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REVIEW ARTICLE

Applications of Bacteriocins of Lactic Acid Bacteria in Biotechnology and Food Preservation: A Bibliometric Review

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Abstract:

Introduction:

Due to the growing prevalence of antibiotic resistance in microorganisms and the demand for safe food, there is increasing interest in using natural bioproducts such as the antimicrobial peptides bacteriocins to extend the shelf-life of foods. This is because of their spectrum of activity, ease of synthesis and applicability. This study reports on the global trends in lactic acid bacteria (LAB) bacteriocins based research publications in the Web of Science core collections within the last 20 years (2000-2019), with specific focus to their applications in biotechnology and food science.

Methods:

Data analysis was undertaken using VOSviewer and HistCite software to evaluate relationships between articles and visualise research linkages amongst authors, institutions and countries.

Results:

In the 20 years under review, a total of 1741 bacteriocin related articles were published, with the most cited publication examining the anti-infective activity of *Lactobacillus salivarius*. The highest research output was recorded by the United States, followed by Spain and China. However, Europe as a continent had the highest research output with a higher inter-institution collaboration network and stronger food safety legislations.

Discussion:

The bibliometric analysis gave insights into the research areas, cooperation network of authors, co-citation maps and co-occurrence of keywords utilized in the research field and indicates that bacteriocin-based research is highly multidisciplinary with a global reach.

Conclusion:

Key focus is on the control of foodborne disease pathogens, search for new producer organisms and approaches to improve bacteriocin yield and application. This class of antimicrobial peptides has the potential to replace chemical food preservatives in the future.

Keywords: Bacteriocin, Lactic acid bacteria, Bibliometric analysis, HistCite, VOSviewer, Food safety, Food security.

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1. INTRODUCTION

There has been a rising trend in the clinical occurrence of drug-resistant microbes in recent times, leading to a high rate of hospitalisations with attendant loss in productivity and associated economic costs [1]. This shows the inadequacies of current prophylactic and therapeutic approaches for microbial disease control. Similarly, there have been growing incidences of foodborne illnesses due to microbial contamination [2], especially in ready-to-eat foods. This increase in microbial resistance to current antimicrobials and the need for safer foods has led research towards alternative antimicrobial agents for food, medical and varied purposes. Within the food safety and food chain system, antimicrobial agents and organic chemicals are employed for food preservation, shelf life extension, and the prevention of food spoilage and foodborne illnesses.

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However, in recent times, consumers have been increasingly demanding minimally processed food products, free from chemical preservatives yet microbiologically safe [3]. Chemical preservatives used in foods may have adverse health effects. An approach to reduce chemical preservatives and mitigate adverse effects associated with them is the use of natural food preservatives. One of such agents is bacteriocins, which are antimicrobial peptides, ribosomally synthesised by a diverse range of lactic acid bacteria (LAB) which have either bactericidal or bacteriostatic effects on bacterial strains closely related to the producers but which do not negatively affect the producer organisms themselves [4, 5]. Bacteriocin production is an adaptation mechanism employed by bacteria in an environment of limited nutrients to aid competition, thus ensuring survivability. Apart from lactic acid bacteria, numerous bacteria genera can produce at least one bacteriocin, although not all have been identified [6]. Bacteriocins have been known by different terminologies, including antimicrobial peptides, antimicrobial proteins [7], bioactive peptides [8], and antimicrobial activity (AMA) peptides [9], amongst others. They are of great interest, especially with regard to food preservation, because of their spectrum of activity and the ease of digestion by the human gastrointestinal tract, thus ensuring that they do not get into the systemic circulation [10].

Bacteriocins have diverse applications as biopreservatives [11]. They can be applied as additives in food either in the crude or purified form by incorporating fermentates of a bacteriocinogenic strain [12]. Furthermore, they can be employed in active packaging of food (such as incorporation into the packaging material for slow release) to extend shelf-life [13] or by the addition of pelleted bacteriocins in semi-permeable sachet into a packaged food which will be slowly released into the food environment throughout the storage period [14]. Unlike antibiotics which are secondary metabolites, bacteriocins are ribosomally synthesised. Thus, they are liable to breakdown by proteases and other proteolytic enzymes [4], making them harmless for human consumption as gastric enzymes in the stomach easily degrade them. Several bacteriocins, including subtilin, cerein, thuricin, and plantaricin, have been characterised and purified for commercial testing, but the most widely utilised is nisin. Nisin is generally regarded as safe and has application as a natural preservative in foods of various origins [15, 16]. A variety of classification schemes have been proposed and applied for bacteriocins. These classifications of bacteriocins are based on the producing bacteria strain, molecular weight, chemical composition or mechanism of action of the bacteriocins. Bacteriocins are generally divided into four groups; Class I bacteriocins contain the uncommon amino acid lanthionine, and class II bacteriocins are small unmodified peptides with molecular sizes less than 10kDa, while class III bacteriocins have molecular weights of more than 10kDA. The class IV bacteriocins, currently termed bacteriolysins are large complexes consisting of carbohydrate and lipid moieties [17].

The bibliometric analysis explores the characteristics of a given set of data by employing mathematical and statistical methods to observe distribution, co-relationships and patterns in the database [18, 19]. The use of bibliometric analysis allows for a better understanding of research trends on a particular topic at a holistic level against a micro-level [20], thus allowing for a comprehensive understanding of the current research direction. This analytical method can be utilized in various disciplines and research topics. It has been used in studies as diverse as Energy performance [21], foodborne diseases [22], and microbiology [23], amongst others. Bibliometric analysis is important as it measures the trend, diversity, productivity and impact of publications in the scientific community and can guide research in the right direction. This is essentially true due to bacteriocins' commercial importance with regards to applications in food preservation, protecting against food poisoning bacteria such as *Listeria monocytogenes* [24], and their potential to replace antibiotics as agents of choice in the treatment of infections. Furthermore, the increasing consumer demand for microbiologically safe food, free of chemical additives [3], whilst maintaining the organoleptic properties of the food can be met by bacteriocins.

Directed analysis of researchers, institutes and countries undertaking leading research on bacteriocins from lactic acid bacteria (LAB) was conducted, allowing the evaluation of collaboration and network strengths between individuals and institutes. Also, the geographical distribution and linkages of published literature on LAB bacteriocins were evaluated. With this bibliometric analysis, gaps in bacteriocin-based research have been identified, and future research perspectives have been discussed. In addition, this article has highlighted the growing field of enquiry and provided insight into the multidisciplinary nature of LAB bacteriocin-based research as well as their applications in biotechnology and food science, providing information for food handling organisations and informing the selection of funding agencies and journals to publish for researchers.

2. BIBLIOMETRIC DATABASE GENERATION

A database was generated for this study by searching the Thomson Reuters Web of Science (WoS) core collection database on November 26, 2020, with the addition of newer publications. The Web of Science was chosen because of its accessibility and wider coverage [25, 26] and taking advantage of the inherent inclination of this search engine to English language publications in the natural sciences and engineering [27]. Furthermore, WoS includes a full index of all authors associated with a paper, institutional addresses and bibliographic references of each article, thus allowing for easy analysis with an interdisciplinary coverage [28]. A focused terminology search was performed on WoS core collection using the keywords: (bacteriocin OR “bacteriocinogenic lactic acid bacteria” OR “lantibiotics”) on the basic search tab, selecting the “Title” option, which allowed an extensive search of publications with the selected keywords in the title only, thus retrieving articles directly involved in bacteriocin research. The Boolean operator (" ") was used to obtain results matching the exact keywords as written in the search box without alterations. These search criteria were utilized to build a comprehensive database for LAB bacteriocin-based research. A 20-year range was applied between 2000 and 2019. This year range was chosen to represent current research trends in the field, allowing for a wider view of how research focus has shifted within this period. Furthermore, very few articles were published before the year 2000 and these publications may have become obsolete due to advances in the research area and new information. The database obtained was filtered/refined to select only research journal articles. This is because they are considered to be original research activities which can be used to infer technological improvements and analytical skillsets being employed in bacteriocin based research. Similarly, non-English language articles were excluded. The selected articles were preliminarily classified using WoS analytical tools before being imported. They were indexed into Clarivates HistCite (12.03.17) software for collation and then into Microsoft Excel spreadsheet for vetting. Vetting was undertaken by individually reviewing the paper title, publishing journal, author names and affiliations to avoid repetition and ensure they were bacteriocin related. When duplications occurred, they were manually deleted. The obtained data were classified based on year of publication, country of origin, citations, author affiliations and funding agencies.

