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Full Length Research Paper

Antibacterial activity of indium curcumin and indium diacetylcurcumin

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Studies on curcumin, the principal element of turmeric powder, have demonstrated several biological actions such as antibacterial activity. Evaluation of new analogs or new compounds of curcumin for their antibacterial effect is interesting for researchers. In this *in vitro* study, we attempted to test the antibacterial activity of indium curcumin ($In(CUR)_3$), indium diacetylcurcumin ($In(DAC)_3$), and diacetylcurcumin (DAC) in comparison with curcumin. The action of these agents were examined on *Staphylococcus aureus* (ATCC 25923), *Staphylococcus epidermidis* (ATCC 14990), *Pseudomonas aeruginosa* (ATCC 27853), and *Escerichia coli* (ATCC 25922). Curcumin was effective against *S. aureus* and *S. epidermidis*, whereas $In(DAC)_3$ showed activity against *S. epidermidis* and *P. aeruginosa*. The effect of $In(DAC)_3$ on *P. aeruginosa* is an advantage. Strikingly, $In(CUR)_3$ exhibited antibacterial activity on all the four mentioned strains. DAC did not show antibacterial effect on any of the four test bacteria. The minimum inhibitory concentration (MIC) of curcumin was 187.5 µg/ml for *S. aureus,* and 46.9 µg/ml for *S. epidermidis*. However, the MIC of $In(CUR)_3$ was lower for the same bacterial strains (93.8 µg/ml for *S.aureus* and 23.4 µg/ml for *S. epidermidis*). Therefore, $In(CUR)_3$ was found to have more antibacterial effect than curcumin itself and could be a suitable candidate for further *in vivo* investigations.

Key words: Antibacterial activity, indium, curcumin, diacetylcurcumin.

INTRODUCTION

Development of bacterial resistance to the available antibiotics and increasing popularity of traditional medicine has led researchers to investigate the antibacterial compounds in plants. *Curcuma longa* is a medicinal plant that botanically is related to Zingberiaceae family (Chattopadhyay et al., 2004). Turmeric powder, derived from the rhizome of *C. longa*, is commonly used as a spice, food preservative, and food-coloring agent (Aggarwall et al., 2007; Di Mario et al., 2007; Menon and Sudheer, 2007). It also has a long history of therapeutic use (Chattopadhyay et al., 2004). Curcumin [1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione; Diferuloylmethane], a yellow bioactive pigment, is the major component of turmeric (Mohammadi et al., 2005; Menon and Sudheer, 2007; Hatcher et al., 2008). It has been shown that curcumin have a wide spectrum of biological actions such as anti-inflammatory (Punithavathi et al., 2000; Siddiqui et al., 2006), antioxidant (Mohammadi et al., 2005; Menon and Sudheer, 2007), anticancer (LoTempio et al., 2005), antidiabetic (Aggarwal et al., 2007), antiallergic (Suzuki et al., 2005), antiviral (Si et al., 2007), antiprotozoal (Reddy et al., 2005) and antifungal activities (Chattopadhyay et al., 2004). Moreover, anti- bacterial activity of curcumin has been reported (Chattopadhyay et al., 2004; Di Mario et al., 2007; Rai et al., 2008).

Synthetic modification of previously described antibacterial agents has been prominent in the development of new compounds which may possess an enhanced antibacterial activity or new pharmacological properties. There are reports on synthesis of mono-carbonyl analogues of curcumin (Liang et al., 2008) or preparation of bioactive conjugates of curcumin (Dubey et al., 2007) in

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order to increase antimicrobial and anticancer activity. Furthermore, it has been shown that indium curcumin complex (a metal complex of curcumin), diacetylcurcumin, and indium diacetylcurcumin have anticancer activity (Mohammadi et al., 2005). The objective of the present study was to evaluate the antibacterial activity of indium curcumin, indium diacetylcurcumin, and diacetylcurcumin compared with curcumin.

MATERIALS AND METHODS

Bacterial strains and maintenance procedure

Staphylococcus aureus (ATCC 25923), *Staphylococcus epidermidis* (ATCC 14990), *Psudomonas aeruginosa* (ATCC 27853), and *Escherichia coli* (ATCC 25922) were used as test organisms. The strains were cultured on brain heart agar (Merck, Germany). Afterwards, grown bacterial colonies were picked from the plate, suspended in sterile skim milk (Merck, Germany) containing 10% glycerol (Merck, Germany) and stored at -20ºC.

Antibacterial activity assay

The test agents in this study were curcumin, indium curcumin ($In(CUR)_3$), indium diacetylcurcumin ($In(DAC)_3$) and diacetylcurcumin (DAC). Curcumin (Sigma) was purchased and then, DAC, $In(CUR)_3$, and $In(DAC)_3$ were prepared as previously described (Mohammadi et al., 2005). Stock solution of the test agents were made up in DMSO (dimethylsulfoxide; Merck, Germany) to ensure complete solubilization (Mohammadi et al., 2005; Liang et al., 2008). The fresh culture of aforementioned strains was prepared and antibacterial activity of each test agent against each bacterium was examined as follows: in the test tube containing Mueller Hinton broth (Merck, Germany), a bacterial concentration of 5×10^5 colony forming units (CFU)/ml (Forbes et al., 2007) was tested with 375 µg/ml of the test agent. Moreover, a tube of the Mueller Hinton broth containing the same bacterial concentration, but without the test agent, was used as growth control, and another tube of the uninoculated Mueller Hinton broth containing the same concentration of test agent was used as negative growth control (Forbes et al., 2007). Also, a tube of Mueller Hinton broth containing the same bacterial concentration and DMSO, but without test agent, was prepared to control and rule out antibacterial effect of DMSO in the test tube. The test tube and three mentioned control tubes were incubated at 37ºC for 24 h. After incubation, antibacterial activity of test agent in the test tube was detected by lack of turbidity (matching the negative growth control) which indicating the inhibition of bacterial growth (Talaro and Talaro, 2002; Forbes et al., 2007).

