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A Review of Phytoestrogens and Their Association with Pelvic Floor Conditions

Olivia Cardenas-Trowers, MD¹, Isuzu Meyer, MD², Alayne Markland, DO, MSc³, Holly E. Richter, PhD, MD², and Ilana Addis, MD, MPH¹

¹Tucson, Arizona, Department of Obstetrics and Gynecology, University of Arizona

²Birmingham, Alabama, Division of Urogynecology and Pelvic Reconstructive Surgery, Department of Obstetrics and Gynecology, University of Alabama at Birmingham

³Birmingham, Alabama, Birmingham/Atlanta Geriatrics, Research, Education, and Clinical Center (GRECC) at the Birmingham VA Medical Center, Departments of Medicine, Division of Gerontology, Geriatrics and Palliative Care, University of Alabama at Birmingham

Abstract

INTRODUCTION—Urinary incontinence (UI), pelvic organ prolapse (POP), and fecal incontinence (FI) are pelvic floor disorders (PFDs) disproportionately experienced by postmenopausal women. Limited data exists suggesting that phytoestrogens may have an impact on the pathophysiology and symptomatology of PFDs.

PURPOSE OF REVIEW—To review the current literature addressing the role of phytoestrogens on PFDs, including the pathophysiology, symptomatology, treatment, and possible prevention.

FINDINGS—Qualifying literature spans from 2003 to 2017 and included 14 studies ranging from in vitro, animal, and observational studies to randomized clinical trials.

SUMMARY—Although the literature is limited, most studies on phytoestrogens and PFDs support associations with pathophysiologic mechanisms, symptoms, and treatment for UI and POP, but not FI. Less is known regarding the prevention of PFDs with phytoestrogen intake over time. Overall, the potential influence of phytoestrogens on PFDs is not well understood and more research is needed.

Keywords

Phytoestrogens; isoflavones; lignans; pelvic floor disorders; urinary incontinence; pelvic organ prolapse; fecal incontinence; postmenopausal women

Corresponding Author: Olivia Orlanda Cardenas-Trowers, MD; Department of Obstetrics and Gynecology, University of Arizona, 1501 North Campbell Avenue, 8th Floor, Tucson, Arizona, 85724; Phone: 850-321-7502 (cell, preferred); Phone: 520-626-6636 (work); Fax: 520-626-1446; ocardenastrowers@obgyn.arizona.edu.

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Introduction

One in four women suffer from a symptomatic pelvic floor disorder (PFD) with 17% having moderate to severe urinary incontinence (UI), 9.4% fecal incontinence (FI), and 2.9% pelvic organ prolapse (POP).[1] The prevalence of PFDs is higher among peri-menopausal and postmenopausal women aged 60 years or older with prevalence rates ranging from 39-50%. [2] With the aging population, the prevalence of PFDs requiring treatment is expected to increase by 56% by the year 2050.[2] Because PFDs impair the quality of life of women affected by them, it is imperative to explore novel prevention and treatment options. Estrogen therapy has been investigated as a treatment modality for pelvic floor symptoms as estrogen receptors are present in the bladder, vagina, pelvic floor, and anal sphincter.[3-7] While oral estrogen worsens UI [8] and use of menopausal hormone therapy may have an effect on increasing FI rates after menopause [9], other studies reported inconclusive effects of oral and topical estrogen to improve FI symptoms [10, 11] and POP [12]. However, topical estrogen has shown to improve vaginal atrophy, overactive bladder, and UI symptoms in the setting of genitourinary syndrome of menopause (GSM).[13] In light of some of the benefits of estrogen, other sources of estrogen-like compounds, such as dietary estrogens, should be investigated as potential modulators of PFDs.

Phytoestrogens, also referred to as plant or dietary estrogens, are biochemically similar to estradiol. They are found in foods such as nuts, flax seed oil, soy products, cereals, breads, and legumes.[14] There are three major classes of phytoestrogens: isoflavones (e.g. daidzein and genistein), coumestans (e.g. coumestrol), and lignans (e.g. enterodiol and enterolactone). [15] Depending on their concentration and bioavailability in foods, phytoestrogens can act as estrogen agonists or antagonists.[16-18] Phytoestrogens have been explored as an alternative to traditional hormone replacement therapy for treatment of menopausal vasomotor symptoms, and more data are needed regarding risks and benefits.[19] This is especially relevant as the results of the Women Health Initiative (WHI) study showed an increased rate of thromboembolic events (VTEs), heart disease, and breast cancer in postmenopausal women taking oral estrogen and progesterone replacement.[19-21] Of note, only VTEs were increased in women in the estrogen only arm of the WHI study.[22] Given the biochemical similarity of phytoestrogens to current oral estrogen replacement (estradiol, estriol, and conjugated estrogen), phytoestrogens may be of use in treating or possibly preventing the development of pelvic floor symptoms and conditions.[19]

The objective of this review is to discuss the available literature on phytoestrogens and their potential role in the pathophysiology, association, and possible treatment and prevention of pelvic floor conditions, specifically UI, POP, and FI. Future research directions will also be discussed.

Methods

Medline/Pubmed, Cochrane, Scopus, and EMBASE databases were searched from Medline's date source year of 1966 to October 9, 2017 using combinations of the following key words: phytoestrogen, incontinence, prolapse, pelvic or pelvis, fecal or anal, urine or urinary, isoflavone, lignan, soy, daidzein, genistein, o-desmethyldangolensin, o-dma, equol,

enterodiol, enterolactone. The literature search was performed independently by the primary author and a certified research librarian. Resulting abstracts were screened for relevant associations of phytoestrogens and PFDs. The manuscripts of relevant articles, or the abstract if no manuscript was available, were reviewed by the group and included in this review. Inclusion criteria were (1) non-descriptive studies, (2) focus on peri- or postmenopausal women, (3) study of or intervention with a phytoestrogen, (5) evaluation of some aspect related to UI, pelvic floor support or prolapse, and/or FI. Studies were excluded if neither the abstract nor the manuscript were available in English. After review, there was limited data with wide variability in study content. Therefore, it was not feasible to perform a systematic review or meta-analysis.