Vosviewer software (1.6.13) [29] was employed to visualize and analyse the bibliometric networks to gain an in-depth view of research trends. Different maps were created, and these include; co-authorship maps to show the level of collaboration amongst experts in the field, co-citation maps showing the journal articles that were most cited together and keyword co-occurrence maps which gives an idea of keywords mainly used in bacteriocin research and are very important to inform future researchers when retrieving published resources. Author affiliation and country maps show which institutions and countries are at the forefront of bacteriocin research. Vosviewer was chosen as the analysis software because of its inherent ability to link research by various parameters such as country, journals, institutions, authors *etc*., grouping them into clusters while providing link strength and connections of the papers. In addition, an overlay visualization is possible showing the activities during the period of study. Fig. (**1**) Presents a flowchart utilized for dataset retrieval and analysis.

3. TRENDS IN BACTERIOCIN PUBLICATION

Using the defined search criteria of ("bacteriocin" OR "bacteriocinogenic lactic acid bacteria" OR "lantibiotics") and refining this further to research articles published in English language only, a database was generated with 1,741 articles written by 4892 authors in 414 journals with a total of 26,954 cited references and 5060 keywords within the 20 years evaluated (2000-2019).

3.1. Yearly Distribution and Research Output

Within the 20 years of analysis, there was a steady increase in the research output in the later years, compared to the year 2000, with a spike recorded in 2012 and 2015. The year 2012 had the highest research output at 124 publications, while the lowest was recorded in 2001 with a total of 55 publications. This trend in the publication is given in Fig. (**2**).

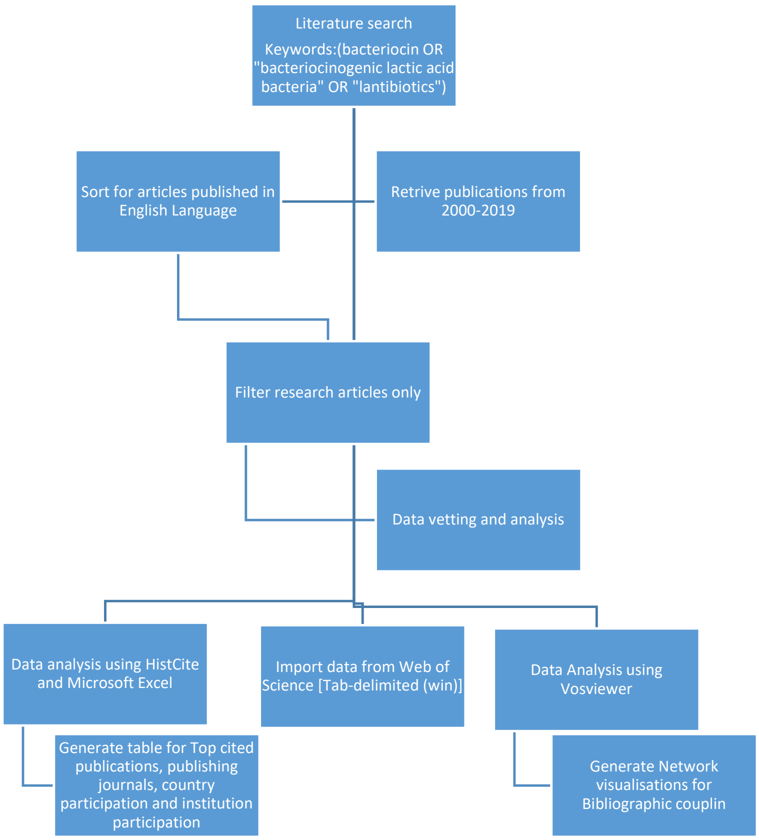

Fig. (1). Data retrieval and analysis flowchart.

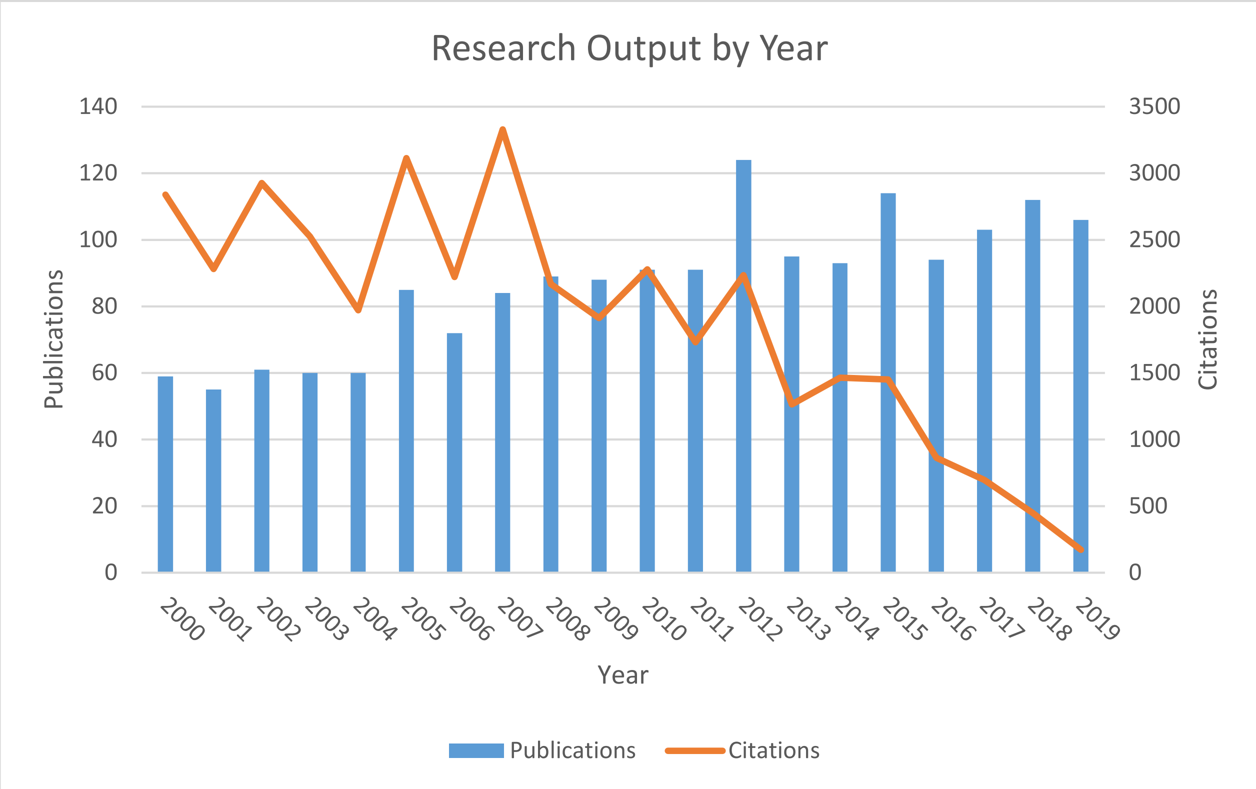

Fig. (2). Number of publications and citations per year for bacteriocin-related research between 2000 and 2019.

The bacteriocin research field is a fast-growing one with almost a doubling in the total research output in the 20 years of study, as shown in Fig. **2**. This can be attributed to increased awareness of bacteriocins, public perception/acceptance and the approval of bacteriocins for commercial usage. Specifically, this growth can be linked to the authorization of the bacteriocin Nisin in the EU as a food additive under Annex II of EC Regulation 1333/2008 which permitted its use in various food categories after evaluation of its safety in 2006 by the EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food [30]. Furthermore, this period coincides with a rise in antimicrobial resistance to commonly used antibiotics, especially in farm animals. This increase in antimicrobial resistance can result in the development of zoonotic diseases as antibiotic-resistant bacteria of animal origin have been shown to persist in meats and other foods of animal origin in retail outlets, causing subclinical colonization of the gastrointestinal tract of man, systemic circulation and clinical infections [31]. It can also be inferred that the constant increase in the number of papers published per year shows the potential for growth in the research area, highlighting the commercial viability of bacteriocins and their biotechnological applications in the food and pharmaceutical sectors [32]. Furthermore, there are vast areas of enquiry on bacteriocin research which has not been exploited, including the use of cutting-edge bioengineering tools to aid in their discovery as they are gene-encoded and ribosomally synthesised [33], which can lead to the production of diverse bacteriocins with improved specificity and activity tailored to specific applications [34]. These vast research gaps drive the increase in yearly research output. On the hand, there was a continual gradual decline in the number of citations averaged per year. This decline in citation does not mean a decline in research intensity as newer publications tend to have lower citations than older articles.

