

Review

# Intraguild predation provides a selection mechanism for bacterial antagonistic compounds

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Bacteriocins are bacterial proteinaceous toxins with bacteriostatic or bacteriocidal activity towards other bacteria. The current theory on their biological role concerns especially colicins, with underlying social interactions described as an example of spite. This leads to a rock–paper–scissors game between colicin producers and sensitive and resistant variants. The generality of this type of selection mechanism has previously been challenged with lactic acid bacterial (LAB) bacteriocins as an example. In the natural environment of LAB, batch cultures are the norm opposed to the natural habitats of *Escherichia coli* where continuous cultures are prevailing. This implies that fitness for LAB, to a large degree, is related to survival rates (bottleneck situations) rather than to growth rates. We suggest that the biological role of LAB bacteriocins is to enhance survival in the stationary growth phase by securing a supply of nutrients from lysed target cells. Thus, this social interaction is an example of selfishness rather than of spite. Specifically, it fits into an ecological model known as intraguild predation (IGP), which is a combination of competition and predation where the predator (LAB bacteriocin producer) and prey (bacteriocin susceptible bacteria) share similar and often limited resources. We hypothesize that IGP may be a common phenomenon promoting microbial production of antagonistic compounds.

**Keywords:** antibiotics; bottlenecks; bacteriocins; colicins; spite; selfishness

## 1. INTRODUCTION

When provided with ecological opportunity, new bacterial genotypes lead to adaptive variation and thereby polymorphic populations [1,2]. One example is provided by colicins—antimicrobial proteins produced by *Escherichia coli* and directed against mainly other *E. coli* lineages [3–5]. Production of colicins imposes a fitness cost on the producing cell but is supported in a heterogeneous (structured) environment, whereas in a homogenous environment, frequency-dependent selection is observed [3,6,7].

Colicins offer a model system for rock–paper–scissor relationships that support biodiversity in communities of competing lineages [3,8]. The fitness cost of colicin production will give advantage to resistant mutants. Colicin-sensitive strains will have a growth rate advantage over the resistant variants but will be susceptible to colicin-producing strains, thus fulfilling the ‘circle’ in a rock–paper–scissor relationship (figure 1*a*). This results in an ‘arms race’ giving rise to several colicin variants [7,9,10] and, because the colicin producer dies when releasing the colicins, it also serves as a good example of a social behaviour known as spite, a social interaction that harm both the actor and the recipient [8,11–14].

Lactic acid bacteria (LAB) are Gram-positive bacteria used extensively in production of fermented foods but with the environment as the primary habitat [15–22]. Many LAB produce bacteriocins, which are effective against various Gram-positive lineages but in general not against Gram-negative bacteria [23–26]. Owing to the industrial applications of food-grade LAB, the molecular genetics and mode of action of LAB bacteriocins have been the subject for extensive research within the last 20 years [23–25,27,28]. The selective forces acting on the evolution of LAB bacteriocins are not as well understood as for colicins [29]. However, what is known about the nature of selective forces and fitness costs associated with the production of LAB bacteriocins does, to some degree, contradict the colicin paradigm. For example, several of the LAB bacteriocins exhibit rather broad antimicrobial spectra contrary to the narrow spectrum of colicins [9,10,29,30] (see the electronic supplementary material, table S1). Furthermore, Dykes & Hastings [29] suggested that the fitness costs of LAB bacteriocin production may be minimized owing to, for example, additional cellular functions [23,31–35], as outlined in §3*b*. This may explain why LAB bacteriocin producers, in some instances, are able to invade and maintain themselves in a population of sensitive clones [29,36]. A reduced fitness cost of bacteriocin production will disrupt the ‘circle’ of the rock–paper–scissor model (figure 1*a*), and thus LAB bacteriocin production cannot be explained by this model.

