

Systematic Review of the Efficacy of Herbal Galactogogues

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Abstract

Exclusive breastfeeding has been linked to many positive health outcomes yet its widespread adoption as the primary mode of providing nutrition to infants remains challenging. The most common reported reason for early breastfeeding cessation is perception of inadequate milk production. To augment breast milk production, a substantial number of women turn to herbal galactogogues despite the limited scientific evidence of their efficacy and safety. We conducted a systematic review of published literature to evaluate the efficacy of herbal galactogogues. PubMed was searched from inception to October 2012 using an iterative search process that proceeded from broad categories to specific herbs. Manuscript references were also reviewed. Only experimental studies with objective outcome measures were included. Six (6) trials met our search criteria. Each trial was evaluated for potential sources of bias in design and reporting using an adapted version of the CONSORT checklist. Shatavari, torbangun, fenugreek, milk thistle and a Japanese herbal medication were the 5 herbal preparations studied. Five (5) trials found an increase in breast milk production. Several limitations exist that affect the validity of the results of the trials, including small sample size, insufficient randomization methods, poorly defined eligibility criteria, use of poly-herbal interventions, and variable breastfeeding practices among enrolled subjects. Given the insufficiency of evidence from these trials, no recommendation is made for the use of herbs as galactogogues. Well-designed and well-conducted clinical trials that address the above limitations are necessary to generate a body of evidence as a basis for recommendations regarding herbal galactogogues.

Introduction

Breast milk has long been accepted as the gold standard of infant nutrition.¹ While breast milk has been linked to many positive health outcomes, widespread adoption of exclusive breastfeeding as the primary mode of providing nutrition to young infants has been challenging. According to the Centers for Disease Control and Prevention's most recent Maternity Practices in Infant Nutrition and Care, in the United States, the exclusive breastfeeding rate for infants under 6 months is 16.3%, and 24.6% of breastfed infants received formula before 2 days of age.² Worldwide, maternal perception of insufficient milk production is the most common reason reported by mothers for early cessation of breastfeeding, with prevalence reported between 30% and 80%.³ For those mothers in whom milk production has declined and is not responding to non-pharmacologic measures, the use of galactogogues is often considered.⁴

Galactogogues are substances thought to assist in the initiation, continuation, or augmentation of breast milk production.⁵ They include pharmaceutical agents and herbal supplements. Recently, the Cochrane Collaboration published a review of pharmaceutical galactogogues given to mothers of preterm hospitalized infants. Two trials of domperidone met the review criteria, and meta-analysis showed a modest increase in expressed breast milk of 99.49 ml/day (95% CI: -1.94 to 201) in mothers of preterm infants given domperidone.⁶ As an alternative to pharmaceutical agents, many clinicians recommend the use of herbs to improve milk output.⁷ In the United States, it is estimated that 15% of breastfeeding women use herbal galactogogues⁸ while in a Norwegian study, this estimate is 43%.⁹ Although some evidence exists regarding pharmaceutical drug-herb interactions, there is limited evidence explaining the mechanism of action of herbs as galactogogues. Given the recency and depth of the Cochrane

review and the common practice of using herbal galactogogues as an alternative to pharmaceutical agents, we sought to evaluate available evidence regarding the efficacy of herbal interventions in increasing breast milk production.

Methods

Search Methodology

Because our goal was to assess *efficacy*, we limited our review to published manuscripts with an experimental design that had an objective outcome measure of breast milk production. The search procedure to identify eligible manuscripts was conducted in three steps. First, PubMed was searched from inception to October 2012 using the keywords “galactogogues” or “galactagogues” or “lactogogues” or “lactagogues” (no field restriction), limited to humans and English language. The search returned 28 articles, 2 of which were randomized controlled trials (RCT) of pharmacologic galactogogues, 15 were reviews, 1 was a practice guideline, 2 were case reports, and the rest were articles that were either observational, survey or commentary in nature. From these 28 articles, 16 different herbal galactogogues were identified: shatavari, torbangun, fenugreek, fennel, milk thistle, chasteberry, goat’s rue, anise, blackseed, caraway, coriander, dill, alfalfa, blessed thistle, nettle, and red clover.

Next, we searched PubMed using each of the herbal galactogogues (no field restriction), limited to humans and English language, and following the search criteria: [common name of the herb] OR [Latin name of the herb] AND (lactation OR breast OR milk OR breastfeed). Appendix A shows a summary of the search results on each herbal galactogogue.

Of the 16 different herbs initially identified, only 7 herbs had articles directly related to the topic of lactation or breastfeeding. As a final search procedure, we reviewed references of these manuscripts. Combining the three searches conducted on these 7 herbal galactogogues and the manual search of associated references resulted in a total of 63 articles. Of the 63 articles, only 6 were RCTs. Further review of the references cited by the 6 RCTs did not yield additional experimental studies. The RCTs were reviewed for study design characteristics as well as proposed mechanism of lactogenesis. The proposed mechanism and primary study outcomes for each trial are summarized in Table 1. Each trial was also evaluated for potential sources of bias in design and reporting, using an adapted version of the CONSORT checklist as a guide¹⁰. The results are summarized in Table 2.

Results

Five of the 6 RCTs were designed to assess the galactogogue activity of shatavari, torbangun, fenugreek, or milk thistle as primary compounds while one was designed to assess the efficacy of a multi-compound regimen consisting of 13 different herbs. All trials were conducted outside the US.

