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Perspective

# On the potential role of naturally occurring carboxylic organic acids as anti-infective agents: opportunities and challenges

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ABSTRACT

Carboxylic organic acids are intermediates of central carbon metabolic pathways (e.g. acetic, propionic, citric, and lactic acid) long known to have potent antimicrobial potential, mainly at acidic pHs. The food industry has been leveraging those properties for years, using many of these acids as preservatives to inhibit the growth of pathogenic and/or spoilage fungal and bacterial species. A few of these molecules (the most prominent being acetic acid) have been used as antiseptics since Hippocratic medicine, mainly to treat infected wounds in patients with burns. With the growth of antibiotic therapy, the use of carboxylic acids (and other chemical antiseptics) in clinical settings lost relevance; however, with the continuous emergence of multi-antibiotic/antifungal resistant strains, the search for alternatives has intensified. This prospective article raises awareness of the potential of carboxylic acids to control infections in clinical settings, considering not only their previous exploitation in this context (which we overview) but also the positive experience of their safe use in food preservation. At a time of great concern with antimicrobial resistance and the slow arrival of new antimicrobial therapeutics to the market, further exploration of organic acids as anti-infective molecules may pave the way to more sustainable prophylactic and therapeutic approaches.



## The antimicrobial potential of carboxylic organic acids

Carboxylic organic acids owe their antimicrobial potential to the lipophilic properties of the undissociated acid form (RCOOH) that crosses the microbial plasma membrane simply by passive diffusion. Because of this, carboxylic acids (CAs) are much more effective as antimicrobials than strong inorganic acids whose toxic effects are largely exerted on the cell exterior [1]. The toxicity of CAs is determined by their pKa and the pH of the milieu (because these define the abundance of the RCOOH form) and by their lipophilicity (more lipophilic acids diffuse easier through the membrane, becoming more toxic) [1]. The dissociation of the acid in the cytosol results in intracellular acidification that, consequently, reduces the activity of pH-sensitive enzymes as those involved in central carbon metabolism, RNA and DNA synthesis, cell wall assembly, and transfer RNA aminoacylation [1]. The accumulation of protons inside the cells also dissipates the electrochemical gradient maintained across the plasma/organelle membrane(s), compromising the activity of secondary transporters and, thus, perturbing nutrient homeostasis and limiting ATP generation [1]. The accumulation of the negatively charged counter-ion also causes multiple negative effects that are determined by its chemical properties and may include the formation of reactive oxygen species, damaging of the spatial organization of plasma/organelle membrane(s), and increased turgor pressure [1]. Microbial cells evolved different mechanisms to cope with pleiotropic effects caused by CA-induced

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stress and the efficiency of these responses determines, to some extent, the different degrees of susceptibility of each species to different acids. The description of such adaptive responses has been reviewed before [1,2], although the individual contribution of each adaptive mechanism in determining the individual tolerance exhibited by each species to each CA remains elusive, likely because of the multi-factorial nature of those adaptive responses.

## How are weak CAs used as food preservatives?

For many years, humans used natural products to preserve foods, including acetic acid (vinegar), citric acid (abundant in citrus fruits), or benzoic and sorbic acids (present in high concentrations in some berries). The natural occurrence of CAs, along with their low toxicity (that favors higher consumer acceptance and allows flexible daily intakes), low cost (as they are obtained easily by microbial fermentation), and high stability when used with different matrixes and under different environmental influences, led to their extensive utilization by the food industry [3]. In this context, organic acids are used as sanitizers to reduce the initial load of pathogenic and spoilage microorganisms present in the surface of foods or equipment or directly added to food products. In both cases, the objective is to improve microbiological stability and assure safe consumption [3]. The naturally occurring organic acids approved for use as food additives include acetic, propionic, butyric, lactic, citric, benzoic, and sorbic acids that, depending on the food matrixes, are used in their acid form or as sodium/potassium salts [3]. Most commonly, these acids (or their salt forms) are used on solutions in which food products are immersed (dipping) in or with which are sprayed with [3].

