Letter to the Editor

Comment on 'Resveratrol in human cancer chemoprevention-choosing the 'right' dose'

I have read with great interest a recent publication in *Mol. Nutr. Food Res.* by E. Scott et al. entitled "Resveratrol in human cancer chemoprevention-choosing the 'right' dose" [1]. The paper raises number of very important points that are unfortunately mostly ignored in both preclinical and clinical research and thus may lead to confusing and misleading conclusions and reports and even expose human subjects to ineffective or unwarranted doses. The same points apply to many if not most natural products which are intended for use as dietary supplements, nutriceuticals, or pharmaceuticals. These misconceptions are further propagated by the press and find fertile ground in lay public which labors under a false perception that all natural products are safe by definition and more is better.

I agree with the authors discussion and suggestions and would only like to add few other limitations associated with in vitro studies which should also be kept in mind. Cell culture studies are almost exclusively done using only the parent compound in cells with very limited, if any, drug metabolism capability. Consequently, molecular targets are exposed to a constant concentration of the parent drug without metabolites. This situation differs from and may not adequately represent that in vivo. As opposed to this static in vitro drug exposure, plasma and tissue concentrations are time dependent. In vivo biological effects, efficacy and/or toxicity, may depend on the maximal concentration (Cmax), threshold concentration, or the total exposure over time (the area under concentration-time curve, AUC). It's important to understand the pertinent in vivo pharmacokinetic-pharmacodynamic profile in relevant animal species prior to attempting translation to humans. Metabolites may be in some part responsible for drug's biological activity or can modulate the activity of the parent compound or target's response to the parent compound, but they are commonly absent from the in vitro systems. As with resveratrol conjugates, they could have biological activity on their own or serve as a depot for the parent drug resveratrol. In addition, it's the free (not protein bound) concentration which is thought to be more pharmacologically and toxicologically important than the total (unbound plus protein bound) concentration; the latter only being commonly measured. Therefore when comparing the in vitro and in vivo concentrations, a more relevant comparison would be based on the free drug concentrations. Also, presence and viability of relevant influx and efflux transporters on cells in vitro may be an important factor in target exposure. These are by no means arguments against using in vitro studies, but only a caution how the results are interpreted and what conclusions are reached based on them. The same consideration are relevant for drugs and health indications in general, not limited to natural products and chemoprevention.

The author has declared no conflict of interest.

Reference

[1] Scott, E., Steward, W. P., Gescher, A. J., Brown, K. Resveratrol in human cancer chemoprevention – Choosing the 'right' dose. *Mol. Nutr. Food Res.* 2012, *56*, 7–13.

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