Milk oligosaccharide patterns in mammalian species: a scoping review protocol

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Abstract

Objective: The aim of this scoping review is to extract and describe the milk oligosaccharide composition of mammalian species and to investigate the similarities and differences between species in relation to the maturity of the new-born.

Introduction: There is a growing interest in milk oligosaccharides because of their numerous benefits for new-born and long-term health. Since their discovery in 1930, a large number of structures has been identified in mammalian milks. Data for non-human species are less abundant but seems to indicate species-specific profiles of milk oligosaccharides. However, as of today, this information is scattered in several publications and not easily findable. A crucial step in understanding the functions of milk oligosaccharides is to characterise the structure of milk oligosaccharides among mammalian species.

Inclusion criteria: This scoping review will include studies analysing the composition of oligosaccharides in the milk of mammalian species. We will only consider studies in English language but irrespective of geographic location or time frame.

Methods: The JBI approach for conduct and reporting of scoping reviews will guide this review process. A preliminary search will be performed on Web of Science, followed by an analysis of titles, abstracts and keywords to refine the search query and extend the search to a second database, PubMed. Two independent reviewers will screen titles, abstracts and full texts of articles based on the inclusion criteria. Relevant studies will be reported in a draft extraction table.

Introduction

Milk is the first food available to neonates in mammalian species i.e., vertebrate animals in which the young are fed with milk produced by the mammary glands of the mother. It provides young mammalian with essential nutritional components and non-nutritional bio-active components. Among the latter, milk oligosaccharides have been studied for their immunomodulatory functions and effect on host microbiome. As the first prebiotics available to new-borns, i.e., fermentable substrates used selectively by host microorganisms (Gibson et al. 2017), milk oligosaccharides regulate the microbial composition. Host enzymes do not have the capacity to digest these molecules, thus they are directed to the gut bacteria. Several studies have been conducted, highlighting the ability of symbiotic bacteria to grow thanks to milk oligosaccharides consumption. Among them *Bifidobacterium* and *Bacteroides* metabolise a wide range of milk oligosaccharides. In addition, bacterial oligosaccharide consumption results in metabolite production, these last being beneficial for intestinal barrier. Some metabolites can also have antimicrobial capabilities (Gibson et al. 2017). Milk oligosaccharide structure in itself plays antimicrobial and non-adhesive roles. They act as decoy for infectious microorganisms by mimicking gut epithelial molecules used by pathogens to invade host intestine. Consequently, pathogens are eliminated and without damaging host gut (Walsh et al. 2020). Finally, milk oligosaccharides can activate immune cell, via direct linkage or indirectly through bacterial metabolites. In that manner, they educate and modulate host immune system (Moubareck 2021; Ayechu-Muruzabal et al. 2018).

These molecules are composed of three to ten monosaccharide units, with 5 building blocks that are glucose, galactose, N-acetyl-glucosamine, fucose and sialic acid residues joined together by glycosidic linkages (McGuire, McGuire, Bode 2017). The core structure of the molecules usually begins with a lactose, although few oligosaccharides have been described starting with an N-acetyl-glucosamine followed by a galactose. This first sequence is completed by an N-acetyl-glucosamine linked to a galactose. Those two monosaccharides can be found in two patterns based on the type of linkage between them. A β1-3 linkage between the two monosaccharides (Galβ1-3GlcNAc) is referred to as Lacto-N-biose. An oligosaccharide with this pattern belongs to the type I oligosaccharides. The second pattern is a β1-4 linkage between the two monosaccharides (Galβ1-4GlcNAc), is referred to as N-acetyllactosamine. This last characterises the type II oligosaccharides (Bode, Jantscher-Krenn 2012).

The pattern can be repeated up until 25 times to create the core structure of milk oligosaccharides. Finally, multiple fucose and/or sialic acid residues can be branched to this core structures under several linkage types. This variability of monosaccharide combinations and their linkage results in structurally complex matrices of linear and branched oligosaccharides. Thus, we distinguish a wide range of milk oligosaccharides, different in length, structure and complexity (Walsh et al. 2020).

