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Sperm and seminal plasma metabolomes and their association with bull fertility

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Abstract

Bull fertility remains critical for livestock production, yet conventional semen evaluations often fail to predict subfertility accurately, leading to economic losses in artificial insemination programs. Metabolomics offers a promising approach by profiling small-molecule metabolites in sperm and seminal plasma to uncover biochemical signatures associated with reproductive performance. This review overviews current research on bull semen metabolomes, highlighting key metabolites such as fructose, citric acid, lactic acid, and GABA in seminal plasma. These metabolites support energy metabolism, motility, capacitation, and antioxidant defence. In spermatozoa, compounds like glycerol, oleic acid, and phosphocholine contribute to membrane integrity and cryotolerance. Studies using GC-MS, LC-MS, and ¹H-NMR have identified distinct profiles between high- and low-fertility bulls: elevated 2-oxoglutaric acid and palmitic acid indicate oxidative stress and poor outcomes, while higher glycine, D-ribose, and propanoic acid correlate with superior freezability and viability. These biomarkers reveal pathways disrupted by cryopreservation, including lipid peroxidation and energy substrate depletion, emphasizing breed- and phenotype-specific variations. Metabolomics enhances sire selection, semen preservation, and fertility prediction beyond traditional parameters, with applications in extracellular vesicle-mediated regulation and multi-omics integration. Challenges include methodological standardization and validation, but future directions such as portable diagnostics and systems biology promise transformative impacts on cattle breeding efficiency. Overall, metabolomics insights bridge molecular defects to field performance, advancing precision reproductive management.

Keywords: Bull fertility, cryo-tolerance, semen metabolomics, sperm biomarkers

Introduction

Bull fertility is crucial for efficient livestock production, particularly in artificial insemination (AI) programs where a single bull can sire thousands of offspring, greatly influencing herd genetics and productivity. Fertility in bulls depends on physiological, biochemical, and molecular factors starting from spermatogenesis to sperm maturation (Kaya *et al.*, 2014) [22]. It was observed that conventional semen parameters like motility and morphology often fail to reliably predict fertility (Srivastava and Pande 2017a; Kumar *et al.*, 2017) [53, 31], as some bulls with normal semen profiles still show poor reproductive performance due to hidden molecular defects (Srivastava *et al.*, 2018) [52], with consequent economic losses. It was because fertility also depends on sperm DNA integrity, proteins, RNAs, and epigenetic factors that influence early embryogenesis (Kaya and Memili, 2016) [23]. Elsewhere, trial results have shown that even frozen semen from proven bulls pregnancy rates can vary upto 20-25% (Jerome *et al.*, 2012) [20]. In natural service systems, especially where bulls breed over 90% of cows, ensuring bull fertility is vital for efficient herd management (Perry and Patterson, 2001) [46]. Hence, accurate prediction of fertility is vital for selecting high-performing sires and improving breeding outcomes. Crossbred bulls tend to have higher infertility rates than purebreds, with culling rates as high as 40-70% due to sub-fertility (Mukhopadhyay *et al.*, 2010) [40].

Though there are several studies related to bull fertility assessment, investigations on metabolic components (metabolomics) of seminal plasma influencing bull fertility have gained prominence recently (Giaretta *et al.*, 2024) ^[14]. In agreement, (Memili *et al.*, 2020) ^[37] reported metabolic components of seminal plasma, rich in metabolites such as amino acids, carbohydrates, lipids, and steroids, plays a key role in sperm function by regulating energy metabolism, oxidative stress, membrane integrity, and other vital processes in bulls.

Metabolomics enables detailed profiling of small molecules in seminal plasma and sperm cells, providing insights into the underlying biochemical pathways affecting fertility (Kumar *et al.*, 2015a) ^[28]. Other studies have identified distinct metabolomic signatures between fertile and sub-fertile bulls, highlighting its diagnostic potential (Menezes *et al.*, 2019; Kumar *et al.*, 2025a) ^[38, 32]. Therefore, integrating metabolomics into fertility assessment programs can enhance bull selection, improve reproductive success, and support more precise livestock breeding strategies.

Metabolites, Metabolome and Bull Fertility

Metabolites are small molecules (<1 kDa) derived from metabolic pathways, which include amino acids, lipids, carbohydrates, nucleotides, and hormones. As end products of cellular processes, they offer key insights into sperm function and gene regulation (Gilany *et al.*, 2017) ^[16]. Though abundant in bovine seminal plasma, especially those involved in energy metabolism, few studies link specific metabolites to bull fertility (Kumar *et al.*, 2015) ^[30]. Extensive research in several species such as goats (Patel *et al.*, 1998) ^[44], boars (Marin *et al.*, 2003) ^[35], bulls (Holden *et al.*, 2017) ^[18] and

humans (Zhao *et al.*, 2018) ^[71] show that both seminal plasma and sperm metabolites correlate with male fertility potential.

