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**Review scientific paper**

# QUORUM SENSING IN FOOD MICROBIOLOGY

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**Summary**
In the last few decades, our perception of bacteria and their communities has changed significantly. In the past, the prevailing opinion was that bacterial communities represent a population of cells that act individually. Today, there is a well-documented fact that the mechanism of intercellular communication, known as "*quorum sensing*", plays an important role in controlling various cellular processes of bacteria such as bioluminescence, virulence, tolerance to disinfectants, sporulation, motility, biofilm formation and antimicrobial resistance.
Understanding the intercellular communication system gives the possibility to control the growth of undesirable bacteria in the food matrix and to develop a new strategy in ensuring the food quality and safety.

**Keywords:** quorum sensing, food quality and safety.

## INTRODUCTION

„*Quorum sensing*“ (QS), term established by Fuqua and Winans (1994), represents a universal mechanism by which bacteria recognize changes in the environment. Recognizing newly established changes, the microbial world has the ability to react in a timely manner, by developing a specific defense strategy in order to adapt to unfavorable conditions in environment and during a time. In this way, by the act of socialization (association) at the moment when the population density reaches a critical level, bacteria synchronize their behavior and thereby optimize the chances of survival in competitive niches.
Numerous gram-negative and gram-positive species of bacteria are capable of adapting their activities to the social community and coordinating collective behavior within a multimicrobial community. The mechanism of combined expression involves the synthesis of low-molecular signal molecules. Bacteria ("emitter" cells) continuously generate a signal, at the beginning of growth in a

low concentration, and then, as the population density increases over time, the signal accumulates. Once, when the concentration of the signal reaches a critical level, which the bacteria perceive as a "quorum", the signal reacts with the receptor protein of the "responder" cell, and through the coordinated expression of certain genes, a unique, common response of the community is triggered in order to survive.

Processes controlled by the "*quorum sensing*" system include bioluminescence, sporulation, competence, production of antimicrobial peptides, biofilm formation, antimicrobial resistance, secretion of virulence factors, toxin production, transfer of conjugative plasmids, as well as production of enzymes whose activity is linked to food spoilage (Smith et al., 2004; Zhao et al., 2020; Wang and Xie, 2020).

## Types of signaling molecules

Basically, the "*quorum sensing*" system involves the production and reading of extracellular signals. Signals are chemicals, signal molecules, so-called autoinductors. Often, although not always, the genes responsible for the synthesis of signaling molecules and the response to them activate their own expression, which explains the name autoinducer. According to Ammor et al. (2008), the identified signaling molecules are divided into 4 categories:

1. N-acyl homoserine lactones (AHL), derivatives of fatty acids, generically called autoinducers 1 (AI-1); they are produced and used by gram-negative bacteria mainly for intraspecies communication. The intracellular accumulation of a sufficient concentration of AHL triggers the transcriptional activation of various promoters within the bacterial genome. Several factors such as temperature, pH, NaCl content, growth medium composition and growth phase can affect the amount of AHLs produced. The production of C4-homoserine lactone by *Aeromonas hydrophila* 519 depends on the growth temperature, glucose and salt concentration, as well as the pH value of the cultivation medium (Medina-Martinez et al., 2006). The same authors determine that at a basic pH value, AHLs become unstable and undergo hydrolysis. As bacteria enter the stationary phase, the amount of AHL decreases (Ravn et al., 2001). Examples of AHL-regulated phenotypes include antimicrobial peptide production, antimicrobial resistance, biofilm formation, DNA uptake competence status, cell differentiation, bioluminescence, growth, plasmid transfer, expression of virulence factors, as well as production of various extracellular enzymes.

