinene, limonene and (*E*)-caryophyllene (Saroğlou *et al.* 2007); and for *H. rumeliacum*, α- and β-pinene (Couladis *et al.* 2003; Saroğlou *et al.* 2007). Samples from several geographic regions of *H. perfoliatum* have been examined for their volatile constituents, with interesting results. The sample from Greece displayed high levels of α- and β-pinene and δ-cadinene (Couladis *et al.* 2001); that from Algeria had high amounts of thymol, T-cadinol and 4,5-dimethyl-2-ethylphenol (Touafek *et al.* 2005); and that from Tunisia had oils rich in α-pinene, allo-aromadendrene and germacrene-D (Hosni *et al.* 2008). The results of these studies indicate the extreme variability of essential oil components, due to both environmental and genetic factors, and suggest that caution must be taken when inferring biosystematic significance from these data (see Petrakis *et al.* 2005; Šmelcerović *et al.* 2007; Nogueira *et al.* 2008).

Work with *H. umbellatum* revealed the presence of flavonoid glycosides and a xanthone, norathyriol (Nedialkov *et al.* 2007a). A more wide-spread xanthone, mangiferin, has been isolated from *H. rochelii* and *H. perfoliatum* (Kitanov and Nedialkov 1998). As with section **12**, the variation in particular biomarker compounds according to ontology and phenology has been studied for some species of this section (Çirak *et al.* 2008; Odabas *et al.* 2008). While bioactivity data for this section is more limited than that for section **9**, *ex vivo* anti-inflammatory activity has been determined for extracts of *H. richeri*, *H. barbatum* and *H. rumeliacum*, although the active constituents have not yet been identified (Šavikin *et al.* 2007; Galati *et al.* 2008). For *H. perfoliatum*, seed germination protocols have been developed that may be applied to additional species of this section threatened by extinction (Çirak 2007).

9. "Euhypericum": Subcluster 4

All species belonging to the "Euhypericum" subcluster 4, which have been the subject of phytochemical study, have been shown to produce simple anthrones, naphthodianthrones, flavonoids and flavonoid glycosides. Most have been shown to produce biflavones and xanthones.

Section Taeniocarpium (**18**): The species belonging to section **18** are distributed across a similar region as section **17**, with the addition of parts of northern Africa. Of these 28 species, seven have been phytochemically studied to some degree. Naphthodianthrones, simple anthrones, flavonoids, flavonol glycosides, and caffeic acid derivatives and the xanthone mangiferin have been reported from *H. pulchrum*, *H. nummularioides*, *H. nummularium* and *H. linarioides* (Netien and Lebreton 1964; Seabra and Alves 1989; Makovetska 2000b; Šmelcerović *et al.* 2006; Ayan and Çirak 2008). Representatives of these classes of secondary metabolites, excepting naphthodianthrones and with the addition of biflavones, have been isolated from *H. hirsutum* (Kitanov *et al.* 1978, 1979b, 1979c, 1988; Umek *et al.* 1999). Extracts of this species as well as specific purified compounds display anti-inflammatory and anti-bacterial bioactivity (Šavikin *et al.* 2007; Cecchini *et al.* 2007; Radulović *et al.* 2007). Similar antimicrobial testing of an extract of *H. havvae* indicated its potency, but the bioactive compounds were not identified (Dulger *et al.* 2008).

Studies of the volatile constituents of *H. hirsutum* and *H. linarioides* revealed that *n*-undecane and patchoulene, and δ-cadinene, (*Z*)-β-farnisene and γ-muurolene, respectively, were major components (Çakir *et al.* 2005; Gudžić *et al.* 2007). The quantitative and qualitative aspects of biomarker compound variation according to ontology, morphology and diurnal fluctuations in *H. pruinatum* plants have also been examined (Ayan *et al.* 2006; Çirak *et al.* 2006, 2007c). As with section **17**, few directed studies toward *ex situ* conservation of endemic species have been undertaken, except for the development of a seed germination protocol for *H. pruniatum* (Çirak 2007).

Section Coridium (**19**): The working group of M. L. Cardona in Spain has published several papers on *H. ericoides* (Cardona and Seone 1982, 1983; Cardona *et al.* 1983), detailing the isolation of flavonoids, flavonol glycosides, as well as a series of xanthones, including 1-, 2-, 3- and 4-hydroxylated representatives, and the xanthonolignoid kielcorin. Naphthodianthrones, simple anthrones, flavonoids and flavonol glycosides are reported from both *H. coris* and *H. empetrifolium* (Makovetska 2000b). An examination of the essential oil of *H. coris* identified α-curcumene as a major constituent (Schwob *et al.* 2002).

