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Research Article

Antiviral Activity of Curcuminoids Derived from *Deverra tortuosa* Plant

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Curcuminoids are natural products with widespread biological activity mostly extracted from *Curcuma longa* and its family. In the current study, we report the first time to isolate curcuminoids from another phyto source. Three compounds (curcumin, desmethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC)) were isolated from the plant Deverra tortuosa using methanolic extract, which was then fractionated and separated by puriFlash. The purity of compounds was monitored by thin-layer chromatography and confirmed by high-performance liquid chromatography. The mass spectrometry identified the isolated compound by their electrospray ionisation. Molecular docking then demonstrated that curcumin and BDMC bind at the same cavity (187 Å) on SARS-CoV-2 M^{pro} protein indicating similarities while DMC binds to a cavity with a larger size (372 Å). Among the three curcuminoids, BDMC was shown to give the highest binding energy (−7.5 kcal/mol) followed by curcumin (−7.4 kcal/mol) and DMC (−7.3 kcal/mol). Calculating the half-maximal cytotoxic concentration and inhibitory median concentration of both DMC and BDMC showed low-to-moderate antiviral activity against SARS-CoV-2.

1. Introduction

The genus *Deverra* DC. (also known as *Pituranthos* Viv.) is an herbaceous widespread from Egypt to Iraq. In the Arabian Ecoregion, the species of the genus are known under the vernacular name "Shabbat al Jabel" and are well known in traditional medicine. Several studies explored the diverse properties and traditional uses of *Deverra* species including treatment of fever and diabetes [1], as natural biopesticides [2], antioxidant agent [3], source of essential phthalide derivatives [4], in wound healing [5] as well as antibacterial, antimicrobial, antifungal, and cytotoxic compound [6, 7]. Furthermore, a recent review detailed all the traditional uses of the plants, which include but are not limited to hypertension, stomachache, intestinal parasites, pain, hepatitis, digestive issues, and urinary infections [8]. The taxa, *Deverra tortuosa*, were recently shown to have potential antidiabetic activity and able to improve blood parameters when methanolic extract was used [9].

From the seeds of *D. tortuosa*, five chemicals were discovered for the first time: marmin 1, pituranthoside 2, isoimperatorin 3, bergapten 4, and isopimpinellin 5. IR spectroscopy, 1D and 2D NMR, and (ESI)-MS were used to clarify their structures [10].

Among the compounds that were found in the pet ether fraction of *D. tortuosa*, which grows in the coastal desert of West Alexandria, the most common classes are terpenes (7.75%), shikimates (20.01%), and acetogenins (3.72%) [11].

The ginger family of the plant turmeric (*Curcuma longa*) has also been involved heavily in both scientific and

traditional medicine for many years due to it being the main source of curcuminoids such as curcumin, desmethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) [12]. These three compounds share high structural similarity (Figure 1) with the presence of two phenolic OH groups linked in conjugation through the β-diketone moiety is thought to attribute the several properties of curcumin and its analogues both in solid and solution states [13]. Such similarity suggests all three may exhibit similar bioactivities, although, in canonical extraction of curcuminoids from turmeric, the highest percentage pertains to curcumin (70.07%) followed by DMC (20.28%) then BDMC (3.63%) [14].

They have been shown to possess many properties although curcumin is considered the most significant among them since it is shown to contain a multitude of uses such as antioxidant, anti-inflammatory, antimutagenic, antimicrobial, and anticancer properties [12, 15–19], to name a few. Furthermore, a review elucidated all the possibilities of curcumin as a potential medicine for numerous metabolic and clinical diseases [20], emphasizing its importance. Nevertheless, the use of curcuminoids as drugs is significantly restricted due to their poor absorption, rapid metabolism, and elimination, especially via the oral route [21–24].

Since its initial outbreak in 2020, coronavirus disease-19 (COVID-19), a highly contagious infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been considered a global pandemic with the World Health Organization (WHO) statistics indicate north of 772 million confirmed cases of COVID-19 including 6.9 million deaths [25]. Scientific research is exceptionally focused on isolating the virus and understanding its genetics for vaccine production or pharmacological-based treatments. Many studies published both routes with few even suggesting curcumin as potential therapy for COVID-19 [26–28].

