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Review

# The impact of phytoestrogens on sexual behavior and cognition in rodents

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ABSTRACT

Phytoestrogens have the potential to influence the effects of other endocrine active-compounds by altering an individual's reproductive development, sexual behaviors, and performance on cognitive tasks. Thus, the following literature review focuses on studies involving the effects that dietary phytoestrogens have on the reproductive behaviors and cognitive abilities of rodents. We found that the bulk of the literature that focused on the cognitive abilities and reproductive behavior of individuals exposed to dietary phytoestrogens does not provide a clear pattern of their effects. We suggest that the mixed results of many studies may be attributed to differences in the type of phytoestrogen administered, the length of time of its administration, the amount or phytoestrogen, the species tested, the sex and hormonal milieu of the subjects, if the exposure to phytoestrogens occurred during gestation, lactation, or adulthood, and if the subject is an herbivore or omnivore. Based on our review, we have provided information that is needed to formulate several testable hypotheses about the effects of phytoestrogens on sexual behaviors and cognitive abilities in rodent species.



## Introduction

Interest in the biological functions of phytoestrogens has increased in recent years because they have been linked to many aspects of human health, including tumor reduction and/or prevention (Setchell 1998) as well as the management of menopausal symptoms (Brzezinski and Debi 1999; Murkies et al. 1995, 1998; Patisaul et al. 1999; Patisaul and Whitten 2005; Wiseman 2000). Several studies have found that people whose diets are rich in soy content, a known source of phytoestrogens, have a lower incidence of breast cancer, osteoporosis, and diabetes (Bhathena and Velasquez 2002; Patisaul and Jefferson 2010) compared to those consuming diets that are lower in soy content (Adlercreutz and Mazur 1997; Brzezinski and Debi 1999). The risk of developing these diseases often rises in women when they go through menopause, and treatments usually involve hormone replacement therapy (Peet 2009). However, long-term hormone replacement therapy carries its own health risks, such as heart disease (Grady et al. 2000; Scharbo-Dehaan 1996), causing many women to search for safer alternatives such as consuming a diet rich in soy or other phytoestrogen dietary supplements (Glazier and Bowman 2001).

Phytoestrogens also have the potential to affect other endocrine active-compounds by their action in altering reproductive development and behavior (You et al. 2002; Lephart et al. 2004). Consequently, much work has focused on the cognitive abilities and reproductive behavior of individuals exposed to dietary phytoestrogens. However, despite this focus, there is little consensus as to the effects of phytoestrogens on reproductive physiology, sexual behavior, and cognition. Much of the lack of consensus is a result of the fact that there are several different types of phytoestrogens and many of their effects differ from one another. Another contributing factor is that males and females often respond differently to phytoestrogens. Moreover, researchers use different methodologies to test the effects of phytoestrogens on behavior. Such differences may include the sex and species selected as the model, whether or not it eats large or small quantities of plant materials that contain phytoestrogens, the phytoestrogen(s) administered to the animal, the amount that was provided to the animal, the length of the treatment, the age of the animal, and its hormonal milieu.

We have three goals in this review. Our first goal was to summarize the findings of selected studies involving the effects that dietary phytoestrogens have on the reproductive behaviors and cognitive abilities of rodents to provide a theoretical framework for future studies. To meet this goal, we first provide a classification for phytoestrogens. We use this classification to discuss the results of experiments that examined the effects of specific phytoestrogens on the three components of sexual behavior: attractivity,

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proceptivity, and receptivity of rodents. We then discuss the effects of phytoestrogens on the performance of rodents on cognitive tasks. Our second goal was to use the results of the empirical studies to create summation points that may be used to develop broad testable hypotheses that examine the effects of phytoestrogens on specific sexual behaviors and cognitive abilities in rodents. Our final goal was to suggest potential areas of research that would involve examining the impact of phytoestrogens on the social behavior, communication, and higher levels of cognition and mate choice in rodents.

## Phytoestrogen classification

Phytoestrogens are nonsteroidal compounds produced by plants that have chemical structures similar to those of natural or synthetic estrogenic compounds (Kurzer and Xu 1997), particularly 17β-estradiol, an endogenous hormone in mammals that is important to reproduction (Adeoya-Osiguwa et al. 2003) and cognition (Barha et al., 2010; Janicki and Schupf 2010). These phytochemicals can be divided into four main categories: isoflavones, coumestans, stilbenes, and lignans (Kurzer and Xu 1997; Murkies et al. 1998). Isoflavones are primarily soy-derived and are the most abundant and potent phytoestrogens found in nature (Boettger-Tong et al. 1998; Lephart et al. 2004). Consequently, they are the most widely studied of the phytochemicals. Well-studied isoflavones include genistein and daidzein, both of which affect development (Irvine et al. 1998; Casanova et al. 1999), sexual behavior (Kouki et al. 2003), and cognitive processes, such as learning and memory (Lephart et al. 2004). Equol, which is a major metabolite of isoflavones, also induces estrogen-like effects on the physiology and behavior of animals (Setchell et al. 2002). Coumestans, including coumestrol, which are found in plants such as clover, alfalfa, and broccoli (Knight and Eden 1995; Ziegler 2004) may antagonize the action of endogenous estrogens in rats (*Rattus norvegicus*) (Patisaul et al. 1999, 2003), but may also have a strong estrogenic effect on reproductive physiology in female rats (Kitts et al. 1983). Other studies, particularly those on sheep (*Ovis aries*) (Newsome and Kitts 1980), suggest that coumestrol has a weakly estrogenic effect on reproductive biology. Stilbenes are found in peanuts and the skin of grapes (Cornwell et al. 2004). The most widely studied stilbene is resveratrol, but few studies exist relating its effects on animal physiology (Cos et al. 2003). Resveratrol may be an estrogen agonist and capable of activating transcription of estrogen-regulated genes (Gehm et al. 1997). The last group of phytoestrogens is the lignans. Lignans are found in oilseeds such as flaxseed. Lignans such as enterolactone and enterodiol have similar effects as estradiol in inducing transcription (Carreau et al. 2008), but lignans do not induce female rats to enter into estrus (Kurzer and Xu 1997). Most work on lignans has focused on their putative effects on longevity and reduced cancer rates in humans (Adlercreutz et al. 1986, 1991).

