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Review

The current status of chemical systematics

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Abstract

Chemical systematics sets out to interpret the phylogenetic implications of the occurrence and distribution of secondary metabolites. In this review, a number of the major contributions from the 1960's and 1970's are identified and re-assessed in the light of recent evidence gained from DNA studies. It is shown that for the most part conclusions drawn on the basis of secondary metabolite distribution have been confirmed by the new techniques and it is concluded that chemical systematics can continue to provide useful insights into plant phylogeny.

Keywords: Chemical systematics; Plant phylogeny; Rutales; *Juniperus*; Belalains; Iridoids; Alkaloids

Contents

1. Introduction

Man, and for that matter a wide part of the animal kingdom, has been carrying out implicit chemical systematics for millennia and the study of this has evolved into its own discipline of chemical ecology. However, this paper restricts itself to the scientific discipline of accumulating information on the distribution of secondary metabolites with a view of using this information to throw light onto systematic or phylogenetic relationships among extant taxa, usually of higher plants.

This subject of chemical systematics has its roots in the early part of the 20th century and exploded into prominence in the 1960's as is illustrated by the publication of *Biochemical Systematics* (Alston and Turner, 1963), the reports of major conferences on the then new topic by Swain (1963, 1966) and the appearance of the initial volumes of

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Hegnauer's *Chemotaxonomie der Pflanzen* (Hegnauer, 1962–1990; Hegnauer and Hegnauer, 1992–2001).

As someone who arrived on the scene at the end of the 1960's I remember the high hopes that were then held for this new discipline. The ability to define unambiguous structures arising from clearly defined biosynthetic pathways would, it was felt, revolutionise our understandings of the phylogenetic relationships among plants. As is always the case, initial expectations are not met in the long term and some of the reasons for this are outlined in the next section. However, failure to live up to the early hype should not be allowed to diminish the considerable success of chemical systematicists following on the early example set by those founding-fathers of the Phytochemical Society, E.C. Bate-Smith, Tony Swain and Jeffrey Harborne.

In the 1990's, small molecule chemical systematics was largely eclipsed by the advent of comparative studies of DNA and RNA and it was amusing to hear the same hype repeated! Now that there is a significant literature arising from DNA studies resulting in some profound re-alignments in our ideas about phylogenetic relationships (Angiosperm Phylogeny Group, 2003) it seems very appropriate to re-examine some of the more successful and extensive chemical systematic studies of small molecules and see how those findings relate to and may have helped shape current thinking (see Section 3).

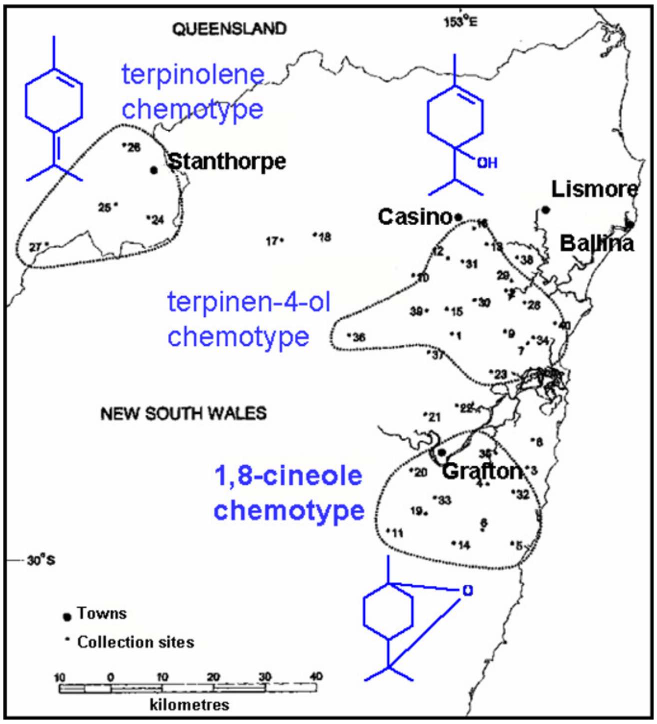


Fig. 1. Major chemotypes of the leaf oil of tea-tree oil (*Melaleuca alternifolia* Cheel.) based on the analysis of 615 individuals (taken from Homer et al. (2000)).

