Vanillic Acid in Endometrial Carcinoma: A Role for Nitric Oxide?

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To the Editor

The recent article by Bhavani et al. [1], reported that vanillic acid (VA) should prevent the effect of the carcinogen N-methyl-N'-nitro-N-nitroso-guanidine (MNNG) on the induction of endometrial carcinoma in Albino female Wistar rats. The study showed that pre-treatment of animals with 100 mg/kg b.w of vanillic acid before the intra-vaginal introduction of 150 mg/0.2 ml olive oil (750 mg/ml) of MNNG, reduced by 70% the tumor incidence [1]. This reduction has to be most probably attributed to the effect of VA, as the protocol in which VA and MNNG were up-taken together by rats in the same experimental setting, did not succeed in reducing tumor incidence with the same extent [1]. The paper by Bhavani et al. [1], showed that VA fundamentally affected the plasma level of some markers of the oxidative stress response, i.e. reducing LOOH and SOD (lipid hydroperoxides and superoxide dismutase) and much more moderately affecting CYP450 (increase), CAT, GPx and GSH (decrease). VA appeared to better counteract plasma SOD reduction induced by MNNG but much less LOOH induced by MNNG-mediated oxidative stress [1]. Interestingly the authors did not seem to address the circadian mechanisms underlying the different levels of plasma SOD or other anti-oxidant markers and the influence of the surrounding environment or of neuro-metabolites from diet [2, 3].

Although VA resulted more efficacy in reducing MNNG-mediated effect if given to rats before the carcinogen, its biological activity did non recover completely the anti-oxidant marker levels observed in controls, an occurrence that has been reported also for metalloproteinases (MMP2, MMP9) and for cyclin D1 [1].

A possible interpretation should come from the evidence that vanillic acid, on l-NAME induced hypertensive rats, increases the expression of endothelial nitric oxide synthase (eNOS) and that, at least in humans, a suggestive correlation between hypertension and endometrial cancer has been reported [4, 5]. It would be very interesting to search for nitric oxide (NO) production in the experimental model published by Bhavani and co-workers. The role of nitric oxide might explain, for example, the systemic effect on SOD observed as an increase in its plasma levels. In the endothelia, eNOS and Cu/Zn SOD are rapidly induced and up-regulated to inhibit the ROS-mediated apoptosis during the shear stress in the endothelium. SOD from endothelia is easily available for plasma. Moreover, vanillic acid might inhibit the superoxide production in the endothelial tissue by modulating HO-1 and preserving the activity of NO. In this model, the production of NO might explain the VA-mediated increase of CYP450, as we should conceive also the existence in the CYP450 group of NOS, such as CYP3A and CYP4E. It is intriguing that VA slightly increases the microsomal cytochrome p450 fraction, increase that was observed, though higher, with MNNG [1]. The possible production of NO from endometrial cancer should be further addressed. NO is a gaseous mediator that may possess both promoting activity towards tumor as well as chemopreventive (anti-tumor) potential, depending on its timing location and the immune microenvironment [6, 7]. The paper by

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Bhavani et al., did not show significantly any direct action on VA on the many anti-oxidant markers, on TBARS, on metalloproteinases and on cyclins, yet, on the contrary, some paradoxical increase. Fundamentally, VA is able to inhibit the pro-carcinogenic effect of MNNG. It is tempting to speculate, on the basis of previous reports with a MNNG-induce gastric carcinogenesis model and the use of sodium nitroprusside, that a possible mediator to be further investigated is NO [8]. In this speculative hypothesis, to be verified, the signaling activity of NO is efficacious if rats were initially treated with VA, which may up-regulate tissue and endothelial NOS, which henceforth would inhibit the effect of the following MNNG. On the contrary, the concurrent intake of VA and MNNG, might slow this effect and give a much lesser extent of positive outcome.

It would be very interesting to reproduce this interesting research study by investigating also the role of nitric oxide in the model and following the different aspects of the circadian rhythms of plasma circulating anti-oxidant enzymes.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Bhavani P, Subramanian P, Kanimozhi S. Preventive efficacy of vanillic acid on regulation of redox homeostasis, matrix metalloproteinases and cyclin D1 in rats bearing endometrial carcinoma. *Indian J Clin Biochem*. 2017;32(4):429–36.
2. Cao H, Qin F, Liu X, Wang J, Cao Y, Tong J, Zhao H. Circadian rhythmicity of antioxidant markers in rats exposed to 1.8 GHz radiofrequency fields. *Int J Environ Res Public Health*. 2015;12(2):2071–87.
3. Sivaperumal R, Subash S, Subramanian P. Influences of aspartate on circadian patterns of lipid peroxidation products and antioxidants in Wistar rats. *Singap Med J*. 2007;48(11):1033–8.
4. Kumar S, Prahalathan P, Raja B. Vanillic acid: a potential inhibitor of cardiac and aortic wall remodeling in l-NAME induced hypertension through upregulation of endothelial nitric oxide synthase. *Environ Toxicol Pharmacol*. 2014;38(2):643–52.
5. Aune D, Sen A, Vatten LJ. Hypertension and the risk of endometrial cancer: a systematic review and meta-analysis of case-control and cohort studies. *Sci Rep*. 2017;7(7):44808.
6. Choudhari SK, Chaudhary M, Bagde S, Gadgil AR, Joshi V. Nitric oxide and cancer: a review. *World J Surg Oncol*. 2013;30(11):118.
7. Salimian Rizi B, Achreja A, Nagrath D. Nitric oxide: the forgotten child of tumor metabolism. *Trends Cancer*. 2017;3(9):659–72.
8. Iishi H, Tatsuta M, Baba M, Yamamoto R, Uehara H, Nakaizumi A. Inhibition of experimental gastric carcinogenesis, induced by N-methyl-N'-nitro-N-nitrosoguanidine in rats, by sodium nitroprusside, a nitric oxide generator. *Eur J Cancer*. 1998;34(4):554–7.