LAB bacteriocin research in the years of study was mainly related to the following areas:

- Microbiology
- Biotechnology and applied microbiology
- Food science and technology
- Biochemistry and molecular biology

Because of the interdisciplinary nature of the research involved and the application of bacteriocins in various fields, there were overlaps in the categorization of articles; thus, some articles belonged to more than one category. Of all the published articles, 840 were published under the microbiology category, accounting for 48.2% of total publications. Microbiology is expected to be top on the list because bacteriocins are microbial products, and most research is geared towards synthesizing new bacteriocins from microorganisms. Also, among the top category is; biotechnology applied microbiology with 632 publications and food science technology with 452 publications, highlighting that research is focused on the biotechnological application of bacteriocins and their potential use in food science for the biopreservation of food products. The treemap (Fig. **3**) provides a visualization of the top 10 categories of research as grouped by the web of science database.

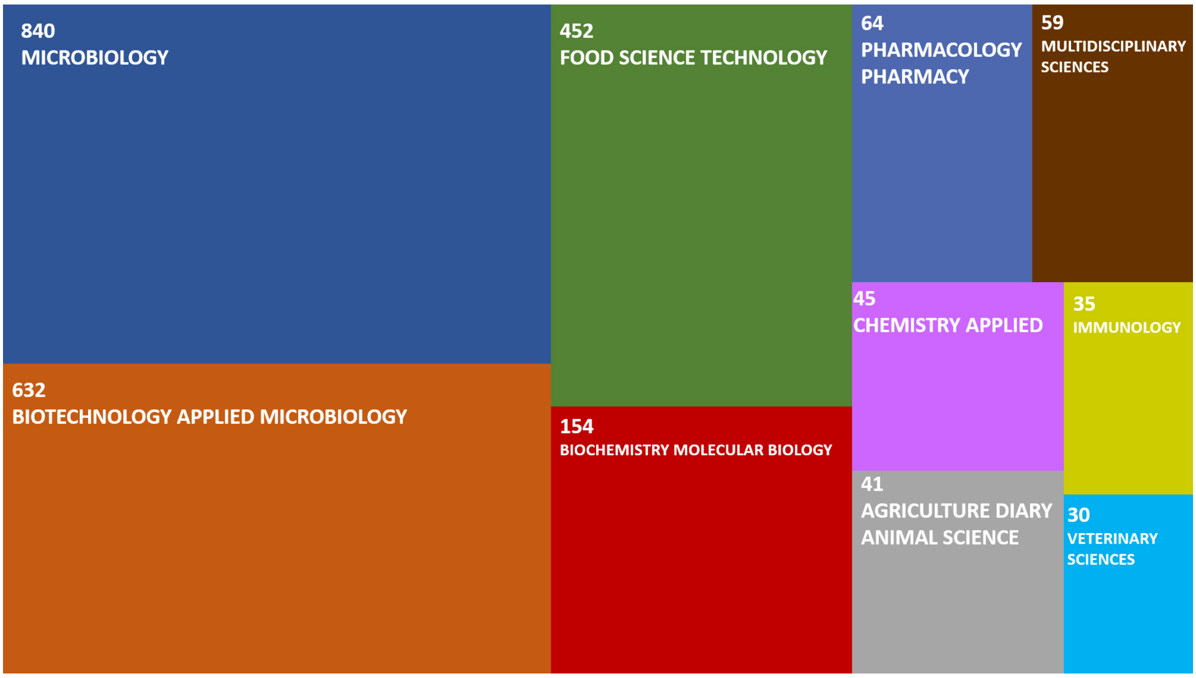

Fig. (3). Tree-map representing research categories of bacteriocin-related publications between 2000 and 2019.

3.2. Research Output by Country/Region

The country of origin of each article can be deduced using the first author's address and affiliation. The collated database shows that publications on bacteriocin research have emanated from 79 countries, representing about a third of the countries in the world. While this represents a wide geographical spread, only 15 of these countries have a minimum of 50 publications, responsible for 82% (1428) of total publications. In these top 15 countries, there are three countries from North America, seven from Europe, four from Asia and one from Africa. All listed countries belong to the top world economies within their regions. The highest number of publications was recorded by the United States of America (165), followed by Spain (151) and the People's Republic of China (145), indicating that these countries are leading the research in bacteriocins and antimicrobial peptides. Amongst all the countries, the highest citation was recorded by the United States of America (4654), followed by Spain (4723) and Norway (2735). The country data on published literature on bacteriocins are presented in Table **1**. The table highlights the total papers, total citations in published literature and average citations per publication for the 15 countries with more than 50 publications.

Table 1. Research Output on bacteriocin-related research by country between 2000 and 2019.

S/N	Country	Total Publications	%	Total Citation	Average Citation per Publication	Most cited Document
1	USA	165	9.48	4654	28.21	[35]
2	Spain	151	8.67	4723	31.28	[36]
3	Peoples Republic of China	145	8.33	2248	15.50	[37]
4	India	126	7.24	1343	10.66	[38]
5	Brazil	116	6.66	2165	18.66	[39]
6	Japan	105	6.03	2073	19.74	[40]
7	France	94	5.40	2350	25.00	[41]
8	South Korea	91	5.23	1437	15.79	[42]
9	Norway	78	4.48	2735	35.06	[43]
10	Canada	68	3.91	2003	29.46	[44]
11	Italy	66	3.79	1654	25.06	[45]
12	Germany	61	3.50	1921	31.49	[46]
13	Belgium	57	3.27	1651	28.96	[47]
14	Ireland	55	3.16	2433	44.24	[48]
15	South Africa	50	2.87	2063	41.26	[49]

The United States of America had both the highest number of published articles and the highest citations, followed by Spain. This is consistent with research trends in antibiotics and drug resistance [50]. Although the United States of America recorded the highest publication and citations, the country with the highest average citation per paper was the Republic of Ireland, thus indicating that the articles published in the country had the most significant impact within the field, followed by South Africa. With regards to the application of bacteriocin-based research, the United States of America is leading. In the USA, nisin, a Type A (1) lantibiotic, was the first bacteriocin to receive FDA approval as a generally regarded as safe compound (GRAS) for food preservation purposes [51] and has been efficacious because of its wide spectrum of antimicrobial activity against both Gram-positive and Gram-negative organisms. Furthermore, the compound has an immunomodulatory function that can activate the adaptive immune response and cancer prevention is being applied medically for therapeutical purposes [51]. Conversely, countries with the least number of publications (1) include; Barbados, Bosnia & Herzegovina, Cuba, Cyprus, Latvia, Mongolia, Qatar, Republic of Congo, Senegal, Sudan and Zimbabwe.

Categorization of all countries based on continent reveals that Europe had the highest participation at 39.24% (31), followed by Asia at 26.58% (21), Africa at 16.45% (13), South America at 8.86% (7), North America at 6.32% (5) and Australia 2.53% (2). This continental distribution is displayed in Fig. **4**. The higher participation of European nations in bacteriocin-based research can be attributed to the emphasis of the European Food Safety Agency on regulating the amount and type of food additives in foods, thus necessitating the need for alternative approaches to food preservation free from chemical additives as exemplified in commission regulation (EU) No 1129/2011 which set out limits for food additives, much lower than acceptable limits in other countries [52].

A visualization of the linkages between the 15 countries with 50 publications and above is presented in Fig. **5**. The country nodes' size indicates the country's contribution level (number of publications). Similarly, lines linking the partnering countries and the thickness represent the strength of such partnerships. These indicators can measure the network strength, co-authorships and co-citations between two country nodes [29]. The visualization shows 105 linkages between the countries. These countries are grouped into two (green and red) clusters based on their collaboration and contribution to article publication. The clusters are differentiated by colours, with countries in the same cluster more strongly linked and connected. Furthermore, the number of papers published in a country can be represented by the size of the circle. Most European nations (Spain, Germany, Ireland, and Norway) belong in cluster 2 (green) with the USA and Canada. This shows a strong regional collaboration amongst the European nations in bacteriocin research. The United States of America has the highest total link strength, collaborating in 167 documents with all the countries. This can be attributed to the number of participatory institutions in this country. This was followed by Spain, which collaborated on 151 documents spread among all the countries. All the featured countries have 14 links, meaning there were collaborations with all listed countries. Spain and Norway recorded the strongest collaboration between the two countries. This analysis shows that bacteriocin-based research is multinational and cuts across geographical regions with collaboration between authors and institutions in different countries and continents.

