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Synergistic inhibition of the urinary tract pathogen *Staphylococcus saprophyticus* by curcumin and berberine

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Abstract
S*taphylococcus saprophyticus* is a Gram-positive pathogen that is most commonly associated with community-acquired urinary tract infections in adolescent and adult women. While antibiotics can be used to treat these infections, they often reoccur and there has been increased interest in using herbal preparations to treat them. Curcumin has been promoted as a treatment for a variety of diseases, but its effectiveness is limited by its low solubility in aqueous solutions and poor bioavailability. The sensitivity of *S. saprophyticus* to curcumin and berberine was determined by plate count assays, minimum inhibitory concentrations in microtiter plates, and growth kinetics. When 100 µg ml^{-1} berberine was combined with 20 µg ml^{-1} curcumin, there was a large increase in the lag phase and a decrease in the growth rate and final yield of bacteria. There was complete inhibition of growth in normal human urine. These studies indicate that a combination of curcumin with berberine allows curcumin to be used at much lower concentrations.

Keywords: Antimicrobial agent, berberine, curcumin, *Staphylococcus saprophyticus*, turmeric urinary tract infection

Introduction
Urinary tract infections (UTIs) commonly occur in infants and small children, in adolescent and adult women, and in patients or older adults fitted with catheters [1-4]. The primary causes are the Gram-negative bacteria *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* and the Gram-positive bacteria *Staphylococcus saprophyticus*, *Enterococcus faecalis*, and *Staphylococcus aureus* [5-6]. Although most UTIs can be treated with antibiotics [7-8], resistant microorganisms are frequently recovered from infected individuals [9-10] and recurrent infections are common [11-12].
Because antibiotics can be relatively expensive and may require prescriptions from physicians, there is a great deal of interest in alternative approaches to preventing or treating UTIs [13-15]. These include the use of over-the-counter plant preparations such as those derived from fruits like cranberries or various herbs [17-19]. Curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione) and its derivatives are the active components of turmeric, a herbal preparation derived from the rhizomes of *Curcuma longa* [20-21]. Curcumin has been reported to have a wide range of pharmacological uses as an antibiotic, antioxidant, and anti-inflammatory agent, with positive effects for the treatment of cancer, ageing, diabetes, neurological, and cardiovascular diseases [22-26]. Although curcumin may be used to treat various illnesses, there are major problems in its application. These include its low solubility in aqueous solutions [27], instability at pH greater than 7.2 [28], poor bioavailability [29], and potential toxicity [26]. Investigators have attempted to improve the effectiveness of curcumin as a therapeutic agent by incorporating it into liposomes or nanoparticles [30-32].
There have been relatively few peer-reviewed reports of the effects of curcumin on renal infections [33-36] but online web sites often promote turmeric as a treatment for UTIs (for example, https://www.turmericforhealth.com/turmeric-benefits/turmeric-and-urinary-tract-infection-uti). Curcumin has been reported to have antimicrobial activity against *S. saprophyticus* [37-38], as well as *S. aureus* [39-41]. I have reexamined the antibacterial activity of curcumin towards *S. saprophyticus* and found that it is much more effective when combined with berberine, an alkaloid found in herbal preparations from Goldenseal (*Hydrastis canadensis*) and other plants.

Materials and methods

Chemicals and herbal extracts

Curcumin was obtained from Sigma Aldrich and berberine HCl was from Bulk Supplements. Herbal extracts were purchased from local health food stores or online distributors.