The metabolome refers to the full set of small-molecule metabolites-such as amino acids, sugars, lipids, and nucleotides-present in a biological system under specific conditions. Metabolomics is the high-throughput analysis of these metabolites, offering insights into sperm quality, oxidative stress, and fertility in bulls (Velho *et al.*, 2018) ^[66]. It connects metabolic profiles with traits like semen freezability and reproductive resilience, aiding livestock breeding, nutrition, and fertility prediction. As the most recent of the “omics” sciences, metabolomics reveals the final outputs of cellular processes (Zhang *et al.*, 2012) ^[70], uncovering key regulatory pathways in sperm such as capacitation, acrosome reaction, and motility modulation (Dipresa *et al.*, 2018) ^[10].

Many bulls produce semen with normal sperm motility and morphology yet exhibit low fertility due to hidden molecular defects (Perumal *et al.*, 2017; Srivastava and Pande 2017b) ^[45, 54]. These non-compensatory fertility issues, where increasing sperm count doesn't improve conception, are undetectable by conventional semen analysis (Darr *et al.*, 2016) ^[7]. In such scenarios, the study of metabolites (metabolomics) offers a more precise evaluation by profiling cellular metabolites-end products of gene and protein activity-that better reflect cell function than transcriptomics or proteomics (Guijas *et al.*, 2018) ^[17]. Metabolite analysis (Table 1 and 2) in sperm and seminal plasma reveals biomarkers linked to fertilizing capacity and supports optimization of sperm storage and capacitation conditions. Metabolomics enables deeper understanding of sperm physiology and improves selection accuracy for AI programs (Morrell *et al.*, 2017) ^[39].

Table 1: Major Metabolites of Sperm

Metabolites	Functions	References
GABA	Induction of capacitation and acrosome reaction	Menezes <i>et al.</i> , 2019 ^[38]
Glycerol	Stimulation of cell dehydration, permeating the membrane and restricting the dehydration effect during cryopreservation	Medeiros <i>et al.</i> , 2002 ^[36]
Serine	Endogenous substrates, Chelating agents, Antioxidant, Reduces lipid peroxidation	Patel <i>et al.</i> , 1998; Paiva <i>et al.</i> , 2015 ^[44, 41]
Stearic acid	Contribute to sperm membrane structure and function	Menezes <i>et al.</i> , 2019 ^[38]
Nonanoic acid	Acrosome reaction by initiating protein tyrosine phosphorylation	Menezes <i>et al.</i> , 2019 ^[38]
Azelaic acid	Act as ROS scavenger, modulates glycolytic enzymes and inhibits tyrosinase	Menezes <i>et al.</i> , 2019 ^[38]
Oleic acid	Represses lipid oxidation, disorders sperm membrane metabolism, lowers ROS species	Tang <i>et al.</i> , 2017; Menezes <i>et al.</i> , 2019 ^[60, 38]
Arachidonic acid	Fluidity modulation and protection against oxidation during freezing and after thawing	Walters <i>et al.</i> , 2018 ^[67]
Inorganic compounds	Contribute to energy metabolism of sperm cell	Menezes <i>et al.</i> , 2019 ^[38]
Lactic acid	Energy source for spermatozoa, important for hyperactivation and capacitation	Menezes <i>et al.</i> , 2019 ^[38]
Benzoic acid	Increases efflux of glutamate	Menezes <i>et al.</i> , 2019 ^[38]
Carbamate	Regulation of intracellular pH	Menezes <i>et al.</i> , 2019 ^[38]
Carnitine	Fatty acid oxidation, beta-oxidation	Paiva <i>et al.</i> , 2015 ^[41]

Table 2: Major metabolites in seminal plasma of bull semen

Metabolite	Function	References
Fructose	Primary energy source for sperm motility	Velho <i>et al.</i> , 2018 ^[66]
Citric Acid	Osmolarity regulation, membrane stability	Velho <i>et al.</i> , 2017 ^[65]
Lactate	Anaerobic energy source	Velho <i>et al.</i> , 2017 ^[66]
Glycine	Antioxidant, protects from oxidative stress	Pessoa <i>et al.</i> , 2023 ^[47]
Propanoic Acid	Energy source and antimicrobial role	Pessoa <i>et al.</i> , 2023 ^[47]
2-Oxoglutaric Acid	Metabolism intermediate and fertility biomarker	Velho <i>et al.</i> , 2018 ^[66]
Phosphocholine	Membrane structure & integrity	Giaretta <i>et al.</i> , 2025 ^[13]
Alanine, Phenylalanine, Tyrosine	Amino acids linked to metabolism, cryotolerance, and oxidative protection	Giaretta <i>et al.</i> , 2025 ^[13]
D-Ribose	Energy source and antioxidant, reducing sperm apoptosis and oxidative stress	Pessoa <i>et al.</i> , 2023 ^[47]
GABA (γ-Aminobutyric acid)	Enhances sperm motility and capacitation	Giaretta <i>et al.</i> , 2025 ^[13]
Histidine	pH buffer and antioxidant, protecting sperm viability	Giaretta <i>et al.</i> , 2025 ^[13]
Citric Acid, Urea, Phosphoric Acid	Osmotic balance and metabolic stability	Velho <i>et al.</i> , 2017 ^[65]

