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Research Article

Antimicrobial and molecular interaction studies on derivatives of curcumin against *Streptococcus pneumoniae* which caused pneumonia

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ABSTRACT

Background: The antimicrobial properties and molecular interaction analysis of curcumin and its derivatives against three different strains of *Streptococcus pneumoniae* (Penicillin-susceptible, Penicillin-intermediate and Penicillin-resistant) are studied.
Results: These properties were analyzed based on the measurement of the inhibition zone, minimum inhibitory concentration (MIC), and rate of kill revealed that curcumin monoglucoside, curcumin diglucoside and curcumin possessed strong antimicrobial properties even on the Penicillin-resistant strains. Additionally, the molecular docking simulation analyses against Penicillin Binding Protein of *S. pneumoniae* also confirm that these compounds docked at the active site of the enzyme. Further, the molecular dynamics simulation validates the conformational stability of the docked ligand–protein complexes in the dynamic environment.
Conclusion: curcumin monoglucoside, curcumin diglucoside and curcumin can be prescribed for treatment against Penicillin-resistant *S. pneumoniae*.

1. Introduction

Streptococcus pneumoniae is a Gram-positive, alpha-hemolytic and facultative anaerobic bacterium which belongs to *Streptococcus* genus [1]. The bacterium is usually present in the human's upper respiratory tract. It is considered as one of the human pathogens for severe infections causing life threatening diseases such as pneumonia, meningitis and sepsis among infants and young children [2,3]. In the recent years, there has been an alarming rise in antibiotic-resistant *S. pneumoniae* strains which has lead to a major concern. Also, the emergence of multi drug resistant strain against the commonly used antibiotics has been observed in several cases. Hence, there is a necessity for developing a novel antibiotic or novel drug or a vaccine. Also, the limitations of recently developed vaccines (protein-capsular polysaccharide conjugate) have kept no choice for the researchers and the scientific community to focus on the developing new therapeutics or novel drug for the anti-biotic resistant *S. pneumoniae* strains [4,5,6]. In the recent year's curcumin, a principal component of turmeric (*Curcuma longa*) and their derivatives has been widely studied because of their potential activity against many diseases such as cancer, Alzheimer's disease, anti inflammatory etc [7,8,9,10]. There are also reports of curcumin possessing anti microbial property [11] which gained our attention on investigating the antimicrobial property of curcumin and its derivatives against three different strains of *S. pneumoniae*. In the present investigation, the antimicrobial activity of these compounds was evaluated against Penicillin-susceptible, Penicillin-intermediate and Penicillin-resistant strains of *S. pneumoniae* by estimating the zone of inhibition of the bacterial growth, Minimum Inhibitory Concentration (MIC) and rate of kill. Furthermore, a molecular docking simulation analysis was performed for curcumin and its derivatives against the Penicillin Binding Protein (PBP) of *S. pneumoniae* to understand the molecular interaction and binding mode of the docked compounds at the active site of the enzyme. The PBP of *S. pneumoniae* are known to involve in the final stages of the peptidoglycan synthesis, which is a major component of bacterial cell walls and essential for bacterial growth and cell division. Thus, Inhibition of PBPs will lead to the irregularities in cell wall structure such as elongation, lesions, loss of selective permeability, and eventual cell death and lysis. Moreover, there are reports of curcumin inhibiting the PBP of certain bacterial species. This enzyme has a penicillin-insensitive trans glycosylase N-terminal domain which is involved in the formation of linear glycan strands and a penicillin-sensitive transpeptidase C-terminal domain involved in cross linking of the peptide subunits [12,13,14]. Furthermore, the docked compounds from the molecular docking result were validated by

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performing a 20 ns molecular dynamics simulation using Gromacs 5.0 [15].

2. Materials and method

2.1. Pathogens

Three *S. pneumoniae* strains used in the present study are the clinical isolates from three different patients of the Department of Respiratory Medicine, Zhangqiu Hospital of Traditional Chinese Medicine, Zhangqiu, 250200, Shandong, China. The descriptions of the strains used in the present study are described in Table 1 below.

2.2. Chemicals

Curcumin and its derivatives curcumin monoglucoside, curcumin diglucoside, hexahydrocurcumin, tetrahydrocurcumin, bisdemethoxycurcumin and demethoxycurcumin along with Penicillin G were purchased from ABI Chem, Germany (Table 6).