Results

Phytoestrogens and Urinary Incontinence

The most commonly studied PFD in relationship to phytoestrogen use was UI. Nine published studies spanning 2003 to 2017 evaluated the influence of phytoestrogens on the pathophysiology, symptoms, treatment, and potential prevention of UI (Table 1). Of these, four were animal and in vitro studies and the other five were clinical studies in peri- and postmenopausal women. Table 1 includes specific data from these studies.

Due to estrogen receptors located in the bladder, vagina, and pelvic floor, and the influence of estrogen in connective tissue metabolism and biosynthesis, estrogen and selective estrogen receptor modulators (SERMs) have been investigated as possible treatment options for stress urinary incontinence (SUI) particularly with respect to their effects on peri-urethral tissue.[23] In 2003, an in vitro study from researchers in Poland demonstrated that both estradiol and the phytoestrogen, daidzein, increased pubocervical fascia fibroblast (PCF) proliferation compared to control fibroblasts harvested from peri-menopausal women with SUI.[23] The authors concluded that the results of their study support the theoretical use of local estrogen and/or phytoestrogens in an attempt to bulk the peri-urethral connective tissue in the treatment of female SUI.

Non-human primates, such as monkeys, are considered a good animal model to study PFDs because similar to humans, they have the ability to walk upright on two legs and have similar gravitational force vectors directed onto their pelvic floors.[24] In animal models, ovariectomized animals are considered analogous to postmenopausal women.[24] A 2008 study in ovariectomized cynomolgus monkeys showed that through a soy enriched diet, chronic (32-month) phytoestrogen treatment increased bladder detrusor muscle and proximal urethral contractile response to carbachol and electrical field stimulation. Other pharmacological stimulation with phenylephrine and endothelin-1 also resulted in significantly higher contractile response in the proximal urethra. A phytoestrogen diet resulted in a thicker and larger mucosal area in all three segments of the urethra compared to the control group.[24] The authors proposed that further studies be designed for human subjects as these findings may translate to treatment options for UI in postmenopausal women.

A 2010 study in ovariectomized mice demonstrated that dietary estradiol and phytoestrogens (equol, genistein, and puerarin) improved urethral closure pressure compared to a control group, adding to the evidence that estradiol and phytoestrogens could possibly be utilized as preventative or treatment options for UI in postmenopausal women.[25] In this study, mice were fed either a 3-month diet enriched with estradiol, equol, genistein, or puerarin. Urodynamics performed on the mice showed that bladder and urethral pressures were highest in the estradiol group followed by puerarin, equol, and then genistein treated animals (Table 1). Phytoestrogen and estradiol treatment resulted in consistently higher pressures in the urethra compared to the bladder during the filling period and in the filled status. Bladder pressure often exceeded urethral pressures in controls.

A long-term phytoestrogen diet in rats also mediated age-related reduced detrusor activity.[26] Similar to the 2008 study in cynomolgus monkeys, a 2011 study in ovariectomized versus sham operated Wistar rats showed that a soy diet was associated with increased bladder detrusor muscle contractile response in aged (52 week old) rats.[26] No change in bladder contractile response was seen in the young (12 week old) rats regardless of the surgery or soy diet. It should be noted that different from menopausal women, ovariectomy in this animal model is associated with decreased circulating progesterone, not estrogen, and should be taken into account when interpreting the data.

From the five clinical studies on phytoestrogens and UI in women, three were cohort studies and two were intervention studies. In the three cohort studies (two cross-sectional and one longitudinal), some evidence linking phytoestrogens to both UI symptoms and possible prevention of symptoms was found.[27] In a cross sectional, population-based cohort survey using the National Health and Nutrition Examination Survey (NHANES) data, the authors reported that increasing concentrations of urinary lignans (enterodiol and enterolactone) were associated with a decreased likelihood of UUI (OR 0.92, 95% CI 0.85-0.99) in postmenopausal women (n=1,789) (Table 1).[28] The authors concluded that lignan phytoestrogens may have a protective association with UI symptoms in postmenopausal women.

In a second cross-sectional population-based household survey of Brazilian women (n=749), the authors reported that current or previous use of soy products to treat menopausal symptoms was associated with a lower prevalence of UI (PR 0.43, 95% CI 0.24-0.78).[29] It is unclear if the study data was controlled for history of both estrogen and phytoestrogen use which might have affected these findings. No data was available for specific types of UI.

As a subset of the longitudinal Study of Women's Health Across the Nation (SWAN) (n=1,459 peri-menopausal women), the SWAN Phytoestrogen Study utilized study investigators to administer food frequency questionnaires to participants at baseline and subsequently at five and nine years.[27] On an annual self-administered questionnaire, participants reported the frequency and type of UI. Discrete proportional hazards models were used to evaluate if daily intake of phytoestrogens (four isoflavones, four lignans, and coumestrol) recorded from the visit preceding the first reported symptom of UI was associated with the development of monthly or more frequent UI versus remaining continent. Although neither low nor high levels of reported phytoestrogen intake were

associated with development of UI in peri-menopausal women, the study investigators recommended that future studies evaluate the influence of serum levels of phytoestrogens and their metabolites on UI.

In addition to the cohort study data, two studies reported efficacy data using phytoestrogen as a treatment for UI. In a small, randomized, cross-over trial comparing the effect of a 12-week soy-rich diet versus an isocaloric soy-free diet with 4-week washout period between treatments on urogenital symptoms in Thai women (n=36), the authors reported that urgency urinary incontinence (UUI) symptoms (0.14 ± 0.35 to 0.25 ± 0.50) and vaginal dryness (0.61 ± 0.84 to 0.92 ± 0.99) significantly increased after a 12-week soy-free diet ($p < 0.05$).