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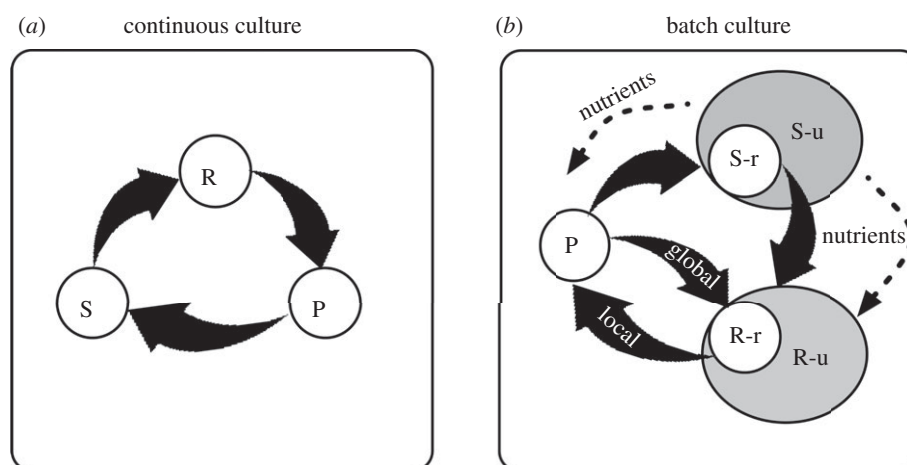


Figure 1. Overview on social models that illustrate distinct types of selection of bacteriocins, (a) the competitive model concerning colicins and (b) the intraguild predation model concerning LAB bacteriocins. P, bacteriocin producer; S, bacteriocin susceptible; R, bacteriocin resistant; -r, related; -u, unrelated. Relatedness is also symbolized by open circles, while un-relatedness is symbolized by grey ovals. In (a) a continuous culture, selection pressure is on high growth rates. In such systems, there is a fitness cost of expressing bacteriocin resistance genes, but an even larger fitness cost of producing bacteriocins (spite). However, the fastest growing bacteriocin susceptible population will be killed by bacteriocins. This phenomenon is described by the rock–paper–scissors model. In (b) a batch culture, selection pressure is shifted towards survival in the bottleneck scenario when resources have been exhausted. Here the cost of producing bacteriocins is outweighed by the benefits gained from uptake of nutrients from the lysed sensitive cells. In situations with a low dispersion factor, resistant and related variants will be selectively favoured, which will not be the case under global conditions.

We here propose that LAB production of bacteriocins serve as an example on intraguild predation (IGP). IGP is a combination of competition and predation in which an IGPredator kills and eats an IGPrey that uses similar and often limited resources as does the IGPredator [37–40]. Our model is based on selection in a bottleneck scenario and suggests that the release of nutrients from lysed sensitive target cells mediated by bacteriocin production during the stationary phase may outweigh the cost of production. This requires that a high degree of bacteriocin activity is first observed in the stationary growth phase to allow a sufficient concentration of bacteriocin-sensitive variants. This is indeed described for many LAB bacteriocins [23,31,41–43].

We will restrain the description of LAB bacteriocins to class I (lantibiotics), and class II (small non-lantibiotic peptides) bacteriocins [24,25,28,35,44,45]—the most well examined of the LAB bacteriocins—and only occasionally include the third class (high molecular weight proteins) of bacteriocins.

## 2. SELECTION OF LACTIC ACID BACTERIAL BACTERIOCIN PRODUCTION DURING POPULATION BOTTLENECKS

We discuss here first the nature of the different environments facing colicin and LAB bacteriocin producers and will bring forward the proposal that LAB populations in their natural environments are facing bottlenecks that offer bacteriocin producers a fitness advantage owing to a higher degree of survival. It is well known that bottlenecks, including those provided by periodic selection, are a prominent cause for selection of bacterial variants [46–49], and we hypothesize here that this is also the case for LAB bacteriocin systems.

### (a) *Effect of habitats on population bottlenecks and selection*

Colicin-producing *E. coli* strains are adapted to live in animal intestines, but they will also face transient

environmental exposures. Experiments that focus on ecological models for colicin systems frequently use the intestine as a model [50–53]. This environment is nutrient-rich and can be considered as providing a continuous culture system. In such an environment, success is expected to depend on fast proliferation, and broad-range bacteriocin production will be of less importance.

On the contrary, it is characteristic that LAB bacteriocin producers can be found in a range of habitats. Although food products predominate among sources of LAB bacteriocin producers [41–43,45,54–63], the external environment or animals must be considered the primary habitat for LAB, whereas food products, in most cases, must be understood as secondary habitats. Here, we will address only the external environment as a LAB habitat, as it provides a striking counterexample compared with the primary habitat facing colicin producers.