2.3. Anti-microbial activity

In the present investigation, curcumin and its derivatives were used to check the bacterial growth inhibitory potency which was determined by susceptibility test using the Kirby–Bauer disk following the protocol developed by Bauer et al. [16,17], and Pathak et al. [18], with slight modifications.

Initially, the samples were infused with a filter paper having a concentration of 250 μg/disk. The disks were then placed on the Mueller–Hinton agar (MHA) plates which were seeded with the target test strains. Penicillin G was used as a positive control. The plates were then kept for incubation at 37°C overnight. After incubation, the zone of inhibition was measured using an antibiotic zone scale. All the experiments were carried out in duplicates.

Further, the quantitative evaluation of the antibacterial activity of curcumin and its derivatives was estimated by MIC of these compounds based on the serial dilution method using micro-well following the protocol developed by Bauer et al. [16,17], and Pathak et al. [18], with slight modifications. The *S. pneumoniae* strains which were cultured in nutrient broth at 37°C overnight were used as the inoculums for estimating the MIC. The wells of the flat bottom 96 well culture plates were diluted with curcumin and its derivatives with different concentrations ranging from 0.0003–2 mg/mL. The wells were then treated with nutrient broth inoculums of the three *S. pneumoniae* strains for around 40–60 μL which was then incubated for overnight at 37°C along with Penicillin G as the positive control and the absorbance was measured at 600 nm.

2.4. Determination of rate of kill

This assay was performed to evaluate the rate of killing *S. pneumoniae* strains by the compounds following the protocol described by Eliopoulos [19] and Cruishank et al. [20]. The compounds were then loaded with McCartney bottles with 10 mL of Mueller Hinton broth at 1× MIC and 2× MIC. The inoculums density having 95 cfu/mL, approximately was further verified by total viable count, and 10 mL volumes of the inoculate bottles. The bottles were then incubated on an orbital shaker at 37°C at 120 RPM. Finally, 100 μL of the aliquot was removed from the culture medium at 5 h and 10 h for the determining the cfu/mL by the plate count technique [21] by plating out 25 μL of the dilutions. The emergent bacterial colonies were counted after incubating at 37°C for 24 h and its cfu/mL was calculated.

Table 1
S. pneumoniae used in the present study.

SN	Strain name	Penicillin resistance
1	SPCH-02	Susceptible
2	SPCH-24	Intermediate
3	SPCH-45	Resistant

2.5. Molecular docking simulation

In the present study, the author's have also performed molecular docking simulation studies of curcumin and its derivatives along with Penicillin G against *S. pneumoniae* PBP to understand the molecular interaction analysis of these compounds and its binding site. For these purposes, the two dimensional structure of curcumin and its derivatives along with Penicillin G was downloaded from the National Center for Biotechnology Information PubChem database [22]. The two dimensional structures were then converted into three dimensional format (sybyl moL2) using ChemOffice 2010 (ChemOffice 2010, CambridgeSoft Corporation, Cambridge, MA, USA) (Table 5).

On the other hand, the X-ray crystal structure of *S. pneumoniae* PBP (PDB ID: 2XD5) was downloaded from the RCSB Protein Data Bank (http://www.rcsb.org/). The potential ligand binding site of the PBP enzyme was predicted using Molegro Virtual Docker 5.0 [23] and the binding site has a volume of 233.984 A3 and a surface area of 701.44 A2. Also, the binding site was set inside a restricted sphere of X: 38.16, Y: 22.31, Z: 62.03 having a radius 14 A with a grid resolution of 0.30 A. For the molecular docking purposes, the compounds were then loaded in Molegro Virtual Docker 5.0 and its bond flexibility was set along with the side chains of the amino acid which were also set inside the restricted sphere. The flexibility was set with a tolerance of 1.10 and strength of 0.90. The RMSD threshold for the multiple cluster poses was set at 2.00 A with 100.00 energy penalty values. The docking algorithm was set for a maximum of 1500 iteration with a simplex evolution size of 50. The docking simulation was run for at least 50 times for 10 poses and the best poses were selected based on the scoring function such as the Rerank score, Moldock score and interaction energy [24].

