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# Histamine accumulation in dairy products: Microbial causes, techniques for the detection of histamine-producing microbiota, and potential solutions

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**Abstract**

Histamine poisoning is a significant public health and safety concern. Intoxication from ingestion of food containing high amounts of histamine may cause mild or severe symptoms that can even culminate in cardiac arrest. Nonetheless, although histamine levels in dairy products are not subject to any regulation, important outbreaks and severe adverse health effects have been reported due to intake of dairy products with a high histamine content, especially ripened cheeses. Histamine, a biogenic amine, can accumulate in dairy products as a result of the metabolism of starter and nonstarter lactic acid bacteria, as well as yeasts that contribute to the ripening or flavoring of the final product, or even as a result of spoilage bacteria. The aim of this review is to describe the microbiological causes of the presence of histamine in fermented milk products, and to propose control measures and potential methods for obtaining histamine-free dairy products. Thus, this manuscript focuses on histamine-producing microbiota in dairy products, highlighting the detection of histamine-producing bacteria through traditional and novel techniques. In addition, this review aims to explore control measures to prevent the access of histamine-producing microbiota to raw materials, as well as the formation of histamine in dairy products, such as a careful selection of starter cultures lacking the ability to produce histamine, or even the implementation of effective food processing technologies

**Nomenclature:** BAs, biogenic amines; bp, base pairs; *C. farciminis*, *Companilactobacillus farciminis*; CFU/g, colony forming units per gram; CFU/mL, colony forming units by milliliter; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; DAO, diamine oxidase enzyme; EFSA, European Food Safety Authority; FAO, Food and Agriculture Organization; GMO, genetically modified organisms; HDC, histidine decarboxylase enzyme; *hdc*, histidine decarboxylase gene; HNMT, histamine N-methyltransferase enzyme; HPB, histamine-producing bacteria; HPH, high-pressure homogenization; HPLC, high-performance liquid chromatography; *L. brevis*, *Levilactobacillus brevis*; *L. buchneri*, *Lentilactobacillus buchneri*; *L. casei*, *Lacticaseibacillus casei*; *L. curvatus*, *Latilactobacillus curvatus*; *L. fermentum*, *Limosilactobacillus fermentum*; *L. hilgardii*, *Lentilactobacillus hilgardii*; *L. kefiri*, *Lentilactobacillus kefiri*; *L. parabuchneri*, *Lentilactobacillus parabuchneri*; *L. paracasei*, *Lacticaseibacillus paracasei*; *L. pentosus*, *Lactiplantibacillus pentosus*; *L. plantarum*, *Lactiplantibacillus plantarum*; *L. reuteri*, *Limosilactobacillus reuteri*; *L. rhamnosus*, *Lacticaseibacillus rhamnosus*; *L. sakei*, *Latilactobacillus sakei*; LAB, lactic acid bacteria; *Lb.*, *Lactobacillus*; *Lb. acidophilus*, *Lactobacillus acidophilus*; *Lb. bulgaricus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*; *Lb. delbrueckii*, *Lactobacillus delbrueckii* subsp. *delbrueckii*; *Lb. delbrueckii* subsp. *lactis*, *Lactobacillus delbrueckii* subsp. *lactis*; *Lb. helveticus*, *Lactobacillus helveticus*; *Lc.*, *Lactococcus*; NSLAB, nonstarter LAB; PCR, polymerase chain reaction; PCR-DGGE, PCR-denaturing gradient gel electrophoresis; RT-qPCR, real-time quantitative PCR; SLAB, starter LAB; SNPs, single-nucleotide polymorphisms; WHO, World Health Organization.

  

to reduce histamine-producing microbiota. Finally, the removal of histamine already formed in dairy products through histamine-degrading microorganisms or by enzymatic degradation will also be explored.

**KEYWORDS**
biogenic amines, dairy products, cheese, histamine-producing microbiota, hdcA, DAO, NSLAB

## 1 | INTRODUCTION

As one of the most important biogenic amines (BAs), histamine is involved in immune system response, gastric acid secretion, and neurotransmission, among other processes. However, histamine is also associated with food intolerance and food poisoning. Strategies to prevent, detect, and overcome food safety problems caused by histamine accumulation will be presented in this review.

Histamine is an organic nitrogenous compound exclusively synthesized via oxidative decarboxylation of the amino acid L-histidine by L-histidine decarboxylase (HDC) enzyme. Fermentation in food (red wine, hard cheese, etc.) or improper preservation may result in the formation of high histamine concentrations. Histamine accumulated in food can cause symptoms such as nausea, headache, abdominal pain, diarrhea, and itching (Benkerroum, 2016; Gardini, Ozogul, Suzzi, Tabanelli, & Ozogul, 2016). An estimated 1% of the population could be histamine intolerant or hypersensitive: in such people, even lower intakes of histamine can lead to severe symptoms (Maintz & Novak, 2007). Fish and ripened cheese are the most common foods associated with histamine intoxication (EFSA, 2011). In fresh raw milk, histamine concentration is usually low; however, in fermented dairy products, such as yogurt and especially ripened cheese, variable concentrations of histamine can be detected. A high concentration of nutrients, marked biochemical changes during extended ripening periods, along with complex microbiota make ripened cheese an ideal matrix for histamine accumulation; it is becoming an increasing health concern (Costa, Rodrigues, Frasao, & Conte-Junior, 2018; Linares, Martin, Ladero, Alvarez, & Fernandez, 2011). Many different genera and species of microorganisms are responsible for histamine production in dairy products. This manuscript reviews histamine-producing microbiota, which can be present in dairy products as starter cultures, usually lactic acid bacteria (LAB), or as nonstarter cultures (naturally present in milk), as well as contaminant microorganisms (due to practices during dairy product manufacture or stemming from the processing environment), mainly members of the *Enterobacteriaceae* family. Some yeasts and molds have been reported as histamine producers in dairy products as well (Barbieri, Montanari, Gardini, & Tabanelli, 2019; Linares et al., 2012).

In the food industry, the determination of histamine is a key aspect for food safety, in spite of the fact that its levels in dairy products are not subject to any regulation. Histamine can be detected and quantified in food by several techniques reviewed by Gagic et al. (2019). However, the detection of potential histamine-producing microbiota, reviewed in the present study, may help to determine whether the starter cultures of dairy products are potential histamine producers. Consequently, histamine accumulation in dairy food might be prevented.

It is important to find solutions for obtaining histamine-free dairy products, and to control histamine production through a series of measures. First of all, good hygienic practices must be implemented during manufacturing processes. Ripening and storage temperatures, pH and salt concentration, among others, are important factors that may also exert an influence on histamine production. Additionally, heat or high-pressure homogenization (HPH) treatments applied to milk have been shown to prevent the production of histamine in dairy products (Benkerroum, 2016; Gardini et al., 2016; Linares et al., 2012).

Histamine degradation, on the other hand, is mainly performed by the diamine oxidase enzyme (DAO) or histamine N-methyltransferase (HNMT) (Maintz & Novak, 2007). Thus, chemical or biological histamine degradation by DAO or the addition of strains with the ability to degrade histamine could also be a preventive measure (Benkerroum, 2016; Gardini et al., 2016; Linares et al., 2012).

This review focuses on providing an overview of previous studies related to histamine production in dairy products, highlighting the implication of the present microbiota. In addition, we review potential solutions designed either to prevent the formation of histamine in manufactured products, or its removal. The increased prevalence of histamine intolerance and food allergies in the general population make this issue an emergent worldwide public health care concern.

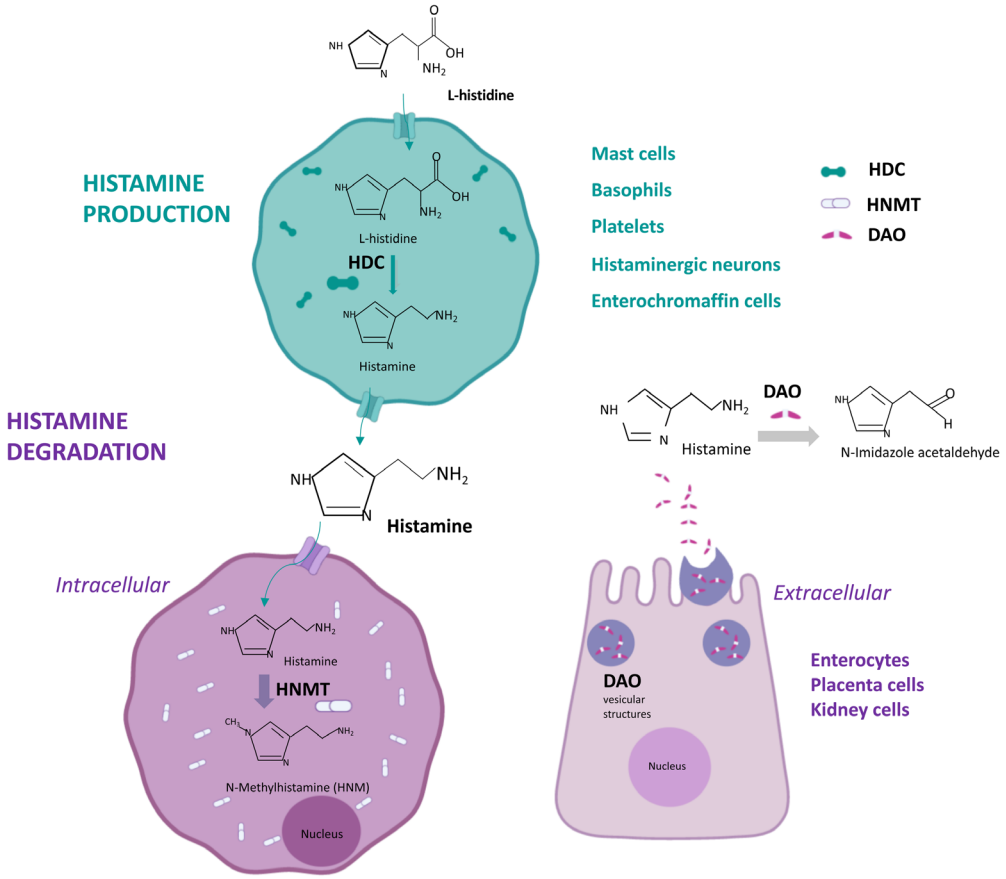


**FIGURE 1** Overview of the main mechanisms of histamine production and degradation in the mammal cell. Histamine is intracellularly synthesized by L-histidine decarboxylase (HDC) from the amino acid histidine by certain mammal cells (mast cells, basophils, platelets, histaminergic neurons, and enterochromaffine cells). Conversely, histamine is intracellularly degraded by histamine N-methyltransferase (HNMT), ubiquitously expressed, and extracellularly by secreted diamine oxidase (DAO), mainly produced in enterocytes

## 2 | HISTAMINE AS A BIOGENIC AMINE: CONSEQUENCES OF ITS ACCUMULATION IN DAIRY FOOD

BAs are low-molecular-weight nitrogenous compounds synthesized by enzymatic decarboxylation of their precursor amino acids, or by amination and transamination of aldehydes and ketones (Benkerroum, 2016; Linares et al., 2011; Pluta-Kubica, Filipczak-Fiutak, Domagała, Duda, & Migdał, 2020). A great variety of BAs exist, with different chemical structures classified as aliphatic (agmantine, putrescine, cadaverine, ethylamine, methylamine, isoamylamine, ethanolamine, spermine, and spermidine), aromatic (tyramine, phenylamine, and phenylethylamine) or heterocyclic (histamine, tryptamine, and pyrrolidine), among others (Linares et al., 2011; Papageorgiou et al., 2018; Spano et al., 2010). From a physiological point of view, BAs are involved in the proper functioning of the human metabolism. On the other hand, histamine and other BAs can serve as indicators of quality and freshness of food and alcoholic beverages (Papageorgiou et al., 2018).

Despite the fact that putrescine and cadaverine have been recently reported as potentially cytotoxic (del Rio et al., 2019), it is well established that histamine and tyramine are the two most toxic BAs; they are the ones most frequently present in dairy products, and the ones which cause the most severe symptomatology. Notably, levels of histamine lower than tyramine appeared to cause typical symptoms in healthy people. This fact, together with the absence of detoxifying mechanisms for histamine in sensitive people who present intoxication symptoms even when exposed to small amounts thereof, makes this BA a major public health concern that needs to be addressed with the appropriate measures (Benkerroum, 2016).

Figure 1 provides an overview of histamine biosynthesis and degradation in the mammal cell. Histamine (2-[4-imidazolyl]ethylamine) is synthesized by oxidative decarboxylation of the amino acid L-histidine, catalyzed by the HDC enzyme. In humans, mast cells, basophils, platelets, histaminergic neurons, and enterochromaffin cells are responsible for synthesizing endogenous histamine, storing a heparin–histamine complex in secretory granules on

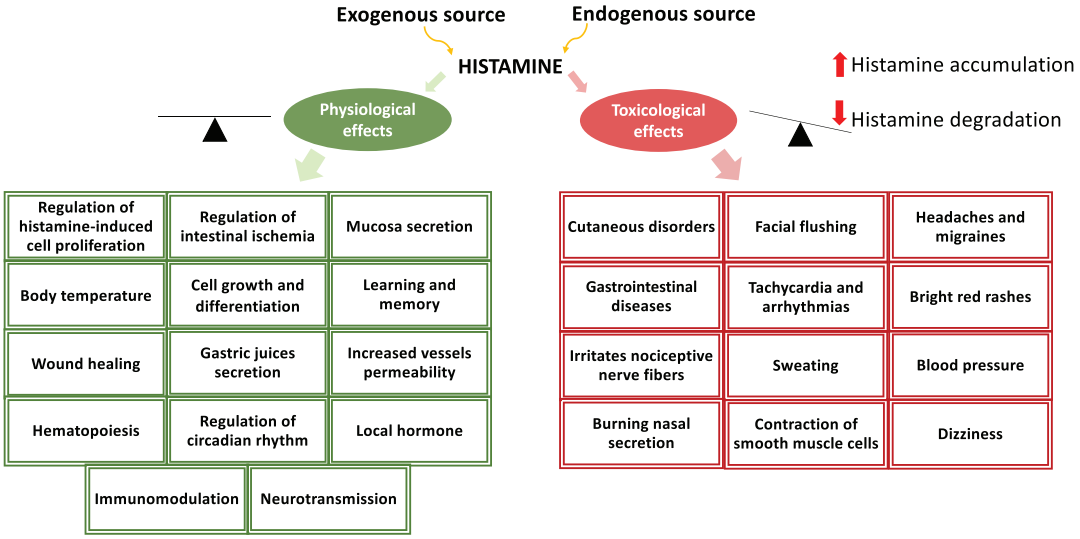


**FIGURE 2** Physiological equilibrium between histamine synthesis/intake and degradation or the consequences of a misbalance due to an increase in histamine accumulation or a decrease in histamine degradation. The physiological and toxicological effects of histamine on the human metabolism are also shown

an intracellular level, and releasing it in response to various stimuli (Maintz & Novak, 2007). Other immune cells, such as T cells, dendritic cells, macrophages, and certain types of epidermal cells, have also been shown to synthesize lower amounts of histamine, which is released without having been stored (Huang, Li, Liang, & Finkelman, 2018).

Present in the brain, lungs, stomach, intestine, uterus, and ureters, histamine is an important mediator of a number of biological processes (Ladero, Calles-Enriquez, Fernandez, & Alvarez, 2010). Figure 2 shows that histamine fulfills important physiological functions, including neurotransmission, regulation of circadian rhythm, immunomodulation, hematopoiesis, gastric juice secretion, vessel permeability, wound healing, learning and memory, mucosa secretion, and regulation of temperature, as well as cell growth and differentiation (Ladero et al., 2010; Maintz & Novak, 2007; Schwelberger, Ahrens, Fogel, & Sánchez-Jiménez, 2014).

Once released, histamine binds one out of the 4 G-protein coupled receptors (H1, H2, H3, or H4) located in target cells, in order to produce those important physiological effects. Most of these effects are caused by the activation of H1 receptors, ubiquitously expressed, and they produce typical type 1 hypersensitivity reactions (allergic and asthma reactions). H2 receptors are involved in immunomodulation, gastric acid secretion, mucus secretion, or vascular permeability. H3 receptors, exclusively expressed in neurons, participate in blood–brain barrier function. H4 receptors are mainly involved in proinflammatory responses (Thangam et al., 2018).

As shown in Figure 1, intracellular histamine can be inactivated by methylation of the imidazole ring, catalyzed by HNMT, a widely distributed enzyme. Conversely, extracellular histamine can be metabolized by oxidative deamination of the primary amino group, catalyzed by DAO, a copper-dependent amino oxidase also called histaminase, which is mainly produced by enterocytes, but also by placenta and kidney cells (Comas-Basté, Sánchez-Pérez, Veciana-Nogués, Latorre-Moratalla, & Vidal-Carou, 2020; Ladero et al., 2010; Schwelberger et al., 2014).

Figure 2 depicts the physiological equilibrium between histamine synthesis/intake and degradation or the consequences of a misbalance. When increased availability of histamine or decreased histamine degradation occurs, histamine accumulation causes unspecific gastrointestinal symptoms as well as extra-intestinal symptoms, mainly immediately after (few min) or even during meals, for a period up to 24 hr (Comas-Basté et al., 2020; Tuck, Biesiekierski, Schmid-Grendelmeier, & Pohl, 2019). The toxicological effects of histamine include vascular disorders (dilation of arteries and increased capillary permeability producing headache, hypotension, edemas, urticaria, facial flushing, etc.), heart disorders (a stimulatory effect leading to palpitations, tachycardia, and arrhythmia), gastrointestinal disorders (contraction of smooth muscle cells causing cramps, diarrhea, and vomiting), and neurological disorders (stimulatory effects resulting in pain and itching) (FAO/WHO, 2013; Ladero et al., 2010; Maintz & Novak, 2007; Schnedl et al., 2019).

