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Lesser-Known Metabolites Influencing Ovarian Function, Follicular Development, and Embryo Viability in Dairy Cows

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Abstract

The intricate processes of ovarian function, follicular development, and embryo viability in dairy cows are tightly regulated by a complex network of metabolites. While conventional biomarkers, such as steroid hormones, amino acids, and glucose metabolites, have been extensively studied, a growing body of evidence suggests that lesser-known metabolites play pivotal roles in bovine reproductive physiology. Dairy cattle fertility is critical for maintaining optimal milk production and herd sustainability, necessitating deeper insights into metabolic influences on ovarian function. This review explores the emerging significance of unconventional metabolic intermediates, including lipid-derived molecules, microbiota-associated metabolites, purine and pyrimidine derivatives, and extracellular matrix components, in modulating ovarian follicular dynamics and embryonic survival in dairy cows. Recent findings highlight that sphingosine-1-phosphate and resolvin D1 contribute to follicular angiogenesis and oocyte protection, while butyrate and propionate influence granulosa cell function and steroidogenesis. In dairy cows, the regulation of ovarian oxidative homeostasis is essential for sustained reproductive efficiency, with reactive oxygen species metabolites, such as hydrogen sulfide and peroxynitrite, exerting direct effects on follicular maturation and luteal function. Emerging evidence also underscores the role of plant-derived phytoestrogenic metabolites in modifying follicular estrogen signaling and embryo implantation potential, which is particularly relevant for dairy cows exposed to phytoestrogen-rich diets. Understanding the physiological roles of these metabolites provides novel insights into ovarian metabolic homeostasis, offering potential therapeutic targets for improving fertility outcomes in dairy cattle. Given the economic significance of reproductive efficiency in dairy herds, this review underscores the necessity of expanding metabolic research beyond classical pathways to unravel novel regulators of ovarian function and embryo viability in dairy cows.

Keywords: Dairy cow, embryo viability, follicular development, lesser-known metabolites, ovarian function, reproductive efficiency

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INTRODUCTION

Ovarian function, follicular development, and embryo viability are tightly coordinated physiological processes that determine reproductive success in dairy cows. These processes are regulated by a complex interplay of hormonal, cellular, and metabolic signals that influence follicular recruitment, oocyte maturation, corpus luteum function, and early embryonic survival. While classical metabolites, such as glucose, amino acids, and steroid hormones, have been extensively studied in bovine ovarian physiology, a growing body of evidence suggests that a diverse array of lesser-known metabolites also contributes to these critical functions. These metabolites originate from various biochemical pathways, including lipid metabolism, gut microbial activity, purine and pyrimidine metabolism, and extracellular matrix remodeling. Their roles in follicular growth, oocyte competence, and embryonic development remain largely underexplored, despite their potential significance in dairy cow fertility and herd productivity.

Recent studies have identified several unconventional metabolites that exert profound effects on ovarian function and embryo viability in dairy cows. Lipid-derived molecules, such as lysophosphatidic acid and sphingosine-1-phosphate regulate granulosa cell proliferation [1], while microbiota-derived metabolites, including butyrate and propionate, modulate ovarian steroidogenesis and follicular maturation. Reactive oxygen species metabolites, such as hydrogen sulfide and peroxynitrite, influence oocyte quality by maintaining oxidative balance within the follicular microenvironment [2]. Additionally, plant-derived phytoestrogenic compounds, including genistein and equol, have been implicated in modulating estrogen receptor activity, thereby affecting follicular responsiveness to gonadotropins [3]. Given the economic importance of reproductive efficiency in dairy herds, the precise mechanisms through which these metabolites influence ovarian physiology require further investigation.

