



Dietary microRNAs from dairy products and their potential relevance to breast cancer: A systematic review

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ARTICLE INFO

Keywords:

Dairy products
microRNAs
Breast cancer
Diet
Epigenetics
Nutrigenomics

ABSTRACT

Background: The potential role of dairy products in breast cancer development remains controversial, with studies reporting both protective and detrimental effects. MicroRNAs, small non-coding RNA molecules involved in post-transcriptional gene regulation, are increasingly recognized as important mediators in cancer biology, including breast cancer. Milk and other dairy products contain extracellular vesicle-associated microRNAs, some of which are conserved, bioactive, and capable of surviving digestion. Additionally, dairy intake may modulate the expression of endogenous microRNAs in humans.

Scope and approach: This review explores the landscape of dairy-related microRNAs—both exogenous microRNAs naturally present in dairy products and endogenous microRNAs influenced by dairy consumption—and examines their potential overlap with those implicated in breast cancer. A structured PubMed search identified studies addressing: (1) the most relevant microRNAs detected in dairy products, (2) human-based studies investigating microRNA modulation following dairy intake, and (3) reported associations with breast cancer across clinical and molecular contexts.

Key findings and conclusions: We identified a group of dairy-associated microRNAs—particularly, *miR-148a-3p*, *miR-21-5p*, *miR-30a-5p-5p*, *miR-125b-5p*, *miR-26a-5p*, *miR-155-5p*, and *miR-146a-5p*—that have been linked to key processes involved in breast cancer development, including cell proliferation, apoptosis, epithelial-to-mesenchymal transition, and chemoresistance. Some of these microRNAs are also differentially expressed in mastitic milk or modulated by farming systems and stress-related conditions, highlighting the need for interdisciplinary approaches bridging food systems and human health. While causal inference is beyond the scope of this review, the widespread and sustained consumption of dairy products supports the need for further research to clarify how dairy intake may influence microRNA-mediated regulatory mechanisms and breast cancer risk in humans. The available evidence also suggests that dairy subtype, origin, and processing may be relevant when considering potential dietary implications.

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<https://doi.org/10.1016/j.tifs.2026.105953>

Received 19 June 2025; Received in revised form 6 July 2026; Accepted 16 July 2026

Available online 17 July 2026

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1. Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of cancer-related mortality among women worldwide, with its prevalence and associated burden steadily increasing over recent decades (Sung et al., 2021). Its incidence varies significantly across countries, influenced by socioeconomic development and lifestyle factors (Falzone et al., 2020). BC comprises multiple subtypes classified based on clinical parameters and molecular profiling. Beyond disease staging, the expression status of key hormone receptors—oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)—is crucial in determining prognosis and treatment strategies. Clinically, BCs are categorized as ER+/PR+, HER2+, or triple-negative BC (TNBC), the latter lacking expression of all three receptors. Additionally, BC subtyping through transcriptome profiling has identified four major subtypes: luminal A, luminal B, and basal-like. ER+/PR+ BC predominantly fall into the luminal A and B subtypes, while TNBC are primarily classified as basal-like (Zabaleta et al., 2020).

Key risk factors for BC include delayed childbearing, fewer children, increased obesity rates, and low or absent physical activity. According to the International Agency for Research on Cancer (IARC), between one-third and two-fifths of new cancer cases could potentially be prevented by reducing exposure to environmental risk factors (Falzone et al., 2020; Sung et al., 2021). Despite advances in detection and

treatment, prevention strategies are critical to reducing the burden of this disease. Among modifiable risk factors, diet has drawn considerable attention, particularly the role of dairy consumption (Riseberg et al., 2024). However, epidemiological studies investigating the relationship between dairy intake and BC risk have yielded conflicting results, ranging from protective to neutral (Arafat et al., 2023; Chen et al., 2019; Riseberg et al., 2024), or even detrimental associations (Fraser et al., 2020; Melnik et al., 2023). This inconsistency underscores the complexity of the relationship and the need to explore molecular mechanisms that may underlie these observations.

MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate gene expression post-transcriptionally by targeting messenger RNAs (mRNAs) for degradation or translational repression. They are initially produced in the cell nucleus as long primary transcripts (called pri-miRNAs), which are processed into shorter, hairpin-shaped precursor molecules (pre-miRNAs). These precursors are then exported to the cytoplasm and cut into a double-stranded structure composed of two strands: one from the 5' arm (5p) and one from the 3' arm (3p) of the hairpin. Typically, one of these strands is selected and incorporated into a protein complex called RISC (RNA-induced silencing complex), which uses the miRNA to recognize and bind specific mRNAs, blocking their translation into proteins or promoting their degradation. In some cases, both the 5p and 3p strands can be active and regulate different target genes (Fig. 1).

The role of miRNAs as master regulators in critical cellular processes,

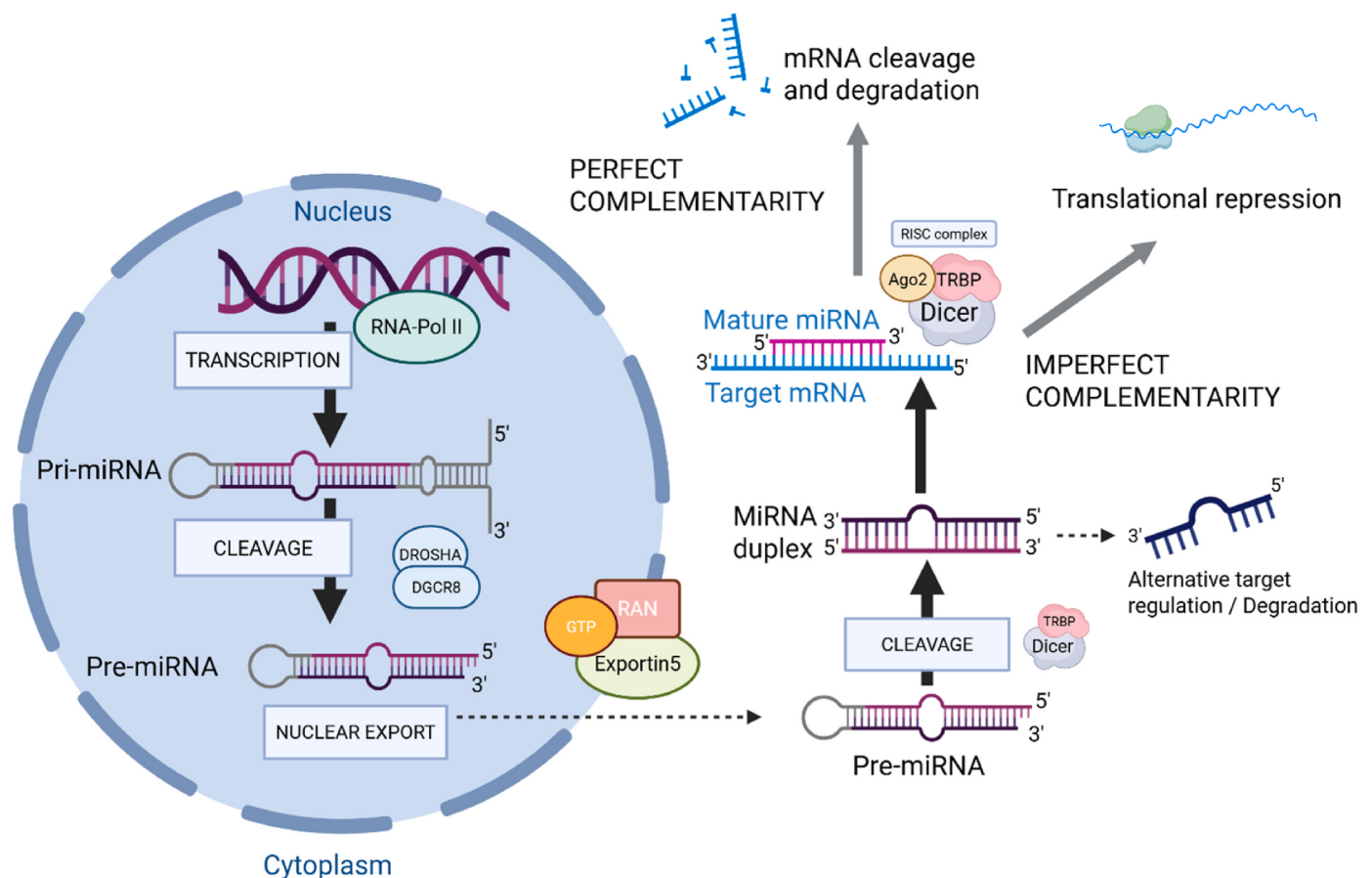


Fig. 1. miRNA Biosynthesis. Primary miRNAs (pri-miRNAs), transcribed in the nucleus by RNA polymerase II, contain characteristic stem-loop structures. These are cleaved by the microprocessor complex at the base of the stem, generating precursor miRNAs (pre-miRNAs) approximately 60–70 nucleotides in length. The pre-miRNA is then exported to the cytoplasm via Exportin-5, where it is further processed by Dicer into a ~22 nucleotide miRNA duplex composed of a 5p and a 3p strand. Typically, one of the two strands is preferentially incorporated into the RNA-induced silencing complex (RISC) to guide sequence-specific targeting of the 3' untranslated region (3'UTR) of mRNAs through seed-based antisense pairing. The other strand may either be degraded or retained for functional loading into RISC under specific cellular conditions, potentially regulating distinct target genes. Perfect complementarity results in mRNA cleavage and degradation, while partial complementarity leads to translational repression. Created in <https://BioRender.com>.

such as proliferation, apoptosis, and inflammation, makes them central to cancer biology. Dysregulation of miRNA expression has been widely implicated in BC development and progression, with specific miRNAs functioning as either oncogenes (OncomiRs) or tumour suppressors (anti-OncomiRs or MiRsupps) depending on their targets (Zabaleta et al., 2020).