Histamine can be expected to be present in all foods containing free histidine or proteins that can suffer proteolysis (Tuck et al., 2019); foods rich in histamine are detailed in Comas-Basté et al. (2020). Histamine may be present in

fermented food as a consequence of the oxidative decarboxylation of L-histidine via the HDC enzymes from the microbiota of these products (Landete, Pardo, & Ferrer, 2008). A fairly efficient detoxification system, based on intestinal and liver amine oxidases, metabolizes the regular dietary intake of histamine (Schwelberger et al., 2014).

However, the presence of high amounts of this BA in food has been associated with histamine intolerance and intoxication (Maintz & Novak, 2007). Several studies of oral administration of histamine have shown that the same histamine dosage produces different effects and severity of symptomatology depending on each participant (EFSA, 2011). For that reason, it is well established that a percentage estimated in 1% of the population suffers from a great sensitivity to this compound, which is known as histamine intolerance (Comas-Basté et al., 2020). It is caused by the ingestion of moderate levels in food, and results from an imbalance between the amount of accumulated histamine and the capacity for its degradation, mainly linked to a DAO deficit. The enzymatic activity and detoxification efficiency of DAO vary significantly among individuals. In some cases related to DAO deficiency, it can lead to hypersensitivity to histamine and subsequent variable symptomatology (Comas-Basté et al., 2020; Ozogul & Ozogul, 2020).

In relation to the etiology of histamine intolerance, several single-nucleotide polymorphisms (SNPs) in the DAO-encoding gene result in decreased activity of the enzyme, whereas other SNPs in the promoter region of that gene produce a diminished transcription level and thus a decreased level of the enzyme. However, DAO deficiency is not only due to a genetic background. It could also be related to impaired DAO activity, caused by inflammatory bowel pathologies or certain functional intestinal disorders, such as carbohydrate malabsorption or nonceliac gluten sensitivity. Finally, temporary and reversible DAO inhibition could also result from the presence of other BAs, alcohol, or even certain drugs as chloroquine, clavulanic acid, metamizol, and so on (Comas-Basté et al., 2020). The diagnostic criteria of histamine intolerance include low serum DAO values, two or more of the typical symptoms exposed above, and clinical improvement as a consequence of histamine-free or reduced diet, or of the intake of antihistaminergic medication (Schnedl et al., 2019; Tuck et al., 2019). Scientific publications referring to histamine intolerance or histaminosis have exponentially increased over the last two decades, thereby indicating the importance of this disorder (Comas-Basté et al., 2020).

On the other hand, histamine intoxication, caused by the ingestion of food containing high levels of histamine (Bodmer, Imark, & Kneubühl, 1999), is an immune system response that usually appears in the course of a short period (up to 24 hr) after ingestion of contaminated food (Hungerford, 2010). The diagnosis is based on increased plasma histamine levels associated with the previous uptake of food with proved high histamine content (Comas-Basté et al., 2020).

Histamine is commonly found in dairy products, such as cheese and yogurt, or raw, pasteurized, and Ultra High Temperature (UHT) milks of different animal species, as well as reconstituted powdered milk (Benkerroum, 2016; Costa et al., 2018; Ladero et al., 2017; Linares et al., 2011; Spano et al., 2010). Amounts of BAs in milk, yogurt, cottage, and unripe cheeses can be expected to range from milligrams to tens of milligrams per kg (Linares et al., 2011; Spano et al., 2010). Histamine is present in higher amounts in fermented or ripened dairy products (Costa et al., 2018). In such products, variable amounts of histamine (7 mg/kg in sour cream, 13 to 21.2 mg/kg in yogurt, and 4 mg/kg in kefir) have been found (Bodmer et al., 1999; Özdestan & Üren, 2010). A drastic increase in histamine content often takes place in the course of cheese production, leading to histamine levels of up to 2,500 mg/kg in aged cheese, a highly toxic amount. Histamine concentration varies among different types of ripened cheese and may differ within the same type of cheese, even within parts thereof, also depending on ripening time, manufacturing process conditions, and the bacterial starter culture used (Madejska, Michalski, Pawul-Gruba, & Osek, 2018; Novella-Rodríguez, Veciana-Nogués, Izquierdo-Pulido, & Vidal-Carou, 2003).

The first outbreak of histamine poisoning related to cheese was reported in 1967, involving Gouda and Swiss cheeses containing 850 to 2,500 mg/kg, but other cheese varieties, including Gruyere, Parmesan, Emmental, Suisse, and Provolone, have also been involved in outbreaks (Fernandez-Garcia, Tomillo, & Nunez, 2000; Maintz & Novak, 2007). A study conducted by Rauscher-Gabernig, Grossgut, Bauer, and Paulsen (2009) concluded that tolerable limits for histamine in cheese would be 100 to 417 mg/kg on the basis of a supposed daily consumption of 60 g. Based on Austrian data for usual serving sizes and histamine concentration in foods, a proposed limit of 400 mg/kg is considered acceptable for cheeses (Rauscher-Gabernig et al., 2009). Given this threshold dose for histamine in cheese, Madejska et al. (2018) found that the amine content exceeded that value in Gorgonzola (400 and 730 mg/kg), and reached that level of toxicity in Camembert.

Maximum legal limits for histamine have been established for fresh fish (200 mg/kg) and cured fish products (up to 400 mg/kg) by European Commission Regulation No. 2073/2005 (European Parliament, 2005). Despite the existing legal limits for fish, the histamine content in dairy products is not regulated by any type of legislation; maximum recommended concentrations have only been

suggested. For instance, the Netherlands Institute of Dairy Research sets a limit of 100 to 200 mg/kg on histamine in foods. In order to guarantee food safety and consumer health, legal histamine limits for dairy products should be established in regulations and enforced.

Overall, ripening cheeses are the most common candidates among dairy products for the potential accumulation of high contents of histamine; they are thus prone to cause significant adverse health effects and thereby constitute a notable health risk for consumers. Further insights into the inherent characteristics of dairy products, including composition, biochemical changes, and above all present microbiota, should enable our health systems to prevent, detect, and overcome the formidable safety issue constituted by histamine in dairy products.

## 3 | INHERENT CHARACTERISTICS OF DAIRY PRODUCTS WITH POTENTIAL IMPACT ON HISTAMINE PRODUCTION

### 3.1 | Composition and biochemical changes in raw milk and fermented (cultured) dairy products

Milk is a secretion from mammary glands, which serves as the basic food for neonates. It contains multiple nutrients whose proportion varies among animal species, explained in Table 1, as well as in the course of the lactation period in order to meet the varying nutritional needs of neonates. Protein content in the milk of several different dairy animals might vary from 3.4% in cow milk to 5.7% in sheep milk (Table 1). This can be of particularly importance because proteins are the main source of histidine in milk as a precursor of histamine. Apart from mother's milk, humans consume milk from certain domestic animals, such as cows, goats, sheep, and buffalos, either in the form of fresh milk or as dairy products. Cow and buffalo milks are the most widely consumed milks in the world, although interest in goat and sheep milks has increased in recent years (OECD & FAO, 2020).

The proportions of chemical components in milk largely determine its nutritional, organoleptic, technological (i.e., chemical and physical reactions that can occur therein), and microbiological (i.e., microbiological species and microbial load) properties (Walstra, Wouters, & Geurts, 2006). Due to the importance of histidine in histamine formation, we will focus on milk proteins, as the main source of amino acids. In cow milk, two groups of proteins can be differentiated according to their pH stability. Caseins represent approximately 80% of total protein, while the remaining approximately 20% is composed of whey (serum) proteins. Caseins (a mixture of

**TABLE 1** Average composition in % w/w and range (in parentheses) of milk from different species (Ballard & Morrow, 2013; Becskei et al., 2020; Jenness, 1980; Recio, de la Fuente, Juárez, & Ramos, 2009; Walstra et al., 2006)

| | Human | Cow | Goat | Sheep | Buffalo |
|---|---|---|---|---|---|
| Fat | 3.4 (3.2 to 3.6) | 3.7 (2.5 to 5.5) | 4.7 (3.0 to 7.8) | 7.1 (5.1 to 8.7) | 6.0 (4.3 to 7.2) |
| Protein | 1.2 (0.6 to 1.4) | 3.4 (2.3 to 4.4) | 3.6 (2.9 to 5.0) | 5.7 (4.8 to 6.6) | 4.6 (4.1 to 5.6) |
| Lactose | 7.2 (6.7 to 7.8) | 4.8 (3.8 to 5.3) | 4.9 (1.0 to 6.3) | 4.6 (4.1 to 5.0) | 5.4 (5.1 to 5.6) |

four heat-stable proteins: $\alpha_{s1}$-, $\alpha_{s2}$-, $\beta$-, and $\kappa$-casein) are present in form of large colloidal particles, known as casein micelles (40 to 600 nm diameter with an average of 5,000 casein molecules/micelle). Casein micelles precipitate either at pH 4.6 or by action of rennet chymosin on $\kappa$-casein. Caseins are susceptible to proteolysis due to their open structure (Fox & Kelly, 2006). On the other hand, whey proteins ($\beta$-lactoglobulin, $\alpha$-lactalbumin, blood serum albumin, and immunoglobulins) are globular, heat-sensitive, soluble at pH 4.6, and very resistant to chymosin and proteolysis. In addition, nonprotein nitrogenous compounds represent 5% of total nitrogen in fresh milk, comprising intermediate products of the animal's protein metabolism (e.g., ammonia, urea, creatine, creatinine, and uric acid), amino acids and their derivatives, as well as small peptides that may serve as essential nutrients for certain bacteria (Croguennec, Jeantet, & Shuck, 2016).

Milk additionally contains indigenous enzymes at trace levels, including proteinases, of which the trypsin-like endopeptidases plasmin (alkaline proteinase) and cathepsin D (acid proteinase) are the ones most relevant for this review. Plasmin is highly heat-resistant and contributes to proteolysis in cheese during ripening. Cathepsin D is less heat-resistant than plasmin; due to its low optimum pH (4.0), it displays a reduced activity in milk but causes proteolysis in cheese (Walstra et al., 2006).

In Europe and North America, the consumption of processed dairy products is greater than that of fresh dairy products. Furthermore, an increase of cheese consumption in those countries is expected for the next decade (OECD & FAO, 2020). Fermentation was a key process for food preservation in ancient times. Dairy products were central in Neolithic food cultures across much of the Old World, and it is likely that milk was often fermented to obtain a safer and more digestible product while avoiding seasonal or logistic fluctuations in the availability of fresh milk. Although it was previously assumed that food fermentation began with agriculture, it is now assumed that storage was and is widely practiced by nonsedentary foragers in order to have portable protein-rich foods at their disposal during travels (Sibbesson, 2019).

Due to its wide range of nutrients, which allow the growth of many spoilage and pathogenic microorganisms, milk is rarely consumed in its raw state. Microbial conversion of lactose is the basis for fermented milks. Microorganisms with lactase activity, such as LAB, metabolize lactose into glucose and galactose, which are degraded to lactic acid. LAB can produce 1% to 2% of lactic acid leading to milk acidification (pH 4.0 to 4.6) that destabilizes dispersed elements and controls bacterial growth (Kelly & Fox, 2012).

Yogurt is obtained from pasteurized milk inoculated with starter cultures containing *Streptococcus salivarius* spp. *thermophilus* (*S. thermophilus*) and *Lactobacillus delbrueckii* subsp. *bulgaricus* (*Lb. bulgaricus*) (Hill, Ross, Arendt, & Stanton, 2017). The Codex Alimentarius Commission (CODEX STAN 243–2003) has established the sum of the specific microorganisms constituting the starter culture in the final product at $\geq 10^7$ colony forming units per gram (CFU/g) (Commission, 2011). *Lb. bulgaricus* is required for acid production, whereas *S. thermophilus* is responsible for the flavor and texture of yogurt: the two bacteria have a synergistic relationship. After fermentation, yogurt is refrigerated to decelerate microbial metabolism and delay excessive microbial acidification or proteolysis (Walstra et al., 2006).

Kefir, on the other hand, is a creamy, aromatic, carbonated acid-alcohol milk beverage (0.7% to 1% lactic acid, pH 4.6) of Eastern European origin. It is prepared by adding "kefir grains" (composed of LAB, acetic acid bacteria, and yeast in a polysaccharide matrix of semihard granules) to milk and incubating for 24 hr at 25 °C (Guzel-Seydim, Kok-Tas, Greene, & Seydim, 2011). Volatile and nonvolatile compounds generated upon fermentation via lipolysis, glycolysis, and proteolysis provide its characteristic flavor. After fermentation, grains are separated and kefir is refrigerated to attain a shelf-life of 2 to 3 weeks (Farag, Jomaa, El-Wahed, & El-Seedi, 2020).

Cheese can be defined as the curd of milk that has been coagulated and separated from whey. Basically, in the cheese manufacturing process, water and whey are removed from milk, and casein and fat are concentrated. Figure 3 shows the basic process for cheese production (Walstra et al., 2006), including the microbiota associated with each step. In brief, the steps involved are the following:

1. The clotting of milk, consisting of the precipitation of casein micelles by acidification (acid coagulation) and/or enzymatically (rennet coagulation), leading to gel formation.
2. Removal of the whey: the separation of curd and whey is achieved by cutting and stirring, and is facilitated by the spontaneous syneresis of the formed gel. Soluble compounds, including whey proteins, small peptides, and most of the lactose, are squeezed out and excluded from cheese. However, certain proteases, such as plasmin and cathepsin D, tend to adsorb onto micelles, which are present during ripening, thereby facilitating amino acid availability.
3. Production of lactic acid by LAB before and/or after steps 1 and 2. After these three steps, a fresh cheese is obtained. For a typical ripened cheese, the following two additional steps are required.

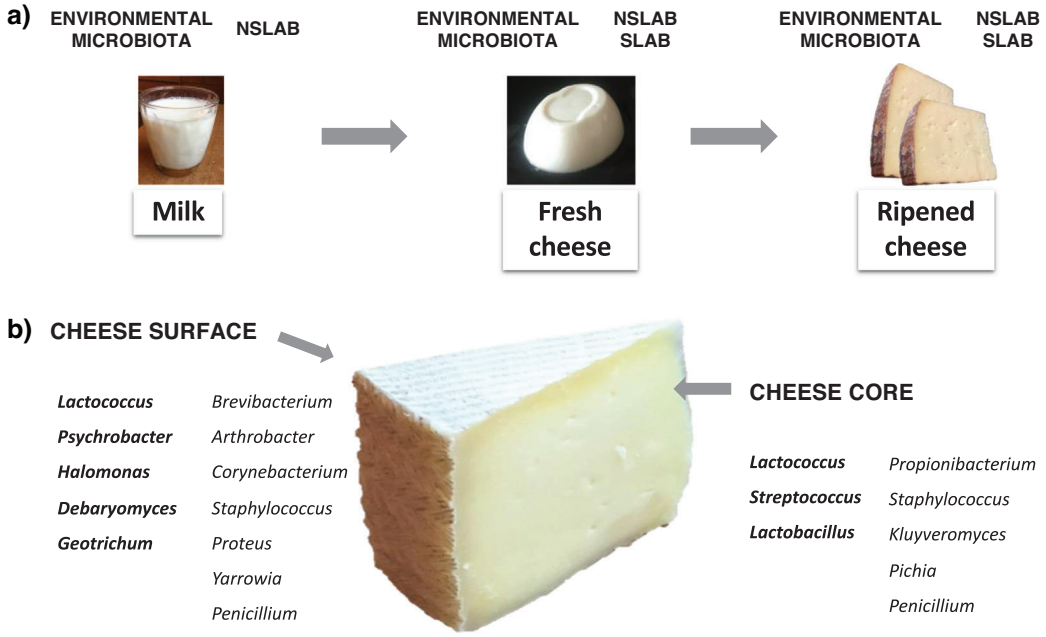


**FIGURE 3** Cheese microbiota. (A) Source of histamine-producing microbiota in cheese making. (B) Microorganisms present in cheese surface versus core: those able to synthesize histamine are highlighted in bold

4. Curd fusion, assisted by pressing. A rind can be formed, shielding the interior of the cheese, which contributes to the limitation of oxygen and water transfer for microbial growth.
5. Ripening or curing: a biochemical process determined by a number of factors (Kelly & Fox, 2012), such as endogenous milk enzymes (e.g., plasmin or lipoprotein lipase), starter and nonstarter LAB, and their enzymes, thoroughly active secondary microbiota, which secrete proteases and lipases (e.g., *Penicillium roqueforti* in blue cheeses or *Leuconostoc* spp. in Dutch-type cheeses), and storage conditions (e.g., temperature, time, and humidity).

Salting (usually after step 2) is another key step designed to modify organoleptic characteristics and improve cheese preservation (by selecting growing microbiota). It involves the direct addition of salt crystals (in curd or rubbed onto surface) and/or immersion in a concentrated brine, in order to achieve a salt-in-water concentration ranging from 1% NaCl in cottage cheese up to 6% NaCl in Pecorino Romano cheese (Walstra et al., 2006). Further optional process steps can be mentioned, such as milk pasteurization (prior to step 1) with the purpose of inactivating pathogenic bacteria as well as microorganisms and enzymes that could be detrimental to ripening; and/or addition of microbial cultures (after steps 1 and/or 2), especially highly selected defined starters of LAB, and other microorganisms that are specific for certain cheese varieties.

