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Assuntos Gerais

UNREMITTING PROBLEMS WITH CHLOROGENIC ACID NOMENCLATURE: A REVIEW

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This paper summarizes a problematic nomenclature of isomers belonging to chlorogenic acid family since its first occurrence until present. During decades, there have been a high number of articles dealing with the family. Unfortunately, researchers who want to get knowledge about this topic may be strongly confused after reading a few articles. Due to gradual discoveries and isolations of the individual isomers from plenty of matrices and because of the changing system of terminology after these discoveries, discrepancies among articles are common. The cause of this confusion is that the main compound of the family, 5-caffeoylquinic acid (also well-known as chlorogenic acid), was truly called as 3-caffeoylquinic acid before 1976, when new rules for nomenclature were published. Many researchers and also chemicals suppliers, however, keep using the "pre-IUPAC" nomenclature and wrongly call 3-caffeoylquinic acid as chlorogenic acid, the main substituent of the family. Despite there have been some works struggling with this issue, the problem is still appearing. Therefore, the present work was written.

Keywords: chlorogenic acid; neochlorogenic acid; nomenclature; coffee.

INTRODUCTION

As is well known nowadays, chlorogenic acids (CGAs) are naturally occurring compounds found in all higher plants. It is a family of esters formed between quinic and certain trans-cinnamic acids.[1,2] However, in spite of the "chloro" in the name, chlorogenic acids do not contain chlorine. This name comes from the Greek, which means light green. This is most likely because of the green color produced when the compounds are oxidized. CGAs are widely recognized to have many beneficial properties such as antioxidant activity, anti-carcinogenic potential and may also slow the release of glucose into the bloodstream after a meal.[3-5] Also, they have strong anti-inflammatory, anti-bacterium and anti-obesity properties.[6-8] Because of these many positive influences on human body, since the middle of the 19th century, when the first references about CGAs appeared, there have been a high amount of articles dealing with extraction and detection techniques of CGAs or studying their influence on human health. CGAs have been observed and isolated in many plant materials such as coffee[9], apple[10], tomato, papaya[11], sweet potato[12], prune[13], pear[14], cabbage[15], yacon[16], burdock[17], cherry[18], apricot[19], orange[20], etc. Coffee beans are undoubtedly the most common observed matrix because coffee is the main source of CGAs.[21] In the final coffee beverage, content of CGAs is supposed to be responsible for cup quality.[22] In potatoes, for instance, the compounds are considered to cause undesirable "after-cooking blackening or darkening", in other words, they seem to be responsible for bluish-grey discoloration of potatoes exposed to air after boiling or steaming.[23,24]

The main purpose of this work is not to bring up some other new extraction or detection possibilities for obtaining CGAs from plant materials neither to reveal some new observed properties of these compounds. It is to point out the considerable differences in articles dealing with the chlorogenic acid esters. During last decade, there has been a big disorder in nomenclature of CGAs. Although there are books or articles also dealing with the nomenclature of chlorogenic acid isomers, some of them are confusing and the majority of them are inaccessible for many researchers. Despite this fact, the wrong nomenclature is still very common, thus the present paper focuses on a possibility of making this problem clear, thus helping further authors to overcome potential misunderstandings of the nomenclature. Unfortunately, it has to be announced sometimes that the direct source (mostly sources published before 1900) are not available and therefore secondary sources might be used here.