2. furanosyl borate diester, known as autoinducer 2 (AI-2); they are created by gram-negative and gram-positive bacteria and thus serve as a universal signal for communication within and between species; responsible for the modulation of several phenotypic changes, such as expression of virulence factors, levels of ABC transporters in *Salmonella* Typhimurium, production of proteases, transcription of numerous genes in *Escherichia coli*, bioluminescence in *Vibrio* spp. Production of AI-2, as in the case of AI-1, is conditioned by the temperature and formulation of the growth medium, as well as changes in intracellular metabolism and the action of stressors.
3. autoinducer 3 (AI-3) is a signal for virulence genes of enterohemorrhagic *Escherichia coli* (EHEC); the production of this autoinducer has also been found in the intestinal microbiota of humans, which implies a possible role in communication between species.
4. autoinduced peptides (AIP) produced and used by gram-positive bacteria. AIPs are synthesized on ribosomes as precursor peptides, transformed into an active peptide and exported outside the cell by the action of ABC transporters in an ATP-dependent process. These peptides are characterized by low molecular weight (5-26 amino acid residues), high stability, specificity and diversity. The signal of these peptides is usually read on the cell surface via the histidine kinase sensor, when the autophosphorylation of the kinase triggers the phosphorylation of the regulatory protein, which ultimately leads to the transcription of the corresponding genes. Examples of phenotypes modulated by the activity of autoinduced peptides include genetic competence and sporulation in *Bacillus subtilis* and *Streptococcus pneumoniae*, virulence in *Enterococcus faecalis*, as well as production of antimicrobial compounds such as nisin (*Lactococcus lactis*) and subtilisin (*Bacillus subtilis*). Nevertheless, a typical example of an AIP-mediated QS mechanism is the *agr* system in *Staphylococcus aureus* (Abisado et al., 2018) and *Listeria monocytogenes*. *Staphyloccus aureus* represents the commensal microbiota of humans, but it also exhibits pathogenic properties after penetrating the host's tissue. The pathogenicity mechanism of staphylococci implies a biphasic strategy: at low population density, staphylococci express proteins that promote adherence to mucosal surfaces and colonization, while at high population concentration, these properties are extinguished, and the secretion of toxins and proteases is initiated, which promotes the dissemination of staphylococci. This "switch" in gene expression is regulated by the *agr* QS mechanism.

More recently, other types of signaling molecules have been described, such as cholera autoinducer 1, diketopiperazines, 4-hydroxy-2-alkylquinoline diffusible signaling factors (Wang and Xie, 2020), various metabolic products such as indole, short-chain fatty acids, secondary bile acids (Buffie et al., 2015).

## *Quorum sensing* in the context of microbial ecology

In most cases, previous studies of the QS mechanism were related to the study of the molecular aspect of intercellular communication, that is, how QS affects virulence, sporulation or conjugation. Less attention was given to the ecological concept at the center of which lies the main question - why do bacteria produce signal molecules in the first place, guided by the basic ecological paradigm - everything is related to everything else, but also how the determinants of the ecological niche affect communication, especially in the case when the niche is represented by complex food ecosystems. Although the production of signaling molecules (AI-1, AI-2) is associated with certain members of the food microbiota (*Pseudomonas* species, members of the *Enterobactericeae* family, lactic acid bacteria), very little is known about the influence of process parameters and storage conditions on quality and quantity of these signals in food. It is known that the dominance of one group of bacteria in the continuum of food production and processing is the result of a complex process of microbial succession, when a specific population, thanks to its implicit characteristics and the adoption of a specific strategy, acquires numerical superiority in a niche that is established as an interplay of the physicochemical characteristics of the food matrix and storage conditions. In most cases, the food matrix implies the association of microbial cells with a solid substrate, and these cells are immobilized and localized in certain microenvironments in high concentration, and growth is present in the form of microcolonies or biofilms. At different places within the food matrix, there are variations in the level of oxygen, water activity, nutrients and pH values. Based on the interaction of all these factors, the food matrix is presented through a series of interconnected microenvironments, some of which can favor the growth of bacteria. The growth dynamics and activity of bacteria present in food, whether they are spoilage agents, pathogenic bacteria or beneficial microbiota, is determined, to a large extent, by *in situ* intercellular ecological interactions. For this reason, an ecological approach is necessary in understanding intercellular communication in different food ecosystems. Very likely, looking at the ecological dimension of the QS mechanism would provide answers to the following important questions:

- What is the critical concentration of the QS signal required for the bacteria to recognize the quorum and initiate gene expression?