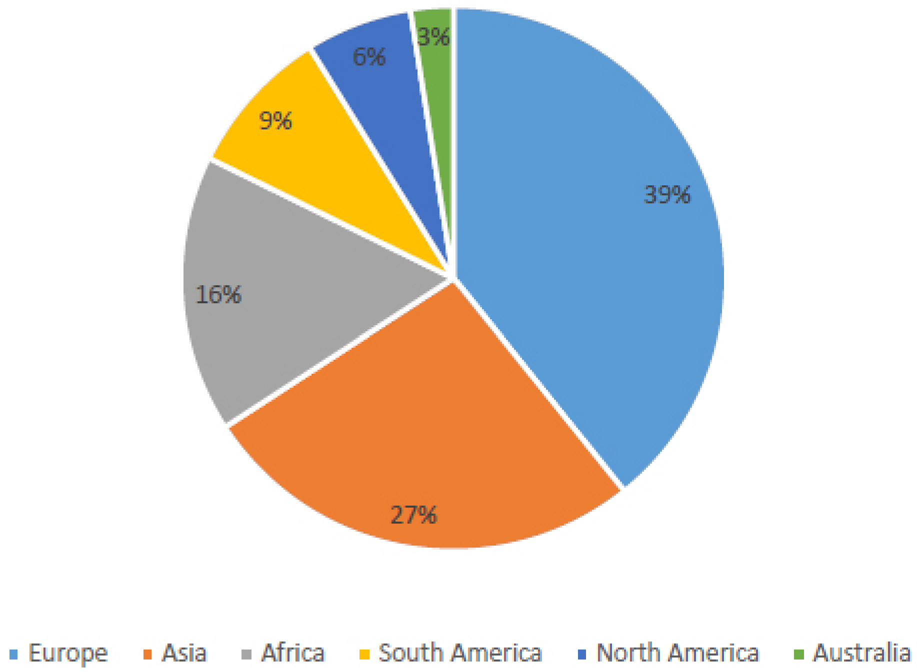

Fig. (4). Number of publications by continent on bacteriocin-related research between 2000 and 2019.

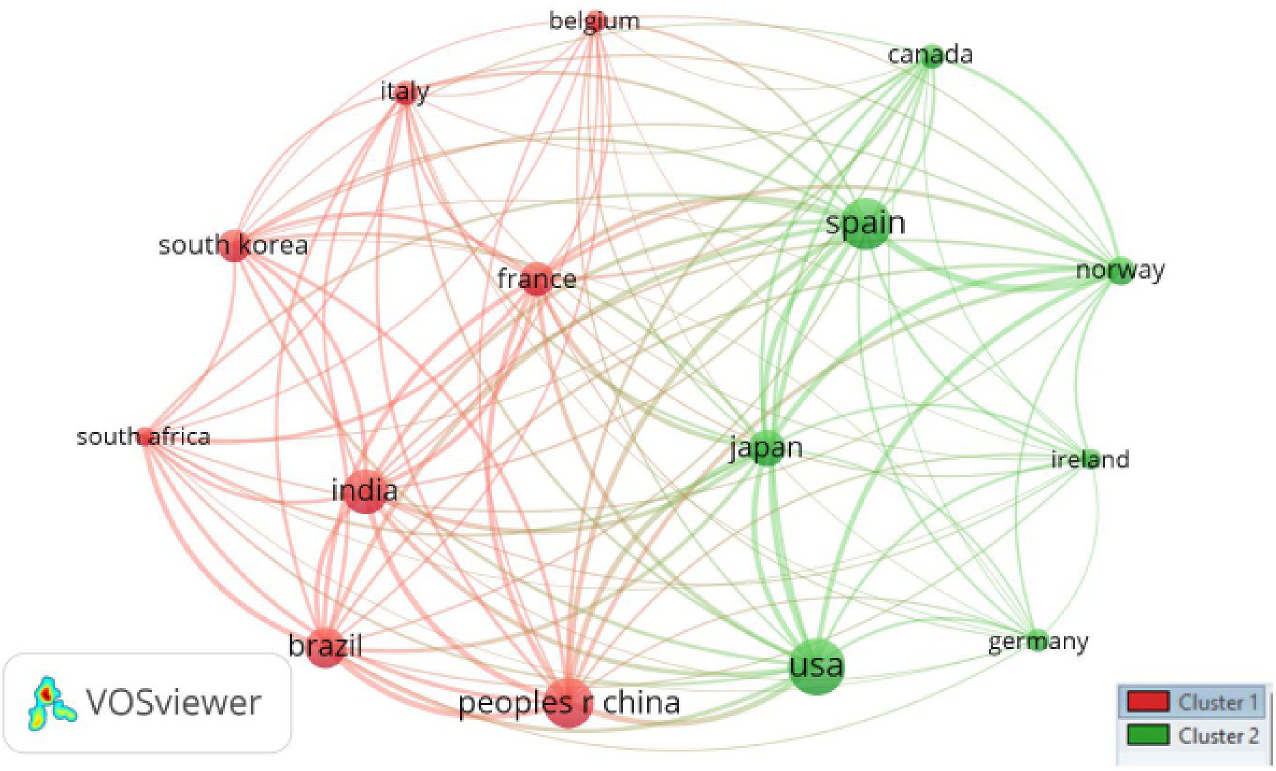

Fig. (5). Network visualization of bibliographic coupling (collaboration) amongst countries with a minimum of 50 publications in bacteriocin-related research between 2000 and 2019.

3.3. Research Output by Institutions

A total of 1391 institutions contributed to bacteriocin-related research as collated on the database. The research output by institutions indicates that the highest paper publications were by authors from the University of Sao Paulo in Brazil (50), followed by the University of Stellenbosch (49), The Spanish National Research Council (Consejo Superior de Investigaciones Científicas, CSIC) (34 publications) and Kyushu University with 32 publications (Fig. **6**). It is of note that although the United States of America had the highest total number of publications and citations, no institution individually from that country featured in the first 10 rankings, thus pointing out that the high output may be related to the large numbers of institutions within the country, GDP and funding available for research [53]. In total, 17 institutions had 20 publications or above, representing 27.68% of the total research output. This information is depicted in Fig. (**6**).

Among the 17 universities with 20 publications or above, Norway had the highest number of representing universities (3), followed by Japan and the Republic of Ireland with 2 representing institutions. Although the University of Sao Paulo had the highest research output at 50, the University of Stellenbosch, with 49 papers, had a higher number of citations (2039) compared to the 833 recorded by the University of Sao Paulo, thus confirming that this university is the leading institute in bacteriocin based research with respect to citation and visibility of publications. Similarly, the National University of Ireland, with only 25 publications, had a very high number of citations (1533), highlighting that an institution's impact on the research field is not solely dependent on the number of publications. The analysis further indicated that Europe is the hotbed of bacteriocin research as 11 of the 17 top publishing institutions are European.

The bibliographic coupling of the selected literature to evaluate the strength of partnerships between institutions with over 20 publications is shown in Fig. (**7**). Each node on the figure denotes an institution, while the colours represent different clusters. The institutions are grouped into two clusters. Institutions in the same cluster are more connected in their research collaboration and output than those from other clusters. However, it is interesting to note that all the top 17 institutions listed were strongly linked. The strongest linkage is between the University of Stellenbosch and the University of Sao Paulo in the green cluster, the two universities with the highest number of publications. This is followed by the University of Oslo and the Norwegian University of Life Sciences in the red cluster. The strong linkage between the University of Oslo and the Norwegian University of Life Sciences may be because they are from the same country; thus, research collaboration is more natural.