This study provides a novel perspective by systematically examining the impact of lesser-known metabolites on ovarian function, follicular development, and embryo viability in dairy cows. Unlike previous reviews that primarily focus on conventional metabolic regulators, this study integrates diverse metabolite classes and highlights their functional significance in bovine reproductive physiology. By identifying and categorizing these metabolites based on their biochemical origins and physiological roles, this review offers new insights into ovarian metabolic homeostasis. Understanding these metabolic interactions has broad implications for optimizing fertility in dairy cattle and developing targeted nutritional and therapeutic interventions for improving reproductive performance. This study thus expands the current knowledge base and underscores the need for further research into the metabolic regulation of ovarian and embryonic function in dairy cows.

LIPID-DERIVED METABOLITES

Lysophosphatidic Acid

Lysophosphatidic acid (LPA) plays a vital role in follicular development and oocyte maturation by promoting granulosa cell proliferation and improving cellular communication. In dairy cows, LPA enhances the secretion of growth factors within the follicle, which is crucial for oocyte maturation and follicular health [4]. By stimulating intracellular signaling pathways, LPA contributes to the selection of dominant follicles and supports the optimal hormonal environment needed for successful ovulation and fertilization. Its role in enhancing oocyte quality directly impacts embryo development and the likelihood of successful conception in dairy cows.

Sphingosine-1-Phosphate

Sphingosine-1-phosphate (S1P) plays a protective role by shielding oocytes from oxidative stress, which is a key factor in reducing oocyte quality and fertility. In dairy cows, S1P maintains oocyte integrity by reducing the damage caused by reactive oxygen species (ROS), which can impair follicular function and oocyte maturation. By modulating cellular stress responses, S1P preserves follicular health, supports proper oocyte maturation, and enhances embryo viability [5]. The protective effects of S1P can improve reproductive outcomes, particularly by ensuring the quality of oocytes available for fertilization and subsequent embryo development.

Prostaglandin F2α Metabolites

Prostaglandin F2α (PGF2α) metabolites are essential for the regulation of luteolysis and corpus luteum function in dairy cows. PGF2α facilitates the regression of the corpus luteum when pregnancy does not occur, helping regulate the hormonal environment during the estrous cycle [6]. By controlling luteal regression and progesterone secretion, PGF2α metabolites ensure proper synchronization of the reproductive cycle and timely ovulation. These metabolites also influence the quality of the luteal phase,

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contributing to the success of embryo implantation and improving overall fertility outcomes in dairy cows by optimizing the hormonal balance during estrus and pregnancy.

RESOLVIN D1

Resolvin D1, a key mediator in inflammation resolution, modulates the ovarian microenvironment, which is crucial for follicular development and oocyte maturation. In dairy cows, resolvin D1 helps regulate inflammatory responses that occur during the follicular phase, ovulation, and luteal phase, creating an optimal environment for follicular growth. By promoting the resolution of inflammation, resolvin D1 prevents excessive inflammatory damage and supports cellular repair, ensuring that the ovarian cells function optimally. This regulation is crucial for maintaining healthy follicles, improving embryo viability, and ensuring successful conception and pregnancy outcomes in dairy cows.

12-HETE

12-Hydroxyeicosatetraenoic acid (12-HETE), a metabolite derived from arachidonic acid, influences granulosa cell proliferation, a key process in follicular development. In dairy cows, 12-HETE promotes the expansion and growth of granulosa cells, which are essential for the proper development of ovarian follicles. The proliferation of these cells ensures that follicles can support oocyte maturation and enhance oocyte quality. By contributing to the optimal growth of healthy follicles, 12-HETE improves the chances of successful fertilization and embryo development, playing a significant role in enhancing reproductive success and embryo viability in dairy cows.

AMINO ACID METABOLITES

Kynurenic Acid

Kynurenic acid, a metabolite of tryptophan, plays a crucial role in modulating ovarian steroidogenesis in dairy cows. By influencing the activity of enzymes involved in steroid hormone production, kynurenic acid helps regulate the synthesis of estrogen and progesterone, two key hormones required for follicular development and oocyte maturation. Through its impact on hormone regulation, kynurenic acid contributes to maintaining the hormonal balance essential for follicular health, optimizing oocyte quality, and improving embryo viability [7]. This regulation is vital for enhancing fertility and ensuring successful reproductive outcomes in dairy cows.

