Lactic Acid Bacteria and Honey Bees

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Honey bees play a pivotal role in the sustainability of ecosystems and biodiversity. Many factors including parasites, pathogens, pesticide residues, forage losses, and poor nutrition have been proposed to explain honey bee colony losses. Lactic acid bacteria (LAB) are normal inhabitants of the gastrointestinal tract of honey bees and their role has been consistently reported in the literature.

honey bee | gut microbiota | lactic acid bacteria

1. Introduction

Honey bees play a crucial role in the maintenance of wider biodiversity, ecosystem stability, and agricultural production through pollination [1][2][3]. While global stocks of managed honey bee colonies appear to be increasing, significant decline and colony losses of wild and domestic bees have been reported in many parts of the world [4][5][6][7].

Multiple biotic and abiotic factors are associated with the honey bee colony losses [4][8][9][10][11][12][13]. Furthermore, there is a growing consensus that parasites and pathogens are among the most significant threats to the management of bee colonies [14][15].

In-depth knowledge of these factors is essential and a prerequisite for developing measures to ensure both healthy bees and sustainable pollination. The aforementioned factors can also influence the honey bees' gut microbiota. Its dysbiosis could weaken the honey bees, thus contributing to the phenomenon of Colony Collapse Disorder (CCD) [16][17][18]. Moreover, the gastrointestinal tract of honey bee's larvae and adult bees is the infection and transmission site of different pathogens, such as Ascosphaera apis, Nosema ceranae, Paenibacillus larvae, Melissococcus plutonius, and viruses. These pathogens may cause economic losses in agriculture, affecting the survival of managed and wild honey bees [19][20][21][22]. Recently, many different control measures, such as fungicides, antibiotics, heterocyclic organic compounds (indoles), and bacteriophages, have been used to control honey bee diseases [23][24]. Most of these products were promising in terms of controlling the growth of pathogens both in vitro and in vivo. Nevertheless, these approaches could be useful as therapy, but are often ineffective for prophylactic purposes, leaving the honey bee colonies vulnerable to diseases. In addition, the use of antibiotics in beekeeping is legally banned in many countries of the European Union [25], due to the risks for both human and honey bee health [17][26], and to the uncontrolled spread of antimicrobial genes [27]. Therefore, there is a growing interest in new effective means of controlling disease and improvement in honey bee health, as well as providing benefits for agriculture by increasing yield and quality of crop production. The use of naturally occurring compounds for disease control could be an interesting approach that needs to be further investigated because the findings to date have not always been of biological relevance [28][29][30].

The gut microbiota is fundamental for honey bee's growth and development, immune function, protection against pathogen invasion [17]. A well-balanced microbiota is essential to support honey bee health and vigor, moreover, the structure of the intestinal bacterial community can become an indicator of the honey bee health [31][32][33].

The gut microbial communities can also provide an important new tool to improve disease management strategies and contribute to the development of novel and sustainable disease monitoring approaches [34][35][36]. More in general, the manipulation and the exploitation of the insect microbiota could be effective in developing strategies for the management of insect-related problems [37][38]. Indeed, this approach, generally defined as 'Microbial Resource Management' (MRM), was described as 'Symbiont Resource Management' (SMR) when applied to symbiotic microorganisms. The MRM refers to the proper management of the microbial resource, present in a given ecosystem, in order to solve practical problems through the use of microorganisms. One of the environmental hot topics is represented by the gastrointestinal tract (GIT) defined as an "outside world within living animals" [39]. The main objective is to control and steer microbial communities, and microbial processes, in the most sustainable way.

Moreover, the protection against pathogens and/or parasites is one of the frequently associated aspects of a balanced intestinal microbiota. Indeed, it is widely known that the early stages of pathogens infection can be eased by any nutritional or environmental stress causing microbial dysbiosis. In several studies, it has been proven that, among the microbial symbionts associated with the honey bee, the lactic acid bacteria have a probiotic effect on bees by stimulating their immunity and helping them to overcome pathogen attacks [40][41][42][43]. Different mechanisms, among which the direct pathogen inhibition by the release of antimicrobial compounds, the stimulation of the immune system, and the competitive exclusion, mediated by the microbial symbionts, could be involved in the honey bee protection.

2. Gut Microbiota of Honey Bee: Presence and Role of Lactic Acid Bacteria (LAB)

The GIT microbiota structure of honey bees (Apis mellifera) is both unique and highly specialized; in detail, the dominant bacterial phyla belong to Proteobacteria, Actinobacteria, Bacteroidetes, and Firmicutes [44][45]. In social insects, such as the honey bees, the intestinal bacteria are transmitted and shared by colony members through oral–fecal and trophallactic transmission. However, consumption of stored pollen or bee bread, contact with older bees within the hive, and hive material during the adult phase are also involved in transmitting and sharing the bacteria [17][44][45].

