Exploring the Safety of S-Equol

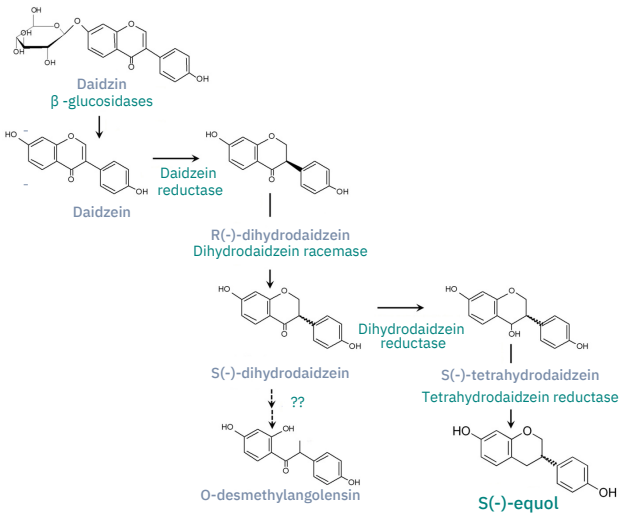
Use of complementary and alternative methods to address symptoms associated with menopause has grown exponentially in recent years, with several surveys reporting up to 50% of women use some form of this care[1]. In addition to critically evaluating the efficacy of dietary supplements purported to offer menopause symptom relief, it is paramount to assess their safety. Here, we review the safety profile of S-Equol, delving into its origins, mechanism of action, benefits, and potential interactions.

Understanding S-Equol

The soybean has been cultivated by humans for over 4500 years, indicating that humans have been consuming isoflavones found in soy-based products for several millennia[2].

S-Equol is an intestinal bacterial metabolite of the soybean isoflavone daidzein. This compound, initially discovered in mare's urine in 1932 gained significant clinical interest in the 1980s[3].

Metabolism of the isoflavone glucoside daidzein by the human gut microbiota and equolbiosynthesis pathway[4]

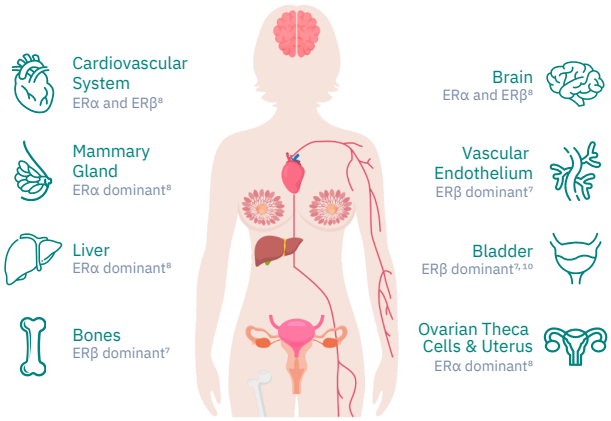


S-Equol exists in two chiral forms: R-(+)equol and S-(–)equol. It is naturally generated in some individuals through the metabolism of daidzein by intestinal bacteria, predominantly in the distal segments of the small intestine and colon[4]. However, only 25-50% of human subjects are deemed "equol producers"[5], showcasing its selective presence.

The Role of S-Equol in Health

Crucial to its significance, S-Equol exhibits estrogenic effects. This enantiomer shares structural similarities with the primary endogenous estrogen estradiol and binds to estrogen receptors (ERs).

While, S-(-)equol displays affinities for both ERα and ERβ, it notably binds more strongly to ERβ with a low binding affinity for ERα - in fact, it possesses a 13-fold higher affinity for ERβ over ERa[6].



Due to its binding affinity, S-Equol exerts multiple benefits for menopause symptom relief, including improvements in hot flash frequency, mood swings, vaginal irritation, sleep quality, and healthy bone support[a,11-13].

S-Equol Safety

An assessment of S-Equol's safety reveals important distinctions from estradiol. While estradiol binds with similar affinity to both ERα and ERβ, S-equol preferentially binds to the latter. As noted earlier, its

preference for binding to ERβ, with reduced affinity for ERα, holds implications for physiological effects. Because ERα is dominant in the uterus and breast, organs with safety concerns associated with estrogen use, an ERβ-selective compound is thought to offer a better safety profile[14]. Additionally, in breasts, ERβ activation inhibits the proliferative effects of ER α activation - a potential benefit[3].

Pharmacokinetic studies have shown S-equol is rapidly absorbed and highly bioavailable, with maximum plasma concentrations occurring between 1-3 hours after oral administration, and clearance with a half-life of 7-10 hours[3]. Over 80% of S-Equol is excreted in the urine within 24 hours after administration[3].

