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Pharmacological and Biotechnological Evaluation of Antimicrobial Metabolites from Controlled Fermentation: Bridging Food Preservation and Clinical Therapeutics

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Abstract: Background: The rising rate of antimicrobial resistance and rising concerns about synthetic food preservatives have fuelled interest in natural food antimicrobial agents. Directed fermentation is a potential and viable method of bioactive metabolite fermentation that could be used to preserve food as well as to treat clinical conditions. **Purpose:** The purpose of this systematic review was to assess the pharmacological and biotechnological potential of antimicrobial metabolites produced by controlled fermentation and also to discuss the twin purpose of antimicrobial metabolites produced by controlled fermentation in foods preservation and therapy.**Methods:** A systematic search was performed according to PRISMA in major databases, as well as other sources. The inclusion criteria were predetermined to study fermentation-produced antimicrobial metabolites. One hundred and fifty studies were chosen to conduct qualitative synthesis. Information was retrieved in microbial sources, type of metabolites, fermentation conditions, antimicrobial activity and context of application. The risk of bias was evaluated narrative because of the heterogeneity of the studies.**Findings:** The included studies have shown that fermentation products by lactic acid bacteria, fungi, and actinomycetes exhibit a great diversity of antimicrobial products in terms of type (bacteriocins, phenolic compounds, and secondary metabolites). These metabolites showed an apparent inhibitory effect on Gram-positive as well as Gram-negative pathogens. Food preservation Applications demonstrated increased shelf life and safety and pharmacological potential was demonstrated via antimicrobial efficacy. But the results were mostly in vitro-based, with little-to-no standardization and clinical validation.**Conclusion:** Fermentation antimicrobial metabolites are an enticing alternative to synthetic preservatives and traditional antibiotics. Nevertheless, it is necessary to conduct additional research to overcome issues associated with standardization, scaling, and clinical translation.
Keywords: Antimicrobial metabolites, controlled fermentation, secondary metabolites, food preservation, lactic acid bacteria, fermentation biotechnology.

INTRODUCTION

The recent surge in antimicrobial resistance (AMR) is becoming a major health issue at the international level, questioning the value of traditional antibiotics and necessitating the search of alternative antimicrobial approaches (1). Simultaneously, the food industry is under pressure to minimize the use of synthetic preservatives, because of related health issues and demand by consumers are products of natural origin, minimally processed. These similar issues have prompted increased efforts to develop bio-derived antimicrobial agents and especially those developed by controlled fermentation processes (2). Fermentation, which was traditionally used in the preservation of food is being reconsidered as an advanced biotechnological platform that has the capabilities of producing a wide range of antimicrobial metabolites with industrial and clinical importance (3).

Controlled fermentation entails the cultivation of microorganisms, including lactic acid bacteria (LAB), Bacillus species, and some fungi under optimized environmental conditions in order to maximize the bioactive production. These metabolites are bacteria-specific fluid acids, hydrogen peroxide, and secondary metabolites which display powerful antimicrobial activity against a wide range of pathogens. (4). Compared to traditional antibiotics, most of them exhibit a specific action of action, decreased toxicity, and smaller propensity to cause resistance. Pharmacologically, these properties make fermentation-based metabolites promising therapeutic development candidates, especially with respect to multidrug-resistant infections.

At the same time, the use of these metabolites in the preservation of foods has become very popular. Examples of bacteriocins such as nisin and pediocin are already used to inhibit food spoilage organisms and food pathogens, extending food shelf life and increasing food safety. Their translational importance is demonstrated by their dual property as preservatives of foods (natural) and as prospective therapeutic agents (3,4). Nevertheless, although there has been a lot of research in microbiology, food science and pharmacology, research tends to be confined to their respective fields. This divisiveness constrains the ability to have an overall picture of how antimicrobials produced through fermentation can be successfully optimized, standardized and adapted across applications.

At the biotechnological perspective, the efforts in the fields of fermentation engineering, metabolic optimization, and genetic modification have gone a long way in enhancing the yield and stability of antimicrobial metabolites. Strain selection, co-culturing and optimization of bioprocess techniques have allowed promoting efficiency in production, and synthetic biology-based techniques provide the opportunity to design metabolite profiles to meet a given need. However, there are still issues concerning scalability, regulatory approval, and reproducibility of bioactivity, especially in the case of moving the laboratory level of study to an industrial or clinical environment (5).

