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Worldwide research on the health effects of bovine milk containing A1 and A2 β-casein: Unraveling the current scenario and future trends through bibliometrics and text mining

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ABSTRACT

The possible adverse effect of consuming bovine milk with A1 β-casein (but not with A2 β-casein) on health aspects due to the release of β-casomorphin-7 (BCM-7) is currently under debate. The aim of this study was to perform a bibliometric analysis of studies extracted from Scopus to explore the relationship between BCM-7, A1 or A2 bovine milk with different aspects of health. Over time, several research groups were formed that are no longer active and although some authors have returned to the field of study, they have focused their efforts mainly on conducting reviews that show the same imprecise conclusions due to the few original articles. Research is concentrated in Europe and Asia, where New Zealand, China and Germany are the countries with the most publications, records and citations on the subject, respectively. On the other hand, no country in Africa or South America has scientific production, which opens the possibility of building collaborations between countries and exploring areas that lack scientific studies. Based on conflicting information from primarily *in vitro* and animal studies, and limited clinical trials with poor designs, A1 milk presents pro-inflammatory and oxidative activity, but the evidence is insufficient to associate its consumption with negative health effects. However, A2 milk may be better tolerated by the digestive system of some individuals, suggesting its possible modulating role in the intestinal microbiota. Stronger scientific evidence is needed to reach a consensus on whether the presence of β-casein A1 can significantly negatively affect health. The information shown will allow a better understanding of the subject and consumers will be able to make their own decisions regarding A1 or A2 milk.

1. Introduction

Milk and dairy products are widely consumed as they are considered important components of a healthy diet (Pereira, 2013). Cattle produce more than 80% of the world's milk (FAO, n.d.) and the high interest is due to its sensory qualities and because its constituents are present in appropriate proportions to meet nutritional needs (Daniloski et al., 2021a). Cow's milk provides 69 kcal/100 mL of energy, is a rich source of high-quality proteins (3.2%), fats (3.6%), sugars (mainly 4.7% lactose), and also contains calcium, magnesium, phosphorus, zinc, potassium, vitamin A, B complex vitamins, vitamin D and E (Pereira, 2013). Caseins (80%) and whey proteins (20%) constitute more than 95% of cow's milk proteins (Fernández-Rico et al., 2022). An important part among the caseins is the β-casein, a subtype that constitutes about 30% of the total proteins and presents thirteen genetic variants, A2 being the oldest variant (Giribaldi et al., 2022). Currently, A1 and A2 variants are the most frequent in dairy cattle and differ in the amino acid at position 67 (His in A1 or Pro in A2) (Brooke-Taylor et al., 2017).

The concentrations of A1 and A2 β-casein vary depending on the breed of cattle that can produce milk with A1 β-casein, A2 β-casein or A1/A2 β-casein (Kay et al., 2021). During β-casein digestion, His67 in the A1 variant allows proteolytic cleavage, releasing β-casomorphin-7 (BCM-7), whereas the presence of Pro67 in A2 β-casein hinders cleavage (Giribaldi et al., 2022). BCM-7 is a peptide that binds to μ-opioid receptors, which exert effects on gastrointestinal physiology, cardiovascular, nervous and endocrine systems (Giribaldi et al., 2022). Due to this interaction, A1 bovine milk has been associated with different adverse

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Abbreviation

A1 milk	Bovine milk with A1 β-casein
A2 milk	Bovine milk with A2 β-casein
A1/A2 milk	Bovine milk with A1/A2 β-casein
ACE	Angiotensin-converting enzyme
BCM-7	β-casomorphin-7
CT	Cluster
EFSA	The European Food Safety Authority
GDP	Gross Domestic Product
WoS	Web of Science database

health such as allergies, type I diabetes, cancer, sudden infant death syndrome, immune alterations, cardiovascular disorders and neurological disorders (Thiruvengadam et al., 2021). Since there is no evidence of negative effects from the consumption of A2 bovine milk and its nutritional composition is similar to that of A1 milk (Kaplan et al., 2022), A2 milk is shown to be a safe alternative for humans. For this reason, New Zealand started the production of A2 milk in 2003 and this trend spread to the United Kingdom, Australia, the United States, the Netherlands and China (Sebastiani et al., 2020).

Several literature reviews on the subject have shown contradictory and inconclusive results. One of the first studies concluded that consumption of A1 bovine milk is not associated with type I diabetes or coronary heart disease (Truswell, 2005), but other studies suggested the correlation between consumption of A1 milk with type I diabetes, sudden infant death syndrome, autism, schizophrenia and cardiovascular disease (Bell et al., 2006; Kamiński et al., 2007). In 2009, The European Food Safety Authority (EFSA) reported that BCM-7 may cause gastrointestinal disturbances, but there was insufficient evidence to associate consumption of A1 bovine milk with non-communicable diseases (Ivano De Noni et al., 2009).

Literature reviews are important in academic research, but they are highly subjective because the choice of studies depends on the researcher, which excludes many papers that could be relevant. For example, Truswell (2005)'s conclusions were criticized because he omitted important studies (Allison and Clarke, 2006; Woodford, 2006). To avoid bias, systematic reviews make it possible to delimit the research problem and select representative studies according to transparent and reproducible criteria and methods that allow researchers to reach similar conclusions (Linnenluecke et al., 2019). Systematic reviews of *in vitro*, animal and human studies (Brooke-Taylor et al., 2017; Daniloski et al., 2021a, 2021b; de Gaudry et al., 2019, 2022) were conducted. However, systematic reviews also present subjectivity when determining the criteria for inclusion and exclusion of papers.

Bibliometric analysis is more methodical, objective and reproducible than literature reviews and systematic reviews (Mahi et al., 2021). Bibliometrics provides a scientific mapping of a large number of documents to fully and simultaneously explore the intellectual structure and dynamic aspects of knowledge (Gonzales-Malca et al., 2022; Tirado-Kulieva et al., 2022a; Zapata-Mendoza et al., 2022). To our knowledge, there is one bibliometric study on A2 bovine milk (Jiménez-Montenegro et al., 2022), but it only collected papers from the Web of Science database (WoS) database and focused mainly on intellectual structure. The most cited papers and the most frequent keywords were also shown to determine research trends, but superficially (Jiménez-Montenegro et al., 2022). The aim of this study was to explore the relationship between BCM-7, A1 or A2 bovine milk with different aspects of health using bibliometric analysis and text mining of studies extracted from Scopus. The importance lay in providing a more accurate and objective understanding of the current status of the A1 and A2 milk dilemma, the evolution over time, as well as research gaps and future directions, of interest to professionals involved in the field. With the information presented, consumers will also be able to make their own decisions about the consumption of A1 and A2 milk.

To achieve the objective of this paper, an attempt was made to answer these research questions (RQ):

RQ1: How has scientific production evolved by type of document in the field of A1 and A2 milk?

RQ2: Which authors and countries are the most influential in the field of A1 and A2 milk?

RQ3: What are the main research focuses in the field of A1 and A2 milk?

2. Materials and methods

In this study, bibliometrics and text mining were combined as proposed by Ranjbari et al. (2022); Villegas-Yarlequé et al. (2023) with some modifications. Fig. 1 summarizes the methodology employed.

2.1. Study selection

The Scopus database was selected because of its broad content and great accessibility (Gonzales-Malca et al., 2022) and because it was not used in the only bibliometric study on the topic (Jiménez-Montenegro et al., 2022). In order to extract all relevant studies, it is essential to use a well-structured research protocol, so based on de Gaudry et al. (2022), several related terms were chosen and four search strings were constructed (Table 1). The terms were grouped into blocks using the boolean operators and quotation marks to refine the document search and minimize false-positives and false-negatives results that negatively influence the robustness and validity of the results. A false-positive result is a document retrieved by the search strategy, but is irrelevant to the object of the study; while a false-negative result is an important document that is missing from the set of extracted documents. Asterisks were also included as wildcard symbols to search for similar terms.