Modifications in these steps allow for the achievement of more than 1,400 cheese varieties worldwide, with different shapes, flavors, and textures (Kelly & Fox, 2012). During ripening, which can take from 2 weeks up to more than 2 years, three major biochemical reactions take place (Croguennec et al., 2016): (1) fermentation of residual lactose and degradation of lactate to ethanol, acetaldehyde, $CO_2$, acetic acid, or propionic acid; (2) hydrolysis of lipids into fatty acids, and of proteins into peptides and amino acids, respectively; and (3) flavor: the production of aroma by the degradation of fatty acids to methyl ketones, esters or lactones, and of amino acids to aldehydes, alcohols, acids, amines, phenolic compounds, indole, or $NH_3$.

Cheese can be considered a solid-like system in which bacteria are immobilized and molecules do not diffuse easily (Floury, Jeanson, Aly, & Lortal, 2010; Walstra et al., 2006). Therefore, microbial growth conditions fluctuate and vary as a function of time and localization in cheese. After production of lactic acid, bacterial metabolism and proteolysis create $NH_3$, which increases pH (Kelly & Fox, 2012). Water evaporation decreases water activity of cheese and facilitates the formation of rind around the cheese, thereby preventing microbial contamination and limiting oxygen diffusion. Oxygen is rapidly used by starter bacteria, favoring the creation of anaerobic conditions inside the cheese. All these physicochemical changes modify the environmental conditions for bacterial development, thereby promoting a dynamic microbiota during cheese ripening.

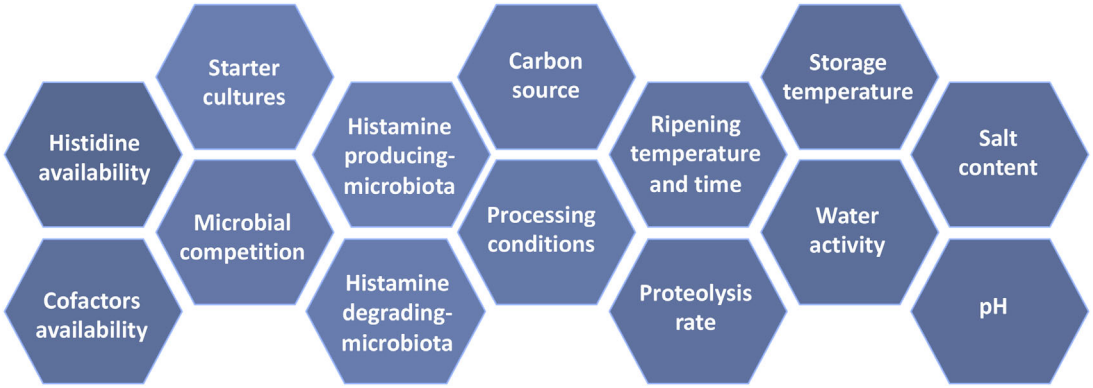


**FIGURE 4** Factors related to histamine production in dairy products, including availability of precursors, environmental conditions, and microbiological factors. All these factors should be carefully controlled in dairy products to avoid histamine accumulation

## 3.2 | Microbiota in dairy food

The detection of the main agents responsible for histamine production should be regarded as an important objective for dairy industries in order to avoid harmful outbreaks. Deciphering the microbiota present in dairy food can be regarded as a first step to elucidate which particular microorganisms are responsible for histamine production. Figure 3 displays the main microbiota involved in the cheese-making process from raw milk to ripened cheese, highlighting the final histamine producers both in cheese surface and core. The formation of this BA by histamine-producing microbiota is modulated by a series of factors that are detailed in Figure 4. In cheese, factors, such as the type of starter cultures, salt content, ripening, and storage temperatures and times, among others, may influence the production of histamine and the amounts of this BA in cheese.

The microbiota of raw milk is mainly composed of LAB (starter and nonstarter), environmental microbiota or contaminants, putative spoilage bacteria, mostly stemming from the teat skin, but also from the farm environment, hygienic practices, or milking and storage equipment (Figure 3) (Jonnala, McSweeney, Sheehan, & Cotter, 2018; Irlinger, Layec, Helinck, & Dugat-Bony, 2015; Odeyemi, Alegbeley, Strateva, & Stratev, 2020). The composition of milk microbiota is diverse, with a high abundance of LAB, and differs depending on the milk's origin: cow, goat, sheep, or buffalo milk (Agrimonti, Bottari, Sardaro, & Marmiroli, 2019; Quigley et al., 2013; Tilocca et al., 2020). In Regulation (EC) No 853/2004, the European Union established the total bacterial plate count limit in raw cow's milk at $\leq 10^5$ colony forming units per milliliter (CFU/mL) at 30 °C, although this limit is allowed to increase to $\leq 1.5 \times 10^6$ CFU/mL for milk from other species (European Parliament, 2004). In general, bacteria present in cooled raw milk include gram-positive species, such as spore-forming bacteria (*Clostridium, Bacillus*), nonstarter LAB (*Lactobacillus* [*Lb.*], *Lactococcus* [*Lc.*], *Streptococcus, Leuconostoc*, and *Pediococcus*), and others (*Corynebacterium, Microbacterium*, and *Staphylococcus*). Gram-negative bacteria are also present in cooled raw milk, usually as environmental or contaminant microbiota: the *Enterobacteriaceae* family and others (*Pseudomonas, Aeromonas, Alcaligenes, Achromobacter, Acinetobacter, Flavobacterium*, and *Chryseobacterium*) (Odeyemi et al., 2020; Settanni & Moschetti, 2010). The *Pseudomonads* family has been reported to be the predominant spoilage bacteria found in cooled raw milk, reaching 70% to 90% of the total microbial load (Odeyemi et al., 2020). Pathogenic foodborne bacteria, such as *Listeria, Campylobacter, Yersinia, Mycobacterium, Escherichia, Salmonella*, *Coxiella*, and *Staphylococcus*, have also been found in raw milk (Agrimonti et al., 2019; Tilocca et al., 2020). The yeasts most commonly present in raw milk are *Kluyveromyces, Yarrowia, Geotrichum, Candida, Debaryomyces*, and *Pichia* (Frohlich-Wyder, Arias-Roth, & Jakob, 2019; Irlinger et al., 2015). Bacteriophages or phages are viruses capable of infecting bacteria, and they can achieve entry into dairy products through raw milk (Fernandez et al., 2017). *Lc. lactis, Lb. helveticus, Lb. delbrueckii, Lactiplantibacillus plantarum* (formerly *Lb. plantarum*), *Lb. acidophilus, Lacticaseibacillus casei* (formerly *Lb. casei*), *L. paracasei*, *S. thermophilus*, and *Leuconostoc* spp. can be infected by phages (del Rio et al., 2007; Marco, Moineau, & Quiberoni, 2012; Muhammed, Krych, Nielsen, & Vogensen, 2017).

Regarding yogurt, in addition to the aforementioned starter cultures *Lb. bulgaricus* and *S. thermophilus* used in adequate proportions to perform lactic fermentation, it can contain other beneficial or deleterious microorganisms. Probiotic bacteria, such as *Bifidobacterium* spp. and *Lactobacillus* spp., which are not part of the starter

cultures, can be found in probiotic fermented milks, namely bioyogurts (Aryana & Olson, 2017; Hill et al., 2017). Flavor can be improved by adding further cultures as *S. diacetylactis* or *Leuconostoc* spp. Phages active against *S. thermophilus* or *Lb. bulgaricus*, and yeast, such as *Torulopsis*, have also been reported for yogurt (Aryana & Olson, 2017). Additionally, viable *L. monocytogenes* and *S. enterica* cells have been detected in certain yogurts, as well as further pathogens, including *Y. enterocolitica, M. tuberculosis*, and *B. cereus*. However, the true hygienic state of yogurt has not been defined by the presence of pathogenic species, but has been suggested to be controlled by monitoring the *Enterobacteriaceae* family (Hervert, Martin, Boor, & Wiedmann, 2017). Other episodes of food poisoning involving yogurts have been caused by *E. coli* O157:H7, *C. botulinum*, and *S. typhimurium* (Aryana & Olson, 2017).

The microbiota of kefir and kefir grains comprises species of bacteria (*Lactobacillus, Lactococcus, Streptococcus, Leuconostoc, Acetobacter*, and *Enterococcus*) and yeasts (*Saccharomyces, Candida, Kluyveromyces, Zygosaccharomyces, Debaryomyces, Issatchenkia, Pichia*, and *Torulopsis*) (Guzel-Seydim et al., 2011; Singh & Shah, 2017; Tang et al., 2020). It should be noted that the Codex Alimentarius Commission (CODEX STAN 243–2003) specifically mentions the presence of *Lentilactobacillus kefiri* (formerly *Lb. kefiri*) and the yeasts *K. marxianus, S. unisporus, S. cerevisiae*, and *S. exiguous*. It also establishes at $\geq 10^7$ CFU/g the sum of the specific microorganisms constituting the starter culture in the final product, and the sum of yeasts at $\geq 10^4$ CFU/g (Commission, 2011). Some species of probiotics, such as *B. lactis, Lb. acidophilus*, or *L. rhamnosus* (formerly *Lb. rhamnosus*), can also be added to kefir (Aryana & Olson, 2017).

The microbiota present in cheese is key for its organoleptic and physicochemical properties. Cheese microbiota varies depending on starter and nonstarter cultures, and changes over time (Figure 3). Bacterial communities present in cheese display an immense diversity, greater than that of fungal communities, depending on cheese variety and manufacturing process (Afshari, Pillidge, Dias, Osborn, & Gill, 2020; Rezac, Kok, Heermann, & Hutkins, 2018). LAB are definitely the most important microorganisms present in cheese microbiota in view of their involvement in the fermentation and maturation processes (Settanni & Moschetti, 2010). Starter LAB (SLAB), including *Lactococcus*, *Streptococcus* and *Leuconostoc*, contribute to the initial ripening process, due to the fermentation of lactose. Thus, SLAB are involved in coagulation of milk and acid development. During cheese manufacture, the SLAB population comprises up to $10^8$ to $10^9$ CFU/g. The most common mesophilic SLAB is *Lc. lactis*, although strains of *Leuconostoc* spp. are also used; whereas thermophilic SLAB usually consist of strains of *S. thermophilus, Lb. delbrueckii, and Lb. helveticus* (Blaya, Barzideh, & LaPointe, 2018; Settanni & Moschetti, 2010). However, the stresses and harsh conditions (high salt, low pH, low sugar availability, low moisture…) that appear in the cheese matrix as a consequence of the cheese-making process lead to a reduction in the population of SLAB due to autolysis (Gatti, Bottari, Lazzi, Neviani, & Mucchetti, 2014; Møller, Christensen, & Rattray, 2021). Instead, adventitious nonstarter LAB (NSLAB), which mainly stem from raw milk, need to be present because they contribute to the development of desirable flavor. NSLAB can grow and survive in more adverse environmental conditions, such as pH as low as 5.0 or energy depletion (Barbieri et al., 2019). For that reason, an initial population of $10^2$ to $10^3$ CFU/g of NSLAB is found in cheese, but it can reach up to $10^9$ CFU/g during the onset of ripening (Blaya et al., 2018; Gatti et al., 2014). Among the NSLAB *Lactobacillus* strains, the obligate homofermentative species *Companilactobacillus farciminis* (formerly *Lb. farciminis*), the facultative heterofermentative species *L. rhamnosus, L. paracasei, L. casei*, *L. plantarum, L. pentosus* (formerly *Lb. pentosus*), and *Latilactobacillus curvatus* (formerly *Lb. curvatus*), and the obligate heterofermentative species *Limosilactobacillus fermentum* (formerly *Lb. fermentum*), *L. buchneri* (formerly *Lb. buchneri*), *L. parabuchneri* (formerly *Lb. parabuchneri*), and *Levilactobacillus brevis* (formerly *Lb. brevis*), are considered to be the main NSLAB found in cheese. Other NSLAB found in cheese are *Pediococcus* species (*P. acidilactici* and *P. pentosaceus*), *Enterococcus* species (*E. durans, E. faecalis*, and *E. faecium*), and *Leuconostoc* spp. (Settanni & Moschetti, 2010). Other microorganisms as enterococci, micrococci, and yeasts are likewise important in cheese microbiota for maturation (Button & Dutton, 2012; Gardini et al., 2006; Gobbetti, Minervini, Pontonio, Di Cagno, & De Angelis, 2016). For instance, *B. linens* or *S. equorum* contribute to the development of flavor, aroma, and color in cheese; even *Propionibacterium freundenreichii* causes the typical holes in Swiss cheeses by producing $CO_2$ during fermentation (Button & Dutton, 2012; Jonnala, McSweeney, Sheehan, & Cotter, 2018). On the other hand, coliforms are considered indicative of nonhygienic conditions and thus regarded as undesirable contaminants; *Pseudomonas* spp., *Serratia* spp., and *Kluyvera* spp. can reduce the sensory quality of cheese (Coton et al., 2012). Foodborne pathogens, such as *L. monocytogenes, Salmonella* spp., *E. coli*, and *Campylobacter* spp., have been detected in soft cheese samples (Cremonesi et al., 2016). Cheese can also contain spoilage bacteria: in fact, the *Clostridium* spore might survive the entire cheese production process (Odeyemi et al., 2020). Bacteriophages active against *S. thermophilus* or *Lc. lactis*, for instance, are also present in cheese, thus helping to modulate the bacterial community (Gobbetti et al., 2016). Yeasts found in cheese

participate in the ripening process, and contribute to its texture and organoleptic properties. *Debaryomyces*, *Yarrowia, Candida, Geotrichum, Kluyveromyces, Saccharomyces*, and *Pichia* are the most commonly described genera (Gardini et al., 2006; van den Tempel & Jakobsen, 2000). Some of them, like *D. hansenii* and *Y. lipolytica*, can be used as starter cultures due to their capacity to grow under hostile conditions and to improve the flavor and quality of cheese (Ferreira & Viljoen, 2003). *Penicillium*, *Scopulariopsis*, and *Fusarium* are important filamentous fungi found in cheese (Irlinger et al., 2015). Opportunistic pathogenic yeasts, mainly the *Candida* species, can also be present in cheese (Frohlich-Wyder et al., 2019). With regard to cheese localization, Figure 3 shows that the microbiota in the cheese rind differs from the microorganisms present in the core. Ripening bacteria (*Brevibacterium, Arthrobacter*, and *Corynebacterium)* and psychrophilic and halophilic bacteria (*Psychrobacter*, *Halomonas*, and *Proteus)* are mostly present on the cheese surface because they cope with the deacidification process. However, LAB are usually found in the cheese core, as well as anaerobic bacteria, such as *Propionibacterium* that grow inside the wheel of cheese (Button & Dutton, 2012; Coton et al., 2012; Frohlich-Wyder et al., 2019). Only yeasts able to ferment carbohydrates, such as *K. marxianus*, *K. lactis*, and *P. fermentans*, can survive in the cheese core, while the yeasts predominant on the surface are acid and salt tolerant: the most abundant ones are *D. hansenii, Y lipolytica*, and *G. candidum* (Frohlich-Wyder et al., 2019). In relation to molds, spores of *P. camemberti* are inoculated into milk of Brie and Camembert cheeses to develop bloomy rind, while *P. roqueforti* grows in the core of blue cheese, producing its blue pigment during sporulation (Button & Dutton, 2012; Jonnala et al., 2018).

## 4 | ENVIRONMENTAL CONDITIONS APPLIED TO DAIRY FOODS MAY INFLUENCE HISTAMINE ACCUMULATION

The amount of histamine in dairy food, and even the presence or absence thereof, is determined by a number of factors, shown in Figure 4, which include available precursors or cofactors, environmental conditions, such as acidic pH, ripening and storage temperatures, water activity, and salt concentration (Costa et al., 2018). Furthermore, microbiological factors, such as microbial competition or the presence of microbiota capable of degrading histamine, could also contribute to modify the amount of histamine present in dairy food (Coton et al., 2012). All these factors should be carefully controlled in order to obtain histamine-free dairy products.

The availability of histidine, the precursor amino acid for the synthesis of histamine during the ripening of cheese, is a limiting factor on histamine formation (Linares et al., 2011). Although histidine can be naturally present in milk in a free state, the proteolysis of casein or other milk proteins is the main cause of the presence of this substrate amino acid in milk and dairy products (Benkerroum, 2016). Since the rate of proteolysis increases with ripening time, long-ripened cheeses present higher concentrations of histamine. Ripening time also contributes to the proteolysis rate, so that long-ripened cheeses have a higher proteolysis rate and thus a higher level of histamine (Fernandez, del Rio, Linares, Martin, & Alvarez, 2006). The addition of exogenous proteinases to milk with the aim of accelerating cheese ripening significantly increases the amount of histamine in a wide variety of cheeses (Linares et al., 2011).

NSLAB are known to survive and grow under very harsh conditions, such as an acidic pH. Since amino acid decarboxylases in bacteria are known to contribute to their adaptation to acidic environment (because the decarboxylation process results in an increase of environmental pH), an acidic pH in the final dairy product could also promote the synthesis of histamine (Barbieri et al., 2019; Linares et al., 2012). The HDC enzyme of *S. thermophilus* seems to be much more active at pH 4.5 than at pH 8 (Tabanelli, Torriani, Rossi, Rizzotti, & Gardini, 2012). It has also been reported that acidic pH may induce structural changes in the HDC from *Lactobacillus* sp. 30a (ATCC 33222) required for the protein to be active (Schelp, Worley, Monzingo, Ernst, & Robertus, 2001). At pH 8.0, however, histamine accumulation was also observed in a culture of *Tetragenococcus halophilus* (Satomi, Furushita, Oikawa, Yoshikawa-Takahashi, & Yano, 2008).

Sodium chloride concentrations higher than 5% (w/v) seem to notably decrease the amount of histamine, probably due to an inhibitory effect on the growth rate of histamine producers (Tabanelli et al., 2012). However, the halophilic bacterium *Tetragenococcus* can produce histamine even at up to 20% (w/v) NaCl (Kimura, Konagaya, & Fujii, 2001; Satomi et al., 2008).