MiRNAs' encapsulation within extracellular vesicles (EVs) or exosomes provides several advantages over freely circulating miRNAs in the blood, including enhanced facilitation of tumour initiation, propagation, immune evasion, and drug resistance. Exosomes are lipid-bilayer EVs, ranging in size from 30 to 150 nm, released by various cell types, including BC cells. They primarily facilitate cellular communication and have been extensively studied for their role in BC biology and treatment. Over the past decade, research has highlighted the pivotal role of exosomes in breast tumorigenesis and progression through the transfer of miRNAs. These miRNAs modulate target mRNAs post-transcriptionally, leading to changes in gene expression or repression and significantly influencing cancer-related pathways (Linares-Rodríguez et al., 2025).

Evidence has highlighted the presence of miRNAs in dietary sources, including dairy products such as milk. Many of these milk-derived miRNAs are highly conserved across mammalian species, suggesting potential functional relevance in cross-species gene regulation (van Herwijnen et al., 2018). These exogenous miRNAs, often associated with milk-derived EVs, are relatively stable and have been proposed to survive digestion and enter the systemic circulation, where they may influence gene expression in human cells (Rani et al., 2017). One study has shown that bovine milk contains several miRNAs with conserved sequences that may exert regulatory effects on human gene expression. Bioinformatic predictions and comparative analyses revealed that multiple bovine miRNAs share identical seed regions with their human homologs, suggesting they may bind the same mRNA targets (Myrzabekova et al., 2022).

In addition to the introduction of exogenous miRNAs through diet, dietary patterns—such as dairy consumption—have also been shown to modulate the expression of endogenous miRNAs, potentially impacting cancer-related pathways (DeLucas et al., 2024).

These observations suggest two complementary mechanisms through which dairy-associated miRNAs may interact with human biology: the direct exposure to miRNAs naturally present in dairy products and the modulation of circulating miRNAs observed following dairy consumption.

Exploring whether dairy-associated miRNAs may functionally or mechanistically overlap with those implicated in BC could shed light on the molecular basis of the conflicting epidemiological findings regarding dairy intake and BC risk.

In this review, the term *dairy-associated miRNAs* refers to both miRNAs naturally present in dairy products (exogenous miRNAs) and circulating miRNAs reported to be modulated following dairy consumption (endogenous miRNAs).

Accordingly, this review aims to systematically map the current literature on (i) miRNAs identified in dairy products and (ii) endogenous miRNAs reported in association with dairy consumption, evaluating their potential relevance to BC biology. While the first category refers to miRNAs directly detected in dairy matrices, the second includes circulating miRNAs measured in human biological samples following dairy intake. In this context, the term *endogenous* is used operationally to refer to miRNAs detected in human circulation after dairy consumption; however, current methodological approaches do not always allow a clear distinction between truly endogenous miRNAs and exogenous dietary miRNAs that may enter the circulation. By identifying overlapping miRNAs, shared pathways, and existing research gaps, this review provides a foundation for future interdisciplinary investigation in nutrition and cancer biology.

2. Methods

This review was conducted in accordance with the PRISMA 2020 guidelines. A structured literature search was initially conducted in PubMed between February and April 2025 using predefined keywords, MeSH terms, and Boolean operators (see Appendix A). To ensure comprehensive coverage of the literature, the search was updated in March 2026 and expanded to include Scopus, and Web of Science. The same conceptual search strategy was applied across databases, with syntax adapted as required. The review was organized into two sequential phases to explore the potential interplay between dairy-associated miRNAs—both exogenous and diet-modulated endogenous—and BC biology. In Phase 1, two distinct literature searches were performed to identify miRNAs associated with dairy: (A) Exogenous miRNAs naturally present in dairy matrices (e.g., milk from bovine, goat, or sheep) and (B) Circulating (here referred to as *endogenous*) miRNAs modulated by dairy consumption. For the second category (B), only human-based studies were included, encompassing dietary interventions and observational research. Animal studies were excluded. In Phase 2, a targeted manual screening in PubMed was conducted using specific combinations of the most consistently reported dairy-associated miRNAs identified in Phase 1 and BC-related keywords to assess their potential involvement in BC-associated processes. Additionally, HMDD v4.0 (Human miRNA Disease Database, version 4) was consulted to retrieve validated or predicted associations between selected miRNAs and BC. Only human-based studies were considered, including cellular models, observational and experimental designs. Eligible studies examined associations between dairy miRNAs and cancer-related mechanisms, such as tumour progression, apoptosis, immune modulation, or treatment resistance, with attention to specific BC subtypes (e.g., ER+, HER2+, TNBC) and pathways.

2.1. Study selection and data extraction

The search included peer-reviewed articles published from 2015 onward. For Phase 2, only studies published from 2023 onward were considered. After duplicate removal, titles and abstracts were screened for relevance, followed by full-text evaluation. Reference lists and PubMed “similar articles” were also reviewed to identify additional studies. Priority was given to original research articles, while review papers were included only when they provided particularly relevant or comprehensive insights aligned with the objectives of the review. Articles were excluded if they were duplicates, unavailable in full text, not peer-reviewed, or not related to the review's scope. Grey literature—including preprints, conference abstracts, and other non-peer-reviewed materials—was excluded to ensure the methodological reliability of the evidence included in this review.

Data extraction was conducted separately for each phase.

- In Phase 1A (exogenous miRNAs), extracted data included: authors and year of publication, the most relevant identified miRNAs, livestock species, health status (e.g., mastitis), type of dairy matrix (e.g., milk, cheese), farming system, and exposure to environmental-related stressors. In Phase 1B (endogenous miRNAs), extracted variables included: type of exposure (e.g., whole dairy, specific components), experimental model (e.g., human in vivo or human-derived in vitro), and reported modulation of miRNA expression.
- In Phase 2, for each miRNA, data were extracted on the biological material and model used (e.g., BC tissue, blood, serum), BC subtype, functional role (oncogenic or tumour-suppressive), validated/predicted targets, and pathway involvement.

3. Results

A total of 1637 records were retrieved across all searches. After removal of duplicates and screening according to the inclusion and

exclusion criteria, a total of 93studies were included in the final synthesis. The selection process and distribution of studies across the two phases of the review are illustrated in the PRISMA flow diagram (Supplementary file 1). Results are presented below according to the review phases: Phase 1 reports studies identifying miRNAs related to dairy (exogenous or endogenously modulated), while Phase 2 focuses on their potential relevance in BC contexts.

3.1. miRNAs in dairy products

The first search (Phase 1A) yielded a total of 560 records, from which 43 studies met the inclusion criteria and were analyzed. These studies reported the characterization of miRNAs naturally present in dairy products derived from various livestock species, including cows (*Bos taurus*), buffaloes (*Bubalus bubalis*), goats (*Capra hircus*), and sheep (*Ovis aries*).

A large number of exogenous miRNAs were identified in different dairy matrices such as raw milk, colostrum, pasteurized milk, cheese, yogurt, and commercial butter. [Supplementary Table 1](#) (S1) lists the subset of miRNAs that were retained based on abundance and cross-species conservation. For clarity and focus, [Table 1](#) reports only those miRNAs identified in at least seven independent sources. This threshold was applied to prioritize miRNAs with higher recurrence and potential biological relevance.