For instance, in human milk, more than 200 different structures of oligosaccharides have been detected (Remoroza et al. 2018). Several reviews have described the composition and structure of human milk oligosaccharides (Thurl et al. 2017; Kobata 2010). Additionally, milk oligosaccharides have also been discovered in the milk of non-human species, but data are less abundant. Among the species studied we can name non-human primates (apes, Old World monkeys, New World monkeys and strepsirrhine primates), ruminants (cows, goats, sheep, camels, reindeers …), horses, pigs, carnivorous mammalian (bears, dogs, lions, seals …), elephants and cetaceans. Urashima, Messer, Oftedal (2017) have listed some of these investigations and have highlighted species specific profiles in terms of oligosaccharide structure diversity. This comparison of milk oligosaccharide patterns among different species and their evolutionary function has led Urashima, Messer, Oftedal (2017) to hypothesize that there is a link between the structure diversity of milk oligosaccharides and their functions in neonates. More specifically, Urashima, Messer, Oftedal (2017) state that

oligosaccharide diversity in human milk could be an evolutionary consequence of the altricial status of human infants that require additional milk-borne protection against pathogens.

Prior to establishing links between neonatal maturity and milk oligosaccharide profiles in mammalian species, it is vital to have an overview of the oligosaccharide profiles. However, those data are scattered among numerous publications and described in non-standardised manners. A scoping review is the appropriate approach to investigate and describe the composition of milk oligosaccharides among mammalian species, to identify the available information and establish similarities and differences among species in terms of structure, quantity and oligosaccharide profile.

The aim of this scoping review is to gather mammalian milk oligosaccharide data in a single database. This review is written in parallel with the construction of a database using artificial intelligence, allowing investigation and comparison of common features and particularities of milk oligosaccharides between mammalian species. This review will also update the state of knowledge on the oligosaccharide composition of milks and detect eventual missing information. At the end, our purpose is to provide clues of links between neonatal maturity and milk oligosaccharide profiles in mammalian, to initiate further research on this topic.

A preliminary search conducted on PROSPERO, Open Science Framework, Figshare and ResearchGate did not enable us to identify any systematic or scoping reviews on the profile of milk oligosaccharides among mammalian species. Existing reviews on the topic only considered milk oligosaccharides in humans (Thurl et al. 2017; Kobata 2010). In addition, to the authors' knowledge no scoping reviews are currently being conducted on this topic.

Review question

What are the common features and peculiarities of the milk oligosaccharide profiles among mammalian species?

Some sub questions will also be addressed:

- What is the state of art on the oligosaccharide composition in the mammalian milk?
- What is the variability in oligosaccharide composition based on maternal metadata?
- Is the species' oligosaccharide profile specificity related to the level of maturity of the species' neonate?

Keywords

Cross species comparison; Mammalian; milk oligosaccharides; milk oligosaccharide diversity; milk oligosaccharide structure

Eligibility criteria

Participants

This review will consider studies on lactating female mammalian, whose milk is analysed in its raw form. In order to capture a wide range of data, there will be no exclusion based on the age of the individual as well as lactation parity. Marsupial and monotremes species will be excluded from this review. Those last belong to mammalian class, however the neonate development displays tremendous particularities in comparison to placental mammalian.

Concept

The overarching concept of interest is the determination of the oligosaccharide composition of milk across mammalian species. Oligosaccharides in mammalian milk can be found either free or conjugated i.e., linked to other molecules such as proteins and lipids. Although both

molecules have the same oligosaccharide core structure, they do not have the same role and the same functional target (Smilowitz et al. 2014). All female metadata, methodology indications and quantification of oligosaccharides will be included, when available.

Context

This review will include all studies irrespective of experimental geographic location. The analysis of milk oligosaccharides can be carried out with several methods i.e., instruments of measurement, products used to prepare samples, techniques to analyse results. In order to include a wide range of evidence, all methodologies will be included in this review. In addition, any intervention on milk can potentially alter its composition, so any studies on transformed products derived from milk (such as yoghurt, whey, cheese) will be excluded.