Results of Trials

None of the trials reported sample size calculations. Only 3 of the 6 trials^{1,19,27} had reproducible recruitment and screening methods. One trial¹⁵ reported its sequence generation and 2 trials^{15,28} reported their mechanism of allocation concealment to ensure that treatment allocation was unbiased. Only 1 trial¹⁵ described how randomization was actually implemented and only 2 trials^{15,19} reported blinding of those assessing outcome. Three trials^{15,19,25} reported

adherence and 5 trials^{15,19,25,27,28} reported absence of side effects. There is insufficient information to verify if side effects were systematically assessed. These potential sources of bias are summarized in Table 2.

1. Sharma S, et al. Randomized controlled trial of *Asparagus racemosus* (Shatavari) as a lactagogue in lactational inadequacy. *Indian Pediatr.* 1996 Aug;33(8):675-7.

Women with uncomplicated term delivery and who reported lactational inadequacy during 14-90 days postpartum were recruited for this multi-center, randomized, double-blind, placebo-controlled parallel arm study of shatavari. Lactation inadequacy was defined either as inability to regain infant's birth weight at 15 days of life, or infant weight gain less than 15 g per day, or mother supplementing greater than 250 ml per day of milk after 4 weeks of birth. All mothers diagnosed with lactation inadequacy were advised to exclusively breastfeed and were instructed on proper position and frequency of feeds, as well as maintenance of adequate rest and nutrition. Sixty-four mothers were enrolled and randomized 1:1 into treatment and placebo arms, with 11 mothers failing to complete the trial. The mothers were randomized to receive either 2 teaspoons twice daily of a 100-g mixture containing 15% shatavari by weight for 4 weeks (N=32), or a physically indistinguishable placebo mixture (N=32). Adherence was not explicitly reported although the authors reported that 26 mothers in the treatment arm and 23 mothers in the placebo arm offered supplementary feeding during the study. The primary outcome was change in serum prolactin level. Additional outcomes were infant weight gain and change in volume and frequency of supplementary feedings. Maternal characteristics at baseline were comparable. Median prolactin level after treatment was 25 ng/ml for the treatment arm and 38

ng/ml for the placebo arm. Although no results of statistical significance testing are reported, these levels were deemed comparable by the researchers. Infant weight gain after therapy for the treatment arm was 30 g/d versus 26 g/d for the placebo arm. These levels were reported as comparable. The researchers concluded that shatavari did not have any effect on milk production.

2. Damanik R, et al. Lactagogue effects of Torbangun, a Batakese traditional cuisine. *Asia Pac J Clin Nutr.* 2006;15(2):267-74.

Women in North Sumatra, Indonesia aged 20-40 years in their last trimester of pregnancy, who were generally healthy and planned to exclusively breastfeed their infants a minimum of 4 months, were recruited to this parallel randomized trial of torbangun leaves (*Coleus amboinicus Lour*). Women were eligible if they delivered a healthy term infant weighing at least 2.5 kg. Starting second post-partum day, 75 subjects were enrolled and randomized 1:1:1 into three arms: 150 g per day of torbangun leaves served as soup 6 days a week (N=25); 1 capsule containing fenugreek seeds 3 times per day (N=25); 1 sugar-coated Moloco+B12 tablet 3 times per day (N=25) for 30 days. Amount of fenugreek in each capsule was not reported. The women were followed for an additional 30 days after the initial 30-day supplementation period. Twenty-three subjects from the torbangun group, 22 subjects from the fenugreek group, and 22 subjects from the Moloco+B12 group completed the two-month study period. Medication count was used to measure adherence for those randomized to fenugreek capsule and Moloco+12 tablet; delivery staff checked daily whether mothers in the torbangun group consumed the soup. Blinding of subjects was not achieved and insufficient information was reported to assess

blinding of researchers. The primary outcome was change in the volume and nutritional quality of breast milk. The difference between pre- and post-feeding weight of the infant in grams was used to calculate milk volume, which was then converted into milliliters using the conversion factor 0.983 ml/g to adjust for breast milk density. There were no significant differences among the 3 groups at baseline. On day 28, the mean breast milk volume for the torbangun group versus the fenugreek group versus the Moloco+B12 group was 479 ml (65% increase from baseline) versus 400 ml (20% increase) versus 385 ml (10% increase). The percent increase for the torbangun group was statistically significant ($p < 0.05$). Data collected on days 42 and 56 showed that the percent increase in milk volume for the torbangun group remained higher than the other 2 groups. The researchers concluded that torbangun leaves enhanced milk production, and the galactagogue effect was sustained even after the supplementation period.

3. Ushiroyama T, et al. Xiong-gui-tiao-xue-yin (Kyuki-chouketsu-in), a traditional herbal medicine, stimulates lactation with increase in secretion of prolactin but not oxytocin in the postpartum period. *Am J Chin Med.* 2007;35(2):195-202.

