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Review Article

Probiotic *Lactobacillus* and the potential risk of spreading antibiotic resistance: a systematic review

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Abstract

Background and purpose: *Lactobacillus*, the most popular probiotic, has recently gained more attention because it is a potential reservoir of antibiotic resistance. This review summarized and discussed the phenotypic-genotypic characteristics of antibiotic resistance.

Experimental approach: Google Scholar, PubMed, Web of Science, and Scopus were searched up to February 2022. The inclusion criteria were all studies testing antibiotic resistance of probiotic *Lactobacillus* strains present in human food supplementation and all human/animal model studies in which transferring antibiotic-resistant genes from *Lactobacillus* strains to another bacterium were investigated.

Findings/Results: Phenotypic and genotypic characterization of *Lactobacillus* probiotics showed that the most antibiotic resistance was against protein synthesis inhibitors (fourteen studies, 87.5%) and cell wall synthesis inhibitors (ten studies, 62.5%). Nine of these studies reported the transfer of antibiotic resistance from *Lactobacillus* probiotic as donor species to pathogenic bacteria and mostly used *in vitro* methods for resistance gene transfer.

Conclusion and implications: The transferability of resistance genes such as *tet* and *erm* in *Lactobacillus* increases the risk of spreading antibiotic resistance. Further studies need to be conducted to evaluate the potential spread of antibiotic resistance traits *via* probiotics, especially in elderly people and newborns.

Keywords: Antibiotic resistance; *Lactobacillus* probiotic, Probiotic safety; Systematic review.

INTRODUCTION

Regarding the growing evidence on the impact of gut microbiota on human health, recent past decades have been spent studying the role of living microorganisms known as probiotics in recovering the host's microbiome balance (1,2). Most of these probiotics colonized in the human host are present in the intestines. The commensal intestinal microbiome can contribute to the synthesis of nutrients, host immune system differentiation, and increased resistance against infections (3,4). Thus, the application of probiotics in various clinical conditions (e.g., diarrhea, diabetes, cancer) is a new and effective alternative to traditional prevention and treatment schemes (5-9).

In recent decades, probiotic production has reached the highest echelon of dietary supplements and has marketing and over-the-counter sales as health supplements under relatively flexible laws (10). One of the most commonly used probiotic microorganisms is the bacterial genus *Lactobacillus*. Since these bacteria are desirable members of the intestinal microflora, they are considered "Generally Recognized As Safe" (GRAS) (11).

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Although probiotic consumption has various health benefits, the increased probiotic entrance into the body *via* dietary routes or pharmaceutical products has raised global concerns due to its side effects (12). The probiotics in commercial dietary supplements often consist of millions to billions of commercially manufactured heterogeneous population bacteria (12). Since the escalating global impact of antibiotic resistance, this large population of probiotic bacteria in dietary supplements has an excellent chance for the spread of resistant determinants especially when sharing residence with intestinal microflora and opportunistic pathogens in the host gut (13). The probiotic bacteria, based on the presence or absence of resistance genes in their genome or imposed plasmid-based antibiotic resistance genes, can be resistant or sensitive to antibiotics (14). Therefore, there is a risk that resistance genes are transferable (15). This is a serious problem and sounds the alarm about the hazard of long-term consuming probiotics. Despite probiotic supplements are gaining popularity all over the world, research on the side effect of this new segment of functional food is lagging. Therefore, this study tried to present a comprehensive and systematic review of available studies on phenotypic and genotypic characteristics of antibiotic resistance in the probiotic *Lactobacillus* present in any supplements and the risk of spreading the resistance.

METHODS

Search strategy and selection criteria

Electronic databases, including Google Scholar, PubMed, Web of Science, and Scopus were searched to select all English language articles published up to February 2022. Full articles of all relevant studies were retrieved and manually searched. Forward and backward citation searching for all included articles was conducted *via* Web of Science and Scopus databases. The literature search strategy in the databases was carried out using the following terms: "probiotic *Lactobacillus*", "antibiotic resistance", "administration *Lactobacillus*", "probiotic supplementation side effects", "phenotypic antibiotic resistance in *Lactobacillus*" "genotypic antibiotic resistance in *Lactobacillus*", “antibiotic resistance in *Lactobacillus* ". In succession to narrow and widen the search results, a Boolean operator (NOT, AND, OR) was used. The inclusion criteria for the phenotypic and genotypic areas were (1) all studies testing antibiotic resistance of probiotic *Lactobacillus* strains in human food/ supplement and (2) all studies in which antibiotic resistance genes were transferred from *Lactobacillus* strains to another bacterium. The exclusion criteria were all studies focused on the other strains of probiotics and non-animal models, studies that were purely descriptive and did not have any statistical tests, and studies with no data based on phenotypic and genotypic resistance tests.