- Is there a concentration gradient or chemical signal degradation due to dynamic (abiotic) conditions?
- Is the spatial distribution of cells more important than population densities in the generation and reading of QS signals?
- Is it possible that other species or strains of bacteria, which coexist in the same niche, deactivate and/or produce the same autoinducer?

## *Quorum sensing* in food microbiology

Intercellular communication attracts the attention of food microbiologists due to the evidence of the connection between QS and food spoilage (Ammor et al., 2008; Skandamis et al., 2009; Galié et al., 2018) and the fact that different signaling molecules have been isolated from the matrix of spoiled food (Blana and Nychas, 2014), but also due to the importance of QS in bacterial pathogenesis (Li et al., 2018). In addition, the role of QS in the formation of biofilm in the process environment is undeniable (Galié et al., 2018).

## *Quorum sensing* and food spoilage

Spoilage of food of animal origin is mainly associated with the activity of gram-negative proteolytic psychrotrophic bacteria, mostly *Pseudomonas* spp., and genera of the *Enterobactericeae* family, i.e. lactic acid bacteria if the food is stored in modified atmosphere conditions. In addition, the activity of hydrolases, mainly phospholipases originating from gram-positive aerobic *Bacillus* spp., is responsible for the spoilage of milk and milk products.

*Pseudomonas* spp. represent the dominant microbiota of aerobically packaged refrigerated meat, reaching a level of $10^9$ CFU/g in case of meat spoilage (Liu et al., 2006). Jay et al. (2003) determined the connection between QS and meat spoilage caused by the activity of *Pseudomonas* spp., *Hafnia alvei* and *Serratia* spp., as dominant psychrotrophic species of the *Enterobacteriaceae* family isolated from spoiled meat packed in vacuum and identified as significant AHL producers. A large number of AHLs is determined in refrigerated beef and poultry meat stored in aerobic conditions, in a situation where a high concentration of *Pseudomonadaceae* (108-109 CFU/g) and *Enterobacteriaceae* (103-104 CFU/g) is recorded, with significant proteolytic activity (Liu and et al., 2006).

Yuan et al. (2018) assume the role of the QS mechanism during the growth and metabolic activity of *Pseudomonas fluorescens*, a frequent cause of spoilage of milk and milk products, due to the ability of the species to synthesize AHL and extracellular proteases. Most (84.5%) strains of psychrotrophic proteolytic microbiota isolated from raw milk are characterized by AHL production (Pinto et al., 2007). Although *Pseudomonadaceae* and *Enterobacteriaceae* cannot be

isolated from pasteurized and sterilized milk, the determined prevalence of AHLs indicates that AHLs produced by the initial microbiota of raw milk retain their activity completely, or at least partially, after thermal treatment. The production of alkaline metalloprotease in *Pseudomonas fluorescens* strain 395, which has a pronounced proteolytic activity, is regulated by the QS system (Liu et al., 2007). The production of extracellular lipolytic and proteolytic enzymes by *Serratia proteamaculans* strain B5a is controlled by the QS system (Christensen et al., 2003).

## *Quorum sensing* and biofilm formation

Biofilm represents a complex ecosystem of one or more types of bacteria immersed in an extracellular polymer matrix. It develops according to patterns of multicellular behavior and in its final form functions as a cooperative consortium of bacteria in a complex but coordinated manner. This sessile way of life offers numerous advantages to associated members - greater resistance to stressful environmental conditions, insensitivity to antimicrobial agents as well as sanitation and disinfection agents, which makes it impossible to eradicate biofilm from the process environment. In addition, the microbial community of the biofilm shows a primitive homeostasis, a primitive circulatory system, the exchange of genetic material and the principle of metabolic cooperation.