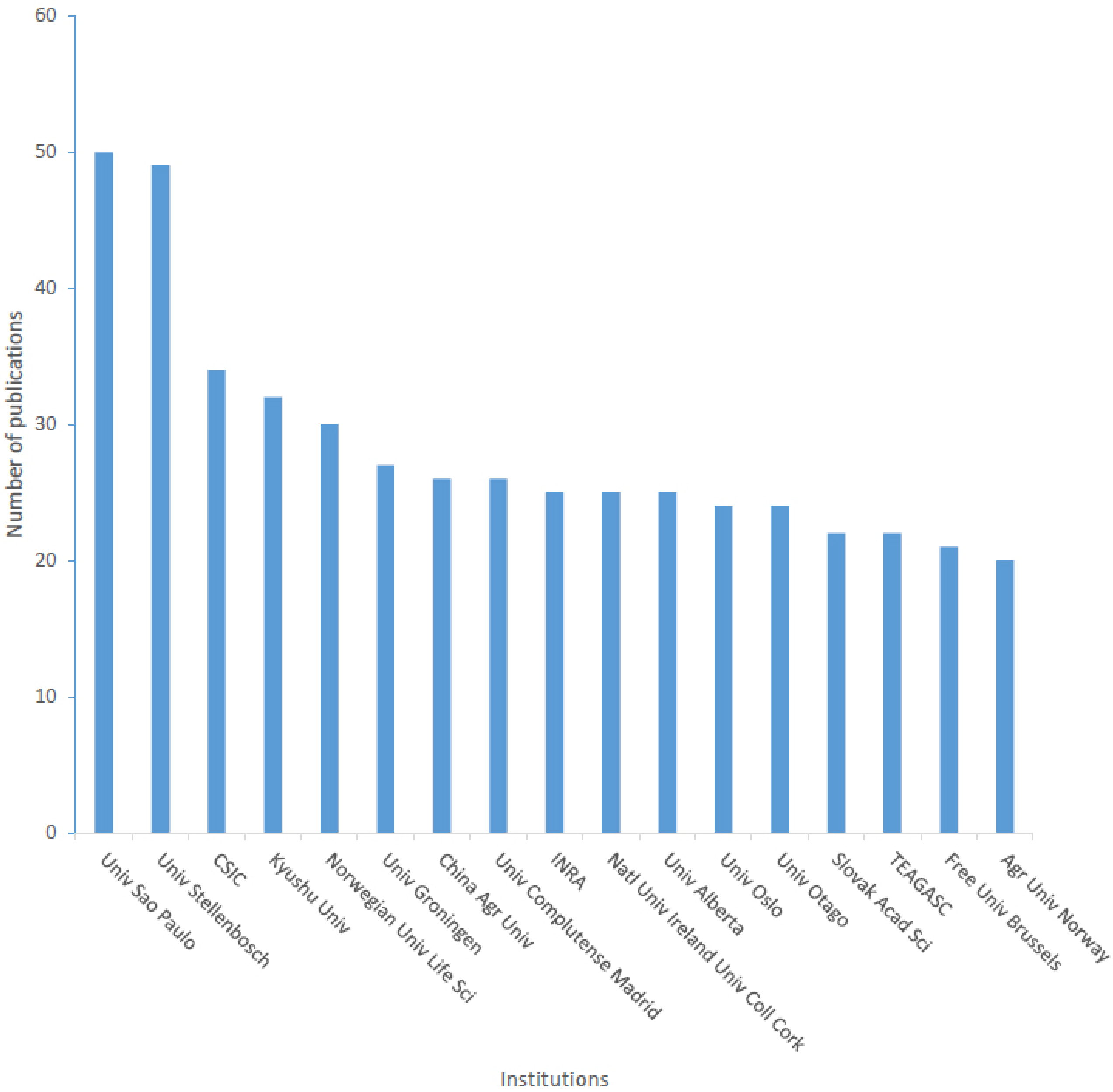

Fig. 6. Number of Publications by institutions on bacteriocin-related research between 2000 and 2019.

3.4. Research Output by Authors

Analysis of publications and citations by authors enables the mapping of co-author relationships, which helps identify the most productive individuals within the field and their affiliations. A total of 4892 authors were involved in bacteriocin-based research in the period under review. There were 14 authors with 20 or more publications to their name. The highest number of publications was by Todorov, S.D. of the Federal University of Viçosa, Brazil, with 56 publications and 1642 citations in the Web of Science database (Table **2**) with key research focus on the screening of bacteriocin producers, characterisation of produced bacteriocins and their application in inhibiting bacteria foodborne pathogens. The next author with a high citation score is Dicks, L.MT. of the University of Stellenbosch, South Africa, with 42 publications and 1702 citations. The highest citation score of 1721 citations was recorded by Nes, I.F. of the Agricultural University of Norway, the third-highest published author with 38 publications. The high citation score of his publications shows the overarching importance and relevance of the studies in bacteriocin research, indicating that he is the most visible author in bacteriocin-based research. This author's works mainly revolve around the production of bacteriocins by different bacteria genera and exploring the genetic/molecular basis of their productions. Although the number of citations a manuscript or an author receives does not always correlate with impact, it shows the visibility of the article and its influence within the research sphere.

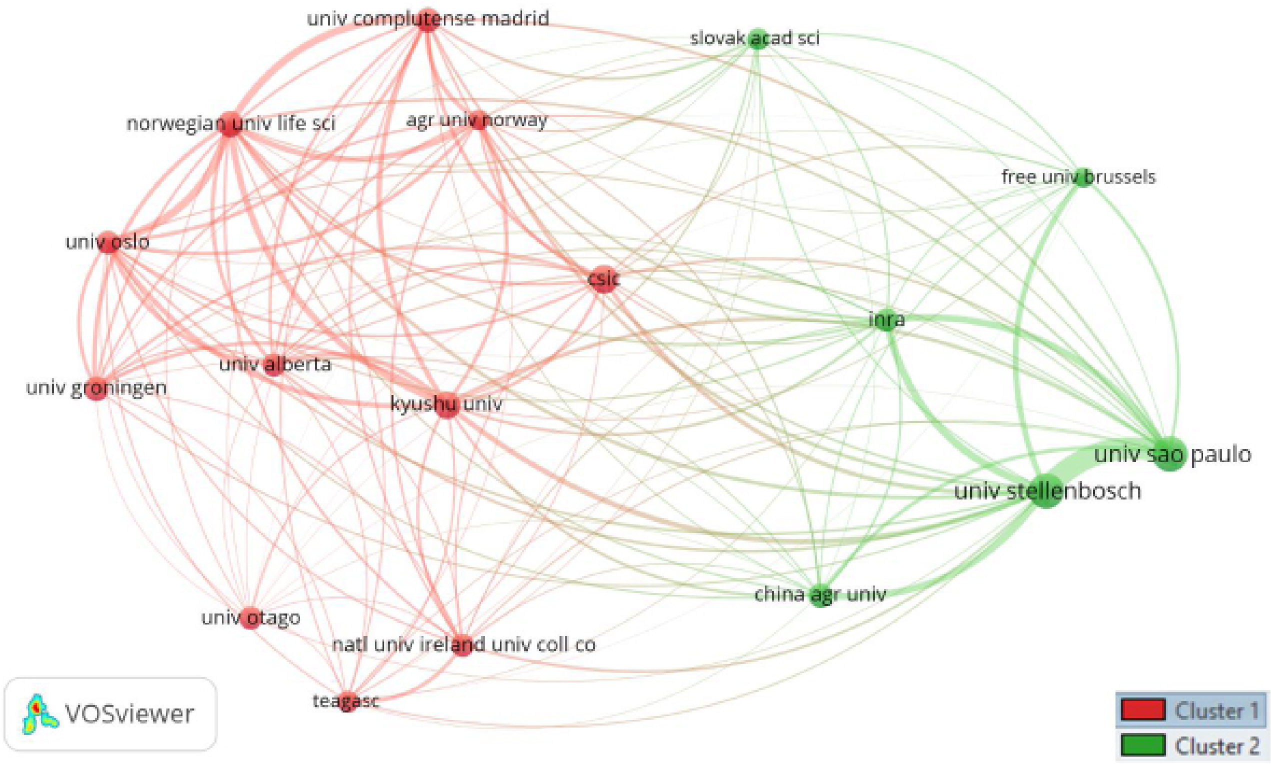

Fig. (7). Bibliographic coupling of bacteriocin-based research publications by institutions with a minimum of 20 research articles.

Table 2. Author contribution to bacteriocin-related publications between 2000 and 2019.

S/N	Author	Publications	Percent (%)	Citations
1	Todorov SD	56	3.22	1642
2	Dicks LMT	42	2.41	1702
3	Nes IF	38	2.18	1721
4	Sonomoto K	32	1.84	827
5	Hill C	31	1.78	1486
6	Zendo T	31	1.78	815
7	Diep DB	30	1.72	729
8	De Vuyst L	28	1.61	1204
9	Ross RP	28	1.61	961
10	Hernandez PE	27	1.55	733
11	Cintas LM	24	1.38	680
12	Herranz C	23	1.32	668
13	Brandelli A	20	1.15	820
14	Nakayama J	20	1.15	629

Fig. **8**. presents a network visualisation of authors who have been cited together. The co-citation of two different authors by a single publication indicates the relatedness of the authors' published work and impact. This is a straightforward approach to establishing connections between authors [54]. For simplicity of data analysis, this was limited to the visualization of authors with a minimum of 100 citations and are cited together in at least 1 published article.

The VOSviewer analysis shows that only 48 authors met the criteria. The authors were grouped into three clusters (red, green and blue). Todorov, S.D. was the highest co-cited author in the green cluster with 640 citations. The highest co-cited author in the red cluster was Cotter, P.D., with 436 citations, while the highest co-cited author in the blue cluster was Citas, L.M. The pairing of authors with the strongest co-citation strength revealed that Todorov, S.D. (Federal University of Viçosa, Brazil) and Klaenhammer, T.R. (North Carolina State University, USA) had the strongest co-citation strength, followed by Todorov, S.D. and Parente, E (University of Basilicata, Italy).