Nonetheless, in spite of the accumulated literature, a synthesis of pharmacologic efficacy, biotechnological production, and real-life application of fermentation-produced antimicrobial metabolites is lacking. The available reviews are typically limited to one or another of the following domains, with no critical bridge gap between them: Food preservation or antimicrobial mechanisms (6). This is a great gap because the use of these compounds in future relies on a combined knowledge base that links lab results with translational and real results.

Thus, the systematic review is intended to critically analyse the pharmacological and biotechnological features of the antimicrobial metabolites of the controlled fermentation process, and their dual application in preserving food materials and treating diseases, in particular. This review attempts to synthesize evidence to draw conclusions on the major trends, limitations, and research gaps, which will lead to the creation of more efficient and sustainable antimicrobial measures.

Material and Methods

This systematic review was carried out under the Preferred Reporting Items guidelines on systematic reviews and meta-analyses (PRISMA) to provide transparency, reproducibility and rigor of the methodology. The purpose of the review was to synthesize the current knowledge on the antimicrobial metabolites produced through controlled fermentation incorporating pharmacological, biotechnological, as well as an application-based approach.

Eligibility Criteria

To guarantee relevance and consistency, a predetermined inclusion and exclusion criteria were used.

Inclusion Criteria:

- Research on the antimicrobial metabolites generated by the controlled or natural fermentation process.
- Research on microorganisms: lactic acid bacteria, fungi, yeast, or actinomycetes.
- Experimental investigations of in vivo, in vitro, applied food model systems.
- Research testing antimicrobial activity, generation of metabolites, optimization or use in food preservation or therapeutics.
- Articles in full-text published in English.
- Articles published in and before 2018.

Exclusion Criteria:

- Research that did not focus on fermentation-generated metabolites.
- Synthesis without biological fermentation applicability.
- Reviews, commentaries and abstracts of conferences that lack any original data.
- Research with no antimicrobial assessment.

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- Research published in any other language.

Information Sources

The targeted literature search was performed on the large scientific databases, such as PubMed, ResearchGate, NIH, and Google Scholar. Besides that, the selected articles reference lists were screened manually to reveal other eligible studies. The search had been narrowed down to those studies which directly corresponded to the scope of fermentation-derived antimicrobial metabolites and their uses.

Search Strategy

A search strategy was constructed in a systematic manner through a combination of keywords and Boolean operators to include the literature of interest. " Key search terms included:antimicrobial metabolites formed during fermentation"

"bacteriocins"

“AND antimicrobial AND secondary metabolites”
“Lactic acid bacteria AND antimicrobial activity”
“
fermentation AND food preservation AND antimicrobial”
AND pharmacological activity bioactive metabolites AND pharmacological activity

Databases were subjected to search string adoptions to achieve wholesome retrievals. There was also consideration of grey literature sources like ResearchGate where there are no peer-reviewed versions, but this has been critically considered.

Study Selection

All the found records were brought into a reference management system, and these were kept free of duplicates. Screening of titles and abstracts was done to determine relevance with the eligibility criteria. Final inclusion was then done based on the full-texts. The discrepancies in the selection process were overcome by means of dialogue and agreement. In this review, 15 studies were chosen as a representative of qualitative synthesis with varied type of fermentation systems and microbial strains and application environments.

Data Extraction

Each study was systematically gathered of relevant information by means of a standardized data extraction framework. Variables that were extracted were:

- Characteristics of the study (authors, year, study design)
- Used microorganism (e.g., LAB, fungi, Streptomyces, yeast)
- Antimicrobial metabolite type generated.
- Conditions and optimization strategies of fermentation.
- Target microorganisms/pathogens
- Determined antimicrobial activity.
- Context of use (food preservation or therapeutic relevance)

This high level of organization guaranteed the control of consistency and promoted comparative analysis between studies.

Risk of Bias Assessment

Since the included studies are heterogeneous, the risk of bias was determined through modified criteria depending on the study design. The evaluation of the study was based on the methodological clarity, reproducibility, and control of variables in the case of experimental studies and on the ecological validity and applicability to the real-world in the case of applied ones. The biases that were commonly identified were small sample sizes, absence of standard measure of outcome and insufficient replication. The changing nature of experimental designs did not allow the application of one standardized instrument, this is why narrative assessment methodology was chosen.

Data Synthesis

Fermentation conditions, microbial system heterogeneity, and outcome measures were found to be very heterogeneous thus a narrative synthesis approach was used. The studies were put together on the basis of theme:

- Antimicrobial metabolites can be of the following types.
- Pharmacological activity
- Biotechnological optimization
- Food preservation and clinical applications.