Asparagine-Derived Polyamines

Asparagine-derived polyamines, such as putrescine and spermidine, are crucial for supporting granulosa cell proliferation during follicular development in dairy cows. These polyamines promote cellular growth and division, which are essential for the expansion of granulosa cells within the ovarian follicle. As these cells play a vital role in oocyte maturation and the production of hormones, polyamines contribute to the development of healthy follicles. By supporting granulosa cell function, these metabolites enhance follicular growth and improve oocyte quality, ultimately improving embryo development and increasing the chances of successful pregnancy in dairy cows.

L-Arginine-Derived Nitric Oxide

L-Arginine-derived nitric oxide (NO) plays a pivotal role in regulating oocyte quality by modulating various ovarian processes in dairy cows [8]. NO influences blood flow to the ovaries, supporting the nutrient and oxygen supply to developing follicles. It also regulates the maturation of oocytes by modulating intracellular signaling pathways, such as those involved in cellular stress response and apoptosis. By improving oocyte quality and facilitating optimal follicular function, L-arginine-derived NO contributes to enhanced fertility and embryo viability, supporting successful reproduction in dairy cows.

Glutathione-Derived Metabolites

Glutathione-derived metabolites are critical for protecting ovarian follicles from oxidative damage, a major factor influencing oocyte and embryo quality in dairy cows. Glutathione, a powerful antioxidant, neutralizes reactive oxygen species (ROS) that can cause cellular damage, impair follicular development, and reduce oocyte quality [9]. The metabolites of glutathione enhance this protective mechanism by maintaining the redox balance within ovarian cells. By preventing oxidative stress, these metabolites ensure healthy follicular development and oocyte maturation, leading to better embryo viability and improved reproductive success in dairy cows.

Γ-Aminobutyric Acid (GABA)

γ-Aminobutyric acid (GABA) plays an important role in modulating ovarian follicular response to gonadotropins, which are essential for follicle stimulating and luteinizing hormone actions in dairy cows. GABA, as an inhibitory neurotransmitter, regulates the signaling pathways that control follicular growth and oocyte maturation [10]. By influencing the response of ovarian cells to gonadotropins, GABA contributes to the proper selection of follicles for ovulation. This modulation ensures optimal follicular development, enhances oocyte quality, and supports successful fertilization and embryo development, ultimately improving fertility and reproductive outcomes in dairy cows.

CARBOHYDRATE METABOLITES

Fructose-6-Phosphate

Fructose-6-phosphate is a crucial metabolite in the energy metabolism of oocytes, particularly in dairy cows [11]. As an intermediate in the glycolysis pathway, it supports ATP production, which is essential for cellular functions, including oocyte maturation and early embryo development. By ensuring a stable energy supply, fructose-6-phosphate helps maintain the metabolic requirements of the oocyte, promoting optimal follicular growth and improving oocyte quality. This enhances fertilization potential and ultimately contributes to improved embryo viability and successful reproduction in dairy cows.

Mannose-6-Phosphate

Mannose-6-phosphate plays a significant role in regulating endometrial receptivity, which is vital for successful implantation and embryo development in dairy cows. This metabolite is involved in glycosylation processes, which affect the expression of cell surface receptors and signaling pathways that mediate embryo attachment to the uterine lining. By influencing the endometrial environment, mannose-6-phosphate ensures that the uterus is optimally prepared to support embryo implantation and early-stage pregnancy, ultimately improving reproductive efficiency in dairy cows.

UDP-Glucose

UDP-glucose is a key metabolite that modulates ovarian steroid synthesis, which is crucial for follicular development and oocyte maturation in dairy cows. UDP-glucose acts as a donor of glucose residues in glycosylation reactions, which are involved in the synthesis of hormones, such as estrogen and progesterone. These hormones regulate the growth and maturation of follicles, influence oocyte quality, and are essential for maintaining the ovarian cycle. By modulating steroidogenesis, UDP-glucose helps optimize follicular health and improves reproductive outcomes in dairy cows.

