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Minireview

Lactic acid bacteria stress response to preservation processes in the beverage and juice industry

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In this review we summarize stress factors that affect the lactic acid bacteria (LAB) and cause different molecular stress responses. LAB belong to a group of bacteria that is very widespread in food and beverages. They are present, and desired, in fermented products like yogurts, cheese, vegetables, meat or wine. In most of them, LAB are providing positive sensory and nutritive features. However, as harmless and desired microbes in one product, LAB can cause spoilage and a bad taste of others, especially in juices and beverages. LAB are resistant to many stress factors which allows them to survive in harsh environments. The most common stress factors they have to deal with are: heat, cold, acidity, NaCl and high hydrostatic pressure (HHP). Their ability to survive depends on their skills to cope with stress factors. Under stress conditions, LAB activate mechanisms that allow them to adjust to the new conditions, which can influence their viability and technological properties. This ability to adapt to different stress conditions may come from the cross-protection systems they have, as resistance to one factor may help them to deal with the other stress effectors. LAB are highly valuable for the food industry and that is why it is important to understand their stress response mechanisms.

Key words: *Lactic acid bacteria*, LAB, stress factors, stress response, cross-protection

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Abbreviations: HHP, high hydrostatic pressure; LAB, lactic acid bacteria

INTRODUCTION

Lactic Acid Bacteria (LAB) are the most widespread group of bacteria that is used in fermented foods. They are natural inhabitants of the human gastric intestine, and can be applied in different fermented products and probiotic foods (Ficco *et al.,* 2009). They are present in products like yogurts, sourdoughs, sour vegetables, cheese, wine or meat and play a crucial role in the development of the organoleptic and hygienic quality of fermented products (van de Gutche *et al.,* 2002). The technological benefit of Lactic Acid Bacteria depends on the ability to enhance safety, flavour, texture and nutritional value (Salminen & von Wright, 2004). Some LAB, due to their probiotic properties, can be used in the production of functional food and potential oral vaccines (Shah 2007; Siragusa *et al.,* 2007; Parente *et al.,* 2010).

At the same time, LAB can cause spoilage of food. They can grow in improperly pasteurized beverages and juices in bottles and cans, in vacuum packed products with a deficit of oxygen. LAB can enter a given product along with the raw material, additives or with packing materials (Lawlor *et al.,* 2009). The most common species that cause spoilage of beverages are *Lactobacillus paracasei* and *Leuconostoc mesenteroides* (Back, 2005), as well as *Lactobacillus brevis, Lactobacillus buchneri, Lactobacillus plantarum, Lactobacillus perolens* and *Weissella confusa.* Many bacteria from these species are also responsible for beer spoilage.

LAB mainly ferment sucrose to lactic acid. Depending on the species and growth conditions, catabolism of sugars can also lead to the formation of ethanol, acetate, formic acid or succinate (Hammes & Hertel, 2009). Some of the bacteria can produce diacetyl that gives a bitter taste and flavour of the products. That is why LAB are undesirable in beverages and juices. It has been reported that formic acid in apple juices can indicate food spoilage (Gökmen & Acar, 2004). The *L. mesenteroides* and *W. confusa* bacteria can synthesize compounds which cause ropiness of the final product (Back, 2005). Ropiness caused by LAB is the reason why these bacteria are believed to be potentially a cider spoilage indicator (Ibarburu *et al.,* 2010).

In alcohol beverages, LAB can influence the bitter flavor by converting glycerol to 3-hydroxypropionaldehyde, which can transform to acrolein and bind with polyphenols creating bitter compounds (Sauvageot *et al.,* 2000; Garai-Ibabe *et al.,* 2008; Juvonen *et al.,* 2011).