However, no symptom changes were observed with a soy-rich diet ($p > 0.05$). [30] Urogenital bother symptoms were based on a non-validated scoring system. Other urogenital variables, including the vaginal health index, vaginal pH, and vaginal cytology did not significantly change. The authors reported good study and diet compliance based on participants' serum isoflavones (daidzein and genistein) levels. Despite a reported significant worsening of UUI and vaginal dryness in the Thai women on a soy-free diet, the authors concluded that a soy-rich diet did not relieve urogenital symptoms. However, key differences at baseline existed with more women having UUI and vaginal dryness in the soy-free intervention group compared to women on the soy-rich diet. In their discussion, the authors stated that a longer treatment period (more than 12-weeks) could be more efficacious for improving urogenital symptoms.

According to a non-randomized single center open label study published in 2017, Dropsordry™, a compounded mixture containing phytoestrogens, reduced mean urgency score by 24.7%, nocturia by 69.4%, and the use of daily panty liners by 66.3% (all $p < 0.05$) in Spanish peri-menopausal women (n=82). [31] No significant difference was noted in the reduction of SUI (no data provided). After an 8-week treatment, 96% of women reported satisfaction with treatment and 92% reported improvement in quality of life. Of note, this study did not have a control or comparison group.

Phytoestrogens and Pelvic Organ Prolapse

Compared to the studies on phytoestrogens and UI, there was a paucity of information on phytoestrogens and POP. From this literature search, we report pathophysiologic data from four in vitro and treatment data from one clinical intervention study (Table 2). Much of the data on phytoestrogens and POP was reported by Tomaszewski, et al in Poland. [23, 32-34] In 2009, Tomaszewski, et al demonstrated that collagen type I levels in cultured pubocervical fascia (PCF) fibroblasts taken from a 56 year old menopausal woman suffering from SUI and POP increased after exposure to estrogen and the phytoestrogen, daidzein. [32] The same research group also demonstrated that PCF fibroblasts produced more type I collagen when exposed to estriol or daidzen regardless of the type of vaginal prolapse mesh applied. In the presence of monofilament mesh, there was a persistent increase in the peak procollagen type I N-terminal propeptide (PINP) concentration with estriol and daidzein, but not with estradiol. [32, 33] Compared to type I collagen, type III collagen only showed a persistent increased production by PCF fibroblasts in cultures containing monofilament mesh stimulated with estriol. Interestingly, the highest total type III collagen production was

observed in culture treated with tamoxifen regardless of the type of mesh.[34] Based on their findings of increased type I collagen production by PCF fibroblasts in the setting of estrogens and daidzein, Tomaszewski, et al concluded that these findings are an indirect rationale for local estrogen and/or phytoestrogen use for female SUI and/or POP.[32, 33]

In a 2016 in vitro and mice study, Iwanaga, et al demonstrated that both estradiol and a phytoestrogen diet increased expression of oxytocin receptors and had a significant impact on oxytocin receptor expression in the uterosacral ligament (Table 2).[35] Estrogen receptor alpha and oxytocin receptors are present in the uterosacral ligament.[35] Oxytocin receptors are involved in tissue regeneration in the body, and estrogen regulates the expression of the oxytocin receptor.[35] These findings further support estrogen and phytoestrogens as potential targets for POP prevention and treatment.

In the one POP treatment study, the phytoestrogen, puerarin, demonstrated therapeutic potential in improving POP symptoms in postmenopausal women.[36] Postmenopausal women with stage II-IV prolapse were divided into two groups, either treated with 0.429 mg/day puerarin versus placebo for 30 days (n=30 and 22, respectively). At the end of the 30-day treatment period (prior to surgery), POP symptoms were assessed using a non-validated score based on a POP-Q exam (defined as “positive” or “strongly positive” improvement in symptoms if 1+ or 2+ stage improvement was noted compared to baseline, respectively). After 30 days, those who were treated with puerarin had significant improvement of POP compared to controls (positive 57% vs. 0%, and strongly positive 35% vs. 0%, $p<0.05$). The women randomized to puerarin or placebo subsequently underwent surgical management of their prolapse where a tissue sample was collected for immunohistochemical analysis. This study showed that the expression of elastin positive rate ($9.8\% \pm 2.8\%$ vs $2.8\% \pm 1.3\%$, $p<0.05$) and collagen I/III ratio (1.1 ± 0.3 vs 0.5 ± 0.3 , $p<0.05$) were significantly increased in the puerarin group. Neuropeptide Y, vasoactive intestinal polypeptide, and transforming growth factor beta levels were also significantly increased compared to controls (all $p<0.05$, individual data not shown).

Phytoestrogens and Fecal Incontinence

No studies were found exploring the role of phytoestrogens on FI pathophysiology, symptoms, treatment or possible prevention.

Discussion

Systemic and topical estrogen therapy has been investigated for pelvic floor symptoms as estrogen receptors are present in the bladder, vagina, pelvic floor, and anal sphincter.[3-7] While oral estrogen worsens UI [8] and use of menopausal hormone therapy may have an effect on increasing FI rates after menopause [9], other studies reported inconclusive effects of oral and topical estrogen to improve FI symptoms[10, 11] and POP [12]. However, topical estrogen has shown to improve vaginal atrophy, overactive bladder, and UI symptoms in the setting of genitourinary syndrome of menopause (GSM).[13] The current literature is limited especially to compare the potential effects of traditional estrogen and phytoestrogen on pelvic floor symptoms.

Except for the in vitro studies, all studies evaluated ingested or dietary intake of phytoestrogens. The majority of the currently existing studies reported data on the potential impact of phytoestrogens on the pathophysiologic mechanisms and modulation of PFDs. Limited evidence also existed on the potential role of phytoestrogens in the treatment of PFDs and scarce data existed on the role of phytoestrogens in the prevention of PFDs. We did not find any evidence supporting the potential impact of phytoestrogens in the pathophysiology or treatment of FI symptoms. More research regarding pathophysiologic mechanisms, associations with symptoms, and response to treatment, especially for POP and FI, are warranted.