In view of the high similarities between *D. tortuosa* and *C. longa* in term of pharmacological properties, it is intriguing to explore the potential of extracting curcuminoids from *D. tortuosa* instead of the canonical *C. longa* and test its antiviral properties against COVID-19.

2. Material and Methods

2.1. Plant Metrical. Plant metrical of *D. tortuosa* was collected from Arar Valley, Northern Border Region, Saudi Arabia, during the summer season of 2020. The sample was identified and named accordingly [29–31]. A voucher specimen (2020/7(DT1)) was deposited in the Department of Chemistry, Faculty of Science, Girls Section, Northern Border University.

2.2. Extraction. The stem part of *D. tortuosa*, (2 kg, collectively) was grounded to fine powder, pulverized, and then extracted for 0.5 hour by ultrasound in an 8-fold volume (w/v) of 80% ethanol and repeated three times. The ethanol solutions were combined and condensed by evaporation to yield 36 g. The extract was then fractionated using liquid-liquid partitioning performed on 10 g of the extract using hexane, dichloromethane, and ethyl acetate. The fractions of all three resulted in 3 g, 0.25 g, and 0.6 g, respectively. Thin-layer chromatography (TLC) was performed on all the fractions using mobile phase dichloromethane: methanol (9.5 : 0.5) [32, 33].

2.3. Purification. The preparative separation of dichloromethane extract was carried out using the puriFlash method; dichloromethane extract (1 g) was dissolved in dichloromethane and then introduced into the column via dry load using 3 g silica. 80 g Flash-NP column (30 μm) was used with dichloromethane : methanol (99 : 1) as the mobile phase. The compounds curcumin, DMC, and BDMC were eluted after 40, 60, and 80 CV, respectively. The identification and purification of each compound were established by TLC, high-performance liquid chromatography (HPLC), and liquid chromatography-mass spectrometry (LC-MS) [34]. Nuclear magnetic resonance (NMR) was also performed but to the DMC and BDMC only.

2.4. Devices Specification. Preparative separations were carried out with a puriFlash 4100 system (Interchim, Montluçon, France) consisting of a mixing HPLC quaternary pump, a PDA-UV-Vis detector 190–840 nm, a fraction collector, and a sample loading module. For system controlling and process monitoring, Interchim Software 5.0 was used.

The proton nuclear magnetic resonance (^{1}H NMR) and carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 500 MHz and at 125 MHz, respectively, in dimethylsulfoxide (DMSO)-d6 (Merck, Darmstadt, Germany) with tetramethylsilane as an internal standard using a BrukerAPX 500 MHz spectrometer. Chemical shifts δ are given in ppm; multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad); coupling constants, J, are reported in Hz. Liquid chromatography-mass spectrometry was verified on Acquity Ultra Performance LC (Waters, Milford, Massachusetts, United States) with ZQ detector in electrospray ionisation (ESI) mode. The UV studies for the compounds were measured on a Shimadzu UV-240 spectrophotometer, distinctly as solutions in methanol and with diagnostic UV shift reagents. Rotary evaporator (Buchi, Switzerland) was used for evaporation and concentration of extracts and fractions. Fractionation was performed by column chromatography using polyamide 6S (Riedel-De Hän Ag, Seelze Hannover, Germany), and compound isolation was completed on cellulose (Pharmacia, Uppsala, Sweden) and/or Sephadex LH-20 (Fluka, Switzerland) columns in diverse dimensions and eluted with various mobile phases. Separation procedures were monitored by TLC. Ultraviolet lamp (VL-215 LC, Marne La Vallee, France) was used for visualization of compound spots on TLC and follow up various column fractions on columns at 254 or 365 nm and with located (sprayed) $FeCl_3$ reagents. NMR spectra were recorded in

