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Taxonomy and Chemotaxonomy of the Genus *Hypericum*

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Abstract

The genus *Hypericum* L. (St. John's Wort, Hypericaceae) includes, at the most recent count, 469 species that are either naturally occurring on, or which have been introduced to, every continent in the world, except Antarctica. These species occur as herbs, shrubs, and infrequently trees, and are found in a variety of habitats in temperate regions and in high mountains in the tropics, avoiding only zones of extreme aridity, temperature and/or salinity. 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 ranges. *Hypericum perforatum* L. (Common St. John's wort, section *Hypericum*), one of the best-known members of the genus, is an important medicinal herb of which extracts are taken for their reported activity against mild to moderate depression. Many other species have been incorporated in traditional medicine systems in countries around the world, or are sold as ornamentals. Several classes of interesting bioactive secondary metabolites, including naphthodianthrones (e.g. hypericin and pseudohypericin), flavonol glycosides (e.g. isoquercitrin and hyperoside), biflavonoids (e.g. amentoflavone), phloroglucinol derivatives (e.g. hyperforin and adhyperforin) and xanthones have been identified from members of the genus. A general overview of the taxonomy of the genus and the distribution of relevant secondary metabolites is presented.

Keywords

antidepressant; hyperforin; Hypericaceae; hypericin; secondary metabolite chemistry; systematics

INTRODUCTION

From the time of Linnaeus, the genus *Hypericum* has been treated as a natural unit by most taxonomists, although the discussion whether to treat this genus and its nearest relatives as a separate family (i.e. Hypericaceae) or as part of subfamily Hypericoideae within Guttiferae *sensu lato* has been contentious (Robson 1977, 1981; Stevens 2001, 2007). Recent molecular phylogenetic analyses of the tremendously diverse flowering plant order Malpighiales, which encompasses more than 16,000 species, support the hypotheses that a) Hypericaceae, including *Hypericum*, is a distinct family apart from other members of Guttiferae *s.l.*; b) the sister family to the Hypericaceae is Podostemaceae, whose representatives are almost exclusively thalloid aquatics; c) the clade of Hypericaceae-Podostemaceae is sister to a taxon (now referred to as Calophyllaceae) formerly subfamily Kielmeyeroideae of Guttiferae *s.l.*; d) and that a clade containing the remaining members of Guttiferae *s.l.*

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(Clusiaceae *sensu stricto*) and Bonnetiaceae forms the base of the broader clade (Korotkova *et al*. 2009; Wurdack and Davis 2009).

Nine genera have been taxonomically assigned to Hypericaceae: *Cratoxylum* Blume, *Eliea* Cambess., *Harungana* Lamarck, *Hypericum* L., *Lianthus* N.Robson, *Santomasia* N.Robson, *Thornea* Breedlove & McClintock, *Triadenum* Rafinesque, and *Vismia* Vand. Approximately 80% of the diversity of the family is within *Hypericum*. The majority of the species belonging to this genus and its nearest relatives (*Lianthus* and *Santomasia*) have capsular (rarely baccate or tricoccoid) fruits and yellow to orange petals (in very rare cases red or white). Species of *Hypericum* (in nearly all species), *Lianthus* and *Santomasia* differ from other genera of Hypericaceae by their conspicuous lack of interstaminal fasciclodes, which are present in other members of Hypericoideae (*Thornea* and *Triadenum*) as well as members of the subfamilies Cratoxyloideae (*Eliea, Cratoxylum*) and Vismioideae (*Vismia* and *Harungana*) (Robson 1977, 1981).

Detailed morphological descriptions of 457 species of *Hypericum* have been given in parts 3-8 of the monograph by Robson (1985 onwards), and an additional 12 species are described in part 9 (Robson in prep.). Species of the genus have been classified into 36 taxonomic sections (Table 1). A general overview of *Hypericum* botany has been included in a volume of Medicinal and Aromatic Plants – Industrial Profiles, with a particular focus on *H. perforatum* (Robson 2003).

Of the currently recognized species of *Hypericum, H. perforatum* L. (Common St. John's wort) is the best-known. This perennial herb is found in its native range distributed throughout Eurasia, but has been introduced to all other continents, except Antarctica (Robson 2002). Other species of *Hypericum* have been incorporated in traditional medicine systems in countries around the world, or are sold as ornamentals (Huxley *et al*. 1992; Moerman 1998). The flowering tops of *H. perforatum* are usually prepared as a decoction or infusion and taken internally for sedative or tonic purposes, or applied externally as a poultice or prepared as an oil-infusion to treat sciatica, neuralgia and speed wound-healing. Extracts of the inflorescences and upper stem leaves have been prescribed for many years in Europe, and are available as dietary supplements in the United States, to treat mild to moderate depression (Müller 2005). *Hypericum perforatum* was among the top ten best-selling herbal dietary supplements sold in the United States in 2008, with sales estimated at *ca*. 8.2 million USD (ABC 2008), and it represented nearly 13% of all European herbal product sales in 2004, valued at more than €70 million in Germany alone (Bäcker *et al*. 2006). The economic value of this plant to the herbal industry is one among several factors that have stimulated research into phytochemical diversity of *H. perforatum* in particular and of other members of the genus in general.

Several classes of bioactive secondary metabolites have been identified from extracts of *H. perforatum*, including naphthodianthrones (e.g. hypericin and pseudohypericin), flavonol glycosides (e.g. isoquercitrin and hyperoside), biflavonoids (e.g. amentoflavone), phloroglucinol derivatives (e.g. hyperforin and adhyperforin) and xanthones (see Fig. 1), and the distribution of these metabolites in related species of *Hypericum* is of considerable interest (Hölzl and Petersen 2003; Avato 2005). The primary focus of research has been on the anti-depressant properties of isolated substances from *H. perforatum*, although many compounds have been isolated from this and other species that additionally display interesting anti-inflammatory, anti-microbial and anti-proliferative activities (Avato 2005; Cuesta-Rubio and Picinnelli 2005; Dell'Aica *et al*. 2007). Numerous reviews of the botanical, phytochemical and pharmacological characteristics of *H. perforatum* have been published during the past 10 years (see particularly Nahrstedt and Butterweck 1997; Ernst and Izzo 2003; Müller 2005; Wurglics and Schubert-Zsilavecz 2006), and readers are

directed toward these specific references (and citations therein) for more detailed information.

The taxonomy of the genus *Hypericum*, as currently treated, is largely based on morphology. A working hypothesis proposing relationships among species of *Hypericum*, formed on the basis of information from numerous original studies in morphology, distribution, floral vasculature and (to a limited extent) cytology, as well as from relevant literature, was initially proposed by Robson (1977) in the first part of his monograph of the genus. Earlier studies of the genus and nearest relatives by Choisy (1821, 1824) and Spach (1836a/b) provided a taxonomic foundation for subsequent studies that focused specifically on *Hypericum* (e.g. Keller 1893, 1925). A phylogenetic network among *Hypericum* species was constructed and elaborated by Robson (1977 onwards) through the analysis of morphological similarities for a broad range of characters across the genus, followed by a closer examination of differences within perceived groups (Table 2). In this way, both stable and variable characters were analyzed, and trends for variable characters were identified. Two important assumptions were made in the construction of this hypothesis: a) character trends identified for currently existing taxa reflect evolutionary trends within the genus and b) a direction for each trend was stated (see overview in Table 2). The phylogenetic network thus formed is a result of the correlation of trends rather than of individual characters, and displays some similarity to a Wagner tree (see Wagner 1969), except that the numerical basis of character assessment is lacking. Due to the extremely time-consuming nature of numerical analysis with a large number of species in the time prior to availability of high-speed computation, this methodology provided an invaluable way to elucidate cladistic relationships among taxa of *Hypericum* (see discussion in Robson, 1981, pp 65-73).