Because the mode of action of CAs is broad, they are used to control a wide spectrum of microbial species, ranging from bacterial pathogens to mycotoxin-producing molds. Among the more prominent food-borne pathogens targeted by organic acid preservation are Shiga toxin–producing *Escherichia coli, Salmonella* spp., *Listeria monocytogenes, Campylobacter jejunii, Yersinia enterocolitica, Vibrio* spp., and mycotoxin-producing fungi [4,5]. Organic acids are also used to reduce the growth of other microbial species that, although not considered true food-borne pathogens, promote spoilage turning the product less attractive for consumption and, in the limit, non-edible. These spoilage species include *Brochothrix thermosphacta, Lactobacillus* spp., *Lactococcus* spp., *Leuconostoc* spp., *Pediococcus* spp., *Streptococcus* spp., *Weisella* spp, *Bacillus* spp, *Clostridium* spp., and yeasts and molds belonging to the *Saccharomyces, Zygosaccharomyces, Candida, Rhizopus, Penicillium*, and *Aspergillus* genera [4,5]. Interestingly, several of these food-spoilage species are recognized as opportunistic human pathogens (e.g. *Candida glabrata, Aspergillus niger*); however, it remains to be elucidated the extent at which the ingestion and/or exposure of susceptible individuals to contaminated food products contributes to the onset of infection, although this has been demonstrated in some cases [6].

## How are carboxylic weak acids applied as anti-infective agents?

Acetic acid (or vinegar) is, by far, the CA that is most used in the clinical setting, as detailed in Table 1, where we summarize the information published in the literature concerning the described clinical uses of organic acids. Reports of its use to treat patients with burn injuries date back from Hippocrates and is still performed today, especially to manage infections caused by antibiotic-resistant recalcitrant strains [7,8]. For this application, acetic acid is used in a diluted form in solutions in which the dressings used to cover the wounds are soaked. More recently, this approach has also been used to control infections in surgical wounds [9,10]. As with all antiseptics of local application, topical treatment with acetic acid is a balance between its microbiocidal activity (most dependent of the microenvironmental pH), local toxicity, and patient tolerability [7]. The use of acetic acid (and of chemical antiseptics in general) to manage infected wounds was largely abandoned with the increase in use of topical antibiotics. However, the increase in nosocomial outbreaks boosted research on alternatives, including the resort to “old-school” antimicrobials [7]. The benefits of using acetic acid–soaked dressings in managing wound infections are consistent with the described potent toxic effects exerted by this acid *in vitro* against *P. aeruginosa* and against other species of the microbial spectrum of a burn unit, such as *Acetobacter baumanii, Staphylococcus aureus*, or *Candida* [7,11,12]. Notably, these inhibitory effects of acetic are observed even against biofilms, usually recalcitrant to antimicrobial therapy [11,12]. Recently, topical application of acetic acid to manage vulvovaginal candidiasis has been deemed as a possible therapeutic approach, adding to the panoply of clinical applications for this acid [13].

The use of lactic acid in the clinical setting is mostly focused on promotion of vaginal health, mainly to counteract the onset of bacterial vaginosis (Table 1) [14]. This utilization is driven by the dominance of the vaginal microbiota by lactic acid–producing lactobacilli, a hallmark of vaginal health [14]. Citric acid has also been used in dressings to control infected wounds resulting from burns or diabetic foot ulcers; however, it is mostly applied in catheter-locking solutions to reduce microbial colonization and avoid blood clots (Table 1). Notably, disinfectants and sanitizers using citric acid and lactic acid proved to be effective against various pathogens and, based on that, were recommended as sanitizers by the US Environmental Protection Agency to control SARS-CoV-2 [15]. Although largely used as food preservatives, benzoic and sorbic acids have limited utilizations in the clinical setting with concentrated benzoic acid solutions being used to alleviate microbial burden in chemical nectromy (Table 1). Benzoyl peroxide, a derivative of benzoic acid, is also a recommended treatment of acne in the acute phase therapy or during remission phases [16]. Once absorbed by the skin, benzoyl peroxide is converted into benzoic acid, which is metabolized by cysteine to generate reactive oxygen species that, eventually, cause a bactericidal effect [16]. The antibiotic therapy used to manage acne is being revised considering the emerging problems with antibiotic resistance, and benzoyl peroxide, as a source of benzoic acid, is believed to represent a valuable approach to manage the disease [16]. Sorbic acid/sorbate has not been used as active ingredient but mainly as a preservative in over-the-counter commercial vaginal products (Table 1).