Bacterial strains and growth media

S. saprophyticus strains ATCC 15305, ATCC 35552, and ATCC 49907 were obtained from the American Type Culture Collection (Manassas, VA, USA). ATCC 15305 is the type strain and ATCC 35552 and ATCC 49907 are well characterized strains that are used as control samples for various clinical test systems. Bacteria were maintained on Difco™ tryptic soy broth agar (Becton, Dickinson and Company, Sparks, MD, USA). Liquid P medium for *S. saprophyticus* was prepared as described by Gatermann *et al.* [42] and contained per liter: 10 g peptone, 5 g yeast extract, 1 g Na_2HPO_4, and 1 g D-glucose. It was adjusted to pH 7.3 or pH 6.5 with 1.0 mol l^{-1} HCl or NaOH as needed. The artificial urine medium (AUM) described by Minuth *et al.* [43] contained per liter: 0.65 g $CaCl_2.2\ H_2O$, 0.65 g $MgCl_2.6\ H_2O$, 4.6 g NaCl, 2.3 g Na_2SO_4, 2.8 g KH_2PO_4, 1.6 g KCl, 1.0 g NH_4Cl, 12 g urea, 1.1 g creatinine, and 10 g tryptic soy broth. The medium was adjusted to pH 6.5 and sterilized by vacuum filtration through membrane filters (PES membrane, 0.22 µm pores, Genesee Scientific, El Cajon, CA, USA,). 50 mM MES (2-(N-morpholino) ethanesulfonic acid) pH 6.5 was added to larger liquid cultures to improve the buffering capacity of the medium and increase the growth yields. Normal morning human urine was collected from laboratory volunteers and sterilized by vacuum filtration.

Growth conditions

Liquid cultures were routinely grown at 37ºC in 300 ml baffled nephelometer flasks containing less than 10% of the total volume of medium and shaken at 250 rev min^{-1}. Turbidities were measured in a Klett-Summerson colorimeter with a red (660 nm) filter. When curcumin or berberine was added to the medium, the turbidities of cultures were read against flasks containing the same curcumin or berberine concentrations. Viable cell counts were determined by serially diluting samples in 0.85% (w/v) NaCl and plating duplicate 100 µl aliquots on tryptic soy broth agar plates. Colonies were counted after two days at 37 ºC. All growth experiments were done at least twice.

Minimum inhibitory concentrations for curcumin

S. saprophyticus strains ATCC 15305, ATCC 35552, and ATCC 49907 were grown overnight in P medium pH 6.5 or AUM pH 6.5 at 37 ºC and diluted 1/100 into sterile 0.85% (w/v) NaCl. Test cultures (150 µl) of P medium pH 6.5 or AUM pH 6.5 containing serial 1/2 dilutions of curcumin dissolved in dimethylsulfoxide (DMSO) ranging from 500 µg ml^{-1} to 16 µg ml^{-1} were set up the wells of sterile Falcon flat bottom polystyrene microtiter plates. Cultures without DMSO or curcumin were included as controls. The wells were inoculated with 5 µl of the diluted bacterial suspensions to give three replicate samples at each concentration and incubated at 37 ºC for 48 hr. The absorbances were measured at 600 nm with a BioTek Synergy HT plate reader. The average for uninoculated wells in each set was subtracted from the averages for other samples to get the net absorbance due to cell growth. Cultures containing 500 µg ml^{-1} curcumin were not included in the data analysis due their very high turbidity.

Inhibition of bacterial growth on agar plates by herbal extracts and berberine

S. saprophyticus strain ATCC 15305 was grown overnight in P medium pH 6.5, diluted into fresh medium, and cultured into exponential phase (about 75 Klett Units). The bacteria were harvested by centrifugation for 10 min at 10,000 rpm in a Bio-Lion XC-H165 centrifuge. The cells were washed once with 0.85% (w/v) NaCl, and resuspended in 0.85% NaCl to give a suspension with a turbidity of 100 Klett Units. Aliquots (100 µl) were spread on agar plates of P medium pH 6.5 supplemented with 0, 20, 50, or 100 µg ml^{-1} curcumin. Small sterile 6 mm 3MM filter paper discs were placed on the plates and 10 µl of various herbal preparations or solutions of berberine HCl in methanol were added to the discs. The plates were incubated at 37 ºC for 24 hr and the zone of inhibition around each disc measured.