From a pathophysiologic role, based on in vitro and animal studies, phytoestrogens, similar to topical estrogen, appear to increase proliferation of the pubocervical musculo-connective tissue[23, 32] and increase the responsiveness of the bladder detrusor muscle and urethra[24-26]. From observational and small clinical studies evaluating dietary influences of phytoestrogens in women, less evidence existed regarding improvement in UI symptoms, except for reported improvement in nocturia[31]. Phytoestrogens could theoretically influence POP pathophysiology by increasing type I collagen production in the pubocervical musculoconnective tissue[32, 33], upregulating oxytocin receptor expression in the uterosacral ligaments[35] resulting in improvement in vaginal connective tissue quality[36]. As estrogen receptors are present in the anal sphincter and pelvic floor, it would be reasonable to investigate phytoestrogen use for FI.[4, 5] Overall, due to the small number of studies, we have noted that the influence of phytoestrogens on PFDs is still exploratory and not well understood.

With regard to the role of phytoestrogens in treatment and possible prevention of PFDs, future studies should consider collecting more data on the bioavailability and metabolism of phytoestrogens in women, as these biologic modulators could potentially affect treatment response.[37] Other important considerations are the safety profile and understanding possible adverse effects of phytoestrogens. Although oral estrogen is associated with an increased risk of endometrial cancer and thromboembolic events, studies evaluating the use of phytoestrogens as hormone replacement therapy have not demonstrated increased risks of these events.[19] In the past, soy intake was thought to increase breast cancer development, but more recent literature appears to support low to normal intake of phytoestrogens (<100 milligrams per day) even in breast cancer survivors.[38]

Conclusion

Current literature on the potential role of phytoestrogens in modulating the pathophysiology, symptom association, treatment and prevention of PFDs is overall scant. Further research is needed to explore these interesting preliminary data to date and ascertain potential risks and benefit of their use for treatment in light of the need for other robust treatment and potential prevention modalities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Wu JM, Vaughan CP, Goode PS, et al. Prevalence and trends of symptomatic pelvic floor disorders in U.S. women. *Obstet Gynecol.* 2014; 123(1):141–8. [PubMed: 24463674]
2. Wu JM, Hundley AF, Fulton RG, et al. Forecasting the prevalence of pelvic floor disorders in U.S. Women: 2010 to 2050. *Obstet Gynecol.* 2009; 114(6):1278–83. [PubMed: 19935030]
3. Copas P, Bukovsky A, Asbury B, et al. Estrogen, progesterone, and androgen receptor expression in levator ani muscle and fascia. *J Womens Health Gend Based Med.* 2001; 10(8):785–95. [PubMed: 11703891]
4. Franz HB, Wendler D, Oettling G. Immunohistochemical assessment of steroid hormone receptors in tissues of the anal canal. Implications for anal incontinence? *Acta Obstet Gynecol Scand.* 1996; 75(10):892–5. [PubMed: 9003088]
5. Haadem K, Ling L, Ferno M, et al. Estrogen receptors in the external anal sphincter. *Am J Obstet Gynecol.* 1991; 164(2):609–10. [PubMed: 1992711]
6. Iosif CS, Batra S, Ek A, et al. Estrogen receptors in the human female lower urinary tract. *Am J Obstet Gynecol.* 1981; 141(7):817–20. [PubMed: 7198384]
7. Oettling G, Franz HB. Mapping of androgen, estrogen and progesterone receptors in the anal continence organ. *Eur J Obstet Gynecol Reprod Biol.* 1998; 77(2):211–6. [PubMed: 9578281]
8. Cody JD, Jacobs ML, Richardson K, et al. Oestrogen therapy for urinary incontinence in postmenopausal women. *Cochrane Database Syst Rev.* 2012; 10 Cd001405. doi: 10.1002/14651858.CD001405.pub3
9. Staller K, Townsend MK, Khalili H, et al. Menopausal Hormone Therapy Is Associated With Increased Risk of Fecal Incontinence in Women After Menopause. *Gastroenterology.* 2017; 152(8):1915–1921.e1911. DOI: 10.1053/j.gastro.2017.02.005 [PubMed: 28209529]
10. Donnelly V, O'Connell PR, O'Herlihy C. The influence of oestrogen replacement on faecal incontinence in postmenopausal women. *Br J Obstet Gynaecol.* 1997; 104(3):311–315. [PubMed: 9091007]
11. Pinedo G, Garcia E, Zarate AJ, et al. Are topical oestrogens useful in faecal incontinence? Double-blind randomized trial. *Colorectal Dis.* 2009; 11(4):390–393. DOI: 10.1111/j.1463-1318.2008.01624.x [PubMed: 18637100]
12. Cardenas-Trowers OO, Borgstrom M, Addis I. Associations Between Type and Route of Hormone Use on Urinary Incontinence and Pelvic Organ Prolapse in Premenopausal and Postmenopausal Women. *Female Pelvic Med Reconstr Surg.* 2017; doi: 10.1097/spv.0000000000000493
13. Rahn DD, Carberry C, Sanses TV, et al. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. *Obstet Gynecol.* 2014; 124(6):1147–56. [PubMed: 25415166]
14. Thompson LU, Boucher BA, Liu Z, et al. Phytoestrogen content of foods consumed in Canada, including isoflavones, lignans, and coumestans. *Nutr Cancer.* 2006; 54(2):184–201. [PubMed: 16898863]
15. Gold EB, Leung K, Crawford SL, et al. Phytoestrogen and fiber intakes in relation to incident vasomotor symptoms: results from the Study of Women's Health Across the Nation. *Menopause.* 2013; 20(3):305–14. [PubMed: 23435028]
16. Carreau C, Flouriot G, Bennetau-Pelissero C, et al. Enterodiol and enterolactone, two major diet-derived polyphenol metabolites have different impact on ERalpha transcriptional activation in human breast cancer cells. *J Steroid Biochem Mol Biol.* 2008; 110(1-2):176–85. [PubMed: 18457947]
17. Kuiper GG, Lemmen JG, Carlsson B, et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. *Endocrinology.* 1998; 139(10):4252–63. [PubMed: 9751507]
18. Pilsakova L, Rieckansky I, Jagla F. The physiological actions of isoflavone phytoestrogens. *Physiol Res.* 2010; 59(5):651–64. [PubMed: 20406033]
19. Lethaby A, Marjoribanks J, Kronenberg F, et al. Phytoestrogens for menopausal vasomotor symptoms. *Cochrane Database Syst Rev.* 2013; (12) Cd001395.
20. Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *Jama.* 2008; 299(9):1036–45. [PubMed: 18319414]

21. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama*. 2002; 288(3):321–33. [PubMed: 12117397]
22. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *Jama*. 2004; 291(14):1701–1712. DOI: 10.1001/jama.291.14.1701 [PubMed: 15082697]
23. Tomaszewski J, Adamiak A, Skorupski P, et al. Effect of 17 beta-estradiol and phytoestrogen daidzein on the proliferation of pubocervical fascia and skin fibroblasts derived from women suffering from stress urinary incontinence. *Ginekol Pol*. 2003; 74(10):1410–4. [PubMed: 14669453]
24. Gratzke C, Jarajapu YP, Christ GJ, et al. Effects of long-term dietary soy treatment on female urethral morphology and function in ovariectomized nonhuman primates. *J Urol*. 2008; 180(5): 2247–53. [PubMed: 18804802]
25. Thielemann A, Wuttke W, Wuttke M, et al. Comparison of urodynamic effects of phytoestrogens equol, puerarin and genistein with these of estradiol 17beta in ovariectomized rats. *Exp Gerontol*. 2010; 45(2):129–37. [PubMed: 19903517]
26. Owen SJ, Rose'Meyer RB, Massa HM. Dietary phytoestrogens maintain contractile responses to carbachol with age in the female rat isolated bladder. *Life Sci*. 2011; 89(7-8):213–20. [PubMed: 21718707]
27. Waetjen LE, Leung K, Crawford SL, et al. Relationship between dietary phytoestrogens and development of urinary incontinence in midlife women. *Menopause*. 2013; 20(4):428–36. [PubMed: 23096248]
28. Kreydin EI, Kim MM, Barrisford GW, et al. Urinary Lignans Are Associated With Decreased Incontinence in Postmenopausal Women. *Urology*. 2015; 86(4):716–20. [PubMed: 26232691]
29. Juliato CR, Baccaro LF, Pedro AO, et al. Factors associated with urinary incontinence in middle-aged women: a population-based household survey. *Int Urogynecol J*. 2017; 28(3):423–429. [PubMed: 27640065]
30. Manonai J, Songchitsomboon S, Chanda K, et al. The effect of a soy-rich diet on urogenital atrophy: a randomized, cross-over trial. *Maturitas*. 2006; 54(2):135–40. [PubMed: 16297576]
31. Marañón JA, Lozano C, Martínez-Campesino L, et al. Clinical Study: Effect of Supplementation with High Genistein Soybean Isoflavones and Pumpkin Standardized Extract on Urinary Incontinence in Western Perimenopausal women. *J Gynecol Women's Health*. 2017; 4(1):555627.
32. Tomaszewski J, Rechberger T, Bogusiewicz M, et al. Collagen type I biosynthesis in culture of pubocervical fascia fibroblast obtained from women suffering from stress urinary incontinence and pelvic organ prolapse. *International Urogynecology Journal and Pelvic Floor Dysfunction*. 2009; 20(3):S336–S337.
33. Tomaszewski J, Adamiak-Godlewska A, Bogusiewicz M, et al. Oestrogen treatment and N-terminal propeptide of type I collagen concentration in culture media of human pubo-cervical fascia fibroblasts surrounding polypropylene mesh used in urogynaecological surgery procedures. *Przegląd Menopauzalny*. 2010; 14(1):5–12.
34. Tomaszewski J, Adamiak-Godlewska A, Bogusiewicz M, et al. Collagen type III biosynthesis by cultured pubocervical fascia fibroblasts surrounding mono and multifilament polypropylene mesh after estrogens and tamoxifen treatment. *Ginekologia polska*. 2010; 81(7):493–500. [PubMed: 20825049]
35. Iwanaga R, Branson ES, Orlicky DJ, et al. Phytoestrogen diet and estradiol rescue oxytocin receptor expression in uterosacral ligaments. *Female Pelvic Medicine and Reconstructive Surgery*. 2016; 22(5):S7.
36. Jiang G, Zhu T, Zhou Y, et al. Effect of puerarin on vaginal connective tissue in patients with pelvic organ prolapse. *International Journal of Clinical and Experimental Medicine*. 2017; 10(1):732–738.
37. Guadamuro L, Dohrmann AB, Tebbe CC, et al. Bacterial communities and metabolic activity of faecal cultures from equol producer and non-producer menopausal women under treatment with soy isoflavones. *BMC Microbiol*. 2017; 17(1):93. [PubMed: 28415978]

38. Fritz H, Seely D, Flower G, et al. Soy, red clover, and isoflavones and breast cancer: a systematic review. PLoS One. 2013; 8(11):e81968. [PubMed: 24312387]

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Phytoestrogens and Urinary Incontinence Studies

