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Assessment of Antibiotic Resistance in Probiotic Lactobacilli

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1. Introduction

Probiotics are live microorganisms that confer a health benefit on the host when administered in adequate amounts (Food and Agriculture Organization of the United Nations-World Health Organization Working Group, 2002). Many microbial species have probiotic properties, but those most commonly used are lactobacilli (Salminen et al, 1998; Caplice & Fitzgerald, 1999; Leroy & De Vuyst, 2004). Lactobacilli have a long history of safe use in the production and consumption of fermented foods and beverages. Over recent decades, as awareness of the beneficial effects of probiotic strains in promoting gut and general health has grown, the development and consumption of probiotic foods has increased worldwide (Saarela et al, 2002). Thus, it is essential to thoroughly investigate the safety of lactobacilli used in probiotic products (Salminen et al, 1998; Borriello et al, 2003).

The human gut is the natural habitat for a large and dynamic bacterial community that has a great relevance for health (Spor et al, 2011). The human gut microbiota is a complex ecosystem colonized by approximately 10^{14} bacterial cells with *Bacteroides*, *Eubacterium*, *Bifidobacterium*, *Ruminococcus*, and *Clostridium* as the pre-dominant genera (Kurokawa et al, 2007). The huge diversity of antibiotic resistance genes detected in the human gut microbiome suggests that antibiotic resistant bacteria in the gastrointestinal tract (GIT) function as reservoir of antibiotic resistance genes (Salysers et al, 2007; Sommer et al, 2009). When probiotic strains enter the gut, they interact with the native microbiota and gene transfer can occur (Teuber et al, 1999; Mathur & Singh, 2005; Salim Ammor et al, 2007). The dissemination of antibiotic resistance genes can reduce the therapeutic possibilities in infectious diseases. It is therefore relevant to look for the presence of transferable antibiotic resistance genes in lactobacilli that are or shall be used as probiotic strains for human consumption or as starter cultures of fermented food or feed products.

This article reviews the experiments to be performed and the criteria for assessment of antibiotic resistance in probiotic lactobacilli. Due to the growing availability of whole bacterial genome sequences, sequence-based identification approaches for antibiotic resistance are also discussed.

2. Antibiotic resistance of probiotic lactobacilli

Many food production is estimated to involve microbial fermentation processes by using lactic acid bacterial (LAB) strains (Food and Agriculture Organization of the United

Nations-World Health Organization Working Group, 2002), for example, sausage, ham, cheese, and dairy products. In addition, probiotics have become available on the market, containing a single strain or a combination of strains. The proposed problem is that probiotic strains might contain acquired resistance genes. From a point of safety, it is necessary to distinguish between intrinsic and acquired resistance genes.

Antibiotic resistance profiles have recently been reported for several lactobacilli. These have been found susceptible to penicillins and ampicillin (cell wall synthesis inhibitor) (Danielsen & Wind, 2003; Coppola et al, 2005) in contrast to vancomycin. Most lactobacilli have been found to be resistant to glycopeptides types of antibiotics. However, the resistance towards vancomycin has been demonstrated being as intrinsic (Tynkkynen et al, 1998). Lactobacilli are usually susceptible to chloramphenicol, erythromycin and clindamycin (protein synthesis inhibitors) (Coppola et al, 2005; Klare et al, 2007). In addition, resistance against trimethoprim (nucleic acid synthesis inhibitor), seems to be intrinsic (Ammor et al, 2007). Resistance to tetracycline has been observed more often among lactobacilli (Roberts, 2005; Korhonen et al, 2008). Resistance against neomycin, kanamycin, streptomycin and gentamicin (aminoglycosides) has been observed more frequently among lactobacilli (Coppola et al, 2005; Danielsen, 2002; Zhou et al, 2005).

Acquired resistance genes which are potentially transferable have been detected in lactobacilli. These have been described in multiple studies and have been reviewed (Ammor et al, 2007). Two of the most commonly observed resistance genes in lactobacilli found so far are *tet(M)* for tetracycline resistance and *erm(B)* for erythromycin resistance, followed with *cat* genes coding for chloramphenicol resistance (Danielsen, 2002; Lin et al, 1996; Gevers et al, 2003a; Cataloluk & Gogebakan, 2004).