The extensive fermentative abilities of LAB indicate that often the natural environment for these bacteria is decaying organic material, which can be viewed as providing the social arena for a batch culture. Thus, the natural habitat of a LAB is characterized by the two very different conditions of feast and famine characteristic for batch cultures (summarized in table 1). The ‘feast’ condition is represented by the start of the fermentation of a suitable substrate in which the LAB, together with other microorganisms that find the conditions favourable, exhibits a logarithmic phase of growth. This growth phase is followed by the ‘famine’ condition, the stationary/death phase causing a bottleneck with exhaustion of substrates and less-favourable key environmental parameters, such as a decrease in pH and increasing concentrations of metabolites (e.g. lactic acid). The selective forces under these two conditions have similarities to the theory of  $r$  and  $K$  selection, which describes two types of selection, one targeting traits in relation to carrying capacity ( $K$ ) and the other traits in relation to the maximal intrinsic rate of natural increase ( $r_{\max}$ ) [64,65].

Table 1. Characteristics of the different growth phases for a bacteriocin producer in a batch culture.

characteristic	growth phase	
	log growth	stationary/death
level of substrates	high	low
level of waste products	low	low to high
duration of phase	short	long
value of high growth rate	high	low
degree of microbial interactions	low	high
growth or survival	growth	survival
presumed value of bacteriocins for producers	low	high

The bottleneck phase can have a prolonged extension because the period of death is not necessarily a steady decrease but may be interrupted by multiple spurts in multiplication [66]. Such spurts might reflect periodic selection events and thereby the addition of extra bottlenecks besides the general one provided by the nutrient limitation. Overall, a strain may survive and dominate the population during a bottleneck in batch fermentations if it has a diminished death rate, similar to what has been argued to be the case for bacterial populations during a transmission phase [49]. This situation is opposed to the conditions during growth, where a strain may survive and dominate the population if it has an increased growth rate.

Production of broad-spectrum bacteriocins allows, in mixed bacterial communities, at least a partial escape from this scenario. Although many LAB bacteriocins have a bacteriostatic mode of action, they may, however, contribute to an indirect bactericidal effect caused by an induction of autolysis of the sensitive target cell (table 2), a phenomenon that has been used for the acceleration of cheese ripening [80]. Bacteriocin producers may therefore have an improved survival during the stationary/death phase by the gain of access to additional sources of nutrients from the lysed cells. Those nutrients will, for a large part, consist of carbohydrates associated with the cell wall and DNA of the target cell, known to be important for bacterial (including LAB) survival [81,82] during the stationary growth phase [83]. Indeed, this role for bacteriocin-producing LAB has been suggested previously as one of the possible functions for *Streptococcus mutans* bacteriocins [31]. It is tempting to speculate that the continuous culture systems that constitute the evolutionary context for colicins do not play a similar role for LAB bacteriocins. Studies examining the effect of selected bacteriocins on the composition of intestinal microbiota, however, gives contradictory results, and this aspect requires further research to reach a conclusion [84,85].

For bacteriocin-producing cells that survive by lysing and eating neighbouring cells, the outcome resembles the cannibalism described for sporulating *Bacillus subtilis* cells or the fratricide mechanism known from *Streptococcus pneumoniae* [86,87]. However, the broad-spectrum activity observed for many LAB bacteriocins fits better into the social model of IGP, which also offers an alternative to direct competition envisaged for colicins (outlined schematically in figure 1).

### (b) Importance of scale of competition for intraguild predation during population bottlenecks

An important parameter regarding selection for bacteriocin production is the dispersion from one habitat to another, i.e. from a bottleneck situation to a new phase of log growth. By dispersion rate, we here mean the probability for separation of bacteriocin producers and sensitive as well as resistant or tolerant target cells during the transition phase(s); so they end up in new distinct habitats during the next round of batch fermentations. If the dispersion rate is low, it will establish competition on a local scale and thereby promote, for example, spiteful behaviour, as for colicin producers [11,88]. Taking into consideration that the bottleneck habitats of LAB in the environment consist of settings, such as decaying vegetables, with a relatively long duration and a continuous dispersion taking place, it is not unreasonable to assume that the rate of dispersion in such a case instead is high, leading to competition on a global scale.