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History of CGAs isolation

The problems with the nomenclature of CGAs are naturally closely-linked to their history. Therefore, the present work paid attention to this fact. The very first references of chlorogenic acid come from the mid-19th century. Since 1837, when Robiquet and Bourton[25] observed physiologically active constituents in coffee and isolated acidic substances with green pigments that included ferulic chloride from green coffee beans, there have been a huge amount of articles dealing with CGAs. In 1846, Payen[26] firstly used the term "chlorogenic acid" (CQA). However, Payen was perhaps affected by Rochleder,[27] who described "caffeotanic acid" in coffee. In 1854, Ludwig and Kromeyer[28] found the compound in sunflower seeds. More than half a century later, in 1908, CQA was first isolated by Gorter[29], who found out that this compound is widely distributed in leaves and seeds of numerous plants. He isolated a crystalline complex, potassium caffeine chlorogenate, from which he prepared the pure compound. He also figured out that chlorogenic acid is decomposed by the action of alkalis with the formation of caffeic and quinic acids. Two years later in 1910, Charaux,[30] who was one of the first workers to attempt the measurement of CQA content in plants, described a possibility of extraction process. He confirmed CQA to be broadly distributed in the vegetable kingdom and said that its quantity is approximately two times more than the amount of caffeic acid in plants. In 1920, Freudenberg[31] described chlorogenic acid, the tannic compound of coffee, as depside of quinic acid and caffeic acid. In 1932, Fischer and Dangschat[32] established the structure of 3-O-caffeoylquinic acid, which is 5-O-caffeoylquinic acid (5-CQA) in current nomenclature (for this terminology see nomenclature section), by its isolation from green coffee beans.

Decades later, in 1950-1960's, the other three "mono-caffeic isomers" of quinic acid were observed. Neochlorogenic acid was

described and isolated from Elberta and Halford peaches as a crystalline material by Corse in 1953.[33] In 1955, Uritani and Miyano[34] succeeded with the isolation of pseudochlorogenic acid (1-CQA) from sweet potatoes infected with black rot. The last possible mono isomer got the name cryptochlorogenic acid (4-CQA) and it was explored and isolated in 1964 by Waiss.[35] These two acids are very easy to distinguish due to the fact their OH groups are placed directly across from the carbon carrying the COOH group or exactly at the carbon carrying the COOH group, respectively.

Also, in 1950, Barnes *et al*.[36] described a compound with a trivial name: isochlorogenic acid. This compound was isolated from coffee beans and it was reported to have similar properties as CQA. The authors determined this compound as a position isomer of chlorogenic acid, which is based on the same molecular weight, ultimate composition, hydrolysis compound or similar UV and IR spectra. Unlike CQA, isochlorogenic acid does not form a complex analogous to the crystalline potassium chlorogenate. Nowadays, the term isochlorogenic acid is used for polyphenolic compounds which are composed of quinic acid and two caffeic acids (di-CQA).[37]

NOMENCLATURE

Problems with the numbering

As said in the Introduction, the main goal of this article is to point out the big problems and common disagreements in the nomenclature of chlorogenic acids isomers. At the very beginning, it has to be announced that the name chlorogenic acid should not be used only for one compound but it should describe one or more family of esters that form between certain cis- or trans-cinnamic acids, mostly caffeic, ferulic or p-coumaric (see figure 1), and quinic acid. For instance, CGAs composition of coffee, one of the most popular beverages in the world, is complex with at least 5 major groups of compounds present. Those are caffeoylquinic acids (CQA), dicaffeoylquinic acids (diCQA), feruloylquinic acids (FQA), p-coumaroylquinic acids (CoQA) and caffeoylferuloylquinic acids (CFQA).[38] In Table 1 and Figure 2 are shown the most common studied types of CGAs composition with correct abbreviations.

The biggest discrepancies are with the designation of two compounds belonging among the caffeoylquinic acids, the 5-CQA and 3-caffeoylquinic acid (3-CQA), which are often commuted. If trivial names are used, it is usual to call them chlorogenic acid and neochlorogenic acid, respectively. Those are optical isomers that are

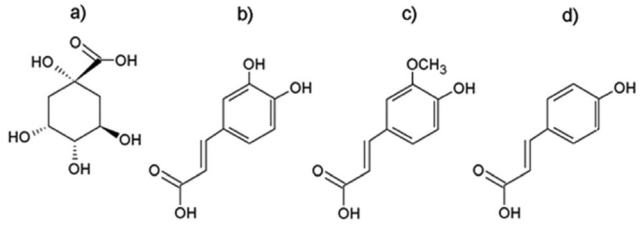

Figure 1. *Structural formulas of quinic acid (a) and three most common trans-cinnamic acids of CGAs family: caffeic acid (b), ferulic acid (c) and p-coumaric acid (d)*