Eighty-two women who had uncomplicated delivery in Osaka, Japan were enrolled in this parallel arm, randomized trial of Xiong-gui-tiao-xue-yin (herein referred to as drug X), a traditional herbal preparation consisting of 13 different herbs. The women were randomized 1:1 to either 6.0 g per day of commercially prepared drug X (N=41) or 0.375 mg per day of ergometrine (N=41). No information was reported to assess how blinding of researchers was achieved and whether subjects were blinded. Outcomes were mean milk volume and mean plasma prolactin and oxytocin levels. Breast milk volume was measured daily until postpartum

day 6 by weighing the infant before and after feeding, and plasma prolactin and oxytocin levels were measured on days 1 and 6. Maternal and infant characteristics at baseline did not differ between the groups. On day 4, the mean milk volume for the treatment group versus the ergometrine group was 276.5 g versus 155.3 g ($p < 0.05$). On day 6, the treatment group continued to have higher mean milk volume of 413.7 g versus 293.3 g for the ergometrine group ($p < 0.05$). On day 6, plasma prolactin level for the treatment group versus the ergometrine group was 167.5 ng/ml versus 117.1 ng/ml ($p < 0.05$). No statistical difference was observed between the two groups regarding their oxytocin level on day 6. No adverse reactions were noted. The researchers concluded that drug X enhances breast milk production among postpartum women.

4. Di Pierro F, et al. Clinical efficacy, safety and tolerability of BIO-C (micronized Silymarin) as a galactagogue. *Acta Biomed.* 2008 Dec;79(3):205-10.

Fifty healthy lactating women in a hospital in Lima, Peru were enrolled in this placebo-controlled trial of micronized silymarin. The mothers were instructed to maintain a diet of about 2600 kcal per day, and were randomized 1:1 into treatment or placebo arms: 420 mg per day of micronized silymarin (BIO-C[®]) (N=25) or placebo (N=25), for 63 days. Treatment and placebo forms were indistinguishable. No information was reported to assess how blinding of researchers was achieved. All mothers completed the study. The women were comparable at baseline. The outcomes were mean quantity of milk in grams and a qualitative assessment of the chemical composition of milk reported as percent water, fats, carbohydrates and protein. Milk was quantified by weighing the infant before and after feeding and adding the quantity taken from manual breast expression. On day 30, the mean quantity of milk for the treatment group versus

the placebo group was 990 g versus 650 g ($p < 0.01$), representing a 64.4% increase in the treatment group and a 22.5% increase in the placebo group over baseline values. On day 63, the percent increase in the quantity of milk remained significantly higher in the treatment group versus the placebo group (85.9% versus 32.1%). No difference was noted in the chemical composition of milk between the two groups on day 30 or day 63. No adverse reactions were noted. The researchers concluded that BIO-C[®] has effective galactagogue activity.

5. Gupta M, and Shaw B. A double-blind randomized clinical trial for evaluation of galactagogue activity of *Asparagus racemosus* wild. Iranian J Pharm Res. 2011;10(1):167-172.

Lactating mothers aged 20-40 years, with an infant younger than 6 months, and at least one of the following symptoms: deficient lactation, pain in breasts during feeding, poor appetite, any anxiety disorder, or an infant that cries just after feeding, were enrolled from a single hospital in Kolkata, India in this double-blind, placebo-controlled, parallel arm trial of shatavari. Deficient lactation was not defined. A total of 60 subjects were randomized 1:1 into treatment and placebo arms: 1 capsule 3 times daily containing shatavari root powder for 30 days (60 mg per kg of body weight) (N=30), or 1 capsule 3 times daily containing rice powder as placebo (N=30) for 30 days (same dosing formula as the treatment group). Those assessing outcomes were blinded to treatment assignments. Subjects were examined weekly and advised during the study period to avoid contraceptives or steroid-containing drugs and to follow normal feeding technique and schedule. The primary outcome was percent change in serum prolactin level from baseline to after treatment (actual prolactin levels not reported). Additional outcomes included

change in mother's and infant's weight, maternal satisfaction with lactation, and maternal satisfaction with the infant's well-being and happiness. Baseline characteristics were not significantly different between the two groups. Mean prolactin level increased by 32.9% for the treatment group compared to 9.6% for the placebo group ($p < 0.05$). Similarly, mean infant weight increased by 16.1% for the treatment group compared to 5.7% for the placebo group ($p < 0.05$). The treatment group had higher mean percent increases in the secondary outcomes compared to the placebo group ($p < 0.05$). No adverse reactions were noted. The researchers concluded that shatavari has significant galactagogue activity.

6. Turkyilmaz C, et al. The effect of galactagogue herbal tea on breast milk production and short-term catch-up of birth weight in the first week of life. *J Altern Complement Med.* 2011 Feb;17(2):139-42.

Healthy mothers from a maternity unit in Ankara, Turkey were enrolled in this placebo-controlled, randomized, double-blind study. To be eligible, the women had healthy term infants, were willing to breastfeed exclusively, and agreed to use a specific breast pump on postpartum day 3. One lactation consultant nurse educated the women on proper positioning, latch-on, and breastfeeding techniques. A total of 66 subjects were enrolled and randomized 1:1:1 into treatment, placebo, and control arms. Mothers in the treatment group ($N=22$) were instructed to consume daily a minimum of 3 cups of a commercially available herbal tea (Still tea, Humana®) containing 100 mg of fenugreek and other ingredients. The placebo group ($N=22$) was prescribed an apple tea daily in the same amount as the treatment group. The fenugreek tea and apple tea were the same color and form. The duration of the intervention was not reported. The control

group (N=22) received routine advice without any specific recommendation. One person randomized the mothers to treatment arms and assessed adherence with tea intake while two other persons blinded to the study collected outcome data. All mothers completed the study. The outcomes were mean breast milk volume, maximum weight loss as a percent of birth weight, and days until birth weight was regained. Each breast was pumped consecutively for 15 minutes using the same model of an electrical breast pump to measure breast milk volume. Baseline maternal characteristics were comparable in the three groups. The mean breast milk volume for the treatment group versus the placebo group versus the control group was 73.2 ml versus 38.8 ml versus 31.1 ml ($p<0.05$). Maximum weight loss was lowest in the treatment group ($p<0.05$). Infants in the treatment group also regained their birth weights faster than the placebo and control groups ($p<0.05$). The researchers concluded that the commercially prepared herbal tea containing fenugreek enhanced breast milk production and might be used to support exclusive breastfeeding in the first week of life.