Applications of metabolomics in bull fertility

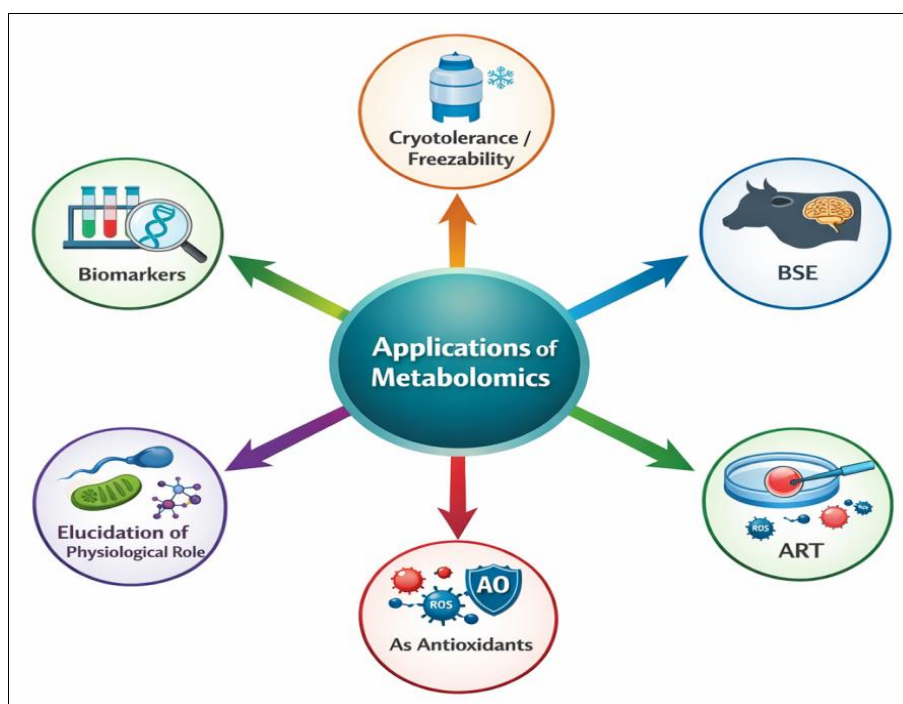


Fig 1: Applications of metabolomics

Metabolomics has emerged as a powerful tool for improving bull fertility diagnostics by profiling the biochemical makeup of sperm and seminal plasma. These real-time metabolic fingerprints reveal sperm health, oxidative stress, and energy status—key factors influencing fertilizing ability and semen cryotolerance (Memili *et al.*, 2020) [37]. Using techniques like GC-MS, LC-MS, and NMR, metabolomics enables rapid, sensitive detection of fertility-associated metabolites in small semen samples.

A major application is identifying fertility biomarkers (Fig. 1). For instance, Velho *et al.* (2018) [66] used GC-MS to find that high-fertility bulls had elevated seminal fructose and humanin (Katiyar *et al.*, 2022) [21], while low-fertility bulls showed higher 2-oxoglutaric acid as in (Table 3 and 6), linked to oxidative stress. Metabolomics also aids in evaluating sperm freezability. Pessoa *et al.* (2023) [47] found that

propanoic acid, glycine, and D-ribose were higher in cryotolerant bulls, supporting antioxidant defense during freezing.

In sire selection, metabolomics complements breeding soundness exams by detecting metabolic deficiencies in bulls with normal semen profiles, preventing subfertile bulls from entering AI programs (Memili *et al.*, 2020) [37]. Additionally, Giaretta *et al.* (2025) [13] linked seminal formic acid, lactate, and glycerol levels to sperm motility and mitochondrial function, offering insights into sperm physiology. Increased expression of ubiquitin on the sperm surface has been shown to be linked with poor-quality ejaculates containing more dead sperm (Bisla *et al.*, 2021) [4].

Overall, metabolomics enhances fertility prediction, semen evaluation, and reproductive efficiency in cattle breeding.

Table 3: Functional metabolites associated with bull fertility

Compound	Role/Impact	Reference
Leucine	Influences calcium transport, affects sperm motility and fertilizing capacity.	Rufo <i>et al.</i> , 1982 [51]
Citrate & Isoleucine	Regulate calcium uptake; excessive levels reduce motility and capacitation.	Ford & Harrison, 1984 [12]
Tryptamine	Modulates acrosome reaction and motility, crucial for fertilization.	Jimenez <i>et al.</i> , 2012 [20]
2-Oxoglutaric Acid	Elevated in low-fertility bulls; linked to oxidative stress and poor semen quality.	Velho <i>et al.</i> , 2018 [66]

Table 4: Lipid metabolism & oxidative injury

Compound	Role/Impact	Reference
Oleic Acid	In humans, associated with poor semen quality; in bulls, maintains sperm viability and reduces ROS when controlled.	Kiernan <i>et al.</i> , 2013 [25]
Palmitic Acid (C16:0)	Elevated in low-fertility bulls; disrupts sperm membrane metabolism, associated with poor motility.	Esmaeili <i>et al.</i> , 2015 [11]
Linoleic & Alpha-linolenic Acid Metabolism	Provide energy for sperm motility; imbalance may impair membrane integrity and function in crossbred bulls.	Tang <i>et al.</i> , 2017 [60]

DNA Integrity and Sperm Health

Deoxyuridine Triphosphate (dUTP): Binds damaged DNA; high levels in sperm can cause genetic instability, affecting fertility outcomes (Webley *et al.*, 2001) [68].

