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# A review of the antimicrobial and immune-modulatory properties of the gut microbiota-derived short chain fatty acid propionate – What is new?

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## REVIEW PAPER



### ABSTRACT

As antimicrobial resistance poses a globally rising health problem, the identification of alternative antimicrobial agents is urgently required. The short chain fatty acid propionate which is physiologically produced by the gut microbiota constitutes a promising molecule given that it has been widely used as a cosmetics and food preservative due to its antimicrobial effects. This literature survey aims to determine the most recent state of knowledge about the antimicrobial and immune-modulatory properties of propionate. Both *in vitro* and *in vivo* studies published between 2011 and 2020 confirmed the ability of propionate to inhibit the growth of several cellular pathogens, including Gram-positive and Gram-negative multi-drug resistant bacteria and fungi. In addition, heterogenous immune-modulatory and in particular, anti-inflammatory effects of propionate could be assessed involving a diverse signaling network that needs further comprehension. In conclusion, our literature survey provides evidence that propionate displays a plethora of health-beneficial including antimicrobial and immune-modulatory effects. Future research is required to further unravel the underlying molecular mechanisms and to set the basis for *in vivo* infection and clinical studies to broaden the path of propionate as a promising adjunct antibiotics-independent option in the combat of infections caused by multi-drug resistant bacteria.

### KEYWORDS

propionate, propionic acid, short chain fatty acids, microbiota, antimicrobial effects, immune-modulatory effects, multidrug-resistant (MDR) bacteria

## INTRODUCTION

### Antimicrobial resistance

Infectious diseases are decreasing as causes of mortality with an observed annual case reduction of approximately 1% between 1990 and 2010 [1]. Especially in middle- and high-income countries, the incidence of infections progressively declined, mainly due to improved living conditions [2, 3], whereas to date most deaths are caused by cardiovascular and neoplastic morbidities [4]. The decrease of infection-related deaths should not be taken for granted, since infectious diseases remain a major threat for the modern health care system. This is mostly due to potential wide-ranging health hazards, possibly gaining epidemical or even pandemical extent [1] and because of the rise of antimicrobial resistance [5].

Primary antimicrobial resistance exists since the emergence of microbial living *per se*, and various microbes display intrinsic resistances against distinct antimicrobial agents. Secondary

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resistance generated by adaptation to antimicrobial substances in course of co-evolution between bacteria, yeasts and plants can result in altered target molecules, inactivating enzymes or increased discharge of the antibiotic agent from the cell by efflux pumps [6, 7]. The dynamics in spread of acquired resistance mechanisms against a multitude of antibiotic compounds is utmost alarming [8, 9]. Furthermore, resistance genes encoding for molecular machineries counteracting antibiotic efficacy can be spread very fast in bacterial populations and even over species or genera barriers via vertical and horizontal gene transfers [6, 7]. In consequence, loss of effectiveness of various groups of antibiotics against multi-drug resistant (MDR) bacterial strains can emerge in very short time intervals. The treatment of infections caused by MDR bacteria poses a major growing challenge in public healthcare since the onset of an efficient antimicrobial therapy and subsequently, the severity and duration of the disease course are significantly delayed. Therefore, morbidity and mortality as well as health care expenses have increased dramatically [5–10]. The need of a holistic strategy against this fatal scenario needs to be enforced. Beside the rational application of antimicrobial compounds in human and veterinary medicine, antibiotic stewardship, and surveillance of antimicrobial resistance, the search for novel molecules with antimicrobial and immune-modulatory properties is of great importance. Hence, the pharmaceutical industry and agriculture need to be involved in this pivotal process [11–13].