Study	Design	Intervention	Comparator (as applicable)	Duration	Outcomes	Results
Tomaszewski (2003) ^[23] Abstract in English Full text in Polish	In vitro, pubocervical fascia (PCF) from n=8 peri-menopausal women with SUI	PCF fibroblast cells serially exposed to 17 beta-estradiol (E2) or daidzein	Human skin fibroblast cells	96 hours	Proliferation ability of fibroblasts from PCF after exposure to E2 or daidzein	PCF fibroblasts from women with SUI exhibited increased proliferation after E2 > daidzein > skin fibroblasts. No objective analytic results in abstract. Summary: Estradiol and daidzein increased PCF fibroblast proliferation from peri-menopausal women with SUI.
Gratzke (2008) ^[24]	Animal, ovariectomized (ovx) cynomolgus monkeys	Soy diet (1.88 mg total isoflavones per gram protein), n=9	Casein lactalbumin diet, n=9	32 months	Contractile responses in vitro were assessed in mid-bladder (BS) and urethral segments, proximal (S1), mid- (S2), and distal (S3) via electrical (EFS) and pharmacological (Carbachol, Phenylephrine, Endothelin-1) stimulation	Soy diet group resulted in higher contractile responses to EFS in BS and S1 (intergroup difference: 53% and 38%, p<0.005 and p<0.05, respectively). No difference noted in S2 (p>0.05). Carbachol stimulation resulted in higher contractile responses in BS and S1 among soy diet group (intergroup difference: 19% and 204%, p<0.05 and p<0.001, respectively) whereas S2 and S3 did not reach significance. Phenylephrine and Endothelin-1 produced significantly higher responses in S1 among soy diet group (intergroup differences: 28% and 55%, respectively, both p<0.05) whereas S2 and S3 did not differ.
Full text					Proximal (S1), mid- (S2), distal (S3) urethral segments tested for urothelial thickness and mucosal area	Dietary soy resulted in higher thickness in all three segments in control vs. soy diet: S1: 24.1 ± 4 vs. 36.6 ± 1.5 µm (difference 52%, p <0.01), S2: 20.7 ± 2.0 vs. 29.6 ± 3.6 µm (difference 43%, p 0.001), S3: 22.4 ± 3.4 to 35.3 ± 1.1 µm (difference 57%, p 0.01). Soy diet resulted in larger mucosal area, S1: 4.3 ± 0.2 vs. 7.3 ± 0.6 mm ² (difference 71%, p 0.01), S2: 3.6 ± 0.1 to 5.5 ± 0.2 mm ² (difference: 52 %, p 0.001). S3: 5.3 ± 0.1 vs. 6.5 ± 0.3 mm ² (difference 22%, p 0.01). Summary: A soy diet resulted in higher contractile responses to EFS and pharmacological stimulation as

Study	Design	Intervention	Comparator (as applicable)	Duration	Outcomes	Results
Thielemann (2010) ^[25] Full text	Animal, ovx, Sprague Dawley mice	Oral E2 vs. phytoestrogen equol, genistein and puerarin	Ovx, untreated mice	3 months	Mice were catheterized with a biluminal catheter with one outlet in the bladder and another in the urethra. Urethral and bladder pressures were recorded during a 240s period of retrograde bladder filling	well as increased mucosal thickness and surface area in certain areas of the bladder and urethra. Bladder and urethra pressures were highest in the E2> puerarin > genistein treated mice, $p<0.05$. Mean differences in pressures (urethra minus bladder) were higher in the phytoestrogen and E2 treatment groups compared to controls during the filling period and in the filled status, $p<0.05$. Results shown in figures, no actual values provided. Summary: Dietary estradiol and phytoestrogens improved urethral closure pressure.
Owen (2011) ^[26] Full text	Animal, female Wistar rats	Ovx rats fed soy chow (soy/ovx), $n=24$ Ovx rats fed non-soy chow (non-soy/ovx), $n=24$ Sham-operated rats fed soy chow (soy/sham), $n=24$	Sham-operated rat fed non-soy chow (non-soy/sham), $n=24$	Bladders dissected at 12, 24, and 52 weeks of age	Detrusor contractile response to carbachol	Contractile response to carbachol did not change with phytoestrogen diet or ovariectomy compared to non-soy/sham at 12 weeks: Soy/sham: 4.22 ± 0.39 , non-soy/ovx: 5.56 ± 0.52 , soy/ovx 4.53 ± 0.55 vs. non-soy/sham: 6.01 ± 0.58 gram tension (g), all $p>0.05$. At 52 weeks, only soy-fed/sham resulted in significantly higher detrusor contraction to carbachol compared to non-soy/sham (6.28 ± 1.08 vs. 4.37 ± 0.76 g), $p<0.01$. Summary: A soy diet was associated with increased bladder detrusor muscle contractile response in aged (52 week old) rats.
Waeijen (2013) ^[27]	Prospective cohort study, women on entry age 42-52 yrs, $n=1,459$ at baseline, $n=981$ at 5 yrs, and $n=883$ at 9 yrs	SWAN Phytoestrogen Study created a phytonutrient database to estimate the usual daily intakes of four isoflavones, four lignans, and coumestrol via a food frequency questionnaire (FFQ)	Not applicable	10 yrs, follow up visits at 5 and 9 yrs	Development of UI: participants reported frequency and type of UI via an annual, non-validated, self-administered questionnaire	Mean intakes of isoflavones were 10 fold lower in non-Asian compared to Asian group. For Asian group, incidence of UI vs remaining continent based on isoflavones intake in mcg (median, quartile range): (111,512.17, 24,748.64) vs (9,717.91, 15,265.30), $p=0.137$. For Black/White: (292.01, 614.30) vs (315.60, 707.26), $p=0.559$. For both unadjusted and multivariable models, no significant association was noted between developing any UI or