The hypothesis has evolved as additional parts of the *Hypericum* monograph have been published (Robson 1981 to present). Members of three sections of *Hypericum* (sections **1**, **3** and **7**, see Table 1) possess character states which are treated as basal, while those sections radiating outward from these three basal sections display character states considered more advanced (sections **2**, **3** and **20**-**30** from section **1**; sections **4**-**6** and **10**-**19** from section **3**; and sections **8**-**9** from section **7**, respectively). Readers are referred to the individual monograph parts for detailed discussions of relationships among members within and between sections as well as character trend analysis for morphological features.

A numerical cladistic analysis of the species of *Hypericum* has recently been performed using 89 morphological characters (originally described in Robson 1981 onwards) that were identified and considered to be phylogenetically informative (Nürk and Blattner submitted) and readers are referred to the original paper for further detailed discussions of sectional relationships proposed on the basis of this analysis. Currently, additional research on taxonomy of the genus *Hypericum* is being performed by several groups in Europe and North America, applying molecular tools to further elucidate phylogenetic relationships within the genus. A final analysis of all available evidence awaits the completion of these studies.

MORPHOLOGICAL CHARACTERS AND VARIATION

Habit

Within the genus, trees, shrubs and perennial and annual herbs occur. True trees, in the sense of having a single stem, are rare within the genus, most woody members having multiple stems arising near the base. However, certain members of section **1** (e.g. *H. bequaertii*) in Africa attain more than 10 m of height and can possess a single woody trunk. Shrubs and dwarf shrubs may have erect or spreading stems, but do not root from nodes that come in contact with the ground. Perennial herbs, however, display a marked tendency to root from

horizontal nodes, particularly among species occurring in wet habitats (e.g. members of section **30** in bogs, marshes and moist páramo habitats), unlike annual herbs, which generally have tap roots and a highly developed system of secondary hair roots.

Indumentum

Many species of *Hypericum* are entirely glabrous, including those in sections **1-10** and **13-16**. An exception is *H. setiferum* in section **13**, which in contrast to other species belonging to this section has scattered appressed hairs on the underside of the leaf. Other species in sections **11-12**, **17-18** and **27** have simple uniseriate hairs that can be described with such terms as scabrid to hirsute, depending on their length. Some species of section **27** as well as *H. elodes* in section **28** have long fine hairs (Robson 1981). Stellate hairs have been observed in particular members of the subfamily Vismioideae, but within subfamily Hypericoideae only simple hairs are found.

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 (i.e. hypericin and/or pseudohypericin, Fig. 1) content (Mathis and Ourisson 1963; Ciccarelli *et al*. 2001a). These glands have been observed in members of *ca*. 2/3 of the taxonomic sections and are often limited to particular organs (Robson 2003). The size and number of these glands correlates positively with the content of naphthodianthrones (Zobayed *et al*. 2006). When tissues containing these glands are crushed between the fingers, the released naphthodianthrones give a red stain, which imbued the plant with magical protective powers, according to folkloric tradition. The name St. John’s wort has to do with the belief that *Hypericum* (ὑπέρεικον or *hyper eikon* – above the image) possessed the power to ward off evil spirits. In the early 16th century, Paracelsus described this red sap as “Johannes-blut,” suggesting that it symbolized the blood of the martyred St. John, thus contributing to the German and English common names used today (Robson 1977; Müller 2005).

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 (Fig. 1) (Ciccarelli *et al*. 2001a; Adam *et al*. 2002). These glands appear as light points or streaks when the leaves are held up to the sun. Numerous studies have examined the anatomy and chemical constituents of these individual gland types in particular species (Ciccarelli *et al*. 2001a, 2001b; Piovan *et al*. 2004; Soeberg *et al*. 2007). Also of interest is the overall distribution of the glands, particularly on leaves, sepals or petals, either intramarginal or laminar.

In the Hypericaceae, pale glands (varying in form, from streaks to dots) have been observed in all three subfamilies, while dark glands occur most prevalently in members of the Vismioideae and Hypericoideae, but are also present in *Cratoxylum* (Cratoxyloideae) (Robson 1974, 1981). The naphthodianthrone hypericin has only, thus far, been reported for flowering plants from species of *Hypericum*. Interestingly, Kusari *et al.* (2008) isolated an endophytic fungus from the stems of *H. perforatum*, cultures of which were shown to produce both hypericin and the supposed precursor, emodin, although this has not yet been proved to be the source of these compounds in the host tissues. Anthraquinones have frequently been isolated from *Cratoxylum* (Boonnak *et al.* 2006) and from members of Vismioideae (Bilia *et al*. 2000; Noungoue *et al*. 2008), while related simple quinones have been identified in other representatives of the Guttiferae *sensu lato* (i.e. Clusiaceae, Calophyllaceae) and Bonnetiaceae (Permana *et al*. 2003; Ee *et al*. 2004). Dark glands have

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been observed in *Marila* and *Mammea* (Calophyllaceae), and it has been speculated that these contain hypericin, but isolation studies have not yet confirmed this (Stevens 2007).

The distribution of such hypericin-containing glands is of particular interest due to the antifeedant activity of this molecule on generalist herbivores. Studies have shown that when generalist insects feed upon *H. perforatum* plants, a chemical defense mechanism is triggered that boosts the production of naphthodianthrones in the affected tissues by 30-100%, and generalist feeders are consequently repelled. In contrast, specialist insects such as the beetle *Chrysolina quadrigemina* that is used to control weedy populations of *H. perforatum* in the United States, can feed upon these tissues without difficulty, simply allowing the compound to pass through their digestive systems unchanged. In addition, the feeding activity of specialist insects upon the plant did not trigger a similar chemical defense cascade to that seen with generalist feeders (Duffey and Pasteels 1993; Sirvent *et al*. 2003). For this reason, such specialist insects are considered serious pests by those cultivating of *H. perforatum*. Such studies support the construction of the hypothesis that evolutionary selective pressures may have influenced the distribution and frequency of dark glands among species of *Hypericum*, and within a species, on particular organs. The trend toward an increase in dark secretory tissue in more advanced members of the genus was initially proposed by Robson (1977, 1981). According to the phylogenetic networks proposed by Robson (1981 onwards) and Nürk and Blattner (submitted), the ability to biosynthesize naphthodianthrones in these tissues seems to have arisen several times independently within *Hypericum*.