By release of nutrients from lysed, sensitive target cells, LAB bacteriocin production provides ‘public good’ to bacteriocin resistant/tolerant lineages similar to, for example, siderophores [89,90]. As for siderophores, it can be anticipated that the proportion of bacteriocin producers in the population will be positively affected if competition acts on a global scale, i.e. with a high degree of dispersion [91]. A critical difference to the siderophore system is that the resource (the sensitive target cells) might mutate into competitors (resistant target cells). The fraction of resources that vanish in this way can also be assumed to depend on the scale of competition being less the more global the social arena is. The importance of scale might however be diminished if more than one type of bacteriocin is produced. The first multiple bacteriocin-producing LAB described was a strain of *Lactococcus lactis* that produced several lactococcins [92,93], with a very narrow inhibition spectrum [62]. Shortly afterwards, multiple bacteriocin production was also discovered in *Carnobacterium maltaromaticum* [56,94,95]. The inhibition spectrum of the carnobacteriocins B1, BM1 and B2 is wider than that of the lactococcins A, B and M (see the electronic supplementary material, table S1) and might reflect the type of niche carnobacteria reside in [19]. Other LAB that produce multiple bacteriocins have subsequently also been found in lactobacilli (e.g. *Lactobacillus plantarum* [96] and *Lactobacillus sakei* [97]), leuconostocs (e.g. *Leuconostoc mesenteroides* [98]) and enterococci (e.g. *Enterococcus faecium*, [43,99–101]). The potential synergy effect by producing multiple bacteriocins probably diminishes the possibility for selection of resistant variants.

In a mixed community of LAB species, bacteriocin-tolerant lineages may proliferate according to the scenario known as ‘tragedy of the commons’ (original concept from Hardin 1968 [102] but for a microbiological context, see for example [13]). Such bacteria that could be considered as cheaters include a variety of Gram-positive lineages as well as Gram-negative bacteria, in general. However, Gram-positive tolerant lineages might be selected against if the scale of competition is global as described earlier, whereas Gram-negative bacteria are selected against owing to their increased sensitivity towards organic acids produced by LAB [103,104].

Table 2. Examples of LAB bacteriocin-mediated lysis of target cells.

bacteriocin (class)	lysis of target organism	due to autolysins	reference
IFPL105 (I)	<i>Lactococcus lactis</i> , <i>Lactobacillus casei</i> subsp. <i>casei</i>	+	[67,68]
lacticin 3147 (I)	<i>Clostridium difficile</i> , <i>L. lactis</i>		[69,70]
lacticin 481 (I)	<i>L. lactis</i>		[71]
nisin (I)	<i>L. lactis</i> , <i>Staphylococcus simulans</i>	+	[68,72]
Pep5 (I) <sup>a</sup>	<i>S. simulans</i>	+	[72]
enterocin AS-48 (II)	<i>Listeria monocytogenes</i>	+?	[73]
lactococcin A, B, M (II)	<i>L. lactis</i>	+	[68,74,75]
pediocin PA-1 (II)	<i>Leuconostoc mesenteroides</i>		[30,76]
pediocin PA-1 (II)	<i>Pediococcus acidilactici</i> , <i>Pediococcus pentosaceus</i>	+	[77]
plantaricin C (I)	<i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i>		[58,78]
plantaricin C (I)	<i>Lactobacillus fermentum</i>	+?	[58,78]
enterolysin A (III)	<i>Enterococcus faecalis</i>	—	[79]

<sup>a</sup>Produced by *Staphylococcus epidermis* that belongs to the Firmicutes but is not a LAB.

### 3. SELECTED FEATURES OF LACTIC ACID BACTERIAL BACTERIOCINS AND THEIR PRODUCERS THAT SUPPORT AN INTRAGUILD PREDATION MODEL

#### (a) *Inhibition spectrum and occurrence of resistant target cells*

Because the LAB bacteriocin producers are likely to meet ever-changing lineages of target cells in successive bottleneck situations, the model requires that the LAB bacteriocins exhibit relative broad target spectra in order to improve fitness of the producing cells. Indeed, several LAB bacteriocins exhibit such broad spectra towards target species that may be only remotely phylogenetically related, i.e. belonging to genera other than the bacteriocin producer. Thus, a survey of the literature showed that among selected class I bacteriocins, all 10 showed inhibition against genera other than that to which the producer organism belonged, and this was also the case for 25 out of 30 class II bacteriocins (see the electronic supplementary material, table S1). There is, however, frequently intraspecific variation in bacteriocin susceptibility among target cells [97,105–109], which result in the likelihood of the presence of tolerant lineages in mixed culture batch fermentations.