Notably, some of these recurrent miRNAs have also been reported among the most abundant miRNAs in milk, milk-derived extracellular

Table 1

Subset of recurrent dairy-associated miRNAs identified across different livestock species and dairy matrices. Each miRNA is reported along with the species in which it was detected, the type of dairy matrix, and the corresponding references. Only selected miRNAs detected in at least seven independent sources and reported among the most abundant or top-ranked miRNAs in the corresponding dairy matrices are included. The table is sorted by the number of studies in which each miRNA was identified, from highest to lowest.

miRNA	Species	Dairy Product	References
miR-148a-3p	Cow (increased expression associated with enhancement of dairy lactation performance), Buffalo, Sheep, Goat	Cheese; commercial butter; raw milk; pasteurized milk; colostrum; milk from different lactation stages; whole and skimmed goat milk powder-derived EVs	Ilori et al., 2025; Rani et al., 2020; Yun et al., 2021; Krupova et al., 2023; Mun et al., 2025; Leroux et al., 2025
miR-21-5p	Buffalo, Cow, Goat	Raw milk; Pasteurized milk; Colostrum; Milk from different lactation stages; Cheese; Yogurt; Commercial butter; Whole and skimmed goat milk powder-derived EVs	; Ilori et al., 2025; Melnik et al., 2023; Rani et al., 2020; Krupova et al., 2023; Mun et al., 2025; Leroux et al., 2025; Krupova et al., 2025
miR-30a-5p	Buffalo, Cow, Goat, Sheep	Milk from all lactation stages; raw milk; colostrum; pasteurized milk; commercial butter; whole and skimmed goat milk powders	Rani et al., 2020; L. Wang et al., 2018; Leroux et al., 2025; Krupova et al., 2023; Mun et al., 2025; Krupova et al., 2025
miR-26a-5p	Buffalo, Cow, Goat, Sheep	Milk from different lactation stages; raw milk; colostrum; pasteurized milk; commercial butter; whole and skimmed goat milk powders	Rani et al., 2020 ; Krupova et al., 2023; Mun et al., 2025; Leroux et al., 2025; Krupova et al., 2025
miR-125b-5p	Cow, Goat, Sheep	Milk; Raw milk; Colostrum; Skim milk; commercial butter	Melnik et al., 2023

vesicles, and processed dairy matrices. In particular, *miR-148a-3p*, *miR-30a-5p*, *miR-26a-5p*, and *miR-21-5p* were frequently reported among highly abundant dairy-associated miRNAs, although their relative ranking may vary according to species, milk fraction, lactation stage, dairy matrix, processing conditions, and analytical approach (Benmoussa et al., 2020; Krupova et al., 2023, 2025; Leduc et al., 2023; Leroux et al., 2025; Mun et al., 2025; Rani et al., 2020).

MiR-148a-3p and *miR-21-5p* were the most widely detected, identified in milk or dairy products from all four species and across multiple lactation stages, with 13 references each. Other highly recurrent miRNAs included *miR-30a-5p* and *miR-26a-5p* (10 studies each), and *miR-125b-5p* (7 studies). These findings highlight a conserved set of miRNAs present in milk from different species, which may retain biological activity and potentially contribute to interspecies epigenetic communication upon consumption. Interestingly, bovine *miR-21-5p* and *miR-30a-5p* have also been reported to increase in human plasma following the ingestion of bovine milk.

The expression levels and abundance of miRNAs in milk are modulated by multiple factors, including the health status of the mammary gland, physiological conditions such as pregnancy, and environmental-related stressors.

[Table 2](#) summarizes the subset of miRNAs reported to be differentially expressed in bovine milk under mammary gland infections. Only miRNAs cited in at least three independent sources were retained to prioritize those with greater consistency across studies. The complete list of differentially expressed miRNAs in different pathological or environmental conditions, including those reported in single studies, is available in [Supplementary Table 2](#) (S2).

Mastitis, a very common inflammatory condition affecting dairy cows and buffaloes, is strongly associated with the differential expression of several miRNAs. Particularly, *miR-21-5p*, *miR-155-5p*, and *miR-146a-5p* were found to be upregulated in mastitis-positive milk samples across multiple independent studies, highlighting their potential as biomarkers of inflammation (see [Table 2](#) and [S2](#) for references).

Processing techniques applied to dairy products substantially affect both the abundance and composition of their miRNA content. Studies have shown that bovine milk retains detectable levels of several miRNAs even after common processing methods such as microwaving, pasteurization followed by fermentation (e.g., yogurt production), and cheese manufacturing. However, all these treatments result in a general reduction in miRNA levels. Among processed dairy products, raw milk and cheese appear to preserve relatively higher concentrations of miRNAs compared to microwaved milk and yogurt, although their specific

Table 2

Differential expression of bovine milk-derived miRNAs in mammary gland infections including mastitis. For each miRNA, the species, condition, direction of modulation (e.g., upregulation or downregulation), and the corresponding references are reported.

miRNA	Species	Condition	Differential expression	References
miR-21-5p	Cow	Mastitis/ mammary gland infection	Significantly upregulated in mastitis test positive milk	Lai et al., 2017; (Kabir & Miura, 2020; Putz et al., 2019; Özdemir, 2020; Ojo & Kreuzer-Redmer, 2023
miR-155-5p	Cow	Mastitis/ mammary gland infection	Significantly upregulated in mastitis test positive milk	Lai et al., 2017; Kabir & Miura, 2020; Özdemir, 2020; Luoreng et al., 2018; Özkan et al., 2024
miR-146a-5p	Cow	Mastitis/ mammary gland infection	Upregulated in mastitis test positive milk	Lai et al., 2017; Kabir & Miura, 2020; Luoreng et al., 2018

miRNA profiles may differ (Ilori et al., 2025; Yu et al., 2017). Kleinjan et al. (Kleinjan et al., 2021) showed that UHT treatment severely damages the integrity of milk-derived extracellular vesicles, compromising their structure and potentially impairing the stability and functionality of their molecular cargo, including miRNAs.

3.2. Endogenous miRNAs and dairy consumption

The second search (Phase 1B) targeting endogenous miRNAs modulated by dairy consumption yielded 115 records, of which only 1 met the eligibility criteria and was included.

In a randomized crossover clinical trial, Khorraminezhad and Rudkowska (Khorraminezhad & Rudkowska, 2022) explored whether dairy consumption modulates circulating miRNAs in individuals with hyperinsulinemia. Microarray analysis identified *miR-223-3p* and *miR-122-5p* as upregulated following high dairy intake, although this finding was not confirmed by subsequent qRT-PCR validation.

3.3. Functional relevance of dairy-associated miRNAs in BC

From phases 1A and 1B, we identified a total of 87 relevant miRNAs associated with dairy products: 85 were exogenous miRNAs detected in dairy matrices (Supplementary Tables 1 and 2), while 2 were endogenous miRNAs whose circulating levels were reported to change following dairy consumption. To preliminarily assess their potential involvement in BC, we first queried the HMDD v4.0 database and cross-referenced the resulting BC-associated miRNAs with the 87 candidates identified from dairy sources. Subsequently, an independent manual search was conducted in PubMed, prioritizing the most relevant and consistently reported dairy-associated miRNAs, particularly those frequently reported among the most abundant or top-ranked miRNAs in dairy matrices and those identified in at least seven independent studies (Table 1), as well as miRNAs implicated in mammary gland inflammation, including mastitis (Table 2). This strategy allowed for the inclusion of both highly recurrent or top-ranked dairy-associated miRNAs and other miRNAs of potential relevance based on their biological context, resulting in the selection of 45 studies in this phase.

All selected dairy-associated miRNAs correspond to human miRNAs that have been reported in BC-related studies. Specifically, *miR-148a-3p*, *miR-21-5p*, *miR-30a-5p*, *miR-125b-5p*, *miR-26a-5p*, *miR-155-5p*, and *miR-146a-5p*, together with the endogenously modulated *miR-122-5p* and *miR-223-3p*, have been associated with BC-related mechanisms, including tumour progression, migration, apoptosis regulation, and treatment response (Table 3).

3.3.1. miRNAs predominantly described as tumour suppressors in BC

miR-148a-3p.

Although *miR-148a-3p* has been reported to act as an oncomiR in ER + BC by enhancing IGF-1 and ER α signaling via suppression of p53 and DNA Methyltransferase 1 (DNMT1) (Melnik et al., 2023), recent evidence suggests that the same regulatory axis may have therapeutic implications in ER α -negative contexts. Specifically, *miR-148a-3p*-mediated inhibition of DNMT1 can reduce ER α promoter methylation, restoring ER α expression and sensitizing triple-negative BC cells to tamoxifen therapy (Dong et al., 2025). In parallel, several functional studies in luminal and TNBC models support a tumour-suppressive role for *miR-148a-3p*, showing inhibition of EMT, stemness, migration and cell viability through targeting pathways such as TGF- β /Smad2, IRS-1 and CYP1B1 (Han et al., 2024; Ma et al., 2025; Zhao et al., 2023). Together, these findings suggest that the biological role of *miR-148a-3p* in BC may depend on the estrogen receptor context and therapeutic setting.

miR-30a-5p.

