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Original article

Biological activity, design, synthesis and structure activity relationship of some novel derivatives of curcumin containing sulfonamides

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ABSTRACT

Five series of curcumin derivatives with sulfonamides **3a**–**3e**, **4a**–**4e**, **5a**–**5e**, **6a**–**6e** and **7a**–**7e** have been synthesized and evaluated for *in vitro* antibacterial activity against selected medically important gram-(+) and gram-(−) bacterial species viz. *Staphylococcus aureus*, *Bacillus cereus*, *Salmonella typhi*, *Pseudomonas aeruginosa* and *Escherichia coli*, and antifungal activity against few pathogenic fungal species viz. *Aspergillus niger*, *Aspergillus flavus*, *Trichoderma viride* and *Curvularia lunata*. The cytotoxicity has been determined by measuring IC_{50} values against human cell lines HeLa, Hep G-2, QG-56 and HCT-116. Among the compounds screened, **3a**–**3e** showed the most potent biological activity against tested bacteria and fungi. Compounds **3a**–**3e** displayed higher cytotoxicity than curcumin. The curcumin derivatives were also evaluated for *in vivo* anti-inflammatory activity. In contrast, the compounds **6a**–**6e** and **7a**–**7e** showed dramatically decrease in biological activity.

1. Introduction

Sulfonamides are the first antibacterial drugs [1], commonly known as sulfa drugs which were introduced clinically in 1934 as the first effective antibacterial drugs. Woods and Paul Flores suggested that sulfanilamide acts by inhibiting the enzyme that incorporates *p*-aminobenzoic acid into folic acid, hence acting as bacteriostatic drug [2]. Humans are not affected by the drug because they do not synthesize folate and get all requirements from diet.

Curcumin, a polyphenol, is an active component of the perennial herb *Curcuma longa* (commonly known as turmeric). The major components of turmeric are curcumin I (~77%), curcumin II (~17%) and curcumin III (~3%) [3]. The curcuminoids complex is also referred to as Indian saffron, yellow ginger, yellow root, kacha haldi, ukon or natural yellow, curcuminoids are present in 3–5% of turmeric. Though principally cultivated in India, Southeast Asia, China and other Asian and tropical countries and regions, turmeric is also common in other parts of the world and recognized by different names in different languages worldwide [4]. A literature survey reveals that curcumin, and its derivatives have various pharmacological activities and medicinal applications such as antioxidant [5], anticancer [6], anti-inflammatory [7], anti-Alzheimer's [8], anti-HIV [9], anti-angiogenesis [10], wound healing [11], antimicrobial [12], anti-venom [13], anti-protozoan [14], antiviral [15], hypoglycemic [16], anti-mutagenic [17], antifungal [18], anti-rheumatic [19], anti-malarial [20] and anti-diabetic [21].

Recently, it has been reported that curcumin derivatives show higher biological activity than curcumin Ref. [22]. Sulfonamides have pharmacological properties and antibacterial activity but bacteria have become resistant. Due to the above action of bacteria and fungi, it was planned that if biological activity of sulfonamides is combined with curcumin than it can lead to better activity as bacteria will not be resistant to new molecule. Thus synthesis and characterization of five new series of compounds was carried out and in *vivo* anti-inflammatory activity, *in vitro* antibacterial, antifungal and cytotoxic activities were evaluated. The possible structure activity relationship (SAR) for the synthesized compounds has been discussed.

2. Results and discussion

2.1. Chemistry

In the present study various sulfonamide molecules have been attached to various reactive sites of curcumin viz. on ketonic group/

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enolic groups (Fig. 1), on both dicarbonyl groups and active methylene group. All these synthesized molecules have been screened for their antibacterial, antifungal, anti-inflammatory and cytotoxic activity. In this paper various sulfonamides viz. sulfanilamide, sulfamethoxypyridazine, sulfamethoxazole, sulfapyridine and sulfadimidine have been used. The physicochemical and analytical data of the synthesized compounds are given in Table 1.