The carbon source could also be a factor that influences bacterial histamine formation, depending on the histamine producer. High concentrations of glucose or lactose have been reported to inhibit the production of histamine, although a recent study showed no effect of the presence of up to 2% glucose on the synthesis of histamine for *L. parabuchneri* and *L. paracasei*, but completely inhibiting histamine formation by *P. pentosaceus* (Calles-Enriquez et al., 2010; Møller, Ucok, & Rattray, 2020).

High storage temperatures and prolonged ripening time increase the microbial production of histamine. For instance, the concentration of histamine was 10-fold higher at 42 °C than at 4 °C in a culture of *S. ther-*

*mophilus* grown in milk after 24 hr, due to the activity of the enzyme rather than to a variation in its gene expression (Calles-Enriquez et al., 2010). *L. parabuchneri*, isolated from cheese, has also been reported to grow and produce histamine at refrigeration temperatures (4 to 8 °C), but this characteristic seems to be strain-dependent (Díaz et al., 2018).

On the other hand, as mentioned above, the *hdc* genes in some bacteria, such as *T. muriaticus*, *T. halophilus*, *Oenococcus oeni*, and *L. hilgardii* (formerly *Lb. hilgardii*), are codified in unstable plasmids (Lucas, Claisse, & Lonvaud-Funel, 2008; Lucas, Wolken, Claisse, Lolkema, & Lonvaud-Funel, 2005; Satomi et al., 2008). In these cases, the instability of the plasmid depends on the bacterial culture conditions, since a poor and acidic medium seems to favor the maintenance of the plasmid and thus the expression of the gene.

## 5 | TECHNIQUES FOR THE DETECTION OF HISTAMINE-PRODUCING MICROBIOTA

A series of techniques for the study of microbial communities in food have been developed in recent years. High-throughput sequencing applications have provided detailed knowledge concerning food-associated microbiota and microbiomes. Not only metagenomics and metatranscriptomics, but also metaproteomics and metabolomics have been thoroughly exploited to decipher the composition and functionality of microbiota, thereby contributing to the improvement of food quality and safety. The expansion of our knowledge of food-associated microbiota by meta-omics technologies would allow us to control their main drivers along with the influence of environmental or technological factors over them. Monitoring food spoilage organisms or even pathogens could also help to improve hygienic practices in food production plants (De Filippis, Parente, & Ercolini, 2018). This multiomics approach applied to cheese has been recently called "Cheesomics", focusing on the ripening process and promoting the identification of biomarkers and bioactive metabolites to improve the attributes of cheese (Afshari et al., 2020). In addition, if we learn to consider the core microbiota of cheese as a superorganism comprising all microbial metabolisms and interactions among individual microbes, we can gain a better understanding of the complex metabolic network of dairy products on the whole (Gobbetti et al., 2016).

Techniques aimed at detecting a putative histamine intoxication in food are currently based on direct analysis of the metabolite, for example, on the detection and quantification of histamine. Nevertheless, it is interesting to highlight the interest in detecting and quantifying the microbiota responsible for synthesizing the metabolite, since putative outbreaks can thereby be prevented or detected even before they cause harmful effects to human health.

For that reason, this review focuses on describing techniques designed to detect histamine-producing bacteria (HPB), which can be classified into three types: culture-based, electroanalytical, and molecular methods. The advantages and disadvantages of these techniques are summarized in Figure 5.

### 5.1 | Culture-based methods

Techniques using chromogenic agar or broth media were implemented in the 80s and 90s as useful tools for the identification of HPB. Several methods were developed to detect histamine accumulation during the growth of bacteria, which is evident in a change of color in the growth medium as a consequence of change in pH. Møllert's group and, many years later, Niven and collaborators developed chromogenic agar media supplemented with L-histidine using bromocresol purple to reveal the change in pH during histamine production (Møller, 1954; Niven, Jeffrey, & Corlett, 1981). Nivent's agar medium was later modified to differentially support bacterial growth (Chen, Wei, Koburguer, & Marshall, 1989) and to be used with increased selectivity for the enumeration of HPB in fish products (Mavromatis & Quantick, 2002). That medium has also been used as a basis for the development of other media adapted to cheese (Joosten & Northolt, 1989) or meat (Maijala, 1993). A liquid decarboxylase medium using bromocresol green and chlorophenol red was also described by Yamani and Untermann (1985) for use in pure or mixed cultures, avoiding solid media that could prevent the growth of certain HPB. A leucocrystal violet detection method was also developed to detect high histamine-producing lactobacilli in cheese (Sumner & Taylor, 1989). A comparative analysis of the composition of some of these published decarboxylase media was reported in Bover-Cid and Holzapfel (1999). Also, an improved decarboxylase medium was proposed by these authors, which proved itself sensitive and suitable for screening the ability not only of LAB but also enterobacteria to produce different BAs. The main problem of these indicator media is the occurrence of false positives, caused by the simultaneous production of alkaline metabolites that lead to a pH-related color change (Bover-Cid & Holzapfel, 1999). For instance, a *P. pentosaceus* isolate from cheese was able to produce ornithine from arginine causing the release of ammonium ion to the medium, which raised the pH and rendered a false positive

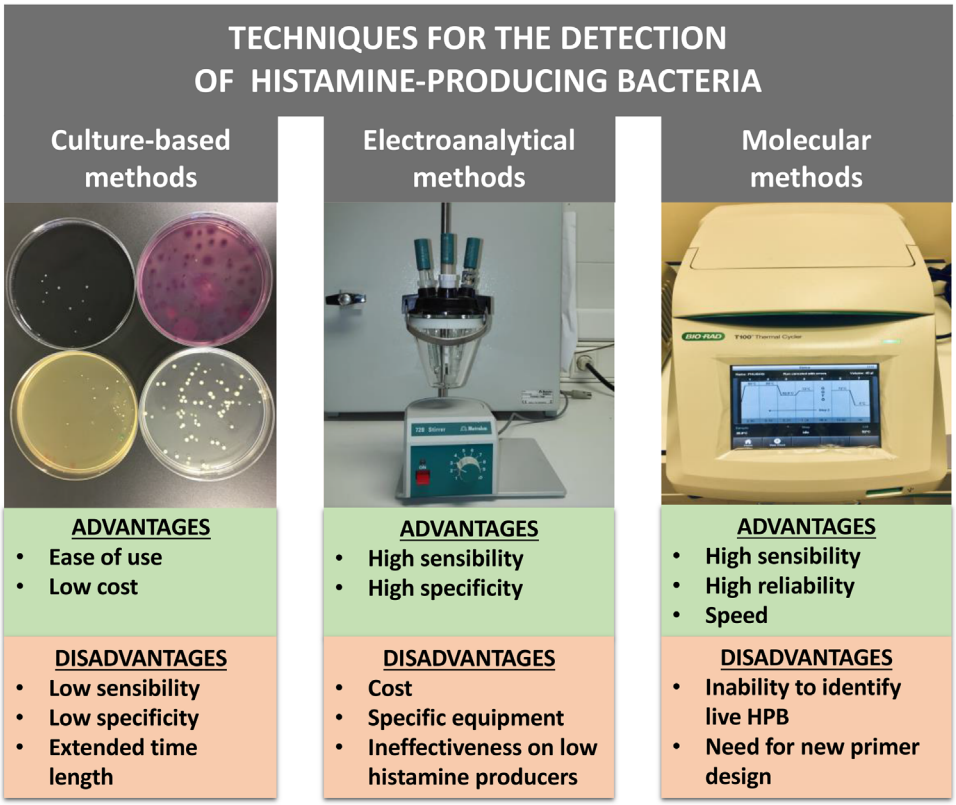


**FIGURE 5** Techniques for the detection of histamine-producing bacteria in dairy products. Their main advantages and disadvantages are listed

result when tested in the indicator medium (Møller et al., 2020).

As shown in Figure 5, ease of use, availability, and low cost are some of the advantages of culture-based methods, whereas false positives, the great amount of time required, and the inability of growth of some HPB due to the conditions of the chromogenic medium are important disadvantages. Furthermore, such methods are not able to detect low histamine producers: thus, other methods might be required to confirm the detection of HPB (Bjornsdottir-Butler, Jones, Benner, & Burkhardt, 2011; Chen et al., 1989; Landete, de Las Rivas, Marcobal, & Munoz, 2007).

In order to solve the time length problem involved in the methods exposed above, a rapid technique has been recently described involving a two-layer membrane filtration assay and a subsequent bacterial culture on agar plates with histidine and bromothymol blue as pH indicator, requiring only 5 hr to analyze HBP in liquid samples as well as in seafood (Tao, Sato, Abe, Yamaguchi, & Nakano, 2009).

## 5.2 | Electroanalytical methods

Many methods based on measurements of potential (volts) and/or current (amperes) have been described in the literature to quantify histamine in food, as reviewed in Yadav, Nair, Sai, and Satija (2019). However, only few studies have applied electroanalytical techniques to reveal HPB, which are difficult to detect since they constitute a minority among the present microbiota. In the late 80s, Klausen and Huss (1987) developed a potentiometric method for the detection of HPB by measuring conductance produced by the histidine-decarboxylase activity of HPB using a histidine-decarboxylase medium: the method was validated in spoiled mackerel. It seems to be highly effective in the detection of high-histamine producers, but is ineffective with low HPB (Figure 5).

Recently, Trevisani et al. (2019) reported an enzyme-based amperometric biosensor designed to detect histamine and HPB in tuna, based on measurements of HDC activity in a histidine decarboxylase broth. However, to our knowledge, no electroanalytical methods for the detection of histamine-producing microbiota in dairy foods have yet been reported.

## 5.3 | Molecular methods

Culture-based as well as potentiometric techniques are nowadays being substituted by modern molecular meth-

ods that enhance sensibility and reliability, even involving the implementation of nucleic acid hybridization techniques. Molecular methods for the detection of BA-producing bacteria in food were reviewed some years ago (Landete et al., 2007), but, from our point of view, an update of that review, focusing on histamine, is required.

Molecular methods are based on the polymerase chain reaction (PCR), a useful and rapid technique that allows the exponential amplification (the increase of number of copies) of target DNA fragments or amplicons from a template by using a DNA polymerase enzyme and a series of cycles of different temperature. To perform this reaction, two short single-strand DNA fragments called oligonucleotides or primers are required. The primers are composed of the complementary sequence of the ends of target DNA (Erlich, 1989). These methods are rapid, specific, and sensitive, although they are unable to distinguish whether the HPB are dead, alive, or even viable but not cultivable (Figure 5) (Landete et al., 2007).

PCR methods to detect HPB are commonly based on the amplification of a fragment of the histidine decarboxylase (*hdc*) gene, sometimes named *hdcA* (Landete et al., 2007; Linares et al., 2011). Bacteria capable of producing histamine exhibit the *hdc* gene in the genome, which is mainly located in the chromosome, but can sometimes be found in an unstable plasmid (Landete et al., 2008). Figure 6 compiles the routes involved in the bacterial histamine metabolism, depicting *hdcA* and other genes involved in the production of histamine, such as *hdcC* (codifying for a histidine/histamine antiporter), *hdcB* (involved in HDC maturation), or *hisS* (codifying for a histidyl-t-RNA synthase like protein) that are usually present in gram-positive bacteria, constituting the typical so-called *hdc* cluster (Benkerroum, 2016; Linares et al., 2011). The genomic structure of the gene responsible for the synthesis of histamine in yeasts or molds has not yet been described.

Two HDC enzyme families have been identified with completely different sequential and biochemical characteristics: gram-positive bacteria, in which the enzyme requires a pyruvoyl moiety, and gram-negative bacteria, which contain pyridoxal phosphate-dependent HDC enzymes (Landete et al., 2008). Nucleotide sequences of enzymes from one or the other group share high similarity (Wuthrich et al., 2017); the nucleotide sequence alignment of the *hdc* gene in gram-positive bacteria was published some years ago (Diaz et al., 2016a). To our knowledge, no genomic studies regarding the putative *hdc* gene in yeasts have been published to date. Taking advantage of this high similarity of the nucleotide sequence of *hdc* genes among groups of bacteria, the design of primers that align in conserved regions within the *hdc* gene would allow for the amplification of the gene from whichever bacteria are present in food. Additionally, to better amplify the same gene from different microorganisms, degenerated primers (a mixture of similar but not identical oligonucleotides) could also be used.

For these reasons, different pairs of primers for the amplification of the *hdc* gene in food through a unique PCR reaction using only a pair of primers to detect each microorganism individually (uniplex PCR) are reported in the literature. However, only few of those studies refer to dairy products. Primers designed to amplify the *hdc* gene of bacteria from dairy products are detailed in Table 2. Specifically, STDEC-F and STDEC-R primers were designed to detect histamine-producing *S. thermophilus* (Rossi et al., 2011) and degenerated HIS1-F and HIS1-R primers were used in cheese to detect gram-positive bacteria (de Las Rivas, Marcobal, Carrascosa, & Munoz, 2006). Some authors adapted the pair of primers HDC3 and HDC4 to detect gram-positive HPB in cheese or homemade yogurt, which had been initially applied to smoked salmon by Burdychova and Komprda (2007) and Coton and Coton (2005). (Berthoud et al., 2017; Gezginc, Akyol, Kuley, & Ozogul, 2013; O'Sullivan et al., 2015) Primers CL1, CL2, JV16HC, and JV17HC, initially published by Le Jeune, Lonvaud-Funel, ten Brink, Hofstra, and van der Vossen (1995), were used by other authors to highlight LAB containing the *hdc* gene in ripened or artisan cheeses (del Valle, Ginovart, Gordún, & Carbó, 2018; Ladero et al., 2015; Møller et al., 2020). Primers HIS2-F and HIS2-R, initially described by de Las Rivas et al. (2006), were used to detect gram-negative HPB in cheese, although no amplification was obtained in any cheese sample (O'Sullivan et al., 2015). Figure 7 shows the regions of *hdc* genes from the alignment of different bacteria where the primers align. As observed, the high similarity among the *hdc* genes allows a good alignment. It is also noteworthy the great sequence similarity of most primers results in alignments in the same regions.

Several multiplex PCR methods (combining multiple pairs of primers in a single and optimized PCR reaction to detect several microorganisms simultaneously) have been reported to detect BAs in food. Coton and Coton (2005) described a PCR method for the simultaneous detection of histamine- and tyramine-producing gram-positive bacteria using HDC3-HDC4 and TD2-TD5 primers directly on bacterial colonies in a single reaction. Some years later, these authors incorporated other pairs of primers to additionally detect ornithine-producing bacteria from wine and cider (Coton et al., 2010). Another multiplex PCR was published for the simultaneous detection of LAB-producing histamine (primers JV16HC and JV17HC), tyramine (primers P1-rev and P2-for, first described by Lucas and Lonvaud-Funel 2002), and putrescine (primers 3 and 16) in food, specifically in wine and grape must (Marcobal, de las

**TABLE 2** List and characteristics of primers aimed to amplify the *hdc* gene of bacteria from dairy products

| Primer name | Primer sequence 5′→ 3′ | Amplicon size | Microorganisms and references | Dairy product sources |
|---|---|---|---|---|
| STDEC-FSTDEC-R | GAATTACCGATCTATGATGC ACACCTTTGTTAGCACAAAC | 121 bp | *Streptococcus thermophilus* (Rossi et al., 2011) | Grana-type and mozzarella cheeses Traditional yogurts |
| HIS1-FHIS1-R | GGNATNGTNWSNTAYGAYMGNGCNGA ATNGCDATNGCNSWCCANACNCCRTA | 372 bp | *Lactobacillus* sp. 30a (ATCC 33222) and *Lentilactobacillus buchneri* StA2 (de Las Rivas et al., 2006) Other bacterial genera as *Micrococcus, Clostridium, Oenococcus* (de Las Rivas et al., 2006) *Streptococcus thermophilus* (Rossi et al., 2011) | Foodborne bacterial strains |
| HDC3 HDC4 | GATGGTATTGTTTCKTATGA CAAACACCAGCATCTTC | 435 to 440 bp | *Lentilactobacillus parabuchneri* (Berthoud et al., 2017), *Lentilactobacillus parabuchneri* DSM 5987 and *Lentilactobacillus parabuchneri* B301 ( Diaz, Ladero et al., 2016), *Lentilactobacillus buchneri* DSM 5987, *Lactobacillus* sp. 30a (ATCC 33222), *Latilactobacillus sakei* LTH 2076 and *Lentilactobacillus hilgardii* IOEB 0006 **(E.** Coton & Coton, 2005**),** *Lentilactobacillus buchneri* and *Latilactibacillus* (O'Sullivan et al., 2015), *Latilactibacillus curvatus, Lactobacillus helveticus* and *Lactobacillus delbrueckii* subsp. *lactis* (Burdychova & Komprda, 2007), *Limosilactobacillus vaginalis* (Diaz et al., 2015) *Tetragenococcus muriaticus* LMG 18498 **(E.** Coton & Coton, 2005) *Oenococcus oeni* IOEB 9204 **(E.** Coton & Coton, 2005) *Streptococcus thermophilus* (Gezginc et al., 2013) | Dutch-type semihard, Cabrales, Emmental, Reblochon, Irish Artisanal, Morbier, Pecorino Sardo, Ossau-Iraty, Emmental, Tête de Moine, Mont Soleil, Tilsit, Alpine, and Raclette cheeses Traditional home-made yogurts Foodborne bacterial strains |
| CL1 CL2 | CCWGGWAAWATWGGWAATGGWTA GAWGCWGTWGTCATATTWATTTGWCC | 150 bp | *Leuconostoc oenos* IOEB 9203 and *Leuconostoc oenos* IOEB 9204 (Le Jeune et al., 1995) *Lactobacillus* sp. 30a (ATCC 33222) (Le Jeune et al., 1995**),** *Lentilactobacillus buchneri, Levilactobacillus brevis, Lacticaseibacillus casei, Lactiplantibacillus plantarum*, and *Lactobacillus delbrueckii* subsp. *lactis* (del Valle et al., 2018) *Lactococcus* sp. (del Valle et al., 2018) | Ripened raw goat milk cheeses Foodborne bacterial strains |