Inhibition of bacterial growth in liquid cultures or human urine by curcumin and berberine

S. saprophyticus strain ATCC 15305 grown overnight in P medium pH 7.3 was diluted 1/100 into P medium pH 6.5 or artificial urine medium pH 6.5 supplemented with 50 mmol l^{-1} MES pH 6.5 containing 20 µg ml^{-1} curcumin. The medium was supplemented 0, 6.25, 12.5, 25, 50, or 100 µg ml^{-1} berberine and the cultures were incubated with aeration at 37 ºC. The turbidities of the cultures were measured periodically for up to five days. Human urine cultures were set up in sterile 13 x 100 mm test tubes and supplemented with 20 µg ml^{-1} curcumin, 100 µg ml^{-1} berberine, or both. Three replicate 2 ml cultures were inoculated with $1/100^{th}$ volume of an overnight culture *S. saprophyticus* strain ATCC 15305 grown in P medium pH 7.3 and incubated without aeration at 37 ºC. The viable cell count was determined after 24 hr and 48 hr.

Results

Survival of *S. saprophyticus* in buffer with curcumin

To determine the effects of curcumin on the viability of *S. saprophyticus*, exponential-phase cells of the type strain ATCC 15305 which had been grown in the standard P medium at pH 7.3 or P medium at pH 6.5 were suspended in 100 mmol l^{-1} sodium phosphate buffer adjusted to pH 7.3 or pH 6.5 containing 2 mmol l^{-1} $MgSO_4.7\ H_2O$. The initial viable counts were determined by making serial dilutions in 0.85% NaCl and spreading 100 µl aliquots on duplicate tryptic soy broth agar plates. Increasing concentrations of curcumin dissolved in dimethylsulfoxide (DMSO) were added and the viable counts determined again after incubation at 37 ºC for four hr (Fig. 1). There was a decrease in viability at concentrations up to 100 µg ml^{-1} but no additional decrease at higher concentrations. Survival was much greater at pH 7.3 than at pH 6.5. These results were consistent with previous studies indicating the curcumin is more stable at acidic pH [28]. Accordingly, most of the additional experiments were done with medium adjusted to pH 6.5.

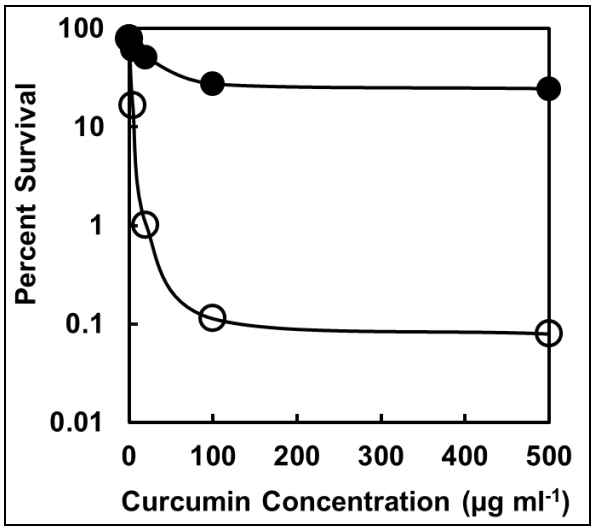

Fig 1: Inactivation of *Staphylococcus saprophyticus* ATCC 15305 in 100 mmol l^{-1} sodium phosphate buffer adjusted to pH 7.3 (●) or pH 6.5 (○) containing 2 mmol l^{-1} $MgSO_4.7\ H_2O$ and different concentrations of curcumin. Viable counts were determined at 0 time and again after 4 hr of incubation at 37 °C.

Minimum inhibitory concentrations with curcumin

The minimum inhibitory concentration (MIC) for curcumin dissolved DMSO then was determined for *S. saprophyticus* strains ATCC 15305, ATCC 35552, and ATCC 49907 during growth in liquid P medium at pH 6.5 or in artificial urine medium (AUM) at pH 6.5 in the wells of microtiter plates (Fig. 2 panels A and B). All three samples of *S. saprophyticus* gave similar results although growth in the standard artificial urine medium (AUM) pH 6.5 used in these experiments resulted in absorbances (turbidities) that were about one-third those seen in P medium pH 6.5. There was a progressive decrease in growth as the curcumin concentration was increased. Strains ATCC 35552 and ATCC 49907 were more sensitive to curcumin than was strain ATCC 15305 in P medium at pH 6.5. The average MIC for P medium pH 6.5 appeared to be 125 µg ml^{-1}. Strain ATCC 49907 was more sensitive to curcumin than the other two strains in AUM at pH 6.5. The average MIC for the strains in AUM pH 6.5 appeared to be 62.5 µg ml^{-1}. It was hard to measure growth in these experiments at curcumin concentrations greater than 100 µg ml^{-1} due to the intense yellow color and insolubility of this compound in aqueous solutions.