Reviewing articles and data extraction

Two investigators (A. Shahali and V. Akbari) independently extracted the data from the selected studies by predefined data extraction form. The following information on phenotypic antibiotic resistance was extracted: type of antibiotic resistance, mechanism of antibiotic action, probiotic origin, and methods of detection. The following information on genotypic antibiotic resistance was extracted: type of antibiotic resistance, mechanism of antibiotic action, resistant genes, localization of the genes, risk of transmission, and probiotic supplementation. The following information on transferable antibiotic resistance was extracted: donor *Lactobacillus* and recipient bacteria, type of gene transferred, and type of antibiotic resistance. Any disagreements were resolved through discussion by the review team (A. Shahali, R. Soltani, and V. Akbari). Data on the identified outcomes were analyzed descriptively and presented in numbers and percentages.

RESULTS

Phenotypic characteristics of antibiotic resistance

A total of 53 records were identified by searching the database in this field. After screening the title and abstract and exclusion of duplicates, full texts of 25 articles were assessed for eligibility. After the full-text assessment, 16 articles ultimately met the inclusion criteria for this study (Fig. 1). In the phenotypic characteristic of antibiotic-resistant *Lactobacillus* probiotics, the most resistance was against protein synthesis inhibitors (87.5%) and cell wall synthesis inhibitors (62.5%). Among these studies, the rate of resistance to antibiotics related to DNA synthesis inhibitors and folic acid synthesis inhibitors (antimetabolites) was 31.25% and 12.5%, respectively. Among antibiotics related to cell wall synthesis inhibitors, the most phenotypic antibiotic resistance was seen against vancomycin, and among protein synthesis inhibitors, the most phenotypic antibiotic resistance was seen against gentamicin and streptomycin followed by tetracycline and erythromycin (Table 1).

Table 1. Phenotypic characteristic of antibiotic resistance in *Lactobacillus* probiotics.

Antibiotic	**Mechanism action**	**Probiotic origin**	**Methods**	**Reference**
Bacitracin, methicillin, cephalosporins, vancomycin, polymyxin, ampicillin, penicillin,	Cell wall synthesis inhibitor	Traditional fermented food, carrot, idli batter, curd, Chinese yogurts, Pakistani yogurt, fermented palm sap	Disk diffusion, MIC test	(19,37-45)
Chloramphenicol, streptomycin, neomycin, gentamycin, tetracycline, erythromycin, aminoglycosides, clindamycin, kanamycin, chlortetracycline	Protein synthesis inhibitors	Traditional fermented food, Chinese yogurts, dairy products, milk, Pakistani yogurt, industrial starter	Disk diffusion, MIC test, E-test	(19, 22, 37, 39-44, 46-49)
Fluoroquinolones, norfloxacin, nalidixic acid, ciprofloxacin	DNA synthesis inhibitors	Industrial starter, fermented food, dairy products, or fruits	MIC test, disk diffusion, E-test	(19, 37, 39, 48, 50)
Trimethoprim/sulfonamides	Folic acid synthesis inhibitors	Isolated from dairy products or fruits	MIC test	(40,50)