Selenocysteine

Essential for spermatogenesis and sperm maturation; both deficiency and excess negatively affect fertility (Atig *et al.*, 2011) [2].

Table 5: Phospholipid metabolism and fertility

Compound	Role/Impact	Reference
Phosphatidylcholine	Key for sperm membrane structure and energy metabolism; disturbances impair sperm function.	Khosrowbeygi & Zarghami, 2007 ^[24]
Carbamate	Potential intracellular pH regulator in spermatozoa, maintaining functional capacity.	Memili <i>et al.</i> , 2020 ^[37]

Secondary Messenger Regulation

Myo-Inositol and Inositol Phosphates (IP3): Regulate calcium-dependent signalling, protein phosphorylation, and flagellar movement; imbalances linked to infertility in bulls and men (Korosi *et al.*, 2017)^[26].

Seminal Plasma and Sperm Metabolome in Bull Fertility

The seminal plasma metabolome functions as a nutritive, protective, and regulatory medium, containing key metabolites such as fructose, citric acid, lactic acid, amino acids, lipids, and antioxidants. Fructose, essential for sperm motility and energy, is predominant in high-fertility bulls, while elevated 2-oxoglutaric acid in low-fertility bulls indicates oxidative stress (Velho *et al.*, 2018)^[66]. Amino acids like glycine and alanine act as osmoprotectants and antioxidants, enhancing membrane stability and capacitation potential (Pande *et al.*, 2017; Ugur *et al.*, 2020)^[45, 62]. Hypotaurine and GABA have also been linked to improved cryotolerance and post-thaw viability (Giaretta *et al.*, 2025)^[13].

Lipid metabolites such as glycerophosphocholine and lysophosphatidylcholine maintain membrane fluidity and resilience during cryopreservation, especially in high-fertility bulls (Srivastava and Pande, 2017c; Longobardi *et al.*, 2020)^[55, 34]. Spermatozoa, though metabolically simpler than seminal plasma, contain crucial metabolites like lactic acid, phosphocholine, and ATP intermediates that regulate motility and energy status (Table 7) (Memili *et al.*, 2020)^[37].

Altered fatty acid synthesis and ketone metabolism have been associated with reduced sperm motility and count, pointing to underlying metabolomic dysfunctions in subfertile bulls (Srivastava and Pande, 2017d; Dasgupta *et al.*, 2022)^[56, 9]. Cryopreservation further alters lipid, amino acid, and antioxidant profiles, affecting sperm viability and membrane integrity, with seminal plasma being particularly vulnerable (Srivastava *et al.*, 2013; Pessoa *et al.*, 2023)^[57, 47]. Table 4 summarizes the roles of key fatty acids in sperm function, highlighting their influence on viability, motility, and membrane integrity.

Energy Metabolism

Energy substrates like fructose, lactic acid, citric acid, and D-ribose in seminal plasma provide ATP necessary for sperm motility and capacitation. High-fertility bulls consistently exhibit higher seminal plasma fructose and lactic acid concentrations (Table 6), facilitating efficient sperm energetics (Velho *et al.*, 2018; Pessoa *et al.*, 2023)^[66, 47].

Membrane Stability and Capacitation

Lipid metabolites such as glycerophosphocholine, lysophosphatidylcholine, and L-acetylcarnitine regulate sperm membrane composition and fluidity, which are vital for successful capacitation and protection against cryo-damage (Longobardi *et al.*, 2020)^[34]. High-fertility bulls exhibit higher levels of these metabolites, preserving sperm viability during storage and post-thaw.

Antioxidant Defense

Metabolites like hypotaurine, glycine betaine, phenylalanine,

and propanoic acid scavenge reactive oxygen species (ROS) and reduce oxidative stress, preventing DNA damage and lipid peroxidation in sperm membranes (Ugur *et al.*, 2020; Kumar *et al.*, 2025b; Giaretta *et al.*, 2025)^[62, 33, 13]. Fertile bulls consistently present higher levels of these antioxidants, enhancing sperm resilience.

Cryotolerance

The metabolomic profile is a key predictor of semen freezability. Bulls with higher seminal levels of glycine, D-ribose, and propanoic acid show improved post-thaw motility and membrane integrity (Pande *et al.*, 2017; Pessoa *et al.*, 2023)^[45, 47].

Capacitation and Acrosome Reaction

Neurotransmitter-like metabolites such as GABA regulate sperm capacitation and acrosome reaction by modulating ion channel activity and intracellular calcium flux. High-fertility bulls possess increased GABA content in spermatozoa, supporting these essential processes (Menezes *et al.*, 2019)^[38].