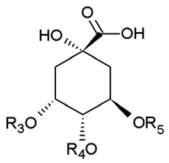

Figure 2. *The structure of quinic acid with possible substituents R_3, R_4 and R_5*

Table 1. Various types of substitution of quinic acid with caffeic, ferulic or *p*-coumaric acid[39]

Compound abbreviation	Identity of R3	Identity of R4	Identity of R5
3-CQA	caffeic acid	hydrogen	hydrogen
4-CQA	hydrogen	caffeic acid	hydrogen
5-CQA	hydrogen	hydrogen	caffeic acid
3-FQA	ferulic acid	hydrogen	hydrogen
4-FQA	hydrogen	ferulic acid	hydrogen
5-FQA	hydrogen	hydrogen	ferulic acid
3-p-CoCQA	*p*-coumaric acid	hydrogen	hydrogen
4-p-CoCQA	hydrogen	*p*-coumaric acid	hydrogen
5-p-CoCQA	hydrogen	hydrogen	*p*-coumaric acid
3,4-diCQA	caffeic acid	caffeic acid	hydrogen
3,5-diCQA	caffeic acid	hydrogen	caffeic acid
4,5-diCQA	hydrogen	caffeic acid	caffeic acid
3,4-CFQA	ferulic acid	ferulic acid	hydrogen
3,4-CFQA	ferulic acid	caffeic acid	hydrogen
3,5-CFQA	ferulic acid	hydrogen	ferulic acid
3,5-CFQA	ferulic acid	hydrogen	caffeic acid
4,5-CFQA	hydrogen	caffeic acid	ferulic acid
4,5-CFQA	hydrogen	ferulic acid	caffeic acid

very difficult to distinguish if researchers are not well-acknowledged with their nomenclature (see below). Figure 3 clearly shows if a spatial structure for illustration of chlorogenic acid is not used, there is no possibility of recognizing the two above mentioned enantiomers between each other. Nevertheless, some authors use such figures in their articles, which can be seen, for instance, in the works of Mills *et al*.[40] or De Maria *et al*.[41] This problem is also common in a plenty of research and web pages. However, according to International Union of Pure and Applied Chemistry (IUPAC) numbering system published in 1976,[42] there are strict rules, which makes easier to differentiate these two enantiomers.

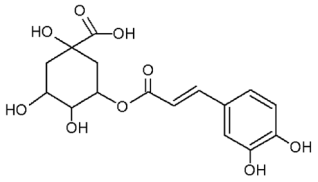

Figure 3. *2-D structure of a compound which could be named 3-CQA or 5-CQA*

Quinic acid according to IUPAC

As was mentioned, CGAs are composed by various types of trans-cinnamic acids always bound to quinic acid. It has to be stated the latter one could be incorrectly considered as a saccharide. However, it is a type of cyclitol which are generally not regarded to be a carbohydrate.[43] Because of that, the nomenclature for cyclitols deals with another rules described in the IUPAC system recommendation.[44] Therefore, the numbering system of CGAs is related to the numbering of cyclitols that was suggested by Maquenne in 1900.[42] He proposed a fractional notation, where numerals in the numerator denote hydroxyl or other group (with exception of hydrogen) above the plane of the ring and numerals in the dominator denote hydroxyl

or other group (with exception of hydrogen) below the plan of the ring. However, Maquenne did not specify the exact way of allocation of the numerals to the specific positions. Afterwards, Posternak[42] developed another system of numbering which was very popular to use until the above-mentioned year 1976, when the IUPAC system for nomenclature of cyclitols was published. Lower in that paper is exactly described how the quinic acid ring should be numbered.[43]

In the literature, there can be found names like D-quinic or L-quinic acid. As is well known, these symbols label whether the configuration at the reference carbon in the Fischer projection is the same (or the opposite) as that one in the D-(+)-glyceraldehyde.[43,45] However, this is an old labeling which occurs mostly with names of natural compounds (or substituents made from natural compounds). Nowadays, enantiomers are distinguished as R- and S- isomers. This system is sometimes called the CIP (as the abbreviation of three authors - Cahn, Ingold, Prelog - who suggested this system) or the R-S system.[46] Also, it is possible to meet names like (-)-Quinic acid or (+)-Quinic acid. Those symbols introduce only information about rotation of plane of polarized light.