2.6. MD simulation

The 2XD5 enzyme and the protein-ligand complexes viz. 2XD5-curcumin diglucoside, 2XD5-curcumin monoglucoside, 2XD5-curcumin complexes and 2XD5-Penicillin complex (control) were carried out for a molecular dynamics simulation. Initially, the system of 2XD5 and 2XD5-ligand complexes was minimized using steepest descent energy minimization and equilibrated for at least 100 ps with NVT (Canonical) and NPT (Isothermal-isobaric) ensemble equilibration for 5000 steps. Finally, the equilibrated systems were subjected to 20 ns MD simulation production. The trajectory file was processed and the RMSD graph was plotted for 2XD5-and the 2XD5-ligand complexes. All simulations were performed in Ubuntu Linux 14.0 LTS with intel i5 processor using GROMACS 5.0 with GROMOS96 43a1 force fields [15].

3. Results

The antimicrobial screening carried out against the *S. pneumoniae* strains revealed curcumin monoglucoside, curcumin diglucoside and curcumin exhibit a strong anti microbial property against all the three *S. pneumoniae* strains. The zones of inhibition of these compounds were found in more than that of Penicillin G (control) which is shown in Table 2. The zone of inhibition of these compounds was more than 20 mm in the Penicillin-resistant *S. pneumoniae* strain. On the other hand, bisdemethoxycurcumin, demethoxycurcumin and tetrahydrocurcumin showed no zone of inhibition in the Penicillin-resistant strain. These three compounds also developed a zone of inhibition, which is less than the threshold value of

Table 2
Zone of inhibition and MIC values of Curcumin and its derivatives against Penicillin-Susceptible, Penicillin-Intermediate and Penicillin-Resistant strains of *S. pneumoniae*.

SN	Compound	Penicillin-susceptible		Penicillin-intermediate		Penicillin-resistant	
		ZI (mm) 250 μg/ml	MIC (μg/mL)	ZI (mm) 250 μg/mL	MIC (μg/mL)	ZI (mm) 250 μg/mL	MIC (μg/mL)
1	Bisdemethoxycurcumin	15	200	13	200	13	200
2	Curcumin	20	10	20	15	>20	>15
3	Curcumin diglucoside	22	7	24	10	>20	10
4	Curcumin monoglucoside	25	5	25	5	>20	10
5	Demethoxycurcumin	–	100	–	100	–	>100
6	Hexahydrocurcumin	–	200	–	200	–	200
7	Penicillin G (control)	18	15	15	20	–	>50
8	Tetrahydrocurcumin	10	80	–	80	–	80

>12 mm which is shown in Table 2 which is considered to be inactive.

Furthermore, to understand the factors which affect the microbial growth inhibition of the *S. pneumoniae* strains the MIC was evaluated against curcumin and its derivatives (shown in Table 2). Curcumin monoglucoside exhibited an MIC of 5 μg/mL each for Penicillin-susceptible and Penicillin-intermediate strains and 10 μg/mL for Penicillin-resistant strain. Curcumin diglucoside and curcumin also exhibited an MIC of 10 μg/mL and >15 μg/mL against the Penicillin-resistant strain. While the MIC values of bisdemethoxycurcumin and hexahydrocurcumin was more than 200 in the Penicillin-resistant strain (Table 2). Also, the results of time kill studies are presented in Table 3. The data are presented in terms of the Log10 cfu/mL which are based on the conventional bactericidal activity standard and greater reduction in the viable colony count.

From the molecular docking simulation studies of curcumin and its derivatives against PBP (PDB ID: 2XD5) of *S. pneumoniae*, it is revealed that curcumin diglucoside, curcumin monoglucoside, and curcumin docked at the active site of the PBP enzyme of *S. pneumoniae* with a favorable Rerank score and docking score compared to Penicillin G (Table 3). The docking result also correlated with the MIC values and zone of inhibition values of these compounds and the details of the ligand–protein interaction analysis are shown in Table 4. The interacting atoms of the amino acid residues and ligand atoms along with their interaction energy and interaction distances are measured and shown in Table 4. Also, Fig. 2, Fig. 3, and Fig. 4 depict the binding mode and electrostatic interaction map of these docked compounds at the binding cavity of PBP.

Further, the result of trajectory analysis of the RMSD backbone of 2XD5, 2XD5–curcumin diglucoside, 2XD5–curcumin monoglucoside, 2XD5–curcumin and 2XD5–Penicillin complexes is plotted in a graph (shown in Fig. 1). The conformational stability of the 2XD5 and 2XD5–ligand complexes in the dynamic behavior is represented in the graph.