The lactic acid bacteria (LAB) are normal inhabitants of the GIT of many insects, and their presence in the honey bee intestinal tract has been consistently reported in the literature [46][47][48]. These bacteria belong to a biologically defined group where lactic acid is produced during homo- or hetero-fermentative metabolism.

Soil and plants are considered the hypothetical first niche of the ancestral LAB, followed by the gut of herbivorous animals [49]; the transition from the soil and the plants to the animal gut occurred by three areas of genomic adaptation [50][51]: resistance to host barriers, adhesion to intestinal cells, and fermentation.

A bees' gut is the optimal microenvironment for LAB as it is defined by microaerobic conditions, presence of nectar and sugars, optimal temperature. Olofsson et al. [52] suggested that bees and their microbiota are mutually dependent, in fact, LABs received a niche in which nutrients were available and bees gained protection [35][53][54].

LABs' importance is further emphasized by their ecological distribution, which is not limited to adult bee gut only, in fact, they have been isolated from larval guts [55] and the honey stomach of adult bees [56]. This latter structure, adjacent to the midgut, is a further relevant microbial niche associated with food storage and liquid transfer (water, nectar, and royal jelly). In addition, LABs are also dominant in the hive environment (beebread, honey, wax, and comb) [46][47][48][52][53][54][56][57][58].

LABs have also been extensively studied in animals and humans because of their probiotic properties, which have led to their well-built commercial exploitation in the food, feed, and pharmaceutical market [59][60][61][62][63]. The finding that a component of the honey bee gut microbiota was represented by LABs has increased the interest of scientists in looking for similarities and analogies with the probiotic bacteria widely investigated in humans and animals.

3. Functional Properties of LAB

There are several properties through which LABs can provide a specific health benefit for the honey bees [60][61][62].

The following section discusses some functional properties of LAB supplemented as probiotics in bee feeding. **Table 1** provides an overview of the main results obtained in several studies.

Table 1. Overview of the main results obtained using LABs as probiotics in the honey bee diet.

LAB Species	Source	Relevant Reported Results	Ref.
L. kunkeei *F. fructosus*	Honey bee gastrointestinal tract	Decreases of the mortality rate and significant enhancement of the longevity of honey bees.	[64]
L. johnsonii		Queen egg-laying stimulation; higher number of honey bees and a significant increase in honey yield, healthier bee colony	[65] [66] [67]
L. johnsonii *L. kunkeei* *L. plantarum* *L. salivarius*		Increased honey production	[42] [68]

LAB Species	Source	Relevant Reported Results	Ref.
Bifidobacterium spp. *Lactobacillus* spp.	Commercial probiotic product	Mild increment in bee survival	[69]
B. lactis *L. acidophilus* *L. casei*		Enhancement of bee health. Increased honey production and size of the wax cells	[70] [71] [72]
B. bifidum *L. acidophilus* *L. delbrueckii* sub. bulgaricus		Administration in pollen substitute resulted in an increase in dry mass and crude fat level	[73]
L. brevis		Increased expression of genes encoding antimicrobial peptides (abaecin, defensin-1)	[74]
L. plantarum, *L. rhamnosus*		Mitigate antibiotic-associated microbiota dysbiosis and immune deficits in adult workers	[75]
LAB mix: *B. breve* *B. longum* *L. acidophilus* *L. casei* *L. plantarum* *L. rhamnosus*	Commercial probiotic product	Enhance honey bee immunity. Higher levels for abaecin and defensin in honey bee larvae	[76]
Multiple LAB species		Boosting colonies' strength. Positive physiological changes in probiotic-treated groups of adult bees	[77]
B. bifidum *E. faecium* *L. acidophilus* *P. acidilactici*		Advantages of probiotic supplementation include better bee survival and higher dry mass and crude fat level	[73]
B. asteroids *F. fructosus* *F. pseudoficulneus* *F. tropaeoli*	Honey bee hive	Induced immune stimulation (higher level of Apidaecin1). Results suggest that the bee immune response to endogenous bacteria is species-specific	[78]
L. kunkeei		Mitigate antibiotic-associated microbiota dysbiosis	[75]
Fructobacillus spp.		Able to utilize lignin and promote the growth of honey bee gut community members	[79]
E. thailandicus *L. curvatus* *W. cibaria* *W. viridescens*	Different sources	The transcription levels of antimicrobial peptide genes, such as abaecin, defensin, and hymenoptaecin, were found to increase significantly	[80]

3.1. Heavy Metals Detoxification

LAB Species	Source	Relevant Reported Results	Ref.
W. paramesenteroides			

Taxonomic references: Lactobacillus kunkeei: Apilactobacillus kunkeei; Lactobacillus plantarum: Lactiplantibacillus plantarum; Lactobacillus salivarius: Ligilactobacillus salivarius.