According to papers, however, it is (-)-quinic acid or D-(-)-quinic acid, which results in different types of CGAs by its conjugation with one or more of the above-named trans-cinnamic acids.[1,47,48] In the IUPAC system, D-(-)-quinic acid is defined as 1L1(OH),3,4/5-tetrahydroxycyclohexanecarboxylic acid. Regarding the R-S system, the name of this acid is (1S,3R,4S,5R)-1,3,4,5-tetrahydroxycycloh exanecarboxylic acid.

As was already written, the biggest problems are with the commutation of 5-CQA and 3-CQA. Nowadays, both of these compounds are available in a pure crystal form purchasable from commercial suppliers. Unfortunately, majority of the suppliers keep the pre-IUPAC nomenclature and sell chlorogenic acid as 3-caffeoylquinic acid. This is probably because of the fact that in 1976, when IUPAC numbering system for cyclitols was published, the name for chlorogenic acid was really 3-caffeoylquinic acid and pure form of neochlorogenic acid was not yet purchasable.

The evidence of unremitting wrong nomenclature can be found in recent studies.[49,50] Besides, in a work of Moeenfard *et al*.,[51] the problems with nomenclature are rightly mentioned and pointed out, although these same authors also used the wrong one. Furthermore, in the discussion they wondered about their results, dealing with CGAs contained in coffee brews, and compared them to the results published in other papers. Some of them are in agreement with Moeenfard's results and some are not. The work in compliance was published by Gloess *et al*.,[52] but they also used the wrong nomenclature. Both of these authors mentioned 3-CQA as chlorogenic acid. Therefore, according to them, 3-CQA was the most abundant compound. On the other hand, in the other compared work of Fujioka,[53] the main compound observed was 5-CQA. Fujioka, however, did not use trivial names. From the mentioned is obvious that authors compared different compounds – chlorogenic and neochlorogenic acid.

According to the current rules, however, the structure of chlorogenic acid for the reason of this term should definitely be 5-CQA. Hence it is clear that 3-CQA is an abbreviation for neochlorogenic acid. These results have to be considered by researchers if CGAs are targets of the research.

CONCLUSION

This short review has been written due to an obvious and unremitting wrong nomenclature occurring in chlorogenic acid family. These discrepancies are caused by the fact that 5-caffeoylquinic acid (5-CQA) was firstly discovered and subsequently isolated already in the middle of 19th century. However, from that time up to 1976, when IUPAC published the exact rules and definitions describing a new system of nomenclature, the right name for the current 5-CQA was actually 3-caffeoylquinic acid. In spite of that fact, researchers and also chemicals suppliers have been still using this pre-IUPAC nomenclature. Therefore, the authors of the present article expect that this work will help further researchers to avoid any mistakes and disagreements, so it could be much easier to correctly compare different studies dealing with the chlorogenic acid family.