4. Discussion and conclusion

From Table 2, it is inferred that curcumin monoglucoside and curcumin diglucoside possessed excellent activity in all the three strains of *S. pneumoniae* (Penicillin-susceptible, intermediate and resistant) strains developing the maximum zone of inhibition, which is shown in Table 2. Moreover, their zone of inhibition was more than 12 mm which are the threshold value to be considered as an active compound. Curcumin also possessed good activity with a zone of inhibition of 20 mm in all the three *S. pneumoniae* strains (Table 2). Meanwhile, Penicillin G (control) showed activity in Penicillin-susceptible and intermediate strains with negative or no activity in the Penicillin-resistant strain.

On the other hand, no zone of inhibition or no activity was observed in demethoxycurcumin, hexahydrocurcumin and tetrahydrocurcumin in the Intermediate and Resistant strains. While the bacterial growth diameter was 16 mm, 14 mm and 13 mm respectively in the case of Penicillin susceptible strain for demethoxycurcumin, hexahydrocurcumin and tetrahydrocurcumin.

Again from the MIC assay, the maximum zone of inhibition exhibited an MIC of 5 μg/mL for susceptible and intermediate strains and 10 μg/mL against resistant strains. Meanwhile, curcumin diglucoside inhibited the bacterial growth at a 7 μg/mL for the susceptible strain and 10 μg/mL each for the intermediate and resistant strain (Table 2). Curcumin also exhibited an MIC of 10 μg/mL, 15 μg/mL and >15 μg/mL for the susceptible, intermediate and resistant strains respectively. Meanwhile Penicillin G (Control) has an MIC of 15 μg/mL for the susceptible, and intermediate strain and >50 for the resistant strain. Overall, curcumin monoglucoside, which exhibits the maximum zone of inhibition, possessed the lowest MIC value for all the three strains. In addition, the MIC values of curcumin were found to be 17 μg/mL, 12 μg/mL, and 21 μg/mL against *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Klebsiella pneumonia*, respectively as reported by Gunes et al. [25]. There are also reports on the derivatives of curcumin possessing more potent antibacterial and antifungal activities than curcumin as described by Chun et al [26]. Also, Sahu et al. [11] reported the derivatives of curcumin also used as antibacterial showed maximum activity against *S. aureus* and *P. aeruginosa*. Thus, confirming that derivatives possessed more powerful anti-bacterial activity compared to curcumin.

Finally, from the antimicrobial activity screening results, it could be inferred that curcumin monoglucoside, curcumin diglucoside and

Table 3
Time kill assessment study of curcumin and its derivatives.

SN	Compound	Penicillin-susceptible				Penicillin-intermediate				Penicillin-resistant			
		Log_{10} Kill MIC		Log_{10} Kill 2× MIC		Log_{10} Kill MIC		Log_{10} Kill 2× MIC		Log_{10} Kill MIC		Log_{10} Kill 2× MIC	
		5 h	10 h	5 h	10 h	5 h	10 h	5 h	10 h	5 h	10 h	5 h	10 h
1	Bisdemethoxycurcumin	1.12	0.92	-0.52	-2.12	1.99	1.21	-0.72	-1.13	1.87	1.18	-0.79	-1.56
2	Curcumin	1.38	0.88	-0.32	-1.12	1.82	1.01	-0.61	-1.14	1.91	1.21	-0.82	-1.36
3	Curcumin diglucoside	1.12	0.92	-0.26	-2.91	1.14	0.98	-0.56	-1.19	1.83	0.92	-0.96	-1.69
4	Curcumin monoglucoside	0.92	0.77	-0.18	-2.54	1.55	1.01	-0.62	-1.95	1.72	1.21	-0.99	-1.41
5	Demethoxycurcumin	1.91	0.98	-0.53	-2.27	1.96	1.21	-0.45	-1.91	1.95	1.18	-0.84	-1.81
6	Hexahydrocurcumin	1.21	0.91	-0.51	-2.16	1.92	1.12	-0.73	-1.78	1.76	1.28	-0.78	-1.62
7	Tetrahydrocurcumin	1.07	0.98	-0.61	-2.97	1.74	1.09	-0.81	-1.92	1.84	1.23	-0.84	-1.77
8	Penicillin G (Control)	1.25	1.02	-0.43	-2.31	1.95	1.02	-0.62	-1.32	1.98	1.2	-0.79	-1.69

Table 4
Docking scores of curcumin and its derivatives with Penicillin G as the control.

