Dear Editor,

Genistein [4’,5,7-tri-hydroxyisoflavone or 5,7-dihydroxy-3-(4-hydroxyphenyl) chromen-4-one] is a plant-derived, hydrolyzed aglycone form of isoflavonoid, genistin (a glycoside) (Nayeem et al., 2019; Sansai et al., 2020). Genistein is mainly found in leguminous plants, especially in soybeans along with other important isoflavones, daidzein and glycitein (Kalaiselvan et al., 2010). Other sources of genistein include broad beans, chickpeas, vegetables, fruits, nuts, soy-based foods and genistein supplements. It has also been reported that unfermented soybeans contain more genistein than the fermented ones (Kuligowski et al., 2017; Li and Zhang, 2017). Further, genistein can be metabolically synthesized by introducing the IFS gene (isoflavone synthase gene) into yeast cells and rice lines, which results in an increased genistein content in rice (up to 30 folds) (Spagnuolo et al., 2015).

Plant flavonoids, especially isoflavonoids, have shown promising pharmacological properties to ameliorate diseases including cancer (George et al., 2016, 2017). Genistein exhibits various pharmacological properties including antioxidant properties, mainly by increasing the activity of antioxidant enzymes. It also has numerous clinical implications in the treatment and prevention of diseases like diabetes, cardiovascular diseases, cancer, and osteoporosis (Kalaiselvan et al., 2010). Genistein has been reported in exhibiting anti-angiogenesis property by regulating vascular endothelial growth factor 165 and matrix metalloprotease-2 and 9 in human bladder cancer cell lines (Su et al., 2005). Due to genistein’s high structural similarity to estradiol, the binding capacity of genistein to the estrogen receptor is notable and thus, genistein is mainly studied in postmenopausal women. Here, we have summarized the most recent findings on the pharmacological activities of genistein in clinical trials.
**Table 1: Recent findings on the pharmacological activities of genistein in clinical trials**

