

# Antibacterial effects of natural compounds: Are they better when acting alone or together?

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## ABSTRACT

With worldwide increase in microbial infections and ever-expanding antibiotic resistance there is growing interest in investigating natural compounds as a potential safe and affordable measure in controlling bacterial infectivity.

Our earlier study showed antibacterial efficacy of a combination of vitamin C and L-lysine against bacterial strains *Acinetobacter baumannii* (*A. baumannii*) and *Escherichia coli* (*E. coli*), the most antibiotic resistant pathogens responsible for urinary tract (UTI) and other infections.

Here we evaluated antibacterial effects of other nutrients carnitine and gallic acid used individually and in combination with vitamin C and L-lysine. The evaluation included inhibition of these bacteria growth (MIC value) and survival (MBC).

The results show that all test compounds were effective in stopping growth and killing of these bacteria strains, with *E. coli* being less susceptible than *A. baumannii* to L-carnitine and a combination of vitamin C with L-lysine, but not to gallic acid. Interestingly, carnitine, not widely considered as an antibacterial agent, was effective in inhibiting growth and survival of both *A. baumannii* and *E. coli*. The study showed both strong synergistic effects of these nutrients and an ability of vitamin C as a substitute for gallic acid in maintaining strong antibacterial efficacy. Other benefits of these nutrients beyond their direct anti-bacteria efficacy was also discussed.

Since *E. coli* and *A. baumannii* have been implicated in urinary tract infections, the tested combination of natural compounds should be further elaborated for its clinical applications, including the long-term prevention of UTI.

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## INTRODUCTION

A steadily increasing spread of microbial infections in human and animal populations, including bacterial infections, has become a global concern. Especially that the occurrence of drug resistant bacterial strains limits the effectiveness of antibiotics and other medical or biotechnological approaches. Therefore, there is an interest in developing alternative means, including natural compounds with anti-microbial efficacy as potential nontoxic affordable measures in prevention and/or complementary therapies in bacterial infections.

In our work, we evaluated the efficacy of natural compounds: L-carnitine HCl, gallic acid, vitamin C and L-lysine HCl against two bacterial strains isolated from urine, *Acinetobacter baumannii* (*A. baumannii*) and *Escherichia coli* (*E. coli*). *A. baumannii* is one of the most antibiotic resistant pathogens in clinical medicine with biofilm-forming ability and is responsible for infections of the urinary tract (UTI), blood, or lungs (pneumonia) with mortality ranging from 26.0% to 55.7%. *E. coli*, which is a part of the normal intestinal flora, can turn into a pathogen causing UTI, but also intestinal illness, abdominal and pelvic infection, pneumonia, and meningitis, among others. There is a growing concern about *E. coli*'s antibiotic resistance as it is the most common Gram-negative pathogen in humans. In the United States, *E. coli* infections have been responsible for approximately 265,000 illnesses and about 100 deaths, each year.

The basis for the rationale of selecting the natural compounds and investigating their antibacterial effects against these two bacteria strains is presented below:

L-carnitine is a ubiquitously occurring substance, essential for the transport of long-chain fatty acids through the inner mitochondrial membrane, important in bio-energy production. In bacteria, the physiological function of L-carnitine is largely unknown. L-carnitine can be synthesized in mammals from lysine and methionine with the help of vitamin C and other nutrients, but it is not produced in bacteria, where carnitine or its immediate precursors are imported into the cells.<sup>1</sup> Although synthetic L-carnitine esters and acylcarnitine analogs were known to have antimicrobial effect, no

such activity has been related to L-carnitine itself so far.