Stem

The presence of 4 thin ridges of tissue along the stems is closely associated with the opposite-decussate nature of the leaves in *Hypericum*. These lines of tissue may be minor, resulting in their being called “ridges” or more prominent, thus becoming “wings.” 2-lined, terete and occasionally 6-lined (in section **20**) conditions occur throughout the genus. Internodes along the branches of most species with a tree and shrub habit generally become terete with age, although some evidence of stem lines can often be detected even in mature plants. The number of lines along the stem is considered an important field character in the distinction between *H. perforatum* (2-lined, most frequently tetraploid) and *H. maculatum* (4-lined, diploid), with which it is most likely to be confused. However, experimental crosses have shown that this is an incompletely dominant character (Noack 1939), and hybrids between these species (which occur in nature in regions where the distributions overlap, e.g. *H.* x *desetangsii*) shown reduced or incomplete lateral ridges, leading to problems with identification. Both pale and dark glands have been observed on the stems of various species of *Hypericum*, but species with eglandular stems are present in various parts of the genus. In section **9**, such glands are confined to the stem lines, while in other sections such as **12** and **17** they may be dispersed over the surface (Robson 1981).

Leaves

Leaf arrangement in *Hypericum* is nearly always opposite and decussate, although whorls of 3-4 leaves occur exceptionally throughout the genus and in all species of section **19**. The leaves lack stipules and may be either sessile or shortly petiolate (longer petioles are seen in species of sections **9** and **27**). A basal articulation may be present (in which cases, the leaves are generally deciduous above or at the articulation) or absent (leaves generally persistent). Several species belonging to sections **1** and **29** have a reflexed leaf-base (auricle-like), while true auricles are observed only in sections **13** and **15/16**. The laminar venation can span the full range from truly dichotomous to pinnate to densely reticulate. Leaf shape can vary from ovoid to elongate to linear (“ericoid”). Leaves are generally shorter than the internodes, but a tendency towards elongation of the latter can be observed in taxa considered as advanced.

As previously noted, pale or dark glands are variously distributed within or at the leaf margin, or on the main laminar surface.

Sepals

Sepal number is 4-5, or rarely 3 in section **20**, and individual sepals that are quincuncial when 5 and opposite, and decussate when 4, are either nearly equal (as in section **17**) or unequal (as in sections **5, 7** and **14**) in size and shape. Species with flowers tending toward tetramery are present in sections **9e** (*H. monanthemum* subsp. *filicaule*) and **20** (e.g. *H. hypericoides, H. microsepalum*). Sepals may be united near the base (obvious in members of sections **17**, **18** and **22**), and free margins may display a variety of elaborations, having protruding marginal glands, (gland-dotted) teeth, or fine hairs. As previously mentioned, the distribution of dark (i.e. potentially hypericin-containing) glands has been considered taxonomically useful. Sepals of sections **2-5**, **7**, **20**, **24-25** and **29-30** lack dark glands, while in sections **9-19**, they are consistently present (see Fig. 2).

Petals

Hypericum petals are almost uniformly yellow, although there are gradations of this color from pale lemon to a deep buttery-orange. White to pinkish petals are seen in *H. albiflorum* var. *albiflorum* (section **12**) and sometimes in *H. geminiflorum* (section **4**), while some species have petals that may become suffused, streaked or otherwise tinged with red (particularly on the outer surface, visible when the flower is in bud). The petals of *H. capitatum* var. *capitatum* (section **17**) are deep crimson. As with the sepals, petal lengths may be unequal or equal. The petals are ± asymmetrical in all species except those belonging to sections **25** and **28**, and marginal elaborations (glands, fine teeth or cilia) occur. In members of sections **25** and **28**, sterile bodies have developed between the stamen fascicles (fasciclodes) that act as lodicules by helping to spread the petals of the pseudo-tubular flower. These species herefore display a specialized insect pollination syndrome.

Glands on petals are present in nearly all species, at least at the lamina. Laminar glands are absent in sections **25** and **30**, and only section **25** possesses entirely eglandular petals. Marginal glands are characteristic for sections **10-17** and occur in some species of sections **9**, **18** and **27**. In sections **17-19**, marginal glands frequently occur on cilia, and in sections **10-16**, they are generally sessile. It has been proposed that the hypericin content of the glands may be inferred from the intensity of their red color, but it is important to consider that other pigments (such as bisanthranone compounds known as skyrin derivatives) can denote a red color (see Wirz *et al.* 2000). For example, both *H. xylosteifolium* (section **6**) and sometimes *H. bupleuroides* (section **8**) have dark (red-colored) glands on the petal margin, although the presence of hypericin and pseudohypericin has not yet been confirmed in these species.

Stamen fascicles and stamens

The stamens, which can range in number from 5 to more than 200, are found in bundles termed fascicles. *Hypericum* flowers have 4-5 stamen fascicles, which may be free from one another (as in sections **1**, **3-7**) or fused in a variety of combinations (mostly in a way described as 2+2+1 resulting in 3 apparent fascicles). In sections **20**, **29** and **30** (in part), the stamens form a continuous ring. Stamens are typically persistent but sometimes deciduous, and possess an anther gland on the connective tissue that varies in color from amber to black. The latter type of gland color (i.e. potentially hypericin-containing) occurs most frequently in sections **12-15**, and occasionally in sections **23, 26** and **27**. Ten types of pollen have been recognized by Clarke (in Robson 1981). It is predominantly of type X (sections **9-11**, **13-19**), although type IV is also common (sections **2-3**, **5**, **8-9**, **12**, **22-23**). Type I

pollen is found only in section **1**; type VII in **20**; type V in **25**; type IX in **28** and type VIII in **29-30**.

Styles and placentae

The ovary in *Hypericum* is (2-)3-5-merous, with a corresponding number of styles (which may be variously free or sometimes united). Fusion of the styles is partial in sections **1**, **3** and **7** (all in part), complete in sections **1** (in part) and **4** and styles are free in sections **5** and **26**. The developing seeds are borne on axile (entirely in sections **17-19**) or parietal (in sections **28-30**) placentae (number of ovules per placenta is ∞-2, depending on the species) and some sections (i.e. **20** and **26**) show a transition between these two states.

Fruit

Hypericum fruits, unlike those of some other members of Hypericaceae, are capsular and dehisce from the apex. When mature, the capsule may be dry or remain (as in some species of sections **3**, **5** and **26**) fleshy, and have particular elongate or punctate glands on the outer surface in a wide variety of shapes and elaborations (termed vittae when narrow and linear and vesicles when short and globose). These are generally pale amber in color, although reddish-black vesicles have been observed for some species of section **13**, but the contents of these vesicles have only rarely been studied. Extractions of the outer surfaces of the fruits of particular species resulted in the isolation of phloroglucinol and other terpenoid derivatives, which may indicate a biosynthetic congruence between these glands and the pale glands of the vegetative tissue (Gronquist *et al.* 2001; Crockett *et al.* 2008).

Seeds

Seeds of *Hypericum* are small (0.3-1.5 mm long), yellowish-brown to dark purple-brown, cylindric to ellipsoid, and may be narrowly winged. In some cases, a basal thickening or ridge may be observed, or rarely an apical caruncle (in section **25**), which acts as an ant attractant to improve seed dispersal. Sculpturing of the seed testa varies from reticulate via foveolate to scalariform or papillose, and linear-reticulate testa sculpturing appears to be the plesiomorphic character state for *Hypericum*. However, evolution towards scalariform or papillose testa sculpturing appears to be homoplastic within the genus.