### Microbiota-derived propionate

Propionate or propionic acid is among the promising molecules for the combat of infections caused by MDR strains [14]. Propionate constitutes a short chain fatty acid (SCFA) containing three carbon atoms [15] and is produced by the commensal intestinal microbiota in the cecum and proximal colon of mammals through anaerobic fermentation of sugar molecules originating from enzymatically digested fiber products. In the human intestinal tract, members of the *Bacteroidetes*, the *Firmicutes* and the *Lachnospiraceae* families generate propionate via the succinate and propanediol pathways, both of which depending on vitamin B12 as a cofactor [16, 17]. In turn, propionate concentrations of up to 10–30 mM can be reached in the proximal large intestines [18]. Together with other SCFAs such as butyrate and acetate, propionate is resorbed by the intestinal epithelium and fuels the energetic metabolism of colonocytes. The SCFAs also pass into the blood stream with propionate reaching portal vein concentrations of 0.02–0.2 mM, whereas concentrations progressively decline after the liver passage [17]. The microbiota is not the only source of propionate. This SCFA is also a naturally occurring dietary component and has been widely used as a food additive. Propionate's antimicrobial properties are utilized as a food preservative and are generally considered to be safe [15].

There has already been various research on the effects of propionate in health and disease. In the gut, propionate promotes intestinal epithelial integrity and barrier function

[19]. As a signal molecule, the SCFA is also suspected to impact glucose homeostasis and lipid metabolism. Furthermore, it affects distinct hormones involved in appetite regulation [17]. Moreover, certain immune-modulatory and anti-inflammatory effects of propionate were shown to be linked to inhibition of histone acetylases and specific G-protein coupled receptors, thus, enabling propionate to control gene expression and cell metabolism [20]. Although the exact pathways of propionate signaling are still subject of current research, this SCFAs could be a promising candidate in the combat of inflammatory, metabolic and oncological diseases [17, 19–23].

Even though the antimicrobial properties of propionate have been known for a very long time, the distinct interactions between propionate, human pathogens and the host's immune system are still not fully understood. Therefore, this literature survey aims to summarize the current state of knowledge concerning antimicrobial and immune-modulatory effects of propionate.

## METHODS

### Inclusion and exclusion criteria

The main inclusion criteria were *in vitro* and *in vivo* studies addressing the interactions between cellular pathogens and propionate as published between 2011 and 2020. Studies focusing on physiological microbiota functions or non-infectious diseases as well as studies in which propionate served as a carrier substance for other agents were excluded.

### Search strategy

The MEDLINE database PubMed was used to implement the literature survey of publications fitting the defined inclusion criteria. The survey was performed between December 15th, 2020 and January 4th, 2021. Applying the Boolean logic through the advanced search option, following steps were carried out (summarized in Table 1).

Using the Boolean operator OR, the database was surveyed for publications containing the key words “propionate OR propionic acid OR short chain fatty acid propionate”. To ensure that the main topic of the publications would be propionate, these terms were applied solely on the title. Secondly, the terms “antimicrobial OR antibiotic OR pathogen reduction” were applied on all fields. Finally, both groups of terms were linked by the Boolean operator AND, whereas the search was limited to the last ten years. Thereby, 34 studies could be found. All of these were carefully evaluated regarding the mentioned inclusion and exclusion criteria. Some studies were excluded since they only focused on propionate derivatives (e.g., the amino acid-derived indole propionate). Certain studies were not applicable since they used microbial propionate as a marker for infection. Moreover, studies concerning metabolic, autoimmune or oncological diseases were excluded. After this selection, eight publications

Table 1. Boolean logic search on PubMed

Search	Query	Results
#1	“propionate”[All Fields] OR “propionic acid”[All Fields] OR “short chain fatty acid propionate”[All Fields]	26,854
#2	“propionate”[Title] OR “propionic acid”[Title] OR “short chain fatty acid propionate”[Title]	5,570
#3	“antimicrobial”[All Fields] OR “antibiotic”[All Fields] OR “pathogen reduction”[All Fields]	373,639
#4	“propionate”[Title] OR “propionic acid”[Title] OR “short chain fatty acid propionate”[Title] AND “antimicrobial”[All Fields] OR “antibiotic”[All Fields] OR “pathogen reduction”[All Fields]	67
#5	“propionate”[Title] OR “propionic acid”[Title] OR “short chain fatty acid propionate”[Title] AND “antimicrobial”[All Fields] OR “antibiotic”[All Fields] OR “pathogen reduction”[All Fields] Filters: published in the last 10 years	34

remained (Table 2). The references of the eight articles and studies considered similar by PubMed were surveyed for other publications fitting the search criteria.