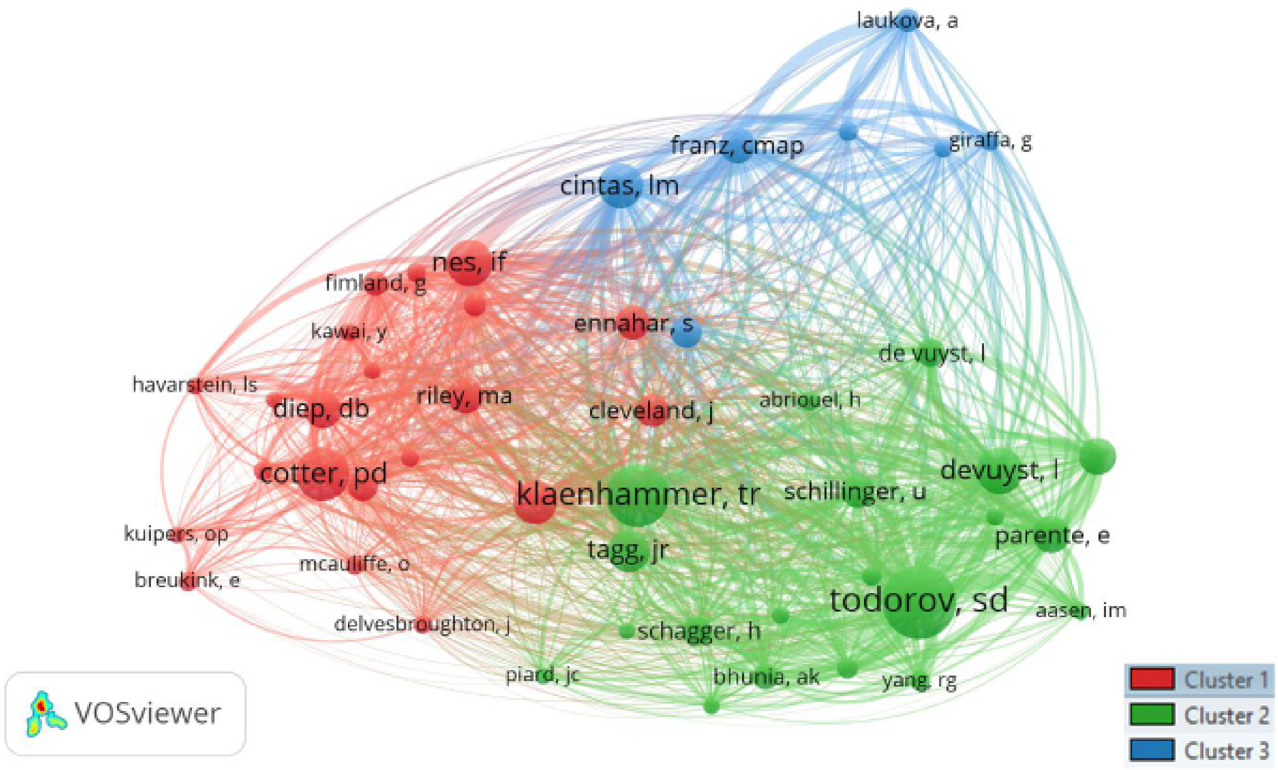

Fig. (8). Network visualization of co-citation of authors with a minimum of 100 citations in bacteriocin-related research between 2000 and 2019.

3.5. Co-occurrence of Keywords

Co-occurrence of keywords used by authors indicates the relevance of these keywords in describing and retrieving research articles on bacteriocins. A total of 5060 keywords were used; 24 occurred a minimum of 100 times. The most encountered keywords are "Bacteriocin" (666), "Lactic-acid bacteria" (541), "Purification" (439), "Nisin" (261) and "*Listeria monocytogenes*" (214). The spread of the keywords indicates that the most prevalent focus of bacteriocin research is the identification of producer strains, their source, type of bacteriocin, characterization and application of produced bacteriocins. Analysis of the co-occurrence of keywords that have occurred a minimum of 60 times groups the keywords into three clusters (green, red and blue), as seen in Fig. **9**. The number of times a keyword appears is calculated as its link strength and indicates the relevance of such keyword within the research domain under evaluation. The blue cluster is focused on the antimicrobial activity of bacteriocins, their production and purification. Within this cluster, the predominant keyword is "bacteriocin," which has a total link strength of 2151 and co-occurred most frequently with lactic-acid bacteria (link strength = 233). This is followed by bacteriocin and purification (Link strength = 218) and lactic acid bacteria with purification (link strength = 172). The green cluster focused more on the bacteriocin-producing strains, pathogens and types of bacteriocin. Within this cluster, the predominant keyword is "Nisin," which has a total link strength of 261 and co-occurred most frequently within the cluster with *"Listeria monocytogenes"* (Link strength = 50) and "Inhibition" (Link strength = 42). The red cluster deals more with the characterization and properties of bacteriocins, with the most prevalent keyword being "Identification" with a total link strength of 780, co-occurring most frequently within the cluster with "Biosynthesis" (Link strength = 23) and "Immunity" (Link strength = 22).

Keyword analysis of bacteria species indicates the highest co-occurring bacterial keyword was *Listeria monocytogenes* which has a total link strength of 864 in 42 links. It is strongly connected to the bacteriocin nisin, indicating that research focuses mainly on this pathogen in food and food products and its inhibition using nisin. *Listeria monocytogenes* is a Gram-positive foodborne pathogen that causes gastroenteritis, abortion, and meningitis and is associated with epidemic listeriosis [55]. Therefore, its inhibition is vital due to the rising pattern of resistance to multiple antibiotics previously effective in its control [56]. Similarly, several correlations were seen between bacteriocin and bacteriocin-producing organisms, including "*Lactococcus lactis"* (Link strength = 46) and "*Lactobacillus plantarum"* (Link strength =39). *Lactobacillus plantarum* is a common bacteria in food and can be present in various sources, including fruits, dairy products, vegetables and cereals [57]. They produce various class IIb bacteriocins called plantaricin, which has application in food quality control, especially regarding inhibition of *Listeria monocytogenes.*

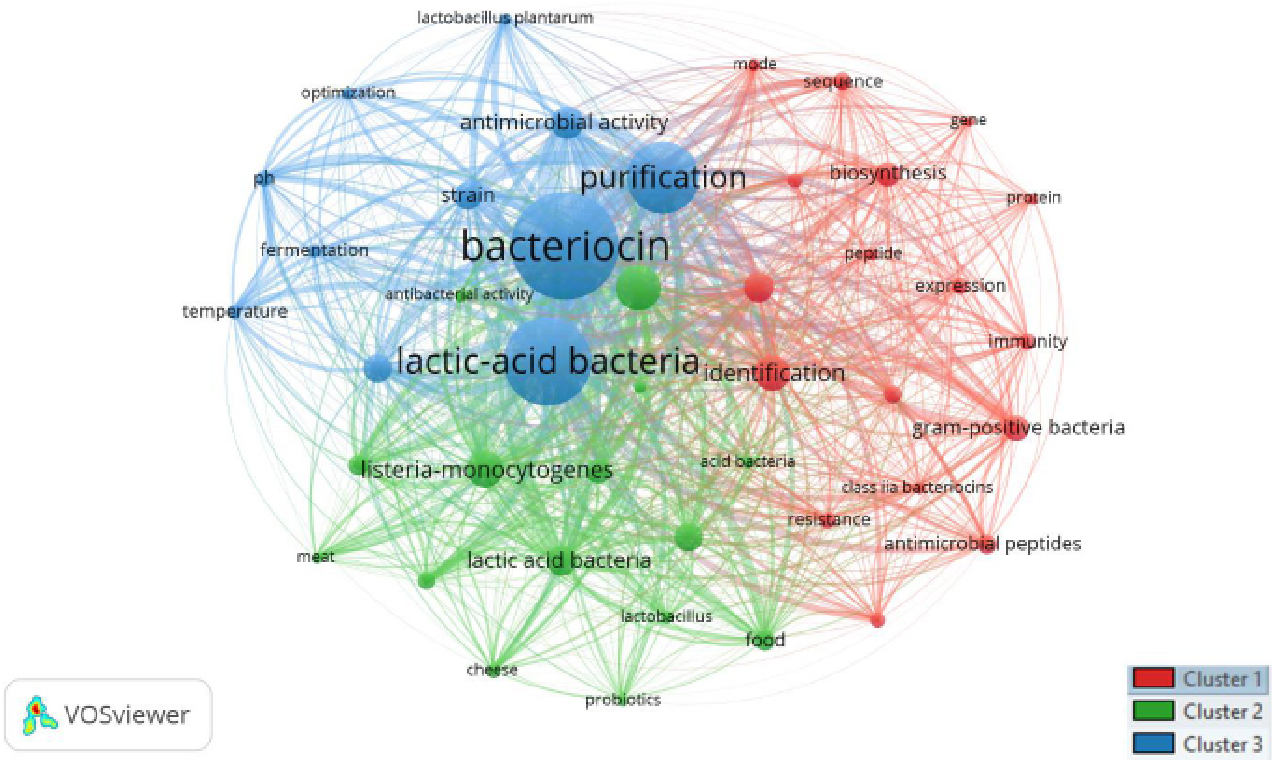

Fig. (9). Co-occurrence of keywords used a minimum of 60 times in bacteriocin-related research between 2000 and 2019.