Types of Sources

This scoping review will consider experimental study designs, analytical observational studies including prospective cohort studies, case control studies and analytical cross-sectional studies. This review will also consider descriptive observational study designs.

We will also consider qualitative studies, that focus on the presence or absence of a dedicated oligosaccharides in the milk of mammalian species.

In addition, primary research studies, systematic reviews, scoping reviews or metaanalyses that meet the inclusion criteria will be included.

Methods

The proposed scoping review will be conducted in accordance with the JBI approach for the conduct and reporting of scoping reviews (Peters et al. 2020). Additionally, the methodology will follow the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) (Tricco et al. 2018).

Search strategy

As recommended by the JBI, the protocol will rely on a three-step search strategy. The first step of this scoping review will be an initial limited search on the Web Of Science database using natural language. We will then look into text words contained in the titles and abstracts of retrieved papers as well as the keyword terms used to describe the articles. Thanks to this analysis, the search query will be refined to undertake a second search across WOS and PubMed, as these databases contain an extensive collections of biology literature (see Appendix 1). Thirdly, we will search for additional bibliographic sources by examining the reference lists of identified relevant reports among the studies selected. This will concern solely the reference lists of the sources that have been included in the review and for whom full text have been analysed. We may intend to contact authors of primary sources or reviews for more information, if relevant. By doing so, we expect to better understand the data in case of misspelling in the name of oligosaccharides for instance, but also to search for additional information such as metadata relevant to describe the milk sample origin. Unpublished materials, so called grey literature, will not be included in the analysis.

The scoping review will be associated with a database registering milk oligosaccharides identified in mammalian species. We intend to make these data FAIR, so that sources will be findable by everyone.

Finally, since this topic is emergent and to extract as much evidence as possible, no restriction in the timeframe will be made. Additionally, we intend to provide a reproducible analysis, accessible and as FAIR as possible for members of the scientific community. Thus, considering English language as the scientific one, only sources in English will be included.

Study/Source of Evidence selection

Following the search, all identified citations will be collected and uploaded into Zotero software version 6.0.19 (Center for History and New Media, USA) and a first screening will

be conducted to remove duplicates. A pilot test will be carried out by two reviewers (SC and MR) for agreement on inclusion and exclusion criteria for 50 potentially relevant sources.

Following this pilot test, the whole text corpus will undergo analysis of titles and abstracts by two independent reviewers (SC and MR) for assessment against the predefined inclusion criteria. Relevant sources will be assessed in full-text form against the inclusion criteria by the two reviewers (SC and MR). Reasons for exclusion of sources at full-text level will be recorded and reported in an appendix of the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion, or with the additional reviewer (CK). The inclusion and exclusion process will be reported in the final scoping review and mapped in a Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping reviews (PRISMA-ScR) flow diagram (Tricco et al. 2018).

Risk of bias analysis

After the source of evidence selection, each study selected will be assessed for quality and bias. Based on the study design of the articles included in our review, quality analysis will be made using the JBI's critical appraisal tools developed by the Joanna Briggs Institute. This tool covers a wide range of types of sources and consists of study-specific check-lists with several questions. Each check-list contains detailed explanations of the questions to guide the reviewers. Two reviewers (SC and MR) will perform critical appraisal independently. A first pilot trial will be made on three to six studies to ensure that quality criteria are the same among reviewers. In case of disagreement, a discussion between the reviewers will take place. If no consensus is reached, a third reviewers (CK) will make the final judgement. The number of studies excluded after this bias risk analysis will be indicated in the flow diagram of the literature search process.