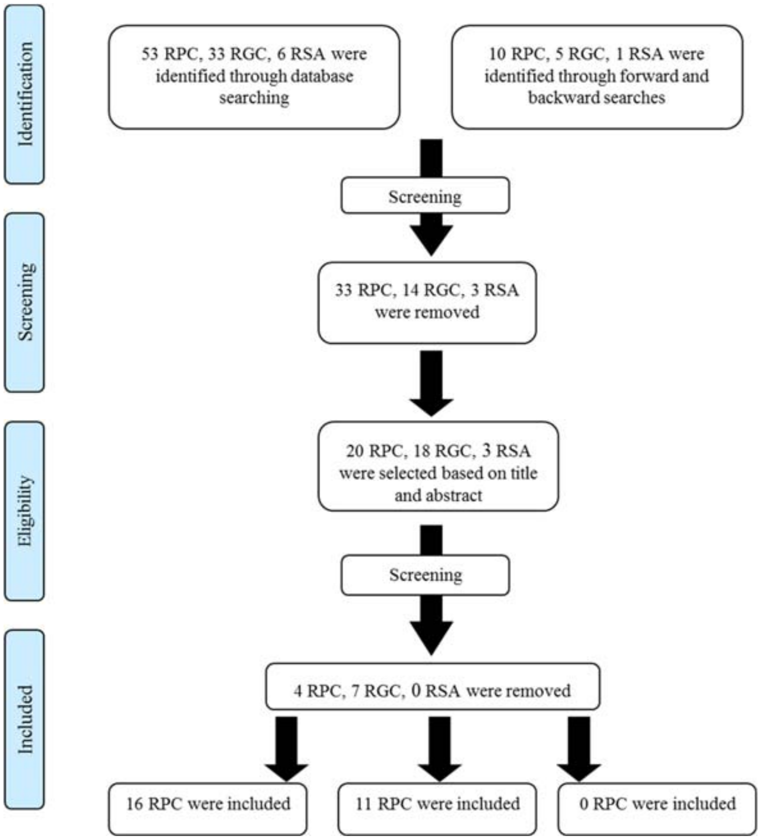

Fig. 1. Prisma flow diagram of literature research. RPC, Phenotypic characteristics of antibiotic resistance articles; RGC, genotypic characteristics of antibiotic resistance articles; RSAR, spreading antibiotic resistance by gene transfer articles.

Genotypic characteristics of antibiotic resistance

A total of 33 records were identified by searching the database in this field. After the screening, the full texts of 18 articles were assessed for eligibility. After the full-text assessment, 11 articles ultimately met the inclusion criteria for this section of the study (Table 2). According to the results, the *tet, erm, gyr, cat, par, ant, aph(3')-IIIa, van,* and *lun* resistance genes were detected (Table 2). The most frequent resistance gene in the probiotics was the *tet* gene (46.61%), leading to tetracycline resistance. This gene is located in the plasmid and is transferable.

Spreading antibiotic resistance by gene transfer

Generally, antibiotic resistance was found to be acquired mainly through conjugation which is a type of lateral gene transfer (i.e., the acquisition of genetic material from other species) (61). For observing conjugal gene transfer from Lactobacillus probiotics to the group of pathogen bacteria, three methods of conjugal transfer including in vitro (e.g., where the recipient (sensitive) and donor (resistant) strains are allowed to mate in a culture medium), in vivo (e.g., where in recipient and donor strains are allowed to mate in the animal gut), and in situ (e.g., where in recipient and donor strains are allowed to mate in a fermented food), have been used (61). To the best of our knowledge, 14 studies exist in this field, 9 of which met the inclusion criteria in the present study (Table 3). These studies used *in vitro* methods and 2 of them used *in vivo* experiments (22.2%) and only one of them had *in situ* experiments (11.1%). The results of these studies suggest that the horizontal gene transfer and natural spread of antibiotic-resistant genes from *Lactobacillus* probiotic as donor species to pathogenic bacteria such as *Enterococcus faecalis*, *Enterococcus hairae, Lactococcus lactis*, and *Listeria monocytogenes* could induce antibiotic resistance (especially tetracycline and erythromycin) in these pathogenic bacteria.

Table 2. Genotypic characteristics of antibiotic-resistant *Lactobacillus* probiotics.

Antibiotics	**Mechanism of action**	**Genes**	**Localization**	**Risk of transmission**	**Probiotic supplementations**	**Reference**
Vancomycin, Ampicillin, Chloramphenicol	Cell wall synthesis inhibitors	*tet(M)* *ant(6)* *aph*(3′)-IIIa	Plasmid - -	Transferable	Fermented milk, dairy products	(51) (41)
		van(E), *van(X),*	Chromosome	Non-transferable		
Chloramphenicol, Neomycin, Streptomycin Gentamycin, Erythromycin, Tetracycline, Clindamycin, Lincosamide.	Protein Synthesis Inhibitors	*gyr(A),* *tet(M)* *erm(B).* *cat* *tet(K)* *Tn916* *erm(C)* *tetS* *ant(6)* *aph(3′)-IIIa* *tet(W)* *lnu(A)* *tet(A)* *tet(W)* *tet(L)*	Plasmid Transposon	transferable	fermented food, Dairy products	(51) (52) (48) (53) (41) (54) (55) (56) (57) (58)
Ciprofloxacin Fluoroquinolones	DNA synthesis inhibitors	*gyr(A),* *tet(M)* *tet(A)* *parC*	Plasmid Transposon	transferable	fermented food, Dairy products	(48) (55)
Sulfonamides	Folic acid synthesis inhibitors	*tet(m)* *tet(A)* *tet(B)*	Plasmid	transferable	fermented food,	(55)

Table 3. Transferring antibiotic resistance *via Lactobacillus* probiotic.