Biologic Plausibility

Little is known about how herbs function as galactogogues. Our review indicates several potential pathways but the studies are mostly done on animal models and untested on humans, limiting their generalizability. In contrast, the biologic pathway for pharmaceutical galactogogues has been extensively researched. Multiple trials of domperidone and metoclopramide have shown that they stimulate the release of prolactin by blocking dopamine receptors in the anterior pituitary gland.^{6,11,12} We present a brief review of the pathways cited by the 5 RCTs (excluding the trial of the 13-compound regimen) to shed light on the possible mechanism of action of these herbs in enhancing breast milk production.

Shatavari

In a study by Sabins et al¹³, among rats, an alcohol extract of shatavari increased milk production concurrent with increased growth of the mammary glands, alveolar tissues and acini. Three other studies have demonstrated the estrogenic effects of shatavari in the mammary glands and genital organs of rats.¹⁴ Chemical analysis of shatavari roots reveals the presence of saponins and steroidal saponins¹⁵, and one hypothesis states that the estrogenic activity results from the hormone-like actions of these steroidal saponins.¹⁴ Another hypothesis states that the growth of mammary tissue is due to the action of released corticoids or prolactin.¹⁴ Although estrogens have a stimulating effect on the ductal epithelial cells causing them to lengthen, their primary role seems to be the potentiation of the production of prolactin.¹⁶

Torbangun

Torbangun has been used as a galactagogue by Batakese people in Indonesia for centuries.¹ It has been hypothesized that torbangun has an effect on the proliferation of secretory mammary cells based on mice models.¹ Increases in DNA and RNA were observed in mice receiving torbangun extract and this effect was dose-dependent.¹ The number of epithelial cells and their secretory activity are thought to determine the shape of the lactation curve, with increases in either number of cells or their secretory activity resulting in increased milk production.¹⁷ Two related studies support this finding. One study involving goats showed that an increase in the number of mammary cells followed by an increase in the secretory activity of each cell were associated with an increase in milk production in the early lactation period.¹⁷ Another study using bovine models showed an increased milk yield due to an increase in the

secretory activity of cells alone.¹⁷ In the latter study, there was no increase in mammary cell number. Despite the use of torbangun in many medical conditions such as malarial fever, hepatopathy, renal calculi, and chronic asthma,¹⁸ little is known about its specific properties. Phytochemical screening of the plant reveals the presence of alkaloids, flavonoids, tannins and saponins in its extracts.¹⁸

Fenugreek

Fenugreek (*Trigonella foenumgraecum*) is the most commonly utilized herbal galactagogue in published literature,^{5,19} although there is conflicting evidence of its efficacy. It is thought that fenugreek stimulates sweat production, and since the breast is a modified sweat gland, this is how fenugreek may affect breast milk production.²⁰ It has also been suggested that fenugreek may have estrogenic activity. One study using in vitro assays found that fenugreek seeds contain estrogen-like compounds, and that they stimulate pS2 expression in MCF-7 cell lines.²¹ pS2 is frequently used as a marker for assessing the estrogenicity of a compound.²¹ The phytoestrogens and diosgenin content (a type of steroidal saponin) of fenugreek appear to account for the increase in milk flow observed from its use,¹⁹ but the exact mechanism of action is as yet undefined. Phytoestrogens are similar in chemical structure to endogenous estrogen and can bind to both alpha and beta estrogen receptors. Thus they have the potential to act as estrogen agonists or antagonists, which could alter the structure or functioning of the endocrine system.^{22,23}

Milk Thistle

The lactogenic activity of milk thistle (*Silybum marianum*) remains largely anecdotal, although its use as a galactagogue is increasing.²⁴ Animal studies suggest milk thistle has promising lactogenic properties. In one study, cows given silymarin (an extract of *Silybum marianum*) were observed to have increased milk production of about 5 to 6 L per day per cow.²⁵ It is thought that the administration of silymarin after calf delivery improves the physiologic status of the cow, which leads to faster recovery of the cow and increased food intake, and thus increased milk production. This finding was supported by the observation of reduction of blood β -hydroxybutyric acid and decreased outcomes of ketonuria in cows treated with silymarin.²⁵ Other experimental studies show a weak anti-estrogenic property arising from the flavonolignans component of silymarin,²⁵ which are the major biologically active components of milk thistle.²⁶ It is rapidly metabolized and measurable in plasma, mainly in the form of glucuronides.²⁶