(Continues)

TABLE 2 (Continued)

| Primer name | Primer sequence 5′→ 3′ | Amplicon size | Microorganisms and references | Dairy product sources |
|---|---|---|---|---|
| HIS2-F<br>HIS2-R | AAYTSNTTYGAYTTYGARAARGARGT<br>TANGGNSANCCDATCATYTTRTGNCC | 531 bp | *Morganella morganii* CECT 173$^T$ (de Las Rivas et al., 2006)<br>*Photobacterium phosphoreum* CECT 4192$^T$ and *Photobacterium damselae* CECT 626$^T$ (de Las Rivas et al., 2006)<br>*Proteus vulgaris* CECT 484$^T$ (de Las Rivas et al., 2006)<br>Other bacterial genera as *Enterobacter, Pseudomonas* (de Las Rivas et al., 2006) | Foodborne bacterial strains |
| JV16HC<br>JV17HC | AGATGGTATTGTTTCTTATG<br>AGACCATACACCATAACCTT | 367 bp | *Lactobacillus* sp. 30a (ATCC 33222), *Lentilactobacillus buchneri* StA2 and *Lentilactobacillus hilgardii* BIFI-87 (Marcobal et al., 2005), *Lentilactobacillus buchneri* B301 (Ladero et al., 2015), *Lentilactobacillus buchneri* StA2, *Lentilactobacillus buchneri* NZHD1, *Lentilactobacillus buchneri* NZHD2, *Lentilactobacillus buchneri* NZHD3, *Lentilactobacillus buchneri* NZHD4, *Lentilactobacillus buchneri* NZHD5 and *Lentilactobacillus buchneri* CIVO29 (Le Jeune et al., 1995), *Lentilactobacillus buchneri, Levilactobacillus brevis, Lacticaseibacillus casei, Lactiplantibacillus plantarum*, and *Lactobacillus delbrueckii* subsp. *lactis* (del Valle et al., 2018), *Lentilactobacillus parabuchneri* KUH1, *Lentilactobacillus parabuchneri* KUH2, *Lentilactobacillus parabuchneri* KUH8, and *Lacticaseibacillus paracasei* KUH3 (Møller, Ucok, & Rattray, 2020)<br>*Clostridium perfringens* ATCC 13124 (Le Jeune et al., 1995)<br>*Leuconostoc oenos* IOEB 9203 and *Leuconostoc oenos* IOEB 9204 (Le Jeune et al., 1995)<br>*Staphylococcus* sp. (de Las Rivas et al., 2005)<br>*Streptococcus thermophilus* (Ladero et al., 2015)<br>*Lactococcus* sp. (del Valle et al., 2018) | Danish Gouda-type and artisanal cheeses Foodborne bacterial strains |

(Continues)

**TABLE 2** (Continued)

| Primer name | Primer sequence 5′→ 3′ | Amplicon size | Microorganisms and references | Dairy product sources |
|---|---|---|---|---|
| 106<br>107 | AAYTCNTTYGAYTTYGARAARGARG<br>ATNGGNGANCCDATCATYTTRTGNCC | 534 bp | *Morganella morganii* CECT 173$^T$ (de Las Rivas et al., 2005)<br>*Photobacterium phosphoreum* CECT 4192$^T$ (de Las Rivas et al., 2005)<br>*Proteus vulgaris* CECT 484$^T$ (de Las Rivas et al., 2005)<br>*Klebsiella planticola* CECT 843 (de Las Rivas et al., 2005) | Foodborne bacterial strains |
| hdcDG-FhdcDG-R | CCTGGTCAAGGCTATGGTGTATGGTC<br>GGTTTCATCATTGCGTGTGCAAA - | 250 bp | *Lentilactobacillus parabuchneri* and *Latilactobacillus sakei/Lentilactobacillus hilgardii* (Diaz, Ladero et al., 2016)<br>*Tetragenococcus halophilus* (Diaz et al., 2016)<br>*Streptococcus thermophilus* (Diaz et al., 2016) | Cabrales, Manchego-type, Idiazabal, Casín, and Gamoneu cheeses |
| hdc1<br>hdc2 | TTGACCGTATCTCAGTGAGTCCAT<br>ACGGTCATACGAAACAATACCATC | 174 bp | *Lentilactobacillus parabuchneri* KUH1, *Lentilactobacillus parabuchneri* KUH2, *Lentilactobacillus parabuchneri* KUH8, and *Lacticaseibacillus paracasei* KUH3 (Møller et al., 2020), *Lentilactobacillus buchneri* B301, *Lentilactobacillus buchneri* B302, *Lentilactobacillus buchneri* B303, *Lentilactobacillus buchneri* DSM 5987, and *Lentilactobacillus hilgardii* 321 (Fernandez et al., 2006)<br>*Enterococcus* 15A (Fernandez et al., 2006)<br>*Oenococcus oeni* 206 and *Oenococcus oeni* 212 (Fernandez et al., 2006)<br>*Pediococcus parvulus* 276 (Fernandez et al., 2006) | Danish Gouda-type and Cabrales cheeses |

Y = C or T; K = G or T; R = A or G; S = C or G; W = A or T; M = A or C; D = G, A or T; N = A, C, G or T.
Reference highlighted in bold is the original manuscript that described the primers for the first time.

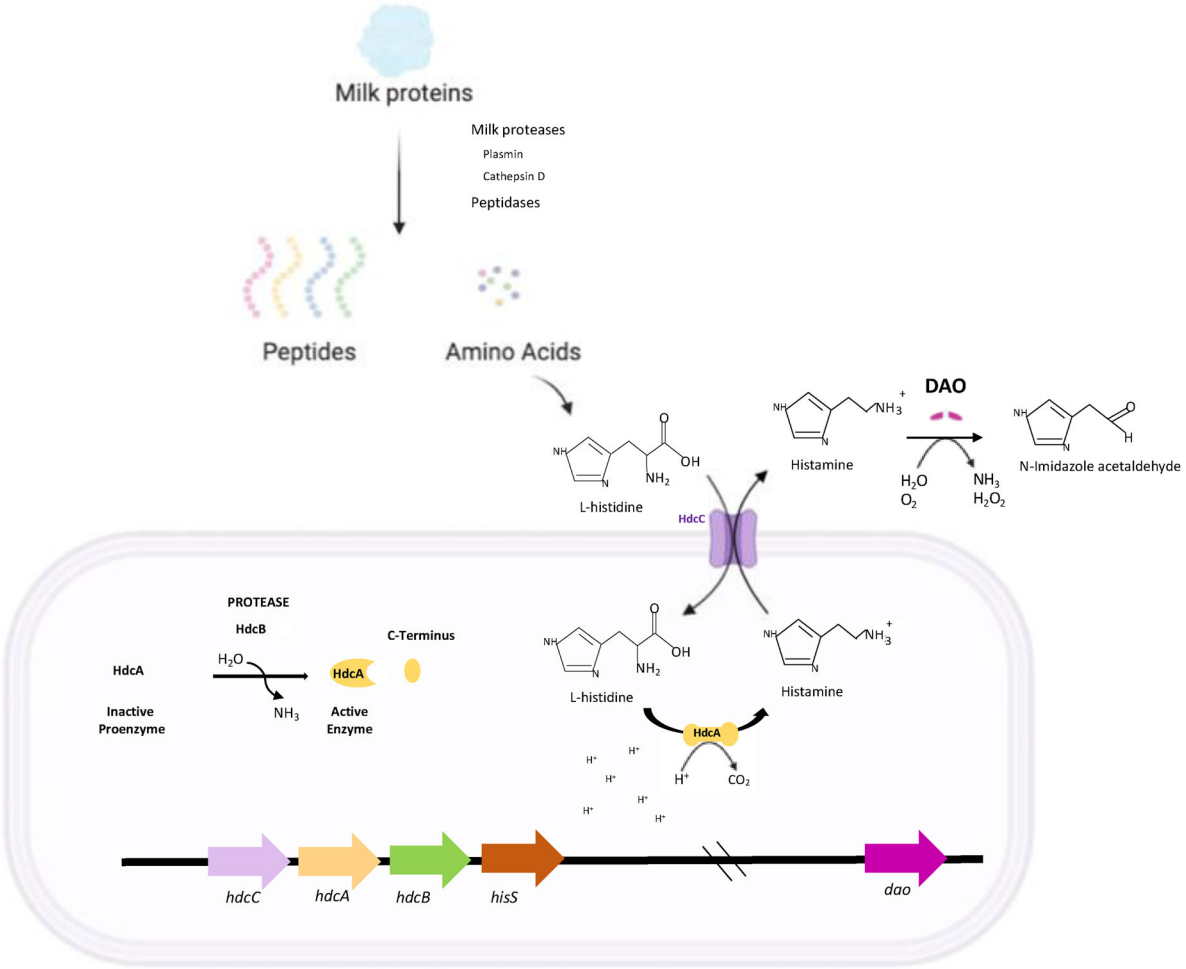


**FIGURE 6** Overview of the mechanisms of histamine formation and degradation by microorganisms. The synthesis of histamine is mediated by the enzyme histidine decarboxylase (HDC or HdcA), codified by the *hdc* (or *hdcA*) gene. In some gram-positive bacteria, this gene takes part in the so-called *hdc* cluster, together with genes codifying for a histidine/histamine antiporter (*hdcC*), a histamine decarboxylase enzyme (*hdcA*), an enzyme involved in proenzyme HdcA cleavage and maturation (*hdcB*), and a protein similar to a histidyl tRNA synthetase (*hisS*). The HdcA enzyme is synthesized as a proenzyme, which requires the proteolysis of the C-terminus, mediated by HdcB, to be an active enzyme. In dairy products, breakdown of milk proteins by plasmin, cathepsin D, and other milk proteases and peptidases results in the formation of free peptides and amino acids, such as histidine, precursor of histamine. When the survival mechanism inducing histamine (no sugar available, low pH…) is activated in histamine-producing bacteria, the antiporter HdcC allows histidine to enter the cell in order to be decarboxylated by HdcA, to form histamine, with the consumption of a proton, that contributes to raise pH. When histamine needs to be metabolized, the same antiporter HdcC secretes this metabolite to be degraded by the enzyme DAO. Since a net positive charge is transported out of the cell by the electrogenic antiport, it results in the generation of proton motive force and energy generation (Molenaar, Bosscher, ten Brink, Driessen, & Konings, 1993)

Rivas, Moreno-Arribas, & Munoz, 2005). These pairs of primers, together with an extra pair (106 and 107 primers) aimed to detect harmful gram-negative HPB, were used in an improved multiplex PCR validated with DNA mixtures of several HPB (de Las Rivas, Marcobal, & Munoz, 2005). It is noteworthy that those multiplex PCR methods are mainly applied for the detection of BA-producing bacteria in wine and its derivatives, but not in dairy foods.

Methods that combine PCR with other techniques have also been used to determine HPB in food. For instance, a PCR-denaturing gradient gel electrophoresis (PCR-DGGE) method for the identification of HPB in cheese on the species level has been recently described. This is a useful and effective method that allows the separation of the *hdc* amplicons with the same size but different sequences, in order to distinguish among different *hdc* variants present in complex microbial communities. The pair of primers used in that study (hdcDG-F and hdcDG-R) aligns in the conserved regions of *hdc*, flanking a variable region, and renders a 250-base pair PCR products that are subsequently subjected to DGGE analysis (Diaz et al., 2016b).

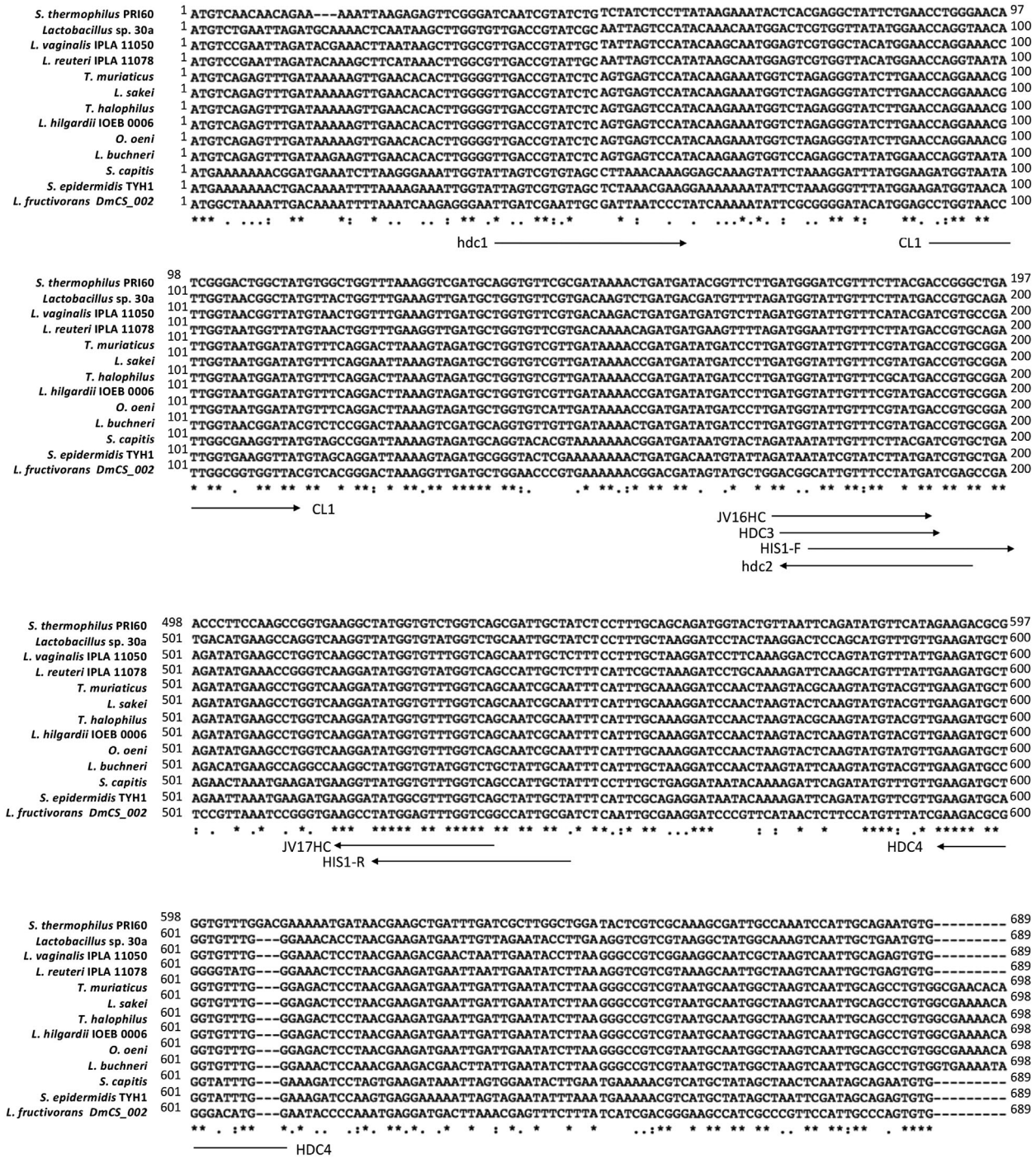


**FIGURE 7** Partial nucleotide alignment of the *hdc* genes from representative gram-positive bacteria, using ClustalW software. The bacterial species, shown at the left of each sequence, as well as the GenBank accession numbers and the references they were taken from (in parentheses), are *S. thermophilus* strain PRI60 (FR693807.2, Rossi et al., 2011), *Lactobacillus* sp. 30a (AAB59151.1, Schelp et al., 2001), *L. vaginalis* strain IPLA11050 (LN828720.1, Diaz et al., 2015), *L. reuteri* strain IPLA11078 (LN877767.1, Diaz et al., 2016b), *T. muriaticus* (DQ132889.1, Kimura et al., 2001), *L. sakei* (DQ132888.1, Diaz et al., 2016b), *T. halophilus* (AB362339.1, Satomi et al., 2008), *L. hilgardii* strain IOEB 0006 (AY651779.1, P. M. Lucas et al., 2005), *O. oeni* (DQ132887.1, P. M. Lucas et al., 2008), *L. buchneri* (DQ132890.1, Diaz et al., 2016b), *S. capitis* (AM283479.1, de Las Rivas, Rodríguez, Carrascosa, & Muñoz, 2008), *S. epidermidis* strain TYH1 (AB583189.1, Yokoi et al., 2011), and *L. fructivorans* strain DmCS_002 (NZ_JOJZ01000009.1, Diaz et al., 2016a). Regions where the primers used in dairy products align are indicated by arrows. Numbers indicate the nucleotide position in the sequence of the *hdc* gene

The main disadvantage presented by end-point PCR methods is the impossibility of quantifying DNA template: thus, real-time quantitative PCR methods (RT-qPCR) have been developed to detect HPB in food, mainly in wine, fish, and cheese (Bjornsdottir-Butler et al., 2011; Lucas et al., 2008; Nannelli et al., 2008). Particularly, in cheese, primers hdc1 and hdc2 were used to detect and quantify gram-positive HPB (Fernandez et al., 2006; Ladero, Linares, Fernandez, & Alvarez, 2008; Møller et al., 2020; Tofalo et al., 2019). A RT-qPCR assay has also been developed in raw milk and cheese to detect and enumerate *L. parabuchneri*, one of the main histamine producers in dairy food, although this method is not based on the analysis of the *hdc* gene but on the unique locus *tmp*, not present in other species (Berthoud et al., 2017).