Indicators of Oxidative Metabolism and Stress

Metabolites like 2-oxoglutaric acid act as markers of oxidative stress and energy pathway efficiency. Its elevated levels in low-fertility bulls reflect mitochondrial dysfunction and compromised fertilizing ability (Velho *et al.*, 2018)^[66] (Table 6).

Steroid Precursors and Hormonal Modulators

Compounds like androstenedione in seminal plasma influence sperm plasma membrane properties and capacitation. Its variations between fertile and subfertile bulls further suggest a role in regulating reproductive function (Velho *et al.*, 2018)^[66].

Modulation by Extracellular Vesicles (EVs)

Recent findings demonstrate that metabolites carried within seminal plasma EVs modulate sperm motility, capacitation, and ROS generation, as evidenced by CASA parameters (Perumal *et al.*, 2016)^[49]. Supplementing subfertile bull sperm with EVs from fertile bulls improves their function, confirming metabolite-mediated regulation (Pal *et al.*, 2025)^[42].

Regulation of the Female Reproductive Tract

Seminal plasma metabolites like androstenedione, phosphoric acid, and myo-inositol modulate the female reproductive tract environment post-insemination, promoting sperm survival and aiding immune tolerance. These metabolites influence cervical mucus viscosity, uterine contractility, and oviductal sperm transport, enhancing fertilization chances (Velho *et al.*, 2018)^[66].

Seminal Extracellular Vesicle (EV) Transfer

Seminal plasma EVs deliver fertility-regulating metabolites and proteins to sperm, enhancing capacitation, motility, and ROS protection. Pal *et al.* (2025)^[42] showed that EV supplementation from fertile bulls improved post-thaw sperm

motility and acrosome integrity in subfertile bulls, confirming a metabolome-mediated functional rescue mechanism.

Cryotolerance Biomarkers

Certain seminal plasma metabolites such as propanoic acid, glycine, D-ribose, and heptadecanoic acid predict sperm freezability. Higher levels of propanoic acid and glycine correlate with superior post-thaw motility, while elevated heptadecanoic acid indicates poor cryoresistance (Pessoa *et al.*, 2023) ^[47].

Oxidative Stress Modulation

Metabolites like formic acid, glutamate, and histidine mitigate oxidative protein damage in thawed semen, preserving sperm viability, linearity, and mitochondrial function. Giaretta *et al.* (2025) ^[13] highlighted these metabolites as biomarkers of oxidative resilience in cryopreserved semen.

Fertility-Linked Steroidal and Lipid Regulation

Steroid-like molecules (e.g., androstenedione) and lipid metabolites regulate sperm membrane lipid remodeling, capacitation, and fusion with the oocyte. High-fertility bulls maintain balanced steroid and lipid metabolome signatures essential for successful fertilization (Velho *et al.*, 2017) ^[65].

Metabolome Profile of High and Low-Fertility Bulls

Table 6: High-fertility bulls

Compound	Role/Impact	Reference
Citrate & Isoleucine	Low levels linked to poor semen quality	Kumar <i>et al.</i> , 2015a ^[28]
Tryptamine, Taurine, Leucine	Higher levels → antioxidant defense, osmoprotection, cryotolerance	Kumar <i>et al.</i> , 2015a ^[28]
Fructose	Main energy source, enhances motility & fertilization	Velho <i>et al.</i> , 2018 ^[66]
Ornithine, L-Leucine, D-Mannitol	Low levels linked to subfertility	Velho <i>et al.</i> , 2018 ^[66]
2-Oxoglutaric Acid	Lower levels → less oxidative stress, better semen quality	Velho <i>et al.</i> , 2018 ^[66]
GABA, Carbamate, Benzoic Acid, Lactic Acid	Higher levels → efficient anaerobic glycolysis	Menezes <i>et al.</i> , 2019 ^[38]
Lactic Acid	Support mitochondrial activity, motility & energy metabolism	Menezes <i>et al.</i> , 2019 ^[66]
Lipid Peroxidation & Antioxidant Levels	Lower peroxidation & higher antioxidants reduce oxidative stress	Dasgupta <i>et al.</i> , 2022 ^[9]
Hypotaurine & GABA	Promote freezability & antioxidant protection	Giaretta <i>et al.</i> , 2025 ^[13]

Table 7: Low-fertility bulls

Compound	Role/Impact	Reference
Citrate & Isoleucine	High content may impair sperm function	Kumar <i>et al.</i> , 2015b ^[30]
Fructose	Low levels → reduced energy for motility	Velho <i>et al.</i> , 2018 ^[66]
Ornithine, L-Leucine, D-Mannitol	Elevated levels linked to subfertility	Velho <i>et al.</i> , 2018 ^[66]
2-Oxoglutaric Acid	Higher levels are associated with oxidative stress and suboptimal fertility.	Velho <i>et al.</i> , 2018 ^[66]
GABA, Lactic Acid, and Metabolic Indicators	Low levels → poor mitochondrial function & sperm motility	Menezes <i>et al.</i> , 2019 ^[38]
Palmitic Acid	High levels reduce motility & membrane fluidity	Menezes <i>et al.</i> , 2019 ^[38]
Lipid Peroxidation & Antioxidant Levels	Higher lipid peroxidation and lower antioxidant levels contribute to oxidative damage and fertility impairment.	Dasgupta <i>et al.</i> , 2022 ^[9]