Discussion

Despite their prevalent use among lactating women, our review finds that herbal galactagogues have limited reported safety and efficacy data. In our extensive review, we found 6 trials of herbal galactagogues with outcomes addressing the effect on breast milk production. These outcomes included effect on serum prolactin and oxytocin levels, breast milk volume, infant weight, weight loss as a percent of birth weight, time to regain birth weight, and the chemical composition of breast milk. Four of the 6 trials showed positive galactagogue activity of 4 herbs based upon different outcome measurements.^{1,15,19,25} Gupta and Shaw¹⁵ observed shatavari to increase serum prolactin level by 3.5 times that of placebo and mean infant weight by almost 3 times that of placebo. The increase change in serum prolactin level, however, contradicts the Sharma et al²⁷ results, which found no galactagogue effect of shatavari. Damanik

et al¹ reported an increase in breast milk volume using torbangun, but not fenugreek, which is in direct contrast with the result of the Turkeyilmaz et al¹⁹ study. Turkeyilmaz et al¹⁹ found that the fenugreek group had almost twice the expressed breast milk volume as placebo. The differing results may stem from different dosages and formulations of fenugreek used, with the Turkeyilmaz et al¹⁹ study using 100 mg of fenugreek while it is unclear how much is used in the Damanik et al¹ study, different study populations, or different measures of breast milk volume: infant weight in the study by Damanik et al¹ versus expressed milk from pumping the breasts in the study by Turkeyilmaz et al.¹⁹ Di Pierro et al²⁵ reported an increase in breast milk volume from the administration of silymarin. There are no other studies evaluating silymarin in which to compare these results. Ushiroyama et al²⁸ reported increases in breast milk volume and serum prolactin level in its study of Xiong-gui-tiao-xue-yin but poly-formulation, duration of the treatment and dates of sample collection make it difficult to draw conclusions about the galactagogue efficacy of this herbal preparation.

Although we reviewed randomized trials, the gold standard for assessing efficacy, the trials had significant flaws: variable recruitment and screening methods, poorly defined eligibility criteria, failure to report sample size calculation, insufficient methods of randomization and blinding, and poor reporting of adherence and assessment of side effects. These design flaws limit reproducibility and generalizability, and introduce significant bias and confounding, such that effects are imprecise and cannot be validly attributed to the treatment tested.

Although 5 of the trials aimed to assess the efficacy of one primary herb, only 2 of the 6 trials^{15,25} used a purified version of the herb. The Sharma et al²⁷ study used a mixture that is 15% shatavari by weight; there were 6 other herbs added to the intervention product. There is insufficient information to determine if the Damanik et al¹ study added other ingredients to the torbangun soup. The Turkyilmaz et al¹⁹ study used a commercially prepared herbal tea containing fenugreek; however, the herbal tea also included fennel, raspberry leaf, and goat's rue, substances that are traditionally used to enhance lactation.²⁴ It is not possible to assess which herb or combination of herbs used in the Ushiroyama et al²⁸ study is responsible for the reported positive galactagogue activity. Because the intervention products contained other substances the concurrent actions of which are unknown, there is potential for erroneously attributing the effect to the main herb. It is recommended that purified individual compounds or derivatives be used such as done by the trials conducted by Di Pierro et al²⁵ and Gupta and Shaw.¹⁵ It is also important to note that, although the studies mentioned here used known preparations of herbs, herbal preparations are not regulated and standardized, posing a safety concern. Under the 1994 Dietary Supplement Health and Education Act, which covers any product taken by mouth that contains a "dietary ingredient" intended to supplement the diet, manufacturers are responsible for ensuring safety of the supplement, but there are no rules that limit the amount of nutrient(s) in any form of these supplements.²⁹

The studies varied in terms of eligibility criteria and outcomes. Three trials^{15,25,27} required inadequate lactation as main eligibility criteria, and of those 3 trials, only 2 trials^{15,27} explicitly defined lactation inadequacy. Inconsistencies in eligibility criteria may attenuate any possible differences observed between treatment and placebo arms,¹¹ particularly if the outcome is change

in breast milk volume from baseline. It is also important to consider infant eligibility criteria, such as whether babies were born term or pre-term given that milk production is affected by local feedback mechanisms. Three of the trials^{1,19,27} explicitly stated including only term infants as subjects while the Ushiroyama et al²⁸ study stated including women who had spontaneous labor pain followed by normal delivery. This information was not reported in the Gupta and Shaw¹⁵ and Di Pierro et al²⁵ studies. For those assessing serum prolactin levels, the timing of the initiation of intervention varied, which is an important consideration given that the role and level of prolactin depend upon the stage of lactation.¹¹ Three trials^{15,27,28} used serum prolactin level as primary outcome. Multiple studies have shown that there is poor correlation between serum prolactin level and milk production;^{11,30} thus, studies that rely on this measure alone do not provide usable evidence of galactagogue activity. Four trials^{1,19,25,28} measured breast milk volume or change in infant weight as primary outcome. However, only 2 trials^{19,25} explicitly described how breast milk volume was measured, and whether it included milk from breast expression. The trials also used different units of measurement, making comparison of the magnitude of effects difficult. Given the paucity and lack of standardization of experimental studies on herbal galactagogues, it is recommended that future studies include lactation inadequacy as an explicitly defined eligibility criteria and that the timing and duration of intervention be considered to yield clinically significant findings.⁶ Additionally, future studies should use the same, multiple outcome measures and units of measurement to enable comparison and extension into a generalizable finding. Outside the review of the trials and biologic plausibility of herbs as galactagogues, there are other limitations to the study of herbal galactagogues. We found variable terminology regarding substances thought to enhance milk production. The use of multiple terminologies makes it difficult to synthesize and pool

information necessary to make a consensus on the safety and efficacy of herbal products in increasing breast milk production.