Phenolic compounds like gallic acid are known to inhibit bacterial growth. It has been shown that gallic acid could significantly reduce the multidrug resistance in *A. baumannii* biofilms with variable degrees dependent on the phenotype–genotype characteristics of the tested isolates.<sup>2</sup> Gallic acid has also shown concentration dependent inhibitory effects on *E. coli* growth and biofilm.<sup>3</sup> This naturally abundant non-flavonoid polyphenol, may reach concentrations up to 220 mg/kg in some foods.<sup>4</sup>

Vitamin C is another widely used antimicrobial compound with its potent antioxidant, immunomodulatory, and anti-infectious effects. The antibacterial effects of vitamin C are, at least in part, due to its low pH and thus milieu-modifying properties and might be both bacterial strain and concentration dependent. Interestingly, vitamin C had only a marginal effect on the growth of *E. coli* ATCC 11775 strain. However, when used in combination with lactic acid it inhibited replication of *E. coli* O157:H7 strain when incubated in Brain Heart Infusion (BHI) broth or in carrot juice. It has been reported that vitamin C could reduce the sensitivity of *E. coli* MG1655 to streptomycin as well.<sup>5</sup>

Our earlier study showed that a combination of vitamin C with L-lysine had a potent antibacterial effect against *A. baumannii* and *E. coli*, while these components used individually did not affect these bacteria.<sup>6</sup> L-lysine has been used for an antibacterial activity in a form of a polymer, i.e., poly- $\beta$ -L-lysine, which due to its positively charged cationic groups was effective in killing bacteria by destroying their membranes. Antimicrobial efficacy of L-lysine evaluated in disk diffusion test by Svediene et al. showed no inhibition on *E. coli* growth at 1.0 mg/ml, while its minimal inhibitory concentration (MIC value) against *E. coli* and *S. aureus* were 500 mg/ml and 125 mg/ml, respectively.<sup>7</sup> Both vitamin C and L-lysine are also important in wider aspects of microbial infections. These nutrients are essential for the synthesis and structure of collagen and extracellular matrix (ECM) components responsible for maintaining integ-

rity of biological barriers- the entry points for various infection agents. Therefore, integrity of the endothelial lining of blood vessels, intestines, lung passages and many other organs largely depends on optimum intake of L-lysine and vitamin C as these two nutrients are not produced in a human body.

The study presented here evaluates the bacteriostatic and bactericidal effects of individual compounds L-carnitine HCl, gallic acid, vitamin C and L-lysine HCl against *A. baumannii* and *E. coli*. The individual effects of these compounds are then compared to the combination of these four ingredients used in various concentrations.

## MATERIAL AND METHODS

*Acinetobacter baumannii* Bouvet and Grimont strain 2208 [81, DSM 6974] is a whole genome sequenced bacterial type strain isolated from human urine. This strain has applications in food testing, media testing, and quality control.

*Escherichia coli* (Migula) Castellani and Chalmers strain NCTC 9001 is a bacterial type of strain that was isolated from urine. This whole-genome sequenced strain can be used for aerosol detection, media testing, and quality control testing.

*Acinetobacter baumannii* was cultured in tryptic soy broth (TSB) in 37°C with 5% CO<sub>2</sub>, while *Escherichia coli* was cultured in nutrient medium (ATCC, Manassas VA) in 37°C with 5% CO<sub>2</sub>. Vitamin C, L-lysine HCl, gallic acid, and L-carnitine HCl were purchased from Sigma (Burlington, MA). A stock solution (50-100 mg/ml) of each compound (depending on solubility of the substance) was prepared by suspending a test compound (individually or in combination) in DMSO and sterilized by 0.22 µm syringe filtration. All stock solutions were prepared just before the start of the experiment and used immediately.

*Evaluation of the bacteriostatic and bactericidal effects of test compounds and their combination against the planktonic form of A. baumannii and E. coli.*

Growth inhibition of test strains was tested using a standard macro-dilution method to establish value of bacteriostatic effect.<sup>8</sup> Briefly, sterile 3 ml two-position-capped test tubes containing 1 ml nutrient broth with 1 x 10<sup>6</sup> cfu/ml of the homogenous bacterial suspension, were supplemented with the test compounds or their combination. The tubes were then incubated at 37°C with 5% CO<sub>2</sub> and growth inhibition as a decrease in the optical density (OD<sub>600</sub>) was registered after 24 hours of incubation. Control cultures were treated with 1 x PBS.