Acquired resistance genes of probiotic lactobacilli have been reported previously (Table 1). In the PROSAFE project, probiotic lactobacilli possessed *erm(B)* and/or *tet(W)*, *tet(M)* or unidentified members of the *tet(M)* group (Klare et al, 2007). In probiotic commercial *L. reuteri* ATCC 55730, *tet(W)* and the lincosamide resistance gene *lnu(A)* were detected (Kastner et al, 2006). Hummel et al determined antibiotic resistances of probiotic lactobacilli and to verify these at the genetic level. *L. salivarius* BFE 7441 possessed an *erm(B)* gene, which was encoded on the chromosome (Hummel et al, 2007). Probiotic lactobacilli of African and European origins were studied and compared for their susceptibility to antibiotics. Acquired resistance genes encoding aminoglycoside (*aph(3')*-III, *aadA*, *aadE*) and *tet(S)* and *erm(B)* were detected (Ouoba et al, 2008). The potentially probiotic strain *L. plantarum* CCUG 43738, which displayed atypical phenotypic resistance to tetracycline and minocycline, was found to contain a *tet(S)* gene located on a plasmid of approximately 14 kb (Huys et al, 2006).

3. Evidence of potential horizontal gene transfer of probiotic lactobacilli

When probiotic strains enter the gut, they interact with the native microbiota and gene transfer can occur. Probiotics might contribute to the transfer of antibiotic resistance genes to other commensal bacteria or pathogens present in the GIT. The occurrence of large numbers of transferable resistance genes within the intestinal microbiota is undesirable due to the potential risk of acquisition by pathogens present in the GIT and subsequent antibiotic treatment failure (Licht & Wilcks, 2005).

Probiotic strains	Antibiotic phenotype	Antibiotic genotype (gene location)	Transferability	Reference
<i>L. rhamnosus</i> GG (ATCC 53103)	Vmr	Not detected	No transconjugants in mating experiment	Tynkkynen et al, 1998
<i>L. brevis</i> KB290	Vmr, Tcr, Cir	Not detected	No transconjugants in mating experiment	Fukao et al, 2009
<i>L. reuteri</i> ATCC 55730	Tcr, Lmr	tet(W), lnu(A) (pLR581, pLR585)	Potentially transferable	Rosander et al, 2008
<i>L. crispatus</i> L-295	Emr, Cmr, Tcr	erm(B), tet(W)	No transconjugants in mating experiment	Klare et al, 2007
<i>L. crispatus</i> L-296	Emr, Cmr, Tcr	erm(B), tet(W)	No transconjugants in mating experiment	Klare et al, 2007
<i>L. plantarum</i> L-437	Tcr	tet(M) group	No transconjugants in mating experiment	Klare et al, 2007
<i>L. reuteri</i> L-285	Tcr	tet(W)	No transconjugants in mating experiment	Klare et al, 2007
<i>L. reuteri</i> L-285-2	Tcr	tet(M) group	No transconjugants in mating experiment	Klare et al, 2007
<i>L. salivarius</i> BFE 7441	Emr, Cir, Gmr, Smr	erm(B) (chromosome)	No transconjugants in mating experiment	Hummel et al, 2007
<i>L. reuteri</i> L4: 12002	Cir, Emr, Gmr, Smr, Kmr, Nmr, Tcr, Vmr	erm(B) (plasmid)	Transferable	Ouoba et al, 2008
<i>L. paracasei</i> L5	Amr, Cir, Gmr, Kmr, Smr, Vmr	aph(3')-III, aadA	No transconjugants in mating experiment	Ouoba et al, 2008
<i>L. plantarum</i> L7	Amr, Cir, Gmr, Tcr, Kmr, Smr, Vmr	aadE	No transconjugants in mating experiment	Ouoba et al, 2008
<i>L. casei</i> L9	Amr, Cir, Gmr, Kmr, Smr, Vmr	aph(3')-III, aadA, aadE	No transconjugants in mating experiment	Ouoba et al, 2008
<i>L. paraplantarum</i> L10	Amr, Cir, Tcr, Vmr	tet(S)	No transconjugants in mating experiment	Ouoba et al, 2008

Vancomycin (Vm), ampicillin (Am), tetracycline (Tc), erythromycin (Em), clindamycin (Cm), gentamicin (Gm), ciprofloxacin (Ci), lincosamide (Lm), Kanamycin (Km), streptomycin (Sm) and chloramphenicol (Cl)

Table 1. Systematic assessment of antibiotic resistance in probiotic lactobacilli have been reported previously

Several of these genetic determinants in lactobacilli are harboured by extrachromosomal elements which are conjugative plasmids and transposons (Mathur & Singh, 2005; Danielsen, 2002; Gevers et al, 2003a; Axelsson et al, 1988; Gfeller et al, 2003). Transfer from lactobacilli to other commensal bacteria has been documented in vitro (Feld et al, 2008;