The role of *miR-30a-5p* in BC appears to be complex and context-dependent, with evidence supporting both oncogenic and tumour-suppressive activities. In vitro experiments using TNBC cell models have reported an oncogenic role of *miR-30a-5p* via inhibition of *BCL2*-

like 11 (*BCL2L11*), a pro-apoptotic gene of the *BCL2* family, thus promoting cell survival (Wang et al., 2024). Conversely, other studies have demonstrated a tumour-suppressive effect. For example, *miR-30a-5p* was shown to downregulate the long non-coding RNA *metastasis associated lung adenocarcinoma transcript 1* (*MALAT1*) and reduce immune-suppressive markers in MDA-MB-231 cells (Ramzy et al., 2025). Furthermore, both human TNBC tissues and MDA-MB-231 cells revealed that *miR-30a-5p* can suppress the *signal transducer and activator of transcription 3/cystathionine gamma-lyase/hydrogen sulfide* (*STAT3/CSE/H₂S*) signaling axis, which is implicated in tumour proliferation and immune evasion (Youness et al., 2025). In addition, an integrated analysis combining TCGA (The Cancer Genome Atlas) BRCA RNA-seq data with transcriptomic profiling of 43 BC and non-cancerous cell lines demonstrated that *miR-30a-5p* can post-transcriptionally repress *estrogen receptor 1* (*ESR1*), which encodes the oestrogen receptor alpha (ER α), possibly also involving epigenetic regulation through promoter methylation (Yang et al., 2025). Collectively, these findings support a dual role for *miR-30a-5p* in BC pathogenesis, potentially modulating key pathways depending on the cellular and molecular context.

miR-125b.

In a multi-omics study focusing on early-stage luminal (ER+) BC, *miR-125b-5p* was associated with oxysterol signaling pathways and ER modulation, suggesting a potential tumour-suppressive role, however, this function was not experimentally confirmed in that context (Holý et al., 2023). In another study analyzing plasma samples from BC patients and drug-resistant BC cell lines, *miR-125b-5p* emerged as a potential predictor of resistance to neoadjuvant chemotherapy, however, its oncogenic role was not functionally validated (Kim et al., 2024). Conversely in TNBC models, *miR-125b-5p* was shown to act as a tumour suppressor by inhibiting the expression of *MAPK12*, *TGF- β 1* (transforming growth factor beta 1), and *SIX1* (*SIX* homeobox 1), thereby reducing TNBC aggressiveness (Sengupta et al., 2024).

miR-26a-5p.

miR-26a-5p has been described as a tumour suppressor in BC across several experimental models. In luminal A (ER⁺/PR⁺) MCF-7 cells, it was shown to inhibit interleukin-6 (IL-6) expression and secretion by targeting its 3' untranslated region (3'UTR), thereby deactivating nuclear factor kappa B (NF- κ B) signalling—a key pro-inflammatory and pro-tumorigenic pathway in BC cells (Farhana et al., 2024). In both MCF-7 and triple-negative MDA-MB-231 cells, the tumour-suppressive role of *miR-26a-5p* was further supported by evidence showing that its maturation is enhanced by Star-PAP, a specialized enzyme that facilitates the processing of primary miRNA transcripts. This enhanced maturation leads to reduced expression of oncogenes, thereby limiting tumour formation (Mohan et al., 2024). Additionally, in a drug-resistant TNBC model (MDA-MB-231-PTX), *miR-26a-5p* was found to enhance sensitivity to the anti-cancer drug paclitaxel by targeting Flap Endonuclease 1 (FEN1), thereby reducing cell migration and chemoresistance (Cai et al., 2023). More recently, circRNA-mediated sponging of *miR-26a-5p* has been shown to promote BC cell proliferation, migration and invasion, further supporting its tumour-suppressive role in BC (Guo et al., 2025).

miR-146a-5p.

miR-146a-5p has been reported to exert context-dependent functions in BC, displaying both oncogenic and tumour-suppressive activities depending on the molecular subtype and cellular environment. In HER2+ BC cell lines, Cabello et al. showed that intracellular *miR-146a-5p* promotes trastuzumab resistance, migration, angiogenesis, and cell cycle progression by targeting *CDKN1A* (cyclin-dependent kinase inhibitor 1A, p21) (Cabello et al., 2023). Notably, exosomal transfer of *miR-146a-5p* was shown to transmit resistance traits to sensitive cells, and high tumour expression levels were associated with poor disease-free survival in HER2+ BC patients. However, several studies support a tumour-suppressive role for *miR-146a-5p* in other BC contexts. Circulating levels of *miR-146a-5p* were found to be downregulated in serum samples from BC patients compared to both healthy

Table 3

Most relevant dairy miRNAs associated with BC-related processes.

MiRNAs	Sample/Model/BC subtype	Function	Involved Pathways/Processes	References
<i>miR-148a-3p</i>	ER + BC	OncomiR	Suppression of p53 and DNMT1 enhancing IGF-1, ER α , and FTO, a m6A RNA demethylase expression, that further enhances ER α expression.	Melnik et al. (2023)
	Human BC cell lines (MDA-MB-231 and MCF7) (TNBC and ER+/PR+)	MiRsupps	Inhibition of BC cell stemness and EMT by targeting the TGF- β /Smad2 signaling pathway.	Ma et al. (2025)
	In vitro TNBC cell lines, supported by in silico analyses	MiRsupps	Inhibition of cell migration and viability in TNBC by targeting IRS-1	Zhao et al. (2023)
	Human cell line MDA-MB-231 (TNBC)	MiRsupps	<i>Mir-148a-3p</i> targets CYP1B1; mediates honokiol-induced apoptosis, inhibits proliferation and migration	Han et al. (2024)
	c-Myc knocked down TNBC cell lines	MiRsupps	When c-Myc is reduced, <i>miR-148a-3p</i> increases and inhibits DNMT1. This reduces methylation of the ER α gene promoter, allowing ER α expression to be restored and making TNBC cells responsive again to tamoxifen.	Dong et al. (2025)
<i>miR-21/miR-21-5p</i> (Significantly upregulated in mastitis test positive milk)	Human TNBC tumor tissues (miRNA-seq, RNA-seq; in silico miRNA-mRNA correlation analysis)	Not defined	Potential downregulation of target genes including CLCN4, PLCB1, CDC25B and AEBP2	Hossain et al., 2025
	Whole blood samples from BC patients at different stages	OncomiR	Positive correlation with ABCA1 expression, contributing to ABC transporter-mediated chemoresistance in BC.	Khalaf et al. (2025)
	Serum-based study on TNBC living patients	OncomiR	As prognostic biomarkers of recurrence	Kujala et al. (2024)
	Bioinformatic analysis using patient-derived transcriptomic data	OncomiR	Promotion of TNBC progression and serving as a marker of unfavorable clinical outcomes.	J. Xu, Guo, et al. (2025)
	MDA-MB-231 (TNBC) stem cells co-cultured with human bone marrow-derived telocytes	OncomiR	Promotion of EMT and metastatic properties in BC stem cells; telocytes counteract these effects by downregulating <i>miR-21-5p</i> -related oncogenic pathways.	Babadag et al. (2024b)
<i>miR-30a-5p</i>	In silico (Boolean network modeling), validated with published experimental data including BC	OncomiR	Promotion of EMT and drug resistance by repressing PTEN in the DNA damage response context.	Gupta et al. (2024)
	In silico analysis integrated with protein-protein interaction network analysis and survival analysis BC cohorts	OncomiR	Associated with a prognostic hub-gene network (STAT3, MYC, PTEN, BCL2, IL1B, MMP9, EGFR, TGFB1, IL10, E2F1, CASP8, RHOA) regulating proliferation, apoptosis and immune signaling in BC.	Tumolo et al. (2026)
	In vitro human cell line MDA-MB-231 (TNBC)	OncomiR	Negative regulation of BCL2L11, a pro-apoptotic gene.	W. Wang et al. (2024)
	MDA-MB-231 cells (TNBC)	MiRsupps	Inhibition of MALAT1 and immune-suppressive markers.	Ramzy et al. (2025)
	Human TNBC tissues and MDA-MB-231 cell line	MiRsupps	Suppression of the STAT3/CSE/H ₂ S axis via direct and indirect regulation	Youness et al. (2025)
<i>miR-125b-5p</i>	TCGA BRCA RNA-seq datasets and 43 BC and non-cancerous cell lines (in silico and in vitro analysis).	MiRsupps	Post-transcriptional repression of ESR1, potential epigenetic regulation through methylation (<i>Mir-30a-5p</i>)	Yang et al. (2025)
	Human TNBC tumour tissues (miRNA-seq, RNA-seq; in silico miRNA-mRNA correlation analysis)	Not defined	Potential downregulation of target genes including CLCN4, PLCB1, CDC25B and AEBP2	Hossain et al., 2025
	TNBC BC datasets; integrative bioinformatics and network analysis	MiRsupps	Regulates genes involved in cell-cycle and mitotic pathways; dysregulation of these targets is associated with TNBC progression and poor prognosis	Dharshini & Mandal, 2025
	Multi-omics study in early-stage luminal (ER+) BC	Not defined	<i>miR-125b-5p</i> involved in oxysterol signaling and ER modulation	Holý et al. (2023)
	Plasma samples from BC patients and drug-resistant BC cell lines	OncomiR (not experimentally defined)	<i>miR-125b-5p</i> as potential predictors of resistance to neoadjuvant chemotherapy in BC patients	Kim et al. (2024)
<i>miR-26a-5p</i>	MDA-MB-231 cells (TNBC)	MiRsupps	Suppression of MAPK12, TGF- β 1, and SIX1 expression, limitation of TNBC aggressiveness (<i>miR-125b-5p</i>)	Sengupta et al. (2024)
	Human BC cell line MCF-7 (Luminal A, ER+, PR+)	MiRsupps	Inhibition of IL-6 expression and secretion via targeting its <i>miR-26a-5p</i> 3'UTR, and by deactivating NF- κ B signaling in BC cells	Farhana et al. (2024)
	MCF-7 (luminal A) and MDA-MB-231 (TNBC) cell lines	MiRsupps	its maturation is promoted by Star-PAP, which limits oncogenes expression and tumour formation.	Mohanani et al. (2024)
	MDA-MB-231-PTX (drug-resistant TNBC line)	MiRsupps	Enhancement of paclitaxel sensitivity in by targeting and downregulating FEN1, reducing drug resistance and migration.	Cai et al. (2023)
	BC tissues and MCF-7 cell line	MiRsupps	Regulates a gene involved in cellular stress response; circRNA-mediated sponging of <i>miR-26a-5p</i> promotes BC cell proliferation, migration and invasion.	Guo et al. (2025)
<i>miR-155-5p</i> (Significantly upregulated in mastitis test positive milk)	Human serum samples (183 female participants)	OncomiR	Upregulated in the serum of BC patients and positively correlated with NF- κ B and TNF- α signaling	Abdel-Samed et al. (2024)
	MDA-MB-231 (TNBC cell line), HUVEC (endothelial cells)	OncomiR	Promotion of migration, invasion, angiogenesis by downregulating PTEN and DUSP14 (Exosomal delivery of <i>miR-155-5p</i> inhibitor reverses these effects)	Razaviyan et al. (2024)
	Human subjects (peripheral blood from 90 BC patients and 30 healthy controls)	OncomiR	Its upregulation is correlated with increased expression of immune checkpoint markers (PD-1, PD-L1, CTLA-4,	Al-Sharabass et al. (2025)