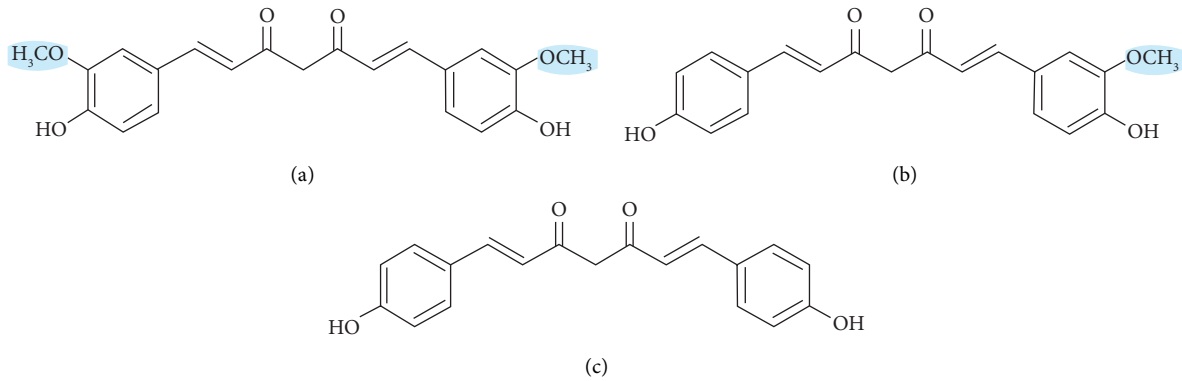


Figure 1: Chemical structure of the curcuminoids isolated from *D. tortuosa*. (a) Curcumin. (b) Desmethoxycurcumin. (c) Bisdemethoxycurcumin.

DMSO-d6. Using a JEOL MS (500 MHz) and 13C NMR (125 MHz) spectra, NMR spectra were recorded in DMSO-d6.

2.5. HPLC and LC-MS Analyses. The experiment was carried out by Waters 2690 Alliance HPLC system equipped with a Waters 996 photodiode array detector. The following specifications were applied: Scharlau C18 4.6 × 150 mm and 5 µm column, mode of elution : isocratic (50 : 50; 0.1% trifluoroacetic acid : acetonitrile), flow rate of 1.5 ml/min, ambient temperature, 425 nm wavelength.

The compact mass spectrometer (Advion, New York, United States) was used following these specifications: ion source: ESI, APCI, or APCI/ASAP; polarity: positive and negative ion switching in a single analysis; flow rate range: ESI: 10 μL/min to 1 ml/min, APCI: 10 μL/min to 2 ml/min, m/z range: Expression S m/z 10 to 1,200, acquisition speed: 10,000 m/z units/sec, ESI: 10 pg reserpine (FIA-5 μL injection at 100 μL/min) 100 : 1S/N with SIM of m/z 609.3, accuracy: ±0.1 m/z units of the entire acquisition range, stability: 0.1 m/z units at m/z 1,200 over 12-hour period operating temperature of 202°C ± 12°C, polarity switching speed: 50 ms, dynamic range: 4.5 orders of magnitude. Method: sample preparation was to dissolve the compounds in acetone prior to they were detected on TLC [35].

2.6. Docking Method. The Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB, https://rcsb.org) was used to acquire the cocrystal structure of SARS-CoV-2 M^{pro}-alpha-ketoamide, a protein-ligand combination of the ligand-binding domain of the SARS-CoV-2 main protease enzyme, and the alpha-ketoamide 13b inhibitor (PDB ID: 6Y2F). The CB-DOCK web server (https://cao.labshare.cn/cb-dock/) was used to investigate the compounds' docking, which needs a target protein in pdb format and ligands in MOL2, MOL, or SDF format. The server is a blind docking tool that automatically prepares the protein and ligands, transforms them to pdbqt format and uses the CB-DOCK server's curvature-based cavity identification algorithm. This method uses AutoDock Vina to execute molecular docking after automatically finding the binding sites, estimating the centre and size, and adapting the docking box size to the docking box size [36, 37].