Study	Design	Intervention	Comparator (as applicable)	Duration	Outcomes	Results
Full text					Discrete proportional hazards models to evaluate whether the estimated daily intake of each phytoestrogen class on the visit previous to the first report of UI was associated with development of monthly or more UI versus remaining continent	subtypes of UI and reported daily intake of phytoestrogen ($p<0.05$). Summary: Neither low nor high levels of reported phytoestrogen intake were associated with development of UI in peri-menopausal women.
Kreydin (2015) ^[28]	Cross sectional, population-based cohort survey, National Health and Nutrition Examination Survey, (NHANES) of women 50 yrs, n=1,789	None	None	2001-2010 datasets	Urinary phytoestrogen levels: <u>isoflavones</u> (daidzein, equol, genistein, and O-desmethylangolensin) <u>lignans</u> (enterodiol and enterolactone)	Increasing urine concentrations of enterodiol associated with decreased odds of UI (odds ratio [OR], 0.92; 95% confidence interval [CI], 0.85-0.99), mixed UI (OR, 0.90; 95% CI, 0.82-0.98), and other UI (OR, 0.90; 95% CI, 0.81-0.99) ($p<0.05$); increasing urine concentrations of enterolactone associated with decreased odds UI (OR, 0.92; 95% CI, 0.86-0.99) and mixed UI (OR, 0.91; 95% CI, 0.84-0.99) ($p<0.05$). No association observed between any isoflavone phytoestrogens and types of UI ($p>0.05$). Summary: Increasing concentrations of urinary lignans were associated with a decreased likelihood of UI in postmenopausal women.
Full text					Prevalence of self-reported SUI, UI, other UI, or mixed UI via non-validated questions	
Juliato (2017) ^[29]	Cross-sectional, population-based household survey, n=749 women, ages 45-60 yrs (mean 52.5 ± 4.4)	None	None	Sept 2012 to June 2013	Reported UI and factors associated with UI based on the International Consultation on Incontinence Questionnaire short form (ICIQ-SF) and the Overactive Bladder (OAB) form	UI prevalence was 24%. Current or previous use of soy products to treat menopausal symptoms was associated with a lower prevalence of UI (PR: 0.43, 95% CI, 0.24-0.78; $p=0.006$). Summary: Current or previous use of soy products to treat menopausal symptoms was associated with a lower prevalence of UI.
Full text						
Manonai (2006) ^[30]	Clinical, randomized, cross-over trial, n=36 women ages 40-59 yrs (mean 52.5 ± 5.1)	Soy-rich diet (25 g soy protein in various forms of soy food containing more than 50 mg/day of	Isocaloric soy-free diet	Two 12 week diets with two 4 week wash out periods	Effect on urogenital symptoms (SUI, UI, urgency, frequency, vaginal dryness, dyspareunia) measured by non-validated questionnaire: no symptoms	UI and vaginal dryness symptoms increased after 12-week soy-free diet: from 0.14 ± 0.35 to 0.25 ± 0.50 and from 0.61 ± 0.84 to 0.92 ± 0.99 , respectively ($p<0.05$). No symptom changes were observed in the soy-diet

Study	Design	Intervention	Comparator (as applicable)	Duration	Outcomes	Results
Full text		isoflavones substituted for an equivalent amount of animal protein)			<p>= score 0, mild= 1, moderate= 2, and severe= 3; vaginal health index (Robert Wood Johnson Medical school method); vaginal pH; and vaginal cytology</p> <p>Serum levels of daidzein and genistein</p>	<p>group ($p > 0.05$). The vaginal health index (12.83 ± 4.20 vs 12.64 ± 4.18), vaginal pH (7.06 ± 0.72 vs 7.11 ± 0.88), and maturation value (38.68 ± 32.66 vs 30.83 ± 30.39) were not significantly changed after soy treatment ($p > 0.05$).</p> <p>Good compliance to diet shown by elevation of serum levels of daidzein and genistein during soy-rich diet period; daidzein: pre- 21.3 ± 2.6 to post-treatment 71.0 ± 4.9 nmol/L and genistein: pre- 77.9 ± 9.1 to post-treatment 249.0 ± 18.6 nmol/L ($p < 0.05$).</p> <p>Summary: UUI and vaginal dryness increased after a 12-week soy-free diet.</p>
Marañon (2017) ^[31]	Non-randomized, single-center, prospective, open label study, n=82 women aged 42-62 yrs (mean 52)	Dropsordry™, a compounded mixture containing phytoestrogens from SOLGEN™ isoflavones and pyrogallol from standardized pumpkin seed extract	None	8 weeks: two 500 mg Dropsordry™ per day for the first 4 weeks, one tablet per day for an additional 4 weeks.	<p>UI symptoms (voiding amount, time, urgency score, leakage episodes and types, number of liners per day) via bladder diary, non-validated urgency score (0-4), treatment satisfaction and improvement in quality of life (QOL) were compared at baseline and post-treatment.</p>	<p>Compared to baseline, mean urgency grade reduced by 24.7%, nocturia reduced by 69.4%, the use of daily panty liners by 66.3% (all $p < 0.05$). No significant difference noted in reduction of SUI (no data provided). After 8-week treatment, 96% reported satisfaction with treatment, 92% reported improvement in QOL.</p> <p>Summary: A compounded phytoestrogen mixture reduced mean urgency score, nocturia, and the use of daily panty liners in peri-menopausal women.</p>

Table 2

Phytoestrogens and Pelvic Organ Prolapse Studies

Study	Design	Intervention	Comparison	Duration	Outcomes	Results
Tomaszewski (2009) ^[32] Abstract in English Full text in Polish	In vitro	Pubocervical fascia (PCF) obtained from a 56 yr old woman with SUI and POP PCF fibroblasts cultured with mono- or multifilament mesh and exposed to 17 β -estradiol (E2), estriol or phytoestrogen daidzein	Same as intervention group but without mesh exposure	Collagen type I (Col I) biosynthesis was assessed after 48, 96, and 144 hrs	Biosynthesis of aminoterminal propeptide of type I procollagen as a marker of Col I biosynthesis in cultured PCF fibroblasts	Fibroblasts from PCF taken from a menopausal woman with SUI and POP are capable of Col I biosynthesis after estrogen and phytoestrogen treatment. There was decreased fibroblast biosynthesis of aminoterminal propeptide of type I procollagen in the study subgroup using multifilament polypropylene mesh. The most significant difference between assessed groups was recorded within the 96 th and 144 th hour. It is possible that decrease of collagen type I biosynthesis after 144 hours of the experiment was caused by aging of the culture (no p-value). Summary: Col I levels in cultured PCF fibroblasts taken from a 56 yo menopausal woman with SUI and POP increased after exposure to estrogen and daidzein.
Tomaszewski (2010) ^[33] Abstract in English Full text in Polish	In vitro	Pubocervical fascia (PCF) obtained from a 56 yo woman with SUI and POP PCF fibroblasts cultured with mono- or multifilament mesh and exposed to 17 β -estradiol (E2), estriol or phytoestrogen daidzein	Skin fibroblasts	Cultures were run for 216 hrs and the media were replaced every 72 hrs	Procollagen type I N-terminal propeptide (PINP) as a marker of Col I synthesis by PCF fibroblasts cultured with mono- or multifilament polypropylene mesh in the presence of estrogens and a phytoestrogen	Fibroblasts exposed to estriol or daidzein produced more Col I than those treated with estradiol regardless of the mesh applied. In the presence of monofilament mesh, peak PINP concentration increased persistently with estriol and daidzein throughout the study whereas the peak PINP was between 72-144 hrs for estradiol. In the presence of multifilament mesh, the rate of Col I production dropped after 144 hrs in all cultures. No data available in abstract. Summary: PCF fibroblasts produced more Col I when exposed to estriol or daidzein regardless of the type of vaginal prolapse mesh applied.