3-Deoxyglucosone

3-Deoxyglucosone influences mitochondrial activity in oocytes, which plays a critical role in oocyte quality and embryo development in dairy cows. This metabolite is produced during the degradation of glucose and interacts with cellular pathways that regulate mitochondrial function. By affecting mitochondrial activity, 3-deoxyglucosone helps ensure proper energy production within the oocyte, supporting the maturation process and reducing cellular stress. This enhances oocyte quality and promotes embryo viability, contributing to improved reproductive success in dairy cows.

Glucosamine-6-Phosphate

Glucosamine-6-phosphate is involved in the expansion of cumulus cells, which surround the oocyte and support its development in dairy cows [12]. This metabolite plays a crucial role in the synthesis of glycosaminoglycans, components of the extracellular matrix that are essential for cumulus cell function. By promoting cumulus cell expansion, glucosamine-6-phosphate ensures proper communication between the oocyte and its surrounding cells, facilitating oocyte maturation and improving oocyte quality. This supports better fertilization rates and enhances embryo viability in dairy cows.

MICROBIOTA-DERIVED METABOLITES

Indole-3-Acetic Acid

Indole-3-acetic acid, a microbiota-derived metabolite, modulates ovarian follicular dynamics by influencing the growth and differentiation of follicles. This metabolite affects the signaling pathways that regulate follicular development, promoting optimal oocyte maturation and quality. In dairy cows, indole-3-acetic acid enhances the balance of hormonal regulation within the ovary, supporting follicular maturation and improving reproductive outcomes. Its impact on ovarian function highlights the important role of microbiota in reproductive health.

Butyrate

Butyrate is a short-chain fatty acid produced by gut microbiota and plays a crucial role in enhancing granulosa cell function in dairy cows. By promoting cell proliferation and improving cellular metabolism, butyrate supports the growth and development of the follicle. Additionally, butyrate helps maintain the integrity of granulosa cells, which are essential for hormone production and oocyte maturation [13]. Through its positive effects on granulosa cells, butyrate contributes to improved follicular health and better reproductive performance in dairy cows.

Propionate

Propionate, another short-chain fatty acid, regulates follicular steroidogenesis, which is essential to produce hormones like estrogen and progesterone. These hormones control follicular development and oocyte maturation in dairy cows. Propionate influences the synthesis of these hormones by modulating enzymatic activity within the ovarian cells. By regulating steroidogenesis, propionate helps maintain the hormonal balance needed for optimal follicular growth, oocyte quality, and overall reproductive efficiency in dairy cows [14].

Acetate

Acetate, a key product of fermentation by gut microbiota, plays a critical role in supporting corpus luteum maintenance in dairy cows. The corpus luteum produces progesterone, a hormone that is essential for sustaining pregnancy. Acetate helps maintain the functionality of the corpus luteum by providing energy for its cellular processes and supporting hormone production. By supporting the corpus luteum, acetate indirectly contributes to enhanced pregnancy rates and reproductive success in dairy cows, making it a crucial metabolite in ovarian function.

Lipopolysaccharide Fragments

Lipopolysaccharide (LPS) fragments, derived from the cell walls of gram-negative bacteria, influence ovarian immune responses in dairy cows. LPS fragments activate immune cells in the ovary, modulating inflammation and immune signaling. These metabolites help regulate the ovarian microenvironment, ensuring proper immune tolerance and preventing excessive inflammatory responses that could interfere with follicular development and oocyte quality. By influencing immune responses, LPS fragments contribute to the overall health of the ovary, supporting reproductive success and embryo viability in dairy cows.

HORMONE-DERIVED METABOLITES

Estrone Sulfate

Estrone sulfate plays a significant role in regulating follicular estrogen dynamics in dairy cows. As a precursor to estrone, this metabolite influences the estrogenic environment of the ovaries, impacting follicular growth and maturation [15]. Estrone sulfate helps modulate the balance between estrogen and progesterone, promoting healthy follicular development. By ensuring the proper estrogenic environment, estrone sulfate contributes to the successful maturation of oocytes and supports optimal reproductive function in dairy cows.