Difficulty in interpreting studies on herbal galactogogues also arises from the lack of attention given to ensuring that enrolled subjects adhere to the same practices throughout lactation. It is requisite in studies of galactogogues that the subjects be comparable not only on their baseline demographic data but also in their breastfeeding practices, such as whether they are exclusively breastfeeding or supplementing, whether they are feeding or expressing at similar frequencies, and whether they received the same advice on supportive measures.^{6,11} If mothers in the study have different breastfeeding practices, this may confound or modify the association observed. The intervention product may not be the only contributing factor to the presence or absence of galactogogue activity of the product.

Three other reviews were published recently on the topic of galactogogues. Zapantis et al²⁴ reviewed the prevalence and types of herbs used as galactogogues without systematic assessment of validity. Budzynska et al³¹ conducted a systematic review to determine the safety and efficacy of herb use during lactation, but studies reviewed included surveys and non-experimental designs and did not include a critical review of validity. Forinash et al³² reviewed the efficacy of galactogogues (pharmaceutical and non-pharmaceutical) in the breastfeeding mother, and although the review included studies with experimental designs, a systematic assessment of validity was not performed. Our review differs from these manuscripts in that we focused on evaluating the efficacy of herbal galactogogues; thus, we included only published manuscripts with an experimental design that had an objective outcome measure of breast milk

production. Given that the available published data on the use of herbs as galactogogues are predominantly based upon case reports or anecdotal evidence, we deemed it more important to highlight the areas of concern regarding the design and reporting of the presently limited experimental studies on herbal galactogogues and make recommendations to guide future studies.

Conclusion

Currently the Academy of Breastfeeding Medicine does not have recommendation for the use of herbs as galactogogues. In this review, 4 herbs (shatavari, torbangun, fenugreek, and milk thistle) have potential as galactogogues. However, the trials assessing these potential galactogogues had several limitations decreasing the validity of their results. Given the insufficiency of evidence from these trials, no recommendation is made for the use of herbs as galactogogues. Well-designed and well-conducted clinical trials that address the limitations are needed to generate evidence for recommendations regarding the use of herbs as galactogogues. More importantly, before the assessment of clinical efficacy, studies must first provide evidence for the mechanism of action of herbs as galactogogues and their safety through phytochemical and pharmacokinetic assays. This will lead to a greater understanding of the herbs' composition, breakdown into active and inactive forms, and bioavailability after ingestion. Any attempt at conducting trials without this a priori information is futile and will add little value to the expansion of our current knowledge. Given the widespread use of herbs among lactating women today, establishing a strong evidence base for herbal galactogogues to guide recommendations is a public health concern.

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References

1. Damanik R, Wahlqvist ML, Wattanapenpaiboon N. Lactagogue effects of Torbangun, a Batakese traditional cuisine. *Asia Pac J Clin Nutr.* 2006;15(2):267-74.
2. Centers for Disease Control and Prevention (CDC). Breastfeeding Report Card – United States, 2012. Retrieved on October 21, 2012. Available at <http://www.cdc.gov/breastfeeding/data/reportcard.htm>
3. Mannion C, Mansell D. Breastfeeding self-efficacy and the use of prescription medication: a pilot study. *Obstet Gynecol Int.* 2012;2012:562704.
4. Asztalos EV, Campbell-Yeo M, Dasilva OP, Kiss A, Knoppert DC, Ito S. Enhancing breast milk production with Domperidone in mothers of preterm neonates (empower trial). *BMC Pregnancy Childbirth.* 2012 Aug 31;12(1):87.
5. Academy Of Breastfeeding Medicine Protocol Committee. ABM Clinical Protocol #9: Use of galactogogues in initiating or augmenting the rate of maternal milk secretion (First Revision January 2011). *Breastfeed Med.* 2011 Feb;6(1):41-9.
6. Donovan TJ, Buchanan K. Medications for increasing milk supply in mothers expressing breast milk for their preterm hospitalised infants. *Cochrane Database Syst Rev.* 2012 Mar 14;3:CD005544.

7. Walker, M. Breastfeeding management for the clinician: using the evidence. 2nd ed. Sudbury: Jones & Bartlett Publishers; 2011.
8. The National Children's Study. Use of herbal products in pregnancy, breastfeeding and childhood workshop. December 2003,
http://www.nationalchildrenstudy.gov/about/stayinginformed/listserv/studyassemblymeetings/2003Dec/Pages/agenda_122003.aspx#day3
9. Nordeng H, Havnen GC. Use of herbal drugs in pregnancy: a survey among 400 Norwegian women. *Pharmacoepidemiol Drug Saf.* 2004 Jun;13(6):371-80.
10. The Consort Group. The CONSORT statement. Available at: <http://www.consort-statement.org/consort-statement/>. Accessed November 12, 2012.
11. Anderson PO, Valdes V. A critical review of pharmaceutical galactagogues. *Breastfeed Med.* 2007 Dec;2(4):229-42.
12. Wan EW, Davey K, Page-Sharp M, Hartmann PE, Simmer K, Ilett KF. Dose-effect study of domperidone as a galactagogue in preterm mothers with insufficient milk supply, and its transfer into milk. *Br J Clin Pharmacol.* 2008 Aug;66(2):283-9.