S-equol is generally well-tolerated in clinical studies with a duration of up to one year without serious adverse events associated with its use[12,14,15]. No effect on the reproductive organs (uterine endometrial thickness and cytological analysis of vaginal epithelium) and mammographic breast density was observed in the two studies which included these endpoints[3]. Furthermore, no notable changes in hormone levels were reported in a recent review[3].

The safety of S-equol is supported by a variety of in vitro and in vivo safety studies, including genotoxicity, acute and subchronic toxicity studies, and reproductive and developmental toxicity tests[16,17].

Potential Interactions and Contraindications

Prudent use of dietary supplements is always important, especially considering potential interactions with medications. The calcium present in Equelle may cause a decrease in absorption of thyroid medication, such as levothyroxine, thus it is important to space such medication intake apart from supplement consumption.

S-equol use is cautioned during pregnancy and lactation, due to insufficient information in this population. It is also contraindicated with soy allergy.

S-Equol is a Safe Dietary Supplement for Menopause Symptom Relief[a]

Healthcare professionals play a critical role in guiding patients towards safe solutions. S-equol is a safe dietary supplement recommended for the management of symptoms associated with menopause[a].

Healthcare professionals can feel confident that Equelle, a supplement made with S-Equol, from the makers of Nature Made, is committed to quality assurance and ensuring that rigorous safety standards are continuously met.

a. These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease

1. Posadzki, P., Lee, M. S., Moon, T. W., Choi, T. Y., Park, T. Y., & Ernst, E. (2013). Prevalence of complementary and alternative medicine (CAM) use by menopausal women: a systematic review of surveys. Maturitas, 75(1), 34–43. https://doi.org/10.1016/j.maturitas.2013.02.005

2. Kiple, Kenneth F., and Kriemhild Coneè Ornelas, eds. The Cambridge world history of food. Vol. 2. Cambridge University Press, 2000

3. Utian WH, Jones M, Setchell KD. S-equol: a potential nonhormonal agent for menopause-related symptom relief. J Womens Health (Larchmt). 2015 Mar;24(3):200-8. doi: 10.1089/jwh.2014.5006. Epub 2015 Feb 18. PMID: 25692726.

4. Mayo B, Vázquez L, Flórez AB. Equol: A Bacterial Metabolite from The Daidzein Isoflavone and Its Presumed Beneficial Health Effects. Nutrients. 2019 Sep 16;11(9):2231. doi: 10.3390/nu11092231. PMID: 31527435; PMCID: PMC6770660.

5. Setchell KD, Clerici C. Equol: pharmacokinetics and biological actions. J Nutr. 2010 Jul;140(7):1363S-8S. doi: 10.3945/jn.109.119784. Epub 2010 Jun 2. PMID: 20519411; PMCID: PMC2884334.

6. Muthyala RS, Ju YH, Sheng S, Williams LD, Doerge DR, Katzenellenbogen BS, Helferich WG, Katzenellenbogen JA. Equol, a natural estrogenic metabolite from soy isoflavones: convenient preparation and resolution of R- and S-equols and their differing binding and biological activity through estrogen receptors alpha and beta. Bioorg Med Chem. 2004 Mar 15;12(6):1559-67. doi: 10.1016/j.bmc.2003.11.035. PMID: 15018930.

7. Nilsson S, Gustafsson JÅ. Clin Pharmacol Ther. 2011;89(1):44-55.

8. Pearce ST, Jordan VC. Crit Rev Oncol Hematol. 2004;50(1):3-22.

9. Kauffman EC, et al. Oncol Rep. 2013;30(1):131-138. doi:10.3892/or.2013.2416

10. Sen A, et al. Immunobiology. 2021;226(1):152020

11. Data on File. 1811 Study Report; Pharmavite LLC.

12. Tousen, Yuko, et al. "Natural S-equol decreases bone resorption in postmenopausal, non-equol-producing Japanese women: a pilot randomized, placebo-controlled trial." Menopause 18.5 (2011): 563-574.

13. Jenks BH, Iwashita S, Nakagawa Y, et al. A pilot study on the effects of S-equol compared to soy isoflavones on menopausal hot flash frequency.

14. Jackson, Richard L., et al. "Single-dose and steady-state pharmacokinetic studies of S-equol, a potent nonhormonal, estrogen receptor β-agonist being developed for the treatment of menopausal symptoms." Menopause 18.2 (2011): 185-193.

15. Natural Medicines. (Accessed 2023, August 17). Equol [monograph]. http://naturalmedicines.therapeuticresearch.com

16. Yee S, Burdock GA, Kurata Y, et al. Acute and subchronic toxicity and genotoxicity of SE5-OH, an equol-rich product produced by Lactococcus garvieae. Food Chem Toxicol 2008;46:2713-2720.

17. Matulka RA, Matsuura I, Uesugi T, Ueno T, Burdock G. Developmental and reproductive effects of SE5-OH: an equol-rich soy-based ingredient. J Toxicol 2009;2009:307618.