The antibacterial effect of test compounds or their combinations on the bacterial strains was evaluated using standard method.<sup>8</sup> The bactericidal values were determined from a broth dilution minimum inhibitory concentration test by sub-culturing the bacterial cell samples removed after 24 hours of incubation, and plated onto nutrient agar plates that did not contain the test agent. The plates were then further incubated at 37°C with 5% CO<sub>2</sub> and bacterial re-growth was assessed after 24 hours by counting the colonies.

A bacteriostatic effect was defined when at least as 2-log<sub>10</sub> cfu/ml, whereas a bactericidal effect was defined when at least as a 3-log<sub>10</sub> cfu/ml decrease from the original inoculum. All experiments were conducted three times independently and each one in three replicates.

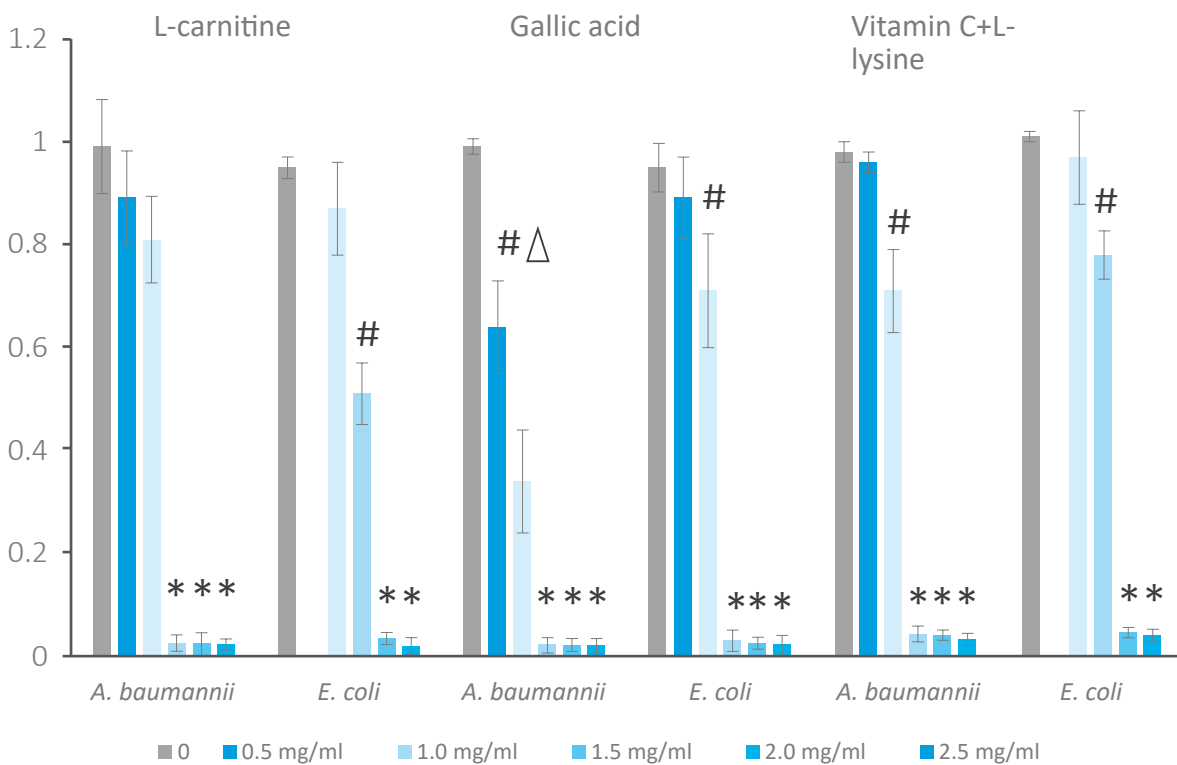
### Statistical analysis.