Name	MolDock score[a]	Rerank score[b]	Interaction[c]	HBond[d]
Curcumin diglucoside	-152.33	-138.77	-202.30	-13.12
Curcumin monoglucoside	-163.70	-137.54	-195.45	-12.27
Curcumin	-150.47	-127.34	-166.04	-9.06
Penicillin G (control)	-135.95	-112.73	-139.09	-12.76
Tetrahydrocurcumin	-133.56	-109.20	-156.67	-7.92
Demethoxycurcumin	-140.25	-109.18	-144.44	-11.69
Bisdemethoxycurcumin	-128.71	-106.83	-145.07	-5.51
Hexahydrocurcumin	-127.10	-104.12	-142.80	-9.65

[a] Moldock score is derived from the PLP scoring functions with a new hydrogen bonding term and new charge schemes [18].
[b] The rerank score is a linear combination of E-inter (Van der Waals, steric, hydrogen bonding, electrostatic) between the ligand and the protein, and E-intra. (Van der Waals, hydrogen bonding, torsion, sp2–sp2, electrostatic) of the ligand weighted by pre-defined coefficients [18].
[c] The total interaction energy between the pose and the protein (kJ moL^{-1}).
[d] Hydrogen bonding energy (kJ moL^{-1}).

curcumin possessed strong antimicrobial activity against susceptible, intermediate and resistant strains of *S. pneumonia*.

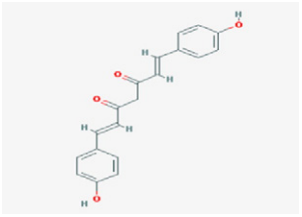
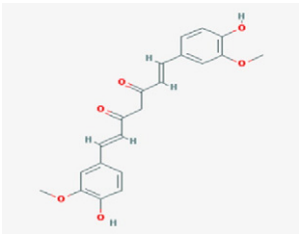
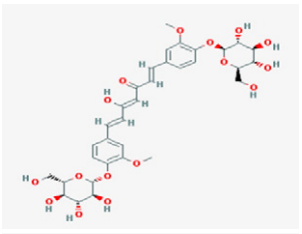
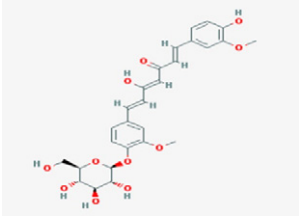
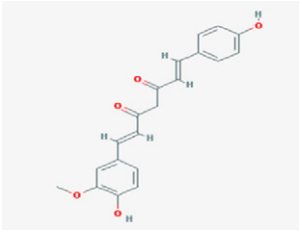
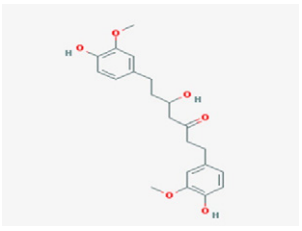
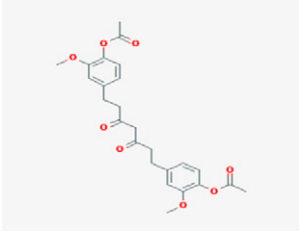
Furthermore, the average log reduction in viable cell count in time-kill assay ranges between -0.99 Log10 to -1.41 cfu/mL for curcumin diglucoside against the Penicillin-resistant strains after 10 h of interaction in 2× MIC. While curcumin monoglucoside ranges between -0.96 Log10 to -1.69 cfu/mL which confirm the validity of these derivatives acted upon the Penicillin-resistant strains (Table 3).

Additionally, the molecular docking simulation studies of curcumin and its derivatives against PBP (PDB ID: 2XD5) also confirmed the effectiveness and inhibitory property of curcumin monoglucoside, curcumin diglucoside and curcumin. The molecular docking result of these tested compounds is shown in Table 3 where the strength of the ligand–protein interaction is considered based on the Rerank score, which is defined as a linear combination of E-inter which is of Van der Waals, steric, electrostatic, hydrogen bonding, energy between

Table 5
Molecular interaction analysis.

