Some Notes on the Chlorogenic Acids.

5. Are dicaffeoyl-*epi*-quinic acids present in Asteraceae?

Version 1 November 2018

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The commonest and best characterised acyl-quinic acids are those containing a (–)-quinic acid moiety.[1] There are increasing reports of acyl-quinic acids in which a different quinic acid stereoisomer is present, generally described as an *epi*-quinic acid on the basis of NMR data,[2-22] but rarely released by hydrolysis / saponification and shown unequivocally to be different from (–)-quinic acid.[22]

The main source of these putative acyl-quinic acids appears to be the Asteraceae. Although not proven, the biosynthesis of (–)-*epi*-quinic acid is plausible, simply requiring D-threose-4-phosphate to replace D-erythrose-4-phosphate in the pathway established for (–)-quinic acid.[23]

If a plant produces acyl-quinic acids then usually a large number of related compounds are present. Typically three (or four) caffeoyl-quinic acids, often with the analogous *p*-coumaroylquinic acids and feruloylquinic acids, plus three (or six) dicaffeoylquinic acids, not infrequently accompanied by further members of this extended family.

However, generally only a single acyl-*epi*-quinic acid is reported and almost always a dicaffeoyl derivative, accompanied by several mono- and diacyl-(–)-quinic acids. Surely one would expect a greater range of acyl-*epi*-quinic acids— even if steric factors prevent all available hydroxyls being esterified, the associated mono-caffeoyl-*epi*-quinic acids would be expected.

Also of note, never has the putative dicaffeoyl-*epi*-quinic acid been accompanied by the full set of three or six *di-trans* dicaffeoylquinic acids (the number expected depending on whether or not 1-acyl-quinic acids are synthesised) always leaving open the possibility that the putative dicaffeoyl-*epi*-quinic acid has been mis-identified.

As discussed in depth elsewhere,[1, 24] isolation, purification and NMR characterisation of dicaffeoylquinic acids is not easy, being further complicated by their susceptibility to acyl migration during preparation, and while the $^{3}J_{HH}$ coupling constants are sometimes provided, the $^{13}C–^{1}H$ coupling constants are not.[25] Accordingly, it is extremely difficult to distinguish between a dicaffeoyl-(–)-quinic acid which favours a carboxy equatorial conformation and a dicaffeoyl-*epi*-quinic acid which is thought to favour the carboxy axial conformer, especially if π–π interaction between the two caffeoyl residues further distorts the conformation.

A simple experiment that would help to provide an answer to this problem is for anyone who has an extract thought to contain a dicaffeoyl-*epi*-quinic acid to subject it to LC–MS^{n} on a reversed phase column packing using a shallow acetonitrile or methanol gradient and compare it with an extract of a green arabica coffee bean as a readily available surrogate standard.[26] This will be much easier with a species which does not produce 1-acyl-(–)-quinic acids, where a quantitatively significant fourth dicaffeoylquinic acid, which is not a *cis*-geometric isomer, must be a novel compound. The presence

of *cis*-geometric isomers could be checked by analysis of extracts before and after UV-irradiation,[27] or by sodium ion complexation.[28] Whatever the outcome, a useful short communication would be possible.

The situation is more complex in the case of a species which does acylate (–)-quinic acid at C1, easily detected by the distinctly rapid elution of 1,3-diCQA IUPAC. An artichoke extract, or similar, is now a suitable surrogate standard, but full resolution of the remaining five *di-trans* dicaffeoyl-(–)-quinic acids is more difficult and becomes even more so if there are *cis* geometric isomers present, to say nothing of a possible novel compound.

Although the elution behaviour of the acyl-(–)-quinic acids can be reasonably well predicted — those with more free equatorial hydroxyl residues eluting more rapidly than those with more free axial hydroxyls, i.e 1,3-diCQA eluting distinctly early and 4,5-diCQA eluting last, with the other four regio-isomers eluting close together just in advance of 4,5-diCQA — the behaviour of the acyl-*epi*-quinic acids is more difficult to predict because of the lack of reliable experimental data. It is not unreasonable to expect analogous behaviour but the orientation of the free hydroxyls will depend on whether or not a carboxy-equatorial or carboxy-axial conformation is adopted.

However, Wang *et al*. who isolated a quinic acid stereo-isomer after saponification, report that 4,5-dicaffeoyl-*epi*quinic acid (IUPAC) elutes in advance of 3,5-dicaffeoyl-(–)-quinic acid which precedes 4,5-dicaffeoyl-(–)-quinic acid.[22]

Are there any volunteers out there?

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