Dehydroepiandrosterone Sulfate (DHEA-S)

Dehydroepiandrosterone sulfate (DHEA-S) is crucial for modifying preantral follicle growth. This hormone-derived metabolite acts as a precursor to both estrogen and testosterone and influences early stages of folliculogenesis in dairy cows. DHEA-S modulates the development of preantral follicles by enhancing granulosa cell proliferation and increasing steroidogenic activity [16]. Its impact on follicular development ensures optimal follicle growth, improving the chances of successful ovulation and subsequent embryo development in dairy cows.

5α-Androstanediol

5α-Androstanediol, a metabolite of testosterone, modulates androgenic effects within ovarian follicles. This hormone-derived metabolite plays a pivotal role in regulating the balance between androgens and estrogens in the ovary. By influencing androgenic signaling, 5α-androstanediol helps maintain proper follicular function and supports oocyte maturation. In dairy cows, this metabolite contributes to the regulation of follicular dynamics, ensuring optimal ovarian function and improved reproductive outcomes.

17α-Hydroxyprogesterone

17α-Hydroxyprogesterone is a key metabolite in the regulation of the luteal phase. This metabolite is involved in the synthesis of progesterone, a hormone critical for maintaining pregnancy in dairy cows [17]. 17α-Hydroxyprogesterone helps regulate the function of the corpus luteum, ensuring the proper production of progesterone necessary for uterine receptivity and embryo survival. By influencing luteal phase regulation, this metabolite plays a crucial role in reproductive success and maintaining pregnancy in dairy cows.

Pregnenolone Sulfate

Pregnenolone sulfate enhances oocyte maturation by modulating steroidogenesis in ovarian follicles. As a precursor to other steroid hormones, pregnenolone sulfate plays a critical role in the biosynthesis of progesterone and estrogen. It supports the maturation of oocytes by influencing the production of these hormones, which are essential for follicular development. In dairy cows, pregnenolone sulfate contributes to the successful maturation of oocytes, thereby improving fertility rates and enhancing embryo viability.

VITAMIN-DERIVED METABOLITES

1,25-Dihydroxyvitamin D3

1,25-Dihydroxyvitamin D3 plays a key role in regulating ovarian follicular development in dairy cows. This active form of vitamin D modulates calcium signaling within the ovary, which is essential for proper follicular growth and maturation. It helps regulate the expression of genes involved in cell differentiation, follicular survival, and oocyte quality. By enhancing follicular development, 1,25-dihydroxyvitamin D3 contributes to overall reproductive health and fertility in dairy cows.

24,25-Dihydroxyvitamin D3

24,25-Dihydroxyvitamin D3 is a metabolite that modulates progesterone synthesis in the ovary. By influencing the enzymatic pathways involved in steroidogenesis, this metabolite helps regulate the production of progesterone during the luteal phase. Adequate progesterone synthesis is essential for maintaining pregnancy and uterine receptivity in dairy cows. 24,25-dihydroxyvitamin D3 ensures that progesterone levels remain optimal for successful conception and embryo survival.

Retinoic Acid Derivatives

Retinoic acid derivatives are critical for granulosa cell differentiation in the ovary. These vitamin A metabolites influence gene expressions associated with cell differentiation, proliferation, and steroidogenesis. By promoting granulosa cell maturation, retinoic acid derivatives help enhance follicular development and oocyte quality [18]. In dairy cows, these metabolites play a crucial role in supporting the formation of healthy, viable follicles necessary for successful reproduction.

Tocopherol Metabolites

Tocopherol metabolites, including those derived from vitamin E, are potent antioxidants that protect ovarian follicles from oxidative stress. Oxidative damage can impair follicular development and oocyte maturation, leading to reduced fertility in dairy cows [19]. Tocopherol metabolites neutralize reactive oxygen species (ROS), helping to maintain follicular integrity and support overall ovarian function. Their protective action ensures healthy oocyte development and contributes to better reproductive outcomes.