The synthetic pathways for the synthesis of the sulfonamides containing curcumin derivatives are illustrated in Schemes 1 & 2. The known starting compound curcumin was isolated according to our previously reported procedure [22]. 3-Sulfonamide curcumin and 3,5-disulfonamide curcumin derivatives were prepared by condensation of one molecule of sulfonamide and two molecules of sulfonamide respectively (Scheme 1). The sulfonamides were diazotized and coupled to curcumin. The products so formed were converted to pyrazoles and oxazoles by treating with phenylhydrazine and hydroxylamine hydrochloride respectively in ethanol using chitosan as catalyst (Schemes 1 & 2) at 60 °C.

The IR spectrum of compounds **3a**–**3e** and **4a**–**4e** revealed the absence of C=O stretching bond of curcumin at 1732 cm^{-1}, appearance of C=N stretching at 1628 cm^{-1}, and S=O stretching at 831 cm^{-1} indicates the participation of C=O in condensation and presence of band at 1628 cm^{-1} and 831 cm^{-1} indicates the presence of C=N bond and S=O respectively which is due to the presence of sulfonamide moiety in the targeted molecule (Scheme 1), furthermore, the disappearance of the primary amine band confirmed condensation of sulfonamides and curcumin at carbonyl group. The disappearance of free ketonic/enolic group band in the synthesized diazotized product confirmed pyrazoles and oxazole ring (Scheme 2). ^{1}H NMR spectra of pure curcumin showed a singlet of H of −OH group at 7.8 ppm, which disappeared in 3-sulfonamide, 3,5-disulfonamide, pyrazole and oxazole derivatives of curcumin which confirmed the condensation of sulfonamide molecule and formation of pyrazole and oxazole to the curcumin molecule. A singlet at 3.51 ppm attributed to protons of the active methylene (>CH_2) group of curcumin which disappears in the diazotized product of sulfonamide hence confirming the proposed Schemes 1 & 2.

2.2. Pharmacological activities

2.2.1. Antibacterial activity

Table 2 showed the antibacterial activity (zone of inhibition, minimum inhibitory concentration) of synthesized molecules against *Staphylococcus aureus, Bacillus cereus, Salmonella typhi, Pseudomonas aeruginosa, Escherichia coli*. Study has been carried out using **3a**–**e**, **4a**–**e**, **5a**–**e**, **6a**–**e**, **7a**–**e**, curcumin and the commercial antibacterial ciprofloxacin at the concentrations 80, 40 and 20 μM.

Compounds **3a**–**e** (MIC 20–40) and **4b**–**e** (MIC 40) exhibited antibacterial activity with greater zone of inhibition compare to curcumin and compounds **5a**, **5c**, **6a**, **6c**, **7a** and **7c** were totally inactive and remaining compounds showed moderate antibacterial activity against *S. aureus* than curcumin. Compounds **3b**–**d** (MIC 20) and **4b**–**e** (MIC 40) exhibited better antibacterial activity against *B. cereus* with greater zone of inhibition compare to curcumin. The compounds **5a**, **5c**, **6a**, **6c**, **7c** and **7d** were totally inactive and remaining compounds exhibited moderate antibacterial activity in comparison to curcumin. Curcumin derivatives **3a**–**e** (MIC 20–40) and **4a**–**e** (MIC 40) showed better antibacterial activity with greater zone of inhibition than curcumin. The compounds **5c**–**e** and **6a** were totally inactive, whereas remaining compounds showed moderate antibacterial activity against *S. typhi*. Compounds **3b** (MIC 20), **3e** (MIC 20), and **4a**–**e** (MIC 40) exhibited better antibacterial activity with greater zone of inhibition than curcumin. Compounds **6a** and **7a** were totally inactive and remaining compounds were moderately active against *P. aeruginosa*. The antibacterial properties of sulfonamides viz. sulfanilamide, sulfamethoxazole, sulfapyridine, sulfadimidine and sulfamethoxypyridazine were studied and the values of MIC have been reported in Table 2.

