Genistein aglycone, one of the soy isoflavones, has been reported to be beneficial in the treatment of menopausal vasomotor symptoms, osteoporosis, and cardiovascular diseases, as well as in a variety of cancers. However, issues of potential harm on thyroid function resulting from soy isoflavones consumption have been raised. Much of the evidence for the goitrogenic effects of isoflavones is derived from experimental in vivo and in vitro studies. Goitrogenic effects were also noted in infants fed non-iodine-fortified, soy-based formula, a problem that was easily solved with iodine fortification. Recent studies suggest that genistein shows a good profile of safety on the thyroid although definitive conclusions have not reached. The aim of this brief review is to summarize and better clarify the effects of genistein on human thyroid health.

**Keywords**: genistein, isoflavones, soy, safety, thyroid
Genistein is also known as a potent, dose-dependent, inhibitor of tyrosine kinase (Ravindranath et al., 2004), as well as thyroid hormone deiodination mediated by 5′-iodothyronine deiodinase (Mori et al., 1996; White et al., 2004).

Using preparations of liver enzymes, Ferreira et al. (2002) found that flavonoids other than genistein inhibited 5′-iodothyronine deiodinase. Indeed, in vivo experiments with the synthetic flavonoid EMD 21388 (Schröder-van der Elst et al., 1991), which inhibits thyroid hormone binding to plasma transthyretin, show a reduction of T3 content in tissues that express type II 5′-iodothyronine deiodinase.

More recently, Šosić-Jurjević et al. (2010) showed that a subcutaneous injection of 10 mg/kg of genistein or daidzein can disturb the pituitary-thyroid axis, causing hypothyroidism in orchidectomized middle-aged rats.

However, overall in vitro and in vivo data from animal studies are not easily to compare with data from human studies, as demonstrated by a recent paper (Sethell et al., 2011).

**HUMAN STUDIES**

In humans, early studies showed that feeding infants with soy milk caused goiter in those with inadequate iodine intake even if this effect was reverted by iodine supplementation (Chorazy et al., 1995; Jabbar et al., 1997). Moreover, of 530 children aged 6–15 years living in iodine-deficient areas of India and consuming large amounts of flavonoids, almost all were goitrous (Brahmbhatt et al., 2000). This enormous rate of thyroid enlargement led the authors to conclude that goiter was due to the combined effect of iodine deficiency and flavonoid excess in their diet (Brahmbhatt et al., 2000).

A more recent human trial reports the effects of short-term soy consumption on thyroid parameters in relation with isoflavone levels in male and female healthy subjects (Hampl et al., 2008). After 7 days of soy consumption, levels of both genistein and daidzein were increased. The statistically significant relationships found at the end of soy consumption were: (i) between basal levels of diadzein and thyrotropin, (ii) between diadzein and antithyroglobulin in males, and (iii) between diadzein and free thyroxine in females. Genistein lacked any correlation with the above thyroid parameters. These results agree with a previous research in 268 children (Milević et al., 2005). The authors investigated whether serum levels of genistein and diadzein were correlated with thyroid hormone function. This study showed only a modest association between isoflavones serum levels and parameters of thyroid function, such as free thyroxine, thyroglobulin antibodies, and thyroid volume.

It is well known that thyroid diseases are most common in women, especially during perimenopause and menopause, perhaps as consequence of an altered balance between estrogens and progesterone. Accordingly, the effects of genistein on thyroid function were also analyzed in postmenopausal women. Results from a 3-month study in postmenopausal women consuming an isoflavone-rich diet (containing 58% of total genistein) showed no significant effect of isoflavones on serum levels of thyroid hormones (Duncan et al., 1999).

Bruce et al. (2003) investigated thyroid function in 38 iodine-repleted postmenopausal women at baseline and after 90

![FIGURE 1| Chemical structure of genistein and estradiol.](image-url)
and 180 days following supplementation with 90 mg (aglycone weight) of total isoflavones/day. Thyroid parameters did not differ between the placebo and the treatment arm.

In a 16-week duration study, 77 postmenopausal women were randomized to receive cow’s milk and a placebo supplement, soy milk and placebo supplement, or cow’s milk and isoflavone supplement. The results showed that daily consumption of isoflavones did not affect the expression of thyroid hormones, as indicated by serum TSH levels that remained within the normal range following the intervention period in all women; cognitive functioning in healthy postmenopausal women was also unaffected. A more recent clinical trial in postmenopausal women evaluated the effects of 3-year administration of pure genistein aglycone (94 mg/day) on thyroid-related markers (Bitto et al., 2010). Specifically, changes in thyroid hormone receptors expression, serum levels of thyroid hormones, and thyroid antibodies were assessed. The results showed that daily consumption of genistein aglycone did not modify circulating FT4, FT3, and TSH levels or thyroid antibodies. Furthermore, genistein aglycone administration over 3 years did not affect the expression of thyroid hormone receptors in peripheral blood mononuclear cells, thus confirming that genistein appears not to alter thyroid function in postmenopausal women.

A 12-week duration randomized, double-blind and placebo-controlled trial in 43 oophorectomized Indian women evaluated the effect of 75 mg/day soy isoflavones (genistein and genistin 25%)

daidzein and daidzin 15%) on serum levels FT3, FT4, TSH, TBG, and anti-TPO antibodies (Mittal et al., 2011). The only variation found was a modest decrease in serum FT3.

Finally, a recent study in men with localized prostate cancer addressed the safety of genistein in the male gender (Lazarovic et al., 2011). Genistein was administered at the dose of 30 mg/day for 3–6 weeks prior to prostatectomy, and thyroid hormones levels were measured as secondary outcome. Serum levels of thyroid hormones remained statistically unchanged.

CONCLUSION

Overall, there is a scarcity of information about the effect of pure isoflavones, such as genistein, on thyroid safety in humans. Results of intervention trials are not easily comparable because the researchers have used (i) mixed isoflavones or isoflavone and protein mixtures with different dosage regimes, soy foods or supplements as the active treatment; (ii) the quality and amount of genistein varied widely in all of these previous studies; and (iii) the trials were of different duration. Although the overall evidence suggests that isoflavone genistein does not affect adversely thyroid function in euthyroid, iodine-replete individuals, further studies are warranted to better define the relationship between genistein and thyroid.

Infants and women deserve particular attention in order to assess the safety of genistein and/or other isoflavones on thyroid function, also considering that thyroid disorders are age- and gender-related.

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