All data are presented as means ± SD (n=3). The Student's two-tailed t test was used to determine statistically significant differences set at 0.05 levels. Statistical analysis was performed using GraphPad software.

## RESULTS

Figure 1 shows the antibacterial effects of different concentrations of L-carnitine, gallic acid and a combination of L-lysine and vitamin C (used in 1:1 ratio) against *A. baumannii* and *E. coli* during a 24h period of incubation with these test compounds. The evaluation of OD600 in these bacterial cultures shows that with increasing concentrations of these test agents, there

was an inhibition of bacterial growth and viability. All test compounds showed antibacterial efficacy when applied at concentrations 1.5 mg or 2.0 mg depending on the bacteria strains. *E. coli* appeared to be slightly more resistant to these natural compounds than *A. baumannii*.



**Figure 1.** Antibacterial effects of L-carnitine, gallic acid and a combination of vitamin C and L-lysine (1:1 ratio) against *A.baumannii* and *E.coli* after 24 hrs incubation with test compounds as described in Materials and Methods. Bacterial growth was evaluated by changes in OD 600nm. #  $p < 0.05$ ,  $\Delta p \leq 0.01$ , \*  $p < 0.001$

Table 1 shows the concentrations of L-carnitine, gallic acid and a combination of vitamin C with L-lysine required to inhibit bacterial growth (MIC) or kill (MBC) these bacteria. All test compounds applied at 1.5 mg/ml concentration were effective in stopping growth of *A. baumannii*. Growth inhibition of *E. coli* by L-carnitine and vitamin C with L-lysine was achieved using higher concentrations of these compounds of 2 mg/ml (MIC value). Only gallic acid was equally effective in inhibiting

growth of both *A. baumannii* and *E. coli* when used at 1.5 mg/ml concentration (MIC value).

The bactericidal effect against *A. baumannii* was achieved with all test compounds applied at 2mg/ml concentration (MBC value). MBC values for *E. coli* were 2 mg/ml for gallic acid and for L-carnitine and vitamin C with L-lysine 2.5 mg/ml.

**Table 1.** MIC and MBC values for *A. baumannii* and *E. coli* exposed to L-carnitine, gallic acid and a combination of vitamin C with L-lysine (ration 1:1).

	L-carnitine		Gallic acid		Vit C – L-lysine (1:1)	
	<i>A. baumannii</i>	<i>E. coli</i>	<i>A. baumannii</i>	<i>E. coli</i>	<i>A. baumannii</i>	<i>E. coli</i>
MBC (log 10 CFU/ml)	3.6 (2.0 mg/ml)	3.4 (2.5 mg/ml)	3.8 (2.0 mg/ml)	3.2 (2.0 mg/ml)	3.3 (2 mg/ml)	3.1 (2.5 mg/ml)
MIC (OD <sub>600</sub> )	0.025 (1.5 mg/ml)	0.033 (2.0 mg/ml)	0.022 (1.5 mg/ml)	0.029 (1.5 mg/ml)	0.043 (1.5 mg/ml)	0.045 (2.0 mg/ml)

**Table 2.** Effects of test nutrients combinations on MIC and MBC and for *A. baumannii* and *E. coli*.

Mix	Vitamin C (mg/ml)	L-Lysine (mg/ml)	L-Carnitine (mg/ml)	Gallic acid (mg/ml)	<i>A. baumannii</i>	<i>E. coli</i>	Final concentration of the Mix (mg/ml)
#1	0.25	0.25	0.5	0.5	MBC (log <sub>10</sub> 3.1)		1.5
#2	0.25	0.5	0.5	-	MIC (OD <sub>600</sub> 0.023)		1.25
#3	0.25	0.5	0.5	0.5	MBC (log <sub>10</sub> 4.1)		1.75
#4	0.75	0.5	0.5	0.5		MIC (OD <sub>600</sub> 0.022)	2.25
#5	1.0	0.5	0.5	0.5		MBC (log <sub>10</sub> 3.1)	2.5
#6	1.0	0.5	0.5	-		MIC (OD <sub>600</sub> 0.022)	2.0