2. Issues that cloud chemical systematics

(a) The presence of similar or identical secondary metabolites with an apparently shared biosynthetic origin in clearly disparate higher plant taxa has always being identified as a major problem for the application of these compounds to resolving phylogeny. While this phenomenon, known as convergence, clearly exists it is usually easily recognisable and can be dealt with in the same common sense manner as convergence in leaf shape, plant habit, and many other features have been dealt with in phylogenetic arguments predating the advent of chemical structures.

Recently, there has been a growing realisation (Wink, 2003) that much of what was thought of as convergence is actually the re-expression of information held in the genome but silent for the evolutionary periods between its repeated exploitation. This phenomenon was observed over 20 years ago by Wink and Witte (1983) in an often overlooked but very important paper. An acceptance that 'apparent convergence' can often be explained in terms of intermittent expression of conserved genetic information is vitally important when using secondary metabolite distribution in phylogenetic studies.

(b) There is ample evidence that a wide range of extrinsic factors can have a major impact on the final products of a biosynthetic pathway (Waterman and Mole, 1989). As an extreme example a study on the volatile oil of genetically uniform *Satureja hortensis* grown in Scotland over three summers (Svoboda et al., 1990) showed strong discrepancies which were attributable to large differences in sunlight between years resulting in variation in efficiency in a 'light-induced' intermediate reaction that was critical in the formation of carvacrol. At a more subtle level an exhaustive survey of the volatile oil of tea tree *Melaleuca alternifolia* over its complete range revealed differences in oil composition (Fig. 1) that were not picked up as genetic differences (Homer et al., 2000).

(c) The recognition that many secondary metabolites appear to play a role in the interactions between the producer and various predators, pathogens or competitors (Harborne, 1993) also has to be taken into account. In particular their role as 'defense' components is often considered in terms of an 'arms race' in which there is strong evolutionary pressure to 'invent' new defense weapons against adaptable opponents. Such pressures lead to a maximising of structural diversity in the end products of secondary metabolism. While this does not necessarily reduce the value of these metabolites as systematic markers it does make them more difficult to interpret and should lead to an emphasis on the biosynthetic pathway being expressed rather than on the structure of the final product.

As part of the defense issue the problem of induced defenses (Harborne, 1993, 1999; Karban and Baldwin, 1997) is particularly difficult to handle as under normal conditions some classes of compounds may be absent but their de novo synthesis and employment under biotic stress can clearly have phylogenetic implications.

(d) The problem of interpreting evolutionary advances through changes in biosynthetic pathways and substrates is exceedingly difficult (for a discussion of this issue in respect to the evolution of alkaloids see Waterman, 1998). As we learn more about the enzymes that govern secondary metabolism it becomes clear that while some are highly specific others are multi-functional and able to catalyse reactions involving a number of substrates (Zenk, 2007 – this volume). This, and the fact that intermediates in biosynthetic pathways can sometimes accumulate at rates faster than they are processed, will lead to the typical situation where isolation studies generate 'families' of structurally related metabolites that occur at varying concentrations. How this phenomenon is interpreted can have a major impact on how metabolites are viewed in a systematic context. For example, should all products in a pathway that are detected be given equal weighting or should it only be those that are clearly being expressed that are used with others being considered as representing a degree of 'leakiness' in the process? As advances in detection techniques allow us to delve more and more into the baseline noise of secondary metabolic profiles resolution of this question becomes increasingly critical. I suspect, as metabolomics evolves, it will become apparent that it is a chemical systematicists 'worst nightmare', and that the noise of secondary metabolism will have to be acknowledged and filtered out of systematic and phylogenetic arguments. For example, an alkaloid occurring at a level of 0.01% is clearly being expressed but what about at 0.000001%? As in so much to do with systematics common sense needs to prevail.

(e) It has to be noted that the acceptance of secondary metabolites in systematics has not always been aided by the actions and attitudes of those involved in generating the chemical data. At the most basic level there has often been, and frequently still is, a failure to follow the requirements of vouchering plant material in an acceptable institution (a drawer in the chemist's laboratory does not do!). The limitations of data from a single collection and extrapolation of findings far beyond what is logical are other factors that contribute to a quite understandable nervousness by general systematicists when it comes to including chemical data.