Lactobacillus **(donor)**	**Recipient bacteria**	**Gene transferred**	**Antibiotic resistance spread**	**Reference**
L. plantarum	*Enterococcus faecalis*	transposon Tn916.	Erythromycin	(59)
L. paracasei	*Enterococcus faecalis*	transposon Tn916	Tetracycline	(60)
L. salivarius *L. reuteri*	*Enterococcus faecalis*	*erm*(B), *tet*(M) *tet*(W), *tet*(L)	Erythromycin and tetracycline	(26)

DISCUSSION

In recent years, one of the topics that have received special attention is the potential side effects of consuming live *Lactobacillus* in dietary supplements or lactic acid fermented foods because this organism may be a vehicle for spreading antibiotic resistance (16). Transferring antibiotic resistance within the gastrointestinal tract from probiotic bacteria or commensal species to other potentially pathogenic bacteria can lead to the failure of antibiotic treatment of common microbial infections (17,18).

In this review, we found 15 studies that reported phenotypic characteristics of antibiotic resistance in *Lactobacillus* probiotics. In these studies, the *Lactobacillus* resistance to vancomycin (a cell wall synthesis inhibitor), gentamicin, streptomycin, tetracycline, and erythromycin (protein synthesis inhibitors) was the most abundant. These studies mostly focused on resistance in cultured *Lactobacillus* rather than *in vivo* resistance determinants. One of the limitations observed in the studies focusing on phenotypic characteristics of antibiotic resistance is the lack of uniform procedures in antibiotic susceptibility testing (minimum inhibitory concentration (MIC), E-test, and disk diffusion) to measure antibiotic isolation susceptibility. The results of these studies are mainly based on the disk diffusion method and MIC (12 studies), and cannot be compared because a few articles used the E-test method. Understanding the molecular mechanism of genotypic resistance of *Lactobacillus* can reveal another piece of the puzzle related to the antibiotic resistance of these bacteria and complete the results of phenotypic observations. The predominance of the tetracycline (*tet*) gene and its transferability confirms a variety of phenotypic reports of antibiotic resistance. Campedelli *et al*. determined the antibiotic susceptibility patterns of 182 dietary *Lactobacillus* strains and they compared *Lactobacillus* phenotypes with their genotypes based on genome-wide annotations of antibiotic resistance genes (19). A combination of homology-based screening and manual annotation showed that the overall correlation between phenotype and genotype was positive when genomic data agreed with the phenotypic test. Thus, phenotypic resistance and susceptibility correlate with the presence or absence of one or more resistance genes (19). In this study, the probiotic *Lactobacillus* had the minimum antibiotic resistance rate to trimethoprim (a folic acid synthesis inhibitor). Previous research showed that the resistance of these bacteria against trimethoprim is natural, due to the lack of the metabolic pathway of folic acid synthesis originating from the resistance to trimethoprim di-hydro-folate-reductase (20), and a genetic determinant of resistance (21). However, careful comment on this issue should be done with caution. Although the data is available regarding the phenotypic characteristics of antibiotic resistance patterns in food/supplement-associated *Lactobacillus*, it has been obtained for only a limited number of strains (16,22). In addition, it is difficult to obtain conclusive evidence and unify all the literature regarding the phenotypic and genotypic characteristics of probiotic *Lactobacillus* due to the small sample sizes and heterogeneity of the data.

This review found that the most resistance of *Lactobacillus* strains (isolated from fermented foods) to protein synthesis inhibitor antibiotics is mediated by the *tet* gene (encoding ribosomal protection proteins for tetracycline resistance) and the *erm* gene (erythromycin resistance). Some previous studies have confirmed that tetracycline resistance genes (i.e., *tetM, tetS,* and *tetW*) encoding a ribosomal protection protein are prevalent in *Lactobacillus* strains (16,23-26). The results of several studies showed that the *tet* gene expression requires tight antibiotic-dependent regulation (23,27). Thus, the relationship between the *tet* and widely different MIC values in different *Lactobacillus* strains could be justified accordingly.