## Interaction of organic acids with currently used antimicrobials in clinical therapy

Studies undertaken *in vitro* show that the molecular targets of CAs differ largely from those of the different types of classes of antibiotics and antifungals [1]. This opens the possibility of exploring combination therapies using an organic acid and an antibiotic/antifungal to enhance the susceptibility of the target species, including of those strains that might be already resistant to the antibiotic/antifungal, as exemplified previously on acne therapy. This combinatorial approach also has the advantage of reducing the doses of antifungals/antibiotics used, resulting in a reduction of the selective pressure for resistance. A search of the literature reveals that this issue has only been little addressed, even *in vitro* studies. The exceptions are (i) acetic acid, shown to synergize with clotrimazole, fluconazole, itraconazole, miconazole, and thioconazole, to inhibit growth of *Candida* species [17,18]; (ii) lactic acid, shown to synergize with azoles to inhibit growth of *C. albicans* [17]; and (iii) citric acid, shown to augment activity of erythromycin, novobiocin, rifampicin, methicillin, gentamicin, and vancomycin against *P. aeruginosa* (including resistant strains) [19]. Besides aiming at

**Table 1**
Description of clinical applications of carboxylic acids with application in food production settings. It is also indicated the pKa of the acid (which directly influences its equilibrium between dissociated and undissociated acid molecules); the species that have shown susceptibility to organic acids; and the PUBMED ID of references linked to those applications.

| Carboxylic acid | pKa | logP | Described clinical applications | Target species | PUBMED ID of relevant references |
|---|---|---|---|---|---|
| **Acetic acid** | 4.76 | −0.2 | Management of infected toe wounds | *Pseudomonas aeruginosa* and fungal species causing local infections *(Trichophyton rubrum, Cladosporium, Candida* spp, *Fusarium* spp) | 30920153 |
| | | | Used in soaked dressings (alone or combination with other antiseptics) in burn wounds | *P. aeruginosa, A. baumanii, Staphylococcus aureus*; undefined | 34862089; 21242734; 29262416; 20731796; 25851059; 20798627; 23999348 |
| | | | Topic agent for the treatment of acute otitis externa | *P. aeruginosa; S. aureus*; undefined | 36791445; 23198673 |
| | | | Sanitizer to clean sinks in intensive care units | methyciline-resistant P. aeruginosa; Undefined *Enterobacteriaceae;* carbapenem-resistant *A. baumannii* | 27346622; 30579969; 34516425 |
| | | | Used in dressings to manage infections in diabetic foot ulcers or surgical superficial wounds | Undefined; *beta-lactamase* producing *P. aeruginosa* strains, *S. aureus* | 37211419; 31155991 |
| | | | Adjunct therapy to clear airways of SARS-CoV-2 infected patients | SARS-CoV-2 | 32449022 |
| | | | Topical agent for management of vulvovaginal candidiasis | Undefined *Candida* species | 37635435 |
| | | | Used as a sanitizer in acrylic resins for dental applications | *Candida* spp; undefined oral pathogens | 25928798; 19082396; 31078286 |
| | | | Adjunct to débridement for lavage of periprosthetic joints | Undefined | 34520439 |
| | | | Sanitizer for cleaning surfaces and nebulizers | Undefined airborne-opportunistic fungi; undefined pathogens of cystic-fibrosis patients; | 30255210; 9253701 |
| **Propionic acid** | 4.9 | 0.33 | *In vitro*, used as a sanitizer to prevent urinary catheter infections and blockages | *Proteus mirabilis, S. aureus* and *Escherichia coli* | 33545216; 33545217 |
| **Citric acid** | $pKa_1$ 3.1<br>$pKa_2$ 4.7<br>$pKa_3$ 6.4 | −1.64 | Used in endodontic irrigation solutions to prevent microbial load in root canals | *C. albicans, E. faecalis, Streptococcus sanguinis*; undefined oral biofilms | 33538336; 36005246; 31226526; 25954488; 36058346; 25206218 |
| | | | Used as a catheter lock solution to prevent microbial colonization and reduce formation of blood cloths | Not defined; *Aspergillus* spp, *Fusarium* spp; *Candida auris; S. aureus; Staphylococcus epidermidis* | 35927733; 17019660; 33996634; 26660041; 16033861; 30148449; 24982071; 21372561; 23669393; 34517829; 29385236; 33006269; 24939191; 24225618; 37344059; 31036689; 30204661 |
| | | | Used in cotton-textiles to prevent nosocomial infections | Undefined | 21328723 |
| | | | Used in wound dressings | *P. aeruginosa*; Undefined | 36362441; 22902057; 33223809;9725693; 20554394; 22781002; 17650189 |
| | | | Used as a component of a vaginal gel to prevent colonization by HPV; used to treat anogenital warts caused by HPV | Human papilloma virus | 34096424; 25922903 |
| | | | Used in osteopromotive composites to promote bone healing after fractures | *S. aureus* and *E. coli* | 35717669 |
| | | | Used to treat diabetic foot infections | Undefined | 20455958 |
| | | | Used in a gel formulation to promote vaginal health | *Chlamydia trachomatis; Neisseria gonorrhoeae* | 33705748 |
| **Lactic acid** | 3.85 | −0.72 | Used in soaked dressings (in the form of poly-lactic acid) in burn wounds | Undefined | 22712440; 37406851 |
| | | | Suppositories to treat bacterial vaginosis | BV-associated anaerobic bacteria | 37406851; 33571286 |
| | | | Used in membranes (in the form of poly-lactic acid) for bone regeneration and prevention of microbial colonization | Undefined | 26114511 |
| | | | As a gel to prevent vaginal urine tract infections and drug susceptible testings | Undefined vaginal/urinary pathogens; *Chlamydia trachomatis; Neisseria gonorrhoeae* | 33772330; 33705748 |