Phytoestrogens are similar in structure to estrogens and capable of interacting with estrogen receptors, but they have lower affinity for these receptors relative to estradiol (Jacob et al. 2000; Luine et al. 2006; Patisaul et al. 2003; Santell et al. 1997; Whitten and Naftolin 1992). Thus, phytoestrogens have been classified as weakly estrogenic compounds and as endocrine disruptors (Ball et al. 2010; Lephart et al. 2004; Patisaul et al. 2003; Whitten and Naftolin 1992). Estrogen receptors are present in several areas of the body, including the cerebral cortex, pituitary, hypothalamus, amygdala, and hippocampus of the brain (Ciocca and Vargas Roig 1995) and in many areas of the reproductive tract (Pelletier and El-Alfy 2000). There are two subtypes of estrogen receptor in rats, mice (*Mus* spp.), and humans, called estrogen receptor α (ERα) and estrogen receptor β (ERβ), which differ in their affinity for various compounds (Kuiper et al. 1998; Morito et al. 2001). Phytochemicals have been shown to interact much more readily with ERβ than they do ERα (Kuiper et al. 1998), which is similar to the action of 17β-estradiol. This is important in that estrogen mediates the onset and maintenance of reproductive behaviors and the estrous cycle (Feder 1981) as well as performance in cognitive tasks (Belcher and Zsarnovszky 2001; Fink et al. 1996; Gillies and McArthur 2010; Rissman et al. 1997). Thus, some phytoestrogens may be capable of acting as estrogenic agonists or competitive antagonists (Morito et al. 2001; Mueller et al. 2004; Santell et al. 1997).

## The effects of phytoestrogens on sexual behavior

The effects of phytoestrogens on reproductive behavior have been studied in several different rodent models and the results of some of these studies are presented here. First, we will describe sexual behavior. Sexual behavior can be divided into three components: attractivity, proceptivity/interest in the opposite sex, and receptivity (Beach 1976). Attractivity refers to any behaviors and/or physiological conditions that an individual may present which act as stimuli to opposite sex conspecifics, relative to same sex conspecifics (Beach 1976). Proceptive behaviors are those displayed by individuals in order to show interest in opposite-sex conspecifics (Beach 1976; Johnston 1979). Attractivity and proceptivity establish communication between potential mates and allow them to coordinate behaviors that facilitate or inhibit direct interactions (Beach 1976; Ferkin 2011; Stopka and MacDonald 1998). Receptivity is characterized as an individual's willingness to mate with an opposite-sex conspecific (Beach 1976).

The majority of research on dietary phytoestrogens has been carried out using laboratory strains of rats and mice (*Mus domesticus*) and has produced mixed results. Zanoli et al. (2009) examined the sexual receptivity of female rats by calculating their lordosis quotient and the number of mounts made by the male. They also recorded hopping and darting behaviors of female rats, which are indicators of their proceptivity (Beach 1967). Zanoli et al. (2009) found that ovariectomized female rats treated with estradiol or the phytoestrogen ferutinin increased their sexual receptivity when compared to that of control animals. However, rats treated simultaneously with both estradiol and ferutinin displayed proceptive behaviors that were similar to those of control rats. In addition, ferutinin alone was not sufficient to increase the frequency of proceptive behaviors in ovariectomized rats (Zanoli et al. 2009), suggesting that the neuroendocrine substrates that mediate receptivity differ from those that mediate proceptivity. Zavatti et al. (2009) discovered that ovariectomized female rats treated simultaneously with estradiol and ferutinin displayed a lower frequency of lordosis and received fewer mounts by the male than did ovariectomized females treated with ferutinin alone. Zavatti et al. (2009) later found that both estradiol and ferutinin alone were capable of inducing partner preferences of ovariectomized Sprague-Dawley rats for male conspecifics. Interestingly, this study also reported that ovariectomized rats treated with ferutinin alone showed increased hopping and darting (proceptive behaviors) relative to ovariectomized females not treated with ferutinin, which contrasts with those results obtained by Zanoli et al. (2009).

Studies have also examined the role of the phytoestrogen resveratrol and isoflavones on sexual behavior of adult rodents. Henry and Witt (2002) found that both high and low amounts of resveratrol were insufficient in inducing ovariectomized female rats to increase their hopping and darting or their receptivity behaviors to those levels found among control ovariectomized rats that had been treated with estradiol. Patisaul et al. (2003) examined the effects of soy-derived isoflavones and the estrogen receptor modulator, tamoxifen, on the proceptive and receptive behaviors