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LETTER TO THE EDITOR

Anthocyanins-based drugs for colon cancer treatment: the nutritionist's point of view

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Dear Editor,

The recent review from Thomasset et al. [1] contributes to the very animated debate in progress in the scientific community regarding the anthocyanin (ACN) health benefits.

Evaluating the ACN future development as cancer drugs, the authors correctly tackle the issue of ACN bioavailability as a crucial point. However, some authors' statements are questionable, particularly when they affirm that:

1. *"Protocatechuic acid…has recently been measured in human plasma at concentrations far in excess of the anthocyanin consumed"*. In the work, they cite [2], it was reported that protocatechuic acid (PCA) is the main human metabolite of cyanidin-3-glucoside (CyG) following to administration of blood orange juice containing mainly cyanidin-3-glucoside and cyanidin-3-(6′-malonyl) glucoside among anthocyanins and no trace of PCA. Anyway measured PCA was never far in excess of the anthocyanin consumed, as it accounted for about 72% of ingested CyG: 44% dose in serum and 28% in the faeces.
2. *"…formation* in vivo *of PCA as a major cyanidin glycoside metabolite seems to be species dependent, as it was not found in the biophase of rats on cyanidin-3-glucoside"*. This point is controversial, as the authors omit to mention the elegant pharmacokinetic study by Tsuda et al. [3], who reported the in vivo formation of PCA in rats following administration of cyanidin-3-glucoside. Wu et al. [4] have very recently shown that PCA is also formed in the gastrointestinal tract of pigs. Thus, to the best of our knowledge PCA is formed from CyG in three species (humans, rats and pigs). The fact that PCA is not retrieved in blood in 100% cases of CyG administration is likely due, apart from differences in the doses, food matrices and experimental model, by the fugitive nature of PCA. Storage conditions, pre-analytical treatments of biological samples and extraction procedure may principally account for this discordance. We also suggest the direct administration of PCA in rodents as an alternative approach to verify its chemopreventive ability.
3. "*Glucuronidated and methylated conjugates are major metabolites of anthocyanins*". Literature data show that glucuronidated and methylated compounds in urine and plasma account for less than 1% of ingested ACN [5]. Thus, the attribute of *major metabolites* to compounds found in a such negligible amount actually has no reason to exist, as recent advances in the field are highlighting the major contribute of ACN-derived phenolic acids, such as PCA for CyG.

We agree with the authors that cell culture studies, although sometimes helpful to elucidate potential chemoprotective mechanisms, have to be considered as a preliminary

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approach. Anymore, we suggest that a great attention has to be paid to their designing. Actually, cell culture studies testing ACN in their native forms, either as standards or as food extracts, are absolutely inappropriate [6]. The bioavailability and biotransformation issue has to be always considered when the health efficacy of compounds from oral administration on target organs is considered. They are ACN metabolites, rather than their native forms, that reach tissues and may exert biological effects. In this regard, we believe that PCA should merit a greater attention, as it has been demonstrated to have promising properties against colon cancer [7–10]. Considering that PCA is abundantly formed in the large intestine, in vitro studies testing PCA at physiologic doses in cellular model of colon cancer may provide preliminary interesting information on in vivo potential chemopreventive effect of CyG.

Conflict on interest statement None.

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