REFERENCES

1. Clifford, M. N.; *J. Sci. Food. Agr.* **1999**, *79*, 362.
2. Clifford, M. N.; Wu, W. G.; Kuhnert, N.; *Food Chem.* **2006**, *95*, 574.
3. Haghi, G.; Hatami, A.; Arshi, R.; *Food Chem.* **2011**, *124*, 1029.
4. Bakuradze, T.; Boehm, N.; Janzowski, C.; Lang, R.; Hofmann, T.; Stockis, J. P.; Albert, F. W.; Stiebitz, H.; Bytof, G.; Lantz, I.; Baum, M.; Eisenbrand, G.; *Mol. Nutr. Food Res.* **2011**, *55*, 793.
5. Tunnicliffe, J. M.; Eller, L. K.; Reimer, R. A.; Hittel, D. S.; Shearer, J.; *Appl. Physiol. Nutr. Metab.* **2011**, *36*, 650.
6. Chagas-Paula, D. A.; de Oliveira, R. B.; da Silva, V. C.; Gobbo-Neto, L.; Gasparoto, T. H.; Campanelli, A. P.; Faccioli, L. H.; Da Costa, F. B.; *J. Ethnopharmacol.* **2011**, *136*, 355.
7. Cho, A. S.; Jeon, S. M.; Kim, M. J.; Yeo, J.; Seo, K. I.; Choi, M. S.; Lee, M. K.; *Food Chem. Toxicol.* **2010**, *48*, 937.
8. Wang, G. F.; Shi, L. P.; Ren, Y. D.; Liu, Q. F.; Liu, H. F.; Zhang, R. J.; Li, Z.; Zhu, F. H.; He, P. L.; Tang, W.; Tao, P. Z.; Li, C.; Zhao, W. M.; Zuo, J. P.; *Antiviral Res.* **2009**, *83*, 186.
9. Ludwig, L. A.; Mena, P.; Calani, L.; Cid, C.; Del Rio, D.; Lean, M. E. J.; Crozier, A.; *Food Funct.* **2014**, *5*, 1718.
10. Liaudanskas, M.; Viskelis, P.; Kviklys, D.; Raudonis, R.; Janulis, V.; *Int. J. Food Prop.* **2015**, *18*, 945.
11. Siriamornpun, S.; Ratseewo, J.; Kaewseejan, N.; Meeso, N.; *Rsc. Adv.* **2015**, *5*, 18579.
12. Sasaki, K.; Oki, T.; Kobayashi, T.; Kai, Y.; Okuno, S.; *Biosci., Biotechnol., Biochem.* **2014**, *78*, 2073.
13. Jabeen, Q.; Aslam, N.; *J. Med. Plants Res.* **2011**, *5*, 1508.
14. Lee, S. W.; Lee, Y. G.; Cho, J. Y.; Kim, Y. C.; Lee, S. H.; Kim, W. S.; Moon, J. H.; *J. Korean Soc Appl. Biol.Chem.* **2015**, *58*, 335.
15. Fernandez-Leon, A. M.; Lozano, M.; Gonzalez, D.; Ayuso, M. C.; Fernandez-Leon, M. F.; *Czech. J. Food Sci.* **2014**, *32*, 549.
16. Oliveira, R. B.; Chagas-Paula, D. A.; Secatto, A.; Gasparoto, T. H.; Faccioli, L. H.; Campanelli, A. P.; Da Costa, F. B.; *Rev. Bras. Farmacogn.* **2013**, *23*, 497.
17. Tang, Y. X.; Lou, Z. X.; Yang, L.; Wang, H. X.; *Eur. Food Res. Technol.* **2015**, *240*, 1203.
18. Xiao, Z. B.; Fang, L. L.; Niu, Y. W.; Yu, H. Y.; *Food Chem.* **2015**, *186*, 69.
19. Kan, T.; Gundogdu, M.; Ercisli, S.; Muradoglu, F.; Celik, F.; Gecer, M. K.; Kodad, O.; Zia-Ul-Haq, M.; *Biol. Res.* **2014**, *47*.
20. Agcam, E.; Akyildiz, A.; Evrendilek, G. A.; *Food Chem.* **2014**, *143*, 354.
21. Bassoli, B. K.; Cassolla, P.; Borba-Murad, G. R.; Constantin, J.; Salgueiro-Pagadigorria, C. L.; Bazotte, R. B.; de Souza, H. M.; *Cell. Biochem. Funct.* **2015**, *33*, 183.
22. Farah, A.; Monteiro, M. C.; Calado, V.; Franca, A. S.; Trugo, L. C.; *Food Chem.* **2006**, *98*, 373.
23. Dao, L.; Friedman, M.; *J. Agric. Food Chem.* **1992**, *40*, 2152.
24. Swain, T., *Economic importance of flavonoid compounds: foodstuffs*. 1962, Pergamon Press, Oxford.
25. Robiquet; *Ann. Pharm.* **1837**, *23*, 93.
26. Payen, A.; *Compte-Rendus de l'Académie des Sciences (Paris)* **1846**, *22*, 724.
27. Hardy, F.; Warneford, F. H. S.; *Ind. Eng. Chem.* **1925**, *17*, 48.
28. Hulme, A. C.; *Biochem. J.* **1953**, *53*, 337.