3. Standing the test of time

In a review Waterman and Gray (1987) identified a number of examples in which the use of chemical characters had had a significant impact on the perceived systematics of a taxonomic grouping. Now, some 20 years later, it is appropriate to re-examine those examples in the light of more recent developments, predominantly involving DNA sequence analysis.

3.1. The 1-benzyltetrahydroisoquinoline (1-btiq) alkaloids

One of several major contributions to chemical systematics made by Robert Hegnauer was his 'taxonomic definition' of alkaloids and his study on the distribution of 1-btiq alkaloids in higher plants (Hegnauer, 1963, reviewed by Waterman, 1999). This was a major factor in the realignment of Papaveraceae and Fumariaceae with the Ranunculales where similar alkaloids were found in families such as Ranunculaceae, Menispermaceae and Berberidaceae. Hegnauer's suggestions were taken up in many phylogenies proposed post-1960 (for example, Thorne, 1968; Dahlgren, 1980).

The pictorial system generated by Dahlgren has proved to be of particular value to chemical systematicists as it allowed known distributions of a class of secondary metabolite to be plotted onto the proposed phylogenetic tree. In Fig. 2 this has been done for the known sources of 1-btiq alkaloids, including the closely allied betalains of the Caryophylliflorae which also arise from tyrosine and have biosynthetic similarities with 1-btiq alkaloids.

The clustering of major alkaloid producing taxa observed in Fig. 2 is not, of course, surprising as their occurrence was taken into account in generating Dahlgren's phylogeny. It does, however, still illustrate how a major group of compounds like the 1-btiq alkaloids do crop up in many other orders, usually as only a few relatively simple compounds but in the case of the Rutales and Fabales in secondary areas of significant diversification.

Recently (Angiosperm Phylogeny Group, 2003) it has been concluded that the long held belief that the Dicotyledonae were monophyletic cannot be sustained and it now seems that the major 1-btiq alkaloid producers Magnoliales and Laurales, together with a number of small groups (collectively the Annonales of Fig. 2) represent a separate taxon that split with the monocots from a line that continued as the eudicots, of which the Ranunculales appears to be among the most ancient. I have depicted this proposed new phylogeny in Fig. 3.

While the change in phylogeny proposed is fundamental it only needs the Annonales in Fig. 2 to be moved to the far left of the diagram and this still leaves a core of 1-btiq rich taxa in close evolutionary proximity to each other. It must now be presumed that the capacity to generate 1-btiq alkaloids arose prior to the split off of the magnoliid/monocot line and the genetic information for their production has been retained, at least into the rosid line (Fig. 3).

3.2. Betalains

The betalains, like the 1-benzyltetrahydroisoquinoline alkaloids, arise from a tyrosine precursor. The unique