Most and Least Predominant Metabolites in Bull Seminal Plasma and Spermatozoa

The most predominant metabolites in bull seminal plasma include fructose, which is the most abundant and serves as the primary energy source for sperm motility and survival (Velho *et al.*, 2018) ^[66]; citric acid, the second most abundant metabolite that acts as a pH buffer, chelates calcium, zinc, and magnesium, and regulates sperm capacitation; lactic acid, which provides rapid energy through anaerobic glycolysis (Darr *et al.*, 2016) ^[7]; urea, reflecting protein metabolism; and phosphoric acid, involved in phosphate availability, energy transfer, and pH regulation (Velho *et al.*, 2018) ^[66].

In contrast, the least predominant metabolites in seminal plasma include androstenedione, a steroid hormone precursor

Comparative Metabolomics of Bull Sperm and Seminal Plasma: Bull semen metabolomics reveals distinct profiles between spermatozoa and seminal plasma due to their unique origins and roles. Seminal plasma, secreted by accessory glands, provides energy substrates, antioxidants, and membrane-stabilizing compounds, while sperm cells possess a focused metabolome supporting motility and fertilization. Seminal plasma contains more and higher-concentration metabolites, including fructose, citric acid, taurine, and glycerol-phosphocholine, essential for sperm support (Memili *et al.*, 2020) ^[37].

Velho *et al.* (2018) ^[66] identified 63 seminal plasma metabolites, while sperm cells showed fewer, such as lactic acid and phosphocholine, linked to mitochondrial activity (Table 7). Lipid-based metabolites like lysophosphatidylcholine aid in membrane fluidity in both compartments but are more abundant in plasma (Longobardi *et al.*, 2020) ^[34].

Giaretta *et al.* (2025) ^[13] correlated seminal plasma and sperm metabolite levels (e.g., formic acid, lactate) with motility and viability, while Pessoa *et al.* (2023) ^[47] found fatty acids and amino acids dominant in plasma, with sperm enriched in ATP-related metabolites. Cryopreservation impacts both, but plasma exhibits greater metabolic shifts.

present in very low abundance; D-xylofuranose, a rare sugar detected in trace amounts; erythronic acid, a minor organic acid; 2-oxoglutaric acid, present at low concentration but associated with oxidative stress and subfertility; and 4-ketoglucose, a rare sugar derivative (Velho *et al.*, 2018) ^[66]. Similarly, in bull spermatozoa, the most predominant metabolites include glycerol, important for osmotic balance and cryoprotection; oleic acid, the most abundant fatty acid contributing to membrane fluidity; phosphoric acid, supporting intracellular energy metabolism; phosphine, associated with reduction of oxidative stress; and carbamate (Table 1 and 5), which regulates intracellular pH (Menezes *et al.*, 2019; Memili *et al.*, 2020) ^[38, 37].

Whereas the least predominant metabolites include acetic

acid, involved in energy metabolism; benzoic acid, with minimal metabolic role; carbonate, acting as a minor buffer; L-serine, participating in phospholipid synthesis; and 2-ketobutyric acid, also involved in phospholipid metabolism (Menezes *et al.*, 2019) [38].

Oxidative Stress and Antioxidant Metabolites of Bull Sperm and Seminal Plasma Metabolomes

Oxidative stress (OS) in bull semen arises when the production of reactive oxygen species (ROS) exceeds the antioxidant capacity, impairing sperm motility, membrane integrity, and fertilizing ability. Both enzymatic and non-enzymatic antioxidants in seminal plasma and spermatozoa mitigate ROS and preserve sperm function (Kumar *et al.*, 2021) [29].

Enzymatic antioxidants in seminal plasma include

- **Superoxide Dismutase (SOD):** Neutralizes superoxide radicals. Higher SOD activity in younger bulls correlates with better sperm motility (Pirsljin *et al.*, 2007) [48].
- **Catalase (CAT):** Decomposes hydrogen peroxide; its activity peaks in autumn (Asadpour & Tayefi-Nasrabadi, 2012) [1].
- **Glutathione Peroxidase (GPx):** Reduces lipid hydroperoxides and hydrogen peroxide; levels vary

seasonally, lower in winter (Asadpour & Tayefi-Nasrabadi, 2012) [1].

- **Non-enzymatic antioxidants:** albumin, uric acid, and bilirubin also contribute significantly, with their concentrations positively correlating with semen motility and quality (Table 8) (Tvrdá *et al.*, 2010) [61].

Markers of Oxidative Status

Thiol groups (R-SH) and Advanced Oxidative Protein Products (AOPP) are associated with improved post-thaw motility and viability (Giaretta *et al.*, 2022) [15]. High-freezability bulls' seminal plasma contains higher levels of glycine, D-ribose, and propanoic acid, offering protection against oxidative and apoptotic damage (Pessoa *et al.*, 2023) [47].

Elevated GABA, histidine, and glutamate concentrations are linked to better post-thaw semen quality (Giaretta *et al.*, 2025) [13].