Gevers et al, 2003b; Jacobsen et al, 2007; Sasaki et al, 1988; Schlundt et al, 1994). Studying the board-host-range conjugative plasmid pAM β 1, transfer was observed in vitro from lactobacilli (*L. plantarum*, *L. reuteri*, *L. fermentum*, and *L. murinus*) to other commensal bacteria (Ouoba et al, 2008; Tannock, 1987; Gasson & Davies, 1980; Shrago et al, 1986; West & Warner, 1985). In the diassociated model pAM β 1 has been transferred from *L. reuteri* to *Enterococcus faecalis* (Morelli et al, 1988). Interspecies conjugative transfer of tetracycline and erythromycin resistance plasmids from lactobacilli has been demonstrated previously in vitro (Gevers et al, 2003a; Ouoba et al, 2008; Feld et al, 2008). Recently, tetracycline-resistant *L. paracasei* strains were identified in samples of milk and natural whey starter cultures. A transposon *Tn916* including *tet*(M) was transferred to *E. faecalis* in vitro (Devirgiliis et al, 2009).

Transfer has been demonstrated in the GIT of rodents, both gnotobiotic (Feld et al, 2008; Jacobsen et al, 2007; Morelli et al, 1988) and those having an indigenous gut microbiota (Feld et al, 2008; Jacobsen et al, 2007; Schlundt et al, 1994; McConnell et al, 1991; Gruzza et al, 1994; Igimi et al, 1996). In addition, the in vivo transfer of vancomycin resistance has recently been shown between enterococci and probiotic lactobacilli in gnotobiotic mice (Mater et al, 2008). Recent experiments of antibiotic resistance transferability in vivo were also conducted from *L. plantarum* to *E. faecalis* (Jacobsen et al, 2007). However, the potential contribution of lactobacilli to the acquisition and dissemination of antibiotic resistance genes in the human GIT is poorly addressed for both conjugative and non-conjugative resistance plasmids. Nevertheless, conclusive documentation of transfer in the GI from probiotic lactobacilli is lacking and therefore more studies need to be carried out.

4. Systematic assessment of antibiotic resistance in probiotic lactobacilli

Antibiotic-resistance screening for lactobacilli intended for use in dairy products such as probiotics or as starters is now tending to become systematic. The European Food Safety Authority (EFSA) has taken responsibility to launch the European initiative toward a “qualified presumption of safety” (QPS) concept which, similar to the GRAS system in the United States, is aimed to allow strains with an established history and safety status to enter the market without extensive testing requirements (European Commission, 2003). The QPS approach together with the recommendations of the FEEDAP panel of EFSA will give a framework for better decision making in safety assessments of antibiotic resistance (Figure 1) (European Commission, 2005; European Food Safety Authority, 2008).

In phenotypic methods, FEEDAP requires the determination of the MICs of the most relevant antibiotics for each bacterial strain that is used as a feed additive in order to eliminate the possibility of acquired resistances. Those microbiological breakpoints define a MICs which, if exceeded, triggers the need for a more extensive investigation to define the genetic basis of the observed resistance and to assess the risk for transfer of this resistance to other bacteria. In genotypic methods, the latest literature indicates that the search for acquired resistance genes using PCR-based techniques (Klare et al, 2007; Hummel et al, 2007; Ouoba et al, 2008; Ammor et al, 2008; Devirgiliis et al, 2008; Fukao et al, 2009; Rizzotti et al, 2009; Comunian et al, 2010) or micro-arrays (Ammor et al, 2008) is a powerful tool to identify resistant LAB strains.