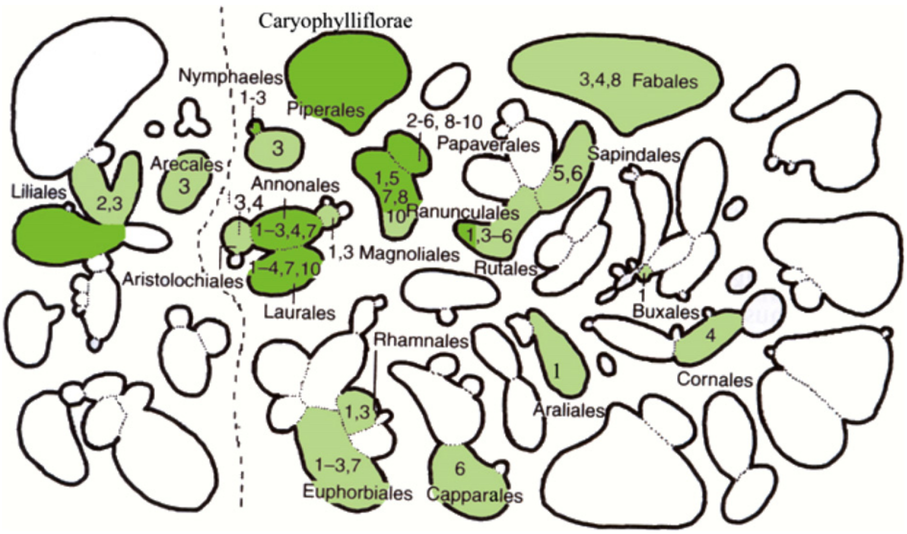


Fig. 2. Distribution of 1-benzyltetrahydroisoquinoline alkaloids (darker green = major sources) superimposed on Dahlgren's classification system (from Waterman, 1998). 1 = tricyclic 1-btiq alkaloids and dimmers, 2 = proaporphines, 3 = aporphines and derivatives, 4 = protoberberines, 5 = protopines, 6 = benzophenanthridines, 7 = morphinans and derivatives, 8 = dibenzazones, 9 = rhoedines, 10 = pavines and isopavines.

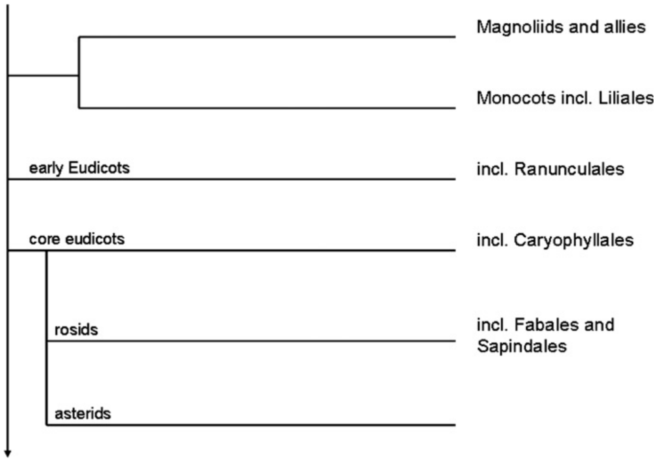


Fig. 3. Recent proposal for the phylogeny of angiosperms (Angiosperm Phylogeny Group, 2003). Major 1-btiq alkaloids taxa are found in the Magnoliids, Monocots and early Eudicots. Betalains occur in the Caryophyllales and there are significant 're-appearances' of 1-btiq alkaloids in the rosids, notably Fabales (Fabaceae) and Sapindales (in Rutales *sensu stricto*).

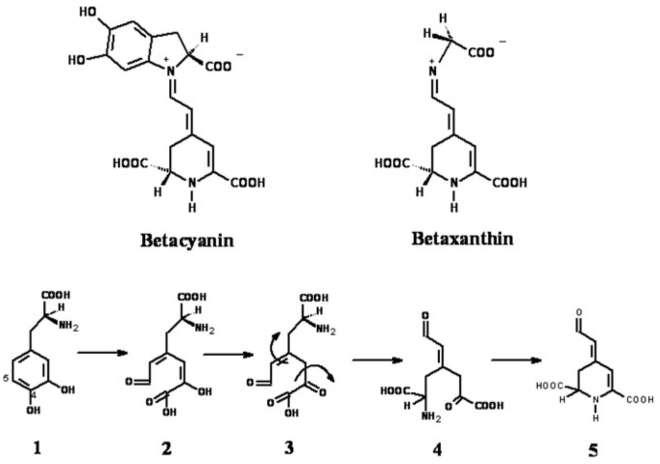


Fig. 4. Formation of the betalains.

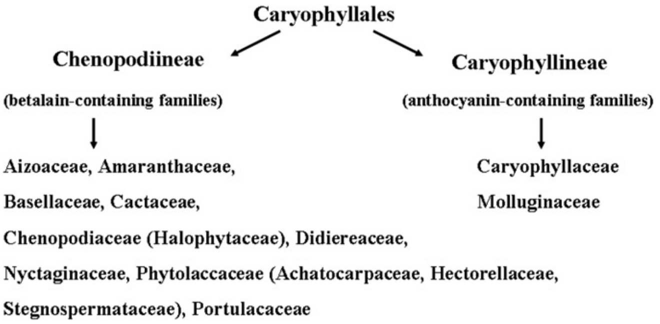


Fig. 5. Mutually exclusive distribution of anthocyanins and betacyanins in the families of the Order Caryophyllales (Mabry, 1977).

feature in betalains (Strack et al., 2003) is the rearrangement from tyrosine (**1**) through a ring-opening and re-closing (**2**–**4**) to yield betalamic acid (**5**) which can condense with an amino acid to give the highly coloured betacyanins and betaxanthins (Fig. 4).