Research articles and reviews published until November 2022 and focused on the influence of consumption of A1 or A2 bovine milk, BCM-7, A1 or A2 β-casein on human health were included. Papers focused on

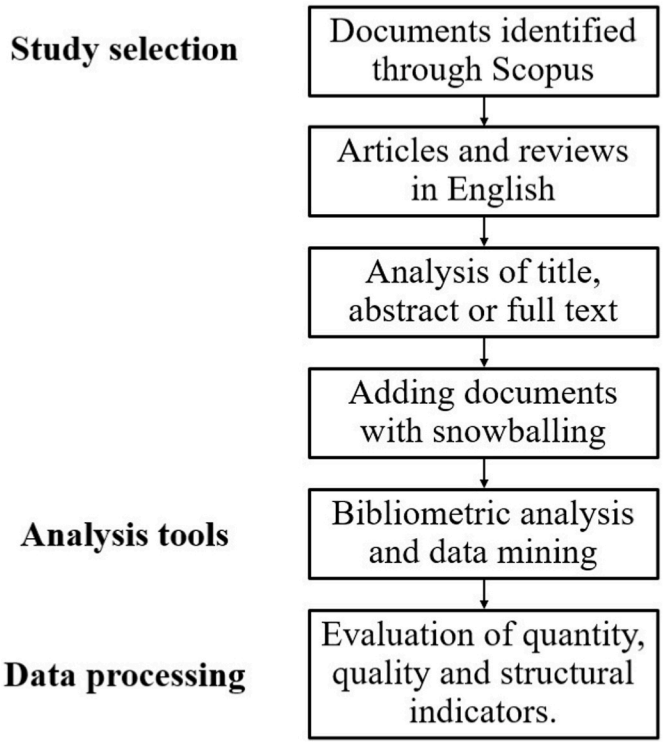

Fig. 1. Flowchart of the steps for the selection and analysis of the studies.

Table 1
Search for documents in Scopus.

Search strings	Results without filter	Results with filter[a]
"A1 milk" OR "A2 milk" OR "A1A2 milk" OR "A2A2 milk"	95	79
milk AND peptide[a] AND opioid[a]	269	224
milk AND (beta-casomorphin[a] OR bcm-7 OR bcm7)	232	205
milk AND ("beta casein[a]" OR "β casein")	3197	2949
Total	3793	3457

[a] Only articles and reviews in English published until November 2022.

β-casein or BCM in general, those that did not mention health effects, and those that included other dairy products were excluded. To avoid duplicates, only documents in English were selected.

Even if search terms are carefully selected, the databases may show false-positives and false-negatives results. Therefore, three authors (M.S. A.-L., W.L. A.-J. and C.M. P.-Z.) of this study independently selected the documents according to title and abstract. If necessary, the papers were subjected to full-text analysis (Daniloski et al., 2021a). Any disagreement was resolved by another author (V.A. T.-K.) of this study. Finally, snowballing was applied, i.e., the reference list of the selected papers was reviewed to identify and include important articles (Tirado-Kulieva et al., 2022b). The approaches adopted were validated after reviewing the suitability of the most cited papers and confirming that important papers were extracted from the most active authors according to their Scopus profiles (Sweileh, 2020).

2.2. Analysis tools

Selected documents were exported in CSV format and loaded into Bibliometrix v. 4.0.0 (in RStudio v. 4.2.1, Aria and Cuccurullo, 2017) and VOSviewer v. 1.6.18 (van Eck and Waltman, 2010) packages for bibliometric analysis and data mining. The analyze search results service from Scopus was used, as well as Datawrapper (Datawrapper GmbH, Berlin, Germany), a visualization tool to present the world's scientific production on a world map. Bibliometrix was used because with its biblioshiny extension it offers the broadest set of techniques by incorporating most of the analyses of other related software (Mahi et al., 2021). VOSviewer was chosen because it offers different types of bibliometric networks especially for use in text mining through keyword extraction and correlation with fantastic visualization and easy interpretation (Moral-Muñoz et al., 2020). In addition, both softwares are freely available.

2.3. Data processing

2.3.1. Pre-processing

Data cleaning is an important step to reduce the presence of useless and redundant information (Ranjbari et al., 2022). Bibliometrix and VOSviewer are powerful, but do not have many preprocessing options such as merging synonyms and acronyms, removing duplicates and stop words (Moral-Muñoz et al., 2020). To refine the analysis and reduce bias, some adjustments were made manually: a) merging of singular and plural keywords, synonyms, full and short forms; b) exclusion of generic and irrelevant keywords.

2.3.2. Analysis

To answer RQ1, information on the number of publications per year was extracted and the distribution was shown according to the type of document.

To address RQ2, the three indicators proposed by Durieux and Gevenois (2010) were evaluated: a) quantity or productivity indicator; b) quality, performance or influence indicator; c) structural, connection or collaboration indicator. Thus, the individual participation of prolific authors and countries in the field of study was determined, as well as cooperation through a co-authorship analysis. The number of documents and citations of authors and countries were evaluated; however, since the number of citations relatively reflects the impact of the paper in the scientific community, the h-index was also evaluated in the case of authors. If an author (or group of authors, countries) has X publications cited at least X times, X is her/his h-index. The h-index was calculated taking into account only the extracted documents. For a fairer comparison of authors with a similar h-index, but with careers of different lengths and with articles with citations above the h-index, the m-(Choudhri et al., 2015) and e-indexes (García-Villar and García--Santos, 2021) were calculated, respectively. Lotka's law, a bibliometric law that measures the productivity of authors, was also applied with the hypothesis that few authors have a high production in a given field, while most authors have only published one paper (Lotka, 1926).

RQ3 was addressed using text mining to define the main areas of research, determine the current state and evolution of the science, detect trends and future lines of research. For this purpose, the maps of co-occurrence and overlapping of the main keywords were analyzed.

3. Results and discussion

3.1. Characteristics of the selected documents

Four search strings were used and 3457 documents were collected (Table 1). After reviewing the title and abstract of each document, only 97 records remained. An additional 22 documents with relevance to the object of study were identified by snowballing to increase the sample number and improve the robustness of the results. Thus, 119 documents were collected ready for analysis (Fig. 2). Most of the studies are literature reviews (36.07%), followed by original articles represented by *in vivo* animal studies (25.41%), *in vitro* studies (17.21%) and clinical trials (13.11%), in addition to systematic reviews and/or meta-analyses (7.38%) and a bibliometric study (<1%). There are more literature reviews because they are general studies that do not only focus on BCM-7, A1 or A2 bovine milk. For example, the first review found (Meisel, 1997) reports in general on peptides derived from milk proteins, including information on β-casomorphins. There are papers (e.g., Kaplan et al., 2022; Kay et al., 2021; Semwal et al., 2022; Summer et al., 2020; Thiruvengadam et al., 2021) that did focus exclusively on the health effects of BCM-7, A1 or A2 bovine milk.

Another question could be why there are more *in vitro* and *in vivo* animal studies than clinical trials. *In vitro* experiments are cheaper and less complex, although they may not simulate the conditions and reactions in the organism. According to Thiruvengadam et al. (2021), using animal models it is easier to perform cause-and-effect experiments because mammals share several characteristics of the human physiological system. The analyses and interpretations may be applicable in humans if the designs simulate in depth the different intestinal microflora, ages, lifestyles, among other characteristics (Thiruvengadam et al., 2021). Clinical trials are difficult to conduct because they are time-consuming and the human system is complex, although many studies only evaluate short-term effects. Thus, Clinical trials are costly, tedious and include many factors that are difficult to monitor and control before, during and after the intervention such as lifestyle, diet and environmental conditions. However, due to the importance of the subject from the point of view of human health and thanks to the results obtained in *in vitro* and animal studies, clinical trials are emerging.

3.2. Prolific actors

Prolific countries were listed according to the number of publications, followed by total citations, while authors were ordered according to the number of papers, followed by the h-index and, finally, total citations. In case of equivalence, the classification in both cases was defined according to alphabetical order.