The first step in biofilm formation involves conditioning the surface of the material and reversibly attaching cells to the same material. Then, binding becomes irreversible and microcolonies are formed. Finally, the film acquires a three-dimensional structure and the complex ecosystem is ready for dispersion. The milk industry, due to the specificity of the raw substrate (fluid) and the variety of technological processes (different temperature profiles), provides numerous opportunities for biofilm colonization. Tanks for raw milk, pipelines, centrifuges, duplicators for cheese, flow plate heat exchangers and packaging machines are examples of the so-called surface substrates on which biofilms are ideally formed. They are of particular importance since they represent a continuous, recurring source of contamination, which in the extreme case damages the quality and microbiological integrity of the final product.

The QS system is involved in all phases of biofilm formation: regulation of population density, synchronization of metabolic activity, so that the activity corresponds to the nutritional requirements, but also to the availability of the nutrient substrate. In addition, biofilm-resident bacteria show a significantly different genome/transcriptional program compared to free-living planktonic cells. The role of the QS system in the formation of biofilms was investigated in most cases in gram-negative bacteria, where acylated homoserine lactones (AHL) act as

signaling molecules. In a situation when the AHL concentration reaches a critical level, AHL binds to the receptor molecule and the formed complex, in response to stressful environmental conditions, triggers the expression and secretion of virulence factors, extracellular proteases, biofilm formation, as well as other physiological functions (Li et al., 2018).

*In vitro* studies show that *Salmonella* spp. readily adhere to work surfaces and form a biofilm (Coughlan et al., 2016). *Salmonella* spp. and *E. coli* do not have the *luxI* gene that encodes AHL synthetase and therefore do not have the ability to synthesize AHL. However, these microorganisms possess a LuxR homologue, SdiA, which detects a signal produced by other bacterial species. The presence of small concentrations of AHL produced by other bacteria induces biofilm formation in *E. coli*, *Salmonella enterica* serovar Typhimurium and *Vibrio* spp. (Jamuna Bai and Ravishankar Rai, 2016). Silagyi et al. (2009) determined that AI2 mediates the formation of *E. coli* biofilm, where the activated QS system also participates in the regulation of chemotaxis, flagella synthesis and expression of genes responsible for motility.

The presence of C12 HSL, one of the AHL signals, affects the formation of *Salmonella* Enteritidis biofilm and promotes the expression of virulence factors in anaerobic conditions (Almeida et al., 2017). Lamas et al. (2016) establish a link between biofilm formation by *S. enterica* and the expression of QS-related genes. In *Campylobacter jejuni*, AI-2 synthesis plays a major role in biofilm formation (Bezek et al., 2016). Biofilm formation in *Vibrio* spp. depends on several key enzymes, involved in the biosynthesis of flagella, pila and polysaccharides, as well as protein regulators that control the expression of the same genes (Giaouris et al., 2015). *Vibrio cholerae, V. vulnificus* and *V. parahaemolyticus* are present in contaminated food and water, especially seafood, where they form densely packed biofilms, which is a key factor in their survival in the environment (Galié et al., 2018). The QS system also controls the formation of biofilms in gram-positive foodborne pathogenic bacteria: *L. monocytogenes*, *Clostridium perfringens* and *B. cereus* (Coughlan et al., 2016). *L. monocytogenes* forms biofilms on abiotic surfaces in community with other bacteria, such as *Pseudomonas* spp. and *E. coli* (Giaouris et al., 2015). It was found that lactose induces biofilm formation in *B. cereus*, in a way that increases the production of AI-2 molecules (Duanis-Assaf et al., 2015). The Agr QS system in *S. aureus* differs from other QS systems since it has been proven that the expression of Agr leads to the down-regulation of genes responsible for bacterial adhesion. Thus, the expression of Agr reduces the adhesion potential of bacteria and indirectly affects the reduced capacity of biofilm formation.