Oxidative Stress Index (OSI), calculated as the ratio of total oxidant to antioxidant status, effectively predicts semen cryotolerance-with higher OSI associated with reduced post-thaw motility and membrane integrity (Unal and Uysal, 2024) [64].

Table 8: Key antioxidant metabolites and their functions

Metabolite / Antioxidant	Function	Reference
Superoxide Dismutase (SOD)	Neutralizes superoxide radicals	Pirsljin <i>et al.</i> , 2007 [48]
Albumin, Uric Acid, Bilirubin	Non-enzymatic antioxidants neutralizing ROS	Tvrdá <i>et al.</i> , 2010 [61]
Catalase (CAT)	Breaks down hydrogen peroxide	Asadpour & Tayefi-Nasrabadi, 2012 [1]
Glutathione Peroxidase (GPx)	Reduces lipid hydroperoxides and H ₂ O ₂	Asadpour & Tayefi-Nasrabadi, 2012 [1]
D-Ribose	Energy source, reduces oxidative stress and apoptosis	Pessoa <i>et al.</i> , 2023 [47]
Glycine	Protects against protein denaturation and oxidative stress	Pessoa <i>et al.</i> , 2023 [47]
GABA, Histidine, Glutamate	Antioxidants enhancing motility and membrane integrity	Giaretta <i>et al.</i> , 2025 [13]
Thiols, AOPP	Markers of oxidative status, associated with better semen quality	Giaretta <i>et al.</i> , 2025 [13]

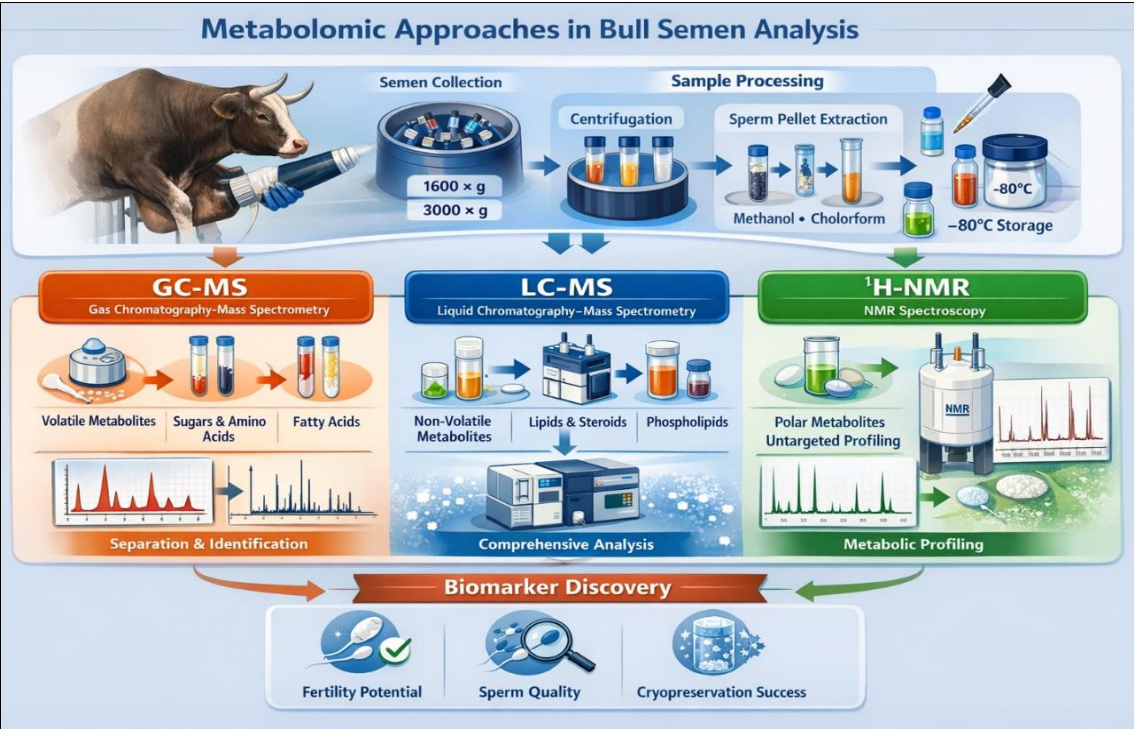


Fig 2: Metabolomic approaches in bull semen analysis

Metabolomic Approaches in Bull Semen Analysis

Metabolomic analysis of bull semen involves profiling small

molecules in sperm and seminal plasma to identify fertility biomarkers. Common analytical platforms include GC-MS,

LC-MS, and $^1\text{H-NMR}$ spectroscopy (Fig. 2) (Velho *et al.*, 2018) ^[66].

GC-MS (Gas Chromatography-Mass Spectrometry)

It is a sensitive technique for detecting volatile and thermally stable metabolites such as sugars, amino acids (post-derivatization), and organic acids. It separates compounds based on their boiling point and identifies them by their mass-to-charge ratio. Velho *et al.* (2018) ^[66] used GC-MS to identify 63 seminal plasma metabolites, including amino acids and fatty acids, highlighting its utility in fertility studies.