Synthesized compounds **3a**–**e** (MIC 20–40), **4b**–**e** (MIC 20–40) and **6b**–**e** (MIC 80) showed better antibacterial activity with greater zone of inhibition than curcumin, compounds **6a** and **7a** were totally inactive and remaining compounds showed moderate antibacterial activity against *E. coli*. Thus, from the antibacterial activity data, it is concluded that the antibacterial activity of inactive sulfonamides when combined with curcumin leads to increased activity. Still the activity was below the results observed with ciprofloxacin. These molecules need further modification.

2.2.2. Antifungal activity

Table 3 showed the antifungal activity (zone of inhibition, minimum inhibitory concentration) activity against *Aspergillus niger*, *Aspergillus flavus*, *Curvularia lunata*, *Trichoderma viride* of the compounds **3a**–**e**, **4a**–**e**, **5a**–**e**, **6a**–**e**, **7a**–**e**, curcumin and the commercial antifungal fluconazole at the concentrations 80, 40 and 20 μM.

Synthesized curcumin derivatives **3c**–**e** (MIC 20–40), **4d** (MIC 40), **5c** (MIC 40) and **5e** (MIC 40) showed better antifungal activity with greater zone of inhibition than curcumin, compounds **6a**–**e** and **7a**–**c** were totally inactive, whereas compound **4d** (MIC > 80), **7e** (MIC > 80) did not show any zone of inhibition and remaining compounds showed moderate antifungal activity against *A. niger*. Compounds **5c**–**e** (MIC 40) showed better antifungal activity with greater zone of inhibition against *A. flavus*, compounds **3a**, **4a**, **6a**–**e**, **7a** and **7b** were totally inactive and remaining compounds showed moderate antifungal activity than curcumin. Compounds **3b** (MIC 80), **3c** (MIC > 80), **3d** (MIC 20), **3e** (MIC 20), **4b**–**e** (MIC 20–80), **5b**–**e** (MIC 20–80), **6b**–**e** (MIC 20–80) and **7e** (MIC 80) showed better antifungal activity with greater zone of inhibition against *C. lunata* and remaining compounds showed moderate antifungal activity than curcumin and sulfonamides. Compounds **3b**–**e** (MIC 20–80), **4b**–**e** (MIC 20–40), **5b**–**e** (MIC 20–80), **6b**–**e** (MIC 20–40) and **7e** (MIC 80) showed better antifungal activity with greater zone of inhibition and remaining compounds showed moderate antifungal activity against *T. viride* than curcumin. The antifungal properties (zone of inhibition and MIC) using sulfonamides viz. sulfanilamide, sulfamethoxazole, sulfapyridine, sulfadimidine and sulfamethoxypyridazine was studied but no observable results were obtained.

Based on above observations, it can be concluded that, newly synthesized sulfonamides containing curcumin derivatives exhibited greater antifungal activity against *A. niger*, *A. flavus*, *C. lunata* and *T. viride*. Moreover, curcumin and fluconazole did not show antifungal activity against *A. niger* and *A. flavus*, whereas synthesized compounds exhibited better antifungal activity against all tested fungal species.

2.2.3. Cytotoxic activity

The results of cytotoxic activity comprise in Table 4 showed that compounds **3b**–**e** were comparatively more cytotoxic against all

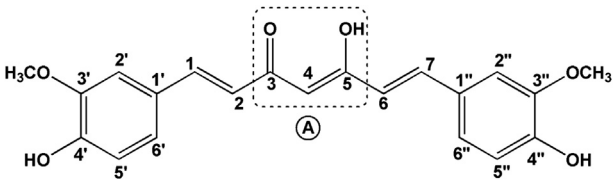

Fig. 1. Showing reactive moiety (A) of curcumin used in the experiment.