PRESERVATION METHODS

Many factors affecting bacteria during the preservation process of beverages and juices can act as potential stress effectors for them. Physical preservation techniques of food are used in order to reduce the number, or to prevent the growth of unwanted microflora in the products (Juvonen *et al.,* 2011). Traditional prevention techniques used in the beverage industry include thermal processing and filtration. Thermal processing is the most efficient technique of food preservation. It can prevent not only the growth of unwanted microflora but also can suppress unwanted enzymatic activity (Back 2005). However, processes that use high temperatures destroy many bioactive and aromatic compounds, causing modification of the flavor, color and nutritional value. The increase of consumer demands for "fresh like" foods brings new challenges for techniques used in food preservation. Nowadays, high hydrostatic pressure techniques (HHP) are used more often, as they can reduce the number of microbes in liquid food products like beverages, juices and alcohol beverages – beer, wine or cider.

High hydrostatic pressure can induce in bacteria many changes, like physiological changes (Wouters *et al.,* 1998; Korakli *et al.,* 2002), changes in gene expression (Welch *et al.,* 1993; Drews *et al.,* 2002; Wemekamp-Kamphuis *et al.,* 2002) and in protein translation (Sato *et al.,* 1995; Ehrmann *et al.,* 2001), and can also lead to cell damage (Ulmer *et al.,* 2002) and death (Vogel *et al.,* 2002; Scheyhing *et al.,* 2004). HHP does not break the covalent bindings. Thanks to this, the primary structure of proteins and fatty acids stays unaffected (Considine *et al.,* 2008; Reundueles *et al.,* 2011). Molecules, like vitamins, amino acids, flavor compounds and other small molecules stay undamaged by HHP, as well as organoleptic characteristics of food. Serrazanetti and coworkers (2009 and 2013) had shown that some proteins undergo induction as a result of HHP, and a few of them are also involved in different types of stress responses including cross-protection.

Stress response to HHP cannot be expected in LAB while it is perfomred in their natural environment, as those bacteria are not normally exposed to this stress factor (Lorca & Font de Valdez, 2009). Compared to other stress factors, LAB response to HHP is more complex, as some of the effects are very similar to those caused by other factors. Their ability to react to HHP can be explained by a bacteria cross-protection system to different stress factors (Scheyhing *et al.,* 2004; Lorca & Font de Valdez, 2009). However, the LAB cross-protection response to HHP is not well documented in the literature as yet. In *Lactobacillus plantarum,* higher sensitivity to HHP was observed when heat shock was used at the same time as HHP.

As shown by Sokołowska and coworkers (2012 and 2014), LAB belong to a group of organisms that are resistant to the effect of high hydrostatic pressure, and their growth can be a valuable tool to evaluate the shelf life of preserved products with this method (Mathias *et al.,* 2013).

LAB STRESS RESPONSE MECHANISMS

It is believed that environmental stress response in LAB can vary between species and depends on the type of stress that has been applied (van de Gutche *et al.,* 2002). The well- known LAB stress responses are those to heat shock (De Angelis *et al.,* 2004), bile (Bron *et al.,* 2006), and oxidative (Serrano *et al.,* 2007), low pH and ethanol stresses (Alegría *et al.,* 2004; Parente *et al.,* 2010).

Bacterial stress response is based on coordinated genes expression that affects different cellular processes (cell division, transport, cell membrane composition, DNA metabolism) (Stortz & Hengge-Aronis, 2000; van de Gutche *et al.,* 2002). LAB achieve an integrated stress response through a regulatory web that allows them to react to environmental changes. Bacteria activate mechanisms allowing them to adapt to new conditions, which can influence the viability and technological properties. Adaptation to stress conditions can also cause morphological changes which affect food spoilage (Asano *et al.,* 2007). Many typical spoilages that occur in beverages, juices and alcohol beverages, like ropiness and volatile phenols formation, are related to stress. LAB have a significance in the food industry and that is why knowing their stress effectors is very important (van de Guchte *et al.,* 2002; Parente *et al.,* 2010). Under stress conditions, in order to protect cells from influence of the same or other type of stress factors, bacteria can trigger a cross-protection response (van de Guchte *et al.,* 2002; Smits & Brul, 2005; Chung *et al.,* 2006).