Pyridoxal Phosphate (Vitamin B6 Metabolite)

Pyridoxal phosphate, the active form of vitamin B6, regulates corpus luteum function by influencing steroid hormone synthesis. This metabolite is involved in the conversion of cholesterol into pregnenolone, a precursor to progesterone. By ensuring adequate progesterone production, pyridoxal phosphate helps maintain luteal function, which is essential for the establishment and maintenance of pregnancy. In dairy cows, this metabolite supports the luteal phase, optimizing reproductive success and fertility rates.

PURINE AND PYRIMIDINE METABOLITES

Adenosine Monophosphate (AMP)

Adenosine monophosphate (AMP) influences granulosa cell proliferation by activating intracellular signaling pathways that promote cell growth and differentiation. In the ovarian follicles of dairy cows, AMP enhances the proliferation of granulosa cells, which are essential for follicular development and oocyte maturation [20]. Increased granulosa cell proliferation facilitates the formation of healthy follicles and improves oocyte quality, contributing to better reproductive outcomes.

Guanosine Monophosphate (GMP)

Guanosine monophosphate (GMP) plays a crucial role in modulating follicular angiogenesis, the process of new blood vessel formation within the ovarian follicles. By regulating the angiogenesis process, GMP ensures the delivery of nutrients and oxygen to develop follicles. This is essential for follicular growth, oocyte health, and overall ovarian function, ultimately supporting improved fertility and embryo viability in dairy cows.

Uric Acid

Uric acid acts as an antioxidant, protecting oocytes from oxidative stress that can impair their quality and viability. In dairy cows, the accumulation of reactive oxygen species (ROS) during follicular development and oocyte maturation can lead to cellular damage. Uric acid neutralizes these harmful ROS, preventing oxidative damage and ensuring healthy oocyte development. This protective function of uric acid contributes to enhanced reproductive performance and embryo viability.

Cytidine Monophosphate (CMP)

Cytidine monophosphate (CMP) supports endometrial receptivity by influencing the expression of genes involved in uterine implantation and trophoblast invasion. In dairy cows, CMP plays a vital role in preparing the endometrium for embryo attachment and implantation, which is essential for successful pregnancy. By enhancing endometrial receptivity, CMP helps ensure the proper establishment of pregnancy, supporting overall reproductive success.

Xanthine

Xanthine affects luteal phase progression by regulating the activity of enzymes involved in steroidogenesis and maintaining the functionality of the corpus luteum. During the luteal phase, xanthine contributes to the production of progesterone, a hormone necessary for pregnancy maintenance. In dairy cows, xanthine's role in supporting luteal function ensures optimal progesterone levels, enhancing the likelihood of embryo survival and successful pregnancy outcomes.

REACTIVE OXYGEN AND NITROGEN SPECIES (RONS) METABOLITES

Hydrogen Sulfide

Hydrogen sulfide regulates ovarian follicular blood flow by acting as a vasodilator, increasing blood supply to the developing follicles [21]. In dairy cows, this improved circulation enhances nutrient and oxygen delivery to the follicles, supporting their growth and maturation. Adequate blood flow is crucial for maintaining follicular health and ensuring optimal oocyte quality, which is essential for successful fertilization and embryo development.

Superoxide Anion

Superoxide anion plays a critical role in influencing ovarian antioxidant defenses. As a reactive oxygen species (ROS), it can induce oxidative stress, if not regulated. In the ovaries of dairy cows, superoxide anion interacts with antioxidant systems to maintain a balance between ROS production and scavenging. This regulation helps protect ovarian cells, including oocytes and granulosa cells, from oxidative damage, preserving their function and viability.