Some species of *Hypericum* seem to require highly specific conditions for germination and survival of the seedling past the 6-leaf stage. For example, *H. lloydii* (section **20**) is native to habitats of degraded granite and, as a seedling, is particularly susceptible to fungal infection when conditions are too moist, while other species germinate and, at least during early stages, grow under water (e.g. *H. lissophloeus* and *H. chapmanii*, section **20**) (Crockett, pers. obs.). For most species of *Hypericum*, germination requirements are poorly known, and this would be an interesting subject for future study.

Basic chromosome number

Summaries of chromosome numbers in *Hypericum* appear in Robson and Adams (1968) and Robson (1981). Basic numbers (*n*) in *Hypericum* are proposed to form a descending series from 12 – 7 and counts of $n = 6$ have been made for *H. setosum, H. cumulicola* (apparently dihaploids) and *H. gentianoides* (if the last is tetraploid), all in section **30**. 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 1981; da Cruz *et al.* 1990). The ploidy level is generally diploid, but tetraploids (on base numbers $n = 8, 9, 10$) have been reported from several sections and hexaploids have been reported from sections **3** (most frequently) and **9**.

PHYTOCHEMICAL CHARACTERS AND VARIATION

A diverse array of secondary metabolites is encountered in nature, each produced through a series of metabolic actions within the cell. In higher plants, specific products of primary metabolism are fed into the acetate, shikimate, mevalonate and deoxyxylulose phosphate pathways leading to the production of secondary compounds. Products of the acetate pathway, starting with the intermediate building block of acetyl-CoA, include fatty acids and aromatic polyketides (including simple phenols and anthraquinones). The shikimate pathway, fed by primary metabolites from glycolysis and the pentose phosphate pathway, leads to aromatic amino acids (often further involved in the biosynthesis of alkaloids), benzoic and cinnamic acids, lignans, phenylpropanes and coumarins. Combinations of the two aforementioned pathways result in the production of flavonoids, stilbenes, flavonolignans and isoflavonids. Both the mevalonate pathway, based upon the acetyl-CoA building block, and the deoxyxylulose phosphate pathway, fed by two intermediates from glycolysis, are responsible for the biosynthesis of terpenoids and steroids (Dewick 2002).

Considerations of bioactivity

Secondary metabolites with demonstrated bioactivity can serve as *biomarkers* (i.e. compounds of pharmaceutical interest, considered specific to a particular taxon), and this type of marker identification and tracking is of particular use at the level of species, population and individual (Crockett and Khan 2003). Much research been conducted on the presence and amount of biomarkers in *H. perforatum*, and a complex of naphthodianthrones (hypericin and pseudohypericin), acylphloroglucinol derivatives (hyperforin), biflavones (I3, II8-biapigenin, amentoflavone) and flavonoid glycosides (rutin, hyperoside, isoquercitrin, quercitrin, quercetin) is generally considered characteristic for this species (Nahrstedt and Butterweck 1997; Hölzl and Petersen 2003 and citations therein). Additional studies have examined the effects of morphological (i.e. organ dependant) and diurnal variability on the qualitative and quantitative aspects of biomarker production (Ayan *et al*. 2006; Kaçar *et al*. 2008). These compounds, as a combined set, have been used to ascertain plant identity, and the presence of rutin has been cited as particularly important for chemical authentication of plant samples as true *H. perforatum*. Certain populations of plants in Italy and Austria have been recognized, however, which are morphologically identified as *H. perforatum*, but lack rutin (Umek *et al*. 1999; Mártonfi *et al*. 2001). Additional studies have shown that although many other species of *Hypericum* contain naphthodianthrones, acylphloroglucinol derivatives and flavonoids, few contain the specific complex of 9-10 biomarker compounds that have been considered typical for *H. perforatum* (Crockett *et al*. 2005; Smecerovic *et al*. 2008; Verma *et al*. 2008).

Due to the extremely large number of compounds from different chemical classes that have been reported from species of *Hypericum*, this article makes no attempt to review the phytochemical literature exhaustively. Readers are referred to reviews by Avato (2005), Nahrstedt and Butterweck (1997), Hölzl and Petersen (2003) and Kitanov and Blinova (1987). Instead, Table 3 provides a general overview of the distribution of particular biomarker compounds (i.e. those with perceived relevance to the pharmaceutical industry) by section within the genus, with reference to selected examples of extant phytochemical literature. During the literature review, isolated reports of naphthodianthrones in species of sections **2** and **21** were found (Salgues 1961; Kartnig *et al*. 1996), however these reports must be treated with care due to the lack of morphological support (i.e. lack of dark glands in these sections) and absence of confirmation from a second source. Interestingly, three taxonomic sections other than section *Hypericum* (**9**) that produce 9-10 of the compounds used as biomarkers for *H. perforatum* have been identified: sections **13** (10), **18** (9) and **27** (10). Due to the morphological distinctness and limited geographic distribution (in their

native ranges) of most species belonging to these sections as opposed to *H. perforatum*, however, the likelihood of adulteration or misidentification is predicted to be quite low.

Considerations of chemotaxonomy

The presence or absence of compounds belonging to a specific class of secondary metabolites, either on the level of plant family, genus, species, within a species (i.e. population analysis), or even within a single plant (i.e. metabolic characterization) is of particular interest in the field of pharmacognosy. These compounds may serve as *chemotaxonomic markers* at higher taxonomic levels (i.e. family to species), indicating that particular biosynthetic pathways have been conserved within a taxon, or alternatively, have arisen two or more times within a taxon through evolutionary convergence.

The clade supported by molecular data (Wurdack and Davis 2009) as containing Guttiferae *s.l.* (Hypericaceae, Clusiaceae *s.s.* and Calophyllaceae), Bonnetiaceae and Podostemaceae is phytochemically unique within the Malpighiales due to the shared possession of xanthones, compounds related to flavonoids with elements derived from both acetate and shikimate pathways, by its members (Kubitzki *et al.* 1978; Bennett and Lee 1989; Burkhardt *et al.* 1992) (see Fig. 1). Excellent reviews of the occurrence of xanthones among members of the Guttiferae *s.l.* (including Hypericaceae) and within *Hypericum* may be found in Bennett and Lee (1989) and Demirkiran (2007), respectively. Biflavones and quinones have also been reported from all families of this clade, but are not restricted to this clade within Malpighiales (Korotkova and Crockett, unpublished data). Dimeric xanthones have been isolated from both Bonnetiaceae and Clusiaceae *sensu stricto* (Bennett *et al.* 1990; Sordat-Diserens *et al.* 1992) as well as from the nearest sister taxon, Calophyllaceae (Cortez *et al.* 1998). Further phytochemical studies of species from Bonnetiaceae are needed to provide additional chemotaxonomic support for the link with Clusiaceae *s.s.* The latter taxon shares the possession of xantholignoids, acylphloroglucinol derivatives, benzophenones and biphenyls with both Calophyllaceae and the more derived Hypericaceae (Pinto and Sousa 2003; Baggett *et al.* 2005). Biphenyls have also been isolated from Podostemaceae, but as with Bonnetiaceae, too few phytochemical studies have been published to speculate further on shared chemical characters between this family and Hypericaceae (Cardona *et al.* 1990; Burkhardt *et al.* 1992; Cortez *et al.* 1998; Seo *et al.* 1999). An overview of the distribution of these compound classes in this clade is shown in Fig. 3.