Minimum inhibitory concentration (MIC)

Broth dilution method was used to determine the MIC of the test agents (Talaro and Talaro, 2002; Forbes et al., 2007). Test agents were added as serial dilutions to a series of tubes containing Mueller Hinton broth so that the concentrations ranged from 375 to 2.9 µg/ml. The bacterial concentration in each tube was 5×10^5 CFU/ml. Three kinds of controls, similar to that described above, were also prepared. After incubation (37ºC for 24 h), the lowest concentration of the agent that led to inhibit the growth of microorganism, was considered as MIC.

RESULTS AND DISCUSSION

In vitro antibacterial activity of $In(CUR)_3$, $In(DAC)_3$, and DAC in comparison with curcumin were investigated against *S. aureus*, *S. epidermidis*, *P. aeruginosa*, and *E. coli* (Table 1). The first step of the work was antibacterial activity assay with 375 µg/ml of each test agent. Curcumin was active against *S. aureus* and *S. epidermidis*, whereas it did not show antibacterial activity on *P. aeruginosa* and *E. coli*. Strikingly, $In(CUR)_3$ exhibited antibacterial effect against all the four test organisms. $In(DAC)_3$ was effective against *S. epidermidis* and *P. aeruginosa*. DAC was not found to be effective against the four mentioned bacteria. The positive results in the antibacterial activity assay were then examined for the determination of MIC (Table 1). The MIC of $In(CUR)_3$ for *S. aureus* and *S. epidermidis* was lower than the MIC of the curcumin for these bacteria. Furthermore, the MIC of $In(CUR)_3$ for *S. epidermidis* was lower when compared with $In(DAC)_3$. Meanwhile, *E. coli* was inhibited only by $In(CUR)_3$ (MIC: 93.8 µg/ml).

Curcumin, the main yellow bioactive component of turmeric powder, has been shown to have several biological effects such as antimicrobial activity (Chattopadhyay et al., 2005; Di Mario et al., 2007). Synthetic modification of antibacterial agents in order to improve antibacterial activity or pharmacological properties is an interesting field in studies. Synthesis of mono-carbonyl analogues of curcumin has been reported which some of these compounds exhibited more antibacterial activity than curcumin (Liang et al., 2008). Other researchers attempted to synthesis of some bioactive conjugates of curcumin which showed relatively more antimicrobial activity than curcumin itself due to their increased solubility, reduced metabolism and better cellular uptake (Mishra et al., 2005; Dubey et al., 2007).

Some metals are known for their antibacterial activity and in some cases as effective therapeutic agents against bacterial diseases. Indium is a major interest metal with antibacterial activity (David et al., 2005). Therefore, two new complexes, indium curcumin and indium diacetylcurcumin, were chosen for the present study.

As shown in Table 1, curcumin was effective against *S. aureus* and *S. epidermidis*, whereas indium curcumin showed antibacterial activity on all the four test organisms. Moreover, the MIC of $In(CUR)_3$ for *S. aureus* and *S. epidermidis* was lower than the MIC of curcumin for the same bacterial strains. Therefore, we found an enhancement in both spectrum and antibacterial activity of indium curcumin complex in comparison with curcumin itself. There is also similar effectiveness in other metal compounds such as silver sulfadiazine, a combination of two antibacterial agents, Ag^+ and sulfadiazine, which has a board spectrum of activity; binding to cell components such as DNA may be responsible for its inhibitory properties (Brooks et al., 2007). Furthermore, it has been shown that formation of metal complexes may lead to change in ability of uptake them by bacterial cells and thus enhance the antibacterial activity (David et al., 2005). Therefore, improve in cellular uptake and/or better binding to cell components could be the reason for increasing the antibacterial effect of indium curcumin.

Table 1. Antibacterial activity and MIC of curcumin, indium curcumin ($In(CUR)_3$), indium diacetylcurcumin ($In(DAC)_3$) and diacetylcurcumin (DAC).

Bacteria	Agent	Antibacterial activity	MIC (µg/ml)
S. aureus ATCC 25923	curcumin	+	187.5
	$In(CUR)_3$	+	93.8
	$In(DAC)_3$	–	
	DAC	–	
S. epidermidis ATCC 14990	curcumin	+	46.9
	$In(CUR)_3$	+	23.4
	$In(DAC)_3$	+	46.9
	DAC	–	
P. aeruginosa ATCC 27853	curcumin	–	
	$In(CUR)_3$	+	23.4
	$In(DAC)_3$	+	23.4
	DAC	–	
E. coli ATCC 25922	curcumin	–	
	$In(CUR)_3$	+	93.8
	$In(DAC)_3$	–	
	DAC	–	

$In(DAC)_3$ was found to be active against *S. epidermidis* and *P. aeruginosa*, but it did not exhibit antibacterial activity on *S. aureus* or *E. coli*. Thus, although $In(DAC)_3$ did not inhibit *S. aureus*, its activity against *P. aeruginosa* is an advantage of this compound over curcumin.

$In(CUR)_3$ showed more antibacterial activity than $In(DAC)_3$. In fact, the reason which suggests that the enhancement in both spectrum and antibacterial activity of $In(CUR)_3$ were not due to antibacterial effect of indium alone, is that we did not find a similar effect by $In(DAC)_3$. Thus, it seems that the roles of both curcumin and indium are essential in the action of $In(CUR)_3$.

In conclusion, indium curcumin complex has more antibacterial activity than curcumin and indium diacetyl-curcumin, and could be a suitable candidate for further *in vivo* investigations.

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