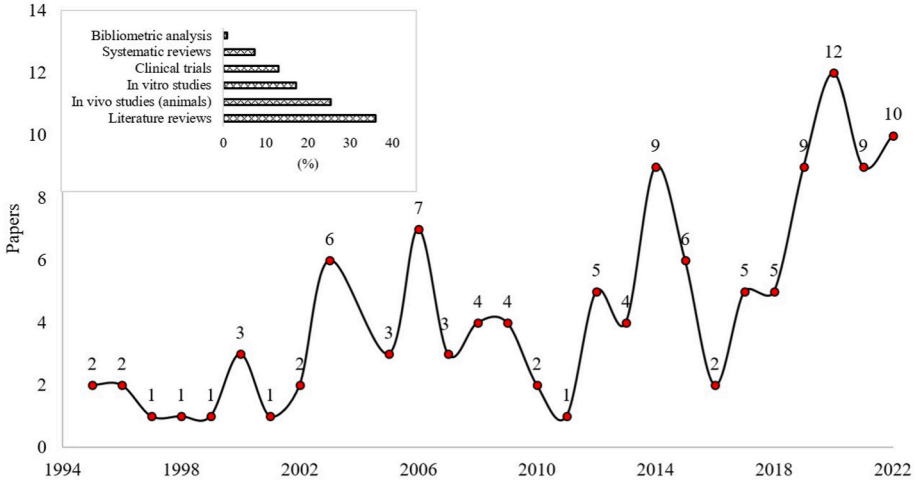

Fig. 2. Extracted papers on the effect of A1 or A2 bovine milk or BCM-7 on health.

3.2.1. Main authors

Recognizing prolific authors in a field of study is key in the functioning of science (Barbosa, 2021). Table 2 shows the 10 authors with the highest production and impact in the field, including indicators such as the h-, m- and e−indexes for greater objectivity by considering the relationship between the number of published papers, citations (within and above the h index) and the length of the author's career according to the date of the first paper. For example, Zhang, Y. (#1) and Kostyra, E. (#2) are the authors with the highest production (7 papers each), but Zhang Y. has a higher h-index (7 vs. 6). Woodford, K. (#3) has higher m- and e-indexes, which would suggest that he is a highly cited scientist despite his younger career.

Co-authorship is the most formal form of intellectual collaboration in a field of study, the analysis of which provides information on the interaction between the most important authors (or countries) (Donthu et al., 2021). The collaborative networks formed can shed light on, for example, scholars from a particular region or those researching a particular topic, which can be useful for contacting colleagues and generating new research (Donthu et al., 2021). Fig. 3 shows co-authorship and its evolution over time to evaluate the path of intellectual development, in addition to observing the career and continuity of the authors for possible collaborations. There are 69 authors distributed in 13 clusters listed according to the number of authors and publications. It is important to note that some authors have links in more than one cluster, indicating collaboration between scholars from different subdisciplines.

The authors of cluster (CT) 1 have mainly focused on demonstrating the association between type 1 diabetes and A1 β casein/BCM-7 according to studies in mice (Chia et al., 2018) and reviews or meta-analyses (Birgisdottir et al., 2006; Chia et al., 2017; Elliott et al., 1999; Laugesen and Elliott, 2003). The authors of CT2 have shown the association of BCM-7 with autism in children (Sokolov et al., 2014) and its positive influence on behavior and learning in rats (Dubynin et al., 2000, 2007, 2008; Maklakova et al., 1995). The authors of CT3 have shown BCM-7 as an indicator of autism (Jarmołowska et al., 2019) and atopic dermatitis in children (Fiedorowicz et al., 2014), in addition to evaluating its immunomodulatory effect *in vitro* (Fiedorowicz et al., 2011). The authors of CT4 obtained positive results in evaluating the effect of BCM-7 on diabetes using rats (Han et al., 2013; Yin et al., 2010, 2012; Zhang et al., 2012, 2013) and *in vitro* (Zhang et al., 2013), as well as improving intestinal mucosal immunity in mice (Yin et al., 2019) and rats (Zong et al., 2007). Research in CT5 determined that A1 milk causes digestive discomfort, gastrointestinal inflammation and/or delayed gastrointestinal transit in rats (Barnett et al., 2014) and humans (Jianqin et al., 2016; Milan et al., 2020; Sheng et al., 2019). According to *in vitro* studies in CT6, BCM-7 induces gastrointestinal mucin secretion (Claustre et al., 2002; Trompette et al., 2003; Zoghbi et al., 2005). In CT7, oral administration of BCM-7 (Haq et al., 2014a) and consumption of A1 β-casein (Haq et al., 2014b) induced inflammatory responses in mice. In CT8, consumption of A2 bovine milk had a positive impact on intestinal immunity in mice (Guantario et al., 2020). In CT9 (Daniloski et al., 2021a, 2021b) and CT10 (de Gaudry et al., 2019, 2022) the systematic reviews showed weak evidence for a positive effect of A2 bovine milk, as opposed to A1 milk. In CT11, BCM-7 delays psychomotor development in infants (Kost et al., 2009). In CT12, administration of BCM-7 in rats modulated the intake of a high-carbohydrate (Lin et al., 1998) and high-fat diet (Lin et al., 1998; White et al., 2000) diet, but not the low-fat diet (White et al., 2000). According to *in vitro* studies in CT13, BCM-7 promotes neuronal survival (Sakaguchi et al., 2001) and stimulates neurite outgrowth (Sakaguchi et al., 2003).

As shown in Fig. 3, many groups are not currently active (CT2-CT4, CT6-CT7, CT11-CT13). CT5 remains active with average publications from ≈2013 to ≈2021, while CT8-CT10 include studies published in 2020–2021. Interestingly, CT1 includes publications from ≈2001 to

Table 2
Top authors with the highest production on the topic of study.

Rank	Author	Number of papers	Percentage	Timespan	Total citations	h-index	m-index	e-index
1	Zhang, Y.	7	5.8824	2007–2015	174	7	0.412	11.1803
2	Kostyra, E.	7	5.8824	2007–2019	334	6	0.353	17.7200
3	Woodford, K.	6	5.0420	2014–2021	325	5	0.500	17.9722
4	Cieślińska, A.	5	4.2017	2007–2019	298	4	0.235	17.2047
5	Fiedorowicz, E.	5	4.2017	2011–2019	130	4	0.308	11.0000
6	Clarke, A.J.	4	3.3613	2006–2016	262	4	0.222	16.2481
7	Elliott, R.B.	4	3.3613	1999–2017	245	4	0.160	17.4356
8	Kukuljan, S.	4	3.3613	2014–2018	210	4	0.400	14.6287
9	Kost N.V.	4	3.3613	2005–2017	199	4	0.211	13.8564
10	Miao, J.	4	3.3613	2010–2013	127	4	0.286	10.7703

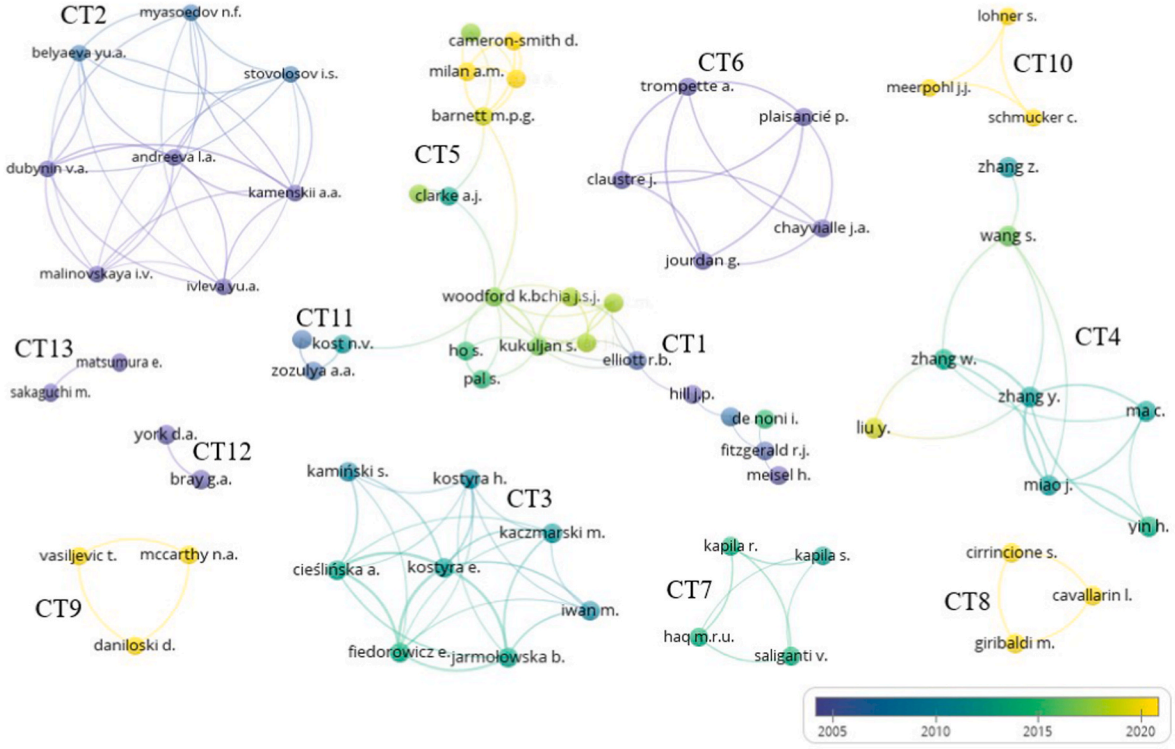

Fig. 3. Overlay visualization network of authors with at least 2 occurrences without removing isolated nodes.