GENE REGULATION IN THE LAB STRESS RESPONSE

In an unfavourable environment, many forms of LAB can convert into VBNC – a viable but nonculturable state. In this state, the bacteria cannot be identified with classical microbiology methods, and this can be achieved only with the use of more advanced molecular biology techniques. Considering niche differentiation that LAB are able to colonize, a high phenotype and genotype diversity is observed (Molenaar *et al.,* 2005; Di Cagno *et al.,* 2010; Siezen *et al.,* 2010; Ricciardi *et al.,* 2012). Gene expression caused by different stress factors allows to identify biomarkers responsible for stress resistance (Juvonen *et al.,* 2011).

Depending on the type of regulation, these genes are divided into six classes (Helman *et al.,* 2001; Darmon *et al.,* 2002; Schumann, 2003; Castaldo *et al.,* 2006).

Class I and III are controlled by two types of transcriptional repressors: HrcA and CtsR. The first class is comprised by heat shock genes, including the *dnaK* and *groEL* operons. They encode proteins belonging to two chaperon complexes, DnaK-GrpE-DnaJ and GroES-GroEL, respectively (Castaldo *et al.,* 2006). Both operons are regulated by the HrcA repressor protein, which binds with the CIRCE operator (Controlling Inverted Repeat for Chaperon Expression) under the stress-free conditions. Genes encoding heat shock proteins and HrcA are being used for taxonomical purposes of several species, including *Lactobacillus* (Blaiotta *et al.,* 2008; Fiocco *et al.,* 2010; Huang *et al.,* 2010; Guidone *et al.,* 2015).

The class II gene expression is dependent on the σB sigma factor, the synthesis and activity of which is increased under different stresses (Hecker *et al.,* 1996; Kruger & Hecker, 1998; Varmanen *et al.,* 2000).

Mechanisms of class IV transcriptional activation are not very well documented, while class V genes undergo regulation by a two-component signal transduction system (2CSs); for class VI, the regulation is still unknown (Schumann, 2003).

Initially, mechanism of the LAB response to stress conditions was compared with that of the documented model species – *B. subtilis* and *E. coli.* The best known stress response mechanisms are those present in the *Bacillus subtilis* species, where, at high temperatures over 200 genes are expressed (as shown by Castaldo *et al.*, 2006). However, it had turned out that there were some differences in these mechanisms. As Ricciardi and coworkers had shown, the Class I and Class III genes' stress response regulation differs in *Lactobacillus plantarum* from *Bacillus subtilis*, a model organism of Gram-positive bacteria. Other data suggest that stress response factors, like sigma factors, that are responsible for stress response in many Gram-positive and Gram-negative bacteria, are not important for LAB. The most striking difference is the lack of the σ^{B} sigma factor, while several stress proteins, like DnaK, GroEL, Clp etc., and their regulators HrcA and CtsR are conserved.

The LAB stress response is regulated by a one-component regulatory system. For the Class I genes, major complexes of chaperons, like GroES-GroEL and GroE-DnaK-DnaJ (Lorca & Font de Valdez, 2009), are induced. Induction of these genes correlates with acid, ethanol, cold, osmotic, starvation and temperature stresses. In some bacteria, regulation of the GroES-GroEL and GroE-DnaK-DnaJ complexes, requires the presence of a σ^{A} sigma factor promoter and a highly conserved inverted repeat CIRCE, which binds the HrcA repressor (Zuber and Schumann 1994).

Table1. Response mechanisms of LAB to various stress conditions encountered during food processing and the major stress proteins or enzymes involved in the response (adapted from Ananta & Knorr, 2004, Pavlovic *et al*., 2005; Jofre *et al*., 2007; Franz & Holzapfel, 2011; Mota *et al*., 2013)