By the 1960's, betalains had been identified and found to be restricted to certain families within the Centrospermae (now Caryophyllales) where they appear to replace anthocyanins (Fig. 5). Today, the presence of betalains remains restricted to the Caryophyllales, where they can unequivocally be considered as chemosystematic markers. However, the idea that betalain-containing and betalain-devoid families within the Caryophyllales represent two monophyletic lines has not been established and it would appear that we still have some way to go before we understand the evolution of this group (Clement and Mabry, 1996; Cuénoud et al., 2002).

3.3. Juniper monoterpenes

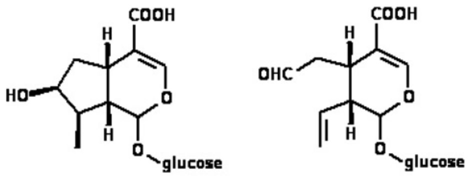
There have been a great number of reports that have concerned themselves with the use of volatile oils in chemical systematics. The techniques for studying these oils, notably GC/MS, lend themselves well to the accrual of data but the complexity and variability of the oils make them difficult to interpret. In the 1987 review (Waterman and Gray, 1987), we highlighted the studies performed by Adams on the *Juniperus* species of North America as an example of just what could be achieved by multiple sampling, sensible selection of useful markers from among the many oil components, and the inclusion of these with other potential systematic markers in cladistic analyses.

With the advent of DNA fingerprinting Adams has also exploited this technique in a series of papers where he examined the phylogenies originating from DNA (RAPDs) data against those derived from presence/absence matching of selected terpene compounds. While the use of the RAPDs method has been questioned the close agreement observed between DNA and terpene phylogenies for smooth leaf-margined junipers of the western hemisphere (Adams, 2000a) and the *J. polycarpos* complex of central Asia (Adams, 2001) indicate the validity of the approach in exploring evolutionary relationships. Unfortunately a study of *Juniperus* sect. *Juniperus* did not show a comparable degree of correlation between the two sets of markers (Adams, 2000b).

3.4. Iridoids

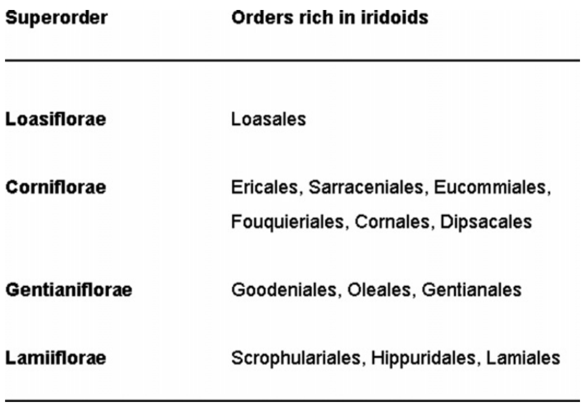
Iridoids, typified by the compounds loganin and *seco*-loganic acid (Fig. 6), have long been recognised as a group of secondary metabolites with a distribution that reflects phylogenetic relationships (Dahlgren et al., 1981). Before the advent of DNA mapping it was clear that these compounds, while found sporadically in a wide range of families, were particularly focussed in the Superorders Loasiflorae, Corniflorae, Gentianiflorae and Lamiiflorae (Fig. 7 – Waterman and Gray, 1987; Sampaio-Santos and Kaplan, 2001).

DNA studies now suggest that the iridoid-producing taxa are a component of the asterid line (cf. Fig. 3). Their distribution within the asterids has been mapped by Grayer et al. (1999), revealing that they occur in all major clades. Grayer et al. (1999) interpret their findings in a manner similar to that proposed above for the 1-btiq alkaloids. That is, the capacity to produce these compounds was already present in ancestors of the present day Asteridae and their absence from a taxon should be viewed in terms of "loss of expression". Furthermore, Grayer et al. (1999) went on to generate alternative phylogenies for the asterid-II clade based on minimising the number of loss/gain events that needed to occur in the production of iridoids and polyacetylenes, suggesting that the lower the number of loss/gain events the more likely the clade was. An example of a phylogeny for the asterid-II clade is shown in Fig. 8.