…nnological …r harmful pollutants [81][82][83][84]. …e damage to the survival, feeding, growth, and impair the behavior of the organisms, including honey bees [85][86][87][88][89]. It has been widely demonstrated that the honey bee populations are susceptible to several environmental threats, including HMs [81]. The honey bees can be exposed to HMs when foraging on contaminated honey and pollen resources and, in some cases, by airborne exposure [90][91]. The HMs also bioaccumulate in larval and adult stages, in the colony's honey, wax, and propolis supplies [86][91], making the honey bees excellent bioindicators of HMs presence in the environment [92][93]. Some reports indicate that the honey bee cell ultrastructure can be adversely affected by HMs, inducing cell apoptosis that can disrupt cell vigor and cell proliferation. HMs can also negatively affect the genetic material, resulting in mutation, and in addition, they also cause neurotoxic effects [86][89][91][94][95][96][97][98][99][100]. Other studies have shown that the HMs may affect antioxidant capacity and immunocompetence in honey bees [87][88][101].

Many bacteria, including the LABs, appear to have the ability to efficiently remove the HMs through two mechanisms: biosorption and bioaccumulation [102][103][104][105].

Biosorption refers to the binding of metals onto the cell wall's surface and it is a simple physicochemical process, whereas the bioaccumulation process refers to the intracellular accumulation of metals that occur in two stages, biosorption and bioaccumulation by transporting the metals across the cell wall and membrane [106][107][108]. Recently, the next generation of probiotics has attracted increasing attention [103][109][110] for their ability to alleviate HMs toxicity, although, most of the studies have been performed with an in vitro digestion or animal model. [75][103][111][112][113][114][115][116][117][118]. Based on this research, specific LABs could be used as a new dietary therapeutic strategy against HMs toxicity. In this regard, Rothman et al. [85] demonstrated that some honey bee symbiotic LABs are capable of in vitro metals' bioaccumulation. However, these results are preliminary and so, more in-depth, systematic, and epidemiological studies need to be performed on honey bees.

3.2. Mitigation of Pesticides Effect

Pesticides, such as insecticides and fungicides, are considered one of the possible stressors causing the general decline in honey bees and colony losses [5][12][119]. The exposure of honey bees to pesticides also causes microbial dysbiosis and immunosuppression, rendering them more susceptible to pathogens; furthermore, the interactions between pesticides and pathogens may exacerbate honey bees' mortality [120][121][122][123][124][125][126][127][128][129][130]. A novel concept may be the administration of lactic acid bacteria to mitigate the harmful effects of pesticides. There are several mechanisms through which the treatment with probiotics could act on pesticide intoxication; for example, the treatment with Pediococcus acidilactici restored the expression of two genes, which were altered by pesticide co-exposure, coding for serine protease 40 and vitellogenin [131]. Moreover, the benefit of LAB supplementation is a reduction in pesticide uptake through their degradation [132][133][134][135] or sequestration of ingested organophosphate pesticides, which has been associated with reduced intestinal absorption and insect toxicity with appropriate models [136][137]. In other model organisms, LABs have been shown to reduce toxicity and exert a protective effect on the host [135][138][139][140], thus establishing a basis for future studies to investigate this potential in honey bees. Recently, some authors have highlighted how the resistance and capacity of LABs for degrading organophosphorus pesticides is strain-dependent [134][141] and showed the feasibility of the LAB to be developed into probiotic products capable of alleviating oxidative damage caused by pesticides in vivo [142].

Based on this knowledge, probiotic supplementation with appropriate LAB cultures could mitigate the sublethal effects of pesticides by reducing pesticide uptake, improving pathogen resistance, and mitigating sublethal effects on colony development. Until chemical agents are no longer used in agriculture, the ability to supplement honey bees with probiotics could help the insects to fight the unintended pernicious effects [143].