Finally, genomic-based tools for the rapid and accurate assessment of microbial communities have been developed in recent years. Target metagenomics is based on the sequencing of selected target genes: it provides variable information depending on the studied gene, for instance, 16S rRNA or BA synthetic genes (Ruiz & Alvarez-Ordoñez, 2019). As an example, high-throughput DNA sequencing has been implemented to assess the presence of bacterial histidine and tyrosine decarboxylases in cheeses. This method consists of amplifying the *hdc* and *tdc* genes with primers HIS2-F and HIS2-R or TD2 and TD5, and then cloning the PCR amplicons to subsequently perform high-throughput sequencing of the created amplicon libraries. Finally, the obtained *hdc* and *tdc* sequences are compared with a nucleotide database to identify bacteria with histaminogenic or tyraminogenic potential (O'Sullivan et al., 2015). Another example of the application of next-generation sequencing techniques combining sequencing and quantification of DNA has also been described in fish: the correlation of the histamine content with the presence of gram-negative harmful bacteria, based on the amplification of the 16S rRNA gene (de Lira et al., 2020; Tsironi et al., 2019). Unlike selected target gene sequencing which only targets 16S rRNA or another key gene, shotgun metagenomics sequences all given genomic DNA from a sample. As an example, several *L. parabuchneri* species isolated from cheese or raw milk were genomically characterized by sequencing their whole genomes to study the *hdc* cluster in profound detail and to conclude that it was gained by horizontal gene transfer among different lactobacilli species (Wuthrich et al., 2017).

In spite of the above-exposed advantages offered by modern molecular methods and summarized in Figure 5 (such as high sensitivity and reliability or rapidity), important disadvantages should be noted. One of the most important drawbacks is the impossibility of identifying *hdc* genes of novel strains with emerging ability of histamine formation by using traditional primers, as explained in Table 2. For instance, Møller et al. (2020) highlighted that, in cheese, the *hdc* genes of *P. pentosaceus* isolates capable of producing histamine could not be detected with the use of both JV16HC/JV17HC and Hdc1/Hdc2 primer pairs, described in the literature and useful for traditional histamine producers, such as *L. parabuchneri* and *L. paracasei*. Alternative methods should, therefore, be developed to allow the identification of all HPB in food. Among them, whole genome sequencing of emerging histamine producers and subsequent metagenomics annotation, or the search for new potential decarboxylase genes based on nucleotide sequencing or tridimensional protein similarity, could yield good results. Once all the putative histidine decarboxylase genes have been identified, the design of new matching primer sets is indispensable.

## 6 | HISTAMINE PRODUCERS IN DAIRY PRODUCTS

The use of the aforementioned techniques in dairy products has allowed the identification of a great variety of microorganisms with the ability to produce histamine (i.e., with histidine decarboxylase activity). Histamine-forming microbiota in dairy products could be classified according to different criteria. For instance, based on their origin and purpose, histamine producers could be divided into (1) NSLAB (naturally present in milk), (2) SLAB (intentionally added to dairy products), and (3) contaminants (due to practices during obtaining and handling the milk through dairy products manufacture, as well as from the processing environment––including insufficient cleaning-disinfection practices and biofilm formation). However,-the traditional classification of microorganisms allows to divide histamine-producing microbiota present in dairy products in gram-positive bacteria, gram-negative bacteria, or yeasts and molds. Specific genera, species, and strains of microorganisms capable of synthesize histamine are detailed in Table 3. Additionally, in bold type, Figure 3 highlights the species of histamine producers present on cheese surface and in cheese core among the total microbiota that can be found in cheese. It is key to consider that histamine formation is influenced by a series of factors, as exposed in Figure 4, which should be carefully controlled during the cheese-making process. Some of these factors directly focus on modulating the growth of histamine producers among total cheese microbiota; for instance, environmental conditions, such as salt content or water activity or even bacterial competition processes.

**TABLE 3** Histamine-producing microbiota present in different dairy products

| Microorganisms | | References | Dairy product source | Techniques applied for identification (I) and confirming (C) histamine-forming ability |
|---|---|---|---|---|
| Gram-positive bacteria | *Lentilactobacillus buchneri* (formerly *Lb. buchneri*) | (O'Sullivan et al., 2015) | Reblochon, Irish artisanal, Morbier, Tête de Moine, and Pecorino Sardo cheeses | High-throughput DNA sequencing of total metagenomic DNA extracts (I) and HPLC quantification (C) |
| | *Lentilactobacillus buchneri* | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Lentilactobacillus parabuchneri* (formerly *Lb. parabuchneri*) KUH8, KUH1, KUH2 | (Møller et al., 2020) | Vintage Danish Gouda cheese | Histidine decarboxylase activity and PCR analysis (I) and UPLC quantification (C) |
| | *Lentilactobacillus parabuchneri* FAM21731, FAM21809, FAM21823, FAM21829, FAM21834, FAM23163, FAM23164, FAM23165, FAM23166, FAM23167, FAM23168, FAM23169 | (Wuthrich et al., 2017) | Emmental, Tête de Moine, Mont Soleil, and Tilsit cheeses | Whole-genome sequencing and HPTLC quantification (C) |
| | *Lentilactobacillus parabuchneri* | (Berthoud et al., 2017) | Emmental, Tête de Moine, Mont Soleil, Tilsit, Alpine, and Raclette cheeses Raw milk | Histidine decarboxylase activity and qPCR analysis (I) and HPLC quantification (C) |
| | *Lentilactobacillus parabuchneri* | (Diaz et al., 2016) | Cabrales, Gamoneu, Manchego-type, Casín, and Idiazabal cheeses | PCR-DGGE analysis (I) and HPLC quantification (C) |
| | *Lentilactobacillus parabuchneri* IPLA 11118, IPLA 11119, IPLA 11120, IPLA 11121, IPLA 11122, IPLA 11123, IPLA 11124, IPLA 11125, IPLA 11126, IPLA 11127, IPLA 11128, IPLA 11129, IPLA 11130, IPLA 11131, IPLA 11132, IPLA 11133, IPLA 11134, IPLA 11135, IPLA 11136, IPLA 11137, IPLA 11138 | (Diaz et al., 2016) | Emmental cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Lentilactobacillus parabuchneri* IPLA 11122, IPLA 11117, IPLA 11150 | (Díaz et al., 2018) | Different types of commercial cheeses | HPLC quantification (C) |

(Continues)

TABLE 3 (Continued)

| Microorganisms | References | Dairy product source | Techniques applied for identification (I) and confirming (C) histamine-forming ability |
|---|---|---|---|
| *Lentilactobacillus parabuchneri* | (Diaz et al., 2015) | Cabrales cheese | Histidine decarboxylase activity (I) |
| *Lactobacillus delbrueckii* subsp. *lactis* (formerly *Lb. lactis*) | (Burdychova & Komprda, 2007) | Dutch-type semihard cheese | PCR analysis (I) and HPLC quantification (C) |
| *Lactobacillus helveticus* | (Burdychova & Komprda, 2007) | Dutch-type semihard cheese | PCR analysis (I) and HPLC quantification (C) |
| *Lactobacillus delbrueckii* | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| *Latilactobacillus sakei/Lentilactobacillus hilgardii* (formerly *Lb. sakei* group) | (Diaz et al., 2016) | Cabrales cheeses | PCR-DGGE analysis (I) and HPLC quantification (C) |
| *Latilactobacillus* gen. | (O'Sullivan et al., 2015) | Ossau-Iraty, Irish Artisanal, Morbier, and Pecorino Sardo cheeses | High-throughput DNA sequencing of total metagenomic DNA extracts (I) and HPLC quantification (C) |
| *Latilactobacillus curvatus* (formerly *Lb. curvatus*) | (Burdychova & Komprda, 2007) | Dutch-type semihard cheese | PCR analysis (I) and HPLC quantification (C) |
| *Levilactobacillus brevis* (formerly *Lb. brevis*) | (del Valle et al., 2018) | Raw goat milk cheese | PCR analysis (I) histamine formation assessment and HPLC quantification (C) |
| *Lacticaseibacillus casei* (formerly *Lb. casei*) | (del Valle et al., 2018) | Raw goat milk cheeses | PCR analysis (I) histamine formation assessment and HPLC quantification (C) |
| *Lacticaseibacillus casei* | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |

(Continues)

**TABLE 3** (Continued)

| Microorganisms | References | Dairy product source | Techniques applied for identification (I) and confirming (C) histamine-forming ability |
|---|---|---|---|
| *Lacticaseibacillus paracasei* KUH3 (formerly *Lb. paracasei*) | (Møller et al., 2020) | Vintage Danish Gouda cheese | Histidine decarboxylase activity and PCR analysis (I) and UPLC quantification (C) |
| *Lactiplantibacillus plantarum* (formerly *Lb. plantarum*) | (del Valle et al., 2018) | Raw goat milk cheese | PCR analysis (I) histamine formation assessment and HPLC quantification (C) |
| *Limosilactobacillus vaginalis* (formerly *Lb. vaginalis*) IPLA11140, IPLA11141, IPLA11142, IPLA11143, IPLA11144, IPLA11145, IPLA11147, IPLA11050, IPLA11051, IPLA11052, IPLA11053, IPLA11054, IPLA11055, IPLA11056, IPLA11057, IPLA11058, IPLA11060, IPLA11062, IPLA11064, IPLA11065, IPLA11067, IPLA11068, IPLA11069, IPLA11070, and IPLA11075 | (Diaz et al., 2015) | Cabrales cheese | Histidine decarboxylase activity and PCR analysis (I) and HPLC quantification (C) |
| *Limosilactobacillus reuteri* (formerly *Lb. reuteri*) | (Diaz et al., 2015) | Cabrales cheese | Histidine decarboxylase activity (I) |
| *Lactococcus lactis* subsp. *lactis* | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| *Streptococcus thermophilus* PRI60 | (Gardini et al., 2012) | Dairy products | HPLC quantification (C) |
| *Streptococcus thermophilus* | (Gezginc et al., 2013) | Home-made natural yogurts | Histidine decarboxylase activity and PCR analysis (I) and HPLC quantification (C) |
| *Streptococcus thermophilus* | (Ladero et al., 2015) | Artisanal raw milk cheeses | PCR analysis (I) and (U)HPLC quantification (no histamine) (C) |

(Continues)

**TABLE 3** (Continued)

| Microorganisms | | References | Dairy product source | Techniques applied for identification (I) and confirming (C) histamine-forming ability |
|---|---|---|---|---|
| | *Streptococcus thermophilus* PRI17, PRI18, PRI21, PRI60, PRI74 | (Rossi et al., 2011) | Mozzarella and Grana-type cheeses. Traditional yogurts | PCR analysis (I) and HPLC quantification (C) |
| | *Streptococcus thermophilus* | (Diaz et al., 2016) | Idiazabal cheeses | PCR-DGGE analysis (I) and HPLC quantification (no histamine) (C) |
| | *Pediococcus pentosaceus* KUH5, KUH6, KUH7 | (Møller et al., 2020) | Vintage Danish Gouda cheese | Histidine decarboxylase activity (I) and UPLC quantification (C) |
| | *Tetragenococcus halophilus* | (Diaz et al., 2016) | Cabrales and Manchego-type cheeses | PCR-DGGE analysis (I) and HPLC quantification (C) |
| | *Leuconostoc* sp. | (del Valle et al., 2018) | Raw goat milk cheese | PCR analysis (I) histamine formation assessment and HPLC quantification (C) |
| | *Enterococcus faecium* | (Tham et al., 1990) | Goat milk cheese | Fluorimetric histamine determination (C) |
| | *Enterococcus faecalis* | (Tham et al., 1990) | Goat milk cheese | Fluorimetric histamine determination (C) |
| | *Enterococcus casseliflavus* | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Microbacterium foliorum* C45 | (Helinck et al., 2013) | French cheeses | HPLC quantification (C) |

(Continues)

**TABLE 3** (Continued)

| Microorganisms | | References | Dairy product source | Techniques applied for identification (I) and confirming (C) histamine-forming ability |
|---|---|---|---|---|
| Gram-negative bacteria | *Citrobacter freundii* | (Marino et al., 2000) | Blue-veined cheeses | HPLC quantification (C) |
| | *Citrobacter freundii* | (Maifreni et al., 2013) | Montasio cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Citrobacter freundii* UCMA 4217 | (Coton et al., 2012) | Livarot cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Citrobacter braakii* CtT 6, CtT 10, CtT 29, CtT 60, CtT 61 | (Chaves-Lopez et al., 2006) | Pecorino Abruzzese cheeses | HPLC quantification (C) |
| | *Hafnia alvei* | (Marino et al., 2000) | Blue-veined cheeses | HPLC quantification (C) |
| | *Hafnia alvei* | (Maifreni et al., 2013) | Montasio cheeses | HPLC quantification (C) |
| | *Hafnia alvei 1* B16 | (Coton et al., 2012) | Livarot cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Hafnia alvei* | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Hafnia paralvei* 920 | (Coton et al., 2012) | Munster cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Halomonas* sp. nov. B39 | (Coton et al., 2012) | Livarot cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Halomonas venusta* 3D7M | (Coton et al., 2012) | Munster cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Halomonas venusta/alkaliphila/hydrothermalis* 4C1A | (Coton et al., 2012) | Munster cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Morganella morganii* 3A2A, 3A5A, 3D4A | (Coton et al., 2012) | Munster cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |

(Continues)

**TABLE 3** (Continued)

| Microorganisms | | References | Dairy product source | Techniques applied for identification (I) and confirming (C) histamine-forming ability |
|---|---|---|---|---|
| | *Providencia heimbachae* GR4 | (Coton et al., 2012) | Epoisses cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Serratia liquefaciens* | (Marino et al., 2000) | Blue-veined cheeses | HPLC quantification (C) |
| | *Serratia liquefaciens* 1B4F | (Coton et al., 2012) | Munster cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Serratia liquefaciens* | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Serratia marcescens* 448 | (Coton et al., 2012) | Munster cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Serratia proteomaculans* 1C2F | (Coton et al., 2012) | Munster cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Serratia odorifera* CtT 28, CtT 57, CtT 58, CtT 74 | (Chaves-Lopez et al., 2006) | Pecorino Abruzzese cheeses | HPLC quantification (C) |
| | *Serratia odorifera* | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Serratia grimesii* UCMA 3895 | (Coton et al., 2012) | Livarot cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Serratia* sp. (close *S. grimesii*) GB3 | (Coton et al., 2012) | Epoisses cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Serratia* spp. | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Chryseobacterium shigense* PCA1 B2.3 | (Coton et al., 2012) | Cow milk Salers cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |

(Continues)

TABLE 3 (Continued)

| Microorganisms | | References | Dairy product source | Techniques applied for identification (I) and confirming (C) histamine-forming ability |
|---|---|---|---|---|
| | *Chryseobacterium* sp. (close *C. bovis*) Pi 18 | (Coton et al., 2012) | St. Nectaire cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Enterobacter hormaechei* 380, 272, INRA 1439 | (Coton et al., 2012) | Munster and Salers cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Enterobacter cloacae* | (Marino et al., 2000) | Blue-veined cheeses | HPLC quantification (C) |
| | *Enterobacter cloacae* | (Maifreni et al., 2013) | Montasio cheeses | HPLC quantification (C) |
| | *Enterobacter gergoviae* | (Marino et al., 2000) | Blue-veined cheeses | HPLC quantification (C) |
| | *Enterobacter aerogenes* | (Marino et al., 2000) | Blue-veined cheeses | HPLC quantification (C) |
| | *Enterobacter sakazaki* CtT 9, CtT 23, CtT 29 | (Chaves-Lopez et al., 2006) | Pecorino Abruzzese cheeses | HPLC quantification (C) |
| | *Enterobacter sakazakii* | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Enterobacter* spp. | (Maifreni et al., 2013) | Montasio cheeses | HPLC quantification (C) |
| | *Pseudomonas* grp *putida* CV 30.6, VRBG 37.3, CFC25.4 | (Coton et al., 2012) | Milk | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Pseudomonas lundensis* PCAi D2.2 | (Coton et al., 2012) | Cow milk Salers cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Pseudomonas stutzeri* UCMA 3883 | (Coton et al., 2012) | Livarot cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Psychrobacter celer* 91 | (Coton et al., 2012) | Camembert raw milk cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Psychrobacter* sp. 580 | (Helinck et al., 2013) | French cheeses | HPLC quantification (C) |

(Continues)

TABLE 3 (Continued)

| Microorganisms | | References | Dairy product source | Techniques applied for identification (I) and confirming (C) histamine-forming ability |
|---|---|---|---|---|
| | *Raoultella planticola* 924 | (Coton et al., 2012) | Munster cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Raoultella ornithinolytica* | (Maifreni et al., 2013) | Montasio cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Sphingobacterium* sp. (close *S. faecium*) PCAi F2.5 | (Coton et al., 2012) | Cow milk Salers cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Acinetobacter* sp. (close genospecies 3) PCA E6.10 | (Coton et al., 2012) | Cow milk Salers cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Alcalingenes faecalis* 1 904 | (Coton et al., 2012) | Munster cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Proteus* sp. (close *P. hauseri*) UCMA 3780 | (Coton et al., 2012) | Livarot cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Proteus heimbachae* 945 | (Coton et al., 2012) | Munster cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Providencia* sp. nov. GB1 | (Coton et al., 2012) | Epoisses cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Escherichia coli* | (Maifreni et al., 2013) | Montasio cheeses | HPLC quantification (C) |
| | *Escherichia coli* | (Marino et al., 2000) | Blue-veined cheeses | HPLC quantification (C) |
| | *Escherichia coli* CtT 1, CtT 24, CtT 43, CtT 75 | (Chaves-Lopez et al., 2006) | Pecorino Abruzzese cheeses | HPLC quantification (C) |