Peroxynitrite

Peroxynitrite modifies oocyte mitochondrial function by interacting with mitochondrial proteins and lipids, affecting their energy production capabilities. In dairy cows, peroxynitrite formation can influence metabolic processes within oocytes, altering their ability to undergo fertilization and embryo development [22]. Balancing peroxynitrite levels is crucial for maintaining mitochondrial health, which is essential for oocyte quality and subsequent reproductive success.

Nitric Oxide-Derived S-Nitrosothiol

Nitric oxide-derived S-nitrosothiols regulate follicular steroidogenesis by modulating the synthesis of steroid hormones, such as estrogen and progesterone. These molecules are essential for follicular maturation and the preparation of the reproductive system for pregnancy. In dairy cows, S-nitrosothiols help ensure proper hormonal balance within the follicles, influencing ovulation and supporting embryo viability by regulating luteal function during the early stages of pregnancy.

Glutathione Disulfide

Glutathione disulfide plays a key role in balancing oxidative homeostasis within the follicles. As an oxidized form of glutathione, it serves as a marker of oxidative stress and helps regulate cellular redox status. In the ovaries of dairy cows, maintaining a balance between glutathione and its disulfide form ensures that oxidative damage is minimized, thereby protecting follicular cells and promoting healthy oocyte development and optimal embryo viability [23].

EXTRACELLULAR MATRIX-DERIVED METABOLITES

Hyaluronic Acid Fragments

Hyaluronic acid fragments modulate cumulus-oocyte expansion by influencing the interactions between cumulus cells and the oocyte. In dairy cows, these fragments play a vital role in promoting the hydration and structural changes of the cumulus-oocyte complex, which is crucial for successful fertilization [24]. This process enhances oocyte quality and ensures proper oocyte maturation, improving the chances of embryo development and overall reproductive success.

Matrix Metalloproteinase-Derived Peptides

Matrix metalloproteinase-derived peptides influence follicular remodeling by breaking down extracellular matrix components, facilitating the structural changes required during follicular growth [25]. In dairy cows, these peptides support follicle development by modulating the composition and integrity of the surrounding matrix, ensuring that the follicles can grow, mature, and ovulate efficiently. Follicular remodeling is essential for optimal oocyte release and embryo viability.

Chondroitin Sulfate Metabolites

Chondroitin sulfate metabolites support ovarian extracellular matrix integrity by contributing to the structural framework of the ovary. In dairy cows, these metabolites help maintain the balance of the extracellular matrix, which is essential for follicle development, oocyte maturation, and ovulation [26]. The integrity of the matrix ensures that follicles can respond to hormonal signals, fostering a conducive environment for successful reproductive processes, including fertilization and embryo viability.

Heparan Sulfate Fragments

Heparan sulfate fragments regulate angiogenesis in the corpus luteum by interacting with growth factors and modulating blood vessel formation [27]. In dairy cows, these fragments contribute to the formation of an efficient vascular network within the corpus luteum, which is critical for luteal function and progesterone secretion. Proper angiogenesis supports early pregnancy by ensuring an adequate blood supply to the developing embryo, thus enhancing embryo viability and supporting successful implantation.

Decorin-Derived Peptides

Decorin-derived peptides modify follicular response to gonadotropins by regulating the extracellular matrix and cellular signaling pathways. In dairy cows, these peptides interact with gonadotropins to modulate granulosa cell function, influencing steroidogenesis and follicular development. The ability of decorin peptides to enhance gonadotropin receptor activity ensures that the follicles respond appropriately to hormonal cues, improving oocyte quality and increasing the likelihood of successful fertilization and embryo development.

METABOLITES FROM PLANT-DERIVED COMPOUNDS

Genistein (Phytoestrogen Metabolite)

Genistein, a phytoestrogen metabolite, modifies follicular estrogen signaling by binding to estrogen receptors and influencing gene expression within the ovarian cells. In dairy cows, genistein enhances the hormonal environment necessary for optimal follicular development. This metabolite's ability to mimic estrogen activity helps regulate steroidogenesis and supports oocyte maturation, improving reproductive outcomes and overall fertility [28]. Genistein may be particularly valuable in environments with hormonal imbalances or where phytoestrogen intake is high.

