Supplementary Materials for Literature Search

Search Strategy

To ensure a comprehensive review of the literature related to this study, the strategy was designed to capture all relevant studies by using a combination of keywords, and the search was conducted based on the PubMed database.

Keywords and Search Terms

The following keywords and search terms were used in various combinations:

“milk”, “miRNA”, “exosome”, “uptake”, “absorption”, and “profile”. The keywords were combined by the Boolean operator AND & OR for comprehensive and specific searches. Several other papers were selected from the reference of these papers and “Similar articles”.

Inclusion and Exclusion Criteria

Studies published from 2014-2023 were included. Only experimental studies were included. Review articles and Studies merely focusing on bioinformatics analysis on milk miRNA are excluded. The research focused only on the metabolism of exosomes without studying the miRNAs inside, which were also included as milk exosomes are one of the major transporters for miRNA. We filtered out those articles on the effect of dietary miRNAs but not specific to the milk diet. Studies that only provide phenotypic change after milk meal without providing detailed mechanisms or direct evidence of miRNA as transferable genetic materials are excluded as well.

Summary

Finally, 16 papers were left. Of those, three showed evidence that milk miRNAs cannot be uptake as functional regulators, while the other 13 studies showed the regulatory effects of milk miRNAs after absorption. Only 16 studies were left, as the majority of miRNA/exosome uptake research does not relate to milk components, and many provide predictions based on phenotypic change after milk meal but do not give direct evidence of BM miRNA uptake. The selected papers are shown in **Supplementary Table S1** below. Studies that provide evidence on either the Functional Hypothesis or the Nutrient Hypothesis are indicated in the last column.

Supplementary Table S1 Comparative Summary of Studies on the Functional vs. Nutrient Hypotheses

	Papers	Key conclusions/results in the studies	Viewpoint

1	Wolf et al., J Nutr., 2015	“This research assessed the transport mechanism of bovine milk exosomes, and therefore microRNAs, in human and rodent intestinal cells.”(1)	Functional Hypothesis
2	Kusuma et al., Cell Physiol., 2016	“Test the hypothesis that human vascular endothelial cells transport milk exosomes by endocytosis.” (2)	Functional Hypothesis
3	Kahn et al., Mol Nutr Food Res, 2018	“For the first time reveal the survivability of preterm milk exosomes following simulated gastric/pancreatic digestion” (3)	Functional Hypothesis
4	Liao et al., Mol Nutr Food Res., 2017	“Reveal the survivability and complexity of human milk exosome microRNAs upon simulated gastric/pancreatic digestion, and the dynamics during lactation stages.”(4)	Functional Hypothesis
5	Wang et al., J Nutr., 2018	“Assessed and identified potential confounders of plasma miR analysis with the intent to develop a consensus of minimal experimental requirements in future studies of dietary miRs.”(5)	Functional Hypothesis
6	Lin et al., Sci Rep., 2020	“Suggested that the milk miRNAs can be absorbed both in vivo and in vitro”(6)	Functional Hypothesis
7	Chen et al., Cell Res., 2021	“Reveal a major mechanism underlying the absorption of dietary microRNAs, uncover an unexpected role of the stomach and shed light on developing small RNA therapeutics by oral delivery.”(7)	Functional Hypothesis
8	Chen et al., Sci Rep., 2016	“Demonstrated that milk-derived exosomes can facilitate intestinal cell proliferation and intestinal tract development”(8)	Functional Hypothesis
9	Baier et al., J Nutr., 2014	"MiRNAs in milk are bioactive food compounds that regulate human genes.”(9)	Functional Hypothesis
10	Pomar et al., FASEB J., 2021	"Milk miR-26a may act as an epigenetic regulator influencing early metabolic program in the progeny, which emerges as a relevant component of an optimal milk composition for correct development”(10)	Functional Hypothesis

11	Manca et al., Sci Rep., 2018	“Assessed the bioavailability and distribution of exosomes and their microRNA cargos from bovine, porcine and murine milk within and across species boundaries.”(11)	Functional Hypothesis
12	Khanam et al., Int J Pharm., 2023	"Conclude that the apparent bioavailability of sMEVs is 45%, and sMEVs are transported to peripheral tissues in C57BL/6J mice” (12)	Functional Hypothesis
13	Munagala et al., Cancer Lett., 2016	"The first report to identify a biocompatible and cost-effective means of exosomes to enhance oral bioavailability, improve efficacy and safety of drugs.”(13)	Functional Hypothesis
14	*Title et al., J Biol Chem., 2015	"Nutritionally derived microRNAs are unlikely to cross the intestinal barrier and influence gene expression”(14)	Nutrient Hypothesis
15	*Laubier et al., RNA Biol., 2015	“Did not detect an increase in miR-30b in tissues of pups fed by transgenic females compared to pups fed by wild-type females.”(15)	Nutrient Hypothesis
16	*Auerbach et al., F1000Research., 2016	Dietary xenomiRs cannot be transfer of into the circulation of adult humans. (16)	Nutrient Hypothesis

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