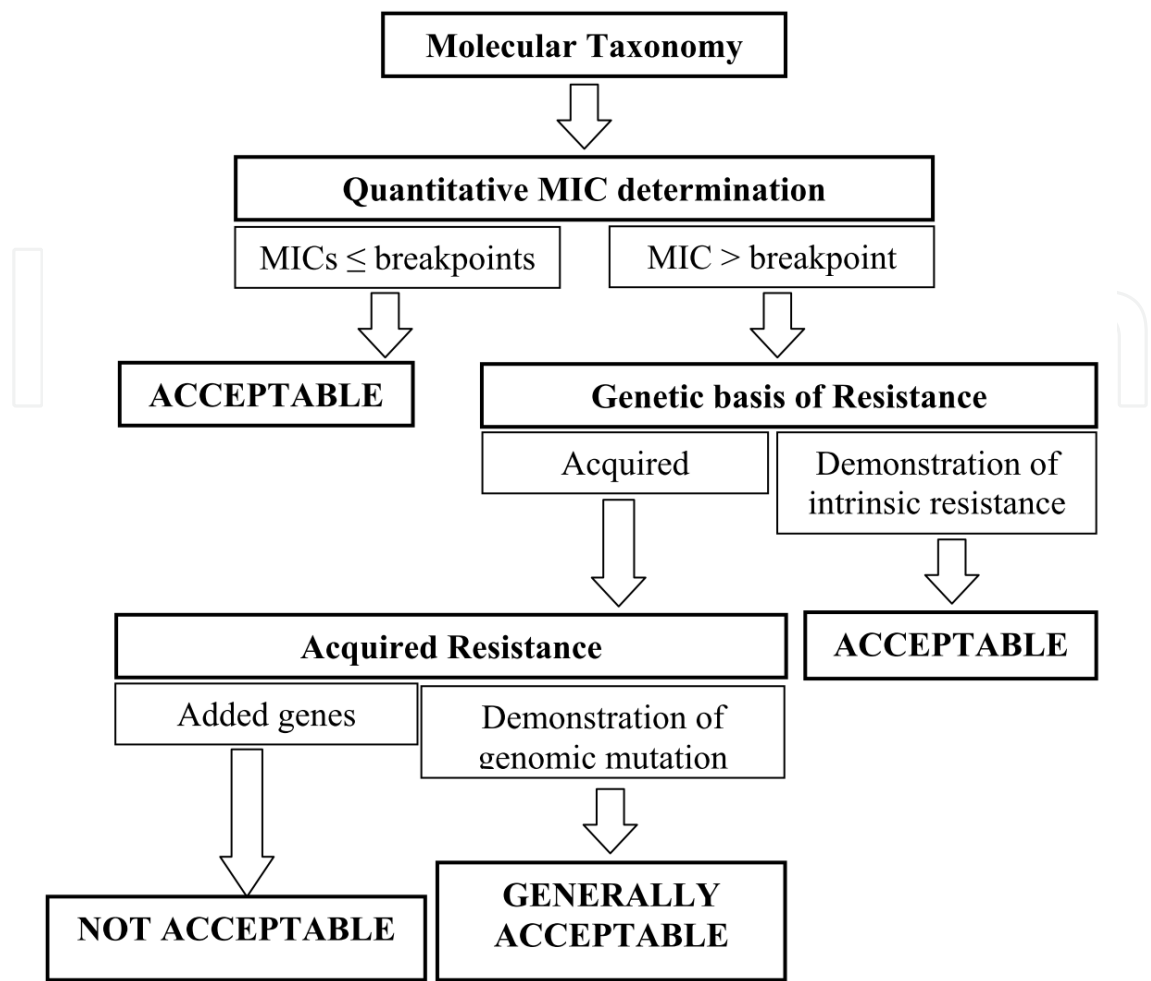


Fig. 1. Proposed scheme for the antibiotic resistance assessment of a bacterial strain (European Commission, 2005; European Food Safety Authority, 2008)

In case of suspected acquired resistance or intrinsic resistance, transferability tests are optional. Conjugation can be detected with bacterial mating experiments. The suspected donor with an antibiotic resistant phenotype is mixed with a recipient strain sensitive to the respective antibiotic, and the transfer of the resistance is subsequently checked. Frequencies of 10^{-6} to 10^{-5} of transconjugant cells are usually the highest experimentally obtainable. If transferability of the resistance is proven, then the strain will not be considered for use in microbial products and further tests are superfluous.

Systematic assessment of antibiotic resistance in some commercial probiotic lactobacilli have been reported previously (Table 1). *L. rhamnosus* GG (ATCC 53103) is a probiotic strain used in fermented dairy products in many countries. Studies have shown that the genes needed for vancomycin resistance in *L. rhamnosus* GG are not related to transferable enterococcal *van* genes and have not revealed any potential risks caused by the vancomycin resistance in this strain (Tynkkynen et al, 1998). The QPS approach was applied to determine the resistance of the probiotic strain *Lactobacillus brevis* KB290 that is used as a probiotic strain in fermented food products in Japan. The authors concluded from their investigation that the antibiotic resistance observed in *L. brevis* KB290 was due not to a potentially acquired mechanisms but to intrinsic resistance. It was concluded that according to the QPS criteria, these results provided safety assurance for the ongoing use of *L. brevis* KB290 as a probiotic (Fukao et al,