13. Sabins PB, Gaitonde BB, Jetmalani M. Effect of alcoholic extract of *Asparagus racemosus* on mammary glands of rats. *Indian J Exp Biol.* 1968;6:55-7.
14. Sharma K, Bhatnagar, M. *Asparagus racemosus* (Shatavari): a versatile female tonic. *Int J Pharm Biol Arch.* 2011; 2(3):855-863.
15. Gupta, M, & Shaw, B. A double-blind randomized clinical trial for evaluation of galactogogue activity of *Asparagus racemosus* wild. *Iranian J Pharm Res.* 2011;10(1):167-172.
16. Bryant CA. Nursing the adopted infant. *J Am Board Fam Med.* 2006 Jul-Aug;19(4):374-9.
17. Capuco AV, Ellis SE, Hale SA, Long E, Erdman RA, Zhao X, Paape MJ. Lactation persistency: insights from mammary cell proliferation studies. *J Anim Sci.* 2003;81 Suppl 3:18-31.
18. Hullatti K, Bhattacharjee P. Pharmacognostical evaluation of different parts of *Coleus amboinicus* Lour., Lamiaceae. *Phcog Commn.* 2011 Aug;3(24): 39-44.
19. Turkyilmaz C, Onal E, Hirfanoglu IM, Turan O, Koc E, Ergenekon E, Atalay Y. The effect of galactagogue herbal tea on breast milk production and short-term catch-up of birth weight in the first week of life. *J Altern Complement Med.* 2011 Feb;17(2):139-42.

20. Gabay MP. Galactogogues: medications that induce lactation. *J Hum Lact.* 2002 Aug;18(3):274-9.
21. Sreeja S, Anju VS, Sreeja S. In vitro estrogenic activities of fenugreek *Trigonella foenum graecum* seeds. *Indian J Med Res.* 2010 Jun;131:814-9.
22. Patisaul HB, Jefferson W. The pros and cons of phytoestrogens. *Front Neuroendocrinol.* 2010 October; 31(4): 400–419.
23. Cassidy A. Potential risks and benefits of phytoestrogen-rich diets. *Int J Vitam Nutr Res.* 2003 Mar;73(2):120-6.
24. Zapantis A, Steinberg JG, Schilit L. Use of herbals as galactagogues. *J Pharm Pract.* 2012 Apr;25(2):222-31.
25. Di Pierro F, Callegari A, Carotenuto D, Tapia MM. Clinical efficacy, safety and tolerability of BIO-C (micronized Silymarin) as a galactagogue. *Acta Biomed.* 2008 Dec;79(3):205-10.
26. Wen Z, Dumas TE, Schrieber SJ, Hawke RL, Fried MW, Smith PC. Pharmacokinetics

and metabolic profile of free, conjugated, and total silymarin flavonolignans in human plasma after oral administration of milk thistle extract. *Drug Metab Dispos.* 2008 Jan;36(1):65-72. Epub 2007 Oct 3.

27. Sharma S, Ramji S, Kumari S, Bapna JS. Randomized controlled trial of *Asparagus racemosus* (Shatavari) as a lactagogue in lactational inadequacy. *Indian Pediatr.* 1996 Aug;33(8):675-7.
28. Ushiroyama T, Sakuma K, Souen H, Nakai G, Morishima S, Yamashita Y, Kamegai H. Xiong-gui-tiao-xue-yin (Kyuki-chouketsu-in), a traditional herbal medicine, stimulates lactation with increase in secretion of prolactin but not oxytocin in the postpartum period. *Am J Chin Med.* 2007;35(2):195-202.
29. US Food and Drug Administration. Dietary supplements. Accessed on December 20, 2012. Available at <http://www.fda.gov/Food/DietarySupplements/default.htm>.
30. Chatterton RT Jr, Hill PD, Aldag JC, Hodges KR, Belknap SM, Zinaman MJ. Relation of plasma oxytocin and prolactin concentrations to milk production in mothers of preterm infants: influence of stress. *J Clin Endocrinol Metab.* 2000 Oct;85(10):3661-8.
31. Budzynska K, Gardner ZE, Duguo JJ, Low Dog T, Gardiner P. Systematic review of breastfeeding and herbs. *Breastfeed Med.* 2012. DOI:10.1089/bfm.2011.0122.

32. Forinash AB, Yancey AM, Barnes KN, Myles TD. The use of galactogogues in the breastfeeding mother. *Ann Pharmacother.* 2012 Oct;46(10):1392-404.

Table 1. Summary of Experimental Trials of Herbal Galactogogues

Ref., location	Herb Common Name (Latin Name)	Proposed Mechanism	Intervention	Outcomes Measured	Primary ^a Outcome Comparing Treatment vs. Placebo (vs. Control, if used)
Sharma et al, 1996 India	Shatavari (<i>A. racemosus</i>)	Estrogenic effect on mammary glands	2 tsp twice daily for 4 weeks of a 100-g galactogogue mixture (15% shatavari by weight) or placebo	Primary outcome: change in serum prolactin level Other outcomes: infant weight gain, change in volume and frequency of supplementary feedings	Median prolactin level (range): 25 (8-210) ng/ml vs. 38 (7-156) ng/ml Median infant weight gain (range): 30 (14-52) g/d vs 26 (10-75) g/d No statistical significance testing provided
Damanik et al, 2006 Indonesia	Torbangun (<i>C. amboinicus Lour</i>)	Proliferation of secretory mammary cells	150g of torbangun leaves served as a soup 6 days per week for one month; or 1 fenugreek capsule 3x a day for one month; or 1 tablet of Moloco+B12 3x a day for one month Amount of fenugreek per capsule not reported	Primary outcome: breast milk volume Other outcomes: nutritional quality of breast milk	Day 28 mean breast milk volume \pm SD: I: 479 \pm 157 ml vs. F: 400 \pm 215 ml vs. M: 385 \pm 202 ml ($p < 0.05$)