(continued on next page)

Table 3 (continued)

MiRNAs	Sample/Model/BC subtype	Function	Involved Pathways/Processes	References
<i>miR-146a-5p</i> (Upregulated in mastitis test positive milk)	Computational/in silico research, based on RNAseq human data integration, bioinformatic analysis and molecular docking simulations	OncomiR	FOXP3) and with elevated levels of MIC-B, which together reflect immune evasion and tumour progression. <i>miR-155-5p</i> as one of the key miRNAs associated with aggressive tumour behavior and poor clinical outcomes in BC	Shornale Akter et al. (2024)
	MCF-7 (ER ⁺ , TAM-sensitive and TAM-resistant)	OncomiR	Promotion of drug (tamoxifen) resistance via upregulation of STAT3 and HK2	Shpigel et al. (2025)
	Primary BC Formalin-Fixed Paraffin-Embedded tissues from patients with different metastatic recurrences	OncomiR	Significantly overexpressed in primary tumours that later develop brain metastasis; high expression predicts BC brain recurrence	Koyama et al. (2025)
	BC cell lines MCF-7 (luminal A) and MDA-MB-231 (TNBC); BC tissues and serum exosomes	OncomiR	Promotes proliferation, invasion and metastasis by targeting NDFIP1, activating the NF-κB signaling pathway	R. Xu, Guo, et al. (2025)
	TNBC patient datasets (TCGA, GEO), multiple BC cell lines (MCF-7, MDA-MB-231, MDA-MB-436, Hs-578T, BT-549, HCC-1395, MDA-MB-157)	OncomiR	Activated by inflammatory signaling and promotes tumor growth, stem-like traits and chemoresistance through activation of oncogenic signaling pathways	Sarcinella et al. (2025)
	HER2 ⁺ BC cell lines (trastuzumab-sensitive and -resistant)	OncomiR	<i>miR-146a-5p</i> promotes trastuzumab resistance, migration, angiogenesis, and cell cycle progression by downregulating CDKN1A (p21); exosomal transfer confers resistance. High levels predict poor disease-free survival in HER2 ⁺ BC.	Cabello et al. (2023)
	Serum samples from 96 BC patients, 30 with benign breast disease, and 25 healthy controls.	MiRsupps (not confirmed)	<i>miR-146a-5p</i> was found to be downregulated in the serum of BC) patients compared to both healthy controls and patients with benign breast disease.	Abd ELhafeez et al. (2024)
	TNBC cell line MDA-MB-231	MiRsupps	Upregulation inhibits inflammatory NF-κB signaling by targeting IRAK1/TRAF6, reducing tumor aggressiveness	Gooran Orimi et al. (2025)
	BC cell line MCF-7 (luminal A)	MiRsupp	Negatively regulates autophagy by targeting TRAF6; reduced <i>miR-146a-5p</i> expression during stress increases TRAF6 and autophagy activity	Alirezade et al. (2025)
	Serum samples from BC patients	MiRsupps	Downregulated in BC; reduced levels associated with metastasis and increased expression of the oncogenic target SIRT1	Sayed et al., 2025
<i>miR-223-3p</i>	MDA-MB-231-derived cancer stem cells (TNBC)	OncomiR	<i>miR-146a-5p</i> promotes stemness, EMT, and expression of tumorigenic markers (e.g., BRCA1, SOX2, P53); its inhibition reduces these properties.	Babadag et al. (2024a)
	BC tissues; integrated microarray profiling and qRT-PCR validation	MiRsupps	Downregulated in BC tissues compared to healthy controls; associated with Wnt, TGF-β, ErbB, and MAPK signaling pathways; potential diagnostic or prognostic marker.	Shahid et al. (2024)
	BC tissues and BC cell lines representing distinct molecular subtypes: MCF-7, SK-BR3, MDA-MB-231, and HCC1500	MiRsupps	Downregulated in BC tissues and cell lines; reduced expression correlates with poorer prognosis; involved in regulation of cell division and cell-cycle progression.	Sahin et al. (2023)
	HDLs isolated from treatment-naïve women with newly diagnosed BC	Not defined	Enriched in HDLs from newly diagnosed BC patients, independently of tumour subtype and particularly in advanced-stage disease; associated with enhanced anti-inflammatory activity of HDLs and modulation of systemic inflammation.	Santana et al. (2023)
	BC cells and clinical samples	MiRsupps	NOTCH3/miR-223-3p/ZEB1 regulatory axis; suppression of ZEB1 inhibits proliferation and invasion in vitro and is associated with favourable prognostic indicators.	Chen et al. (2024)
	BC cells	MiRsupps	Inhibits cell proliferation and invasion while promoting oxidative stress-mediated apoptosis through downregulation of KIF4A.	Zhi et al. (2025)
	ER + MCF-7, TNBC MDA-MB-231, and long-term oestrogen-deprived models	MiRsupps/context-dependent	Modulation of miR-223-3p combined with cholesterol depletion reduces tamoxifen resistance; associated with lipid raft disruption.	Palma and Kaur (2023)
<i>miR-122-5p</i>	Serum from BC patients	OncomiR	Significantly upregulated in BC patients, suggesting a potential oncogenic role.	Elghoroury et al. (2024)
	BC cells	OncomiR	Crocin suppresses BC cell proliferation by downregulating miR-122-5p, resulting in upregulation of the tumour suppressor genes FOXP2 and SPRY2, direct targets of miR-122-5p.	Jia et al. (2023)
	TNBC transcriptomic data from The Cancer Genome Atlas	MiRsupps/context-dependent	Low intratumoral miR-122-5p levels are associated with poorer overall survival; reduced expression is linked to pathways related to proliferation, migration, invasion, and apoptosis, supporting a tumour-suppressive role in TNBC.	Flores Fortis et al. (2023)

Abbreviations: ABCA1: ATP-binding cassette transporter A1; CDKN1A: Cyclin-Dependent Kinase Inhibitor 1A; CSE: Cystathionine γ-lyase; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; DNMT1: DNA Methyltransferase 1; DUSP14: Dual Specificity Phosphatase 14; EMT: Epithelial-to-mesenchymal transition; ERα: Oestrogen Receptor alpha; ESR1: Estrogen receptor 1; EVs: Extracellular vesicles; FEN1: Flap Endonuclease 1; FOXP3: Forkhead box P3; FTO: Fat mass and obesity-associated protein; HK2: Hexokinase 2; IGF-1: Insulin-like Growth Factor 1; IL-6: Interleukin 6; IRS-1: Insulin Receptor Substrate 1; MAPK12: Mitogen-Activated

Protein Kinase 12; MALAT1: Metastasis-Associated Lung Adenocarcinoma Transcript 1; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PTEN: Phosphatase and tensin homolog; SOX2: SRY-box transcription factor 2; SIX1: Sixes oculis homeobox homolog 1; Star-PAP: Speckle-targeted PIPKI α -regulated Poly(A) Polymerase; STAT3: Signal Transducer and Activator of Transcription 3; TCGA: The Cancer Genome Atlas.

and benign controls, and lower expression was associated with metastasis and increased levels of the oncogenic target SIRT1 (Abd Elhafeez et al., 2024). In line with these findings, in TNBC MDA-MB-231 cells, upregulation of *miR-146a-5p* was shown to inhibit inflammatory NF- κ B signaling by targeting IRAK1 and TRAF6, thereby reducing tumour aggressiveness (Gooran Orimi et al., 2025). In luminal A MCF-7 cells, *miR-146a-5p* was also shown to regulate autophagy through targeting TRAF6, with reduced miRNA expression leading to increased autophagic activity under cellular stress (Alirezade et al., 2025). Supporting its oncogenic role, Babadag et al. (Babadag et al., 2024a) demonstrated in triple-negative MDA-MB-231-derived cancer stem cells that *miR-146a-5p* enhances stemness, EMT, and the expression of tumorigenic markers such as BRCA1, SOX2, and TP53.

miR-223-3p.