Data Extraction

Two independent reviewers (SC and MR) will carry out the data extraction process from publications included in the scoping review. Beyond basic descriptive data about the included sources of evidence (authors, title, year published, type of sources, study design and country), we will focus the data extraction of the oligosaccharide composition to characterize the milk oligosaccharide profiles among mammalian species. This will include richness in oligosaccharides (i.e., number of structures evidenced in a study), the presence or absence of around 40 pre-selected relevant milk oligosaccharides, with their relative quantification when specified, and key findings relevant to the review questions. The 40 entities will be representative of the different types of structures present in milk: neutral or sialylated, fucosylated or not, longitudinal or branched, short (at least 3 monosaccharides) to the longest. Elements regarding study methodology, context and characteristics of the participant groups with sample size will be extracted, when available.

A draft extraction table will be used (see Appendix 2) to detail the data to be extracted. To test the feasibility of this draft extraction tool, we will pilot it on a subset of sources to be included in the review. This draft data extraction tool can be refined as necessary during the process of extracting data for the scoping review. The final updated data extraction tools will be detailed in the scoping review report. Any disagreements that occur between reviewers will be settled by discussion or with the third reviewer (CK).

Data Analysis and Presentation

The extracted data will be presented in tabular form accompanied by a narrative summary that aligns with the objective of this scoping review.

Oligosaccharide richness and patterns (if identified) will be illustrated using figures and or diagrams, and summarized narratively. If outcomes are identified in relation to a specific group of species and in particular with neonate maturity or metadata characteristic, for example, this will be presented and explained. Final conclusions will be drawn from the mapped evidence and recommendations will be made for future research in this area. Where

gaps or inconsistencies are identified, recommendations for further studies to be undertaken may be proposed.

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Conflicts of interest

There is no conflict of interest in this project.

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Appendices

Appendix I: Search strategy

#	Search Query	Results
1	TI=(oligosaccharide* OR glycan*)	28720
2	AB=(oligosaccharide* OR glycan*)	58887
3	AK=(oligosaccharide* OR glycan*)	15729
4	#1 OR #2 OR #3	73135
5	TI=(milk OR "breast feed*")	120167
6	AB=(milk or "breast feed*")	169285
7	AK=(milk or "breast feed*")	58499
8	#5 OR #6 OR #7	227381
9	#5 OR #6 OR #7	227381
10	TI=(quantification OR composition OR content* OR concentration* OR structure*)	2519746
11	AB=(quantification OR composition OR content* OR concentration* OR structure*)	10797899
12	AK=(quantification OR composition OR content* OR concentration* OR structure*)	969925
13	#10 OR #11 OR #12	12111944
14	#13 AND #9 AND #4	1602
15	ALL=(fructose OR galacto-oligo* OR galactooligo* OR yogurt* OR cheese OR whey OR FODMAPS* OR fructo-oligo* OR fructooligo* OR "enzymatic synthesis" or "enzymatic production" or BSSL or "nutritional yeast")	144993
16	TI=("Infant formula*" OR galactosidase* or "skim* milk" OR supplementation)	78829
17	((#14) NOT #15) NOT #16	1161
18	((#14) NOT #15) NOT #16 and Article or Review Article or Proceeding Paper or Early Access (Document Types)	1134
19	((#14) NOT #15) NOT #16 and Article or Review Article or Proceeding Paper or Early Access (Document Types) and English (Languages)	1108

Appendix II: Data extraction instrument

Research details	
Title	
Year	
Author	
Type of source	
DOI	
PMID	
WOS	
Study details and characteristics	

Study design	
Quantitative or qualitative data	
Country	
Context	
Methodology	
Participant's information and sample size if available	
Details/results extracted from study	
Richness in oligosaccharides	
Indications about a selected list of main neutral oligosaccharides: • Presence (relative quantity when available) • Absence • Not studied in the article (NA)	
Indications about a selected list of main neutral fucosylated oligosaccharides: • Presence (relative quantity when available) • Absence • Not studied in the article (NA)	
Indications about a selected list of main sialylated oligosaccharides: • Presence (relative quantity when available) • Absence • Not studied in the article (NA)	
Indications about a selected list of main sialylated fucosylated oligosaccharides: • Presence (relative concentration when available) • Absence • Not studied in the article (NA)	
Finding relevant of this study	
Result diffusion media	
Distribution	
Presence of Neu5Gc (specific to non-human mammalian)	