No meta-analysis was done because of the unavailability of similar quantitative data in studies. Rather, focus was put on determining similarities, intersections, and gaps that are of critical significance in the literature.

Results

Study selection

The process of selection of the study was priced on PRISMA and shown in Figure 1. Database searching (n = 890) and other sources (n = 342) helped in identifying a total of 1,232 records. Before the screening, 781 records were eliminated such as duplicates (n = 141), records tagged as ineligible by automation tools (n = 280), and records that

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were eliminated due to other reasons (n = 360). After this, 451 records were filtered because of titles and abstracts with 193 being left out as irrelevant. The number of reports that were requested to be retrieved was 258 reports; the number of reports that were not retrieved was 167 reports. Then, 91 of the full-text articles were evaluated based on their eligibility. Among these, 69 studies were eliminated based on such criteria as no focus on fermentation (n = 39), no antimicrobial results (n = 11), and study design (n = 19). Lastly, 15 studies were presented in the qualitative synthesis.

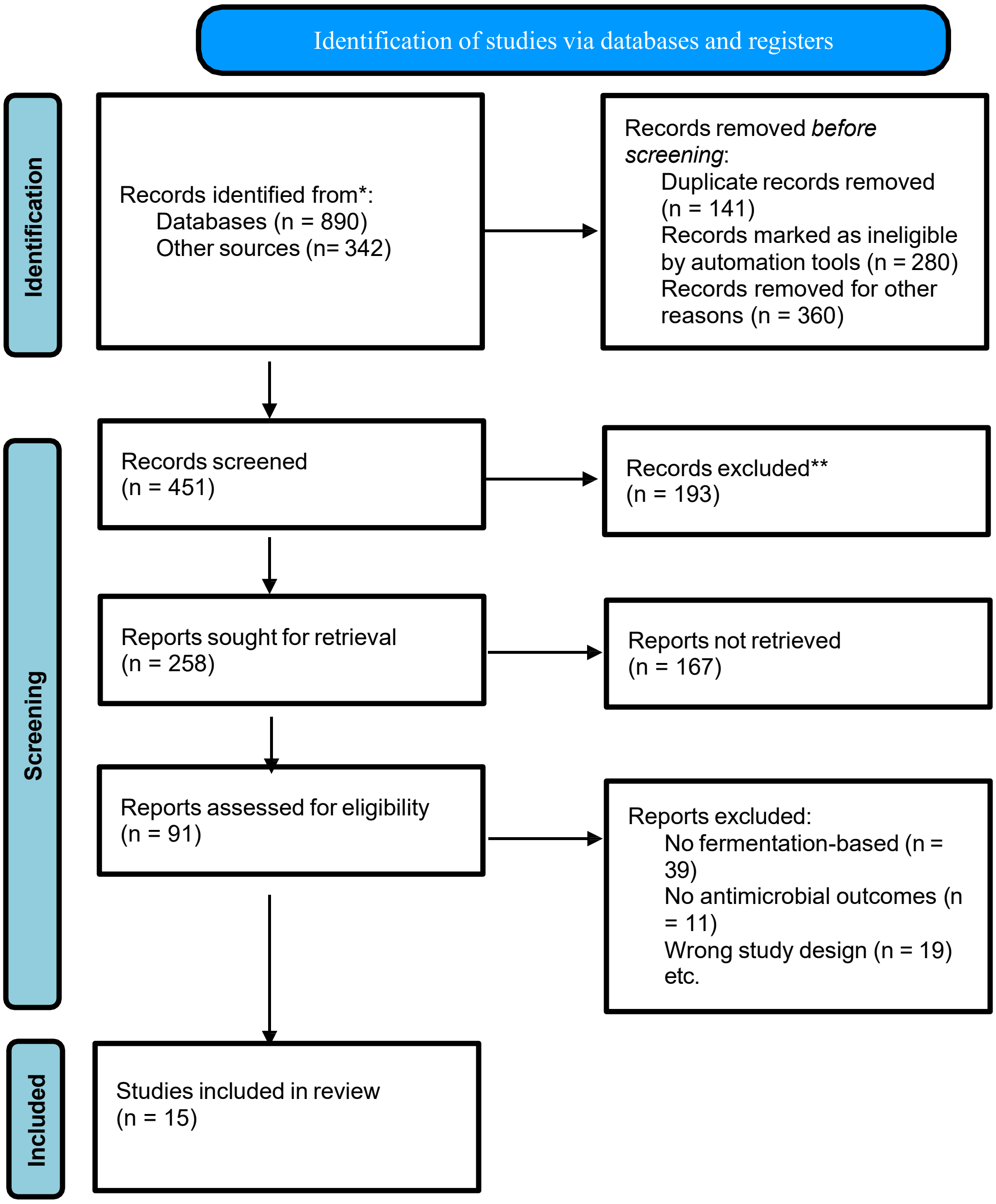

Figure 1: Prisma framework

Study Characteristics

The studies included were experimental in nature with several of them being conducted in the controlled laboratory environments with some involving applied food model systems to test the real-world applicability. There was a variety of microorganisms used in the studies, including actinomycotes, i.e., Streptomyces species (7), lactic acid bacteria (8,14,19), filamentous fungi, i.e., Trichoderma viride (10) and Phomopsis longicolla (12,16), and yeast species, i.e., Saccharomyces cerevisiae (15). Fermentation approaches were widely different, as the objectives of the studies and the contexts of their application were dissimilar. These were submerged

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fermentation systems (7,12) to produce metabolites and solid-state fermentation (10,20) to increase the yield of bioactive compounds in plant substrates, and natural fermentation processes (8,14), which are typically linked to traditional food systems. Some of the articles aimed at streamlining fermentation conditions including nutrient concentration, temperatures, pH, and incubation period to enhance the production of antimicrobial metabolites (7,18). Implications of fermentation-based metabolites have been widely divided into food preservation systems, such as dairy and bakery products (9,11,20), and antimicrobial testing regarding pathogenic microorganisms, such as Escherichia coli, Staphylococcus aureus, Listeria monocytogenes, and Salmonella enterica (8,14). This heterogeneity indicates diversity of the research area that includes microbiology, food science, and pharmacology.

Classes of Metabolites of Antimicrobial