It has been shown that *miR-223-3p* is significantly downregulated in BC tissues compared to healthy controls, as demonstrated by Shahid et al. (Shahid et al., 2024) through integrated microarray profiling and qRT-PCR validation. This miRNA appears to be involved in critical oncogenic pathways, including Wnt signaling, TGF- β , erythroblastic leukemia viral oncogene homolog (ErbB), and mitogen-activated protein kinase (MAPK) signaling, suggesting a potential role in BC pathogenesis and its utility as a diagnostic or prognostic marker. Moreover, integrated bioinformatic and experimental analyses have shown that *miR-223-3p* is significantly downregulated in BC tissues and in cell lines representing distinct molecular subtypes—namely MCF-7 (luminal A), SK-BR3 (HER2+), MDA-MB-231 (TNBC), and HCC1500 (luminal B). Its reduced expression correlates with poorer prognosis, and several oncogenic targets have been identified, highlighting its involvement in regulating cell division and cycle progression (Sahin et al., 2023).

Evidence suggests that *miR-223-3p* is enriched in high-density lipoproteins (HDLs) isolated from newly diagnosed BC patients, independently of tumour subtype. This elevation was particularly evident in advanced-stage disease and was associated with enhanced anti-inflammatory activity of HDLs, suggesting a potential role of *miR-223-3p* in modulating systemic inflammation in BC (Santana et al., 2023).

Chen et al. (Chen et al., 2024) identified a regulatory axis involving NOTCH3, *miR-223-3p*, and ZEB1, which modulates the invasive behaviour of BC cells. Specifically, NOTCH3 upregulates *miR-223-3p* expression, which in turn suppresses the transcription factor ZEB1, a known promoter of epithelial-mesenchymal transition and metastasis. This mechanism was shown to inhibit proliferation and invasion in vitro and was associated with favourable prognostic indicators in clinical samples.

A very recent study demonstrated that *miR-223-3p* acts as a tumour suppressor in BC by inhibiting cell proliferation and invasion while promoting oxidative stress-mediated apoptosis through the downregulation of kinesin family member 4A (KIF4A) (Zhi et al., 2025).

Palma and Kaur (Palma & Kaur, 2023) demonstrated that modulation of *miR-223-3p*, combined with cholesterol depletion, significantly reduced tamoxifen resistance across BC cell lines representing distinct subtypes—including ER⁺ (MCF-7), TNBC (MDA-MB-231), and long-term oestrogen-deprived models mimicking endocrine resistance. This effect was associated with lipid raft disruption, suggesting that *miR-223-3p* may serve as a therapeutic target to counteract cholesterol-mediated drug resistance in heterogeneous BC contexts.

Collectively, the evidence suggests that *miR-223-3p* primarily exerts tumour-suppressive functions in BC, although its role appears to be context-dependent, influenced by tumour subtype, disease stage, and microenvironmental factors such as lipid metabolism and inflammatory status.

miR-122-5p.

3.3.2. *miRNAs predominantly described as oncomiRs in BC* *miR-21-5p.*

Several studies have characterized *miR-21-5p* as an oncomiR (Syed et al., 2024), particularly in TNBC. *miR-21-5p* has been linked to various malignant features in BC, including an increased risk of recurrence based on serum analyses (Kujala et al., 2024), as well as disease progression and poor prognosis, as shown by bioinformatic analysis of patient-derived transcriptomic data (J. Xu, Guo, et al., 2025). Integrative bioinformatic analyses further indicate that *miR-21-5p* is associated with a prognostic hub-gene network involved in proliferation, apoptosis and immune signaling pathways in BC (Tumolo et al., 2026). Additionally, it promotes EMT and enhances the metastatic potential of BC stem cells (Babadag et al., 2024b). Mechanistically, *miR-21-5p* has been shown to contribute to chemoresistance by upregulating ATP-binding cassette transporter A1 (ABCA1) (Khalaf et al., 2025) and to promote drug resistance and EMT by repressing phosphatase and tensin homolog (PTEN) within the context of the DNA damage response (Gupta et al., 2024).

miR-155-5p.

miR-155-5p is a well-established OncomiR in the context of BC (Otmani et al., 2024). Its overexpression has been detected in the serum of BC patients and is positively correlated with the activation of pro-inflammatory signaling pathways such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and tumour necrosis factor alpha (TNF- α), supporting its role in tumour-promoting inflammation (Abdel-Samed et al., 2024). Consistently, *miR-155-5p* has also been reported to be significantly overexpressed in primary breast tumours that later develop brain metastasis, suggesting its potential value as a predictor of metastatic recurrence (Koyama et al., 2025). In TNBC models, *miR-155-5p* has been shown to enhance migration, invasion, and angiogenesis via downregulation of PTEN and dual specificity phosphatase 14 (DUSP14), while exosomal delivery of a *miR-155-5p* inhibitor reversed these effects (Razaviyan et al., 2024). Moreover, elevated *miR-155-5p* levels in patients' peripheral blood samples were associated with increased expression of immune checkpoint markers—programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and forkhead box P3 (FOXP3)—as well as of major histocompatibility complex class I chain-related protein B (MIC-B), indicating a contribution to immune evasion and tumour progression (Al-Sharabass et al., 2025). In silico analyses have also identified *miR-155-5p* as a key regulator associated with aggressive tumour phenotypes and poor prognosis in BC (Shornale Akter et al., 2024). Experimental evidence further shows that *miR-155-5p* can promote proliferation, invasion and metastasis through activation of NF- κ B signaling pathways (R. Xu, Guo, et al., 2025). In line with this, recent integrative analyses indicate that inflammatory signaling can induce *miR-155-5p* expression, promoting tumour growth, stem-like traits and chemoresistance in TNBC models (Sarcinella et al., 2025). Additionally, in ER⁺ MCF-7 cells, *miR-155-5p* was implicated in the development of tamoxifen resistance through the upregulation of signal transducer and activator of transcription 3 (STAT3) and hexokinase 2 (HK2), both involved in survival signaling and metabolic reprogramming (Shpigel et al., 2025).

miR-122-5p.

A recent case-control study conducted by Elghoroury et al. (Elghoroury et al., 2024) found that serum *miR-122-5p* is significantly upregulated in BC patients, suggesting a potential oncogenic role.

Another study by Jia et al. (Jia et al., 2023) further provides additional evidence supporting the oncogenic role of *miR-122-5p* in BC. The authors demonstrated that crocin, a natural compound with known antitumour properties, suppresses BC cell proliferation by downregulating *miR-122-5p*. This downregulation results in the upregulation

of two tumour suppressor genes, *FOXP2* and *SPRY2*, which are direct targets of *miR-122-5p*. These findings not only highlight *miR-122-5p* as a tumour-promoting miRNA, but also suggest that modulating its expression may offer therapeutic potential. In contrast, Flores Fortis et al. (Flores Fortis et al., 2023) investigated the role of *miR-122-5p* specifically in TNBC using transcriptomic data from The Cancer Genome Atlas. They found that low intratumoral levels of *miR-122-5p* were associated with poorer overall survival. Gene coexpression network analysis revealed that TNBC tumours with reduced *miR-122-5p* expression were enriched in pathways related to cell proliferation, migration, invasion, and apoptosis. Moreover, the network was enriched with predicted *miR-122-5p* target oncogenes, many of which are involved in cell differentiation, supporting a tumour-suppressive role for *miR-122-5p* in this subtype. Based on the studies reviewed in this work, *miR-122-5p* displays a context-dependent role in BC, exhibiting both oncogenic and tumour-suppressive activities depending on the biological and clinical setting. **4. Discussion.**

