Research Paper
Impact Factor: 4.164
Refereed Journal

IJMDRR
E- ISSN –2395-1885
ISSN -2395-1877

GALACTOGOGUE - ITS STIMULATION ON HUMAN MILK PRODUCTION: A REVIEW

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Abstract

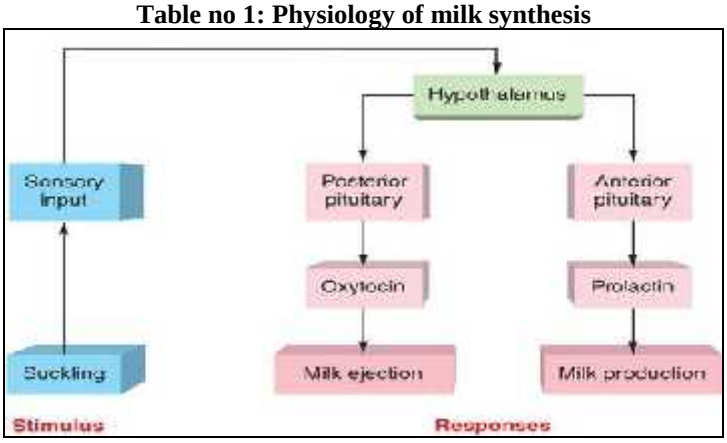
Breast milk is considered the optimal food source for newborns through 1 year of age. Poor production of breast milk is the most frequent cause of lactation failure. To augment breast milk production, a substantial number of women turn to herbal galactogogues. Galactogogues are synthetic or plant molecules used to induce, maintain, and increase milk production. The objective of this review is to review the literature relating to the efficacy and safety of galactogogue including both herbs and drugs on maternal lactation. A systematic review of published literature from 2008-2016 to evaluate the efficacy of galactogogues using the keywords "galactogogue, herb, drugs, maternal milk production, breast feeding efficacy, safety" in Pub med, Google scholar were searched. Additional relevant articles were obtained from article reference list. Six research articles were identified which emphasized on effect of galactogogue on human breast milk production. The galactogogues and 2 drugs have been studied with their mechanism of action, bioactive compound, effectiveness and potential side effects.

Keywords: Galactogogue, Herb, Drugs, Lactation, Breast Milk Production.

Introduction

The current slogan 'breast milk for brain growth and cow's milk for body growth stresses the importance of breastfeeding in mental development. Breast milk is the best nutrition for infants and is used as the 'gold' standard for good infant nutrition at birth (By Elizabeth, 4th edition). The World Health Organisation (WHO), the American Academy of Paediatrics (AAP), and the American College of Obstetricians and Gynaecologists (ACOG) all recommendation breastfeeding for the first six months of age. Knowledge of the biology of human milk and the physiology of its production, secretion and delivery is critical in deeply understanding the benefits of breastfeeding (Abeer El Sakka et al, 2014).

Table no 1: Physiology of milk synthesis



(HumanPhysiology2011)

Infant suckling stimulates the nerve endings in the nipple and areola, which signal the pituitary gland in the brain to release two hormones, prolactin and oxytocin. Prolactin causes the alveoli to take nutrients (proteins, sugars) from your blood supply and turn them into breast milk. Oxytocin causes the cells around the alveoli to contract and eject your milk down the milk ducts. This passing of the milk down the ducts is called the "let-down" (milk ejection) reflex. (2008, Sutter Health).

Reduced or poor breast milk production is called as hypogalactia. (Wilinska, M. &Schleußner, E, 2015)Many factors influence overall maternal milk production, including maternal pain, illness, balance of time when returning to work, anxiety, or emotional stress.**(**Alicia B Forinash et al,2012).Mothers of very preterm infants struggle to maintain a supply of breast milk and poor milk supply can result from less than perfect positioning and attachment of the baby at the breast resulting in incomplete breast drainage. Infrequent, restricted, limited feeds, reduction in milk supply is frequently noted after premature delivery with milk supply maintained only by expression over a period of weeks **(**Abeer El Sakka et al,2014).

The infant can also cause low milk production in the mother by failing to remove enough milk in an effective manner, as milk production is dependent upon both the volume of milk removed and the quality of the sucking stimulation.**(**Geddes 2008)Examples of infant factors include oro-motor dysfunction, hypotonia, and abnormalities of the oral cavity such as clefts of the hard or soft palate**(**Amir 2006;Kent 2012**;** McClellan 2012).It can be increased in several ways, such as; psychological support and relaxation techniques. Non pharmacological measures such as added emotional support, kangaroo care/skin to skin, compressing and massage, relaxation techniques, expressing breast milk at the baby's bedside, increasing pumping times, and alterations in mechanical expression contribute to a variable level of success in augmenting milk production.(Alexander C Allen,2006)