Of the 9 genera of Hypericaceae, four (*Eliea, Harungana, Lianthus* and *Santomasia*) are monotypic, *Thornea* has only 2 species and *Triadenum*, fewer than 10. It is perhaps not surprising, therefore, that the phytochemistry of these plants is poorly known. *Harungana madagascariensis* is an exception due to its use as a traditional medicinal plant against bacterial, viral and fungal infections, and has been the subject of several chemical investigations that have revealed the presence of triterpenes, prenylated anthrones, anthraquinones, flavonoids, xanthones and benzophenones (Iinuma *et al.* 1995, 1996; Kouam *et al.* 2005). Compounds belonging to these classes of secondary metabolites have also been isolated from species of *Cratoxylum* and *Vismia*, emphasizing the evolutionary ties and shared biosynthetic capabilities of these taxa (Bennett *et al.* 1993; Seo *et al.* 2002; Cuesta-Rubio *et al.* 2005; Pattanaprateeb *et al.* 2005; Boonnak *et al.* 2009; Noungoue *et al.* 2009). Xanthones have more frequently isolated from *Cratoxylum*, and anthraquinones and benzophenones, from *Vismia*. Both of these genera, however, display an interesting tendency to biosynthesize dimeric and/or conjugated secondary metabolites such as anthraquinobenzophenones (Seo *et al.* 2002), bisxanthones (Laphookhieo *et al.* 2006), and xanthonolignoids (Delle Monarche *et al.* 1993; Iinuma *et al.* 1996), which have not yet been isolated from *Harungana*.

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Of all genera in Hypericaceae, *Hypericum* has been the subject of the highest number of studies but, although phytochemical investigations have been conducted on at least one or more representatives belonging to 34 of the 36 taxonomic sections, the secondary chemistry of an estimated 60% of the species is still largely unknown. Representatives of all secondary metabolite classes that have been identified from members of Cratoxyloideae and Vismioideae also occur in *Hypericum*, making subfamilial chemotaxonomic distinctions challenging. It is, however, relevant to note that the highly prenylated anthrones, anthraquinones and xanthones frequently found in *Vismia* and *Cratoxylum* (Bilia *et al.* 2000; Boonnak *et al.* 2006) are uncommon in *Hypericum*, although certain specialized bianthrones such as hypericin have been isolated exclusively from the latter. Simple benzophenone derivatives, in some cases glycosylated or oxidized, have been isolated from some species of *Cratoxylum* (Seo *et al.* 2002; Yu *et al.* 2009), but compounds with elaborate prenylation patterns upon phloroglucinol base structures (acylphloroglucinols or prenylated benzophenones) have been more frequently isolated from *Hypericum* (Winkelmann *et al.* 2001; Baggett *et al.* 2005; Hashida *et al.* 2008) as compared to other members of Hypericaceae.

Although numerous benzophenones and acylphloroglucinols that vary considerably according to their acylation, prenylation, methylation, oxidation and cyclization patterns have been isolated from genera within Guttiferae *s.l.*, representatives of less than a third of the taxonomic sections of *Hypericum* have been surveyed for these compounds. Thus, the examination of structural diversity for these compounds across the genus has not been thoroughly investigated enough to draw any firm conclusions regarding their utility as chemotaxonomic markers. However, it is encouraging to note that such compounds as uliginosin B and japonicin A have been each independently isolated from two species of section **30** (uliginosin B: Ferraz 2002; Taylor and Brooker 1969; japonicin A: Gu *et al.* 1984; Rocha *et al.* 1995), and that chinensin II has been isolated from two species of section **3** (Decosterd *et al.* 1991; Nagai and Tada 1987), indicating that these compounds may have some chemotaxonomic utility at the sectional or subsectional level.

Researchers have suggested that the oxygenation and prenylation patterns of xanthones have potential chemotaxonomic value due to their variability (Bennett and Lee 1989; Demirkiran 2007). More than 100 xanthones have been isolated and identified from *Hypericum*, many of which differ according to patterns of hydroxyl, methoxy, prenyl, butenyl and glycoside substitutions on the base structure. Two of the most common xanthones isolated from *Hypericum* (mangiferin and isomangiferin), however, belong to the group of 1,3,6,7-tetrahydroxyxanthones. A study by Kitanov and Blinova (1987) found xanthones with this specific pattern of oxygenation in *Hypericum* species representing 17 taxonomic sections of the genus, and they have been isolated from the most basal member of the family, *Cratoxylum* (Kitanov *et al.* 1988), indicating that they represent a conserved chemical character. The distribution of xanthones with a 1,3,5,6-tetrahydroxylation pattern seems to be more limited within *Hypericum* (sections **1**, **3**, **5** and **30**), although they have been reported additionally from two species of *Cratoxylum* (Sia *et al.* 1995; Boonnak *et al.* 2006). Xanthonolignoids have been to date reported from only a few species of *Hypericum* belonging to sections **3**, **21** and **27**. Although many papers detailing the isolation of xanthones from *Hypericum* in recent years have appeared, many species remain to be investigated. The chemotaxonomic utility of these compounds, therefore, can not be properly assessed until their distributions and chemical characteristics among more members of the genus have been evaluated.

CONCLUDING REMARKS

Despite preliminary findings that indicate that certain classes of secondary metabolites might have chemotaxonomic utility at lower taxonomic levels, a cautionary note must be added. Most phytochemical investigations of these species were conducted using material collected from their native habitats, although a small subset of species were either collected from cultivation in a botanical garden or micropropagated. Results of such studies are, for various reasons, notoriously difficult to repeat and verify. Advantages to using cultivated material include the facts that native populations are not damaged by collection of the large amounts of material generally needed for phytochemical investigation; environmental conditions can be recorded and, in some cases, controlled; studies can be planned so that an adequate amount of material exists for the isolation of minor components; and seasonal and/or temporal changes in chemical composition can be more easily tracked. Many herbacous *Hypericum* species can be grown from seed (see Faron *et al.* 2004), while woody species are readily grown from cuttings (Crockett unpublished data), and researchers who plan to perform intensive phyotchemical investigations of particular *Hypericum* species – particularly endemic taxa – may obtain better results using cultivated material, rather than relying upon material collected from wild populations.

For those researchers who wish to continue working with material collected from the wild, a careful consideration of the multitude of available analytical tools, many of which allow the detection and identification of secondary metabolites starting with extremely small amounts of plant material, is valuable. Metabolic characterization studies of various parts of a single plant and for single cells within a particular tissue type have recently been conducted, primarily with *H. perforatum*. In these studies, the significant effects of ontogenetic, diurnal and seasonal variation on the production of secondary metabolites, particularly the naphthodianthrones, has been described (Southwell and Burke 2001; Seidler-Łożykovska 2003; Ayan *et al*. 2006; Coucerio *et al*. 2006). Hyperforin and hypericin accumulation has been measured through microcapillary sampling of single glands in *H. perforatum* (Soelberg *et al*. 2007). A recent study combining the tools of laser microdissection with laser desorption/ionization mass spectrometry allowed the single-cell localization and identification of naphthodianthrones and biflavones in this species (Hölscher *et al*. 2009). The increased sensitivity of detection of secondary metabolites provided by the use of these techniques, as well as the broader availability of such instruments, will allow much more detailed and efficient studies of the phytochemistry of *Hypericum* species in the future.