LC-MS (Liquid Chromatography-Mass Spectrometry)

It enables detection of non-volatile, polar, and thermolabile compounds such as lipids, phospholipids, and steroids without derivatization. It combines liquid chromatography for separation with mass spectrometry for identification. LC-MS has been used to detect fertility-linked metabolites in sperm and seminal plasma (Longobardi *et al.*, 2020; Dasgupta *et al.*, 2022) ^[34, 9].

$^1\text{H-NMR}$ (Proton Nuclear Magnetic Resonance)

It is a non-destructive, reproducible method that identifies proton-containing metabolites with minimal sample preparation. Though less sensitive than MS, it offers broad, untargeted profiling. Giaretta *et al.* (2025) ^[13] applied $^1\text{H-NMR}$ to distinguish high- and low-motility bulls by analyzing seminal plasma metabolites related to motility and cryotolerance.

Cryopreservation and Metabolomic Changes in Bull Semen

Cryopreservation is vital for AI but causes biochemical disruptions in sperm and seminal plasma, reducing motility, viability, and membrane integrity. Key energy substrates like fructose, citric acid, and phosphocholine decline during freezing, impairing sperm function (Giaretta *et al.*, 2025) ^[13]. Additionally, Rai *et al.* (2010) ^[50] observed the development of skin infections under extreme conditions of oxidative stress. Oxidative stress markers such as AOPP increase, elevating ROS and reducing post-thaw viability.

In sperm, protective metabolites like glycerophosphocholine, L-acetylcarnitine, and formic acid decrease, while lysophosphatidylcholine rises, compromising membrane stability and mitochondrial function (Longobardi *et al.*, 2020) ^[34]. Amino acid profiles also shift-glutamic acid remains dominant, while phenylalanine, alanine, and tyrosine influence freezability and antioxidant defense. Phenylalanine is positively linked to post-thaw survival (Ugur *et al.*, 2020) ^[62].

High-fertility bulls show elevated levels of glycerol, lactate, glycerophosphocholine, and L-acetylcarnitine, supporting motility and antioxidant capacity (Giaretta *et al.*, 2025) ^[13]. Lipid profile changes include decreased phosphatidylcholines and increased lysophospholipids, further compromising membrane integrity after freezing (Longobardi *et al.*, 2020) ^[34].

Breed and Phenotype-Specific Studies on Sperm and Seminal Plasma Metabolomes associated with bull fertility

Substantial evidence confirms that bull fertility traits are influenced by both breed-specific genetic factors and individual semen phenotype variability. These differences affect the metabolomic, proteomic, and molecular composition of sperm and seminal plasma, directly impacting fertility outcomes.

Memili *et al.* (2020) ^[37] demonstrated that seminal plasma metabolite profiles significantly vary across bulls with different fertility phenotypes, identifying specific small molecules correlated with conception rates.

Velho *et al.* (2018) ^[66] identified lactic acid, 2-oxoglutaric acid, and glycerophosphocholine as discriminating metabolites between high- and low-fertility bulls within the same breed.

Azizah *et al.* (2024) ^[3] profiled seminal plasma proteins by molecular weight across Friesian Holstein, Belgian Blue Cross, and Ongole Grade bulls, finding that proteins in the 22-33 kDa range differed among breeds and correlated with ovulatory induction potential.

Willforss *et al.* (2021) ^[69] performed seminal plasma proteomics via LC-MS/MS in Holstein bulls, identifying fertility-associated proteins like osteopontin and N-acetylglucosamine-1-phosphotransferase consistently correlating with fertility.

Ugur *et al.* (2020) ^[62] found that amino acids such as phenylalanine, alanine, and glycine were significantly higher in bulls with superior semen freezability and post-thaw viability.

Talluri *et al.* (2022) ^[59] used integrated multi-omics (proteomics, transcriptomics, metabolomics) to distinguish high- from low-fertility bulls, identifying metabolic pathways and small molecules influencing sperm function and fertility.

15. Conclusion and Future Perspectives

Bull fertility is vital for livestock productivity, yet conventional semen analysis often fails to detect subfertility (Srivastava and Pande, 2017) ^[53]. Metabolomics offers a powerful solution by profiling sperm and seminal plasma metabolites to identify fertility-linked biomarkers such as fructose, glycerophosphocholine, and GABA. These insights help distinguish high- and low-fertility bulls and improve cryopreservation outcomes. Combining sperm and seminal plasma metabolomic data will likely yield more robust fertility biomarkers than either compartment alone. Despite challenges such as breed variability and methodological inconsistencies, metabolomics is a promising tool for early subfertility detection and improved reproductive management. Integrating it with other omics and developing portable diagnostic tools will accelerate its practical application, making it a transformative approach for improving bull fertility and herd genetic advancement. Future directions include integrating metabolomics with other omics for a systems-level fertility view, exploring seminal extracellular vesicle biomarkers, and developing portable diagnostic tools like point-of-care MS devices and biosensors for on-site fertility assessments. These advances could make metabolomics practical for AI and breeding programs.

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Competing Interests

Authors have declared that no competing interests exist.

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