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Stress response	Reported cross--resistance	Stress related resistance mechanism	Stress-related proteins/enzymes involved
Acid stress response Two general types: During log growth phase (L-ATR; induced by nonlethal low pH) In stationary phase, induction of general stress response	Heat, osmotic, oxidative (varies between species)	ATP-dependent expulsion of proteins by protein pump Activation of arginine deiminase pathway-production of basic compounds (e.g. ammonia) Amino acid decarboxylation reactions & electrogenic transport Change in cell envelope composition of damaged proteins, DNA & cell components Incremental expression of regulators that promote minor or global responses Induction of heat shock proteins	F_0F_1-ATPase K^+-ATPase Arginine deiminase Urease Ornithine/arginine/lysine decarboxylase Lo18 Ffh Heat shock chaperones & regulators (DnaK, GroEl, HrcA, CtsR) recA, AP endonuclease, UvrSystem
Oxidative stress response	Heat, acid, general stress resistance	Reducing intracellular environment Prevention of reactive oxygen species formation Target protection Repair of oxidative damage	Glutathione peroxidase, glutathione reductase Thioredoxin, thioredoxin reductase NADH oxidase Catalase Pseudocatalase Superoxide dismutase Methionine sulfoxide reductase Mannose phosphotransferase system FLP (FNR-like protein) RecA Phosphate ABC transporter
Cold stress response Transient adaptive response i.e. cold shock response	Heat shock, freezing (cryotolerance)	Production of cold-induced proteins (CIPs) to maintain membrane fluidity DNA supercoiling Transcriptional & translation	CIPs involved in Sugar metabolism (Hpr, CcpA, β-PGM, β-phosphoglucomutase) Chromosome structuring (HslA) Signal transduction (LlrC) Stress adaptation (OsmC) Proteolysis of misfolded proteins (ClpX ATPase) Cold shock protein (CSPs) CspA-CspG, vary in number according to species
Osmotic stress response	Heat shock	Exchange of compatible solutes to maintain osmotic balance	ATP-dependent uptakte system (QacT) or ABC transporter (OpuA or BusA) (species-dependent) for uptake of glycine--betaine, carnitine and proline during hyperosmotic stress conditions, efflux by unidentified channel protein General stress proteins (GroEL, GroES, DnaK) Proteases FtsH, HtrA
Heat shock response	Acid, oxidative, cold, osmotic, alcohol	Production of heat-inducible chaperones Production of heat-inducible proteases Production of heat shock proteins	Chaperon complex DnaK-GrpE-DnaJ & GroES-GroEL HtrA/DegP protease, FtsH/HflB protease, Clp protease (ClpB,C,E,P,Q,X & Y), Lon protease Trigger factor, HrcA, HSP10, HSP23 (ClpP), HSP26, HSP33, HSP40, DnaK/HSP70, GroEL/HSP60, HSP84, HSP85, HSP100 Small heat shock proteins (sHSPs), e.g. Lo18, HSP18.5, HSP18.55, HSP19.3, HSP16.4, HSP20
Bile stress response	Heat	Metabolism of bile salts Adaptation to bile stress MDR efflux	Bile salt hydrolase (BSH) DnaK, GroEL MDR transporters
Nutrition starvation stress response	Heat, oxidative, ethanol, acid, osmotic	Modification of cell morphology Regulation of metabolism Amino acid (arginine) catabolism	General stress proteins Proteins involved in carbon metabolism (triose phosphate isomerase, putative dihydroxy-acetone kinase, Gls24 protein) Proteins involved in amino acid catabolism (carbomate kinase, putative glycine cleavage system, L-serine dehydrogenase)

Ethanol stress response	Heat, acid	Production of heat shock proteins	sHSPs, HSP18
High pressure stress response	Heat, cold	Biosynthesis of proteins preventing thermal degradation Expression of ribosomal protein genes Synthesis of translation factors Transcription factors Protein folding and stabilization Energy metabolism-glycolysis Cellular processes- adaptation to atypical conditions Nucleotide and nucleoside interconversion DNA replication, recombination and repair	Chaperones & ATP-dependent protease Translation factors (EF-G, EF-TU), genes changing translation or chaperones (GroEL, ClpL) Proteins HSP60, gryA Ribosome recyclingfactor (Rrf)Lsa1262 Transcription antitermination protein (NusG) Lsa1674 DnaK chaperone protein (DnaK) Lsa1236 Glyceraldehyde 3-P-dehydogenase (Gap) General stress protein Lsa0169 General stress protein Lsa0170 Universal stress protein (Usp6) Lsa0836 Universal stress protein (Usp5)Lsa0038 Cold shock protein A family (Csp1) Lsa 0768 Adenylate kinase; Ec 2.7.4.3 (Adk) Lsa1744 Single-standed DNA binding protein (Ssb) Lsa0008

Regulation of heat stress response genes in Gram-positive bacteria was described as HrcA or CtsR dependent. This statement is still valid for *B. subtilis* and closely related to them *Clostridum perfingens* or *Listeria monocytogenes* bacteria (Chastanet *et al.,* 2003, Chastanet and Msadek 2003, Lorca and Font de Valdez 2009).

