

CORRESPONDENCE/REBUTTAL

Comment on Safety and Antioxidant Activity of a Pomegranate Ellagitannin-Enriched Polyphenol Dietary Supplement in Overweight Individuals with Increased Waist Size

For researchers, it is a most interesting and rewarding experience to confirm the effects and discover the mechanisms of the health-enhancing power of traditionally valued foods. No doubt pomegranate fruit is such an asset. In the paper by Heber and collaborators (1), recently published in this journal, antioxidant properties, corresponding to a decrease of plasma thiobarbituric acid reactive substances after 4 weeks of daily ingestion of 1000 mg of a pomegranate ellagitannin-enriched polyphenol extract have been described. These results confirm previous reports of the antioxidant potential of pomegranate (2–4) not only *in vitro* but also *in vivo*, in mice and in humans (5).

Although pomegranate consumption has not been reported to possess deleterious health effects, apparent innocuousness cannot be simply extended to enriched pomegranate extracts. Heber et al. (1) reported no difference in adverse effects between pomegranate extract-treated and placebo groups, as well as no apparent treatment-related changes of clinical significance or laboratory results in the chemistry, hematology, or urinalysis testing. Moreover, they invoke the results of Farkas et al. (6) on the lack of interference of pomegranate juice with midazolam (as a probe for cytochrome P450 3A activity) to corroborate a lack of pomegranate juice–drug interaction. However, there is a case report describing that moderate pomegranate juice consumption might cause food–drug interaction (7). We stress that our group recently showed that continuous consumption of pomegranate juice decreases CYP 1A2 and 3A hepatic expression in mice (8). The consequences may be positive, for example, decreasing bioactivation of toxics such as aflatoxin B₁, benzo[*a*]pyrene, or other procarcinogens, or negative, as with decreased drug inactivation with toxicological consequences. Therefore, although an occasional, moderate consumption of pomegranate or pomegranate juice as regular food probably carries no problems and is instead beneficial to health, high dose and long-term ingestion, with “pharmacological” intention, needs much more investigation to avoid placing people at serious health risk. Consumption of very high levels of polyphenols can be deleterious, not only through effects on the cytochrome P450 enzymes but also through cytotoxic and apoptotic properties (3, 9). However, the human study on POMx by Heber et al. (1) used very moderate polyphenol

concentrations, which are equivalent to those used with pomegranate juice and with POMx, in mice and in humans with no adverse effects at all (5, 10).

It is important to understand why this is a hot topic. At this time, an increasing proportion of people around the world are more health conscious than ever before. This may be due to an increased awareness that the most prevalent diseases (i.e., obesity, heart disease, cancers, osteoporosis, arthritis, and type 2 diabetes mellitus) are preventable and probably also a continuous shift of the population toward a more advanced age. Along with age comes an increased incidence of disease and thus individual concern with the prevention and treatment of such disorders. A high medicine consumption by this population group adds much importance to putative drug–drug, food–drug, and dietary supplement–drug interactions.

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