Our review identified several dairy-associated miRNAs frequently reported across multiple livestock species and dairy matrices, including, *miR-148a-3p*, *miR-21-5p*, *miR-30a-5p*, *miR-125b-5p*, *miR-26a-5p*, *miR-155-5p*, and *miR-146a-5p*. Among these, *miR-148a-3p* and *miR-21-5p* emerged as the most frequently detected across diverse dairy products and animal sources. Importantly, several recurrent miRNAs, particularly *miR-148a-3p*, *miR-30a-5p*, *miR-26a-5p*, and *miR-21-5p*, have also been reported among highly abundant milk miRNAs, although their relative ranking may vary depending on species, milk fraction, lactation stage, and analytical approach. These dairy-associated miRNAs overlap with miRNAs reported in BC-related studies, where they have been associated with tumour-suppressive or oncogenic functions. Specifically, *miR-148a-3p*, *miR-30a-5p*, *miR-125b-5p*, and *miR-26a-5p* predominantly demonstrated tumour-suppressive roles, although their functions may vary depending on the biological context and BC subtype. Conversely, *miR-21-5p* and *miR-155-5p*, —frequently associated with inflammatory conditions such as mastitis in dairy cattle—were predominantly related to tumour-promoting processes, including EMT, chemoresistance, and immune evasion.

miR-146a-5p, which is also linked to mastitis, appears to exert context-dependent effects in BC, displaying both tumour-suppressive and oncogenic activities depending on the cellular environment and disease subtype. Of note, bovine mastitis, particularly in its subclinical form, is among the most widespread diseases affecting the global dairy industry. A recent study conducted in China reported that subclinical mastitis in dairy cows can reach prevalence rates as high as 72% (Chen et al., 2022). Intensive dairy farming practices have been linked to an increased risk of both clinical and subclinical mastitis in cows. This heightened risk is primarily due to factors such as physiological stress, high milk yield demands, and varying hygienic conditions (Moschovas et al., 2023). Beyond infection-related conditions, various stressors associated with intensive farming, —such as group relocation—have also been shown to modulate miRNA expression (Colitti et al., 2019). In parallel, some studies have suggested that the consumption of milk from pregnant cows may contribute to the promotion of hormone-sensitive cancers, such as BC, due to increased levels of bioactive molecules, including oestrogens and potentially oncogenic miRNAs (Fraser et al., 2020; Melnik et al., 2023). In modern dairy farming, it is common practice to re-inseminate cows within a few weeks after calving to optimize milk production efficiency. As a result, a large proportion of commercially available milk is derived from cows that are simultaneously lactating and pregnant—conditions characterized by significant hormonal and immunological changes. While no studies have directly addressed this question, it is plausible that such physiological conditions may influence the miRNA content of milk, with potential, yet unconfirmed, implications for human health.

Although *miR-451* was not among the most recurrent dairy-associated miRNAs selected for detailed analysis in this review, it is worth mentioning as an example of a milk miRNA potentially influenced

by farming system and with reported tumour-suppressive relevance in cancer (Degheidy et al., 2025; Zhang et al., 2020). Expression of the tumour-suppressive *miR-451* has been reported to be higher in milk-derived EVs/exosome-enriched fractions from cows raised in grazing systems compared with those in intensive settings (Abou El Qassim et al., 2024). This miRNA is known to inhibit cell proliferation in several cancer types, including HER2+ BC (Woo et al., 2022).

The miRNA content of milk may be influenced by processing methods, including bacterial fermentation, pasteurization, and refrigeration. Notably, certain miRNAs appear to be differentially degraded during fermentation (Abou el qassim et al., 2023), while pasteurization and cold storage preserve the structural integrity and potential bioactivity of EV-associated miRNAs. Industrial-scale implementation of these processes—originating during the Industrial Revolution—has reduced the activity of naturally occurring milk-fermenting bacteria, while allowing the continuous and widespread presence of stable dietary miRNAs in the human food chain. This prolonged exposure to milk-derived epigenetic signals may have implications for human health, including potential effects on BC risk.

In this context, epidemiological evidence indicates that the health effects of dairy products may depend on the degree and type of processing. Studies conducted in Sweden—a country with traditionally high milk consumption—have shown that higher intake of non-fermented, pasteurized milk is associated with a dose-dependent increase in all-cause mortality (Melnik & Schmitz, 2021; Tognon et al., 2017). In contrast, fermented dairy products, particularly yogurt, are consistently linked to beneficial health effects. Several studies suggest that fermented dairy is associated with a reduced risk of BC, whereas non-fermented milk shows a potential adverse association (Kaluza et al., 2021; McCann et al., 2017). Together, these observations raise the question of whether dairy-associated miRNAs could contribute not only to mechanistic pathways but also to clinically relevant risk assessment strategies. Fig. 2 summarizes the overlap between dairy-associated miRNAs and miRNAs implicated in BC-related processes, together with the main factors influencing the interpretation of their potential biological relevance.

3.3.2.1. Potential clinical implications of dairy-associated miRNA profiling. The profiling of dairy-associated miRNAs may have potential relevance beyond mechanistic insights. Several of the exogenous miRNAs identified from dairy products—such as *miR-21-5p*, *miR-155-5p*, and *miR-148a-3p*—are identical to endogenous miRNAs already under investigation as diagnostic or prognostic biomarkers in BC. Although the contribution of dietary exposure to circulating miRNA levels remains poorly defined, integrating dietary assessment with miRNA profiling could help generate new hypotheses regarding the interaction between diet, miRNA regulation, and BC-related pathways. In the longer term, a better understanding of how specific dairy products influence miRNA signatures may provide insights relevant to dietary exposure assessment in populations at increased BC risk. However, these potential applications require rigorous validation in well-designed human studies before any clinical translation.

3.3.2.2. Collective effects of miRNAs in breast cancer. Most evidence discussed in this review refers to individual miRNAs; however, miRNAs involved in BC may also act as part of coordinated regulatory networks. A single transcript can be targeted by several miRNAs, and a single miRNA can regulate multiple transcripts, creating complex layers of post-transcriptional control. As a result, the functional outcome of miRNA dysregulation may depend not only on the expression of individual miRNAs, but also on their combined activity within shared pathways.

This concept is supported by evidence showing that miRNAs can cooperate in BC-related processes. For example, Hu et al. (2014) showed that *miR-155-5p* can act as a regulatory node linking inflammatory