## Data extraction

In order to conduct a systematic review, each included article was carefully read and evaluated regarding the inclusion and exclusion criteria. Distinct pathogens under investigation, applied animal trials, main findings, relevance for the topic of this survey and possible errors were taken into account.

## RESULTS

Investigations of the anti-inflammatory properties of propionate in murine macrophages, which were stimulated with *Staphylococcus aureus*-derived lipoprotein in the presence or absence of SCFAs *in vitro* [24] revealed that propionate inhibits nitric oxide secretion, which was due to attenuated expression of the inducible nitric oxide synthase (iNOS). A reporter gene assay further confirmed that the propionate induced reduction in iNOS expression was linked to transcriptional inhibition of NF- $\kappa$ B, STAT1 phosphorylation and IFN- $\beta$  expression via inhibition of histone deacetylase [24].

The effects and interactions of sodium propionate during *S. aureus* skin infection were analyzed both *in vitro* and *in vivo* [25]. Therefore, various *S. aureus* strains including clinical methicillin-resistant *S. aureus* (MRSA) and other MDR isolates were grown in the presence or absence of

Table 2. Overview of the included studies

Reference	Setting	Pathogen	Host model	Antimicrobial effect	Immune-modulatory effect
[24]	<i>in vitro</i>	<i>S. aureus</i> incl. MRSA and other MDR strains	Murine macrophages	Not assessed	Anti-inflammatory
[25]	<i>in vitro</i> and <i>in vivo</i>	<i>S. aureus</i> , incl. MRSA and other MDR strains	Mice	Bacteriostatic (250 mM)	Anti-inflammatory, but supposed to be indirect
[26]	<i>in vitro</i> and <i>in vivo</i>	<i>S. aureus</i> , <i>E. coli</i> , <i>K. pneumoniae</i>	Human and murine immune cells (macrophages, dendritic cells, splenocytes), living mice	None	Overall anti-inflammatory, but highly stimulus- and cell-dependent
[27]	<i>in vitro</i>	MRSA, <i>E. coli</i> , <i>C. albicans</i>	-	pH-independent bactericidal and fungicidal (10–25 mM)	Not assessed
[28]	<i>in vitro</i> and <i>in vivo</i>	<i>E. coli</i> (wild type), adherent-invasive <i>E. coli</i> (AIEC)	Intestinal epithelial cells and mice	Bactericidal in wild type (25 mM), AIEC resistant and virulence enhancing	Not assessed
[29]	<i>in vitro</i> and <i>in vivo</i>	<i>Salmonella</i> Typhimurium	None	Growth inhibition, reduced motility and invasion	None
[30]	<i>in vitro</i>	Several <i>Salmonella</i> serotypes	Mice	Bactericidal (50.5 mM), reduced motility and biofilm formation	None
[31]	<i>in vitro</i>	<i>Salmonella</i> Typhimurium	Human Hep2-cells	Specific inhibition of expression of invasion-related genes (10mM)	Not assessed

*S. aureus* – *Staphylococcus aureus*, MRSA – methicillin-resistant *S. aureus*, MDR – multi-drug resistant, *E. coli* – *Escherichia coli*, *K. pneumoniae* – *Klebsiella pneumoniae*, *C. albicans* – *Candida albicans*; incl. – including.



sodium propionate at different concentrations. A dose-dependent growth reduction was observed for every strain with a minimal inhibitory concentration (MIC) of 250 mM propionate. A bactericidal effect, however, remained undetected. In the following *in vivo* study, mice were subcutaneously infected with MRSA and treated with 50 mM propionate. Not only did the propionate application significantly reduce abscess size and weight as well as bacterial loads, but also led to reduced concentrations of pro-inflammatory cytokines including IL-1 $\beta$  and IL-6. The authors hypothesized that the induced immunopathological responses following propionate treatment were more likely due to the reduced bacterial loads, rather than due to direct immune-modulatory effects of the SCFA. Interestingly, *S. aureus* strains without D-alanine motifs in the teichoic acids were more susceptible towards propionate as compared to the wild-type strain. In order to verify this effect, sodium propionate was combined with the D-alanine inhibitor AMSA, which led to an almost complete growth inhibition of MRSA [25].