≈2006 on average, but authors such as Woodford, K.B. and de Noni, I. have returned to the field of study with literature reviews reporting the effect of BCM-7, A1 or A2 bovine milk on health (Summer et al., 2020; Woodford, 2021). Apparently, efforts would focus on summarizing the existing evidence and since the increase in original research is low, review articles evaluate the same results and offer similar conclusions. In the period 2021–2022, six clinical trials, *in vitro* or *in vivo* animal studies (Hohmann et al., 2021; Liu et al., 2022; Mori et al., 2021; Osman et al., 2021; Prodhan et al., 2022; Ramakrishnan et al., 2020) and fourteen reviews, systematic reviews or bibliometric studies were published (Daniloski et al., 2021a, 2021b; de Gaudry et al., 2022; Fernández-Rico et al., 2022; Giribaldi et al., 2022; Jaiswal and Worku, 2022; Jiménez-Montenegro et al., 2022; Kaplan et al., 2022; Kay et al., 2021; Leischner et al., 2021; Li et al., 2022; Semwal et al., 2022; Thiruvengadam et al., 2021; Woodford, 2021).

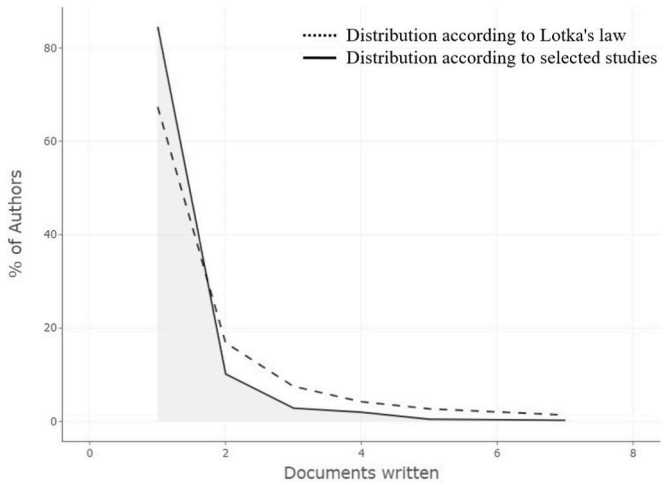

Fig. 4. Author productivity through Lotka's Law.

In Fig. 4, the solid line shows the number of articles written with the corresponding proportion of authors and the dashed line represents the distribution of authors according to Lotka's law. 85% of authors have published one paper, 9.35% of authors have published two papers, 2.61% of authors have published three papers, 1.96% of authors have published four papers, 0.43% of authors have published 5 papers, 0.22% of authors have published six papers and 0.43% of authors have published 7 papers. The documents evaluated do not comply with Lotka's law; the production of most of the authors is lower than expected and a very small group of authors has published most of the papers. This negative correlation presented an r value of −0.67.

Although the topic has been studied for several decades, it is not yet possible to define the existence of established authors or groups of authors in the field.

3.2.2. Main countries

It is important to assess how different countries contribute to the advancement of knowledge in the field of A1 and A2 milk to recognize the outstanding presence of countries who can serve as role models, determine where to look for subject matter experts, and promote international collaboration. Identifying where a field of study lacks or deserves attention is also important for policy decisions by governments

Table 3
Top countries with the highest production on the topic of study.

Rank	Country	Number of papers	Percentage	Total citations
1	New Zealand	19	15.9664	895
2	China	18	15.1261	449
3	Australia	16	13.4454	691
4	India	14	11.7647	305
5	United States	13	10.9244	442
6	Poland	9	7.5630	339
7	Russian Federation	9	7.5630	225
8	Germany	8	6.7227	1003
9	Italy	6	5.0420	136
10	United Kingdom	5	4.2017	134

to promote research through the allocation of resources. To determine which countries are at the forefront in this field of study, Table 3 shows the 10 countries with the highest production and impact in the field. New Zealand is the most productive country with 19 papers (895 citations), while Germany has the highest number of citations (1003 for 8 papers). Based on the number of records, the ranking would be different: China (67) > Australia and India (56) > Poland (44) > New Zealand (41) > USA (39) > Italy (34) > Germany (27) > France (21) > Japan and Spain (19). According to a bibliometric study of papers extracted from WoS, the countries with the most studies on BCM-7, A1 or A2 milk are the United States, New Zealand and Australia (#5, #1 and #3 in this study, respectively) (Jiménez-Montenegro et al., 2022). These data can be useful to determine how many researchers per country contribute to the field, regardless of the number of publications. For example, in Jarmołowska et al. (2019) all eight co-authors have affiliation from Poland, i.e. one paper, but eight records.

As Fig. 5 shows, several countries in most continents have published studies on BCM-7, A1 or A2 milk, which would indicate that these are global topics. However, few countries show interest in the subject according to the color bar in the upper left corner, where the absence of color means the absence of scientific production. No country in Africa or South America has scientific production, except for French Guiana, which is administered by France. Considering that the topic is related to the biotechnological field, this can be associated with the results obtained in a previous study (Gonzales-Malca et al., 2022). The interest in biotechnological development in countries is associated with their Gross Domestic Product (GDP). The GDP of Latin America and Africa are lower than those of North America, Europe, Central Asia and East Asia, but higher than those of East Asia (STATISTA, 2021). One East Asian country (Bangladesh) has contributed to the topic with one paper. Another reason could be that poverty affects bovine milk production in Africa, reducing interest and research in the field (FAO, n.d.). The low interest in the subject could also be caused by the population's lack of knowledge. A questionnaire showed that more than 50% of Brazilian respondents did not know about A2 bovine milk or had never heard the term (Mendes et al., 2019) because the topic is highly specific. Consumers with basic notions could be more demanding and the frequency of milk consumption would vary substantially. This could lead to further research on the subject that would help reach a consensus on the role of A1 or A2 bovine milk in health.

Fig. 6 shows the collaboration between countries distributed in seven clusters listed according to the number of countries and publications. Among the key findings, the only isolated country is Poland (CT7), despite being the sixth country with the highest scientific production with 44 records and 9 papers (Table 3). There are countries with one collaboration, such as Hungary with Germany, China with Japan, India with South Korea, France with Spain and Denmark with Mexico. CT1 integrates more countries and in CT3, New Zealand has the highest total link strength (14) of all clusters. Thus, New Zealand has cooperated with countries in America, Europe, Asia and Oceania. There are many countries without scientific production on the topic and there is little cooperation in those that have done research. This is of interest to start researching new areas around the world and also to build collaborations between countries.

3.3. Main keywords

Keyword co-occurrence analysis makes it possible to detect subfields and the relationship between different themes (Mahi et al., 2021) and since it does not take into account article citations article citations, it is a more objective and appropriate approach (Linnenluecke et al., 2019). Fig. 7 shows the clusters of the main and most interrelated keywords. To refine the results and improve visualization, keywords with lower frequency and interrelation were omitted. The red CT focuses on type 1 diabetes, as well as cholesterol associated with cardiovascular disease. The green CT includes terms related to antioxidant activity with emphasis on cell lines and glucose, which is associated with research on the protective activity of BCM-7. The blue CT blue is related to inflammation and its role in the intestinal mucosa and flora. The yellow CT focuses on peptide bioactivity, especially immunomodulation, which adds to the positive studies on BCM-7. However, it also includes the term autism for its natural opioid activity. The purple CT is associated with the role of A1 and A2 β-casein in the digestive system and, particularly, in the hypothesis that milk A1 plays a role in lactose intolerance.