The mechanism that confers resistance or tolerance to target cells is, in some instances, owing to differences in the membrane composition [108,110,111], but other mechanisms (e.g. mutations related to phosphotransferase systems or cell wall alterations) have also been reported [28,112]. There are indications that resistance phenotypes are associated with fitness costs [113,114]. As mentioned previously, bacteriocin-producing LAB contains an immunity gene(s) that confers resistance towards own bacteriocin(s). In a few cases (putative orphan), immunity genes without any clear bacteriocin partner have been reported [94,115,116]. The mechanisms for maintaining the presence of such genes in LAB populations will require additional studies, but their occurrence might be explained by the Black Queen hypothesis (BQH) proposed by Morris *et al.* [117], which suggest the loss of genes essential for producing (leaky) common goods (here, bacteriocin structural genes) by many members of microbial communities (here variants with orphan immunity genes).

#### (b) *Cost of bacteriocin production*

We propose that the lack of fitness cost of bacteriocin production is not of overall importance in an IGP model but

this devaluates the usefulness of the rock–paper–scissor model for LAB bacteriocins.

Some, but far from all, LAB bacteriocin operons are located on chromosomes [24,25,44,118], which may reduce fitness cost as argued by Dykes & Hastings [29], assuming that no other selective forces are relevant. Another way to reduce the fitness cost of bacteriocin production is to assess whether the bacteriocin has moonlighting properties [119], meaning that it serves cellular functions other than interbacterial warfare. An example is LAB bacteriocins that can also act as signal molecules in a quorum-sensing context [23,32,34,35]. Here, it is of interest that quorum-sensing-controlled bacteriocin production observed for many LAB bacteriocin systems fits into an IGP/bottleneck model, as it delays bacteriocin production relative to growth. Also, some bacteriocin-related molecules may exert biological roles unrelated to antagonism [31,33,120,121].

On the other hand, evidence exists that points towards additional cost of LAB bacteriocin production as LAB loci frequently contain numerous genes involved in bacteriocin production, immunity and secretion [19,23–27,34,35,44,118,122]. However, it should be noted that in the context of bottlenecks in batch fermentations, it is more relevant to study the presence of fitness costs associated with survival. Use of nutrients in an IGP/bottleneck model that increases survival of the producer offers a potential selection mechanism, but there are currently no experimental studies that have examined this issue.

### 4. CONCLUSIONS

Selfishness, as a social interaction, appears to be promoted by bacteriocin-producing LAB in batch culture habitats that allow for IGP. Contrarily, the production of colicins has been extensively used as a convenient microbial model for the social interaction spite [89,123]. The LAB bacteriocin systems described here may also be perceived, to some degree, as an example of altruism rather than of selfishness when tolerant or resistant lineages in addition to sensitive target cells are present in the environment of the producer. This combination of potentially two types of social interactions makes LAB bacteriocins an interesting model to explore.

It can be argued that bacteriocin producers and tolerant/resistant lineages could be labelled as helpers and

beneficiaries, respectively, according to the BQH (referring to the queen of spades in the game Hearts) [117], provided they do not compete for carbon and energy sources. In our scenario, bacteriocin-producing and bacteriocin-tolerant lineages share the same limiting resources and are therefore synonymous with the provider/cheater terminology used in an altruistic context [12,13,89]. There is, however, one potential similarity between the IGP model and BQH that is of interest. This concerns the fact that in many complex microbial communities, the majority of species lose genes necessary for providing (leaky) common goods when this instead can be provided by a few key species, the black queens. As bacteriocin producers consume metabolites provided by sensitive strains, at least in theory, the producers may lose genes necessary for metabolizing specific substrates (e.g. carbohydrates) as long as these are used by some of the IGPrey lineages. In this analogy, IGPrey may, to some extent, resemble black queens with the difference that there most likely are more than just a few such lineages present in a typical LAB batch environment. It would be of interest to examine whether bacteriocin producers may in fact carry fewer genes for metabolizing, for instance, specific carbohydrates than is the case for IGPrey lineages. Staying in the cards game analogy, one could compare LAB bacteriocin production to the game of Casino. One aim is here to capture as many cards as possible (equivalent to nutrients) from a layout. However, one can only obtain cards (bacteriocin sensitive cells) that match the cards of the players' hand (bacteriocin producers). To increase a capture, a player can make a build (broad spectrum and/or multiple bacteriocins), which can only be captured in the next round and thus in danger of getting captured by other players (competing tolerant/resistant variants).