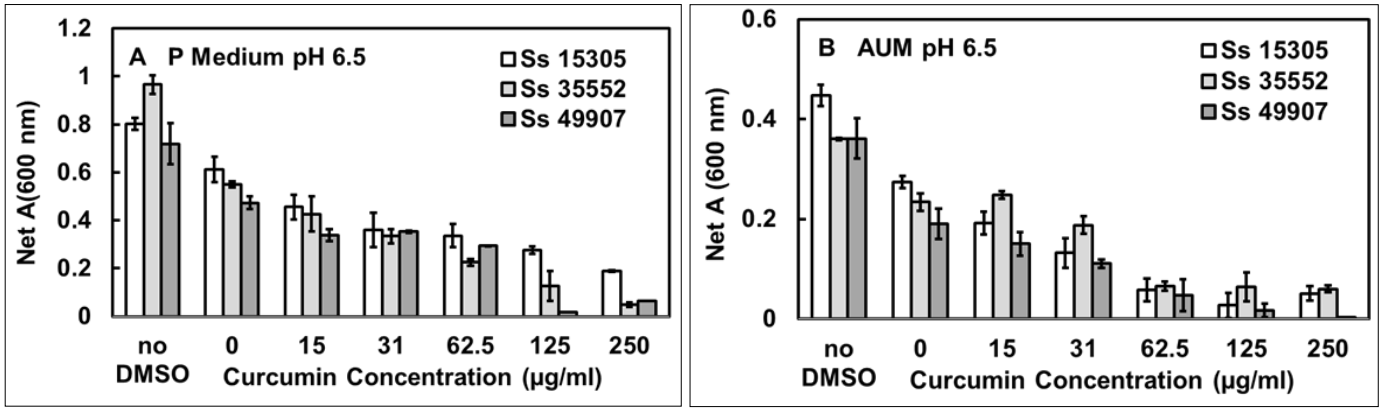

Fig 2: Determination of minimum inhibitory concentrations of *S. saprophyticus* in P medium pH 6.5 (panel A) or artificial urine medium (AUM) pH 6.5 (panel B).

Inhibition of growth of *S. saprophyticus* by curcumin

To extend these results, *S. saprophyticus* strain ATCC 15305 was grown in nephelometer flasks containing P medium pH 6.5 or AUM pH 6.5 supplemented with different concentrations of curcumin. Turbidity was measured periodically in a Klett-Summerson colorimeter. With P medium at pH 6.5, there was a progressive increase in the length of the lag phase and a decrease in the growth rate as the curcumin concentration was increased (Fig. 3 panel A). The final yield in cultures containing up to 50 µg ml^{-1} curcumin was the same but there was no growth at a concentration of 100 µg ml^{-1}. With AUM pH 6.5, there was a less obvious increase in the length of the lag phase (Fig. 3 panel B). While the growth rate was not affected at curcumin concentrations up to 100 µg ml^{-1}, the final yield of cells was progressively reduced.