To investigate the host immune responses upon bacterial and fungal infections and under the influence of different propionate concentrations ranging between 0 and 4 mM *in vitro*, human and murine macrophages, dendritic cells, splenocytes and whole blood cells were either stimulated with pathogen-associated molecules, namely lipopolysaccharide (LPS) and the lipopeptide Pam<sub>3</sub>CSK<sub>4</sub>, or with viable bacteria, including *S. aureus* and *Escherichia coli* [26]. The real-time PCR and ELISA analyses revealed that human and murine macrophages secreted lower amounts of pro-inflammatory cytokines such as TNF, IL-6 and IL-12p40 in a propionate dose-dependent fashion. However, this was not the case for TNF concentrations in LPS- or *E. coli*-challenged macrophages, where propionate failed to exert anti-inflammatory effects. In contrast, dendritic cells were much more resistant to propionate when compared to macrophages, monocytes and whole blood cells. Hence, propionate was able to exhibit anti-inflammatory effects, which correlated with the applied concentration, the inflammatory stimulus and respective stimulated immune cell type. The authors further treated mice with 200 mM propionate via the drinking water for three weeks and subsequently either challenged the animals with LPS to induce endotoxemia or infected them with *S. aureus*, *Klebsiella pneumoniae* or *Candida albicans*. Surprisingly, no differences in pro-inflammatory cytokine responses could be observed in propionate and placebo treated mice. The authors concluded that prophylactic propionate application does neither affect the host's susceptibility to infections nor alleviate pro-inflammatory immune responses. In addition, prophylactic propionate application does not prevent from inflammatory toxic shock in the vertebrate host [26].

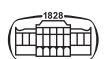
Another *in vitro* study tested whether the antimicrobial effect of propionate was due to its acidity [27]. Therefore, the community-acquired MRSA strain USA300 was incubated with different concentrations of propionate. Whereas growth inhibition could be observed upon co-incubation with 25 mM propionate, 100 mM of the SCFA were found to

exert bactericidal effects. When applying 25 mM propionate at unbuffered pH 5.8 or buffered pH 6.8, the growth-inhibiting effects of propionate were independent from the pH of the medium. The pH reduction within the bacterial cell indicated a direct antimicrobial effect by propionate. Furthermore, propionate was tested against *E. coli*, *Propionibacterium acnes*, and *C. albicans*. While growth rates for *P. acnes* were not affected at the highest propionate concentrations, the other microbes were efficiently reduced at relatively low minimal inhibitory (10 mM for *E. coli* and *C. albicans*) and minimal bactericidal and fungicidal concentrations of 25 mM for *E. coli* and of 50 mM for *C. albicans*, respectively. The lack of anti-*P. acnes* induced effects by propionate was not surprising given that *P. acnes* is known to be the main propionate producer within the commensal skin microbiota. Moreover, the authors demonstrated that an esterified derivative of propionate, which is more resistant against metabolism, exhibited similar growth-inhibiting effects [27].

The impact of the SCFA on the virulence of Crohn's disease-associated adherent-invasive *E. coli* (AIEC) as compared to several commensal *E. coli* strains was studied in male C57BL/6 mice treated with 20 mM propionic acid. Although the growth of commensal *E. coli* isolates was inhibited by propionic acid, the virulence of the AIEC strain surprisingly increased. Moreover, AIEC exhibited reversible epigenetic and transcriptional changes, which was associated with an increased expression of distinct virulence factors involved in epithelial cell adherence and invasion as well as in biofilm formation. The authors concluded, that i.) propionic acid can be regarded as a driving force for AIEC virulence without exhibiting antibacterial effects and that, ii.) broadly acting microbiota-derived antimicrobials may induce resistance mechanisms and even reinforce pathogenicity in distinct bacterial strains [28].

