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A Comprehensive Overview of Galactagogues: Herbal and Synthetic Agents for Enhanced Milk Production

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Introduction

Galactagogues are medications that aid in initiating and maintaining adequate milk production. Most exert their pharmacologic effects through interaction with dopamine receptors, resulting in increased prolactin (PRL) levels and thereby augmenting milk supply. These may be synthetic or plant molecules that induce, maintain or increase milk production which mediates complex processes involving action between physical and and physiological factors. They act through exerting an influence on Adreno hypothalamo-hypophyseal-gonadal axis by inhibiting hypothalamic dopaminergic receptors or by inhibiting dopamine producing neurons. Galactagogues stimulate the activity of alveolar tissue and raise the secretory activity and thereby restore and regulate milk yield.

Herbal Galactagogues

Different plants have been used since long in different cultures for the purpose of stimulating milk production in women and in dairy animals. Galactagogue effect of various plants has been studied in the recent years which give the clear evidence that use of herbal galactagogues can increase milk synthesis and are found to be safer especially in case of humans. Several herbal galactagogues have been reported as safe substances that in appropriate and economic doses can be therapeutically used in domestic animals and in dairy food supplements. Plants with galactagogue component include Fenugreek, Fennel, Milk Thistle, Shatavari, Goat's Rue and Anise**.** Nowadays herbal preparations are known to significantly increase milk production in women, goats, cows and other species. Some of the examples of natural galactagogues is mentioned in the text below.

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a) Shatavari *(Asparagus racemosus*)

The word Shatavari means "one who is acceptable to many". It is considered both a general tonic and a female reproductive tonic. This herb is found to have many medicinal and therapeutic uses one of them being its effect in increasing milk production. Shatavari is known to be composed of about more than 50 organic chemical compounds of different groups such as steroids saponins, glycosides, alkaloids, polysaccharides, mucilage, racemosol and isoflavones which possess numerous medicinal properties.

Various efforts have been made till date to explore the use of Shatavari in dairy animals to improve the productive and reproductive performance of animals. In a study it was found that supplementation of roots of Shatavari at the rate of 0.5 kg at milking time alongwith concentrate is found to increase milk yield of buffaloes significantly. Similar results were also seen in freshly calved crossbred cattle that when oral supplementation of root powder of Shatavari @100gms on alternate day, there was significant improvement in milk production. Shatavari contains steroidal saponins (as shatavarins I and IV). Shatavarin I is the most glycosided molecule with 3 glucose and a rhamnose moieties attached to sarsasapogenin, and a hypothesis states that estrogenic activity of Shatavari results from hormone like action of these steroidal saponins. Another hypothesis states that the growth of mammary tissue is caused by the action of released corticoids or PRL. Estrogens along with having potentiating effect on PRL production also have stimulating effect on ductal epithelium causing them to lengthen.

Systemic administration of alcoholic extract of Shatavari showed lactogenic effect in weaned rats as there was increase in weight of mammary glands, inhibition of involution of lobulo-alveolar tissue and maintained milk secretion. Other studies also showed estrogenic effect of Shatavari in genital organs and mammary glands of rats with hyperplasia in alveolar tissue and acini along with increased milk production. In pigs and goats, feeding Lactare (commercial galactagogues containing Shatavari) also increased growth of mammary glands alveolar tissue and acini.

b) Fenugreek (*Trigonella graecum foecum*)

It is a leguminous herb cultivated in India. The endosperm portion of the plant seeds is found to be rich in galactomannan and young seeds mainly contain carbohydrates and sugar. Mature seeds contain the amino acids, fatty acids, vitamins and saponins. It has numerous

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pharmacological effects which include hypoglycemic, hypolipidemic, carminative, antidiabetic and galactagogue activity.

Numerous reports indicate that the seeds of plant have mastogenic effect, stimulating growth of mammary gland. It is being used as a galactogogue due to significant levels of phytoestrogens present in it. In a study it was found that fenugreek seeds contain estrogen like compounds that stimulate pS2 (estrogen induced protein) expression in a breast cancer cell line. pS2 is being used to assess the estrogenecity of a compound. Although limited research has been conducted on its pharmacodynamic and pharmacokinetic properties to determine the extent to which its components are excreted in milk but phytoestrogens such as diosgenin, a type of steroidal sapogenin could explain significant increase observed in milk flow. Moreover, this plant has been also shown to influence the maintainence of lactation in ruminants, ad buffaloes fed with fenugreek seeds showed increase in milk production. In goats also, feeding 10gm of fenugreek seeds daily increase milk production.