(*continued on next page*)

**Table 1** (*continued*)

| Carboxylic acid | pKa | logP | Described clinical applications | Target species | PUBMED ID of relevant references |
|---|---|---|---|---|---|
| **Benzoic acid** | 4.19 | 1.87 | Used for chemical nectrotomy to treat wounds from burns or necrotizing fasciitis | *Vibrio vulnificus*; Undefined | 33856245; 28869382 |
| | | | Used to treat campylobacteriosis in mice | *Campylobacter jejunii* | 37007531 |
| | | | *In vitro* inhibits activity of oral plaque-pathogens | *Porphyromonas gingivalis; Treponema socranskii* | 25790996 |
| | | | Used for acne therapy in the initial form of benzoyl peroxide | *Cutibacterium acnes* | 30725905 |
| **Sorbic acid** | 4.76 | 1.33 | Used to reduce gastric microbial burden in ventilated patients | Undefined | 16253799 |
| | | | *In vitro* inhibits biofilms by *Enterococcus faecalis* | Undefined | 22985004 |

different targets in the cell than those targeted by the antifungal/antibiotic, the organic acid may facilitate entrance of the antifungal/antibiotic to the inside of the cell, considering the deleterious action of the RCOOH form on the spatial organization of the plasma membrane and the cell wall [1]. An important conditioning factor for the success of this combinatorial approach is the local pH because this parameter not only determines the amount of undissociated acid but also influences the efficacy and/or stability of antibiotics/antifungals, increasing it in some cases (e.g. ceftolozane/tazobactam, sulphamethoxazole, tetracyclines, nitrofurantoin, and some $\beta$-lactams are more active at acidic pHs) and decreasing it in others (e.g. azoles and echinocandins are less active against *Candida* at acidic pHs) [20].

## Opportunities for the implementation of CAs as anti-infective agents

The fact that CAs have a long track record of safe use in the food industry, along with the already established use of some of these molecules as anti-infective agents (it is relevant to mention that they are legally allowed to use) and, in some cases, also antiseptics, opens the door to a possible intensification of their use. In this context, we identify as interesting opportunities the exploration of what can be the potential of further exploration of benzoic and sorbic acids because they are among the most powerful antimicrobials used in the food production settings but have limited utilization in the clinical context. A thorough investigation of how these acids counteract growth and activity of relevant human pathogens is due *in vitro* and in the clinical context (either as part of antiseptic solutions and/or as topical anti-infectives). Such approach gains further interest considering that sorbic and benzoic acids are much more toxic for microbial cells than acetic or citric acid owing to their higher lipophilicity, resulting in the need of using lower concentrations of these molecules to obtain the same antimicrobial effect. Another opportunity that, in our opinion, is also worthwhile of attention concerns the continuation of studies involving the combined use of organic acids and antimicrobials already used in the clinical context. In this case, besides the new combinations of antibiotics/antifungals/organic acids, it is also essential to investigate the role of key environmental parameters (e.g. the pH) in the establishment of the synergistic effect. Again, this proposal is inspired by what is performed in food production settings that already explore multiple combinations of acids to improve the efficacy of CA preservation. This possibility of using mixtures of organic acids because antimicrobials have not been explored at all in the clinical context (not even in *in vitro* studies) but shows some potential considering that different organic acids have very different biological targets, a trait that limits genetic resistance traits that pathogenic microorganism can transmit to the progeny and to other species. Finally, it is also worthwhile mentioning the numerous possibilities that might arise from combining the antimicrobial properties of organic acids with materials that are compatible for clinical application (e.g. nanoparticles, biopolymers, etc.), also in analogy with the food sector where this is already been performed to produce a novel generation of preservatives using biopolymers such as chitosan or alginate.

## Declaration of competing interest

The authors have no competing interests to declare.

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## Ethical approval

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## Author contributions

NPM coordinated the writing of the paper with contributions from RM, SAD, MJFP, NS, KR, PAL, DDB. The conceptualization of the manuscript was made by all the authors during the scope of their participation in the activities of WG3 of the COST Action EuroMicropH.

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