Loganin *Seco*-loganic acid

Fig. 6. Typical iridoid structures.



Superorder	Orders rich in iridoids
Loasiflorae	Loasales
Corniflorae	Ericales, Sarraceniales, Eucommiales, Fouquieriales, Cornales, Dipsacales
Gentianiflorae	Goodeniales, Oleales, Gentianales
Lamiiflorae	Scrophulariales, Hippuridales, Lamiales

Fig. 7. Major sources of iridoid compounds.

3.5. The Rutales

A PSE symposium on the chemistry and chemical taxonomy of the Rutaceae and allied families (Meliaceae, Simaroubaceae) was held in Glasgow in 1982 (Waterman and Grundon, 1983). As the review in Natural Product Reports (Waterman and Gray, 1987) followed soon after it did not highlight the Rutales s.s. as a whole but used as an example the distribution of limonoids in the Meliaceae.

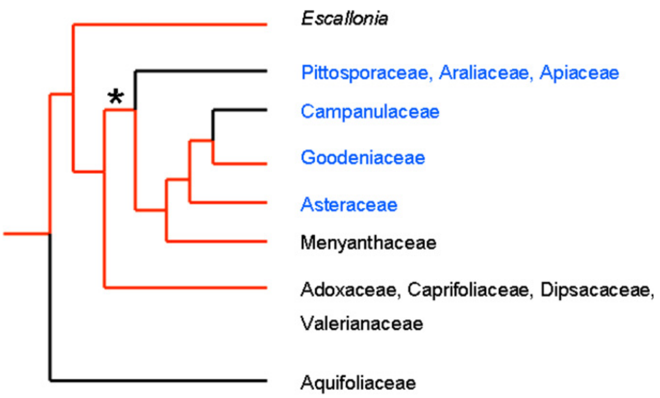
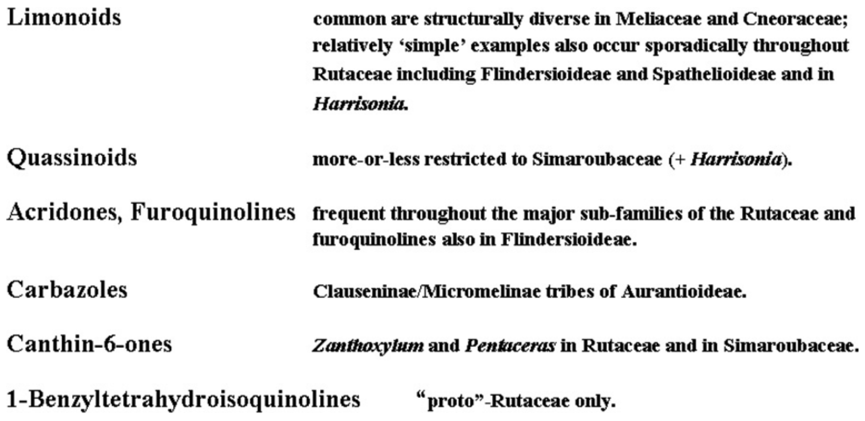


Fig. 8. Putative phylogeny for the asterid-II clade based on the presence (red line) or loss (black line) of the capacity to express iridoids and/or *seco*-iridoids and gaining the ability to synthesise polyacetylenes (*). Polyacetylene-containing taxa in blue. Modified from Grayer et al. (1999).



Limonoids	**common are structurally diverse in Meliaceae and Cneoraceae; relatively 'simple' examples also occur sporadically throughout Rutaceae including Flindersioideae and Spathelioideae and in *Harrisonia*.**
Quassinoids	**more-or-less restricted to Simaroubaceae (+ *Harrisonia*).**
Acridones, Furoquinolines	**frequent throughout the major sub-families of the Rutaceae and furoquinolines also in Flindersioideae.**
Carbazoles	**Clauseninae/Micromelinae tribes of Aurantioideae.**
Canthin-6-ones	***Zanthoxylum* and *Pentaceras* in Rutaceae and in Simaroubaceae.**
1-Benzyltetrahydroisoquinolines	**"proto"-Rutaceae only.**

Fig. 9a. Summary of distribution of some major classes of secondary metabolite within the Rutales s.s.