Log > 2 equivalent to OD<sub>600</sub> < 0.03

Table 2 shows the effects of test compounds combined as mixes containing L-carnitine, gallic acid, vitamin C and L-lysine at different concentrations on MIC and MBC values for *A. baumannii* and *E. coli*. All six nutrient combinations contained L-carnitine and L-lysine at 0.5 mg/ml concentrations except for Mix #1, where L-lysine was used at a concentration of 0.25 mg/ml. Gallic acid was present at 0.5 mg/ml in all mixtures except for Mix #2 and Mix #6. Concentrations of vitamin C varied in the mixes from 0.25 mg/ml to 1.0 mg/ml.

The results show that growth inhibition of *A. baumannii* could be achieved using Mix #2 lacking gallic acid. However, MIC values for *E. coli* show that two effective mixtures contained either all ingredients with 0.75mg/ml of vitamin C (Mix #4) or as in the case of Mix #6 a lack of gallic acid was compensated by higher vitamin C concentration of 1.0 mg/ml.

Bactericidal effects for both *A. baumannii* and *E. coli* were achieved with mixes containing gallic acid. MBC for *E. coli* required higher vitamin C concentration (1.0 mg/ml) in the mixture than required for *A. baumannii* (0.25 mg/ml).

## DISCUSSION

This study provides important information on antibacterial efficacy of individual natural compounds and their combinations against bacterial strains largely responsible for UTI and other infections with dangerous health consequences.

### Direct antibacterial effects

The results show that similar antibacterial efficacy could be achieved by different compositions of natural compounds containing varying amounts of these individual agents in the mixture. Examples are the bacteriostatic effects of Mix #4 and Mix #6 against *E. coli* and bactericidal effects of Mix #1 and Mix #3 against *A. baumannii*. It appears that to inhibit growth of *E. coli* a mixture lacking gallic acid should contain a higher concentration of vitamin C. The mechanisms responsible for this effect should be further evaluated.

It appears that these two bacterial strains have different sensitivity to the tested mixtures, with *A. baumannii* being more affected than *E. coli*. As such, growth inhibition of *A. baumannii* could be achieved by the mixture containing low 0.25 mg/ml concentration of vitamin C and lacking gallic acid (Mix #2). Killing effects of this bacteria was also achieved by lower concentration of the mixes than required for *E. coli*. As such, MBC for *A. baumannii* were at mixture concentrations of 1.5 and 1.75 mg/ml, while for *E. coli* at 2.5 mg/ml.

*A. baumannii* was equally sensitive to individually applied L-carnitine, gallic acid and vitamin C with L-lysine with MIC value at 1.5 mg/ml and MBC value at 2.0 mg/ml. However, *E. coli* was less susceptible than *A. baumannii* to L-carnitine and vitamin C with L-lysine, but not to gallic acid. MBC values for L-carnitine and vitamin C with L-lysine against *E. coli* were at 2.5 mg/ml. Gallic acid was equally effective against *A. baumannii* and *E. coli* with MIC value at 1.5 mg/ml and MBC value at 2.0 mg/ml.

It is important to note that the ingredients in the mixes were applied at lower concentrations compared to those that showed any effects against these bacterial strains when used individually (Figure 1). However, these compounds used together displayed antibacterial efficacy, confirming the importance of additive or synergistic effect when combining different ingredients. Such an effect was clearly observed in our earlier work with the combination of vitamin C and L-lysine against both *E. coli* and *A. baumannii*.<sup>6</sup>

Enhanced antibacterial effects were also indicated in other studies using combinations of vitamin C with other natural components. As such, synergistic antibacterial effects could also be observed upon co-administration of vitamin C and quercetin against *E. coli* and *Staphylococcus aureus*.<sup>9</sup> The combination of vitamin C with natural extracts from pomegranate rind and white tea resulted in enhanced anti-*S. aureus* properties of the tea.<sup>10</sup> Also, co-administration of vitamin C with epigallocatechin gallate (EGCG) could enhance the antibacterial effects even against methicillin-resistant *S. aureus* or multidrug-resistant (e.g., MRSA) bacterial species.<sup>11</sup>