3.6. Research Output by Journals

A total of 414 journals were involved in bacteriocin-based research publications. The prevalent journal for bacteriocin bacteriocin-based research publication in Applied and Environmental Microbiology has 120 publications and a total citation of 4471. This is followed by the Journal of Applied Microbiology, with 74 publications and 2638 citations. The 414 journals which published a total of 1741 publications indicate an average of 4.20 papers per journal. Of the journals, 4 (Applied and Environmental Microbiology, Journal of Applied Microbiology, Food Control and International Journal of Food Microbiology) had more than 50 publications. Overall, a total of 26 journals had a minimum of 15 publications and is presented in Table **3**. The majority of the top publishing journals have a high impact factor, as seen from the table, which is an important index for the measurement of the significance of a journal [58].

Table 3. Publications on bacteriocin-related research by Journal house between 2000 and 2019.

S/N	Journal	Impact Factor	Publications	Citation	Average Citation
1	Applied and Environmental Microbiology	4.077	120	4471	37.258
2	Journal of Applied Microbiology	2.683	74	2638	35.649
3	International Journal of Food Microbiology	4.006	58	3178	54.793
4	Food Control	4.248	58	1427	24.603
5	Probiotics and Antimicrobial Proteins	2.962	37	301	8.135
6	Journal of Bacteriology	3.234	33	1248	37.818
7	Letters in Applied Microbiology	1.805	31	853	27.516
8	Food Microbiology	4.089	28	1044	37.286
9	Journal of Microbiology and Biotechnology	1.975	27	320	11.852
10	Microbiology-SGM	1.922	27	1283	47.519
11	FEMS Microbiology Letters	1.994	26	661	25.423
12	Journal of Food Protection	1.559	24	523	21.792
13	Antimicrobial Agents and Chemotherapy	4.715	23	846	36.783
14	World Journal of Microbiology & Biotechnology	2.652	23	323	14.043
15	Current Microbiology	1.595	19	396	20.842
16	African Journal of Microbiology Research	0.539	18	104	5.778

(Table 3) contd.....

S/N	Journal	Impact Factor	Publications	Citation	Average Citation
17	Annals of Microbiology	1.431	18	117	6.500
18	BMC Microbiology	3.287	18	584	32.444
19	Brazilian Journal of Microbiology	2.857	18	316	17.556
20	Applied Biochemistry and Biotechnology	2.14	17	244	14.353
21	Frontiers in Microbiology	4.259	17	77	4.529
22	Scientific Reports	4.011	17	221	13.000
23	Applied Microbiology and Biotechnology	3.67	16	445	27.813
24	LWT-Food Science and Technology	3.714	16	226	14.125
25	Molecular Microbiology	3.649	15	831	55.400
26	PLOS One	2.776	15	342	22.800

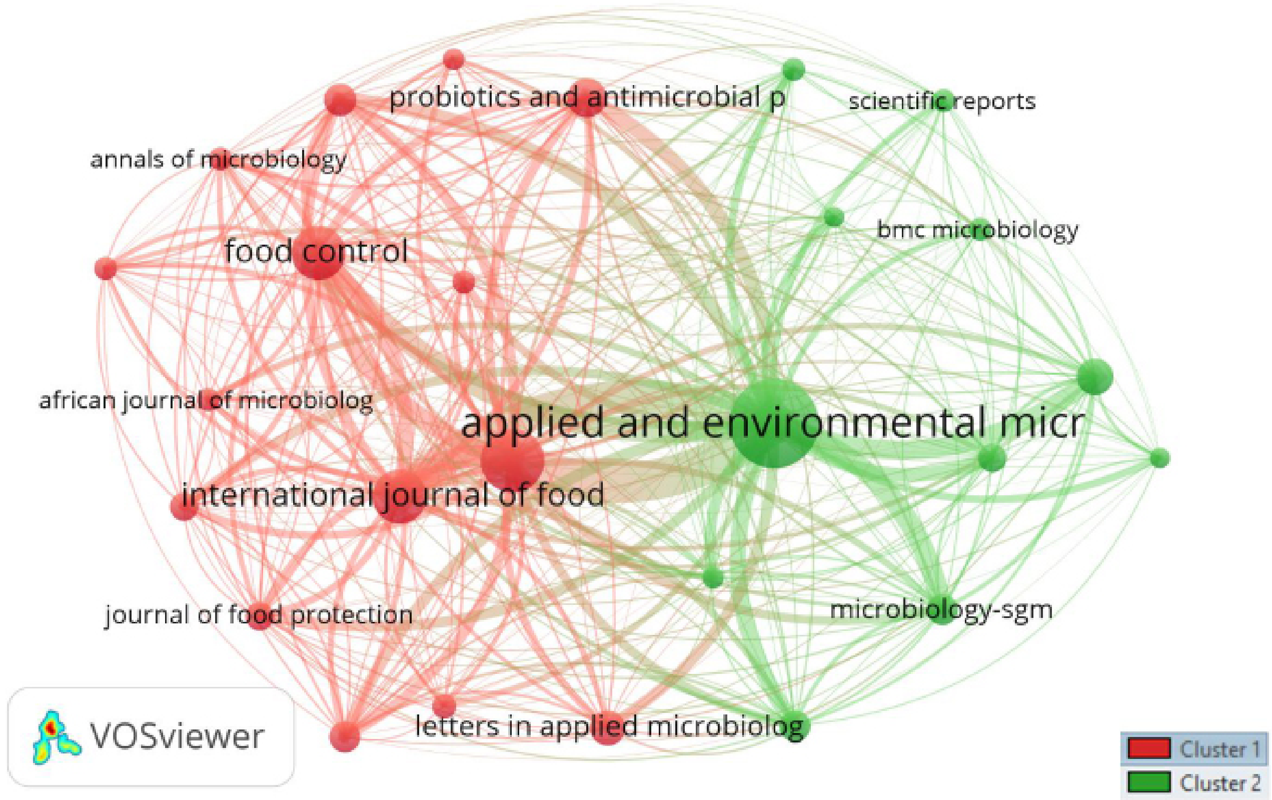

Fig. (10). Bibliographic coupling with relation to publications sources with a minimum of 15 articles in bacteriocin-related research between 2000 and 2019.

The visualisation of the 26 journals with more than 15 publications is shown in Fig. (**10**). It highlights the co-citation association of articles published within them. As indicated in Table **3**, Applied and Environmental Biology have the strongest total link strength, with connections to all the top papers. This is closely followed by the Journal of Applied Microbiology and the International Journal of Food Microbiology. The strongest link was between the Journal of applied microbiology and the Applied and environmental Biology journal, and the International Journal of Food Microbiology and Applied and Environmental microbiology. The visualization shows that these three journals are the leading sources of information on bacteriocin-based research, and articles published within these journals are closely related. This is expected as the scope of these journals is in applied microbiology research, a niche for bacteriocin-based research. Similarly, the International Journal of Food Microbiology has amongst its focus subjects related to food preservation and shelf life elongation, which is the thrust of most bacteriocin-based research.

In terms of citation, the top 26 journals identified (6.28%) out of a total of 414 journals had 23019 (60.75%) of the total 37,887 citations. This shows the high impact and contribution of these journals to the research field. Although Applied and Environmental Microbiology has the highest number of publications and citations, the International Journal of Food Microbiology had the highest average citation of 54.793, thus, showing that bacteriocin research articles published in it are highly cited (Table **3**).

Table 4. Highest cited articles in bacteriocin-related research between 2000 and 2019.