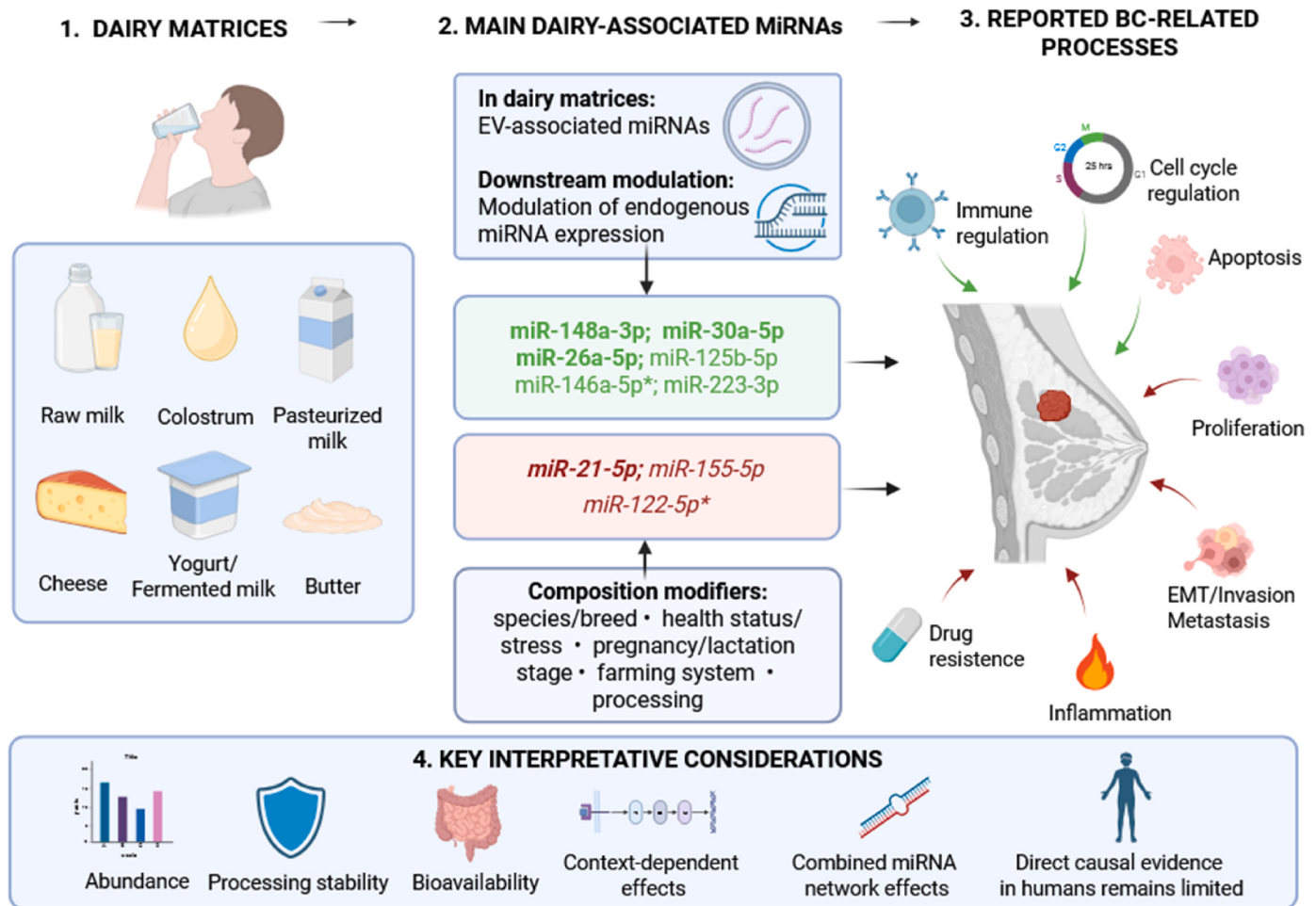


Fig. 2. Overview of dairy-associated miRNAs and BC-related processes. The figure illustrates the conceptual framework of this review, linking dairy-associated miRNAs with miRNAs implicated in BC-related pathways. This overlap should be interpreted cautiously, as its potential biological relevance depends on miRNA abundance, processing stability, bioavailability, context-dependent effects, and possible combined miRNA network effects. MiRNAs shown in bold indicate those repeatedly reported among highly abundant miRNAs in milk and dairy matrices. Asterisks indicate miRNAs for which more clearly context-dependent and/or conflicting roles have been reported in BC studies. Direct causal evidence in humans remains limited.

signaling to broader changes in cancer-related miRNA expression in BC (Hu et al., 2014), including the upregulation of several oncomiRs such as *miR-21-5p*. Network-based analyses have also shown that multiple BC-associated miRNAs can converge on common gene regulatory circuits (O'Day & Lal, 2010). In addition, *miR-21-5p* and *miR-155-5p* have been associated with the regulation of genes involved in prostaglandin metabolism in human BC cell lines, with evidence of cumulative effects on selected targets, including the tumour suppressor 15-HPGD and the potential oncogene COX-2 (Nikiforova et al., 2015). These observations suggest that miRNA effects in BC should be interpreted at both the individual and network levels.

3.3.2.3. Dietary implications and potential interventions. From a translational and practical perspective, and building on the considerations discussed above, some cautious dietary implications may be proposed. First, dairy products should not be considered as a single exposure category, and a preference for fermented dairy products over high intakes of non-fermented milk may be a prudent approach. Second, attention should also be paid to the origin of milk and to the production system from which it derives. In particular, a high consumption of milk from intensive production systems may deserve greater caution, whereas milk from grazing systems may differ in its biological profile. The effect of processing (e.g., pasteurization, UHT treatment, or fermentation) should therefore be interpreted in relation to the

characteristics of the raw milk, since it could reduce exposure to potentially unfavorable miRNAs in some contexts while preserving potentially beneficial ones in others. However, these considerations remain hypothesis-generating and require validation in controlled human studies.

3.3.2.4. Research gaps and future perspectives. To translate these potential clinical implications into practice, several critical knowledge gaps must be addressed. First, although several miRNome studies have increasingly characterized the miRNA composition of dairy products, comparative data across farming systems, processing methods, livestock health status, and lactation stages remain fragmented and methodologically heterogeneous. In particular, the influence of physiological conditions such as pregnancy, mastitis, or stress, as well as genetic factors such as species and breed, on milk miRNA profiles in dairy animals remains insufficiently characterized in the context of human health and warrants systematic investigation.

Second, the bioavailability of exogenous milk-miRNAs in humans—particularly their capacity to withstand digestion, enter systemic circulation, and reach target tissues such as the mammary gland—remains underexplored. Although some studies suggest that EV-associated miRNAs can be absorbed and exert regulatory functions, robust evidence in human-based models is lacking. Notably, the high abundance and reported persistence of several recurrent dairy-

associated miRNAs in dairy products further strengthen the rationale for investigating their potential biological relevance to consumers.

Third, while growing evidence supports the role of diet in modulating miRNA expression, studies specifically investigating the impact of dairy product consumption on human miRNA profiles remain scarce. To date, only a few clinical studies have explored this relationship, and none have directly addressed BC-related outcomes. E.g., it has been shown that high dairy intake may upregulate specific circulating miRNAs (*miR-223-3p* and *miR-122-5p*) (Khorraminezhad & Rudkowska, 2022). Notably, both miRNAs showed correlations with fasting glucose and insulin levels, indicating a potential link between dairy-induced miRNA modulation and metabolic pathways involved in Type 2 Diabetes (T2D) risk. These findings are particularly relevant in light of mounting epidemiological evidence linking T2D with an increased risk of several common cancers, including BC (Pearson-Stuttard et al., 2021). Current mechanistic models explaining the obesity/T2D/BC axis have emphasized the central role of insulin and IGF-1 signaling (Kang et al., 2018). Importantly, milk-derived components—such as insulinotropic effects, IGF-1, and miRNAs including exosomal *miR-148a-3p* and *miR-21-5p*—have been implicated in the pathogenesis of both T2D and BC (Doghish et al., 2021; Melnik, 2015, 2021; Melnik & Schmitz, 2022). Thus, the observed upregulation of miRNAs following high dairy intake may reflect a broader interplay between diet-induced miRNA modulation and oncogenic or diabetogenic signaling pathways.

Beyond growth factor-driven mechanisms, emerging evidence indicates that nutrient availability can directly reshape tumour immunometabolism. Metabolic adaptations within the tumour microenvironment influence immune cell function and immune checkpoint regulation, thereby modulating antitumour responses. For instance, Tong et al. (2024) demonstrated that dietary serine and glycine restriction exerts dual effects in colon cancer models, enhancing antitumour immunity while simultaneously promoting immune evasion through PD-L1 lactylation. Early clinical observations further suggest that dietary modulation may influence systemic immune parameters in patients, supporting the translational relevance of these immunometabolic mechanisms (Tong et al., 2024).

Although the direct contribution of dairy-derived miRNAs to immunometabolic regulation in BC remains unproven, several of the miRNAs identified in this review—particularly *miR-21-5p* and *miR-155-5p*—are known regulators of inflammatory signaling, NF- κ B activation, and immune checkpoint pathways (Fu et al., 2025; Sikder et al., 2024). Given their involvement in both metabolic and immune-related processes, diet-associated modulation of these miRNAs may plausibly intersect with immunometabolic circuits within the breast tumour microenvironment. Future research should clarify how different types and amounts of dairy products influence human miRNA expression and determine whether such modulation intersects with metabolic and immune regulatory pathways relevant to BC, ideally through human-relevant experimental systems capable of capturing tumour-immune complexity. Finally, although simplistic in vitro and animal-based models can offer valuable mechanistic insights, most available studies rely on these systems, which frequently fail to capture the full complexity of human physiological and pathological processes, particularly in the context of cancer biology. Notably, over 220 studies were considered not eligible for inclusion in this review because they relied on animal models or non-human experimental systems. To overcome these limitations and enhance translational relevance, future research should prioritize the use of human-relevant models—including organoids, organ-on-chip technologies, and high-resolution transcriptomic profiling—to better elucidate the potential role of dairy-derived miRNAs in BC development and progression (Gastélum-López et al., 2023; Herbst et al., 2025; Palcau et al., 2025; Testa et al., 2025).

An interdisciplinary approach—integrating nutritional science, oncology, molecular biology, and animal production—is essential to

advance this emerging field and better understand the implications of dairy consumption in the context of BC prevention and health promotion.

CRediT authorship statement

Cassotta Manuela: Conceptualization, Methodology, Writing - Original Draft. Diaz Yasmany Armas: Conceptualization, Methodology, Writing - Original Draft. Cianciosi Danila: Investigation, Validation. Chen Ge: Investigation, Validation. Zexiu Qi: Software. Zhng Bei: Software. Cao Qingwei: Writing - Review & Editing. Haixia Hu: Writing - Review & Editing. Diaz Esteban Yanetsi: Data Curation. Rabeiro Martinez Carlos Luis: Data Curation. Gracia Villar Santos: Validation. Lopez Dzul Luis Alonso: Validation. Battino Maurizio: Project administration, Resources, Writing - Review & Editing. Giampieri Francesca: Project administration, Supervision, Writing - Review & Editing.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT (OpenAI) solely to improve the readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Acknowledgements

Dr Danila Cianciosi was supported by a Fondazione Umberto Vernesi fellowship.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tifs.2026.105953>.

Data availability

No data was used for the research described in the article.

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