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Letter to Editor Open Access

Comment on: Pomegranate Flower Extract Does Not Prevent Cisplatin-induced Nephrotoxicity in Female Rats

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DEAR EDITOR,

We read with interest the recently published letter[1] which was commented on an article previously published in the "International Journal Prevention Medicine" by Jilanchi *et al*., entitled "Pomegranate flower extract does not prevent cisplatin-induced nephrotoxicity in female rats." The author of the commentary letter has pointed to the results of Jilanchi *et al*. and concluded that phytoestrogens are the cause of aggravation or negative results response of pomegranate flower extract (PFE) on nephrotoxicity induced by cisplatin (CP) in female rats.[2] Here, we would like to discuss the results of the main paper[2] and explain about the commentary letter[1] written on the results of this article.

In the main experiment Jilanchi *et al*. designated 23 female rats into four groups and treated as follows. Groups 1 and 2 respectively received 25 and 50 (mg/kg/day) PFE, for 9 days, and cisplatin (CP) (2.5 mg/kg) daily from day 3 on. Group 3 was treated the same as Group 1 except saline instead of PFE, and Group 4 received PFE (25 mg/kg/day) alone. In this study, CP increased the serum blood urea nitrogen, creatinine, and nitrite levels; as well as kidney tissue damage score. PFE aggravated the renal tissue damage induced by CP.[1] As it was mentioned, in his letter related this effect to phytoestrogens present in PFE. Several studies have proven that oxidative stress contributes to not only CP but also a lot of other drugs induced renal toxicity.[3-8] In this regard, oxidative stress induces processes involved in chronic renal scaring such as inflammation, apoptosis, cell proliferation, and vascular injury. For example, mitogenesis, apoptosis of tubular and mesangial cells, and hypertrophy of tubular cells are mediated by oxidative stress. Oxidative stress induced by free radicals activates expression of the genes for inflammatory chemokines, selectin species, adhesion molecules, and pro-inflammatory cytokines. These are considered as processes closely related to vascular injury.[9] Furthermore, several studies have demonstrated that plants with antioxidant activity have positive effects in prevention and treatment of oxidative stress induced renal injury.[10-14] In fact various mechanisms have been considered by which reno-protection might be achieved, from them, anti-oxidative properties have been considered as one of the most important of them.[15-17]

More importantly, some phytoestrogens such as soy bean phytoestrogens have shown protective effects against oxidative stress induced renal injury.[18] Pomegranate is a potent antioxidant and therefore, other mechanisms seem to be involved in aggregative or negative effect of pomegranate in Jilanchi *et al*. (2014) study.[1] This possibility is discussed below:

Under certain conditions antioxidants may act as pro-oxidants and promote the oxidation of other compounds. The pro-oxidant activity of antioxidants is directly proportional to the total number of their hydroxyl groups. The pro-oxidant property of antioxidants seems to be concentration-dependent. The production of superoxide anion and lipid peroxidation is increased with increasing concentrations of flavonoid antioxidants. Furthermore, the antioxidant compounds were able to induce DNA strand breakage in a concentration-dependent manner. This effect might be explained by enhancing hydroxyl radical formation of flavonoids. The reported pro-oxidant activity has been related to the structural characteristics of these compounds.[19]

In rat liver microsomes, gossypol, quercetin, and myricetin powerfully inhibited iron-induced lipid peroxidation

at low micromolar concentrations (IC_{50} = 1.5 μM). However, all three compounds at 100 μM concentration increased the formation of hydroxyl radical up to eight-fold.[20] In a similar pattern, human leucocytes protection by quercetin against superoxide-induced oxidative DNA damage was ambiguous. So that quercetin at doses of 1–50 μM reduced the levels of oxidative DNA damage, however, at the high dose of 100 μM the damaging level was increased. Other studies have supported these results on quercetin in showing a pro-oxidant effect at 100 μM dose.[21] These paradoxical actions of antioxidants have been demonstrated by other antioxidant compounds.[1,22-25] Therefore, the lack of protective effect of pomegranate in CP induced nephrotoxicity seems to be the pro-oxidant activity of pomegranate extract or low dose of this plant extract.[26,27]

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