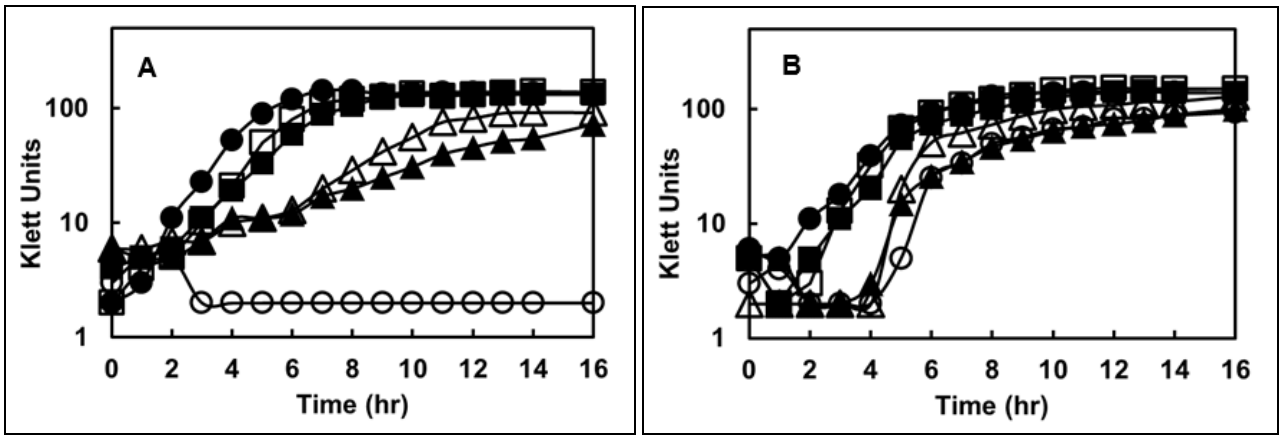

Fig 3: Effect of different concentrations of curcumin on the growth of *S. saprophyticus* ATCC 15305 in P medium pH 6.5 (panel A) or artificial urine medium pH 6.5 (panel B). The curcumin concentrations were 0 (●), 100 µg ml^{-1} (○), 50 µg ml^{-1} (▲), 25 µg ml^{-1} (△), 12.5 µg ml^{-1} (■), and 6.25 µg ml^{-1} (□).

Inhibition of *S. saprophyticus* by curcumin and herbal extracts

Previous studies indicated that commercial preparations of turmeric or curcumin had relatively little effect on the urease activity of *S. saprophyticus* or on its ability to form biofilms [44-45]. Other herbal preparations such as Sprouts Green Tea extract or Nature's Answer Uva Ursi extract were much more effective. To determine if any of these herbal preparations might enhance the inhibitory effect of curcumin on *S. saprophyticus*, the bacteria were spread on agar plates of P medium at pH 6.5 or P medium at pH 6.5 containing 20, 50, or 100 µg ml^{-1} curcumin. Aliquots (10 µl) of various herbal preparations were spotted on small paper discs and the zones of inhibition measured after one incubation at 37ºC. The bacteria formed well-defined lawns on both the plates with and without curcumin. The Sprouts green tea extract and Nature's Answer Uva Ursi extract gave visible zones of inhibition on P medium pH 6.5, which did not increase in size when the medium contained 20 µg ml^{-1} or 50 µg ml^{-1} curcumin (Table 1).

Table 1: Zones of inhibition in mm of *S. saprophyticus* by herbal extracts and berberine in combination with curcumin[a]

Inhibitor	P Med pH 6.5	P Med pH 6.5 + 20 µg ml^{-1} curcumin	P Med pH 6.5 + 50 µg ml^{-1} curcumin	P Med pH 6.5 + 100 µg ml^{-1} curcumin
Sprouts Green Tea Extract	15	13	15	16
Nature's Answer Uva Ursi Extract	12	12	12	14
Herb Pharm Golden Seal Extract	10	19	22	22
Botanic Choice Cranberry Extract	19	20	20	21
Herb Pharm Horehound Extract	11	9	9	10
10 mg ml^{-1} berberine	12	22	26	23
5 mg ml^{-1} berberine	14	20	26	22
2.5 mg ml^{-1} berberine	13	19	24	18
1.25 mg ml^{-1} berberine	11	15	20	19
0.62 mg ml^{-1} berberine	12	15	18	16

[a]Zones of inhibition were measured after 18 hr of incubation at 37 ºC for two to three replicate plates.

The zones of inhibition were less obvious on plates of P medium containing 100 µg ml^{-1} curcumin. The Herb Pharm Goldenseal preparation gave larger and clearer zones of inhibition both in absence and presence of curcumin. The diameter of the zone of inhibition increased with the curcumin concentration. The Botanic Choice cranberry preparation gave similar zones of inhibition on plates without or with curcumin. Other herbal preparations including Herb Pharm horehound extract, Nature's Answer ginger extract, Nature's Answer Horsetail extract, Kyolic aged garlic extract, Nature's Answer Gingko biloba extract, Herb Pharm horehound extract, Herb Pharm horseradish extract, Nature's Answer blueberry extract, Hawaii Pharm broccoli extract, Wishgarden UTI herbal suspension, and Nature's Remedies UTI clear herbal supplement had no effect on *S. saprophyticus* on either regular P medium or P medium containing curcumin.