2009). In the PROSAFE project, probiotic lactobacilli displayed phenotypic resistance to tetracycline and/or erythromycin possessed *erm*(B) and/or *tet*(W), *tet*(M) or unidentified members of the *tet*(M) group. In vitro intra- and interspecies filter-mating experiments failed to show transfer of resistance determinants. *L. reuteri* ATCC 55730, a commercially available, well-documented probiotic bacterium, has been shown to carry unusual resistances to tetracycline and lincosamides (Kastner et al, 2006). Deletion of the two plasmids was achieved by use of a protoplast-formation technique. BioGaia concluded that *L. reuteri* strain DSM 17938, except for the deletion of plasmids pLR581 and pLR585, was substantially equivalent to its parent strain *L. reuteri* ATCC 55730. Additionally, BioGaia concluded that the evidence demonstrating the safety of strain ATCC 55730 is equally applicable to strain DSM 17938 (Rosander et al, 2008). Hummel et al determined antibiotic resistances and to verify these at the genetic level according to the QPS system. *L. salivarius* BFE 7441 possessed an *erm*(B) gene, which was encoded on the chromosome and which could not be transferred in filter-mating experiments (Hummel et al, 2007). Probiotic lactobacilli of African and European origins were studied and compared for their susceptibility to antibiotics. Acquired antibiotic resistance genes encoding aminoglycoside (*aph*(3')-III, *aadA*, *aadE*) and *tet*(S) and *erm*(B) were detected. Only the *erm*(B) gene found in *L. reuteri* 12002 could be transferred in vitro to enterococci (Ouoba et al, 2008).

5. Whole genome based assessment of antibiotic resistance in probiotic lactobacilli

Due to the growing availability of whole bacterial genome sequences, sequence-based identification approaches have in recent years been intensively explored for safety evaluation such as antibiotic resistance in probiotic lactobacilli. Commercial probiotic *L. acidophilus* NCFM and *L. reuteri* DSM 17938 were assessed with whole genome and no known acquired resistance genes were detected (Agency Response Letter GRAS Notice No. GRN 000357; (Heimbach, 2008). Whole genome sequences were used to screen for acquired antibiotic resistance genes in lactobacilli strains which could be used in human nutrition (Bennedsen et al, 2011).

Moreover the overall NCBI clusters of orthologous groups (COGs) analysis is recommended (Heimbach, 2008). The COG category V (termed defense mechanisms) consists of many COGs that may have a potential safety interest, such as antibiotic resistance (Heimbach, 2008). Although it doesn't imply that these genes in COG category V are involved in antibiotic resistance, it is recommended to be assessed that there is nothing unusual about the number of COGs belonging to category V and none of the each gene was a part of a detectable mobile element such as predicted transposase genes (Heimbach, 2008). The overall COG analysis of *L. reuteri* DSM 17938 with complete genomes revealed that several COGs belonging to category V were found (Heimbach, 2008). The data indicated that there was nothing unusual about the number of COGs belonging to category V among these strains. Further analysis of each of the genes revealed that no gene was clustered with complete transposons or ISs. Thus none of the genes was a part of a detectable mobile element (Heimbach, 2008).

6. Conclusions

In this context, probiotic lactobacilli are considered to pool the resistant genes and might transfer these to pathogenic bacteria. In order to eliminate this possibility, resistance to the

most relevant antibiotics for each strain used as probiotic lactobacilli, food or feed additives could be determined using the systematic QPS protocols. Moreover, due to the growing availability of whole bacterial genome sequences, sequence-based identification approaches have been employed. These can be used to screen strains for unwanted genetic content such as antibiotic resistance. This screening supports normal safety assessment of probiotic lactobacilli.

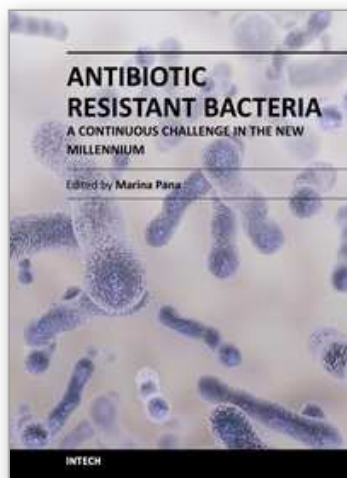
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Antibiotic-resistant bacterial strains remain a major global threat, despite the prevention, diagnosis and antibiotherapy, which have improved considerably. In this thematic issue, the scientists present their results of accomplished studies, in order to provide an updated overview of scientific information and also, to exchange views on new strategies for interventions in antibiotic-resistant bacterial strains cases and outbreaks. As a consequence, the recently developed techniques in this field will contribute to a considerable progress in medical research.

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