Selfishness has, compared with altruism and spite, received little recent attention in microbial models. However, this type of social behaviour is suitable for exploring general ecological interactions such as IGP, which is a very common phenomenon in nature [37,124]. Microbial examples have primarily focused on ciliates acting as predator and intraguild prey, whereas bacteria provided the common resource [39,125]. There are few reports, if any, on IGP including only bacteria, but it has to be kept in mind that the example offered here does not include a genuine IGP mechanism as the general resource for the IGPredator and IGPrey is nutrients from decaying organic material and thus not a prey organism as such. Still, the LAB bacteriocin mechanism offers a model that might be useful for examination of more general aspects of IGP, such as the relationship between IGP and resource competition.

It has been shown theoretically [126] and experimentally, using ciliates and bacteria [39], that nutrient-rich environments allows predominance of the IGPredator. This is similar to the population dynamics predicted and observed for colicin producers [5,7,10,127]. Contrarily, an interesting aspect of the issue of LAB bacteriocins as an IGP mechanism is that it is relevant in habitats that include a bottleneck scenario but not habitats with plenty of availability of 'prey', i.e. nutrients. IGP under these circumstances allows the organisms to respond dynamically to the environmental variation by enabling them to change the trophic level upon which they feed, as suggested by Banerji & Morin [125] for a ciliate with inducible trophic polymorphism. Indeed, the induction

of bacteriocins in the late exponential or stationary growth phase by quorum sensing appears to present just such a polymorphism.

Production of toxic substances within an IGP/bottleneck model may be a common survival strategy not restricted to lactic acid bacteria. An example could be the *Streptomyces* genus, which produces the majority of the natural antibiotics known to man. The genus is primarily found in the soil where it gets nutrition from decaying vegetation [128]. The habitat is thus expected to create a bottleneck situation as has been discussed for LAB in this review. Interestingly, like LAB bacteriocin production, antibiotic production in *Streptomyces* is not initiated before entering the stationary phase, where growth rate slows down and production of aerial mycelium begins [129]. Both protection against other microbes and recycling of killed sensitive cells have been proposed [128] as an explanation for this timing of antibiotic production. The induction of antibiotic production upon nutrient exhaustion (bottleneck) coinciding with the production of aerial mycelium (dispersion) fits very well into the IGP model presented here and it would be of interest to examine experimentally whether this model could be used to explain *Streptomyces* antibiotic production.

We have until now only discussed fitness of LAB bacteriocin producers during population bottlenecks in environments where they have experienced a previous logarithmic phase of growth. We have described the dispersion to new potential habitats only as a parameter to adjust the scale of competition with a high degree of dispersion leading to a global scale of competition. It can, however, be expected that the transition phase present its own bottleneck scenario and selective parameters as shown by Handel & Bennett [49], which will influence the outcome of the IGP scenario discussed here. Even so, it can be anticipated that IGP is an important component of the social behaviour of bacteriocin-producing LAB. Future studies should test the validity of this mechanism on both a mathematical and an empirical level. Such studies would quantify the magnitude of selection for bacteriocin producers under different bottleneck scenarios using microcosm evolution experiments. This would also illuminate the effects of habitats on the selection of types of social interactions. In this regard, it should be considered that bottleneck scenarios may promote other survival strategies in addition to bacteriocin production, with the phenomenon of persister cells as an example [130].

Alternative explanations for the function of antibiotic/bacteriocin production have included roles as tools for interbacterial warfare and more recently, for example, in chemical signalling processes [131], involvement in biofilm and swarming development or fratricide [132]. The strength of the IGP model proposed here and in contrast to the majority of these suggestions is that it demonstrates the advantage of production of antimicrobial compounds in bottlenecks during the stationary growth phase.

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