These extracts usually contain a mixture of compounds and there is no standardization of their concentrations from one supplier to another [63]. The primary active ingredient in Goldenseal extracts is believed to be the alkaloid berberine [47]. To determine if berberine affects the growth of *S. saprophyticus* alone or in the presence of curcumin, the disk assays were repeated with pure berberine HCl dissolved in methanol. Aliquots (10 µl) of 10, 5, 2.5, 1.25, or 0.62 mg ml^{-1} were spotted on small filter paper discs and the zones of inhibition measured after 24 hr incubation at 37 ºC. While there was some inhibition on regular P medium at pH 6.5, the zones of inhibition were much larger and clearer on plates containing 20, 50, or 100 µg ml^{-1} curcumin (Table 1). There were no resistant colonies within the zones of inhibition even after 7 days of incubation.

Inhibition of *S. saprophyticus* by curcumin and berberine

To extend these results, ATCC 15305 was again grown in nephelometer flasks containing P medium or AUM at pH 6.5 supplemented with different concentrations of berberine. With P medium pH 6.5, berberine alone had only limited inhibitory effects (Fig. 4 panel A). A concentration of 100 µg ml^{-1} berberine increased the length of the lag phase and decreased the growth rate but did not affect the final yield of cells. On the other hand, when the same concentrations of berberine were combined with 20 µg ml^{-1} curcumin, there was a much

greater increase in the length of the lag phase and a slower growth rate (Fig. 4 panel B). A complete growth cycle took about 60 hr rather than 12 hr. There was no growth when 50 µg ml^{-1} or 100 µg ml^{-1} berberine was combined with 20 µg ml^{-1} curcumin. With AUM pH 6.5 supplemented with 50 mmol l^{-1} MES buffer pH 6.5 to increase the yield, there was little inhibition by berberine concentrations up to 100 µg ml^{-1} (Fig. 4 panel C). When the same concentrations of berberine were combined with 20 µg ml^{-1} curcumin, there was again an increase in the lag phase and a decrease in the growth rate (Fig. 4 panel D). The bacteria continued to grow in AUM pH 6.5 containing 20 µg ml^{-1} curcumin together with up to 100 µg ml^{-1} berberine, but the yield was reduced by about 60%.