The use of *Lactobacillus* probiotics may be associated with the risk of horizontally transferring antibiotic-resistant genes (i.e., acquired resistance) to pathogen bacteria. Although these studies are still in their infancy, the presence of resistance genes in mobile genetic elements can bring about the acquisition of resistance genes by bacterial conjugation (28). The evidence of spreading antibiotic resistance in probiotics by gene transferring is scarce. The limitation of understanding the inherently or non-inherently transfer of resistance genes *in vivo* from *Lactobacillus* probiotic to pathogen bacteria caused the frequent employment of the *in vitro* models of conjugation (28). Plasmid transfer of antibiotic-resistant genes (especially tetracycline and erythromycin) from *Lactobacillus* probiotics to pathogen bacteria has been frequently reported *in vitro* or *in situ* studies. However, it is necessary to carry out natural condition-based studies to determine the true transfer of resistance genes in probiotic *Lactobacillus* strains (29). Although this evidence emphasized the potential of food probiotics and human gut microbiota as reservoirs of antibiotic resistance genes (18,24), there is still a long way to go before conclusions, and clinical studies should be done. The complexity of the relationships between the probiotic *Lactobacillus* and diverse populations of host microflora caused difficulty in interpreting how metabolic and biochemical exchanges take place. In addition, the studies are still on animal models, and few studies have examined the possibility of antibiotic resistance due to *Lactobacillus* probiotic administration, and they reported no antibiotic resistance (30,31).

Lactobacillus probiotics administration is generally considered safe for a healthy population; however, the precise mechanisms of these bacteria mediating clinical benefits are unclear (1,62). It is conjectured that *Lactobacillus* probiotics act by revamping gastrointestinal tract microbiota, reduction of inflammation, and modulating the immune profile. From a theoretical point of view, probiotic administration with or without antibiotics may cause systemic infections and excessive immune stimulation in susceptible individuals. Furthermore, it might lead to deleterious metabolic activities and antibiotic resistance *via* gene transfer in patients with underlying medical conditions (2). Vice versa, some clinical evidence demonstrated the beneficial effect of the administration of *Lactobacillus* probiotics during antibiotic treatment on the imbalance of intestinal flora. Also, the administration of local *Lactobacillus* probiotics enhances antibiotic effects in periodontal inflammation like chronic periodontitis and other infections (11). Therefore, care should be taken in the concurrent use of probiotics and antibiotics. Regarding the limited evidence for the effects of *Lactobacillus* administration from several probiotic intervention studies, owing to the variability in a target population, clinical and statistical heterogeneity, probiotics formulations administered, study limitations, and small sample sizes, it is necessary to do a comprehensive safety evaluation on the at-risk population groups.

Nowadays, the use of probiotics in preventive therapy has attracted wide attention and *Lactobacillus* probiotics have extensive applications in replenishing infant gut microbiome and treating antibiotic-associated diarrhea. On the other hand, the beneficial effects of *Lactobacillus* probiotics in reducing antibiotic resistance and succeeding in antibiotic administration have been clinically proven (32-34). However, information on the exact effects of probiotic strain, the duration of administration without clinical side effects, and the mechanism of action of these probiotics are recommended points for future studies In addition, the co-administration of antibiotics and probiotics (e.g., *Lactobacillus*) can influence probiotics efficiency (35). This co-administration may allow opportunistic pathogens to be colonized in the gut or increase opportunities for horizontal gene transfer with major implications of resistance and can result in increased susceptibility to subsequent disease (35,36). Therefore, recognizing the physiological and pharmacological effects of simultaneous administration of antibiotics and probiotics could be the potential goal of future clinical research.

CONCLUSION

To conclude, the data presented in this systematic review indicated that *Lactobacillus* probiotics that are naturally present in fermented foods have phenotypic and genotypic antibiotic-resistant characteristics, especially against protein synthesis inhibitors and cell wall synthesis inhibitors. These characteristics may represent an important reservoir of antibiotic resistance. *In vitro* studies confirmed that the resistance gene can be transferred into *Lactobacillus*. Thus, it is possible to transfer antibiotic resistance determinants to the intestinal microbiota during the ingestion of large numbers of these probiotics. The results of this systematic study highlight the importance of screening *Lactobacillus* probiotics in foods and supplementations in terms of the presence of antibiotic-resistance genes before their use. However, clinical studies on this probiotic for a specified time duration in the patient population would be more helpful to get a better conclusion. Current studies have some limitations in various items such as the bias of the type of food from which the probiotic was isolated, data heterogeneity, and limitation to *in vitro* studies. We advise researchers to focus on the spread of clinical antibiotic resistance due to *Lactobacillus* probiotic administration, especially in high-risk subjects like elderly people and newborns.

Conflict of interest statement

All authors confirmed no conflict of interest in this study.

Authors' contributions

A. Shahali made a substantial contribution to the concept and design of the article; R. Soltani and V. Akbari potentially interpreted the data and revised the article critically. The finalized article was approved by all authors.

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