Investigations on the role of microbiota-derived propionate in the colonization resistance of mice against the enteropathogen *Salmonella* Typhimurium revealed that propionate produced by intestinal commensal *Bacteroides* species preserved the physiological colonization resistance against *Salmonella* Typhimurium at basal conditions [29]. The growth suppression of the pathogen and the resulting colonization resistance against *Salmonella* Typhimurium *in vivo* were caused by disturbing the pH homeostasis towards an intracellular acidification, but neither via extracellular acidification nor by modulating the host's immune responses. Furthermore, propionate had no effect on the invasive properties of *Salmonella* Typhimurium but led to reduced intestinal expansion and fecal shedding of the bacteria. The authors concluded that microbiota-derived propionate constitutes a key molecule mediating physiological colonization resistance of the vertebrate host against *Salmonella* Typhimurium [29].

The analysis of the antimicrobial activity of propionate against *Salmonella enterica* strains isolated from poultry revealed that propionate exhibited a minimal inhibitory and bactericidal concentration of 3,750 mg/L (i.e., 50.6 mM) against all isolates under investigation [30]. In addition,





propionate was able to reduce motility and biofilm formation at sub-inhibitory concentrations. The authors hypothesized that this effect might have been due to disturbed flagella and fimbria synthesis during intracellular acidification. In contrast to other SCFAs such as acetate and butyrate, propionate did not alter virulence gene expression in the *S. enterica* isolates tested. The obtained results provide further evidence that SCFAs such as propionate constitute promising compounds in the combat of foodborne pathogens such as *Salmonella*. However, an application at sub-inhibitory concentrations should be avoided in order to keep the risk of increased virulence at a minimum [30].

A study addressing the antimicrobial effect of propionate on the invasive capacities of *Salmonella* Typhimurium revealed that the observed dampening of bacterial invasiveness was not due to acidification but post-translational regulation of HilD, a transcriptional regulator of the AraC family [31]. It is notable that propionate was able to repress gene expression at physiological pH conditions. This effect was linked to attenuated secretion of bacterial effector proteins involved in cell invasion. The authors further investigated that the invasion repressive effects of propionate in *Salmonella* Typhimurium was specifically due to the post-translational inactivation of HilD, acting as the central activator of the *Salmonella* Typhimurium Pathogenicity Island 1 (SPI1), which is essential for cell invasion. In fact, this effect was mediated by the intestinal metabolite propionyl-CoA. Further investigations confirmed that gene deletions necessary for the production of propionyl-CoA resulted in a significant restoration of bacterial invasion gene expression in the presence of propionate. Thus, propionyl-CoA derived from commensal bacteria can be applied as a *Salmonella* virulence regulating molecule instead of a direct anti-*Salmonella* treatment option [31].

## DISCUSSION

### Main findings

The in-depth literature survey presented here revealed that four out of eight studies verified the antimicrobial effects of propionate against distinct bacterial strains, including antibiotic susceptible and MDR strains. Propionate was found to act as an antimicrobial agent against MRSA, *E. coli*, *Salmonella* Typhimurium and even *C. albicans* [25–28, 30]. The propionate-mediated bacterial growth reduction occurred in a dose-dependent manner and was mainly associated with intracellular acidification [25, 29]. Moreover, propionate application was able to impact bacterial morphology by disturbing flagella and fimbria synthesis in *Salmonella* strains [30]. Another study affiliated the antimicrobial properties of propionate and propionyl-CoA to the post-translational regulation of HilD [31]. However, contrasting results were found in a murine *in vivo* study against AIEC, where propionic acid unexpectedly increased the bacterial virulence [28].

