Hormesis, resveratrol and plant-derived polyphenols: some comments

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Hum Exp Toxicol published online 9 May 2011
DOI: 10.1177/0960327111408153

Human and Experimental Toxicology
000(00) 1–4

DOI: 10.1177/0960327111408153
het.sagepub.com

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Abstract

Hormesis is a dose–response phenomenon, usually present in plants and animals, characterized by a low-dose stimulation and high-dose inhibition, often resulting in typical U-shaped or J-shaped curves. Hormesis has become an interesting model for toxicology and risk assessment, as it has been described for several nature-derived phytochemicals but also because this adaptive response to stressors might hide an underlying more general behaviour of cell towards low doses.

Keywords

polyphenols, hormesis, quercetin, low doses

The recent debate on resveratrol dose–response published in the latest number of Human and Experimental Toxicology,[1–7] on the basis of an article by Mukherjee et al.[8] and by Calabrese et al.,[9] has expanded the long lasting issue about health benefits of low doses of natural substances even among the general population, whose abuse (high doses) is normally associated with health risks: although presenting strong cytoprotective and cardiovascular disease preventive effects, resveratrol, as well as other dietary polyphenols, can have negative consequences through the generation of more reactive and harmful metabolites, mainly because of the interaction with detoxification responses and gene induction effects due to uncontrolled nutritional supplementation.[10] Therefore, people are asking whether regular wine consumption is really useful for human health. The question remains unresolved even if a good answer probably was that of my father-in-law when he used to say *in vino veritas*, particularly when a good bottle of Amarone exalted a nicely laid table.

In this popular scenario, hormesis would appear as the scientific version of how a moderate life style can be healthy and this may actually be the view of most people. But why do most plant-derived polyphenols exhibit a hormetic mechanism? The biphasic behaviour attributed to resveratrol is not the only hormetic mechanism observed in polyphenolic plant-derived substances.[11]

Dietary consumption of vegetables is often associated with the prevention of damage by oxidative free radicals, with a reduced incidence of cancer, a reduction of neurodegenerative damage and of cardiovascular diseases, so the increase in dietary intake of fruit and vegetables, can prevent age-related decline in brain function and cognitive performance; moreover, many of these substances behave as good tools to prevent inflammatory and allergic affections.[11] What is intriguing is that most evidence has been reported for complex-chaotic systems such as the immune system, the brain and the heart.

The mechanisms through which antioxidants from diet may be useful to prevent free radical-related pathologies are related to their ability to counteract toxic production of both reactive oxygen and nitrogen species, along with the up-regulation of members of the heat shock protein (Hsp) family heme oxygenase-1 and Hsp70.[12] Actually, most of the hormetic property described for a plant-derived compound appears to be related with the anti-

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oxidant potentials of the latter, in the context of the cellular stress response and of so-called vitagenes, a group of genes which encode for Hsp Hsp32, Hsp70, the thioredoxin, and the sirtuin protein systems[12]; nevertheless, many other biphasic mechanisms concerning polyphenols have been described in literature. Hormesis is a biphasic dose–response relationship for which low doses display stimulation and high doses inhibition.[13] In colon cell lines HCT-116 and HT-29, the flavonol quercetin showed a biphasic modulation of cell proliferation, while on adenocarcinoma cell lines MCF-7 it promoted cell proliferation in the whole concentration range used.[14] Stimulation of cell proliferation by quercetin was related to the involvement of the estrogen receptor, as physiologically relevant concentrations of the flavonoid could exert phytoestrogen-like activity quite similar to that observed with other plant polyphenols, such as genistein.[15,16] Also another flavonoid, such as kaempferol, has been reported to posses a biphasic effect on human breast cancer cells: kaempferol might regulate a suitable level of estrogenic activity with a potential benefit in preventing estrogen imbalance pathologies, such as osteoporosis, breast cancer, cardiovascular diseases, and so on.[17] As with what concerns quercetin many biphasic mechanisms have been reported but this flavonol could interact synergistically with many pathways and molecular components, thus leading to the suggestion that a more complex picture of the biphasic behaviour of many polyphenolic compounds does exist.[18] Hormetic effects in the context of inflammatory and allergic mechanisms have also been reported: in human basophils triggered with bacterial formylated peptides quercetin exhibits a classical hormetic dose–response, reaching the stimulatory effect at nanomolar concentration ranges.[19,20] Although factors such as heme oxygenase-1 have been reported for the anti-allergic potential of quercetin,[21] the biphasic effect of quercetin on basophils has not been related to detoxifying mechanisms or to the up-regulation of heat shock family proteins.[20] What is interesting is that several toxic heavy metals act by a hormetic dose-responsiveness on the same intracellular targets reported for many polyphenols such as quercetin.[22,23] This evidence appears to assess the stress-response model of hormesis. Many plant polyphenolic compounds are actually considered as hormetic dietary phytochemicals: the state-of-art hypothesis is that these noxious substances, which in an evolutionary perspective should dissuade insects and other animals to eat plants, activate adaptive cellular stress response pathways.[24] This perspective claims for an assessment of the concept of hormesis in public health and addresses to improve research on this field. The low-dose zone of many molecules that are intrinsically noxious is not necessarily beneficial, however, for human health as many standard dose–response models show their failure in making accurate predictions of safety or health potentials of natural compounds.[1]

The biphasic effect observed with several polyphenolic compounds should be considered as a forthright hormetic mechanism? According to some authors[25] a need for a better definition of the concept of hormesis and a reappraisal of whether all biphasic dose–response curves should be considered representative for hormesis, should be addressed. Hormesis is a mechanism that probably should not be reduced to an adaptative cellular response but related to a more complex process of cellular homeodynamics: in the case of resveratrol, for example, one has to consider not only its effect on nitric oxide (NO) pathway but also the biphasic behaviour of NO in itself.[26,27] Biologists have to face low or very low concentrations on cell function as the starting point to comprehend such intriguing phenomena such as hormesis, as low doses are the playground of many cellular functions.[28] Many intracellular mechanisms are chaotic in nature and low doses might play a fundamental role in bifurcation phenomena and complex adaptive systems regulation, as these phenomena depend on timing, cell type and state.[29,30] So, it is arguable that cellular pre-condition would result in more complex effects on a cell as an oscillating system.[30,31,32] In this view, hormesis may lead to a profound contribution in the comprehension of biological systems: the question is pursued of whether there might be some new law of biology yet to be discovered, able to elucidate many paradoxical phenomena observed in literature. Although a general consideration might be forwarded taking into account that hormesis is restricted to phenomena that proceed by mechanisms that are broadly generalizable and represents possibly beneficial overcompensation in response to an adverse stimulus, thus highlighting the importance of hormesis in toxicology and risk assessment, many issues possibly suggest that hormesis may be the tip of an iceberg of a more general and complex function underlying cell biology and pharmacology.[33]

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

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