## Inhibition of QS system

As the QS system relies on the creation and transfer of small signaling molecules between bacteria, it is realistic to expect that the same molecules (AI) can be used to control the growth and survival of bacteria, as well as to modulate their virulence profile. Inhibition of the QS system, a mechanism known as "Quorum Quenching" (QQ), represents a new strategy in the control of specific bacterial phenotypes (bioluminescence, biofilm formation, virulence, swarming effect).

There are several possible ways of inhibiting the QS system:

1. Inhibition of AHL synthesis,
2. Degradation of AHL signal by enzyme activity (AHL-acylase and AHL-lactonase)
3. Interference with receptors or blocking of the AHL/receptor complex (Lade et al., 2014).
4. Post-transcriptional control of QS enzymes via sRNA.

Natural (isolated from various sources) and synthetic QS inhibitors are intensively studied. Extracts of different herbs show great potential. Methanolic extract of mango leaves reduces the production of protease, elastase, pyocyanin, as well as exopolysaccharides, and the swarming effect and biofilm formation in *Pseudomonas aeruginosa* (Husain et al., 2017). In the study of the same authors, more than 14 ingredients, including trifluoromethylketones and phenothiazines, were identified in the extract of mango leaves, with possible anti-QS action, namely by inhibiting "*efflux*" pumps, although it is very likely that they act on more than one target site.

Teas, especially polyphenols extracted from tea leaves, represent a traditional source of natural components, which have recently been intensively tested as possible anti-QS agents. Epigallocatechin gallate, the most abundant polyphenolic antioxidant metabolite from green tea, shows a strong inhibitory effect in relation to the expression of genes (biofilm formation, and motility) regulated by the QS system of *E. coli* (Lee et al., 2009). Spices such as black pepper, garlic, cumin and cinnamon show promising results as anti-biofilm agents.

Fruits, such as cranberries, strawberries and blackberries, contain, among other ingredients, phenols, quinones, flavonoids, alkaloids, terpenoids and polyacetylenes, which have proven to be successful as anti-QS agents, based on interference with AHL synthesis, inhibition of the production of AI- 2 (Bezek et al., 2016) or down-regulation of QS-related genes.

Quercetin (present in fruits, vegetables, nuts and cereals) shows a significant reduction of QS-dependent phenotypes of certain pathogenic food-borne bacteria (*P. aeruginosa*, *Y. enterocolitica* and *K. pneumoniae*), especially biofilm formation, exopolysaccharide production and motility (Gopu et al., 2015).

Vegetables and grains such as rice, tomatoes, soybeans, onions and broccoli also produce substances that mimic the activity of AHL signals (Jakobsen et al., 2012). Essential oils have proven to be good inhibitors of biofilm formation, primarily through the mechanism of AHL signal degradation or inhibition of AHL synthesis.

As alternative sources of QS system inhibitors, bioactive components originating from bacteria are mentioned, since it is quite certain that bacteria have adopted this mechanism in order to provide a competitive advantage in the niches in which they exist. In this sense, the members of soil microbiota are particularly interesting, which have been confirmed to produce enzymes (AHL-lactonases and AHL-acylases) capable of breaking down QS molecules, but also many so-called -ocins, such as bacteriocins, lactocins, enterocins and nisin (Choyam et al., 2019).

Bee products are also recognized as a significant source of molecules with an anti-QS mechanism of action, especially propolis (Bulman et al., 2011) and honey (Maddocks and Jenkins, 2013).

One of the possible solutions in "turning off" the QS system is the application of paraoxonases, enzymes isolated from the serum of mammals, fungi and various plants. These enzymes block the QS system based on the hydrolysis of the lactone ring of N-acyl homoserine lactone (AHL) (Galié et al., 2018).

## CONCLUSION

The QS system regulates the expression of genes responsible for coding many vital functions, which enable bacteria to survive in unfavorable environmental conditions. In an effort to bring the QS system under control, numerous antagonists of signaling molecules have been identified. It is important that food microbiologists are aware of the importance, but also understand the QS system, since strategies that "turn off" the quorum sensing mechanism in the bacterial population represent an effective tool for controlling the growth of undesirable bacteria in food.

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