Regarding the immune-modulatory effects of propionate, the data basis is less evident, since only five of eight studies assessed parameters to address this question [24–26, 29, 30]. Although two studies did not detect any effect immune-modulatory effects of the SCFA at all [29, 30], propionate was found to inhibit nitric oxygen secretion in murine macrophages via its histone deacetylase inhibitor activity, leading to a transcriptional inhibition of pro-inflammatory signaling pathways [24]. Moreover, human and murine macrophages were found to secrete lower amounts of pro-inflammatory cytokines upon cocubation with propionate. However, this was not the case for TNF expression, which did not change upon prophylactic propionate application [26]. Another study linked the anti-inflammatory properties of propionate to an indirect effect via reduction in pathogen loads [25]. Overall, propionate appears to elicit specific effect mechanisms on a wide range of immune cells and other cells. Notably, the impact of propionate is highly dependent on the modulated cell type, attacking pathogen and distinct cytokines, chemokines and effector molecules. Thus, propionate may exhibit an anti-inflammatory effect, but the distinct immune-modulatory properties remain hardly predictable.

### Open questions and area for future research

This literature survey is based on different *in vitro* and *in vivo* studies and due to this heterogeneity, results are not always concordant. For instance, one study revealed considerably higher MICs if compared to other publications [25], whereas especially the extent of immune-modulatory effects was inconsistent. Some studies rather questioned the health-beneficial effects due to potential immune-modulatory responses elicited by propionate [25], since these were suspected to be even counterproductive for the host when fighting the infection [26]. Propionate's immune-modulatory activities can therefore be regarded as an essential part of its effect range, but might also be linked to differences in experimental set-ups [24]. Therefore, more studies with consistent methods need to be performed. Apart from an approach for the use of propionate to combat infections, many studies found propionate to exhibit anti-inflammatory properties [21–23]. The physiological impact of propionate with regard to prophylactic or therapeutic treatment of infections is still not fully understood. Further research is needed to clarify the signaling pathways involved and the extent of the antibacterial effect, facilitating our comprehension of the interaction between propionate and the host. Thereby, it is of particular interest to study the differential effects of propionate on pathogens and immune cells in more detail.

Moreover, translational findings regarding propionate and human infectious diseases are still scarce. Given that the antimicrobial effects of propionate are evident and no relevant side effects have been shown in humans to date, an implementation of the SCFA into human medicine poses as a potential goal for future research. Therefore, further investigations need to analyze the application of propionate as a supportive therapy against bacterial infections. Hence,



future animal trials with more clinically oriented and standardized experimental setups are needed.

In conclusion, propionate exhibits a wide range of antimicrobial effects and seems to be a promising agent in the battle of infections caused by MDR bacteria. Therefore, future studies should address whether natural antimicrobial agents like propionate can act as a supportive adjunct antibiotic-independent and immune-modulatory treatment option in the combat of infections.

### Limitations of this survey

This systematic literature survey displays methodological limitations. High efforts were made to perform a searching strategy as sensitive as possible. Relevant studies may have not been included in this review. Given that several studies investigated propionate, butyrate and acetate together, potential propionate-focused surveys could have been overlooked. In addition, the full-text versions of distinct articles were not available. It should be mentioned that the selection of included studies was carried out by a single investigator. The included publications are of heterogeneous methodology, which is why in-between comparisons are limited. Generalized conclusions should be drawn with caution. In spite of the careful data extraction, inaccuracies and mistakes may have occurred as well. Conclusions taken from this literature survey should be evaluated attentively.

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*Conflict of interests:* SB and MMH are Editorial Board members.

### LIST OF ABBREVIATIONS

iNOS	Inducible nitric oxide synthase
LPS	Lipopolysaccharide
MIC	Minimal inhibitory concentration
MDR	Multi-drug resistant
SCFA	Short chain fatty acid
SPI1	<i>Salmonella</i> Typhimurium Pathogenicity Island 1

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