Equol

Equol enhances ovarian response to follicle-stimulating hormone (FSH) by increasing granulosa cell sensitivity to gonadotropins. In dairy cows, equol promotes follicular growth and oocyte maturation by influencing key signaling pathways involved in steroidogenesis and cellular proliferation [29]. This metabolite is produced during the metabolism of certain soy isoflavones and plays a crucial role in improving reproductive efficiency. By optimizing the ovarian response to FSH, equol contributes to increased follicular recruitment and better-quality oocytes, supporting successful fertilization.

Resveratrol-Derived Metabolites

Resveratrol-derived metabolites protect against ovarian oxidative damage by acting as potent antioxidants. In dairy cows, oxidative stress can impair oocyte quality and follicular development, leading to reduced fertility. Resveratrol metabolites neutralize free radicals and reduce inflammation, thus safeguarding the ovarian environment from oxidative damage [30]. Their protective role ensures better follicular function, oocyte integrity, and improved embryo viability, making resveratrol-derived compounds a potential strategy for enhancing fertility in dairy cows under stressful conditions.

Quercetin Metabolites

Quercetin metabolites influence ovarian inflammatory responses by modulating cytokine production and inhibiting oxidative stress. In dairy cows, quercetin-derived compounds act as anti-inflammatory agents that reduce follicular inflammation, which can otherwise impair oocyte quality and follicular development [31]. By regulating inflammatory pathways, quercetin metabolites help maintain a balanced ovarian microenvironment, supporting optimal follicular maturation, hormone production, and enhancing the overall success of reproduction.

Curcumin-Derived Metabolites

Curcumin-derived metabolites modulate luteal phase stability by influencing the secretion of key reproductive hormones, such as progesterone. In dairy cows, these metabolites promote luteal function, which is critical for maintaining early pregnancy. By supporting progesterone production, curcumin-derived metabolites help sustain the luteal phase, allowing for the proper implantation and growth of the embryo. Their role in modulating luteal phase dynamics also contributes to better pregnancy rates and fertility outcomes in dairy cows.

CONCLUSIONS

Lesser-known metabolites play crucial roles in regulating ovarian function, follicular development, and embryo viability in dairy cows through diverse biochemical pathways. While conventional metabolic regulators, such as glucose and steroid hormones, are well established, emerging evidence highlights the significance of lipid-derived molecules, microbiota-associated metabolites, purine and pyrimidine derivatives, and extracellular matrix components in bovine reproductive physiology. These metabolites influence key processes, such as granulosa cell function, steroidogenesis, oxidative homeostasis, and embryonic survival, all of which are critical for optimizing fertility in dairy cattle. Understanding their roles offers novel insights into ovarian metabolic regulation and potential therapeutic targets for improving reproductive efficiency. This study underscores the need for further research to elucidate the precise mechanisms underlying these metabolic interactions, paving the way for advancements in both dairy herd fertility management and clinical reproductive treatments.

Future Directions

Future research should focus on elucidating the precise biochemical pathways through which lesser-known metabolites influence ovarian function, follicular development, and embryo viability in dairy cows. Advanced metabolomic and transcriptomic approaches should be integrated to identify metabolic signatures associated with enhanced reproductive efficiency in bovine species. Investigating the crosstalk between microbiota-derived metabolites and ovarian physiology can provide deeper insights into gut-reproductive axis interactions. Additionally, exploring the role of oxidative stress-related metabolites in follicular aging and oocyte quality may offer novel strategies for improving fertility in dairy cattle. Studies should also assess the impact of dietary interventions on modulating metabolite availability and ovarian responsiveness. Further, controlled in vivo and in vitro studies are required to validate the functional relevance of these metabolites in dairy reproductive management. Applying these findings in livestock systems can enhance fertility optimization strategies, improve assisted reproductive technologies, and contribute to sustainable dairy herd productivity.

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