To explore current or future relationships between topics in the field of A1 and A2 milk, the evolution of the use of keywords over time (from 2000 to 2022, data not shown) was also. To better determine research trends, Table 4 shows the key findings obtained in the clinical trials and *in vivo* animal studies selected in this study. Keywords related to type 1 diabetes mellitus were widely used from 2003 to 2018. It is suggested that BCM-7 activates μ-opioid receptors, altering metabolic processes, which deregulates insulin and glucose levels (Fernández-Rico et al., 2022). The term cardiovascular disease was only used in 2006, but a related study in mice was recently conducted (Sheng et al., 2020). In contrast to rabbits fed A2 β-casein, A1 β-casein promoted elevated levels of triglycerides, serum cholesterol, HDL cholesterol, and LDL cholesterol (Tailford et al., 2003), which are risk factors for cardiovascular disease. However, no significant differences were found when assessing the consumption of A1 or A2 β-casein in men (Venn et al., 2006). Terms related to gastrointestinal system and digestive intolerance (or lactose intolerance) were used from 2014 to 2020. The term immunology (2014–2019) was grouped with the term inflammation (2014–2020)

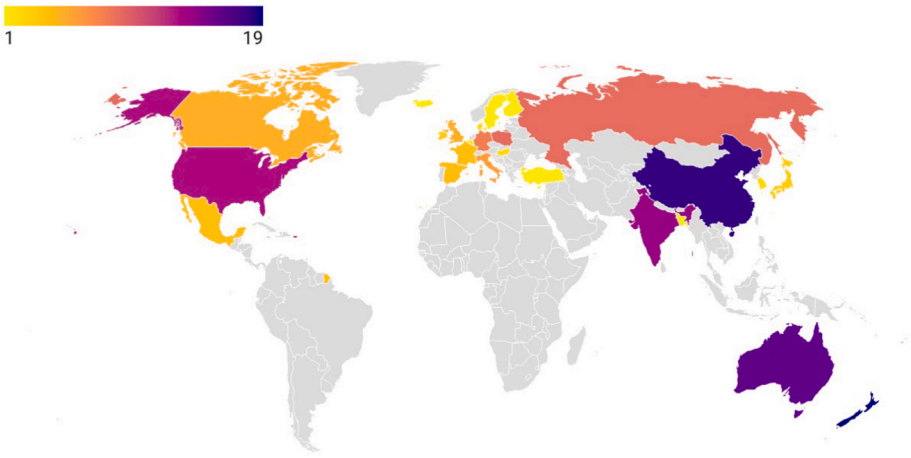

Fig. 5. Map of countries with scientific production on the subject.

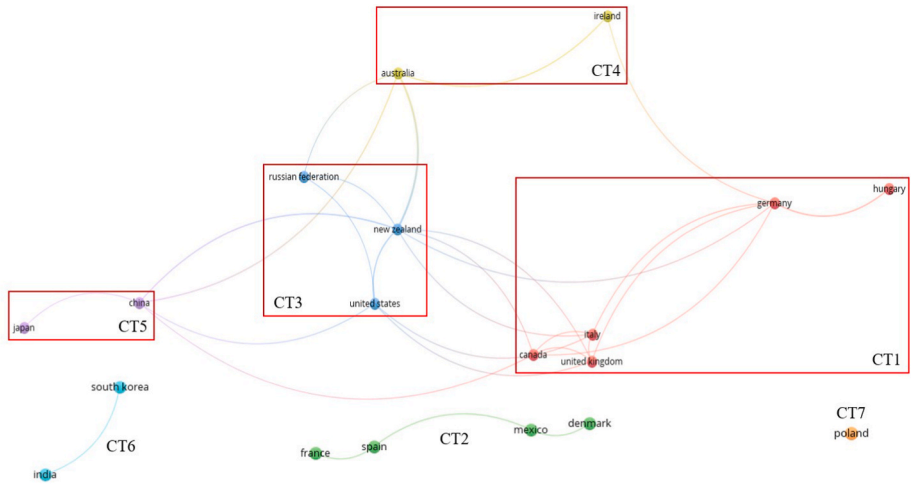

Fig. 6. Network visualization map of countries with at least 2 occurrences without removing isolated nodes.

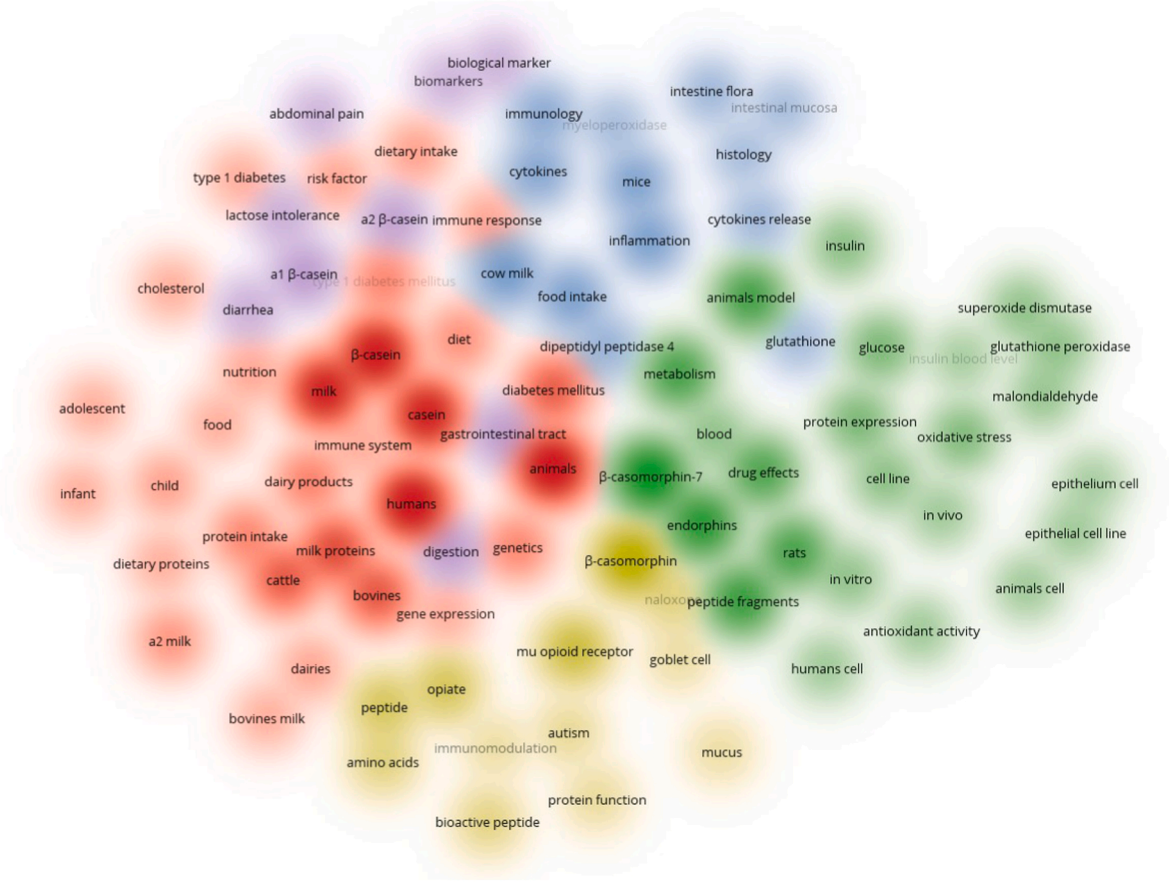

Fig. 7. Cluster density visualization map of keywords with at least 5 occurrences.

and the keywords oxidative stress and antioxidant activity (2012–2018) because oxidative stress is associated with different diseases and occurs naturally when immune and inflammatory responses are generated. In turn, oxidative stress causes alterations in, for example, metabolism and cell signaling, increasing the severity of the inflammatory state.