Study	Design	Intervention	Comparison	Duration	Outcomes	Results
Tomaszewski (2010) ^[34] Abstract in English Full text in Polish	In vitro	Pubocervical fascia (PCF) obtained from a 52 yo premenopausal woman undergoing SUI surgery PCF fibroblasts cultured with mono- or multifilament mesh and exposed to 17β-estradiol (E2), estriol, phytoestrogen daidzein, or tamoxifen	PCF's without treatment	Cultures were run for 216 hrs and the media were replaced every 72 hrs	N-terminal propeptide of type III procollagen (PIIINP) as a marker of collagen type III (Col III) synthesis by PCF fibroblasts cultured with mono- or multifilament polypropylene mesh in the presence of estrogens, a phytoestrogen, and an anti-estrogen	High collagen type III synthesis persisted throughout the study period only in cultures containing monofilament mesh stimulated with estriol. The highest total PIIINP production was observed in culture treated with tamoxifen regardless of mesh types. No data available in abstract Summary: Col III only showed a persistent increased production by PCF fibroblasts in cultures containing monofilament mesh stimulated with estriol. The highest total Col III production was observed in culture treated with tamoxifen regardless of the type of mesh.
Iwanaga (2016) ^[35] Abstract only	In vitro and animal, mice	For human subjects: Oxytocin receptor (OXTR) mRNA expression in human USL collected from 11 premenopausal women with normal pelvic support (controls, CTL) vs. 6 premenopausal women with POP vs. 7 postmenopausal women with POP. For mice; OXTR expression was compared between i. mice with prolapse and age-matched mice without prolapse (n=3 and 10, respectively) ii. Ovx mice for 2 months (nulliparous or NP, n=6, multiparous or MP, n=6) iii. Ovx mice for 2 months further treated with and without 2-day estradiol treatment (n=5 and 6, respectively) iv. 12 months mice undergoing sham surgery and treated with vs. without 2-day estradiol treatment (n=5 and 6, respectively) v. 70 weeks old NP mice raised on a phytoestrogen diet (n=10) vs. phytoestrogen-free diet (n=10)	For human subjects: Oxytocin receptor (OXTR) mRNA expression in human USL For mice; OXTR expression was compared in mice USL i) with vs. without prolapse ii) Ovx in NP and MP mice vs. sham surgery iii) Ovx vs. without E2 treatment to sham and OVX mice v) phytoestrogen diet vs. phytoestrogen-free diet	Up to 70 week old mice	For human subjects: Oxytocin receptor (OXTR) mRNA expression in human USL For mice: OXTR expression was compared in mice USL i) with vs. without prolapse ii) Ovx in NP and MP mice vs. sham surgery iii) Ovx vs. without E2 treatment to sham and OVX mice v) phytoestrogen diet vs. phytoestrogen-free diet	For human subjects: OXTR expression was decreased by 65% in the premenopausal POP group and by 78% in the postmenopausal POP group (both p<0.05) compared to premenopausal CTL. For mice: OXTR was decreased by 90% in mouse USL with POP compared to CTL (p<0.05). OVX resulted in significantly decreased OXTR expression in NP and MP mice compared to sham (p<0.05)*. Treatment with E2 to a MP sham and OVX mice increases expression of OXTR (p<0.05)*. Phytoestrogen diet had a significant impact on OXTR expression in USL compared to phytoestrogen free diet (p<0.05)*. *no specific data available in abstract. Summary: Both estradiol and a phytoestrogen diet increased expression of OXTRs and had a significant impact on OXTR expression in the USL.

Study	Design	Intervention	Comparison	Duration	Outcomes	Results
Jiang (2017) ^[36]	Prospective cohort of women having transvaginal surgery for POP and/or SUI	Puerarin 0.429 mg/day for 30 days, n=30	Placebo for 30 days, n=22	June 2010 to Nov 2012	POP symptoms: non-validated score based on POP-Q exam (positive or strongly positive improvement in symptoms if 1+ or 2+ stage improvement, respectively) Vaginal tissue: biopsies of participants' prolapsed tissue obtained. Expression of elastin, collagen, neuropeptide Y (NPY), vasoactive intestinal polypeptide (VIP) and transforming growth factor beta (TGF- β) was evaluated in all patients using immunohistochemistry	Patients treated with puerarin had significant improvement of POP vs. control patients (positive: 57 % vs. 0%, and strongly positive 35% vs. 0%, $p<0.05$). Elastin positive rate ($9.8\% \pm 2.8\%$ vs $2.8\% \pm 1.3\%$, $p<0.05$), collagen I/III ratio (1.1 ± 0.3 vs 0.5 ± 0.3 , $p<0.05$), NPY, VIP and TGF- β was significantly increased in the puerarin group compared to control (all $p<0.05$). Summary: After 30 days, women treated with puerarin had significant improvement of POP. The expression of elastin positive rate and collagen I/III ratio were significantly increased in the puerarin group. NPY, VIP, and TGF- β levels were also significantly increased.
Full text						