In the reported studies, there was a diverse range of antimicrobial metabolites, which is the evidence of the diversity of metabolism of fermentation systems. The most common compounds which were reported were bacteriocins and bacteriocin-like-inhibitory-substances (BLIS), which were mostly produced by lactic acid bacteria (8,18,19). These proteinaceous compounds showed specific antimicrobial action, especially on Gram-positive bacteria, and generally were emphasized to have application in preservation of foods. Besides bacteriocins, secondary metabolites of actinomycetes and fungi were reported in several other studies. Streptomyces species were found to secrete antibacterial compounds, which possessed high levels of inhibitory effects (7), fungal systems like Phomopsis longicolla produced metabolites which had greater effects on antimicrobial effects (12,16). The substrates of plant origin were fermented to produce more phenolic compounds and organic acids, which were involved in antimicrobial and antioxidant activities. Indicatively, solid-state fermentation of ginger and rice bran had a great effect on the production of bioactive phenolic compounds that possessed antifungal properties (10,20). Moreover, microorganisms that include yeast-derived metabolites of Saccharomyces cerevisiae were also reported to have abilities against bacteria even though these compounds were not characterized in detail (15). Although metabolites are diverse, several studies had a significant drawback of the fact that no standardized methods of identification and characterization were established, and this limited the direct comparison of results across the studies.

Pharmacological Activity

All the studies that were incorporated assessed antimicrobial activity, most of which were carried out in vitro with agar diffusion analysis and zone of inhibition being the most frequently used techniques. The results repeatedly indicated that fermentation-derived metabolites have important antimicrobial potentials against many microorganisms. Bacteriocins were very active inhibitors of Gram-positive pathogens, in particular, Staphylococcus aureus and Listeria monocytogenes (8,14,19). On the contrary, the fungal and actinomycete derived metabolites had broader spectrum activity and included Gram-negative bacteria such as Escherichia coli (7,12). More so, the value-added fermentation-enhanced phenolic compounds were also demonstrated to have bilateral functions, having antimicrobial and antioxidant properties, especially in fermentation-based systems on plants (10,20). Research with Phomopsis longicolla also indicated the directed antimicrobial use against plant pathogens which showed that it could be used across domains in both agriculture and clinical microbiology (12,16). The main drawback of all the studies, however, was the use of laboratory-based tests where there was little standardization in the antimicrobial testing methods. This heterogeneity decreases the possibility of a direct comparative study of antimicrobial potency in the different studies.