2.7. SARS-CoV-2 Antiviral Activity

2.7.1. Cytotoxicity Assay. Stock solutions of the test compounds were produced in 10% DMSO in ddH_2O and further diluted to the working solutions with Dulbecco's Modified Eagle Medium (DMEM) in order to determine the half maximum cytotoxic concentration (CC50). With a few minor adjustments, the 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) technique was used to assess the compounds' cytotoxic activity in Vero E6 cells. The cells were seeded at a density of 3×10^5 cells/ml in 96 well plates with 100 μl of liquid per well and then incubated for 24 hours at 37°C with 5% CO_2. Cells were treated in triplicate with varying doses of the investigated substances after a 24-hour period. After 24 h, cells were treated with various concentrations of the tested compounds in triplicate. 24 h later, the supernatant was discarded, and cell monolayers were washed with sterile 1x phosphate buffered saline (PBS) three times, and MTT solution (20 μl of 5 mg/ml stock solution) was added to each well and incubated at 37°C for 4 h, followed by medium aspiration. In each well, the formed formazan crystals were dissolved with 200 μl of acidified isopropanol (0.04 M HCl in absolute isopropanol = 0.073 ml HCL in 50 ml isopropanol). Absorbance of formazan solutions was measured at λ max 540 nm with 620 nm as a reference wavelength using a multiwell plate reader [38]. The percentage of cytotoxicity compared to the untreated cells was determined with the following equation:

$$\text{Cytotoxicity\%} = \frac{(\text{absorbance of cells without treatment} - \text{absorbance of cells with treatment})}{\text{absorbance of cells without treatment}} \text{ X } 100. \quad (1)$$

Table 1: ^{1}H NMR, ^{13}C NMR, and coupling constant (J) of desmethoxycurcumin and bisdemethoxycurcumin.

	Desmethoxycurcumin		Bisdemethoxycurcumin	
	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR
H1, H1/	5.79	105	5.00	101.42
H2, H2/	6.86–6.89 ($J = 15$)	184	6.80–6.78	183.73
H3, H3/	6.50–6.46	120.51	6.55–6.68 ($J = 15$)	121.36
H4, H4/	7.72–7.76 ($J = 15$)	145.41	7.50–7.55 ($J = 15$)	140.88
H5, H5/	7.50–7.55	125.63	7.53	126.38
H6, H6/	7.26	115.25	6.80	116.45
H7	—	152.69	6.00	—
H7/	—	134.78	—	—
H8.8	9.8	164.55	10.0	160.32
H9, H9/	6.86 ($J = 8.2$)	—	6.68	130.22
H10, H10/	7.26	—	6.65–6.64	116.22
CH_3	3.8 s	—	—	—

2.7.2. Inhibitory Median Concentration Determination. 2.4×10^4 Vero-E6 cells were seeded into each well of 96-well tissue culture plates, and the plates were incubated for the entire night at 3°C in a humidified environment with 5% CO_2. After that, the cell monolayers were treated to one hour of room temperature viral adsorption (hCoV-19/Egypt/NRC-03/2020; accession number on GSAID: EPI_ISL_430820). This was followed by a single wash with 1x phosphate buffer saline. The test chemicals were added to 100 μl of DMEM that contained different concentrations and applied on top of the cell monolayers. After being incubated for 72 hours at 37°C in an incubator with 5% CO_2, the cells were fixed for 20 minutes with 100 μl of 4% paraformaldehyde and stained for 15 minutes at room temperature with 0.1% crystal violet in distilled water. Next, 100 μl of 100% methanol was used to dissolve the crystal violet dye using a multiwell plate reader). The inhibitory median concentration (IC_{50}) of the compound, which is required to reduce the virus-induced cytopathic effect (CPE) by 50%, was then calculated [39]. Both CC_{50} and IC_{50} values were then used to calculate the selectivity index (SI), which is CC_{50}/IC_{50}.

3. Results

Three curcuminoid compounds were isolated for first time from new source other than normal source, *Curcuma longa*, the compounds were isolated from dichloromethane fraction of methanol extract of plant *D. tortuosa* as shown in Figure S1 (Supplementary material), and antiviral activity of compounds was assayed by CPE inhibition assay.

3.1. Identification of the Curcuminoids. The three curcuminoids (curcumin, DMC, and BDMC) were separated with purity above 97%. Thin-layer chromatography was performed for all three compounds showing a single spot then the purity was confirmed by HPLC (Figures S2–S4).

3.2. Characterisation of the Curcuminoids. Compound 1: curcumin (20 mg) was identified to have molecular formula of $C_{21}H_{20}O_6$ and ESI-MS of 366.9 (Figure S5, supplementary material).

Compound 2: DMC (18 mg) was obtained as a yellow-orange powder after purification by HPLC, and after recyclization by MeOH, the purity 98% according to HPLC analysis, the structure was identified and confirmed by comparison of spectral data (1H NMR, 13C NMR, and MS) by previous literature [40], and molecular formula was C20H18O5. MS: 337 [M-H] as described in Figure S6, supplementary material.