Compound	Interaction	Interaction energy	Interaction distance (Å)
Curcumin diglucoside	Gln687(OE1)—O(3)	-2.5	2.94
	Asn656(O)—O(10)	-1.92	3.22
	Asn656(OD1)—O(10)	-0.04	2.65
	Asn656(ND2)—O(10)	-2.24	2.85
	Asn656(ND2)—O(0)	-1.83	3.23
	Ser457(OG)—O(6)	-2.1	2.72
	Gly559(N)—O(8)	-2.5	3.25
	Gly557(O)—O(8)	-2.1	3.38
	Ser460(OG)—O(14)	-1.4	3.30
	Asn518(ND2)—O(16)	-1.67	2.64
Curcumin monoglucoside	Gln687(N)—O(1)	-2.5	2.63
	Tyr690(N)—O(2)	-0.89	3.30
	Gln686(O)—O(2)	-2.1	2.68
	Ser460(OG)—O(7)	-1.73	3.47
	Lys463(NZ)—O(7)	-1.89	3.50
	Asn518(OD1)—O(7)	-1.5	3.05
	Ser460(N)—O(7)	-0.70	3.32
	Asn518(ND2)—O(10)	-1.23	3.04
	Thr654(OG1)—O(4)	-2.5	2.81
	Thr652(OG1)—O(6)	-2.14	3.00
	Val628(O)—O(5)	-2.47	2.63
Curcumin	Met556(O)—O(2)	-1.5	3.13
	Asn656(N)—O(0)	-2.18	3.05
	Ser460(OG)—O(4)	-0.78	2.90
	Thr654(N)—O(4)	-2.31	2.86
	Thr654(OG1)—O(4)	-2.11	3.47
	Ser516(OG)—O(5)	-0.94	3.13
	Asn656(N)—O(0)	-2.18	3.05
	Ser460(OG)—O(4)	-0.78	2.90
	Thr652(OG1)—O(5)	-2.5	2.98
	Gln686(O)—O(3)	-1.76	3.11
	Gln686(OE1)—O(3)	-2.1	3.13

Table 6
Structures.

SN	Compound	Structures
1	Bisdemethoxycurcumin	
2	Curcumin	
3	Curcumin diglucoside	
4	Curcumin monoglucoside	
5	Demethoxycurcumin	
6	Hexahydrocurcumin	
7	Tetrahydrocurcumin	

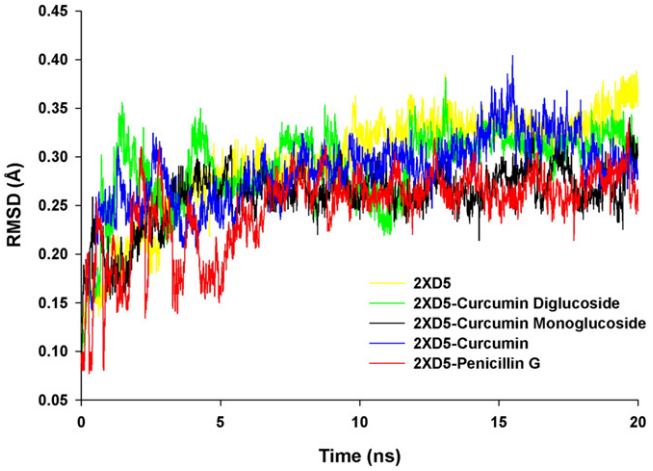


Fig. 1. RMSD backbone of 4XD5, 4XD5–curcumin diglucoside complex, 4XD5–curcumin monoglucoside complex, 4XD5–curcumin complex and 4XD5–penicillin G complex.

the ligand and the protein, and E-intra which is of Van der Waals, hydrogen bonding, torsion, electrostatic, sp2–sp2 energy of the ligand weighted by pre-defined coefficients [18]. From the docking result, curcumin diglucoside, curcumin monoglucoside, and curcumin formed bonds and non-bond interaction at the binding cavity of the PBP as evident from the interaction energy and hydrogen bonding energy (Table 4).

Moreover, the zone of inhibition values and MIC values corresponds with the docking scores of curcumin diglucoside, curcumin monoglucoside, and curcumin (Table 4). These compounds docked at the binding cavity with a Rerank score of -138.77 kJ moL^{-1}, -137.54 kJ moL^{-1} and -127.34 kJ moL^{-1} respectively.

Furthermore, to comprehend the deepness of the ligand-protein molecular interaction, the ligand energy inspector was employed for analyzing the ligand–protein interaction. The ligand–protein interaction analysis for curcumin diglucoside, curcumin monoglucoside and curcumin, which represents the interacting residues, interaction energy and interaction distances are shown in Table 4. The snapshots of the ligand–protein molecular interaction illustrating the binding mode of these compounds at the binding cavity of PBP and their electrostatic interaction map are shown in Fig. 2, Fig. 3, and Fig. 4 respectively.