(Continues)

**TABLE 3** (Continued)

| Microorganisms | | References | Dairy product source | Techniques applied for identification (I) and confirming (C) histamine-forming ability |
|---|---|---|---|---|
| | *Escherichia coli* | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Escherichia fergusonii* | (Maifreni et al., 2013) | Montasio cheeses | HPLC quantification (C) |
| | *Klebsiella oxytoca* | (Maifreni et al., 2013) | Montasio cheeses | HPLC quantification (C) |
| | *Klebsiella oxytoca* | (Marino et al., 2000) | Blue-veined cheeses | HPLC quantification (C) |
| | *Klebsiella pneumoniae* | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Arizona* spp. | (Marino et al., 2000) | Blue-veined cheeses | HPLC quantification (C) |
| | *Salmonella enterica* spp. *arizonae* CtT 31, CtT 33, CtT 37 CtT 50 | (Chaves-Lopez et al., 2006) | Pecorino Abruzzese cheese | HPLC quantification (C) |
| | *Kluyvera* spp. CtT 3, CtT 26, CtT 49, CtT 53 | (Chaves-Lopez et al., 2006) | Pecorino Abruzzese cheese | HPLC quantification (C) |
| | *Cedecea* spp. | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Edwarsiella* spp. | (Roig-Sangüés et al., 2002) | Spanish traditional cheeses | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| Yeasts and molds | *Geotrichum candidum* | (Roig-Sangüés et al., 2002) | Cabrales cheese | Histidine decarboxylase activity (I) and HPLC quantification (C) |
| | *Debaryomyces hansenii* LM21, LM24, LM26 | (Gardini et al., 2006) | Pecorino Crotonese cheese | Histidine decarboxylase activity (I) |
| | *Debaryomyces hansenii* 304 | (Helinck et al., 2013) | French cheeses | HPLC quantification (C) |

## 6.1 | Gram-positive bacteria

LAB are the main histamine producers in dairy products; *Lactobacillus* species, such as *L. parabuchneri, L. buchneri, Lb. helveticus*, and *L. curvatus*, among others, seem to be responsible for histamine accumulation in cheese (Barbieri et al., 2019). Some of these species can be present in cheese because they were either already contained in milk (above all, NSLAB), or because they took part as contaminants or starter cultures in the course of the cheese production process (Linares et al., 2012). Notably, *L. buchneri* and *L. parabuchneri*, present as contaminants in fermented dairy products and closely related with one another phylogenetically, have been reported to be the major histamine producers in cheese, capable of synthesizing high amounts of histamine even at low temperatures (Berthoud et al., 2017; Díaz et al., 2018; O'Sullivan et al., 2015; Wuthrich et al., 2017). *L. parabuchneri* has been reported to produce histamine in a wide variety of cheese samples, even at low refrigeration temperatures (Diaz, Del Rio et al., 2016; Diaz, Ladero et al., 2016; Díaz et al., 2018; Møller et al., 2020). From several cheeses containing histamine, Berthoud et al. (2017) isolated certain *L. parabuchneri* strains with the *hdc* gene, and developed a molecular method to detect and enumerate *L. parabuchneri* in raw milk and cheese. Later on, the same authors investigated the genome variability of these strains and concluded that the *hdc* cluster is located in a genomic island that can be transferred within the *L. parabuchneri* species. Some strains have lost that island and thus the capacity to synthesize histamine (Wuthrich et al., 2017). Relative to *L. buchneri*, one isolate of a histamine-forming strain was detected in Spanish traditional cheeses, and was shown to be the predominant LAB with histaminogenic potential in 10 different cheese varieties, as evidenced by high-throughput DNA sequencing (O'Sullivan et al., 2015; Roig-Sangüés, Molina, & Hernández-Herrero, 2002). On the other hand, Diaz et al. (2015) isolated (for the first time from cheese) and typified several *L. vaginalis* (formerly *Lb. vaginalis*) strains capable of producing histamine, as well as a number of histamine-producing isolates identified as *L. reuteri* (formerly *Lb. reuteri*). Burdychova and Komprda (2007) also studied the histamine-producing potential displayed by certain bacterial communities in a Dutch-type semihard cheese. Among the histamine-producing strains isolated from the cheese, the authors found that *Lb. delbrueckii* subsp. *lactis* and *L. curvatus* played a role as contaminants, whereas *Lb. helveticus* originated from a starter culture used for cheese production. Other species, such as *L. brevis*, *L. casei*, and *L. plantarum*, were found to contain the *hdc* gene in cheeses prepared with raw milk, and some of those species had not been added as starter cultures (del Valle et al., 2018). The *Lb. delbrueckii* species was also reported as a histamine producer (Roig-Sangüés et al., 2002). *L. hilgardii*/*L. sakei* may present histaminogenic potential as well; the indistinguishable *hdc* genes of these species have been detected in two Cabrales cheeses and even highlighted by high-throughput DNA sequencing (Diaz, Ladero et al., 2016; O'Sullivan et al., 2015). An *L. paracasei* isolate from cheese was also shown to be a fast producer of high levels of histamine, together with several isolates of *L. parabuchneri* (Møller et al., 2020).

In addition to *Lactobacillus* species, the *Streptococcus* genus is also an important histamine producer in cheese, although the source of this microorganism in the product is unclear (O'Sullivan et al., 2015). However, not all of the strains actually contain the *hdc* gene. A recent study classifies most *S. thermophilus* strains into two major clusters: Cluster A and Cluster B. Strains belonging to Cluster A present larger genomes or complete histidine biosynthesis gene clusters, among other characteristics. The *hdc* cluster is also present in all *S. thermophilus* strains pertaining to Cluster A, supporting the hypothesis of acquisition by horizontal gene transfer from a satellite phage (Alexandraki et al., 2019). In fact, up to 6% of *S. thermophilus* strains isolated from natural sources contain the *hdc* gene, and some of them are able to produce histamine in milk under conditions relevant to cheese-making, or even at low temperatures (Calles-Enriquez et al., 2010; Gardini et al., 2012; Rossi et al., 2011). However, certain *S. thermophilus* strains isolated from cheeses or home-made natural yogurt were also shown to contain the *hdc* gene, although only a low amount or even no histamine at all was found in the supernatant in culture media (Diaz, Ladero et al., 2016; Gezginc et al., 2013; Ladero et al., 2015).

Apart from *Lactobacillus* and *Streptococcus*, other LAB genera have been shown to synthesize histamine in dairy products. Recently, Møller et al. (2020) reported *P. pentosaceus* for the first time as a histamine producer in cheese. *T. halophilus* has been previously described as a histamine producer in fish or soy sauces, although it was reported for the first time as a histamine-producing species in certain Cabrales and Manchego cheeses (Diaz, Ladero et al., 2016; Satomi et al., 2008). The *hdc* gene was also amplified in a *Leuconostoc* sp. strain isolated from raw goat milk cheese (del Valle et al., 2018). Potential histamine formation by *E. faecium* or *E. casseliflavus* in cheese has also been reported, but the contribution of enterococci to the level of histamine in cheese is probably irrelevant (Roig-Sangüés et al., 2002; Tham, Karp, & Danielsson-Tham, 1990).

### 6.2 | Gram-negative bacteria

On the other hand, common contaminants of milk or spoilage bacteria, such as the microbial families *Enterobacteriaceae* or *Pseudomonads*, could also be responsible for histamine production in food. Many members of the *Enterobacteriaceae* family can act as histamine producers in cheese, but they only produce low amounts thereof, usually in early steps of the cheese-making process (Barbieri et al., 2019; Costa et al., 2018).

Several studies have isolated gram-negative bacteria present in different cheese varieties, and some of them have also quantified the amount of histidine that every bacterial isolate was able to produce *in vitro* or even in cheese model. Coton et al. (2012) obtained gram-negative bacterial isolates from French cheeses or milk, and then evaluated their ability to produce histamine *in vitro*. Many of the isolates were able to produce histamine in a culture medium, but only few of them produced more than 1,000 mg/kg of histamine, namely *Morganella morganii* and *Serratia* sp. Additionally, *H. alvei, C. freundii, Halomonas* spp., *Raoultella planticola*, and *Providencia heimbachae* also produced more than 500 mg/kg of histamine (Coton et al., 2012). Many isolates of enterobacteria obtained from Montasio cheeses produced low amounts of histamine (<300 mg/kg), but only four isolates, two corresponding to *E. cloacae* and two more to *C. freundii*, produce more than 1,000 mg/kg (Maifreni et al., 2013). According to another study, more than 50% of the 104 bacterial isolates from blue-veined cheeses were able to form histamine; although the histamine production was very low (<20 mg/kg), isolates corresponding to *Enterobacter gorgoviae, S. liquefaciens, E. coli, H. alvei, E. cloacae, E. aerogenes, C. freundii, Arizona* spp., and *Klebsiella oxytoca* were confirmed to produce histamine (Marino, Maifreni, Moret, & Rondinini, 2000). The analysis of isolates of enterobacteria obtained from Pecorino cheese resulted in the production of very low amounts of histamine by all the strains (< 3 mg/kg), namely *E. coli, S. enterica* spp. *Arizonae, E. sakazakii, C. braakii, Kluyvera* spp., and *S. odorifera* (Chaves-Lopez et al., 2006).

Other studies have also analyzed the presence of histamine-producing microbiota but have failed to obtain quantitative results. For instance, Roig-Sangüés et al. (2002) isolated total microbiota from certain Spanish cheeses: most of the gram-negative isolates, identified as enterobacteria, displayed histamine-forming activity. The authors detected *H. alvei, E. coli, E. sakazakii, Edwarsiella* spp., and *Serratia* spp. as histamine producers in cheese. Additionally, one isolate of *Cedecea* spp., a genus genetically very close to *Serratia*, was reported for the first time to produce histamine (Roig-Sangüés et al., 2002).

On the other hand, *Psychrobacter* sp. was reported for the first time to produce histamine *in vitro* in a culture medium containing histidine, and even in a cheese model with the yeast *D. hansenii* as coculture (Helinck, Perello, Deetae, de Revel, & Spinnler, 2013).

### 6.3 | Yeasts and molds

Certain yeasts and molds can also produce histamine in food, although few studies have analyzed that production specifically in cheese. The major histamine producer in cheese belonging to this group is *D. hansenii*, but this seems to be a strain-specific characteristic (Gardini et al., 2006). In a cheese model, *D. hansenii* was able to produce histamine only in the presence of the bacterium *Psychrobacter* (Helinck et al., 2013). *G. candidum* was also mentioned as a histamine-forming mold in Cabrales cheese (Roig-Sangüés et al., 2002).

## 7 | POTENTIAL SOLUTIONS TO COUNTERACT HISTAMINE ACCUMULATION IN DAIRY FOOD: FROM PREVENTION TO HISTAMINE DEGRADATION

In order to avoid the release of dairy products with high levels of histamine to the market, the main measure the food industry could take would be the reduction of HPB in dairy products by (1) preventing their access to raw materials, (2) inactivating them, and/or (3) controlling environmental conditions. If those measures are not effective, (4) microbial or enzymatic degradation of histamine is the alternative. Figure 8 compiles the potential strategies for obtaining histamine-free dairy products, aimed at preventing histamine formation or promoting histamine degradation.

The promotion of hygienic conditions during milking and food processing could decrease and even inactivate histamine-producing microbiota. Additionally, the selection of suitable starter cultures unable to synthesize histamine is an appropriate alternative for the reduction of histamine production in dairy products, although it is necessary to assess whether the organoleptic characteristics of the final product are eventually thereby altered.

To obtain a safe product with an extended shelf-life, it is necessary to apply food preservation treatments designed to reduce the microbial load and guarantee milk safety in the cheese-making process (Quigley et al., 2013; Tilocca et al., 2020). Heat treatment (sterilization or pasteurization) is currently the most commonly applied process for

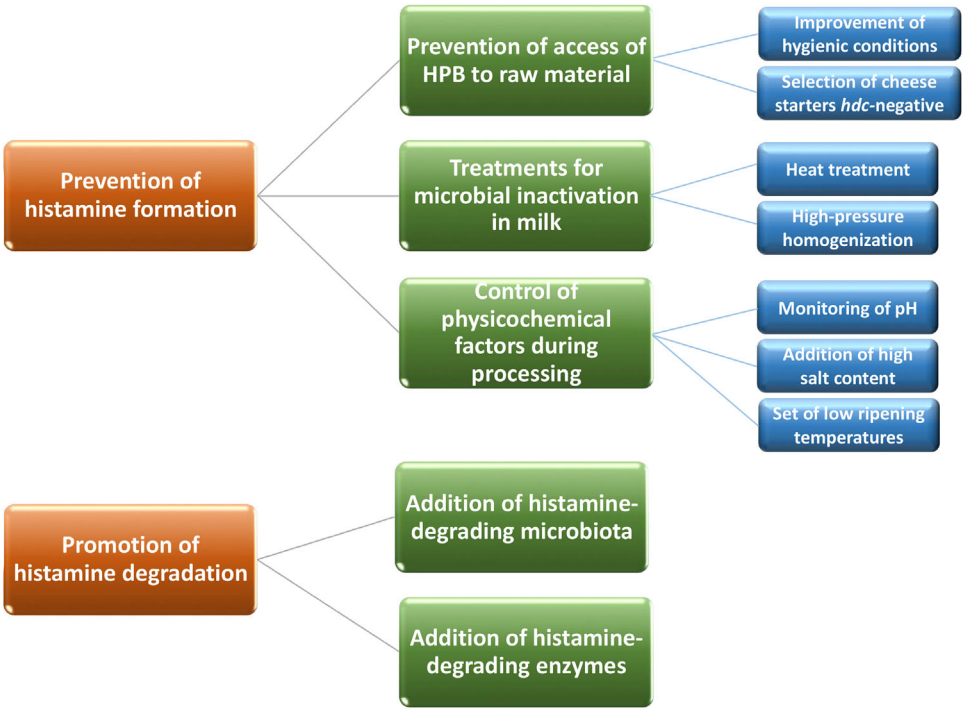


**FIGURE 8** Strategies aimed at preventing histamine formation or promoting histamine degradation in dairy products

the preservation of liquid milk (Walstra et al., 2006). Nevertheless, nonthermal technologies, such as HPH, or irradiation, have also been proposed as alternative technologies to preservation of milk, although these methodologies are not currently being used industrially for this purpose (Ramaswamy, Ahn, Balasubramaniam, Rodriguez Saona, & Yousef, 2019).

As mentioned above, the production and quantity of histamine synthesized in dairy products, such as cheese, depends on a number of factors, such as histidine availability, ripening and storage temperatures, pH, sodium concentration, decarboxylation potential of the HPB, and carbon source (Benkerroum, 2016; Linares et al., 2012). These factors can be occasionally modified to prevent or reduce the rate of histamine production. In case the strategies for the prevention of histamine formation in dairy products fail, the degradation of histamine can be considered as a crucial alternative (Linares et al., 2012). Figure 8 summarizes the main strategies aimed at preventing or reducing histamine content in dairy products.

## 7.1 | Measures aimed to prevent histamine formation during processing of dairy products

One of the most important measures aiming to reduce histamine production is the overall improvement of hygiene during production and storage of dairy food. Other changes in food processing designed to inhibit or reduce HPB in dairy products include the selection of *hdc*-negative starters, pasteurization, HPH, and control of physicochemical factors during dairy processing (Linares et al., 2012; Naila, Flint, Fletcher, Bremer, & Meerdink, 2010).

### 7.1.1 | Preventing access of HPB to raw materials

*Improving hygienic conditions along the dairy food chain*

Hygienic conditions during milking are a very important factor for the dairy industry. The milk of healthy animals produced under hygienic conditions should contain less than $5 \times 10^5$ CFU/mL (Bereda, Yilma, & Nurfeta, 2012). The initial microbial load of milk varies between $10^3$ and $10^5$ CFU/mL, rising to $10^6$ to $10^7$ CFU/mL before processing (depending on its handling), and increasing during cheese ripening to up to $10^8$ CFU/g in the final product (Benkerroum, 2016; Mlejnkova et al., 2016; Schirone, Tofalo, Visciano, Corsetti, & Suzzi, 2012). The microbiological quality of milk is clearly influenced by the way in which milk is handled from milking to consumption. The environment, handlers, equipment, and packaging materials can all be a reservoir for microbial contamination of milk and dairy products (Pal, Devrani, & Pinto, 2018). Lack of hygiene in the handling of milk, the misuse of milking equipment, and the lack of drinking water for cleaning purposes can contribute to the poor hygienic quality

of milk. Strict hygienic measures must be applied during preparation, storage, and delivery of a variety of dairy products for human consumption. It is thus necessary to educate food handlers regarding the basic principles of hygiene and manufacturing of dairy products, which ensure their quality and safety for consumption.

On the other hand, histamine-producing microorganisms are likely to appear in the food chain in the form of food contaminant microbiota or NSLAB contained in the raw material (Linares et al., 2012). Pintado et al. (2008) indicate that the production of BAs in cheese made from raw milk depends, among other variables, on the level of enterobacteria, enterococci, and lactobacilli present in raw milk, which can attain levels of $10^7$ CFU/g. This level of contamination in raw milk appears to be frequently associated with a high histamine content in raw milk cheeses. The number and diversity of histamine-producing microorganisms increases as the total count in raw milk rises (Benkerroum, 2016). Ascone et al. (2017) reported repeated contamination of *L. parabuchneri* in milk from providers, capable of forming biofilms on stainless steel surfaces in dairy processing equipment, and thus constituting a reservoir and a source of contamination of postripening-processed cheeses (Diaz, Ladero et al., 2016). To reduce the histamine content in such cheeses, it would be necessary to perform routine screening of provided milks and to control the formation of biofilms containing HPB in the dairy food processing industry (Diaz, Ladero et al., 2016). This would allow the identification and exclusion of contaminated raw milk in order to prevent the production of contaminated raw milk cheeses (Ascone et al., 2017).