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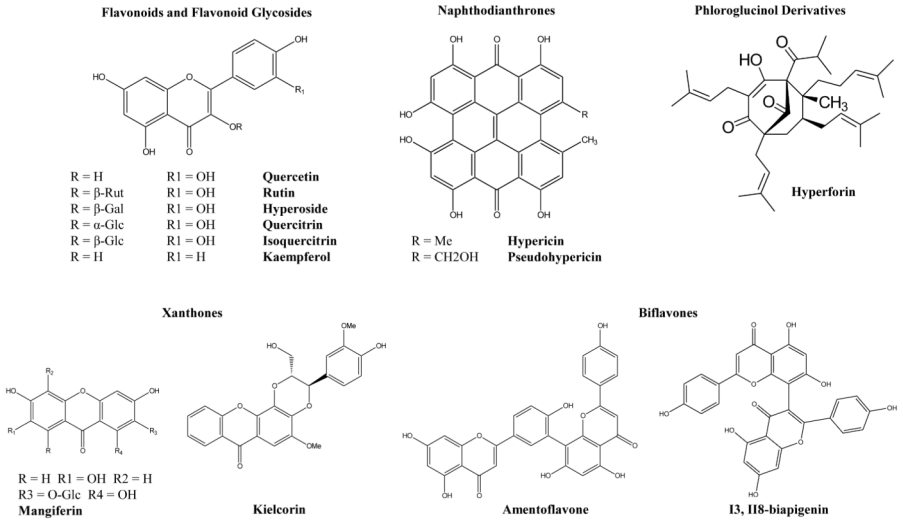

Fig. 1. Some bioactive secondary metabolites in *Hypericum*

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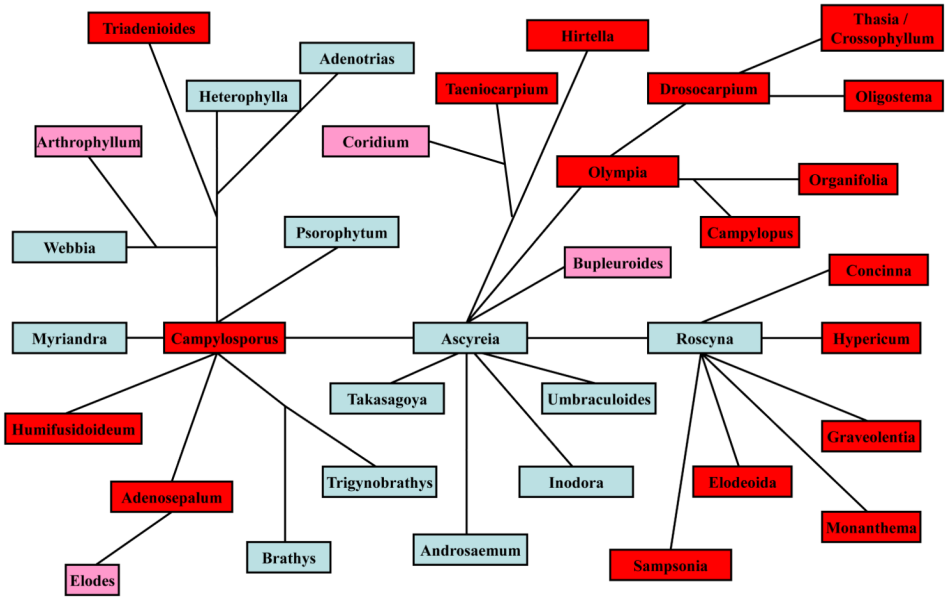

Fig. 2. Relationships among sections of *Hypericum* adapted from Robson (2003)

Sections denoted in blue lack naphthodianthrones; sections in pink produce naphthodianthrones in fewer than 2 organs; sections in red produce naphthodianthrones in 2 or more organs.

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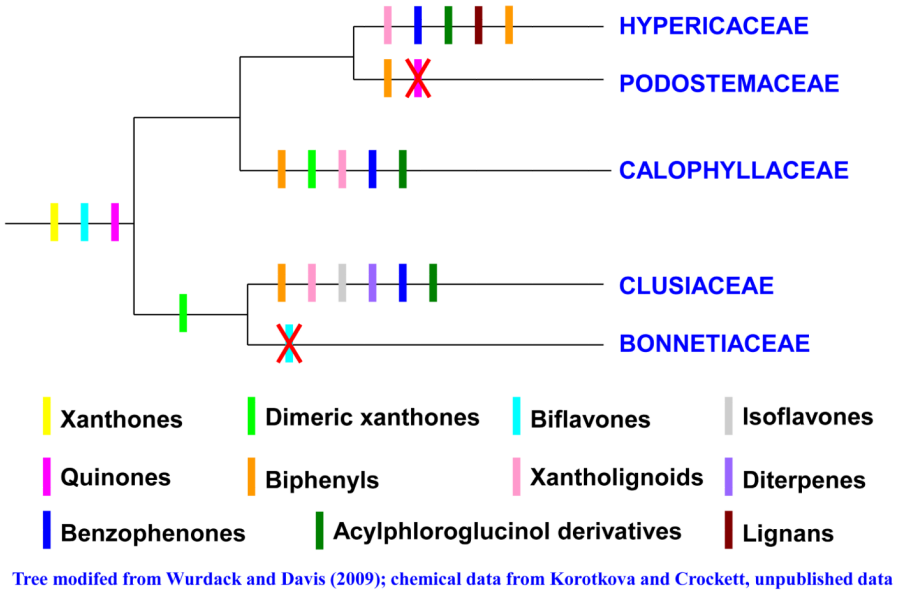

Fig. 3. Distribution of relevant compound classes in Guttiferae *s.l.*, Podostemaceae and Bonnetiaceae

A colored bar at the base of a clade indicates the presence of this class of compounds in all families in the clade; a colored bar along the tree branch indicates the presence of this class of compounds in that specific family; a red “X” indicates the absence of the indicated class of compounds in the specified family. Tree modifed from Wurdack and Davis (2009); chemical data from Korotkova and Crockett, unpublished data.

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Table 1

(modified from Nürk and Blattner (submitted) with permission). Classification of the genus *Hypericum* L.[A] detailing sections, subsection and series (*sensu* Robson 1981 onwards), number of species per section, general distribution and specific citation for the systematic treatment. E = east, S = south, W = west, N = north.