Curcumin diglucoside formed molecular interaction with Ser457, Ser460, Asn518, Gly557, Gly559, Asn656 and Gln687 (Fig. 2); curcumin monoglucoside formed molecular interaction with Ser460,

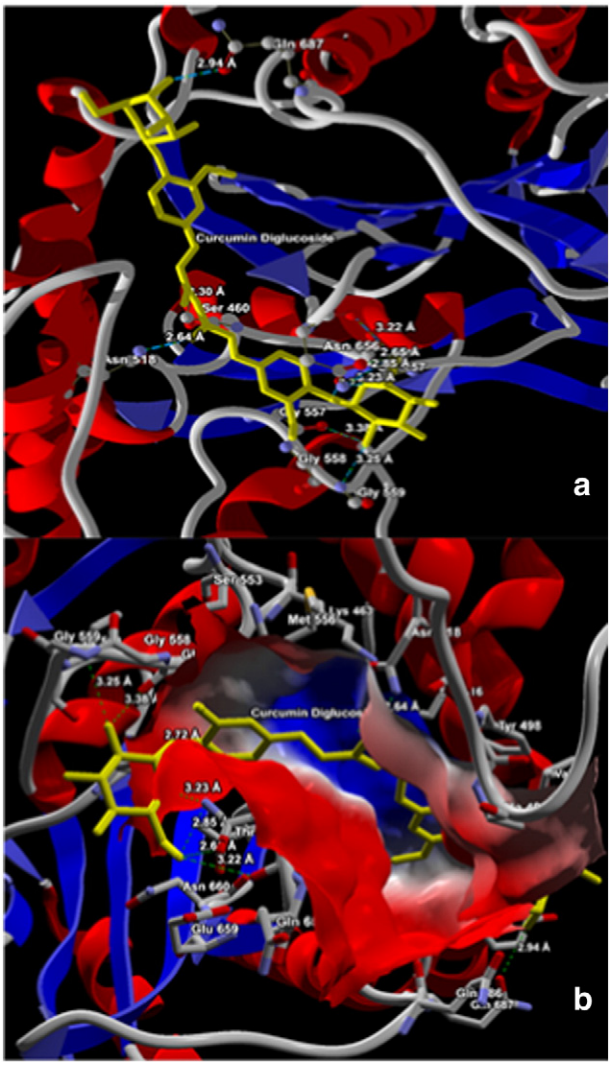


Fig. 2. a: Ligand–protein molecular interaction illustrating the binding mode of curcumin diglucoside (yellow color) at the binding cavity of PBP (PDB ID: 2XD5); b: Electrostatic interactions map of curcumin diglucoside (yellow color) at the binding cavity of PBP.

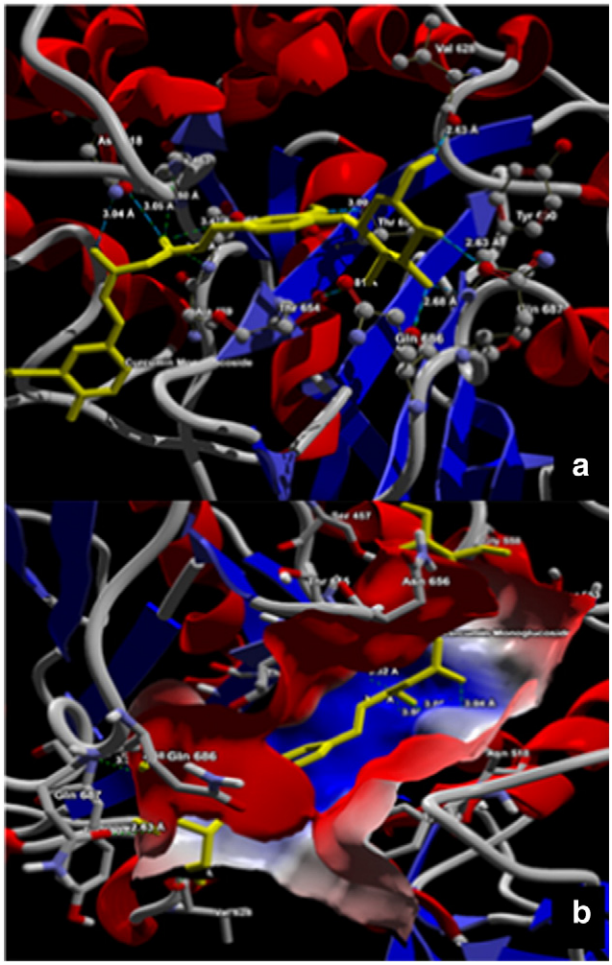


Fig. 3. a: Ligand–protein molecular interaction illustrating the binding mode of curcumin monoglucoside (yellow color) at the binding cavity of PBP (PDB ID: 2XD5); b: Electrostatic interactions map of curcumin monoglucoside (yellow color) at the binding cavity of PBP.