The studies shown in Table 4 have associated oxidative stress and inflammation with their results. Based on *in vivo* animal experiments, BCM-7 reduced oxidative stress and the inflammatory response, providing protection against kidney damage (Zhang et al., 2013, 2019), myocardial hypertrophy (Sheng et al., 2020) and diabetes (Yin et al., 2010, 2012). The influence of BCM-7 on improving intestinal mucosal immunity was also reported (Yin et al., 2019), but negative results were obtained when evaluating the influence of BCM-7 (Haq et al., 2014a) and A1 bovine β-casein (Haq et al., 2014b) on the gastrointestinal immune system. Barnett et al. (2014) obtained similar results when they determined that A1 β-casein affected the gastrointestinal system by aggravating the inflammatory state and/or inducing oxidative stress. In other studies, A2 bovine milk showed an antiinflammatory effect on the lungs, modulated the intestinal microbiota and prevented the oxidative effects of aging (Guantario et al., 2020; Liu et al., 2022; Yadav et al.,

Table 4
Summary of findings when evaluating the effect of BCM-7, A1, A2 or A1/A2 bovine milk on health according to clinical trials and *in vivo* animal studies.

Reference	Evaluated phenomena	Samples	Evaluated factor					Treatment	Brief conclusion
			BCM-7	A1 milk	A2 milk	A1/A2 milk	Other		
Clinical trials: Digestive system									
Crowley et al. (2013)	Chronic functional constipation	Children (1–12 years old) (n = 39)		x	x			1) consumption of alternative milk (at least 400 ml) every day for 2 weeks, 2) 2-week washout, c) step 1)	No significant differences
Ho et al. (2014)	Gastrointestinal health	Men and women (19–68 years old) (n = 36)		x	x			1) 2-week washout, 2) consumption of alternative milk (750 ml/day) for 2 weeks, 3) step 1), 4) step 2)	A1 milk was associated with softer stools and greater abdominal pain.
Jianqin et al. (2016)	Digestive intolerance	Men and women (25–68 years old) (n = 45)		x	x			1) 2-week washout, 2) consumption of alternative milk (250 ml twice a day) for 2 weeks, 3) step 1), 4) step 2)	A1 milk was associated with increased gastrointestinal inflammation and digestive discomfort, and delayed intestinal transit
He et al. (2017)	Digestive intolerance	Men and women (20–50 years old) who reported lactose intolerance and digestive discomfort after consuming milk (n = 600)		x	x			1) 3-day washout, 2) single consumption of alternative milk (300 ml), 3) 7-day washout, 4) step 2)	A1 milk increased undesirable gastrointestinal symptoms by reducing lactase activity
Sheng et al. (2019)	Digestive intolerance	Children (5–6 years old) (n = 75)			x	x		1) 10-day washout, 2) consumption of alternative milk (150 ml twice a day) for 5 days, 3) 9-day washout	A2 milk attenuated gastrointestinal symptoms associated with milk intolerance
Milan et al. (2020)	Digestive intolerance	Women (19–50 years old) (n = 40)			x	x	Lactose-free A1/A2 cow's milk	Single consumption of some type of milk (750 ml)	Digestive comfort was better when consuming A2 milk
Ramakrishnan et al. (2020)	Digestive intolerance	Men and women (19–50 years old) (n = 33)			x	x	Lactose-free A1/A2 cow's milk	Single consumption of some type of milk (245 ml)	A2 milk was associated with fewer gastrointestinal symptoms
Prodhan et al. (2022)	Digestive intolerance	Women (20–30 years old) (n = 40)			x	x	Lactose-free A1/A2 cow's milk	Single and random consumption of each type of milk (750 ml)	No significant differences
Clinical trials: Nervous system									
Kost et al. (2009)	Psychomotor development	Infants (younger than 1 year) (n = 90)					Breast milk and infant formula with A1/A2 cow's milk	ns	Infants with delayed psychomotor development showed higher concentration of BCM-7
Sokolov et al. (2014)	Autism spectrum disorders	Children (4–8 years old) (n = 20)	x					[a]	Autistic children presented higher BCM-7 concentrations
Jarmołowska et al. (2019)	Autism spectrum disorders	Children (3–10 years old) diagnosed with autism (n = 137)	x					[a]	BCM-7 concentration was higher in children diagnosed with autism spectrum disorder
Clinical trials: Others									
Chin-Dusting et al. (2006)	Cardiovascular disease	Men and women (32–67 years old) at high risk of developing cardiovascular disease (n = 15)					A1 or A2 β-casein supplementation	Daily supplementation of either A1 or A2 β-casein (25 g) for 12 weeks each	No significant differences
Venn et al. (2006)	Blood cholesterol concentrations	Men (20–65 years old) (n = 55)			x	x	A2 and A1/A2 low-fat milk, cheese made with a) full-fat A2 milk and b) full-fat A1/A2 milk	Consumption of either A2 milk and cheese or A1/A2 milk and cheese (500 ml/day and 28 g/day respectively) for two four-and-a-half week periods	No significant differences
Deth et al. (2016)	Plasma glutathione concentration	Men and women (25–68 years old) who reported			x	x		1) 2-week washout, 2) consumption of alternative milk (250 ml	A2 milk increased glutathione concentration and

(*continued on next page*)

Table 4 (*continued*)

Reference	Evaluated phenomena	Samples	Evaluated factor					Treatment	Brief conclusion
			BCM-7	A1 milk	A2 milk	A1/A2 milk	Other		
		digestive discomfort after consuming milk (n = 45)						twice a day) for 2 weeks, 3) step 1), 4) step 2)	reduced BCM-7 concentration
Kirk et al. (2017)	Muscle damage after exercise	Men (≈23 years old) (n = 21)			x	x	A2 semi-skimmed milk	Single consumption of some type of milk (500 ml)	A2 milk accelerated muscle recovery, improving subsequent performance
in vivo animal studies: Digestive system and related subject									
Zong et al. (2007)	Regulation of gastrin and somatostatin in gastric mucosa	Sprague-Dawley rats (n = 24)	x				Poly-Gly	Oral administration of BCM-7 or poly-Gly (equivalent content 7.5 × 10^{-7} mol) for 30 days	BCM-7 modulated the expression of D- and G-cell-associated genes
Barnett et al. (2014)	Gastrointestinal health	Wistar rats (4 weeks old) (n = 48)					Diets based on skim bovine milk: A1 or A2 milk plus saline or plus naloxone	Consumption of either A1 (44.89% of the diet) or A2 milk (44.36%) *ad libitum* for 36 or 84 h. Then, single injection of naloxone (0.03%, 1 mg/kg bw) or saline (equivalent volume) at 12 or 60 h	A1 milk showed proinflammatory effects and its consumption delayed gastrointestinal transit
Haq et al. (2014a)	Gastrointestinal health	Swiss-albino mice (n = 18)	x				BCM-5	Oral intubation with BCM-5 or BCM-7 (7.5 × 10^{-8} mol/day) for 15 days suspended in 200 μL of phosphate buffer saline	BCM-7 promoted an inflammatory immune response in the gut
Haq et al. (2014b)	Gastrointestinal health	Swiss-albino mice (n = 24)					A1 or A2 or A1/A2 β-casein	Consumption of some type of β-casein (85 mg/day) for 15 days suspended in 200 μL of phosphate buffer saline	A2 milk did not promote an inflammatory immune response in gut, compared to A1 and A1/A2 variants
Yin et al. (2019)	Intestinal mucosal immunity	KM mice (11 months old) (n = 40)	x					Intragastric administration of BCM-7 (2 × 10^{-7}, 1 × 10^{-6} or 5 × 10^{-6} mol/day) for 30 days	Modulation of intestinal mucosal immunity, reducing the effects of aging
Guantario et al. (2020)	Gut health	BALB-c mice (20 months old) (n = 24)					A1/A2 or A2 milk diet	Consumption of either A1/A2 or A2 milk diet (both 44.36% of the diet) *ad libitum* for 4 weeks	A2 milk modulated the gut microbiota, slightly counteracting the effects of aging
Hohmann et al. (2021)	Growth and gastrointestinal health	Dairy calves (3 weeks old) (n = 47)		x	x			Single consumption of either A1/A2 or A2 milk three times a day (mean 6.53–6.78 L) for 21 days	No significant differences in weight. A2 milk induced a higher prevalence of diarrhea and softer fecal consistency
Liu et al. (2022)	Immune and gut health	BALB-c mice (3–4 weeks old) (n = 30)			x		A2/A1 milk	Consumption of either A2/A1 or A2 milk (10 ml/kg bw) for 4 weeks	Improved diversity and composition of the gut microbiota when consuming A2 milk, which improves the immune response
in vivo animal studies: Diabetes									
Kim et al. (2000)	Circulating concentrations of hyperglycaemic insulin and glucose	Non-lactating Friesian cows (n = 9)					Glucose plus somatostatin or plus a mixture of BCM-4, -5 and -7	Single intra-abomasal administration of a bolus of mixture of BCM (240 mg, 1:1:1 ratio) with and without intravenous infusion of somatostatin (52 pg/kg bw/min) for 15 min	BCM-7 modulated insulin secretion, but did not significantly affect glucose concentration
Beales et al. (2002)	Type 1 diabetes	NOD/Ba mice (30 weeks old) (n = 270), NOD/NZ mice (30 weeks old) (n = ns) and BB rats (n = 234)					Hydrolyzed casein-based formula (F1), soy-based infant formula (F2), F1 or F2 + whole casein, F1 + A1 or A2 β-casein (10%), F2 + A1 or A2 β-casein (10%)	Consumption of some type of formula *ad libitum* for 150 days for the rats and 250 days for the mice	Both variants of β-casein showed protective effect