Biotechnological Aspects of Fermentation

Some reports have pointed how biotechnological optimization is critical towards improving the production of antimicrobial metabolites. The parameters that were important to the yield were nutrient composition, pH, temperature, and incubation time (7,18). The optimization strategies proved to make a big difference in the number and the activity of antimicrobial compounds. Submerged fermentation systems were also found to be very useful in producing bacteriocins, whereas solid-state fermentation showed an increased production of phenolic compounds and antimicrobial activity in plant-based fermentations (10,20). Moreover, the importance of strain selection and strain optimization with respect to maximizing the production of metabolites was highlighted, and microbial genetics were imperative in defining the yield and functionality (17). There were also innovative methods like immobilization of bacteriocins which were used to enhance stability and ease their use in the food systems (21). Irrespective of these developments, issues of scalability, reproducibility and cost-effectiveness are major limitations to large-scale adoption.

Food Preservation Applications

A significant percentage of the literature explored the use of antimicrobial metabolites produced through fermentation of food in food preservation. Bacteriocins and phenolic extracts were proven to have a positive impact on spoilage organisms and foodborne pathogens inhibition, thus improving the food safety and the increase of shelf life (8,19,20). Common models that were used in applications were

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fermented dairy products and sourdough systems. As an example, hop extracts were used in sourdough fermentation and showed antifungal activity as well as the extension of bread shelf life (9), mastic gum was used as an antimicrobial agent and as a structural ingredient in fermented milk items (11). Such results suggest that the use of natural anti-microbial compounds in food systems as substitutes to synthetic preservatives is promising. Nevertheless, it was determined that these compounds had uneven efficacy with regard to food matrix, storage, as well as interaction with other food elements, which showed that further standardization is necessary.

Clinical and Therapeutic Potential.
The studies included also suggested possibilities of the utilization of fermentation-derived metabolites in clinical and therapeutic settings. Some of the metabolites proved to be active against clinically interesting pathogens such as Staphylococcus aureus, Escherichia coli, and Salmonella enterica (8,14). The development of synthetic fermentation strategies also indicates that there is a potential that bioactive molecules will be made with improved pharmacological properties and antimicrobial target (13). The above changes underscore the prospects of the use of fermentation-produced molecules as substitutes to traditional antibiotics, especially with the emergence of increased antimicrobial resistance. Nevertheless, there is a lot of evidence mostly in vitro only and no in vivo or clinical support. This is a big hole in translating the laboratory results to therapeutical uses.

DISCUSSION

This is a systematic review that consolidated the evidence of antimicrobial metabolites produced through controlled fermentation, which combines the pharmacological activity, biotechnological production, and practical applications. The results show that ferment systems can produce a wide spectrum of bioactive substances, which have a high antimicrobial potential. Nonetheless, it has also been shown that there is a patchy research landscape, and that microbiological, technological and clinical dimensions have frequently been pursued independently as opposed to being viewed as a component of an integrative translational system.
The main conclusion in the reviewed studies is the regular antimicrobial activity of fermentation-based metabolic compounds, especially bacteriocins and secondary metabolites. Bacteriocins secreted by lactic acid bacteria were very active against Gram-positive pathogens, including Staphylococcus aureus and Listeria monocytogenes (8,14,19), which confirmed their proven use in the biopreservation of food products. However, in comparison, metabolites of actinomycetes and fungi were found to be of broader spectrum activity, such as Gram-negative bacteria (7,12). This difference is of pharmacological importance, in that it brings into focus the complementary functions of various microbial systems, against different sets of pathogens. However, the overproduction of in vitro assays constrains the clinical application of the results because the activity of the antimicrobial in controlled laboratory systems may not necessarily be directly applicable in the clinical setting.

Biotechnologically, the review is significant in the optimization of fermentation to improve the yield and functionality of the metabolites. Several reports indicated that nutrient composition, pH, and temperature are important parameters affecting antibiotic production (7,18). Solid-state fermentation was linked to the generation of more phenolic compounds and antimicrobial action in plant-based feeds (10,20). Although these results demonstrate the opportunities of fermentation engineering, it also indicates an absence of standardization in process design. The experimental conditions of studies vary forcing them to come up with reproducible protocols or compare results in systematic manner. This variation is a dire scalability and industrial usability obstacle.