Compound 3: BDMC (15 mg) was obtained as a yellow-orange powder after purification by HPLC, and after recyclization by EtOH, the purity 96% according to HPLC analysis, the structure was identified and confirmed by comparison of spectral data (^{1}H NMR, ^{13}C NMR, and MS) by literature [41], and molecular formula was $C_{19}H_{16}O_4$. MS: 307 (M-H) as described in Figure S7 supplementary material.

The ^{1}H NMR and ^{13}C NMR for DMC and BDMC demonstrated hydrogen atoms' position, the chemical shifts of the signals, and the corresponding coupling constants (Table 1).

3.3. Docking Study. Using the CB-DOCK tool, ten docking cavities were predicted on the SARS-CoV-2 M^{pro} (PDB ID: 6Y2F), and the three curcuminoids were docked to each cavity. The docking pose with the highest vina score was considered the best binding cavity (Figure 2). Molecular docking showed curcumin and BDMC binding at the same cavity (187 Å) on the target protein while DMC binding at a different cavity (372 Å). Among the three curcuminoids, BDMC showed the best binding energy of −7.5 kcal/mol followed by curcumin (−7.4 kcal/mol) and DMC (−7.3 kcal/mol). Each of the three curcuminoids showed binding to nine or ten amino acid residues on the target protein via

Table 2: Docking results of the curcuminoids with SARS-CoV-2 M^{pro} protein.

Compound	Vina score	Cavity size (Å)	Centre			Size			Binding residues
			X	*Y*	*Z*	*X*	*Y*	*Z*	
Curcumin	−7.4	187	−15	−9	13	27	27	27	Chain A: GLU240[a], ILE200[b], VAL202[b], HIS246[c], ASN202[a], PRO293[a], GLN110[b], THR292[b], PHE294[b], ASN151[a]
DMC	−7.3	372	−14	4	6	24	24	24	Chain A: ASN151[a], THR111[a], ASP295[a], PHE294[b,c], ILE249[b], VAL202[a], GLY109[a], GLN110[b], THR292[b]
BDMC	−7.5	187	−15	−9	13	27	27	27	Chain A: GLU240[a,b], HIS246[c], ILE200[b], VAL202[b], ASN203[a], THR292[b], GLN110[b], PHE294[b], ASN151[a]

[a]Hydrogen bond, [b]hydrophobic bond, and [c]pi-pi interaction.