S/N	Author	Title	Citation	Journal	Year	Citation Intensity	Refs
1	Corr SC, Li Y, Riedel CU, O'Toole PW, Hill C, *et al*.	Bacteriocin production as a mechanism for the anti-infective activity of *Lactobacillus salivarius* UCC118	464	Proceedings of the National Academy of Sciences of The United States of America	2007	4.33	[48]
2	Leverentz B, Conway WS, Camp MJ, Janisiewicz WJ, Abuladze T, *et al*.	Biocontrol of Listeria monocytogenes on fresh-cut produce by treatment with lytic bacteriophages and a bacteriocin	249	Applied and Environmental Microbiology	2003	8.04	[35]
3	Rea MC, Sit CS, Clayton E, O'Connor PM, Whittal RM, *et al*.	Thuricin CD, a posttranslationally modified bacteriocin with a narrow spectrum of activity against *Clostridium difficile*	248	Proceedings of the National Academy of Sciences of The United States of America	2010	8.10	[44]
4	Aasen IM, Moretro T, Katla T, Axelsson L, Storro I	Influence of complex nutrients, temperature and pH on bacteriocin production by *Lactobacillus sakei* CCUG 42687	192	Applied Microbiology and Biotechnology	2000	10.42	[43]
5	Li C, Bai JH, Cai ZL, Fan OY	Optimization of a cultural medium for bacteriocin production by Lactococcus lactis using response surface methodology	181	Journal of Biotechnology	2002	11.06	[37]
6	Cintas LM, Casaus P, Herranz C, Havarstein LS, Holo H, *et al.*	Biochemical and genetic evidence that *Enterococcus faecium* L50 produces enterocins L50A and L50B, the sec-dependent enterocin P, and a novel bacteriocin secreted without an N-terminal extension termed enterocin Q	177	Journal of Bacteriology	2000	11.30	[36]
7	Flynn S, van Sinderen D, Thornton GM, Holo H, Nes IF, *et al*.	Characterization of the genetic locus responsible for the production of ABP-118, a novel bacteriocin produced by the probiotic bacterium *Lactobacillus salivarius* subsp *salivarius* UCC118	169	Microbiology-SGM	2002	11.85	[60]
8	van der Ploeg JR	Regulation of bacteriocin production in *Streptococcus muttans* by the quorum-sensing system required for the development of genetic competence	155	Journal of Bacteriology	2005	12.94	[61]
9	Stern NJ, Svetoch EA, Eruslanov BV, Perelygin VV, Mitsevich EV, *et al.*	Isolation of a *Lactobacillus salivarius* strain and purification of its bacteriocin, which is inhibitory to *Campylobacter jejuni* in the chicken gastrointestinal system	155	Antimicrobial Agents and Chemotherapy	2006	12.94	[62]
10	Kommineni S, Bretl DJ, Lam V, Chakraborty R, Hayward M, *et al*.	Bacteriocin production augments niche competition by enterococci in the mammalian gastrointestinal tract	151	Nature	2015	13.34	[63]

3.7. Highest Cited Articles

A search for the most prominent publications showed that 10 papers had citations above 150. These are highlighted in Table **4**. The most impactful article in bacteriocin research is "Bacteriocin production as a mechanism for the anti-infective activity of *Lactobacillus salivarius* UCC118" [48], with 464 citations which focused on the ability of a newly isolated lactic acid bacteria to produce bacteriocins which can inhibit the activity of the foodborne pathogen *Listeria monocytogenes* and investigated the mechanism of this anti-infective activity. Whereas the next highly cited paper investigated the biocontrol of *Listeria monocytogens* using a bacteriophage and nisin [35]. Notably, most of the highly cited papers are from earlier years. This shows the foundational nature of these initial researches and the key roles in contributing to the emerging field of bacteriocin research. With regards to the citation count of a paper, the time effect is an important parameter to be considered [59]. This is because the older a paper is, the more likely it will be cited. Thus, the citation intensity indicates a paper's performance in relation to the number of years since its publication. The citation intensity score shows that although the highest cited paper is Corr *et al.,* [48]. the article with the highest number of citations per year is Kommineni *et al.,* [63], which demonstrated that bacteriocin production by commensal microorganisms in the intestines can affect gut microbiota and can be employed as a therapeutic approach for the elimination of multi-drug resistant bacteria. The citation intensity of this article underscores its high visibility and usage within the field and the key effect the number of years post-publication has on the number of citations an article receives.

The top-cited papers were published in predominantly two journals; The Proceedings of the National Academy of Sciences of the United States of America and The Journal of Bacteriology.

4. SCIENTIFIC ADVANCES IN LAB BACTERIOCIN RESEARCH AND FUTURE PERSPECTIVES

In addition to the major applications of bacteriocins in food preservation to reduce incidences of food spoilage and foodborne illnesses, a variety of medical advancements and applications of bacteriocin have been demonstrated recently. The bacteriocins nisin and fermenticin are spermicidal and decrease sperm motility (in rabbits), with the potential for use as birth control agents [64, 65]. However, the concentration of bacteriocin, which is effective in inhibiting spermatozoa in rabbits, may negatively affect the normal flora of the human vagina [66], and thus studies to modify the bacteriocins to be effective as a birth control agent must factor in its spectrum of activity and potential to destabilise the microbiota of humans. Similarly, the bacteriocins nisin is effective in inhibiting *Streptococcus mutans* which is implicated in cases of dental caries. A study has shown that a formulation of nisin and polylysine is effective in completely eradicating *Streptococcus mutans* in the oral cavity of individuals [67], showing their potential use in the prevention of dental caries and halitosis when incorporated into dental care products. Other potential applications include their use as anti-cancer agents. The nisin variant (Nisin ZP) showed *in-vivo* and *in-vitro* activity by inducing apoptosis in HNSCC cells and further resulted in a reduction in cell proliferation [68] highlighting the promising nature of this agent for the treatment of cancers.

With the global increase in microbial resistance to conventional antibiotics, the ability to effectively control pathogens and undesirable microorganisms continue to dwindle. It is estimated that by 2050, this will lead to more than 10 million deaths annually, with a financial burden of up to 100 billion USD [69]. Thus, there is a need for an effective replacement for antibiotics. Bacteriocins are a promising alternative, and their research should focus more on the engineering of more stable forms that can be applied freely for food preservation and medical uses. Furthermore, genetic engineering, the application of proteomics and metabolomics techniques which results in a rapid advance in the process development for bacteriocin production at the industrial scale, needs to be given more attention. Hence, greater emphasis on collaboration between research institutes/universities, companies and government agencies to encourage the development of this promising line of research is needed. These collaborations have been evidenced in this bibliometric analysis between research institutes. However, for effective product development, collaborations should not be limited to research institutes or universities but between funding bodies, start-up ventures and government policymakers. The future of bacteriocin application may be found in nanotechnology and microencapsulation for the slow release of an antimicrobial particle within food products or food packaging materials. This is because antimicrobial peptides such as bacteriocins can be rapidly inactivated in food matrixes through binding to proteins and lipids. Furthermore, they can be degraded by proteolytic enzymes in foods, thus reducing their efficacy [70]. Therefore, to maintain their stability, microencapsulation and slow-release systems for bacteriocins need to be further explored for effective food utilization for a shelf-life extension. The currently published literature has not fully explored these areas of research; thus, future perspectives may be directed towards addressing concerns on the practical long-term application of bacteriocins, especially in foods and the process industries.

CONCLUSION

The research focused on the antimicrobial peptides bacteriocin is growing rapidly, cutting across various fields including; food, pharmaceutical, medicine and industrial technology. More than 2000 documents related to bacteriocins and anti-microbial peptides have been published in the last 20 years, with about 1741 of these being research articles in the English language. The present study observed a doubling in the research output per year compared to those in the earlier years. This shows that the research field is growing. The United States, Spain and The People's Republic of China are the leading nations in bacteriocin research output. The bibliometric analysis performed in this study enabled the identification of institutes and authors with the highest research output and showed inter-institute, country and regional collaboration in bacteriocin research. The review further highlighted trends in bacteriocin research, pointing out that bacteriocin research is focused mainly on biotechnology and food safety, with numerous publications on the application of these antimicrobial peptides in food preservation. It is expected that this is the direction the field may take in the coming years.

LIST OF ABBREVIATION

LAB	=	Lactic Acid Bacteria
WoS	=	Web of Science

AUTHORS' CONTRIBUTIONS

Conceptualization and Design, H.O., T.M. and C.K.A. methodology, C.K.A.; software and Analysis O.O. and C.K.A; writing—original draft preparation, C.K.A.; writing—review and editing, C.K.A, AH and U.A.E.; visualization, C.K.A. and O.O.; project administration, H.O. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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