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Table 4 (*continued*)

Reference	Evaluated phenomena	Samples	Evaluated factor					Treatment	Brief conclusion
			BCM-7	A1 milk	A2 milk	A1/A2 milk	Other		
Yin et al. (2010)	Type 1 diabetes	Diabetic Sprague-Dawley rats (n = 30)	x					Oral administration of BCM-7 (7.5×10^{-8} mol/day) for 15 days	BCM-7 showed antioxidant activity and protective effect against hyperglycemia
Zhang et al. (2012)	Diabetic nephropathy	Diabetic Sprague-Dawley rats (n = 24)	x					Intraperitoneal administration of BCM-7 (7.5×10^{-6} mol/day/kg bw) for 30 days	BCM-7 reduced deterioration of renal function impairment and renal tubular fibrosis
Zhang et al. (2013)	Glucose -induced renal oxidative stress	Diabetic Sprague-Dawley rats (n = 24)	x					Oral administration of BCM-7 (7.5×10^{-6} mol/day/kg bw) for 30 days	BCM-7 reduced Ang II levels and improved antioxidant markers, alleviating renal oxidative stress
Chia et al. (2018)	Type 1 diabetes	NOD/ShiLtJArc mice (3–4 weeks old) (n = ns)					A1 or A2 skim milk diet	Consumption of either A1 or A2 milk diet *ad libitum* for 30 weeks	A1 milk affected glucose homeostasis in mice and increased diabetes incidence
Thakur et al. (2020)	Diabetogenic activity	Diabetic Wistar rats (6 weeks old) (n = 36)					A1 or A2 β-casein hydrolysate	Consumption of either A1 or A2 β-casein (800 mg/kg bw) for days	No significant differences
in vivo animal studies: Learning and behavior									
Maklakova et al. (1995)	Learning	White rats (n = 292)	x					Single intraperitoneal injection of BCM-7 (0,1–5 mg/kg bw) 5 min before the start of each learning session	BCM-7 facilitated learning involving positive reinforcement (food-procuring habit) and promoted defensive function in a stressful situation (learning of the active avoidance response).
Blass and Blom (1996)	Behavior	Sprague-Dawley rats (10 days old) (n = 180)	x				BCM-4 and BCM-5	Single intraperitoneal injection of BCM-7 (0,1 to 2,5 mg/kg)	BCM-7 caused hypoalgesia
Dubynin et al. (2000)	Behavior	Pups of albino rats (10–23 days old) (n = 98)	x					Single intraperitoneal injection of BCM-7 (1 mg/kg)	BCM-7 produced delayed anxiolytic effects
Dubynin et al. (2007)	Mother-oriented ("Child's") behavior	Pups of white rats (10 and 17 days old) (n = 480)	x					Single intraperitoneal injection of BCM-7 (5 mg/kg)	BCM-7 increased the pup's attachment to the mother.
Dubynin et al. (2008)	Learning	Pups of albino rats (n = 340)	x					Single intraperitoneal injection of BCM-7 (1 mg/kg)	BCM-7 negatively affected passive avoidance conditioning
in vivo animal studies: Cardiovascular system									
Tailford et al. (2003)	Atherosclerosis	White/Lop cross rabbits (16/24 weeks old) (n = 60)					Pellets: whey protein, whey protein plus A1 o A2 β-casein	Consumption of one of the pellets *ad libitum* for 6 weeks.	A1 β-casein was atherogenic compared with A1 β-casein
Han et al. (2013)	Cardiomyopathy	Diabetic Sprague-Dawley rats (8 weeks old) (n = 32)	x					Oral administration of BCM-7 (7.5×10^{-8} mol/day) for 30 days	BCM-7 reduced oxidative stress in the blood and myocardium and improved energy metabolism in the myocardium
Sheng et al. (2020)	Myocardial hypertrophy	C56BL/6 mice (8 weeks old) with induced hyperthyroid heart disease (n = 30)	x					Intraperitoneal injection of BCM-7 (15 mol/L) for 30 days	Prevention and improvement of myocardial hypertrophy status
in vivo animal studies: Others									
Maslennikova et al. (2008)	DNA synthesis	Newborn outbred albino rats (n = 42)	x					Single or 5-fold intraperitoneal injection of BCM-7 (1 mg/kg mol/L)	BCM-7 stimulated DNA synthesis in lingual, gastric and duodenal epithelium
Kamiński et al. (2012)	Blood parameters	Sibling gilts (Polish large White x Polish Landrace) (n = 6)		x	x			Consumption of either A1 or A2 milk (progressively, 0.32–1.5 kg/day) for 6 weeks	No significant differences
Yin et al. (2012)	Oxidative stress in pancreas	Diabetic Sprague-Dawley rats (n = 30)	x					Intragastric administration of BCM-7 (1×10^{-6} mol/d) for 30 days	BCM-7 reduced oxidative stress and inhibited the NF-κB-

(*continued on next page*)

Table 4 (*continued*)

Reference	Evaluated phenomena	Samples	Evaluated factor					Treatment	Brief conclusion
			BCM-7	A1 milk	A2 milk	A1/A2 milk	Other		
									iNOS-NO signaling pathway
Zhang et al. (2019)	Sepsis-induced acute kidney injury	Sprague-Dawley rats (7–8 weeks old) (n = 48)	x					Single intraperitoneal injection of BCM-7 (7.5 × 10^{-8} mol)	Reduction of inflammation and oxidative stress
Yadav et al. (2020)	Pulmonary inflammation	BALB-c mice (3–4 weeks old) (n = 32–40)					A1 or A2 or A1/A2 β-casein	Oral gavage of either some type of β-casein (10 mg/kg bw, 5 days/week) for 30 weeks	A1 milk showed proinflammatory effects

Note: All experiments included control or placebo groups. The milks were denominated A1/A2 or A2/A1 if A1 or A2 β-casein predominated, respectively. If this information is not available, they were denominated as in the study evaluated. Unless otherwise indicated, the A1 or A2 or A1/A2 milk used contained lactose. bw: body weight, ns: not specified.

[a] BCM-7 concentration was measured in urine and serum.

2020). In clinical trials, some individuals who consumed bovine milk containing only β-casein A2 experienced less severe gastrointestinal symptoms compared to consumption of A1 or A2/A1 milk, the results of which highlighted the association between exposure to β-casein A1 and gastrointestinal inflammation (He et al., 2017; Ho et al., 2014; Jianqin et al., 2016; Ramakrishnan et al., 2020; Sheng et al., 2019). Consumption of A2 milk increased glutathione concentration in humans, which confers a higher antioxidant capacity (Deth et al., 2016).