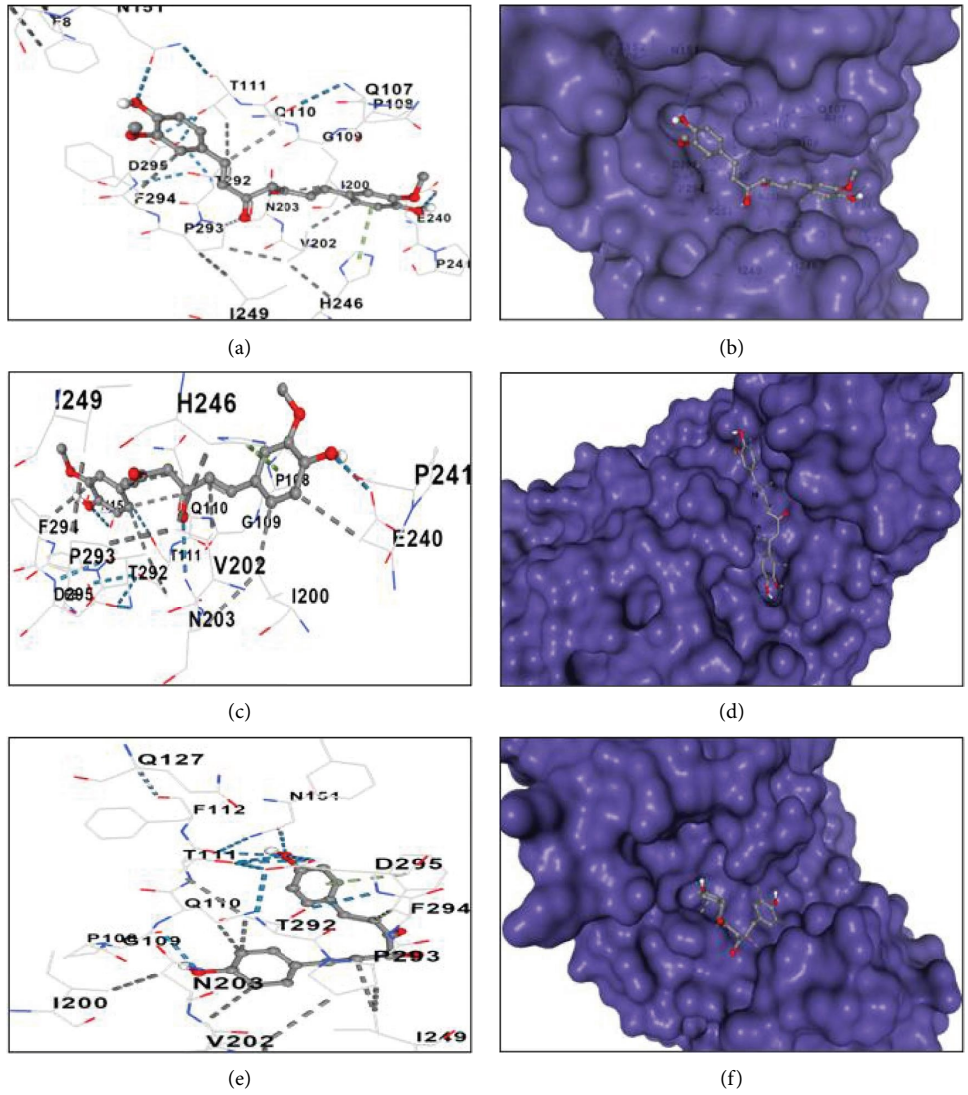


FIGURE 2: Docking positions of curcuminoids. (a) Stereochemistry of curcumin and its bonds with amino acids in the protein cavity. (b) 3D representation of curcumin docking with SARS-CoV-2 M^{pro} cavity. (c) Stereochemistry of DMC and its bonds with amino acids in the protein cavity. (d) 3D representation of DMC docking with SARS-CoV-2 M^{pro} cavity. (e) Stereochemistry of BDMC and its bonds with amino acids in the protein cavity. (f) 3D representation of BDMC docking with SARS-CoV-2 M^{pro} cavity.

hydrogen bond, hydrophobic bond, and/or pi-pi interaction with some residues being common between the three curcuminoids (Table 2). Curcumin and BDMC shared eight amino acid residues (GLU240, ILE200, VAL202, HIS246, GLN110, THR292, PHE294, and ASN151) while DMC only shared five amino acid residues with curcumin and BDMC (ASN151, PHE294, VAL202, GLN110, and THR292).

3.4. Antiviral Activity. Both DMC and BDMC showed low antiviral activity with IC_{50} of 97 ± 1.25 and $105 \pm 1.22\ \mu g/ml$, respectively, as well as CC_{50} of 357 ± 1.15 and $319 \pm 1.18\ \mu g/ml$, respectively. The SI was calculated at 3.68 for DMC and 3.04 for BDMC as shown in fig 3.

Not DMC or BDMC, but curcumin, one of the main derivatives of curcuminoid, is the ingredient that gives the plant its activity, whereas BDMC is a more highly active molecule than curcumin and DMC, according to the docking results.

4. Discussion

Curcuminoids (curcumin, DMC, and BDMC as the main compounds) have been the centre of extensive research given their plethora of properties and uses. All of which have them as the main extract of *C. longa* (turmeric). The novelty of this study is to find an alternative for curcuminoid extraction and test its similarities against the body of literature. The *D. tortuosa* was the chosen plant given the shared