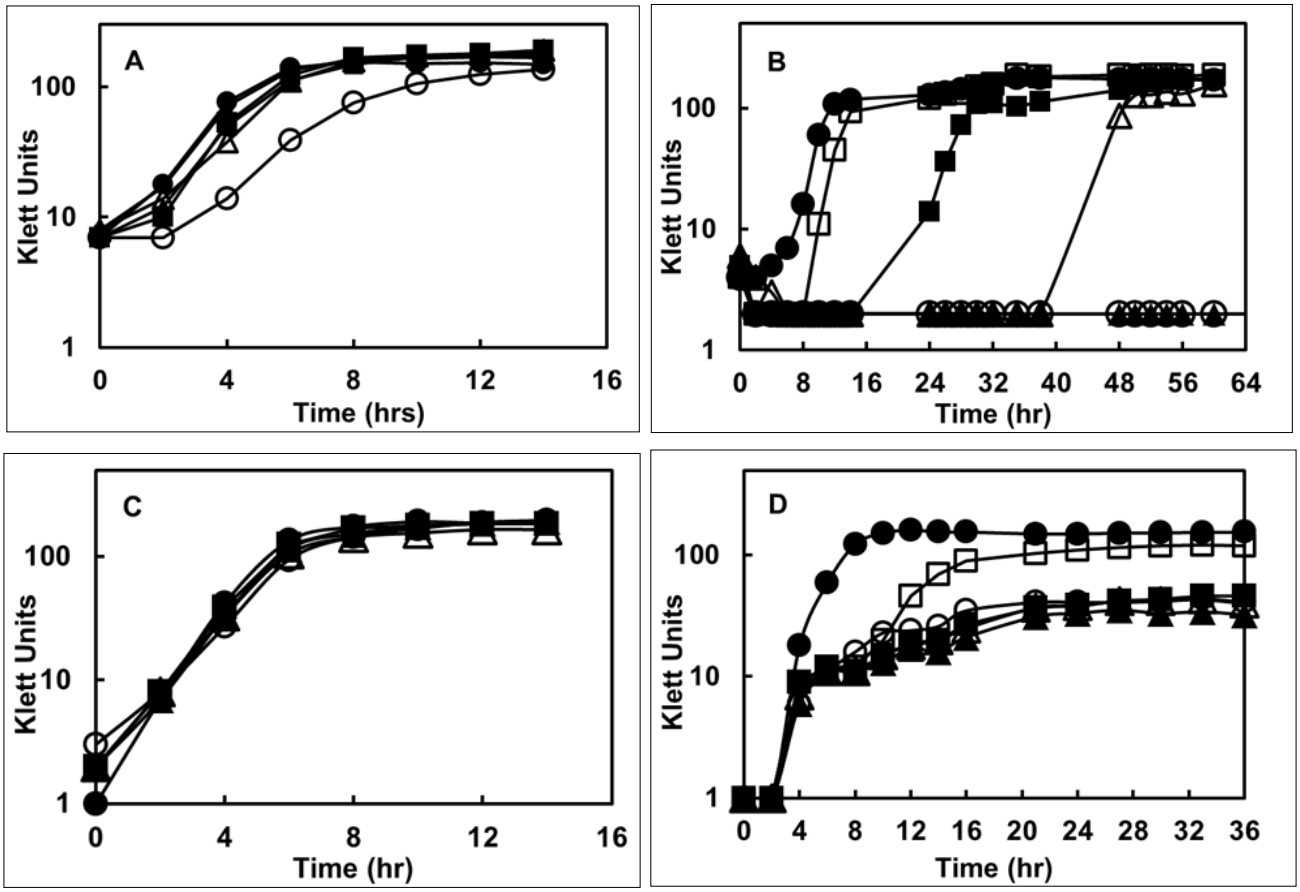

Fig 4: Effect of berberine and berberine in combination with curcumin on the growth of *S. saprophyticus*. Panel A shows the results for P medium pH 6.5 containing 0 (●), 100 µg ml^{-1} (○), 50 µg ml^{-1} (▲), 25 µg ml^{-1} (△), 12.5 µg ml^{-1} (■), and 6.25 µg ml^{-1} (□) berberine. Panel B shows the results for P medium pH 6.5 containing 20 µg ml^{-1} curcumin and 0 (●), 100 µg ml^{-1} (○), 50 µg ml^{-1} (▲), 25 µg ml^{-1} (△), 12.5 µg ml^{-1} (■), and 6.25 µg ml^{-1} (□) berberine. Panel C shows the results for artificial urine medium (AUM) pH 6.5 containing 0 (●), 100 µg ml^{-1} (○), 50 µg ml^{-1} (▲), 25 µg ml^{-1} (△), 12.5 µg ml^{-1} (■), and 6.25 µg ml^{-1} (□) berberine. Panel D shows the results for artificial urine medium (AUM) pH 6.5 containing 20 µg ml^{-1} curcumin and 0 (●), 100 µg ml^{-1} (○), 50 µg ml^{-1} (▲), 25 µg ml^{-1} (△), 12.5 µg ml^{-1} (■), and 6.25 µg ml^{-1} (□) berberine.

Inhibition of *S. saprophyticus* in human urine

To determine if curcumin or berberine could inhibit the growth of *S. saprophyticus* under the physiological conditions found in the urinary tract, small cultures of 2 ml sterile human urine were set up in sterile 13 x 100 test tubes. The cultures were supplemented with 20 µg ml^{-1} curcumin, 100 µg ml^{-1} berberine, or both and the viable cell count determined after 24 hr and 48 hr (Table 2). Curcumin alone at a concentration of 20 µg ml^{-1} reduced the viable count by about 30% after 24 hr. After 48 hr, the viable count in the control culture decreased about 50% and there was little difference between the control and the curcumin-treated culture. Berberine alone at a concentration of 100 µg ml^{-1} reduced the viable count about 90% after 24 hr and about 99.9% after 48 hr. The colonies from the berberine-treated cultures were noticeably more variable in size on tryptic soy broth agar plates after two days incubations and there were many more small pin-size ones. The combination of 20 µg ml^{-1} curcumin and 100 µg ml^{-1} berberine was much more effective and almost completely inhibited growth after 24 hr or 48 hr. There were only a few isolated colonies on the viable count plates.