More than 40% of selected clinical trials focused on digestive intolerance or gastrointestinal health (Table 4). In 6 of 7 studies, the results associated consumption of A1 or A1/A2 bovine milk with aggravation of abdominal pain, diarrhea, gastrointestinal inflammation, delayed intestinal transit, among other undesirable symptoms. He et al. (2017) drew attention by reporting that A1 milk reduced lactase activity. Three studies included a lactose-free A1/A2 milk group, but only two of them found adverse effects of A1 β-casein (Milan et al., 2020; Ramakrishnan et al., 2020), so more research is required. In this line, A2 milk modulated the intestinal microbiota in mice, improving its composition and diversity (Guantario et al., 2020; Li et al., 2022). Considering that a microbiota with a higher number and type of bacteria reduces the symptoms of lactose intolerance (Zhong et al., 2004), it should be evaluated whether the relationship between lactose intolerance and A1 milk is associated with the effect of its consumption on the microbiota. Recently, a study showed that A2 β-casein can promote the proliferation of bifidobacteria in intestinal bacteria, reducing borborygmus, abdominal distension, increase the frequency of defecation and stool characteristics (Lijun et al., 2021). Another study indicated that the symptoms of patients with lactose intolerance may be due to the abundance of bifidobacteria (Gois et al., 2022).

In the extracted documents, the term autism was used from 2016 to 2020 and the term brain was used in 2021. These keywords were associated because consumption of A1 bovine milk has been linked to the pathogenesis or aggravation of symptoms of neurological disorders or psychiatric diseases such as schizophrenia, autism spectrum disorder and sudden infant death; however, the evidence is limited and further research is needed (de Gaudry et al., 2022; Kaplan et al., 2022; Kay et al., 2021; Summer et al., 2020; Thiruvengadam et al., 2021). Two clinical trials (Table 4) found higher BCM-7 concentrations in children diagnosed with autism than in healthy children (Jarmołowska et al., 2019; Sokolov et al., 2014). This is also related to the hypothesized inflammatory and oxidative activity of A1 β-casein or BCM-7, since autism in children was associated with low glutathione concentrations and higher numbers of proinflammatory cells in the intestines (Kay et al., 2021). The limited synthesis of glutathione is due to decreased uptake of cysteine, its precursor due to oxidative stress (Fernández-Rico et al., 2022). Also, BCM-7 influenced the alteration of epigenetic mechanisms, associating abnormal DNA methylation patterns with the aforementioned neurological conditions (Daniloski et al., 2021b). Gut permeability and inflammation increase the concentration of BCM-7, so it crosses the blood-brain barrier (Fernández-Rico et al., 2022). Due to the underdeveloped central nervous system and intestinal mucosa in infants and children, they are more susceptible to negative effects.

Since milk is a fundamental food in the diet, more extensive research is needed to obtain accurate and conclusive results. Clinical trials should include a larger number of participants and with more heterogeneous characteristics, e.g., diet, age, ethnicity, geographic location, microflora and physiological states (Brooke-Taylor et al., 2017; Daniloski et al., 2021a; Kay et al., 2021; Thiruvengadam et al., 2021), which will allow determining whether A1 β-casein or BCM-7 have an exclusive or secondary role on any aspect of health. Interventions should be conducted for short-, medium- and long-term evaluations and the results can be complemented with *in vitro* and *in vivo* animal studies. Studies focused on determining the mechanisms of action of A1 and A2 milk are also required to provide essential information on the origin of the effects in the organism. Until this is addressed, the issue will remain controversial and public health authorities cannot suggest that A1 milk should not be consumed, although with the limited evidence, A2 milk is already gaining prominence in the market (Daniloski et al., 2021a).

4. Scope and limitations of the study

Since the study was limited to publications indexed in Scopus, it is recognized that not all publications on the topic of study were captured. Future research could use Scopus and another major database, such as WoS, to extend the results and improve the reliability of the study. The descriptors used in the search string also imply that important documents have been ignored, but this limitation was somewhat reduced by considering terms from related studies as a reference and manually addressing false-positive and false-negative results.

In line with Choudhri et al. (2015), the publication count is fundamental, but it does not take into consideration the degree of participation of authors or the prestige of the journal. Similarly, the citation count does not distinguish between positive and negative citations (e.g., criticism of Truswell, 2005) and also accounts for self-citations. These uncontrolled variables may have influenced the results of this study.

The h-index is advantageous for measuring productivity because it focuses on the quantity and quality of documents, but does not consider citations above the index. For example, an author with h-index 3 may have many influential papers with more than 3 citations. To reduce bias, the e-index was used to provide information on citations above the h-index (see Choudhri et al., 2015). The h-index also does not measure productivity over time and, therefore, many authors have a high h-index due to their older papers. This limitation was overcome with the m-index that evaluates the relationship between the h-index and the age

of the first published paper, but the results can be improved with related metrics such as the h5 index and the contemporary h-index (hc) (see García-Villar and García-Santos, 2021). The h-index scores all authors of a paper equally, regardless of whether they are young researchers, their authorship position or their collaborative tendencies. Complementary indicators such as the A-index, Ab-index and p-index are suggested to fairly rank researchers (García-Villar and García-Santos, 2021).

Regarding data analysis, the techniques used have shown good results, but there are also other methods with which different results would have been obtained. For example, Reference Publication Year Spectroscopy and Words' Frequency over Time for papers; Corresponding Author's Countries and Production over Time for countries; Thematic Evolution and Factorial Analysis for keywords, titles and abstracts. Information about the institutions can be included, in addition to evaluating journal characteristics such as Bibliographic Coupling and productivity according to Bradford's law. Specifically, co-authorship analysis of authors and countries and co-occurrence analysis of keywords showed results according to the minimum number of occurrences leading to a corresponding number of clusters. At least 2 occurrences of authors and countries were considered to reduce bias when presenting collaborative networks and networks with at least 1 occurrence were not selected because the number of data is large, contains many isolated nodes and are difficult to interpret. When analyzing the co-occurrence of keywords, a mínimum of 5 occurrences was established to show a reduced and accurate picture. In addition, when assessing temporal dynamics, important keywords that may have been overlooked were covered.

The analysis included original studies that were highly heterogeneous in terms of type (*in vitro*, animal models and clinical trials), study population (different animals, ages of participants), samples (e.g., type of milk and β-casomorphin) and phenomenon evaluated (e.g., diabetes, gastrointestinal health, cardiovascular disease, neurological conditions, oxidative stress and inflammatory reactions), which made it difficult to synthesize the information. Although some fundamental characteristics of the study designs (dose, frequency and time of intake or exposure) were detailed, they were not evaluated in depth, focusing efforts on showing an overview of this topic. However, shortcomings were noted in several studies such as insufficient sample size, short age ranges, lack of long-term follow-up, lack of blinding, inadequate randomization, and lack of washout period that could have significantly influenced the robustness of the results. Therefore, no solid and generalizable conclusions can be drawn.

5. Conclusion

This work is a first contribution on research trends on the effects of A1 and A2 bovine milk on health, where a low increase in scientific production is observed, highlighting few original articles, mainly clinical trials. A significant number of authors contributed to the field of study, but most were transient (85%) with one published paper, so the authors' publication frequency did not comply with Lotka's law. Similarly, the co-authorship analysis showed that few research groups are active and that efforts are mainly focused on summarizing existing evidence on the topic and conducting reviews. Research is concentrated in Europe and Asia, represented by New Zealand and China with more documents and records (frequency of researchers with Chinese affiliation), respectively. However, no country in Africa or South America has scientific production, which could be associated with factors such as low development in biotechnology and lack of knowledge among the population. This information opens possibilities to determine where to look for experts in the field, to build collaborations between countries and to explore areas that lack scientific studies.

Keyword analysis showed that the influence of BCM-7, A1 or A2 β-casein on multiple health effects was studied. It has been suggested that A1 milk may induce pro-inflammatory and oxidative effects due to the presence of BCM-7, but there is insufficient evidence to associate its consumption with negative health effects and some studies have even shown positive results. However, A2 milk may be better tolerated by the digestive system of some individuals due to its possible modulating role in the intestinal microbiota. The findings obtained are based primarily on *in vitro* and animal studies, and limited clinical trials with poor designs. Therefore, more solid scientific evidence is needed to reach a consensus on the role of A1 or A2 bovine milk on health.

CRediT authorship contribution statement

Jhony Alberto Gonzales-Malca: Methodology, Conceptualization, Formal analysis, Writing – original draft, Funding acquisition. **Vicente Amirpasha Tirado-Kulieva:** Methodology, Conceptualization, Formal analysis, Writing – original draft. **María Santos Abanto-López:** Conceptualization, Writing – review & editing. **William Lorenzo Aldana-Juárez:** Writing – review & editing, Supervision. **Claudia Mabel Palacios-Zapata:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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