Different studies suggest that stimulation of endogenous hormone secretion may be the way by which fenugreek exerts its action on increasing milk production. In goats feeding fenugreek increased milk production and this effect might be mediated *via* PRL stimulation because PRL concentration was found to be significantly higher in fenugreek fed goats when compared with control group. It is also suggested that in buffaloes plasma growth hormone could be responsible in mediating fenugreek's action. In a study it was found that feeding fenugreek seeds to dairy cows have been found to improve the profile of functional fatty acids in the milk, produced lower cholesterol in milk without altering milk flavour and taste. A study in Saudi goats leads to an observation that goats fed with 60gm/day fenugreek seed powder had significantly higher milk yield than control group. Similar results were seen in goats fed with fenugreek along with decrease in milk fat content with an inconsistent pattern of protein, lactose and SNF.

c) Milk Thistle (*Silybum marianum)*

It is a plant native to mediterranean, Europe and also commonly cultivated in Jammu and Kashmir. The bioactive components include flavonolignans- silybin, sylidianin and silychristin which are together called as silymarin, and are similar to steroid hormones responsible for its protein synthesis facilitatory actions. The primary constituent of silymarin is 60% of silybin primarily found in fruits and seeds. Milk thistle has various medicinal

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properties like anti-oxidative, hepatoprotective, immunomodulatory, anti-fibrotic, anti-carcinogenic activity *etc*. This herb is great for removing toxins from the body and works as a great tonic for liver.

Human and animal studies have shown that milk thistle has promising lactogenic properties. In a study it was found that after treatment with 10kg silymarin/cow/day *per os* in the peripartum period, there was an increase in milk production of 5 to 6 litres/day/cow. Administration of Milk Thistle improves physiological status of cow, which leads to faster recovery, increased feed intake and increased milk production. Silymarin is well tolerated when administered orally. Silymarin present in Silybum increases the activity of mammary gland and therefore production of milk. Therefore, silymarin increases PRL levels on consumption during pregnancy and lactation. Studies also suggested that silymarin does not have any adverse allergic reactions and report no toxicity. In an animal study milk thistle seed extract containing 70% silymarin was tested for its galactagogue effect in rabbits during pregnancy and lactation and it was found that the seed extracts help in milk production through increased hormonal levels. Milk thistle is known to be best lactation supporting plant its use in dairy cows contributing to an increase in daily milk yield by 3 to 4 kg in various studies.

Synthetic Galactagogues

Synthetic molecules that are used to increase lactation include dopamine antagonists such as antiemetics (metoclopramide, domperidone) and antipsychotics (sulpiride and chlorpromazine). Hormone synthetic analogues include oxytocin, recombinant bovine somatotropin (rBST), Thyrotropin-Releasing Hormone (TRH) and medroxyprogesterone, are also included in list of synthetic galactagogues.

a) Oxytocin

The major sites where this peptide hormone is expressed include magnocellular neuron region in the supraoptic and paraventricular hypothalamic nuclei. Oxytocin is released into the general circulation from the neural lobe of the pituitary by the milking stimulus, induces milk discharge during lactation.

Oxytocin binds to specific receptors present on myoepithelial cells surrounding the alveoli and small intralobular ductules and induces contraction of myoepithelium cell which leads to collapse of alveolar lumen and shortens ducts leading to expulsion of milk in cisterns. A number of reports are known to show that administering exogenous oxytocin at the time of

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machine milking can increase milk production. It has been used to induce milk ejection in cases where dysfunction has been noticed. This hormone induces contraction *via* G protein receptor, and Phospholipase C (PLC) is activated and induces the formation of diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP_3), by hydrolysis of membrane lipid phosphatidylinositol 4,5-bisphosphate (IPI_2). IP_3 induces intracellular Ca^{++} release, and this active Ca^{++}-calmodulin system triggers the activation of myosin light chain kinase (MLCK) which initiates smooth muscle contraction in mammary myoepithelial cells. Other *in vitro* studies have revealed the role of oxytocin on mammary epithelial cell proliferation. Expression and immunolocalization of oxytocin receptors in lactating monkey and human mammary epithelium and binding of oxytocin in lactating rabbit mammary epithelial cells have also been reported. In rabbits, oxytocin not only stimulates milk ejection by the contraction of mammary myoepithelial cells, but also induces exocytosis of milk in myoepithelial cells. Oxytocin can increase milk production and is indicated in agalactia or hypogalactia or dysfunction of milk ejection reflex in stress or premature birth cases. When used appropriately at reasonable dosages oxytocin rarely cause significant side effects. The use of oxytocin in dairy animals is banned in India and other countries because its continuous use in each milking affects the animal welfare. The dosage in dogs and cats is 0.5 to 0.2 IU/kg, SC every 2 hours. In bovine, SC injection dose of 20 IU/animal at each milking throughout lactation increases milk production. The doses most commonly used in sheep and goats are 1-5 IU SC every milking. In swine reported doses are between 0.025 and 0.05 IU given as intravenous rapid injections at each milking. In equines the dose is 20 IU IM per animal every miking.