Classification Section / Subsect. / Series				Number of species	Distribution	Systematic treatment
1.	***Campylosporus*** (Spach) R. Keller			**10**	Tropical & SE Africa + adjacent islands, SW Iran	Robson, 1985: 178
2.	***Psorophytum*** (Spach) Nyman			**1**	Spain (Balearic Islands)	Robson, 1985: 202
3.	***Ascyreia*** Choisy			**43**	SE Europe, W to SE Asia, S China	Robson, 1985: 206; 2001: 49
4.	***Takasagoya*** (Y. Kimura) N. Robson			**5**	Japan (Ryuku Island), Taiwan, Philippines	Robson, 1985: 288
5.	***Androsaemum*** (Duhamel) Gordon			**4**	Macaronesia, W & S Europe to Iran, Saudi Arabia & Yemen	Robson, 1985: 297
6.	***Inodora*** Stef.			**1**	NE Turkey, Georgia	Robson, 1985: 314
6a.	***Umbraculoides*** N. Robson			**1**	Mexico (Oaxaca)	Robson, 1985: 317
7.	***Roscyna*** (Spach) R. Keller			**2**	Central to E Asia, NE America	Robson, 2001: 52
8.	***Bupleuroides*** Stef.			**1**	NE Turkey, Georgia	Robson, 2001: 49
9.	***Hypericum*** L.			**42**	Europe, NW Africa, Asia, NW America; introduced (H. perforatum) into many other parts of the world	Robson, 2002: 66
	1.	***Hypericum***		19		Robson, 2002: 66
		1.	***Hypericum***	*12*		Robson, 2002: 66
		2.	***Senanensia*** N. Robson	*7*		Robson, 2006: 28
	2.	***Erecta*** N. Robson		23		Robson, 2006: 42
9a.	***Concinna*** N. Robson			**1**	USA (N California)	Robson, 2001: 61
9b.	***Graveolentia*** N. Robson			**9**	SE Canada, eastern USA to Guatemala	Robson, 2006: 79
9c.	***Sampsonia*** N. Robson			**2**	NE India to S Japan	Robson, 2001: 63
9d.	***Elodeoida*** N. Robson			**5**	E & SE Asia (China to Kashmir)	Robson, 2001: 66
9e.	***Monanthema*** N. Robson			**7**	E & SE Asia (China to Sri Lanka)	Robson, 2001: 75
10.	***Olympia*** (Spach) Nyman			**4**	S Balkan peninsula, W Turkey, Aegean Islands	Robson, 2010a in press.
11.	***Campylopus*** Boiss.			**1**	S Bulgaria, NE Greece, NW Turkey	Robson, 2010a in press.
12.	***Origanifolia*** Stef.			**13**	Turkey, Georgia, Syria	Robson, 2010a in press.
13.	***Drosocarpium*** Spach			**11**	Madeira, Mediterranean to W Caucasus	Robson, 2010a in press.
14.	***Oligostema*** (Boiss.) Stef.			**6**	Europe, Macaronesia, Mediterranean	Robson, 2010a in press.

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Classification Section / Subsect. / Series			Number of species	Distribution	Systematic treatment
15.	***Thasia*** Boiss.[B]		**1**	Greece, Bulgaria, Turkey	Robson, 2010a in press.
16.	***Crossophyllum*** Spach[B]		**3**	N Aegean region, Turkey, Caucasus	Robson, 2010a in press.
17.	***Hirtella*** Stef.		**30**	W Mediterranean & S Europe to Altai	Robson, 2010b in press.
	1.	***Stenadenum*** N. Robson	12		
	2.	***Platyadenum*** N. Robson	18		
		1. ***Lydia*** Sennikov	*5*		
		2. ***Scabra*** N. Robson	*3*		
		3. ***Abbreviata*** Semikov	*10*		
18.	***Taeniocarpium*** Jaub. & Spach		**28**	Europe, Mediterranean to Iran & Mongolia	Robson, 2010b in press.
19.	***Coridium*** Spach		**6**	Mediterranean, Alps, Caucasus	Robson, 2010b in press.
20.	***Myriandra*** (Spach) R. Keller		**29**	E & central North America to Honduras, Bermuda & Caribbean Islands; introduced (?) into the Azores	Robson, 1996: 92
	1.	***Centrosperma*** R. Keller	14		Robson, 1996: 94
	2.	***Pseudobrathydium*** R. Keller	1		Robson, 1996: 112
	3.	***Suturosperma*** R. Keller	7		Robson, 1996: 113
	4.	***Brathydium*** (Spach) R. Keller	2		Robson, 1996: 122
	5.	***Ascyrum*** (L.) N. Robson	5		Robson, 1996: 124
21.	***Webbia*** (Spach) R. Keller		**1**	Canary Islands, Madeira	Robson, 1996: 133
22.	***Arthrophyllum*** Jaub. & Spach		**5**	S Turkey, Syria, Lebanon	Robson, 1996: 137
23.	***Triadenioides*** Jaub. & Spach		**5**	S Turkey, Syria, Lebanon, Socotra	Robson, 1996: 141
24.	***Heterophylla*** N. Robson		**1**	Turkey (NW & W-central Anatolia)	Robson, 1996: 146
25.	***Adenotrias*** (Jaub. & Spach) R. Keller		**3**	S Morocco to Mediterranean	Robson, 1996: 147
26.	***Humifusoideum*** R. Keller		**12**	Tropical & S Africa, Madagascar, SE to E Asia	Robson, 1996: 153
27.	***Adenosepalum*** Spach		**25**	Canary Islands, Madeira, Europe, Africa, SW Asia	Robson, 1996: 170
	1.	***Aethiopica*** N. Robson	7		Robson, 1996: 172
	2.	***Pubescentes*** N. Robson	6		Robson, 1996: 181
	3.	***Caprifolia*** N. Robson	3		Robson, 1996: 189
	4.	***Adenosepalum***	9		Robson, 1996: 193
28.	***Elodes*** (Adans.) W. Koch		**1**	Azores & W Europe	Robson, 1996: 208

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Classification Section / Subsect. / Series			Number of species	Distribution	Systematic treatment
29.	***Brathys*** (Mutis ex L. F.) Choisy		**87**	Central & South America, Caribbean Islands, SE Canada & eastern USA (S to Florida)	Robson, 1987: 12; 1990: 12
	1.	***Styphelioides*** N. Robson	2		Robson, 1990: 16
	2.	***Phellotes*** N. Robson	32		Robson, 1990: 16
	3.	***Brathys***	39		Robson, 1990: 27
	4.	***Spachium*** R. Keller	14		Robson, 1990: 29
30.	***Trigynobrathys*** (Y. Kimura) N. Robson		**52**	South America to S Canada, E to SE Asia, the Hawaiian Islands, Australia, New Zealand, Africa; introduced into Europe	Robson, 1990: 47
	1.	***Connatum*** (R. Keller) N. Robson	27		Robson, 1990: 51
	2.	***Knifa*** (Adans.) N. Robson	25		Robson, 1990: 95