On the other hand, in the final histamine content, contamination stemming from food processing seems to be more important than contamination stemming from the raw material. Ladero, Fernández, and Álvarez (2009) studied the effect of postripening processing of different types of cheese on the presence of HPB and on the average histamine concentration of the final product. The highest concentrations of histamine (734 mg/kg) were reported in grated cheese samples in comparison with whole Emmental cheeses (115 mg/kg). In this case, the presence of HPB during cheese manufacturing was due to poor hygiene practices in product processing: the contact of the cheese with equipment surfaces increased the risk of microbiological contamination.

Thus, in sum, it is necessary to control and improve microbiological and hygienic conditions along the entire production chain (i.e., from farm to fork) in order to reduce the amounts of BAs or to avoid their presence altogether in dairy products (Benkerroum, 2016).

### *Selection of cheese starters unable to synthesize histamine*

To guarantee the quality of dairy products and minimize the adverse health effects of histamine, starter cultures must be carefully selected on the basis of their inability to produce histamine and their capacity to degrade it (Naila et al., 2010; Spano et al., 2010).

Raw milk cheeses are particularly vulnerable to the formation of histamine, favored by high levels of secondary proteolysis as a consequence of the action of starter and nonstarter cultures, along with a higher microbial load and, in some cases, long ripening times (Guarcello et al., 2016; Linares et al., 2011; O'Sullivan et al., 2015; Schirone et al., 2013). The addition of proteinases to milk or curd has been widely used with the purpose of accelerating cheese ripening (Fernandez-Garcia et al., 2000). The effect of the selection of starter cultures on the proteolytic pattern and thus on histamine production in cheese was demonstrated by Gardini et al. (2012) by using a histaminogenic *S. thermophilus* strain (PRI60) and, alternatively, a nonhistamine-producing strain (PRI40) as starter cultures. Nieto-Arribas, Poveda, Seseña, Palop, and Cabezas (2009) suggested *L. plantarum* and *L. paracasei*, isolated from an artisan cheese, as possible starter cultures for cheese production due to their inability to produce BAs and, at the same time, because they do not alter the sensory characteristics of cheeses.

As a promising approach to the strain selection procedure, the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas technique, commonly used for gene editing (Jiang, Bikard, Cox, Zhang, & Marraffini, 2013; Jinek et al., 2012), could also be applied either to inactivate the *hdc* gene and thus to obtain fermentative *hdc*-negative strains, or to ensure a greater phage resistance to starter LAB (Roberts & Barrangou, 2020). By generating these kinds of strains, fermented foods could be developed with similar sensory characteristics to those obtained with traditional strains, but with no histamine content or a greater phage resistance. CRISPR/Cas systems are present in many LAB, predominantly in *Streptococcus*, *Lactobacillus*, and *Bifidobacterium*. However, to our knowledge, no approaches based on CRISPR/Cas techniques in dairy products have been published to date, since in the European Union, CRISPR/Cas methods are considered as genetically modified organisms (GMO) and thus regulatorily restricted. Consumers, and specifically those in the European Union, do not accept the use of GMOs. The United States, for instance, has recently allowed the use of CRISPR-Cas9 edited plants (Plavec & Berlec, 2020). Therefore, although the CRISPR/Cas technique is currently not approved for the production of starters in the European

market, it could serve as an alternative for other international markets.

### 7.1.2 | Treatments for microbial inactivation in milk

*Heat*

Heat treatment is an important step in the manufacturing of most dairy products, since high temperature can inactivate the bacterial species responsible for histamine formation (Naila et al., 2010).

-Sterilization virtually inactivates all present microbiota. Sterile milk is microbiologically stable, even at room temperature. Its shelf-life is usually limited by age-gelation (Deeth & Lewis, 2016), a progressive increase in viscosity leading to gel formation that can be associated with the action of heat-resistant proteases (e.g., plasmin or proteases of *Pseudomonas*) or other physicochemical factors (e.g., changes in micelles, availability of calcium ions, etc.).

-Pasteurization inactivates vegetative pathogenic microbiota. However, bacterial spores and vegetative spoilage microbiota (e.g., heat-resistant micrococci and thermophilic streptococci) might survive heat treatment, thus limiting shelf-life. Subsequent bacterial growth to $10^6$ CFU/mL causes noticeable undesirable changes, such as acid production, protein breakdown, and lipolysis. Thus, it is necessary to refrigerate pasteurized milk in order to limit bacterial growth, allowing for up to 2 to 3 weeks of storage at 4 °C, depending on the milk's hygienic properties. As mentioned for sterile milk, heat-resistant proteases can also be active in pasteurized milk.

In artisanal dairies, a thermization process is applied to milk at 57 to 68 °C for 15 s or more, whereas in industrialized dairies, the milk is pasteurized at 72 °C for 15 s (Martuscelli et al., 2005).

In general, bacterial counts in cheeses made from pasteurized milk are lower than raw milk cheeses (Novella-Rodríguez et al., 2003). The decrease of the initial microbial load by pasteurization can lead to lower levels of BAs detected in dairy products obtained from pasteurized milk compared to those obtained from raw milk (Benkerroum, 2016). In this regard, Novella-Rodríguez, Veciana-Nogués, Roig-Sagués, Trujillo-Mesa, and Vidal-Carou (2004) reported lower levels of BAs in pasteurized milk cheeses in relation to raw milk cheeses. Tabanelli et al. (2012) determined that the inactivation of the HDC enzyme of *S. thermophilus* required a heat treatment of at least 75 °C for 2 min.

However, once histamine is formed, high-temperature treatment could not destroy it, since BAs appeared to be stable and difficult to degrade (McCabe, Frankel, & Wolfe, 2003).

Milk pasteurization thus contributes to reduce the risk of histamine content in the final cheese. However, survival of HPB or their HDC enzymes to the thermal treatment, and/or contamination with HPB in the subsequent steps of cheese formation (see Section 3.1), might be responsible for histamine outbreaks reported even in pasteurized cheeses (EFSA, 2011).

*High-pressure homogenization*

Currently, the food industry is particularly interested in nonthermal techniques for the inactivation of microorganisms, including foodborne pathogens. These techniques allow to increase shelf-life while achieving a "fresh-like" product presentation. HPH treatment is one of the most promising food preservation strategies that can help to inactivate microorganisms while likewise avoiding traditional thermal treatments (Lanciotti et al., 2007). In milk, for instance, an HPH treatment in pressure ranges between 100 and 1,200 MPa helps to maintain flavor, body, texture, and nutrients while improving rennet or acid coagulation. Pressure treatment also improves the preservation and rheological properties of yogurt (Chawla, Patil, & Singh, 2011).

HPH treatment can promote histamine synthesis because it produces a higher proteolysis rate than pasteurization, thereby leading to a higher availability of histamine precursors (Novella-Rodríguez, Veciana-Nogués, Saldo, & Vidal-Carou, 2002). Both aminopeptidase activity and free amino acid concentration of ripening cheeses are significantly increased by treatment at 400 or 600 MPa for 21 and 35 days. However, HPH can also inhibit BA formation in cheese depending on the level of pressure applied (Novella-Rodríguez et al., 2002). Total BA formation decreased by about 50% in cheeses treated at 600 MPa compared to untreated cheeses, thus suggesting that HPH exerts an antimicrobial effect (Calzada, Olmo, Picon, Gaya, & Nuñez, 2013). Lower doses of 100 MPa applied to milk before cheese-making also resulted in decreased microbial counts and a lower histamine concentration at the end of the ripening process (Lanciotti et al., 2007).

Therefore, HPH could be regarded by the dairy industry as a suitable treatment aiming to decrease the population of potentially histamine-producing microorganisms and, consequently, to inhibit BA production. This technique is also useful in the development of innovative dairy foods without harmful effects on safety and milk coagulation, as well as for the improvement of cheese yields (Lanciotti et al., 2007). Moreover, HPH can help to achieve improved nutritional and sensory quality combined with longer shelf-life, while maintaining a food's original texture (Chawla et al., 2011).

### 7.1.3 | Control of physicochemical factors during processing of dairy products

During the production of fermented dairy products, decarboxylase activities and the growth of BA-producing microorganisms are affected by a number of physicochemical factors, such as pH and salt concentration (see Section 4 and Figure 4) (Linares et al., 2012). If good hygiene conditions, controlled pH, and high salt content are achieved, the formation of BAs in cheese is decreased (Valsamaki, Michaelidou, & Polychroniadou, 2000).

Although some authors have proposed that low pH inhibits the accumulation of BAs in ripened cheese (Pintado et al., 2008; Valsamaki et al., 2000), most studies have suggested that acidic pH can encourage the formation of BAs in the course of cheese production (Coton, Rollan, & Lonvaud-Funel, 1998; Ladero et al., 2017; Landete et al., 2008; Marcobal, De Las Rivas, Moreno-Arribas, & Muñoz, 2006). The fermentation of lactose to lactic acid produces a low pH that is difficult to modify, since it is inherent to the milk fermentation process (Linares et al., 2012). In order to neutralize acid stress caused by dairy fermentation, it is assumed that specific amino acid decarboxylases produce BAs (Linares et al., 2012); in fact, the optimal pH for certain amino acid decarboxylases has been reported to be acid. Furthermore, histamine-producing NSLAB are able to survive and grow at low pH, and even produce high amounts of histamine at acidic pH (Barbieri et al., 2019; Frohlich-Wyder et al., 2015). Since formation of BAs raises pH (Barbieri et al., 2019), monitoring of pH could detect increases in pH which might be associated with histamine production. This change of pH could be used as a decision-making tool, for example, for determining the period allotted to the ripening of the monitored cheese.

On the other hand, high salt content seems to reduce BA-producing microbiota and amino acid decarboxylase activity (Linares et al., 2012; Pintado et al., 2008). Salt has been conventionally added to prevent spoilage and food poisoning, while indirectly inhibiting the production of histamine in the final product (Linares et al., 2012). Gardini et al. (2001) demonstrated that a concentration of 5% NaCl minimizes the production of BAs in culture medium and milk by inhibiting microbial growth. However, excessive addition of NaCl should be avoided (Dotsch-Klerk, Goossens, Meijer, & Van het Hof, 2015), since a limited intake of NaCl is recommended (less than 5 g per day) in order to avoid health issues.

Additional preventive measures that could be adopted during processing include low temperatures for ripening. It has been shown that refrigeration can help to reduce the final BA concentration (Calles-Enriquez et al., 2010). Thus, cheese ripening in cold storage and the freezing of cheese samples can reduce the rate of histamine production, probably due to a reduction or inhibition of microbial growth, as well as to a decrease in enzymatic activity of HDC at low temperatures (Martuscelli et al., 2005; Santos, Souza, Cerqueira, & Glória, 2003). However, it is noteworthy to mention that low temperatures could not always be an effective preventive measure, since it has been described that *L. parabuchneri* is capable of producing histamine even in refrigerated cheese (Díaz et al., 2018).

## 7.2 | Histamine degradation: addition of histamine-catabolizing strains or enzymatic degradation

The food preservation measures expounded above can be useful in preventing the production of histamine, but are in fact unable to eliminate accumulated histamine. As explained in Figure 6, histamine can be biologically catabolized by histamine-degrading microbiota through the activity of DAO enzyme (in the same or a different cell), which breaks down histamine to produce aldehyde, ammonia (which contributes to raise pH), and hydrogen peroxide (Pugin et al., 2017). Thus, to degrade histamine already formed in dairy food, the addition of histamine-degrading bacteria (biological degradation) or degrading enzymes, such as DAO (enzymatic histamine degradation), should also be considered (Naila et al., 2010).

### 7.2.1 | Addition of histamine-degrading microbiota

Histamine-degrading microbial strains can be used as starter cultures to reduce histamine content in dairy products (Benkerroum, 2016; Dapkevicius, Nout, Rombouts, Houben, & Wymenga, 2000). Guarcello et al. (2016) identified the enzymatic activities responsible for BA degradation in LAB isolated from Italian cheeses. They selected 431 isolates unable to synthesize histamine (*hdc*-negative); 94 of them were also able to degrade histamine during culture in chemically defined medium. Those isolates belonged to the *Lactobacillus, Leuconostoc, Pediococcus, Lactococcus, Streptococcus, Enterococcus*, and *Weissella* genera. Among them, *L. paracasei* subsp. *paracasei* CB9CT exhibited the highest histamine-degrading activity. These results pointed toward a useful strategy to improve safety while maintaining the sensory characteristics of traditional cheeses. Tittarelli, Perpetuini, Di Gianvito, and Tofalo (2019) studied 24 isolates of a raw ewe's cheese unable to produce histamine and, at the same time, able to degrade it. The most interesting strains appeared to be

*L. casei* A422 and *E. casseliflavus* A143, with degradation rates higher than 50%; thus, they were proposed to be used as starter cultures to reduce the concentration of histamine in raw milk cheeses. Herrero-Fresno et al. (2012) also identified 17 histamine-degrading isolates of *L. casei* from cheese, among which two strains (*L. casei* 4a and 5b) with the highest histamine degradation rates (over 40%) were tested in a Cabrales-like mini-cheese manufacturing model. Due to their validated ability to degrade histamine during cheese ripening, those two *L. casei* strains are proposed as adjunct cultures for the reduction of histamine content in cheese. Leuschner and Hammes (1998) observed a degradation of 55% histamine content during a 4-week ripening period by the *B. linens* strains LTH456 and LTH3686 in a phosphate buffer. A reduction in histamine content was observed throughout the fermentation period of Munster cheese with both strains. Regarding yeasts, the strains of *D. hansenii* H525 and *Y. lipolytica* H446 were demonstrated to degrade several BAs, including histamine, when cultivated in red grape juice with each amine and in phosphate buffer (Baumlisberger, Moellecken, Konig, & Claus, 2015). It is interesting to once more point out the ability of *D. hansenii* to produce histamine as well, but in a strain-dependent manner (Gardini et al., 2006). Physicochemical and sensorial characteristics of dairy products should, nevertheless, be carefully assessed to guarantee their quality.

### 7.2.2 | Addition of histamine-degrading enzymes

Apart from histamine-degrading strains, the addition of the DAO enzyme represents another strategy for the degradation of preformed histamine (Naila et al., 2012). Although the ability of DAO to degrade histamine has not yet been studied in dairy products, Dapkevicius et al. (2000) and Naila et al. (2012) analyzed the use of DAO to degrade histamine in buffer and fish products. Dapkevicius et al. (2000) concluded that in fish slurry, the addition of DAO was more effective than histamine-degrading bacteria. Histamine degradation by DAO is pH- and temperature-dependent, whereas the addition of sucrose or NaCl does not affect histamine degradation. Naila et al. (2012) also evaluated the action of DAO in a tuna soup, corroborating that it is more efficient than histamine-degrading microorganisms in the removal of histamine from food. Enzymatic degradation of histamine by DAO might be considered a safe strategy in raw milk, since the enzyme would be inactivated by heat treatment before its consumption.

Although DAO is presented as an innovative and promising alternative for the degradation of histamine in food, important drawbacks are also associated with its use, especially in dairy products. First, as mentioned above, the enzymatic activity of DAO strongly depends on pH, temperature, and other environmental conditions. Thus, these parameters need to be adjusted and maintained within the enzyme's optimum ranges of activity, which can turn out to be extremely complicated in certain dairy products since yogurts, for instance, have a very acidic pH and must be stored in refrigerated condition. Second, DAO can be easily added to liquid or semiliquid dairy products, such as milk, yogurt, or kefir, without any inconvenience. It would be quite complicated, however, to add DAO to a complex and heterogeneous matrix as cheese, mainly because of putative problems and limitations of enzyme diffusion. The composition, heterogeneity, and microstructure of the cheese matrix would condition the diffusion pattern of the enzyme (Floury et al., 2010; Silva, Peixoto, Lortal, & Floury, 2013), and subsequently its ability to migrate and find the substrate histamine. Finally, although most dairy products are regarded as basic consumer goods, DAO is an expensive commercial product, and its addition would significantly increase retail prices. The production of greater amounts of DAO at a competitive price could represent an interesting challenge to help promote the implementation of this effective solution for the degradation of histamine from dairy products.

## 8 | CONCLUSION

Histamine in dairy products constitutes an important safety and health concern, specifically in fermented and ripened products. This BA is produced by present microbiota (gram-positive and gram-negative bacteria, as well as yeasts and molds) from the precursor amino acid histidine via oxidative decarboxylation by the HDC enzyme. It is important to detect and quantify histamine-producing microbiota, particularly through the *hdc* gene, which is responsible for the synthesis of histamine. The accumulation of histamine in dairy products can be additionally prevented by controlling specific environmental and microbiological conditions (pH, temperature, salt concentration, etc.) when preparing dairy products, and/or by applying milk treatments (pasteurization, HPH, etc.). The use of starter cultures unable to produce histamine is another strategy designed to prevent histamine from dairy products. Finally, once histamine is accumulated, it could be necessary to implement its biological or enzymatic degradation through the addition of histamine-degrading microbiota or DAO. Obtaining histamine-free dairy food is a formidable challenge: if met, it would improve the quality of life of histamine-intolerant individuals, but also of the rest of the population, since it would prevent histamine

outbreaks that cause significant harmful health effects on the public at large.

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## AUTHOR CONTRIBUTIONS

M. Moniente collected test data and drafted the manuscript. D. García-Gonzalo designed the study, drafted and reviewed the manuscript. I. Ontañón reviewed the manuscript. R. Pagán designed the study, reviewed the manuscript, and carried out project administration and funding acquisition. L. Botello-Morte designed the study, collected test data, interpreted the results, and drafted, reviewed, and edited the manuscript.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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