b) Thyrotropin releasing hormone (TRH)

Thyrotropin releasing hormone is synthesized in the hypothalamus stimulating the secretion of Thyroid stimulating hormone (TSH) and PRL by the anterior pituitary. Synthetic thyrotropin hormone (TRH) L-(Pyro)-Glu-His-Pro-NH2(2, 5), increases serum thyroxine, PRL and growth hormone concentration of lactating dairy cows.

Synthetic thyrotropin releasing hormone applied intravenously can significantly increase serum PRL by the anterior pituitary. TRH is the principle physiological factor stimulating the fast release of PRL. Synthetic TRH applied intravenously can significantly increase serum PRL in proestrus female and in normal and estrogen primed male rats, 10 minutes after injection. Subcutaneous administration of TRH was also found to be effective in

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increasing plasma PRL levels in lactating cows. The TRH molecule binds to its receptor in the lactotrophic cells triggering the activation of PRL and increasing the formation of DAG and IP_3. DAG activates protein kinase C (PKC) and PKC promotes phosphorylation pathways that culminate in PRL gene expression, IP_3 induces release of Ca^{++} from endoplasmic reticulum, forming the complex Ca^{++}-calmodulin (CaM), and this complex induces the PRL gene expression. Furthermore, the increase of intracellular Ca^{++} and CaM stimulates the release of the PRL stored in the vesicles.

c) Dopamine antagonists

There are various examples of dopamine antagonists like metoclopramide, domperidone, chlorpromazine *etc*. which are being used as galactagogues. These antagonists generally block the dopamine 2 receptors (D2R) which ultimately results in an increase of PRL synthesis in lactotrophic cells of anterior pituitary whereas the dopamine agonists induce opening of K^+ channels through G-protein receptor subunit G-alpha-0, leading to increase in K^+ ion concentration and decrease in Ca^{++} ion and its intracellular concentration. This low Ca^{++} inhibits vesicle formation and PRL secretion. When an antagonist binds, it blocks all the pathways by which agonist decrease Ca^{++} concentration and inhibits PRL secretion thus, activating the synthesis and release of PRL. Metoclopramide is used to treat cases of secondary hypogalactia at the dose rate of 0.1-0.2mg/kg subcutaneously every 6-8 hours for 4-6 days. Domperidone is recommended at the dose rate of 2.2mg/kg subcutaneously every 12hours for 4-6 days in case of dogs and cats. In equines domperidone is administered at the dose rate of 1.1mg/kg *per os* every 12 hours to increase PRL blood concentration. Chlorpromazine is found to increase lobulo-alveolar growth and initiate milk secretion when administered at the dose rate of 15mg/kg body weight in rats with 10 µg priming with estradiol daily.

Homeopathy galactagogues

Homeopathy offers a range of galactagogues, which are believed to stimulate and enhance lactation. Homeopathic remedies are derived from natural sources and are administered in highly diluted forms that are believed to trigger the innate healing mechanisms of body. These remedies can help address issues of low milk production, hormonal imbalances, or stress that may affect milk production. However, the efficacy of homeopathic preparations is debated, and scientific evidence supporting their use is limited. Some of the commonly used homeopathic galactagogues include *Ricinus communis*, *Urtica urenes*, *Pulsatilla pratensis*, Lac

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Defloratum *etc*. *Ricinus communis*, prepared from castor seed and available in potency of 200 and 1000. *Urtica urenes* is a potent medicine for agalactia, and available in potency of 200 and 1000. Lac Defloratum is prepared from skimmed milk and known to stimulate lactation and also available in potency of 200 and 1000.

Conclusion

Galactagogues play a significant role in supporting lactation across animals as well as humans. Both herbal and synthetic galactagogues have been extensively studied and utilized to enhance milk production by influencing mammary gland function and levels of prolactin. Herbal galactagogues like Shatavari, Fenugreek and Milk Thistle have demonstrated effectiveness in stimulating milk synthesis through their bioactive compounds and hormonal interactions. Similarly, synthetic galactagogues such as oxytocin and dopamine antagonists like metoclopramide and domperidone have shown efficacy in clinical settings, although they are associated with some side effects and some scientific guidelines need to be followed. Homeopathic galactagogues are popularly used, but lack major scientific evidences but are still used due to their natural approach. The choice of galactagogue depends on factors such as species-specific physiology and individual health considerations, and they are very helpful in lactation management practices.

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