29. Moores, R. G.; McDermott, D. L.; Wood, T. R.; *Anal. Chem.* **1948**, *20*, 620.
30. Charaux, C.; *J. Pharm. Chim.* **1910**, *102*, 292.
31. Thomas, A. W.; *J. Ind. Eng. Chem.-U.S.* **1922**, *14*, 829.
32. Feldman, J. R.; Ryder, W. S.; Kung, J. T.; *J. Agric. Food Chem.* **1969**, *17*, 733.
33. Corse, J.; *Nature* **1953**, *172*, 771.
34. Uritani, I.; Miyano, M.; *Nature* **1955**, *175*, 812.
35. Waiss, A. C.; Lundin, R. E.; Corse, J.; *Chem. Ind.* **1964**, 1984.
36. Barnes, H. M.; Feldman, J. R.; White, W. V.; *J. Am. Chem. Soc.* **1950**, *72*, 4178.
37. Guo, W.; Wang, L.; Gao, Y.; Zhao, B.; Wang, D.; Duan, W.; Yu, Z.; *J. Chromatogr. B* **2015**, *981–982*, 27.
38. Clifford, M. N.; Wight, J.; *J. Sc.i Food Agric.* **1976**, *27*, 73.
39. Clifford, M. N.; Johnston, K. L.; Knight, S.; Kuhnert, N.; *J. Agric. Food Chem.* **2003**, *51*, 2900.
40. Mills, C. E.; Oruna-Concha, M. J.; Mottram, D. S.; Gibson, G. R.; Spencer, J. P. E.; *Food Chem.* **2013**, *141*, 3335.
41. De Maria, C. A. B.; Moreira, R. F. A.; *Quim. Nova* **2004**, *27*, 586.
42. IUPAC Commission on the Nomenclature of Organic Chemistry (CNOC); IUPAC-IUB Commission on Biochemical Nomenclature (CBN); *Biochem. J.* **1976**, *153*, 23.
43. De Azevedo, W. F.; Leclerc; S.; Havlicek; L.; Strnad, M. H.; *Eur. J. Biochem.* **1997**, *243*, 518.
44. IUPAC Commission on the Nomenclature of Organic Chemistry (CON); IUPAC-IUB Commission on Biochemical Nomenclature (CBN); *Arch. Biochem. Biophys.* **1968**, *128*, 269.
45. Kovacs, L.; *Magy. Kem. Foly.* **1997**, *103*, 178.
46. Cahn, R. S.; Ingold, C.; Prelog, V.; *Angew. Chem. Int. Edit.* **1966**, *5*, 385.
47. Hemmerle, H.; Burger, H.-J.; Below, P.; Schubert, G.; Rippel, R.; Schindler, P. W.; Paulus, E.; Herling, A. W.; *J. Med. Chem.* **1997**, *40*, 137.
48. Farah, A.; De Paulis, T.; Trugo, L. C.; Martin, P. R.; *J. Agric. Food Chem.* **2005**, *53*, 1505.
49. Fu, X.; Yin, Z. P.; Chen, J. G.; Shangguan, X. C.; Wang, X. Q.; Zhang, Q. F.; Peng, D. Y.; *J. Agric. Food Chem.* **2015**, *63*, 262.
50. Sun, P. C.; Liu, Y.; Yi, Y. T.; Li, H. J.; Fan, P.; Xia, C. H.; *Food Chem.* **2015**, *168*, 55.
51. Moeenfard, M.; Rocha, L.; Alves, A.; *J. Anal. Methods Chem.* **2014**, *2014*, 965353.
52. Gloess, A. N.; Schonbachler, B.; Klopprogge, B.; D'Ambrosio, L.; Chatelain, K.; Bongartz, A.; Strittmatter, A.; Rast, M.; Yeretzian, C.; *Eur. Food Res. Technol.* **2013**, *236*, 607.
53. Fujioka, K.; Shibamoto, T.; *Food Chem.* **2008**, *106*, 217.