3.3. Adhesion to Intestinal Mucosa and Enhancement of the Epithelial Barrier

Adhesion to intestinal epithelial cells is a prerequisite for the colonization of probiotic bacteria, leading to transitory colonization that would foster the immune response and, at the same time, stimulate the intestinal barrier and metabolic functions. In addition, this ability to adhere to the host may serve a protective role against undesirable microorganisms through competition for host cell-binding sites [108][144][145][146].

As reported in a number of studies, during this adaptation phase, bacteria produce extracellular polymeric substances (EPS), containing biological macromolecules, some of which (polysaccharides, proteins, nucleic acids, and lipids) are also responsible for the cohesion of microorganisms and are implicated in the production of biofilms [146][147].

3.4. Participation in the Digestive Process

The honey bee gut microbiota, as well as that of other insects, synthesize essential nutritional compounds and improve the digestion efficiency and availability of nutrients [17][47][148]. A properly functioning gut microbiota is closely connected to the health of the honey bee since it provides countless enzymatic activities to break down the complex sugars of the honey bees' diet. Iorizzo et al. [48] proved that some Lactiplantibacillus plantarum (previously Lactobacillus plantarum) strains isolated from honey bee gut possess both alpha- and beta-glycosidase activities. The enzyme beta-glycosidase in association with other enzymes, cellulase, and hemicellulase produced by bee intestinal symbionts, such as Gilliamella, contributes to the hydrolysis of cellulose [149]. The alpha-glycosidase converts maltose to glucose and with alpha-amylase, is involved in the starch breakdown [150].

Honey bees collect food rich in carbohydrates, such as sucrose, glucose, and fructose, which are important for the development and well-being of their colonies [151]. However, other carbohydrates present in their diet in lesser quantities, such as monosaccharides (e.g., mannose, galactose, xylose, arabinose, rhamnose) and oligosaccharides (e.g., lactose, melibiose, raffinose, and melezitose), may be toxic to bees as they do not have specific enzymatic activity for their metabolization [152][153]. Iorizzo et al. [154][155] evidenced that some Apilactibacillus kunkeei (previously Lactobacillus kunkeei) and Lp. plantarum strains can metabolize arabinose, galactose, lactose, mannose, melibiose, melezitose, and raffinose. As they are able to simultaneously intervene in the breakdown of complex polysaccharides and metabolize toxic sugars, the role of LABs in enhancing food tolerance and maintaining the health of their hosts could be considerable [156].

3.5. Antioxidative Activity

Recent research demonstrated that several biotic and abiotic factors, induce oxidative stress and impair the antioxidant defensive capacity of honey bee larvae [9][157][158][159][160].

Oxidative stress is an important process that can cause severe negative effects in eukaryotic organisms. Reactive oxygen species (ROS) are produced during normal metabolic processes and are responsible for oxidative stress. To prevent or reduce ROS-induced oxidative stress, insects use various enzymatic mechanisms that cause oxidative inactivation (superoxide dismutase, catalase, and peroxidase) or removal of ROS at the intracellular level through the enzymes glutathione peroxidase (GPX) and glutathione reductase (GSR) [161][162][163].

These particular enzyme activities are relevant for the health of honey bees when they are under biotic and abiotic stressors, such as nutritional and thermal stress, parasites, heavy metals, and/or pesticides [9][129][157][164][165][166][167][168]. Oxidative stress can also be a consequence of some honey bee diseases; in fact, during the excessive growth of pathogens, the levels of ROS in the infection site increase [160]. Dussaubat et al. [169], and more recently Li et al. [158], reported that the oxidative stress in honey bee larvae and the decreased levels of metabolites involved in mitigating oxidative stress induced by Ascosphera apis could disrupt the antioxidant defenses of the infected larvae. Antioxidant enzymatic activity and the amounts of certain metabolites (e.g., taurine, docosahexaenoic acid, and L-carnitine) involved in reducing oxidative stress were significantly decreased in the gut of infected larvae [158]. In recent years, particular attention has been focused on the application of LABs as natural antioxidants. Some strains belonging to this group have both enzymatic and non-enzymatic antioxidant activity, which can reduce the oxidative damage caused by the accumulation of ROS during the digestive process [170][171][172]. Probiotic LABs have complex antioxidant mechanisms, and different strains use different mechanisms: chelation of toxic ions (Fe^{2+} and Cu^{2+}); synthesis of antioxidant compounds (e.g., glutathione, butyrate, folate, and exopolysaccharides); activation of transcription of enzymes that neutralize free radicals [173][174][175]. Further research aimed at the selection, and diet utilization, of appropriate probiotics that can contribute to the reduction in oxidative stress in honey bees, would be interesting.

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