Effect of Selected Drugs Andbotanical Herbs on Milk Production

Two Dopamine antagonists, Metoclopramide and Domperidone are reviewed in this article. These drugs block the dopamine 2 receptors (D2R) in the central nervous system which induces an increase of PRL synthesis in lactotrophic cells of the anterior pituitary. Activation by an agonist of D2R, a G protein receptor, the K^+ channels opening, increases intracellular concentration of this ion and reduces Ca^{2+}entry and its intracellular concentration. When an antagonist binds to the receptor, those pathways are blocked, and the synthesis and release of PRL are activated. This high blood level of PRL increases milk protein synthesis rate and mammary epithelial cells (MEC) proliferation. In the pituitary gland, antagonists bind to the receptor (D2R) dopamine 2 and induce PRL gene expression, blood level of PRL increases, milk protein synthesis rate increases, and mammary epithelial cells (MEC) proliferation is stimulated**(**Felipe Penagos Tabares,2014)

Some of the more popular botanical galactagogues include fenugreek (*Trigonellafoenum-graecum*), fennel *(Foeniculum vulgare)*, shatavari *(Asparagus racemosus)*, anise *(Pimpinellaanisum),*milk thistle *(Silybummarianum),*barley *(Hordeuml vulgare)*, malunggay *(Moringaoleifera),*and goat's rue (*Galega officinalis*) (Abascal 2008;Bingel 1994;Bruckner 1993;Sim 2014).

Herbal galactogogues effect could be mediated by phytoestrogenic action and that some molecules may have effects similar to 17β-estradiol (E2), an endogenous estrogen that promotes the proliferation of MEC(Felipe Penagos Tabares,2014).

Phytoestrogen molecules have E2-like action; these molecules could induce the expression of PRL receptor (PRLR) and EGF receptor (EGFR) and could up regulate casein production and lactose synthetase activity in MEC.E2 triggers PRL gene expression through at least two independent and undetermined pathways in pituitary lacto tropic cells. A first route is characterized to act through the intracellular receptor E2 (E2R) that finally increases levels of PRL and increases secretion of milk. These effects are mediated by the pathway triggered by α isoform of the membrane-associated estrogen receptor (mE2R). The second route inhibits the pathway activated by D2R dopamine receptor, stimulating PRL production and proliferation of lactotrophic cells by increasing cAMP ending in PKA phosphorylation pathways that trigger PRL gene expression (Felipe Penagos Tabares,2014).

Table No 3: Mechanisms and Effects of Herbal Galactogogues

Oral Herbal Galactogogue	Picture	Bioactive compound	Mechanism	Harm	Reference
1)Fenugreek (*Trigonellafoenum-graecum*)		Phytoestrogen & diosgenin	Increases milk flow by its phytoestrogens and diosgenincontents.	Digestive upset, loose stools, light headedness, maple smell in the urine and sweat.	, Barone 1999, Doggrell 2014, Forinash 2012, Hale 2007, Zuppa 2010
2) Fennel (*Foeniculum vulgare*)		Anethole	Anethole, considered weakly estrogenic; may increase breast milk production or assist with the 'let-down' reflex.	Essential oil, may be toxic in large amounts	Abasca 2008, Bingel 1998, Bruckner 1993, Humphrey 2007, Low Dog 2009, Mills 2006, Mortel 2013, Romm 2010
3)Shatavari*(As*		Saponins	Estrogenic; may	Runny nose, itchy	Chaudhury

paragus racemosus)			stimulate production by increasing prolactin.	conjunctivitis, contact dermatitis and cough. May have laxative effect	1983, Mortel 2013, Zapantis 2012
4)Torbangunle aves(*Coleus amboinicuLour*)		-	May stimulate proliferation of secretary mammary cells	Hypoglycaemia and stimulation of the thyroid gland.	Bingel 1994,Zapantis 2012, Mortel 2013
5) Goat's rue (*Galega officinalis*)		Galegin	Galegin, a precursor to metformin. May exert effects via contents of steroidal saponins stimulates mammary growth	No data for humans.	Abasca 2008, Bruckner 1993, Humphrey 2007, MacIntosh 2004, Rasekh 2008, Romm 2010
6)Anise *(Pimpinellaanisum)*		Anethole	Anethole, considered weakly estrogenic; the aromatic compound in anise acts as a dopamine receptor antagonist	Possible allergen for some people	Bingel 1994, Bruckner 1993, Humphrey 2007, Low Dog 2009, Romm 2010
7) Milk thistle *(Silybummarianum)*		Silybin ,silychristin, silydianin	Appears to stimulate prolactin; possibly estrogenic	None known	Abascal 2008, Bingel 1994, Capasso 2009, Low Dog 2009, Mills 2006, Mortel 2013
8) Barley *(Hordeum vulgare)*		Lignans	Polysaccharide stimulates prolactin	None known.	Bingel 2014, Humphrey 2007, Koletzko 2000, MacIntosh 2004, Sawagado 1988
9)Malunggay or Drumstick*(Moringaoleifera)*		Saponins	Increases prolactin	None known.	Bingel 2014

(Foong, S. C., Tan, M. L.,2015)