<p>Ushiroyama et al, 2007 Japan</p>	<p>Xiong-gui-tiao-xue-yin Drug X contains: 2 g each of Japanese angelica root, cnidium rhizome, rehmannia root, atractylodes rhizome, hoelen, citrus unshiu peel, cyperus rhizome, moutan bark, and lindera root, 1.5 g each of jujube fruit, Siberian motherwort, ginger rhizome, and glycyrrhiza root</p>	<p>Regulation of prolactin and oxytocin secretion</p>	<p>6.0 g per day of commercial compound Xiong-gui-tiao-xue-yin or 0.375 mg per day of ergometrine</p>	<p>Outcomes: mean breast milk volume, plasma prolactin and oxytocin levels</p>	<p>Day 4 breast milk volume: 277 ± 21 g vs. 155 ± 61 g (p<0.05) Day 6 breast milk volume ± SD: 414 ± 68 g vs. 293 ± 98.5 g (p<0.05) Day 1 plasma prolactin level ± SD: 158 ± 78 ng/ml vs. 129 ± 65 ng/ml (p<0.05) Day 6 plasma prolactin level ± SD: 168 ± 95 ng/ml vs. 117 ± 54 ng/ml (p<0.01)</p>
<p>Di Pierro et al, 2008 Peru</p>	<p>Milk Thistle (<i>S. marianum</i>)</p>	<p>Unknown, possibly estrogenic</p>	<p>420 mg per day of BIO-C® (micronized Silymarin) or placebo</p>	<p>Primary outcome: breast milk quantity Other outcome: macronutrient analysis of breast milk</p>	<p>Day 30 mean breast milk quantity ± SD: 990 ± 102 g vs. 650 ± 78 g (p<0.01)</p>

<p>Gupta & Shaw, 2011 India</p>	<p>Shatavari (<i>A. racemosus</i>)</p>	<p>Steroidal action of saponins in plant</p>	<p>1 capsule 3x daily containing shatavari root powder for 30 days, based on dosing formula: 60mg per kg of body weight or placebo</p>	<p>Primary outcome: change in serum prolactin level Other outcomes: change in infant's weight and mother's weight, subjective satisfaction of mother, and overall well-being and happiness of the infant</p>	<p>Mean percent increase in prolactin level ± SD: 32.9 ± 6.5 % vs. 9.6 ± 4.6 % (p<0.05) Mean percent increase in infant weight ± SD: 16.1 ± 3.7 % vs. 5.7 ± 2.6 % (p<0.05)</p>
<p>Turkyilmaz et al, 2011 Turkey</p>	<p>Fenugreek (<i>T. foenumgraecum</i>)</p>	<p>Possibly estrogenic; stimulate sweat production</p>	<p>At least 3 cups daily of commercial herbal tea (Still tea, Humana®) containing fenugreek; or apple tea (placebo); or no intervention (control) Humana® Still tea contains 100 mg fenugreek and other ingredients</p>	<p>Outcomes: breast milk volume, maximum weight loss (% of birth weight), and time to regain birth weight (day)</p>	<p>Mean breast milk volume ± SD: I: 73.2 ± 53.5 ml vs. P: 38.8 ± 16.3 ml vs. C: 31.1 ± 12.9 ml (p<0.05)</p>

^aFor comparison purposes, only serum prolactin level or breast milk volume outcomes were shown
SD, standard deviation

Table 2. Potential Sources of Bias in Study Design and Reporting

Study measure	Sharma et al ²⁵	Damanik et al ¹	Ushiroyama et al ²⁶	Di Pierro et al ²³	Gupta et al ¹⁵	Turkyilmaz et al ¹⁹
Reproducible recruitment and screening methods	Yes	Yes	No	No	No	Yes
Reproducible eligibility criteria	Yes	Yes	Yes	Yes	No	Yes
Reproducible intervention administration	Yes	No	Yes	Yes	Yes	Yes
Sample size calculation	NR	NR	NR	NR	NR	NR
Adequate sequence generation	NR	NR	NR	NR	Yes	NR
Allocation concealment mechanism	NR	NR	Yes	NR	Yes	NR
Randomization implementation (enrollment and assignment of subjects)	NR	NR	NR	NR	Yes	NR
Blinding of subjects	Yes	No	Unclear	Yes	Yes	No
Blinding of care providers/those assessing outcome	Unclear	No	NR	NR	Yes	Yes
Methods of maintaining blinding of researchers reported	NR	Unclear	NR	NR	Yes	Yes
Intention to treat analysis	Yes	Yes	Yes	Yes	Yes	Yes
Groups balanced at baseline	Yes	NR	Yes	Yes	Yes	Yes
Number lost to follow-up reported by arm	Yes ^a	Yes	Yes	Yes	Yes ^a	Yes
Exclusions after randomization reported by arm with reasons	No	No	No	Yes	Yes	Yes
Adherence reported	Unclear	Unclear	No	Yes	Yes	Yes
Harms of treatment (i.e., side effects) reported	Yes	No	Yes	Yes	Yes	Yes

NR indicates Not Reported or no information is reported to assess the measure.

Yes: Sufficient information was reported, and the measure was appropriately addressed.

No: Sufficient information was reported, and the measure was not appropriately addressed.

Unclear: Insufficient information was reported to fully assess whether the measure was appropriately addressed.

^aTotal number of subjects lost to follow-up was reported but no information was provided for the distribution between treatment and placebo arms