Two bicyclic acylphloroglucinol derivatives were isolated from *H. amblycalyx* by Winkelmann *et al.* (2003) and displayed moderate cytotoxic activity (KB and Jurkat T cancer cells) and strong antibacterial (gram-positive) activity. Several structurally similar compounds, demonstrating *in vitro* antioxidant activity, were isolated from *H. jovis* by Athanasas *et al.* (2004). One of these compounds, along with an additional acylphloroglucinol derivative, was subsequently isolated from *H. empetrifolium* (Crockett *et al.* 2008), supporting the potential for acylphloroglucinol derivatives to be used in chemotaxonomy, at least at sub-generic levels. Alali *et al.* (2009) identified the bicyclic acylphloroglucinol adhyperforin using HPLC-MS in a sample of *H. empetrifolium* collected in Jordan, although this compound was not detected in the sample from the preceding sample (cultivated in Great Britain from seed). This case serves as an additional example that environmental conditions (particularly biotic and/or chemical elicitation such as with herbivory) can significantly affect the biosynthesis of these compounds (also demonstrated by Sirvent *et al.* 2003 for *H. perforatum*). Anti-inflammatory and analgesic effects of the polar extract of *H. empetrifolium* have been demonstrated *in vivo* in mice, but the active constituents have not yet been identified (Trovato *et al.* 2001).

Section Hirtella (**17**): The species of section **17** are distributed primarily from the eastern Mediterreanean region to Asia Minor, with the highest diversity centered in Turkey. Naphthodianthones, simple anthrones, flavonoids, flavonol glycosides have been isolated from *H. helianthemoides* and *H. elongatum* (Makovetska 2000b). Additionally, biflavones, flavonoid glycosides and hypericin, which displayed antioxidant activity, were identified from the latter species by Çakir *et al.* (2003, published under the synonym *H. hyssopifolium* ssp. *elongatum*). Major volatile constituents for this species (also published as *H. hyssopifolium* ssp. *elongatum*) are α- and β-pinene (Çakir *et al.* 2004) and γ-terpinene (Ghasemi *et al.* 2007). In contrast, the volatile constituents of *H. hyssopifolium* ssp. *hyssopifolium* are dominated by spathulenol, tetradecanol and dodecanol (Schwob *et al.* 2006). Antimicrobial activity (gram-positive and –negative) has been cited for the polar extract of this species, but no active compounds were isolated (Cecchini *et al.* 2007). Naphthodianthrones have been reported from *H. hyssopifolium* (Ayan and Çirak 2008), *H. hirtellum*, *H. lysimachioides* and *H. helianthemoides* (Jaimand *et al.* 2008).

The volatile components of *H. microcalycinum* (published as *H. hyssopifolium* var. *microcalycinum*) have been studied, revealing the major compound to be caryophyllene oxide (Toker *et al.* 2006), while spathulenol was identified as the major volatile constituent of *H. thymposis* (Ozkan *et al.* 2009). A single report on the fatty acid chemistry of *H. retusum* has been published, reporting primarily acids with C14, C16 and C18 chain lengths (Özen *et al.* 2004a). Studies of the fatty acid constituents of *H. scabroides*, *H. amblysepalum* and *H. lysimachioides* revealed linolenic and palmitic acids to be major components (Özen and Basham 2003; Özen *et al.* 2004b). Naphthodianthrones, flavonoids, flavonoid glycosides and caffeic acid derivatives have been isolated from *H. lydium* (Çirak 2006; Çirak *et al.* 2007c). While extracts of this species have demonstrated anti-cholesterolemic activity (Hakimoğlu *et al.* 2007), mutagenic activity has been also reported (Tolan *et al.* 2009), and active constituents have not yet been isolated.

In contrast to most other species in this section, considerable phytochemical work has been done on *H. scabrum*, in part due to its extensive distribution. The earliest report was of flavonol glycosides by Bandyukova and Khalmatov (1966). Additional flavonoids and flavonol glycosides were reported by Zaichikova and Barabanov (1980), as well as simple anthrones and naphthodianthrones (Makovetska 2000b). Polyprenylated benzophenone derivatives were isolated (albeit from a sample collected in Uzbekistan) and identified (Matsuhisa *et al.* 2002). From samples collected in Turkey, α-pinene has been identified as a major component of the essential oil (>70%, Çakir *et al.* 1997), Uzbekistan (>10%, (Başer *et al.* 2002) and Iran (>40%, Morteza-Semnani *et al.* 2006). Sixteen other members of this section are yet phytochemically unstudied, in part due to their highly endemic nature. Despite this, little work has yet been published on *ex situ* conservation strategies for these species, with the exception of one report on the establishment and maintenance of cell cultures for *H. capitatum* (Sokmen *et al.* 1999).

CONCLUDING REMARKS

The immense richness of diversity, both morphological and phytochemical, displayed by species of *Hypericum* distributed in the Mediterranean Basin (especially Turkey) and the adjacent regions of Macaronesia and the northeastern African highlands (especially Socotra) is both inspiring and somewhat daunting. A pressing need for further research on *ex situ* conservation methods exists for many of these species, particularly endemic and monotypic representatives of the taxonomic sections described above. Some solid work in this direction with endemic species in Turkey has been admirably pursued by the research group of Çirak and Radusiene, and researchers in other countries in this region of the world are urged to follow their lead. For many of these species, very little data is available concerning their specific habitat requirements, population dynamics and structure, and further collaborative work between phytochemists and botanists in this region would be particularly helpful.

ACKNOWLEDGEMENTS

Dr. Norman K. B. Robson is thanked for many helpful discussions about *Hypericum*. Funding for S. Crockett was provided by a Hertha Firnberg Stipend (T345) from the Austrian Science Foundation (FWF).

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