Letter to the Editor DOI: 10.2478/aiht-2024-75-3823

A follow-up on the hesperetin issue in modelling the first electrochemical oxidation potential and antioxidant activity of flavonoids

Ante Miličević

Institute for Medical Research and Occupational Health, Zagreb, Croatia

Dear Editor,

In Volume 70 (pages 134-139) of *Arhiv za higijenu rada i toksikologiju – Archives of Industrial Hygiene and Toxicology*, I published a paper entitled "The relationship between antioxidant activity, first electrochemical oxidation potential, and spin population of flavonoid radicals" (1). The paper detected a problem with hesperetin, a flavonoid (flavanone) with 4'-methoxy and 3'-hydroxyl groups on the B ring. That problem was later resolved in a paper published in the *Journal of Molecular Liquids* (2021;335:116223) on a set of 29 flavonoids (2), which I believe is worth reporting as a follow-up to my aforementioned article published in the *Archives*.

More precisely, in my paper (1), I detected hesperetin as an outlier in regression models for the estimation of both oxidation potential (E_{p1}) and antioxidant activities (AA), on a set of 14 flavonoids. The models [Models 2 and 7, Figures 2 and 3 in (1)] were based on the sum of atomic orbital spin populations over the carbon atoms in the skeleton of a flavonoid radical, $\sum_{s(C)} AOSP_{Rad}$, calculated using semiepirical PM6 method. Later, in our paper on E_{p1} models for 29 flavonoids (2), we succeeded in resolving a problem with hesperetin and its glycosides, hesperidin and neohesperidin, thanks to studies on the electron donation potential of the *ortho*-methoxy group in quinones (3, 4). When we fixed the methoxy group, placing it outside of the plane (orthogonally to the B ring) during optimization, the calculated $\sum_{s(C)} AOSP_{Rad}$ for hesperetin, hesperidin, and neohesperidin fit into the model perfectly, Figure 1 in (2) [see more details about approaching certain flavonoids, like flavanones, isoflavones, and flavonoids with *O*-glycosyl, galloyl and methoxy substituents, as well as a new models that we introduced in (2, 5, 6)].

Figures 1 and 2 show that $\sum_{s(C)} AOSP_{Rad}$ values for hesperetin calculated in this way fit the quadratic regression models in (1).

Acknowledgement

Funded by the European Union – Next Generation EU [Interactions between Human and Environmental Health: Determinants of Health Preservation (HumEnHealth) under Program Contract of 8 December 2023, Class: 643-02/23-01/00016, Reg. no. 533-03-23-0006].

REFERENCES

1. Miličević A. The relationship between antioxidant activity, first electrochemical oxidation potential, and spin population of flavonoid radicals. Arh Hig Rada Toksikol 2019;70:134–9. doi: 10.2478/aiht-2019-70-3290
2. Miličević A, Novak Jovanović I. The relationship between the first oxidation potential and changes in electronic structures upon the electrochemical oxidation of flavonoids: Approach to *O*-glycosyl, galloyl and methoxy substituents. J Mol Liq 2021;335:116223. doi: 10.1016/j.molliq.2021.116223
3. Robinson HH, Kahn SD. Interplay of substituent conformation and electron affinity in quinone models of quinone reductases. J Am Chem Soc 1990;112:4728–31. doi: 10.1021/ja00168a017
4. de Almeida WB, Taguchi AT, Dikanov SA, Wraight CA, O'Malley PJ. The 2-methoxy group orientation regulates the redox potential difference between the primary (QA) and secondary (QB) quinones of type II bacterial photosynthetic reaction centers. J Phys Chem Lett 2014;5:2506–9. doi: 10.1021/jz500967d
5. Miličević A. Application of changes in atomic charges resulting from different electrochemical oxidation mechanisms for the estimation of the first oxidation potential of flavonoids. MATCH Commun Math Comput Chem 2022;88:67–78. doi: 10.46793/match.88-1.067M
6. Miličević A. Estimating flavonoid oxidation potentials: mechanisms and charge-related regression models. Arh Hig Rada Toksikol 2023;74:99–105. doi:10.2478/aiht-2023-74-3721

Corresponding author: Ante Miličević, Institute for Medical Research and Occupational Health, Ksaverska cesta 2, HR-10001 Zagreb, Croatia
E-mail: *antem@imi.hr*, ORCID: 0000-0003-1536-6278

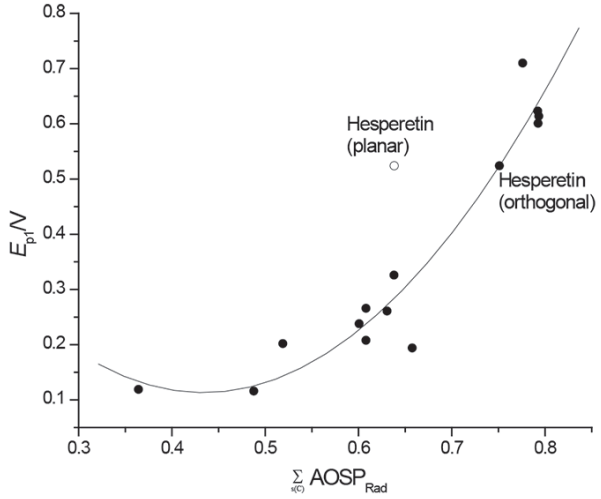

Figure 1 The dependence of experimental E_{p1} (pH = 7) on $\sum_{s(C)}$ AOSP$_{Rad}$, calculated using the PM6 method, for 14 flavonoids from (1). Empty circle represents $\sum_{s(C)}$ AOSP$_{Rad}$ of hesperetin calculated using methoxy group planar with the B ring plane [as in (1)]. When the methoxy group was set orthogonally to the B ring plane (filled circle), the $\sum_{s(C)}$ AOSP$_{Rad}$ of hesperetin fit the regression model, yielding R^2=0.930, SE=0.053, and SE_{cv}=0.069

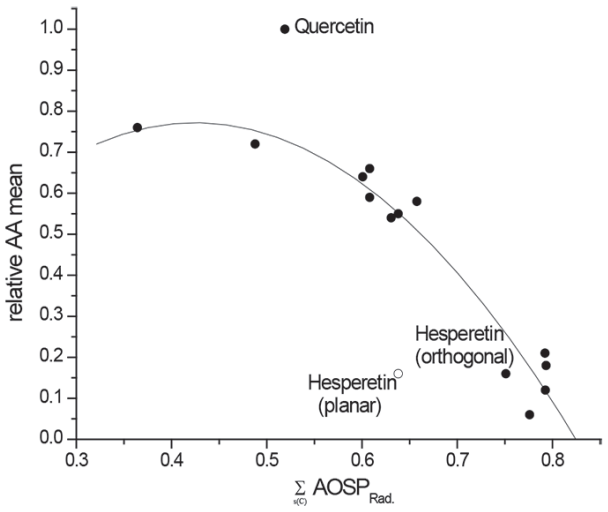

Figure 2 The dependence of experimental relative AA mean on $\sum_{s(C)}$ AOSP$_{Rad}$, calculated using the PM6 method for the set of 14 flavonoids from (1). Empty circle represents $\sum_{s(C)}$ AOSP$_{Rad}$ of hesperetin calculated using methoxy group planar with the B ring plane [as in (1)]. When the methoxy group was set orthogonally to the B ring plane (filled circle), the $\sum_{s(C)}$ AOSP$_{Rad}$ of hesperetin fit the regression model well, yielding R^2=0.942, SE=0.059, and SE_{cv}=0.073 (after exclusion of quercetin)