What makes the Rutales so interesting is the diversity of types of secondary metabolite that are either unique to or attain a particular high diversity in the Order (Fig. 9a). Within the Rutaceae itself there is a quite extraordinary proliferation of alkaloids arising from anthranilic acid (Fig. 9b).

In the 1982 Rutales Conference Proceedings Taylor (1983) on the Meliaceae and Waterman (1983) on the Rutaceae both made phylogenetic conclusions based on the distribution of secondary metabolites. Based on the known distributions of limonoids, quassinoids, coumarins, chromones Waterman (1983) suggested the phylogenetic scheme depicted in Fig. 10.

The conclusions made by Waterman (1983) may be summarised as follows:

(a) Rutaceae, Simaroubaceae and Meliaceae, together with a number of small taxa, formed a clade linked by unique secondary metabolism.
(b) Of the three major subfamilies of the Rutaceae the Aurantioideae could be sustained but the other two (Rutoideae and Toddalioideae) could not be reliably separated.
(c) The largely Australian genus Flindersia, which was sometimes regarded as a separate family, had close chemical affinities to the Rutaceae.
(d) The Cneoraceae, Ptaeroxylaceae, and minor subfamilies of the Rutaceae (Dictylomatoideae, Spathelioideae) shared chemical characters that suggested they were closely related.
(e) The genus Harrisonia, traditionally placed in the Simaroubaceae, exhibited a complex secondary metabolite profile that indicated it was closer to the small taxa named in (d).
(f) A group of five genera in the Rutaceae (Zanthoxylum, Phellodendron, Fagaropsis, Tetradium, Toddalia) were unusual in producing a range of 1-benzyltetrahydroisoquinoline alkaloids, notable benzophenanthridines which are otherwise found in the far more primitive Ranunculales (see Fig. 3).

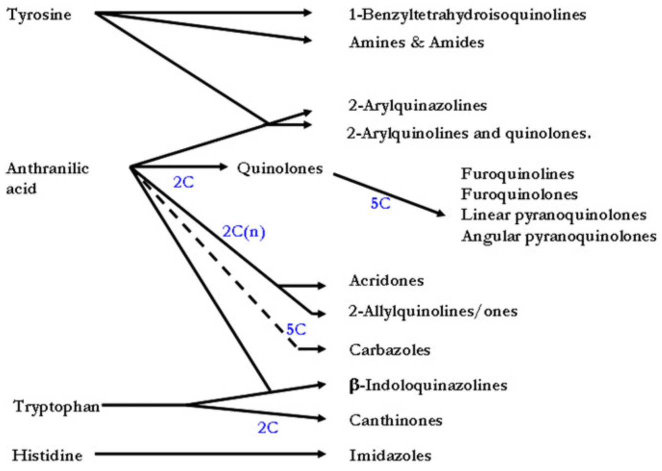


Fig. 9b. A biogenetic classification of the alkaloids of the Rutales (after Waterman (1975). 2C = acetate, 5C = mevalonate.

Waterman (1983) coined the name proto-Rutaceae for this group and proposed their presence indicated

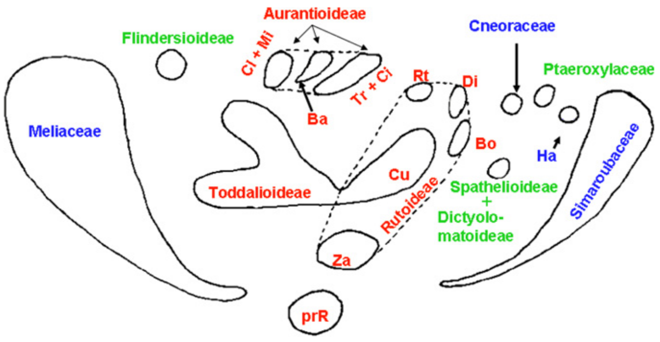


Fig. 10. Taxonomic groups within the Rutales s.s. for which significant secondary metabolite data is known. Blue – widely accepted families other than Rutaceae. Ha = *Harrisonia* (aberrant genus). Green – small taxonomic units, usually considered as separate families or sub-families within Rutaceae. Red – three major sub-families of the Rutaceae (sub-tribes – Ba = Balsamocitrinae; Bo = Boronieae; Ci = Citrinae; Cl = Clauseninae; Cu = Cusparieae; Di = Diosmeae; Mi = Micromelinae; prR ="proto-Rutaceae"; Rt = Rutinae; Tr = Triphasiinae; Za = Zanthoxyleae.

