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Review

# Phytosteroids beyond estrogens: Regulators of reproductive and endocrine function in natural products

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ABSTRACT

Foods and botanical supplements can interfere with the endocrine system through the presence of phytosteroids – chemicals that interact with steroids receptors. Phytoestrogens are well studied, but compounds such as kaempferol, apigenin, genistein, ginsenoside Rf, and glycyrrhetinic acid have been shown to interact with non-estrogen nuclear receptors. These compounds can have agonist, antagonist, or mixed agonist/antagonist activity depending on compound, receptor, cell line or tissue, and concentration. Some phytosteroids have also been shown to inhibit steroid metabolizing enzymes, resulting in biological effects through altered endogenous steroid concentrations. An interesting example, compound A (4-[1-chloro-2-(methylamino)ethyl]phenyl acetate hydrochloride (1:1)) is a promising selective glucocorticoid receptor modulator (SGRM) based on a phytosteroid isolated from *Salsola tuberculatiformis Botschantzev*. Given that $6.9 billion of herbal supplements are sold each year, is clear that further identification and characterization of phytosteroids is needed to ensure the safe and effective use of botanical supplements.



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## 1. Introduction

Phytosteroids are a class of specialized metabolites derived from plants that bind to steroid receptors in animals and can trigger or

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repress downstream receptor-mediated signaling events. Phytosteroids have diverse structures, sometimes very different from the endogenous steroid (Fig. 1); yet they can act as agonists, antagonists, or frequently have mixed agonist/antagonist activity for steroid receptors (Lesovaya et al., 2015; Toh et al., 2012). In addition, some phytosteroids interact with multiple steroid receptors (Pihlajamaa et al., 2011) or interfere with steroid metabolizing enzymes (Blachley and Knochel, 1980), thus having complex effects on the endocrine and reproductive systems.

## 2. Herbal and dietary effect on fertility

Botanicals have been used to treat disease and control reproduction for centuries (Noumi and Tchakonang, 2001; Yun, 2001), a phenomenon that continues, as evidenced by the growing market for dietary herbal supplements (Smith et al., 2016). Phytosteroids have the potential to interfere with multiple aspects of the endocrine system, with early examples involving reduced fertility (Bennetts et al., 1946; De Lange, 1961). The first phytosteroids were reported when it was found that sheep grazing on subterranean clover in western Australia suffered from reduced fertility (Bennetts et al., 1946). Since then, molecules that activate the estrogen receptor (phytoestrogens; typically isoflavones, lignans, and coumestans) have been identified as steroidogenic constituents responsible for reduced fertility (Adams, 1995; Hughes, 1988). In a study examining the effects of caffeine on fertility, high consumption of tea was associated with double the frequency of pregnancies, while caffeine or other caffeinated drinks had no effect (Caan et al., 1998). A double-blinded placebo-controlled study of the herbal supplement FertilityBlend® found that the herbal supplement increased the pregnancy rate likely through enhanced luteal phase progesterone concentration increases in women trying to conceive (Lm et al., 2005). However, since herbal supplements likely influence reproductive biology in multiple ways, more research is required to identify the mechanisms responsible and determine whether these effects are the result of steroid receptor signaling (Dennehy, 2006).

Identification of novel phytoestrogens and characterization of their biological activities continues to be an area of active research (Nie et al., 2015). A thorough literature search reveals that many other phytosteroids exist and bind the progesterone, androgen, and corticoid receptors. However, though their potential biological activities have been characterized to widely varying degrees.

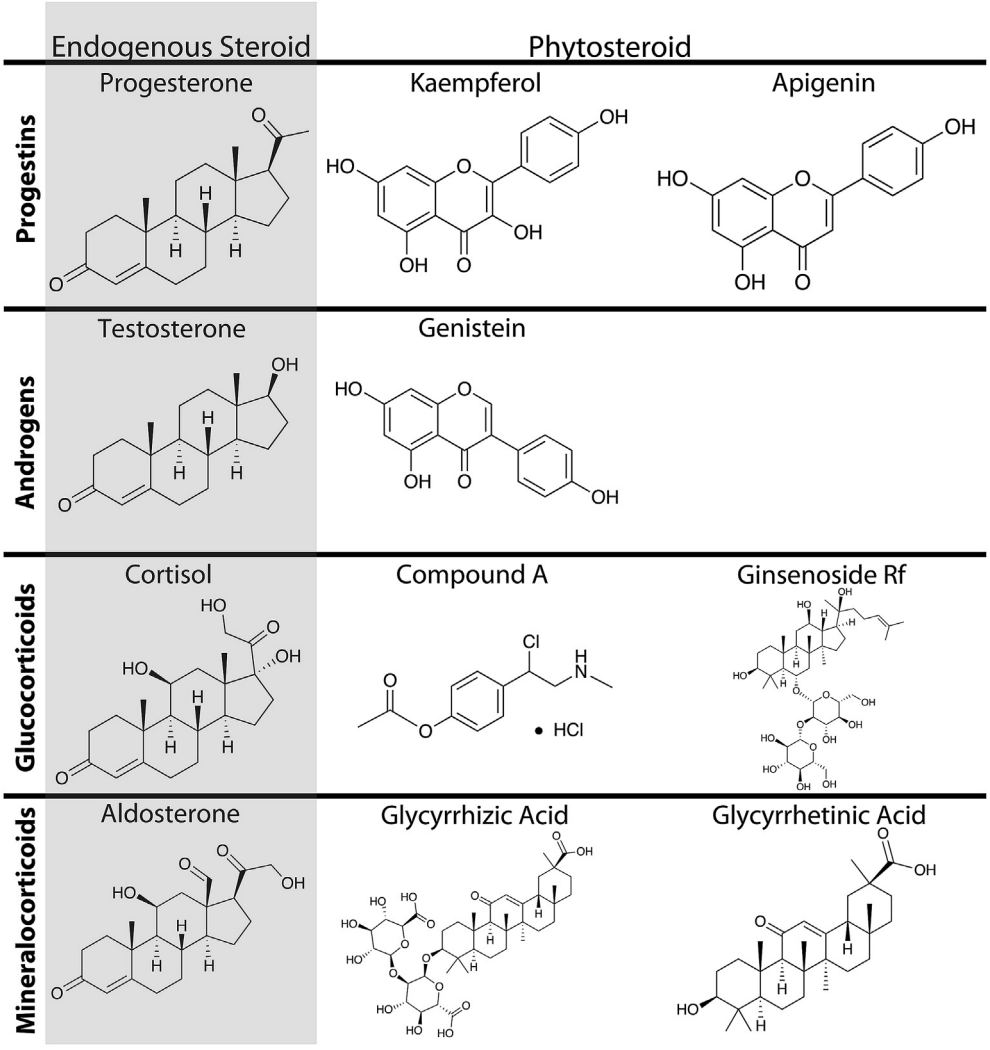


**Fig. 1.** Structure of the major endogenous steroid in each class, the phytosteroid(s) best supported by scientific literature, and compound A (4-[1-Chloro-2-(methylamino)ethyl] phenyl acetate hydrochloride (1:1)) a synthetic compound based on a phytosteroid.