



# Free radical scavenging potency of quercetin catecholic colonic metabolites: Thermodynamics of $2\text{H}^+/2\text{e}^-$ processes



Ana Amić<sup>a</sup>, Bono Lučić<sup>b</sup>, Višnja Stepanić<sup>b</sup>, Zoran Marković<sup>c</sup>, Svetlana Marković<sup>d</sup>,  
Jasmina M. Dimitrić Marković<sup>e</sup>, Dragan Amić<sup>f,\*</sup>

<sup>a</sup> Department of Biology, Josip Juraj Strossmayer University of Osijek, Cara Hadrijana 8a, 31000 Osijek, Croatia

<sup>b</sup> Ruđer Bošković Institute, Bijenička 54, 10002 Zagreb, Croatia

<sup>c</sup> Department of Chemical-Technological Sciences, State University of Novi Pazar, Vuka Karadžića bb, 36300 Novi Pazar, Serbia

<sup>d</sup> Faculty of Science, University of Kragujevac, Radoja Domanovića 12, 34000 Kragujevac, Serbia

<sup>e</sup> Faculty of Physical Chemistry, University of Belgrade, Studentski trg 12-16, 11000 Belgrade, Serbia

<sup>f</sup> Faculty of Agriculture, Josip Juraj Strossmayer University of Osijek, Kralja Petra Svačića 1d, 31000 Osijek, Croatia

## ARTICLE INFO

### Article history:

Received 11 March 2016

Received in revised form 11 July 2016

Accepted 5 September 2016

Available online 13 September 2016

### Keywords:

Quercetin

Colonic metabolites

Catecholic compounds

Radical scavenging

Double HAT

Double SPLET

## ABSTRACT

Reaction energetics of the double ( $2\text{H}^+/2\text{e}^-$ ), i.e., the first  $1\text{H}^+/1\text{e}^-$  (catechol  $\rightarrow$  phenoxyl radical) and the second  $1\text{H}^+/1\text{e}^-$  (phenoxyl radical  $\rightarrow$  quinone) free radical scavenging mechanisms of quercetin and its six colonic catecholic metabolites (caffeic acid, hydrocaffeic acid, homoprotocatechuic acid, protocatechuic acid, 4-methylcatechol, and catechol) were computationally studied using density functional theory, with the aim to estimate the antiradical potency of these molecules. We found that second hydrogen atom transfer (HAT) and second sequential proton loss electron transfer (SPLET) mechanisms are less energy demanding than the first ones indicating  $2\text{H}^+/2\text{e}^-$  processes as inherent to catechol moiety. The Gibbs free energy change for reactions of inactivation of selected free radicals indicate that catecholic colonic metabolites constitute an efficient group of more potent scavengers than quercetin itself, able to deactivate various free radicals, under different biological conditions. They could be responsible for the health benefits associated with regular intake of flavonoid-rich diet.

© 2016 Elsevier Ltd. All rights reserved.

## 1. Introduction

Numerous epidemiological evidences throughout the years have indicated that regular consumption of food and beverages of plant origin is associated with a decreased incidence of cardiovascular diseases, cancer, and neurodegenerative diseases, which all in their etiology include oxidative stress (Del Rio et al., 2013). Natural plant products contain many macro- and micronutrients that may be responsible for their health promoting effects (Hollman, 2014). The beneficial effects of fruits, vegetables, grains, olive oil, red wine and tea have been mostly ascribed to polyphenols, ubiquitously present in plant kingdom. In the last decades, one of the most popular explanations of such effects has been ascribed to antioxidant activity of flavonoids, polyphenols present in many fruits and vegetables at concentrations in the low  $\mu\text{M}$  to  $\text{mM}$  range, and which possess strong *in vitro* free radical scavenging activity (Del Rio et al., 2013). This notion has been questioned and almost abandoned by studies of bioavailability, which indicate that

*in vivo* flavonoid concentrations in systemic circulation rarely exceed low  $\mu\text{M}$  values (Dangles, 2012; Hollman, 2014). Instead, it has been suggested that not parent flavonoid molecules but their metabolites can act as protectors against oxidative stress mediated diseases (Aura, 2008).

Only some 5% of ingested flavonoids are metabolized in small intestine (Clifford, 2004) and over 95% reach colon and undergo microbial metabolism (Duenas, Surco-Laos, Gonzalez-Manzano, Gonzalez-Paramas, & Santos-Buelga, 2011). Gut microbiota can hydrolyse flavonoid glycosides and their conjugates. They also perform degradation reactions of flavonoids such as C-ring cleavage, reduction, decarboxylation, demethylation, and dehydroxylation reactions (Selma, Espin, & Tomas-Barberan, 2009). The resulted metabolites may be potentially more biologically active than the parent compounds. Hydroxylated aromatic compounds can be formed from the A-ring and phenolic acids from the B-ring of flavonoids. Many of the structurally diverse food flavonoids are broken down into the common set of simpler phenolic compounds (e.g., hydroxybenzoic, hydroxyphenylacetic and hydroxyphenylpropionic acids) by action of colonic bacteria (Selma et al., 2009). For example, quercetin glycosides transform, *via* C-ring fission by gut

\* Corresponding author.

E-mail address: [damic@pfos.hr](mailto:damic@pfos.hr) (D. Amić).