[A] Up to now, 457 species in 36 sections have been described in the monograph (Robson 1981 onwards). However, 9 species have been described additionally by several authors: *H. dogonbadanicum* Assadi (section *Campylosporus*, Iran), *Iran. Joum. Bot.* **2**, 89 (1984); *H. fosteri* N. Robson (section *Ascyreia*, China), *Acta Phytotax. Sin.* **43**, 271 (2005); *H. wardianum* N. Robson (section *Ascyreia*, China), *Acta Phytotax. Sin.* **43**, 273 (2005); *H. enshiense* L.H. Wu & F.S. Wang (section *Hypericum*, China), *Acta Phytotax. Sin.* **42**, 76 (2004); *H. chejuense* S.-J. Park & K.-J. Kim (section *Hypericum* subsection *Erecta*, Korea), *Novon* **15**, 258 (2005); *H. jeongjocksanense* S.-J. Park & K.-J. Kim (section *Hypericum* subsection *Erecta*, Korea), *Novon* **15**, 260 (2005); *H. hubeiense* L.H. Wu & D.P. Yang (section *Elodeoida*, China), *Acta Phytotax. Sin.* **42**, 74 (2004); *H. austroyunnanicum* L.H. Wu & D.P. Yang (section *Elodeoida*, China), *Acta Phytotax. Sin.* **40**, 77 (2002); *H. haplophylloides* Halácsy & Bald. (section "24a." *Haplophylloides* N. Robson [in prep.: *Hypericum* monograph part 9], Albania), *Verh. Zool.-Bot. Ges. Wien* **42**, 576 (1893). The following species were omitted from the monograph in error: *Hypericum huber-morathii* N. Robson (section *Adenosepalum*, Turkey), *Notes Roy. Bot. Gard. Edinburgh* **27**, 197 (1967); *H. minutum* Davis & Poulter (section *Adenosepalum*, Turkey), *Notes Roy. Bot. Gard. Edinburgh* **21**, 182 (1954); *H formosissimum* Takht. (section *Adenosepalum*, Turkey, Armenia, Iran), *Not. Syst. Bot. Tiflis = Zametki po Sistematike i Geografii Rastenii* **9** (1940).

[B] Sections 15 (*Thasia*) and 16 (*Crossophyllum*) have been recently merged (Robson 2010a, in press).

Table 2

Character trends used for classification (according to Robson 1977)

Character	Trend	
Habit	trees → shrubs → perennial herbs → annual herbs	
Indumentum	absent → present	
Glands	pale → dark	
	pale channels → pale dots	
	dark dots → dark lines or streaks	
	fewer dark glands → more dark glands (concentration and number)	
Stem	4-lined → 2-lined → terete	
Leaves	sessile	→ shortly petiolate
		→ amplexicaul → perfoliate
	deciduous → persistent	
	opposite → 3-whorled → 4-whorled	
	parallel venation → reticulate venation	
Perianth	5-merous → 4-merous → 3-merous	
Sepals	persistent → deciduous	
	unequal → nearly equal	
	free → united	
	margin entire → dentate → ciliate → fimbriate	
Petals	persistent → deciduous → persistent	
	asymmetric → symmetric	
Stamen fascicles	persistent → deciduous → persistent	
	5 → 4	
	free → variously united	
Styles and placentae	5 → 4 → 3 → 2	
Placentation	loosely axile	→ definitely axile
		→ parietal
Ovules per placenta	∞ → 2	
Seeds	narrowly winged → carinate → cylindrical	
Basic chromosome numbers	12	→ 7 (6, dihaploids of 12?)
		→ 14

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Table 3

Distribution of Biomarker Compounds *Hypericum*

	Section	quercetin	rutin	hyperoside	quercitrin	isoquercitrin	amentoflavone	I3, II8-biapigenin	hypericin	pseudohypericin	hyperforin	Selected References
1	*Campylosporus*	X		X					X	X		Cardona and Seone 1983; Kitanov 2001
2	*Psorophytum*	X	X	X	X	X						Alberto et al. 1981; Mathis and Ourisson 1963
3	*Ascyreia*	X	X	X	X	X						Doğanca and Öksüz 1993; Seabra and Alves 1990
4	*Takasagoya*	X			X							Chen et al. 1989
5	*Androsaemum*	X		X	X	X		X			X	Crockett 2005, Bonkanka 2008
6	*Inodora*	X	X	X	X	X						Makovetska 1999a; Zapesochnaya et al. 1967
7	*Roscyna*	X	X	X	X	X						Komissarenko et al. 1992; Park et al. 2000
8	*Bupleuroides*	X	X	X	X	X					X	Makovetska 1999a, Kitanov 2001; Ayan et al. 2009
9	*Hypericum*	X	X	X	X	X	X	X	X	X	X	Makovetska 1999b, Kitanov 2001; Butterweck 2007
9a	*Concinna*								X			Mathis and Ourisson 1963
9b	*Graveolentia*	X	X	X	X	X		X	X		X	Makovetska 2000a; Mathis and Ourisson 1963; Crockett 2005
9c	*Sampsonia*								X			Mathis and Ourisson 1963
9d	*Elodeoida*								X			Mathis and Ourisson 1963
10	*Olympia*	X	X	X			X		X	X		Akhtardzhiev et al. 1973; Kitanov 1987; Mathis and Ourisson 1963
11	*Campylopus*		X							X		Makovetska 1999a; Crockett 2005
12	*Organifolia*								X	X	X	Mathis and Ourisson 1963; Çirak et al. 2008
13	*Drosocarpium*	X	X	X	X	X	X	X	X	X	X	Crockett 2005; Çirak and Radušienė 2007
14	*Oligostema*	X	X	X	X	X		X	X	X		Kitanov et al. 1979; Kitanov 1988a; Seabra and Alves 1990; Mathis and Ourisson 1963
15	*Thasia*									X	X	Mathis and Ourisson 1963
16	*Crossophyllum*	X	X	X	X	X	X		X	X		Doğanca and Öksüz 1989; Crockett 2005, Çirak et al. 2009
17	*Hirtella*	X	X	X	X				X	X		Mathis and Ourisson 1963; Zaichikova and Barbanov 1980; Makovetska 2000b; Ayan et al. 2009
18	*Taeniocarpium*	X	X	X	X	X	X	X	X	X		Kitanov 1988b; Mathis and Ourisson 1963; Shatunova 1978
19	*Coridium*	X		X	X	X			X	X		Mathis and Ourisson 1963; Crockett 2005; Alali et al. 2009
20	*Myriandra*	X	X	X	X	X	X				X	Alyukina 1970; Crockett 2005
21	*Webbia*	X		X	X			X				Cardona et al. 1989; Makovetska 2001a; Mathis and Ourisson 1963
22	*Arthrophyllum*	X		X	X							Makovetska 2001a; Crockett 2005
23	*Triadenioides*	X	X	X					X	X		Makovetska 2001a; Mathis and Ourisson 1963
24	*Heterophylla*	X	X	X	X	X						Makovetska 2001a

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	Section	quercetin	rutin	hyperoside	quercitrin	isoquercitrin	amentoflavone	I3, II8-biapigenin	hypericin	pseudohypericin	hyperforin	Selected References
25	***Adenotrias***		X									Makovetska 2001a; Crockett 2005
26	***Humifusoideum***	X	X	X	X				X	X		Makovetska 2001a; Mathis and Ourisson 1963
27	***Adenosepalum***	X	X	X	X	X	X	X	X	X	X	Umek et al. 1999; Crockett 2005, Alali et al. 2009
28	***Elodes***	X	X	X	X	X			X	X		Seabra and Alves 1990; Mathis and Ourisson 1963
29	***Brathys***	X	X	X	X	X						Makovetska 2001b
30	***Trigynobrathys***	X	X	X	X	X						Makovetska 2001b; Rocha et al. 1995