L-lysine contains positively charged cationic groups, which are very effective in destroying the membranes of the bacteria, thereby killing the bacteria.<sup>12,13</sup> It has been shown that L-lysine can be used in decreasing resistance to aminoglycosides antibiotic of some bacteria strains, such as Gram-negative *A. baumannii*, *E. coli* and *Klebsiella pneumoniae* and a Gram-positive bacterium (i.e., *Mycobacterium smegmatis*). Importantly, the combination of L-lysine with aminoglycosides killed clinically isolated multidrug-resistant *A. baumannii*.<sup>14</sup> Also, polymers of lysine as poly-L-lysine have been investigated as they showed antibacterial properties, and do not induce inflammation of the tissue,<sup>15</sup> however, it can be toxic but only in high doses.<sup>16</sup>

Our study increases our knowledge on antibacterial properties of L-carnitine, by showing its direct biocidal and biostatic effects against *A. baumannii* and *E. coli*. Interestingly, L-carnitine is not known for its antibacterial effects, but rather its opposite. Some studies indicated that L-carnitine can act as osmo-protectant in the *E. coli* helping these bacteria to survive extreme osmotic stress<sup>1</sup> and can also stimulate growth of some microorganisms.<sup>17</sup>

However, L-carnitine is important for the shift from carbohydrate to fat metabolism, which plays a role during inflammatory crises such as sepsis. Recent clinical application of L-carnitine in patients with sepsis resulting from upper respiratory infection with *Pseudomonas sp.* has shown positive effects. L-carnitine supplementation demonstrated the ability to ameliorate inflammation, boost antioxidative status, and most notably, reduction in mortality after just 7 days of treatment.<sup>18</sup> In this aspect, also gallic acid with its anti-inflammatory benefits including the reduced release of inflammatory cytokines, chemokines, adhesion molecule, and cell infiltration is expected to be a potential candidate for the application in various inflammation-related diseases.

### Wider implications of the study findings

There are other important aspects to be considered when selecting and combining various natural compounds. By using compounds with different mechanisms of action and biological effects in the body we can address infections in their wider aspects. The range of beneficial natural compounds effects would include strengthening biological barriers against penetrating infectious agents, improved bioenergy of the host cells, antioxidant and anti-inflammatory effects, or the immune response, all in addition to a direct biocidal effect.

Such pleiotropic effects could be expected by our selection of natural compounds as well. As such, vitamin C and L-lysine essential in collagen production can address the protection of biological barriers used as entry points for various infectious agents by preserving integrity of the endothelial lining of blood vessels, intestines, lung passages, and many other organs. In addition, vitamin C is the most important antioxidant, it is essential for the immune system function, as an anti-inflammatory agent and for its numerous functions in the body. It is important to note that neither vitamin C nor L-lysine are produced in the human body and their supplementation is vital. However, bacteria can synthesize all 20 proteinogenic amino acids, including L-lysine and other essential amino acids. L-carnitine, with its anti-sepsis benefits is not produced in bacteria, but here we have shown that the exposure of *A. baumannii* and *E. coli* to L-carnitine can inhibit growth and eliminate these bacteria.

Since *E. coli* and *A. baumannii* have been implicated in urinary tract infections, the combination of natural compounds tested in our study may also be considered as a prophylactic treatment especially for the long-term prevention of UTI. Nutrients are cost-effective, readily available, safe to use, with fewer reported side effects, and do not induce bacterial resistance. The antimicrobial effects these natural compounds could be attributed to multiple mechanisms, including directly killing microbes, stopping their multiplication but also improving the host protection acting on natural barriers, serving as immunomodulators, restoring intestinal dysbiosis, or boosting body oxidant status.<sup>19</sup>

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