The Class III heat shock genes CtsR repressor binds directly to a specific repeat sequence (the CtsR Box: a/ggtcaaaNaNa/ggtcaaa)(Derre *et al.,* 2000). This sequence was found in other Gram-positive bacteria, like: *Listeria monocytogenes, Streptococcus salivarius, Streptococcus pneumonia, Streptococcus pyogenes, Streptococcus thermophilus, Enterococcus faecalis, Staphylococcus aureus, Leuconostoc oenos, Lactobacillus sake, Lactobacillus lactis,* and *Clostridium acetobutylicum* (Smeds *et al.,* 1998, Derre *et al.,* 1999, Ingmer *et al.,* 1999).

In *Lactobacillus plantarum,* CtsR regulates transcription of the ctsR-clpC operon, hsp1 and ftsH (Russo *et al.,* 2012). Deletion of CtsR influences the temperature sensitivity and changes morphology of cells under stress. It suggests that in *L. plantarum,* CtsR has a significant role in the heat shock tolerance by controlling the processes of protein quality (Fiocco *et al.,* 2009, Fiocco *et al.,* 2010). CtsR gene homologs were also identified in other bacteria: *Listeria*, *Streptococcus*, *Leuconostoc*, *Lactococcus* or *Clostridium,* which indicates that heat shock gene regulation by CtsR is highly conserved in those bacteria. That allows us to state that heat shock response regulation by CtsR is highly conserved in the Gram-positive bacteria (Derre *et al.,* 1999).

Stress response to HPP has been well studied in the *L. sakei* and *L. sanfranciscensis* strains (Hörmann *et al.,* 2006; Jofré *et al.,* 2007). Hörmann *et al.,*(2006) had observed changes in the expression of 16 genes in *Lactobacillus sanfranciscensis* as an effect of HPP. Nine of those genes were over-expressed and seven were silenced as a result of stress. That can suggest that in LAB the stress response to HPP is negatively regulated by a one component protein system HrcA or CtsR, and by a two-component system of signal transduction (2CSs).

An overview of different types of the LAB stresses, their reported cross-resistance and the resistance mechanisms are shown in Table 1.

CONCLUSION

Growing pressure to lower the use of thermal processes and chemical preservatives in beverages and juices leads to maintain more natural products. However, this process may cause higher contamination by unwanted compounds produced by LAB. Although they may be harmless and desired microbes in one product, LAB can cause spoilage of other products.

A comparative study of the response of different bacterial strains to the same stress factors shows their diverse characteristics. In the context of food protection treatment, it is important to take under consideration that even closely related organisms can posses their individual, specific stress response mechanisms.

That is why, for different bacterial strains, there is a cross-response to various stress factors and cross-protection to different food preservation systems, like HHP, acidic, cold, and salt treatment, which needs to be taken under consideration.

Therefore the identification of stress response regulatory genes, like HrcA, CtsR, DnaK and FtsH, is necessary to control and evaluate the relationship between polymorphism of LAB in food products and the ability to cope with stress. At the same time, as a consequence of a highly conserved status in bacteria, these genes can be use as biomarkers.

Although present molecular methods allow to better understand the LAB taxonomy, it is believed that more data is needed to understand the stress related physiological dependence of those bacteria (De Angelis & Gobetti, 2011).

Genetic diversity evaluation of lactic acid bacteria, as an effect of stress factors that can occur during beverage and juice preservation processes, is important to control LAB in those products. A better understanding of the stress response related mechanisms in LAB allows to understand the basis of adaptation response and cross-

protection mechanism they undergo (Van de Guchte *et al.,* 2002), and thus can make these bacteria more useful in industrial processes.

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