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<td>Higher intake of soy food mainly containing genistein along with other soy isoflavones by pregnant women before and during pregnancy was proved to decrease gestational diabetes mellitus occurrence among them.</td>
<td>Dong et al., 2020</td>
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<td>Genistein reduced blood glucose (fasting blood glucose), glycated hemoglobin, serum triglyceride and malondialdehyde levels in postmenopausal women with type 2 diabetes mellitus. Not much effect was seen on the bodyweight of postmenopausal women.</td>
<td>Braxas et al., 2019</td>
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<td>Genistein has the ability to increase the levels of genes that are responsible for regulating metastasis and cell mortality (MALAT1 and BASP1 respectively) in prostate epithelial cells. Genistein administration also decreased the level of HCF2 gene responsible for the cell migration. Increased levels of BASP1 and decreased levels of HCF2 in prostate tissue led to decreased prostate cancer cell invasion. It was also found that the levels of MEK4, a target of genistein, led to decreased cell motility and metastasis of human prostate cancer and was almost 50 % lower in the Chinese men’s prostate tissues when compared to those of US men, who were exposed to genistein for a short period of time in contrast to the Chinese men. Further, the levels of MMP-2 were increased in the Chinese men, where it should have been lower because of the direct proportionality of MEK4 and MMP-2 levels. Hence, it was concluded that the long term exposure of genistein alters the biomarker response profile in these populations and probably prevents/delays prostate cancer occurrence.</td>
<td>Zhang et al., 2019</td>
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<td>Upregulation of Plasminogen activator inhibitor 1, (PAI-1) leads to asthma exacerbations. Genistein is found to decrease the levels of TGF-β-1- induced PAI-1 in the epithelial cells of the airways in asthmatic patients with genotype 4G4G/4G5G and 5G5G.</td>
<td>Cho et al., 2019</td>
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<td>Serum calcium levels affects the action of genistein on bone mass density. When calcium levels were high, it was observed that genistein containing isoflavone increased the bone mass density.</td>
<td>Nayeem et al., 2019</td>
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<td>PhytoSERM contains an equal combination of 16.7 mg genistein, 16.7 mg daidzein, and 16.7 mg S-equol (to formulate a 50 mg tablet), which when given to postmenopausal women with associated vasomotor symptoms were established as a safe dose and did not elicit any adverse effects, but improved health conditions.</td>
<td>Schneider et al., 2019</td>
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<td>Oral treatment with genistein prior to chemotherapy with FOLFOX or FOLFOX-Bevacizumab in metastatic colorectal cancer patients has significantly reduced chemotherapy-related adverse events and was found to be safe and tolerable.</td>
<td>Pintova et al., 2019</td>
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<td>Genistein present in the isoflavone diet showed no changes in the fertilizability of sperm but showed mild changes in libido and testis function in rabbit bucks. This could be due to the antioxidant properties of isoflavones or other dietary components.</td>
<td>Hashem et al., 2018</td>
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<td>A 60 mg genistein supplementation with other isoflavones in menopausal women showed an increase in calcium level, decrease in chlorine level, lower albumin level and no effect on the sodium and potassium levels in their serum. Thus, calcium monotherapy with genistein containing isoflavones might decrease the risk of cardiovascular diseases. It was also noted that the genistein excretion is not a good predictor of chloride, calcium and albumin levels in the serum.</td>
<td>Lu et al., 2018</td>
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<td>90 mg of genistein given to postmenopausal women along with calcium and vitamin supplements showed not much beneficial effect on the levels of vitamin D and bone markers. Further, the group who received only calcium and vitamin supplements exhibited no effect on the markers of bone re-modeling.</td>
<td>Perez-Alonso et al., 2017</td>
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<td>Isoflavones containing 55 % of genistein, when administered to ischemic cardiomyopathy patients showed improvement in flow-mediated dilation, antioxidant activity, anti-inflammatory properties, and lipid profile. Moreover, the antioxidant properties were improved because of the increased levels of Nrf2-mediated antioxidant system. It was thus proved that the treatment with genistein was safe for ischemic cardiomyopathy patients.</td>
<td>Li and Zhang, 2017</td>
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Key findings

When genistein was given to patients with non-alcoholic fatty liver disease, it was noted that their insulin resistance was decreased as shown by a decrease in the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). Other observations included lower triglyceride level, decreased weight and body fat, and improved antioxidant property.

Postmenopausal women who were undergoing resistance training, when given soy protein containing 32 mg of genistein along with other isoflavones in soy milk, showed an increase in muscle strength but not much change in muscle mass.

When 54 mg of pure genistein was given to postmenopausal women suffering from metabolic syndrome, it was found that the ejection fraction of left ventricle was improved with no negative effects on the left ventricular chamber size or its function. It was also observed that increased adiponectin levels are most likely the reason for the improved left atrial re-modeling.

30 mg treatment with genistein was found to decrease the methylation of many genes including ADCY4, NEU1, CYTSB, RBM28 in patients with localized prostate cancer. A reduction in MYC and PTEN activity further proved that these genes can be the targets of genistein for prostate cancer treatment. Some of these genes also showed varied gene expression profiles in the developmental processes, stem cell markers, proliferation, and transcriptional regulation.

When genistein was topically applied on postmenopausal women, the facial skin collagen (both type I and type III) levels were found to be increased. But when compared to the topical application of estradiol, genistein had inferior results.

Supplementation of soy drink containing genistein along with other isoflavones in nursing women resulted in increased isoflavone content (12 nmol/L) in the breast milk samples compared to the normal level. Further, there were no changes observed in the total antioxidant capacity of the breast milk.

When 54 mg of genistein along with calcium and vitamin D3 were given for over two years to postmenopausal women suffering from osteoporosis, it was observed that the bone mineral density and the bone turnover increased significantly in a time-dependent manner. This also led to a decreased fracture risk in these women.

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Conflict of interest

The authors declare no conflict of interest.

REFERENCES