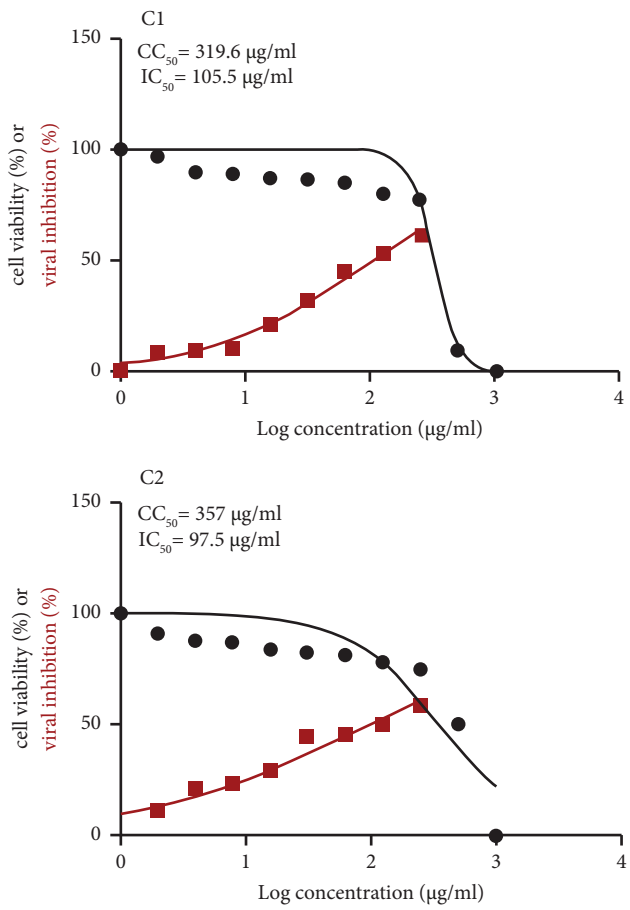


FIGURE 3: CC_{50} and IC_{50} of curcuminoid compounds C1 (BDMC) and C2 (DMC).

properties and activities with the turmeric. The extracted compounds were identified by comparing spectral data (NMR and ESI-MS) with literature [40, 41]. In addition, ^{1}H NMR and ^{13}C NMR data for DMC and BDMC also concord their characterisation with previous literature [42, 43], confirming the novelty of extracting curcuminoids from *D. tortuosa* rather than the canonical *C. longa*.

To avoid redundancy given the established potential of curcumin as antiviral agent against COVID-19, only DMC and BDMC were tested for antiviral activity against the SARS-CoV-2 protein. Both DMC and BDMC have relatively high IC_{50} values, indicating low-to-moderate antiviral activity compared to curcumin from literature (IC_{50} of ~23.73 μg/ml and CC_{50} of 44.83 μg/ml) tested against SARS-CoV-2 [44–46]. Even though it was not as strong as curcumin, the antiviral activity of DMC and BDMC against SARS-CoV-2 is in line with earlier research on the two compounds that were isolated from *C. longa* [42, 43]. The plausible explanation for DMC and BDMC having lower antiviral capabilities compared to curcumin might be due to the absence of the methoxy group in them, which, in turn, decreases the stability of the keto-enol structure [27, 47].

Taken together, the results confirm *D. tortuosa* as a new source of curcuminoids and imply the possible use of them as antiviral agents against COVID-19.

5. Conclusion

The first-time isolation of curcuminoid compounds from a new natural source other than the usual source represents good work due to the high importance and biological activity of curcumin derivatives. The analysis of compounds was performed spectroscopically (^{1}H NMR, ^{13}C NMR, and MS). Moreover, puriFlash method and TLC were developed for rapid qualitative and quantitative analysis of chloroform extract, antiviral activity against SARCOv-19 was assayed, BDMC and DMC compounds show low activity when compared with curcumin, and docking results demonstrate that curcumin and BDMC bound at the same cavity of the target protein having the same cavity size (187 Å) while DMC bounds to a cavity with different sizes (372 Å). Among the three compounds, BDMC was shown to have the best binding energy, followed by curcumin and DMC, respectively. Further analysis and *in vivo*/*in vitro* experimentation are recommended for the future.

Data Availability

All data generated or analysed during this study are included in this published article.

Conflicts of Interest

All authors declare that they have no conflicts of interest.

Acknowledgments

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Supplementary Materials

Figure S1: isolation and identification methods of isolated compounds. Figure S2: HPLC chromatogram of curcumin. Figure S3: HPLC chromatogram of desmethoxycurcumin. Figure S4: HPLC chromatogram of bisdemethoxycurcumin. Figure S5: mass spectrum of curcumin. Figure S6: mass spectrum of desmethoxycurcumin. Figure S7: mass spectrum of bisdemethoxycurcumin. (*Supplementary Materials*)

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