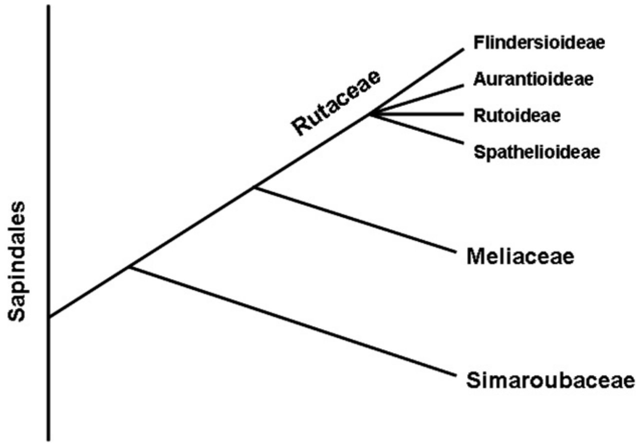


Fig. 11. Current view of relationships within the Rutales s.s.

that the Rutaceae had a far closer relationship to primitive angiosperms than had hitherto been recognized.

DNA studies reported in the last few years (Chase et al., 1999; Morton et al., 2003; Stevens, 2006) have shed further light on the above conclusions (a–e). For example, Chase et al. (1999) concluded that (1) Simaroubaceae and Meliaceae were the closest relatives of the Rutaceae; (2) The Flindersioideae belonged to the Rutaceae; (3) the Dictyolomatoideae and Spathelioideae are both part of a clade that also includes Cneoraceae, Ptaeroxylaceae and *Harrisonia* and it was proposed that all five taxa be circumscribed as Spathelioideae and form part of the Rutaceae; (4) Toddalioideae and Rutoideae should be merged. Under these conditions monophyly was achieved for the Rutaceae. Morton et al. (2003) confirmed that the other subfamily of the Rutaceae, the Aurantioideae, was monophyletic.

Consequently, as a result of the DNA studies Fig. 10 remains essentially the same as predicted by Taylor (1983) and Waterman (1983) with the Rutaceae now being considered to include all the taxa other that Meliaceae and Simaroubaceae (Fig. 11). For the Rutaceae the situation is simplified by recognizing four sub-families, Flindersioideae, Rutoideae (inc. Toddalioideae), Aurantioideae and Spathelioideae (inc. Cneoraceae, Ptaeroxylaceae, Dictyolomatoideae, *Harrisonia*). No support is forthcoming for any link between the proto-Rutaceae (all included in Rutoideae) and the Ranunculales and in that light it seems that the 1-btiq alkaloids that characterize these few genera are an example of the re-expression of genetic information that has been retained by the genome.

4. General conclusion

The number of 'big' insights into plant phylogeny offered by secondary metabolites is really rather small and most of them had been identified by the end of the 1960's. For all the reasons noted in Section 2 the discipline progressed slowly in terms of acceptance by the systematic community but by the 1980's and 1990's chemical information was being used to develop putative phylogenies, notably by Dahlgren and Thorne.

What is now clear is that the majority of those early insights have withstood the test of re-examination with macromolecular techniques (for further examples, see Wink, 2003), illustrating that chemical systematics was built on a correct premise even though the vagaries in distribution mean that comprehending systematic meaning is often less obvious and more ‘‘open to interpretation’’ in a manner comparable to non-chemical characters than was anticipated by the founding fathers. Today it is encouraging to see that modern taxonomic descriptions arising from the most recent attempts at identifying phylogenies do include secondary metabolite characters. In as much as this is the case chemical systematics can be judged to be alive and well as a discipline.

For the future, providing phytochemical data are generated using acceptable procedures, the chemical database available for assessing phylogenetic relationships will continue to grow and to provide a valuable counterpoint to DNA fingerprinting.

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