Food preservation using metabolites produced through fermentation is one of the most established fields that have been researched in this review. Research showed the use of these compounds in inhibiting spoilage organisms and increasing the shelf life of certain produce like dairy and bread (9,11,20). The application of natural antimicrobial products, such as bacteriocins and phenolic extracts, is consistent with the current demand of consumers toward clean-label and minimally processed foods. The efficacy of these compounds, however, is very contextual, as the effect of these compounds depends on the composition of the food matrix in storage conditions, and in the interaction of the compounds with other food components. This inconsistency indicates that more standardized application models and real-life validation studies should be implemented.

Comparatively, translation of metabolites generated during fermentation to therapeutic agents use in clinics is limited. Whereas multiple studies had shown activity against clinically relevant pathogens (8,14), there is a clear deficiency of in vivo and clinical research. This is especially important considering that alternative antimicrobial agents are in demand to reduce the increasing antimicrobial resistance. The development of synthetic fermentation and metabolic engineering provides an opportunity to generate custom bioactive compounds with an improved pharmacological profile (13). Nevertheless, issues of

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safety, standardization of doses, approval of regulatory agencies, and mass production should be overcome before these compounds can be regarded as an option of viable therapeutic alternatives.
One essential limitation that has been found throughout the read works is the absence of methodological reliability. The disparities between antimicrobial testing procedures, characterization of metabolites, and reporting guidelines develop a high level of heterogeneity, which restricts comparability and synthesis. Small-scale experimental designs that lack sufficient controls are also used in most studies, which makes them less reliable. In addition, there were no long-term stability studies and toxicity research, which limits the estimation of the applicability of the practice, especially in clinical settings.

Notably, one of the basic gaps in the literature, identified in this review, is the absence of integration of food science with clinical research. Although metabolites produced by fermentation have proven useful in food preservation, little is known about their possible use as therapeutic agents. The solution to this gap would involve interdisciplinary studies that involve integrating of microbiology, pharmacology, and bioprocess engineering to come up with standardized, scalable and clinically proven solutions.
In summary, fermentation-resistant antimicrobial metabolites are a promising but underused source in solving the food safety issue as well as the antimicrobial resistance issue. Standardization of methods, testing in living systems and the investigation of possible translational pathways should be considered the priorities of future research to close the gap between the results of laboratory and real-world approaches.

Limitations

This systematic review has a number of limitations which must be taken into account when interpreting the findings. To begin with, the review covered only articles written in English, which could have caused omission of other possible studies that had been done and written in different languages thus language bias. Second, there was a large degree of heterogeneity in the included studies in the microbial strains, fermentation conditions, types of metabolites, and methods of antimicrobial evaluation. This heterogeneity restricted what would have been achieved in making direct comparisons between studies and it also precluded the possibility of quantitative meta-analysis.

Also, the majority of the studies were in-laboratory and were highly dependent on in vitro antimicrobial testing and the little validation of in vivo or clinical. This limits the externalisability of the results especially within the therapeutic application. Differences in experimental design such as variability in outcome measure and in the absence of standardized protocols to characterize metabolites also added to reporting variations. The other weakness is connected with the fact that the number of included studies could be considered rather limited, and thus the research could be not fully reflected in this field. In addition, the fact that some sources of grey literature are mentioned, though they are needed to fill gaps in peer-reviewed evidence, can raise certain issues about methodological rigor and the quality of publications.

CONCLUSION

This review paper demonstrates the high potential of antimicrobial metabolites produced through controlled fermentation as versatile antimicrobials in food preservation and medicine. Its results indicate that a wide array of microorganisms such as microorganisms of lactic acid, fungi and actinomycotes can produce bioactive compounds that have significant antimicrobial properties against diverse pathogens. These metabolites especially bacteriocins and phenolic compounds have demonstrated effectiveness in improvement of food safety and shelf life as well as promising pharmacological characteristics. Nevertheless, in spite of these benefits, there is still a lack of translation of fermentation-derived antimicrobials in clinical applications. The existing body of evidence is mostly limited to in vitro research, and it has not been validated in in vivo and clinical setting. Moreover, issues of standardization, scalability as well as regulatory certification remain a barrier to the widespread adoption.

To maximize the potential of such bioactive compounds, the research in the future must be aimed at combining the microbiological, biotechnological, and pharmacological strategies. The focus should be on creating standard production processes, performing strict clinical trials and trying to find scalable fermentation technology. These efforts are critical to close the gap between antimicrobial applications in the field of food and clinical therapeutics, which will eventually build sustainable and effective antimicrobial strategies.

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