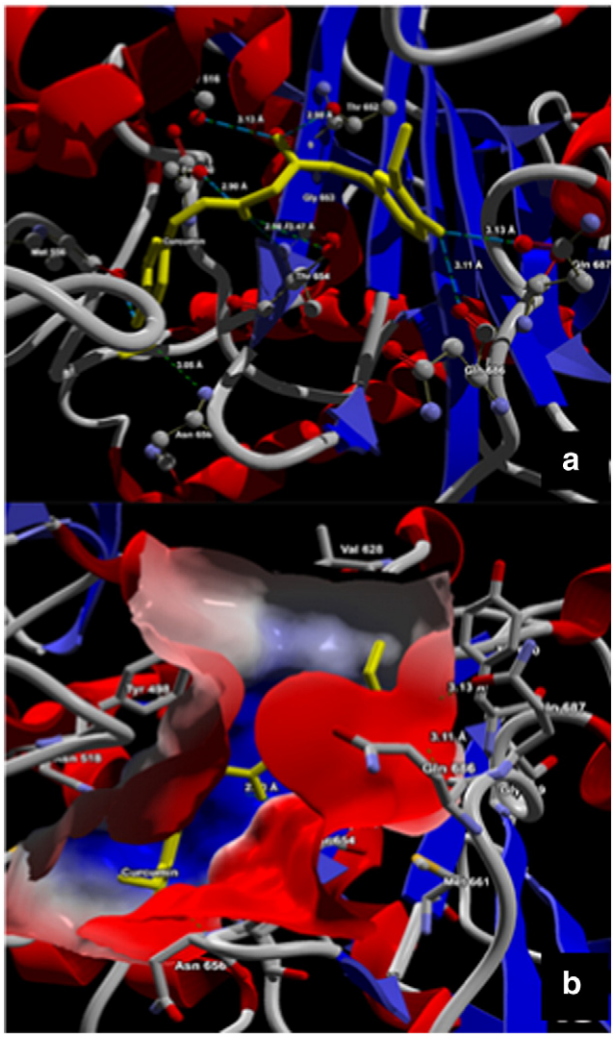


Fig. 4. a: Ligand–protein molecular interaction illustrating the binding mode of curcumin diglucoside; b: electrostatic interactions map of curcumin (yellow color) at the binding cavity of PBP.

Lys463, Asn518, Val628, Thr652, Thr654, Gln686, Gln687 and Tyr690 (Fig. 3), and curcumin formed molecular interaction with Ser460, Ser516, Met556, Thr652, Thr654, Asn656 and Gln686 (Fig. 4).

Lastly, from the molecular dynamics simulation analysis, the backbone root mean square deviation (RMSD) values of protein and the protein-ligand complex during 20 ns of MD simulations (Fig. 1), indicates the RMSD values for 2XD5-Monoglucoside ligand complex is more stable than 2XD5 and 2XD5-Penicillin G complex, indicating the conformational flexibility in the dynamic behavior.

To conclude, curcumin and its derivatives were evaluated for there antimicrobial property against Penicillin-susceptible, Penicillin-intermediate and Penicillin-resistant strains of *S. pneumoniae* where three derivatives possessed strong anti microbial property against all the three strains based on the diameter of the zone o inhibition and MIC values. The compounds were further screened for molecular docking simulation against the Penicillin Bonding protein (PDB ID: 2XD5) where the compounds exhibit favorable docking score compared to Penicillin G (Positive Control).

Again, from the 20 ns molecular dynamics simulation revealed that the 2XD5–curcumin diglucoside, 2XD5–curcumin monoglucoside and 2XD5–curcumin docked complexes showed stable RMSD backbone in the dynamic behavior. Hence, the authors conclude that curcumin and its derivatives curcumin diglucoside and curcumin monoglucoside can be prescribed in treating in Penicillin-Resistant strains of *S. pneumoniae*.

Conflict of interesting

The authors declare that there is no conflict of interest.

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