Table 2: Inactivation of *S. saprophyticus* in urine cultures[a]

Addition	Viable cells ml^{-1} at 24 hr	Viable cells ml^{-1} at 48 hr
none	4.17 ± 0.28 x 10^7	1.86 ± 0.33 x 10^7
20 µg ml^{-1} curcumin	2.93 ± 0.24 x 10^7	1.72 ± 0.20 x 10^7
100 µg ml^{-1} berberine	3.99 ± 0.54 x 10^6	2.12 ± 0.82 x 10^4
20 µg ml^{-1} curcumin + 100 µg ml^{-1} berberine	<10	<10

[a]Viable counts reflect the means and standard deviations for three replicate cultures of each condition.

Discussion

Staphylococcus saprophyticus is an important Gram-positive urinary tract pathogen and is most often associated with community-acquired UTIs in adolescent or adult women [48-49]. These infections can be treated with commonly-used antibiotics including beta-lactams, ciprofloxacin, nitrofurantoin, and trimethoprim/sulfmethoxazole but resistant microbes can be recovered from infected individuals [50-51]. A key virulence factor for *S. saprophyticus* is the enzyme urease, which hydrolyzes urea to form ammonium [42]. This raises the pH and leads to the formation of urinary stones [52]. A number of chemical inhibitors of the *S. saprophyticus* urease have been identified, which fall into several different classes [53]. However, only one of these, acetohydroxamic acid (AHA) has been subjected to rigorous clinical trials and it not widely used because of its side effects [54]. As a result, there has been a great deal of interest in the identification of herbal extracts that might inhibit the urease activity and be used to treat UTIs. Because the urease from *S. saprophyticus* lacks any cysteine residues [55], only a small subset of these compounds actually inhibit its activity [44]. Curcumin was not among them.

Although curcumin does not inhibit urease activity, it has been tested as an antimicrobial agent for *S. saprophyticus* [38], and the minimum inhibitory concentration for different turmeric fractions in a rich medium was reported to be 2.5 mg ml^{-1}. The experiments described in this paper extend these results and gave a lower value of about 125 µg ml^{-1}. This study also indicated that the MIC in artificial urine medium is still lower, perhaps because growth is simply less extensive. The effectiveness of curcumin is limited by its low solubility in aqueous solutions and poor bioavailability. The mechanism of curcumin action is poorly understood, but it may be related to the nonpolar nature of the compound and its ability to insert into cellular membranes and damage them [56]. Berberine is an alkaloid with a very different structure, although it is able to damage cellular membranes and inhibit efflux pumps [57-58]. A combination of 100 µg ml^{-1} berberine with 20 µg ml^{-1} curcumin could completely inhibit the growth of *S. saprophyticus* in the rich P medium at pH 6.5. Berberine alone or 100 µg ml^{-1} berberine in combination with 20 µg ml^{-1} curcumin caused a partial inhibition of growth in artificial urine medium. More significantly, the combination of 20 µg ml^{-1} curcumin and 100 µg ml^{-1} berberine completely inhibited growth of *S. saprophyticus* in standing cultures of normal human urine.

Conclusions

The experiments described here indicate that the effectiveness of curcumin as an antimicrobial agent can be enhanced by combining it with berberine. A combination of curcumin and berberine has also been found to be an effective treatment for other diseases including infections by methicillin-resistant *Staphylococcus aureus* [59], obesity [60], liver disease [61], and Alzheimer's Disease [62]. Mixtures of curcumin and berberine are not commercially available, but physicians who are interested in treating urinary tract infections in a novel way may want to try them.

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Contributor Role

All of the experiments were designed and performed by Charles E. Deutch as was preparation of the manuscript.

Conflicts of Interest

The author declares there are no conflicts of interest.

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