Compilation of Researches, 2008-2016

Source	Author	Title	Method	Major findings	Conclusion
Ochsner journel,2016	Alessandro N.Bazzano, RAEBECCA Hofer, Shelley Thibeay, VernoicaGillispies	Effect of herbal & Pharmaceutical galactogogue on milk production	PUBMED, Indian journal of Paediatrics, Google scholar. Between July,15, 2015- August 18,2015. Study on galactogogues, herbal, pharmaceutical, domperidone, metoclopramide. Keywords-herbal galactogogue-dates,fenugreek, shatavri,garlic.	Only 1 study showed significant result on lactation on use age of herbal galactogogue Shatavri- no significant result, needs to be mixed with other herbs. Fenugreek- very effective in daily milk production. Malunggay- moderate effect not as strong as fenugreek. Domperidone(D)- has side effects, though 2 studies showed + result. Metoclopramide less side effects than D but more effective in lactation than D.	More studies and information is needed to guide the use of pharmaceutical and herbal galactogogue.

Source	Author	Title	Method	Major findings	Conclusion
Iranian red crescent medical journal, 2015	Vida ghasemi, MassomehKheirkhah, Mohsen vahedi	Effect of herbal tea containing fenugreek seed on the sign of breast milk sufficiency in iranian girl infants	Conducted between July 2014-august 2015. at Tehran university of medical sciences, Tehran city. Subjects-78 girl term infants of 0-4 months. Treatment group(n=39) -given herbal tea with fenugreek seeds powder (7.5gm) + 3 gm black tea, 3ice a day, 2 hrs after each meal, for 4 weeks Control group (n=39) were only on herbal tea with added black tea.	At the end of 4th week compared to pre-intervention condition, weight, head circumference, no. of wet diapers, frequency of defecation and number of times of infants of the treatment group significantly increased though there was no change in height growth.	Thus fenugreek seeds increases breast milk sufficiency including infants growth parameters such as weight, HC, & no. of wet diapers/day along with frequency of defecation.

Source	Author	Title	Method	Major findings	Conclusion
British journal of clinical pharmacology , April 2008	Elise W-X.Wan, Kaye Dvey, Madhu Page- Sharp, Peter.E. Hartmann Ketien Slimmer, KenethF.Ilett.	Dose effect study of domperidone[D] as a galactogogue in preterm mothers with insufficient milk supply & its transfer into milk.	Location:- King Edward Memorial Hospital, Australia. To study the effect of different doses, 3 groups were made:-Run in(no drug group), Phase 1(30 mg of D daily) and Phase 2 (60 mg.). The phase 1 & phase 2 doses were given 10 or 20 mg every 8 hrs, and their duration was 1 & 2 weeks respectively. Their effect was assessed by pumping both the breast simultaneously to measure the volume over 15 sessions on arrival at the clinic when morning dose of D was given and further after 1 hr, 2 hr & 3 hr after this dose. Parameters checked:- serum prolactin & concentration of D in milk.	4/6 mothers showed increased milk production with both the doses & 2 did not show any response. Among responders, Run in phase showed mean milk production of 8.7 +/-3.1gh Phase 1=23.6+/- 3.9gh Phase 2=29.4+/-6.6gh .Also few mothers dropped in the middle of the study because of the side effects like dry mouth abdominal cramping, headache, constipation,. More no. of women were affected with the symptoms by 60 mg dose. In all participants serum prolactin was increased significantly for both doses.	In one third of mothers, domperidone did not increase milk production, but in remainder milk production increased at both the doses.

Source	Author	Title	Method	Major findings	Conclusion
BMJ Jornal, ADC Fetal and neonatal edition, 2012	Jennifer Ingram, Hazel Taylor, Cathy Churchill, Alison Pike, &Rosemary Greenwood	Metoclopramide or domperidone for increasing maternal breast milk output	Study took place at NICU. 80 mothers expressing breast milk for their infants (mean gestational age 28 weeks) based in NICU and the amounts expressed fell short of the prescribed target. Mothers were randomised to receive domperidone or metoclopramide for 10 days (10 mg three times a day). Parameters checked- Total milk volume daily for 10 days before the medication, 10 days during the trial and 10 days after medication. Adverse side effects were also recorded.	More milk was produced in the domperidone group & a mean of 96.3% increase in milk volume compared with a 93.7% increase for metoclopramide was seen.Prior to medication, the mean amount of milk produced for those on domperidone was greater than the mean for those on metoclopramide. Mothers on metoclopramide showed more side effects than those on domperidone.	Oral domperidone and metoclopramide increased the volume of milk produced by mothers who are expressing to feed their babies in NICU. There were small differences in milk output between the two medications and in the incidence of side effects, but the differences were non-significant.

Conclusion

Despite of the use of herbal and pharmacological galactogogues, there are limited data on their safety and efficacy. However, pharmacokinetics and pharmacodynamics active ingredients present in galactogogues plants are not well characterized and further research is compulsory to determine their mechanisms of action and to establish therapeutic ranges, dosage, and possible side effects in different domestic species and humans. Future studies needs to be undertaken to study the safety and recommended doses that stimulate breast milk production.

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