Molecular Structure, Interactions and Antimicrobial Properties of Curcumin-PLGA Complexes – A DFT Study

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Abstract

Density functional calculations are performed to study the molecular structure, interactions, and antimicrobial activity of curcumin-poly Lacto glycolic acid (Cur-PLGA) complexes. The calculations are performed on curcumin, Glycolic acid (SSC and AAT conformers), Lactic acid (LA), Cur-SSC, Cur-AAT, Cur-LA, and Cur-PLGA complexes using dispersion corrected M06-2X functional with 6-31 + G* basis set. The condensed Fukui functions of curcumin are calculated to identify the favorable reactive sites. Inter- and intramolecular H-bond interactions are analyzed in detail through natural bond orbital, Atoms in Molecule, and Reduced density gradient analyses. The interaction energy values indicate that the interaction between curcumin and AAT is stronger than the other studied complexes. Further, our calculations show that the PLGA interacted with curcumin is having lower LUMO energy and density values. This indicates that the antimicrobial activity is high in this complex.

Introduction

Curcumin is the dried rhizome of the plant *Curcuma domestica* [1]. The Food, Agriculture, and World Health Organization have approved curcumin as a food additive product [2]. It is used as a herbal supplement, coloring agent, and flavoring in food, and as a cosmetic ingredient [3]. Further, it has a wide range of therapeutic properties in medicinal activities such as anti-inflammatory [9], anti-amyloid [7], anticancer [4], anti-ischemic [8], antimicrobial [6], antioxidant [5] activities, etc. Poly(lactic-co-glycolic acid) (PLGA) is an a popular polymeric material known for its unique properties over other amphiphilic materials. [10–13]. PLGA and other similar materials like PGA are used as a drug carrier in targeted cancer therapy [14–16].

The combination of curcumin and PLGA in the complex form was studied both experimentally [17–24] and theoretically [25–27]. Earlier, Mukerjee *et al.* have studied the curcumin-loaded PLGA for cancer therapy using experimental techniques. They have concluded that PLGA can be used as a drug carrier [17]. Later, Song *et al.* have experimentally studied the curcumin-loaded PLGA-PEG-PLGA triblock copolymeric micelles. They concluded that these micelles are promising candidates for drug carriers for poorly water-soluble drugs [18]. Recently, Karataş *et al.* have studied the interaction of curcumin with Poly(lactic-co-glycolic acid) and Montmorillonite. From their theoretical studies, they found that PLGA complexation with curcumin, MMT complexation with curcumin, and PLGA complexation with MMT complexes have strong interaction. That is the interaction energy is large for these complexes. Then, they concluded that MMT or PLGA composite can be used as carrier for curcumin [26]. Also, Chereddy *et al.* have studied the PLGA and curcumin for wound healing activity experimentally. They found that PLGA-based drug delivery systems are promising particularly for wound healing activity [19]. More recently, Akl *et al.* have studied curcumin-loaded PLGA nanoparticles for oral colon targeting and they found that CS-coated CPLGA nanoparticles can form electrostatic interaction with the cells [23]. From the above literature, we have concluded that the curcumin-loaded PLGA compound is used in many cancer therapy applications as well as antimicrobial, antioxidant, anti-infective, and anti-inflammatory, activities.

Antimicrobial resistance is one of the topical studies in the last few years. For instance, recently, Hussain *et al.* have reviewed the recent developments to improve antimicrobial efficacy, anti-inflammatory, and antioxidant activity of curcumin. They found that curcumin and its derivatives have got wide attention due to its antimicrobial efficacy, anti-inflammatory, and antioxidant activity [22]. Further, it is widely believed that the presence of hydroxyl and methoxyl groups in curcumin (Cur) is responsible for antimicrobial activity. Recently, Krausz *et al.* [21] have calculated the pharmaceutical significance of CUR-encapsulated polymeric NPs. They have successfully fabricated the CUR-loaded polymeric NPs. Even though extensive experimental and theoretical studies were reported in the literature, limited attention has been given to study the molecular scale information on Cur-PLGA complexes using theoretical methods. Because the molecular-level understanding of the interaction between curcumin and PLGA is necessary for future studies on the design and development of new antimicrobial agents. In general, curcumin is less soluble in water. Because of this, bioavailability of curcumin is limited. In particular, it is difficult to interact with microorganisms in the liquid phase [28]. To improve the bioavailability of curcumin, here we employed polymer-molecule based approach. That is we have studied the structure and interaction of curcumin with PLGA using DFT method. The Food and Drug Administration approved PLGA polymer is widely used in various pharmaceutical applications in areas like targeted drug delivery, delivery of active agents and gene therapy [29, 30]. Recently, Mary *et al.* have studied the antimicrobial properties of the chalcone-based Schiff bases using the DFT method [31]. They found that the $HL(1-3)-Cu^{2+}$ complexes show higher antimicrobial activities. This indicates that the antimicrobial properties can be studied using theoretical methods in particular density functional theory. To explore more detailed molecular-scale information about the structure and antimicrobial activity of curcumin, it is necessary to study curcumin and curcumin-PLGA complexes. Hence, in the present study, we investigate the structure and antimicrobial activity of curcumin, curcumin interaction with glycolic acid conformers such as SSC (Cur-SSC) and AAT (Cur-AAT), curcumin interaction with lactic acid (Cur-LA), and curcumin interaction with Poly(lactic-co-glycolic acid) (Cur-PLGA) using density functional theory method. Recently, Karataş *et al.* have studied the interaction of curcumin with PLGA. They have used periodic DFT calculations and molecular dynamics for their study [26]. However, to obtain the molecular level information about the interaction between curcumin and PLGA, DFT cluster approach is necessary. Further, inter-and intramolecular H-bond interactions have been analyzed in detail through Natural Bond Orbital (NBO), Atoms in Molecule (AIM), and Reduced Density Gradient (RDG) analyses using the M06-2X/6-31 + G* method. We believe that this study will be helpful to future studies focusing on the design and the development of new antimicrobial agents.

Computational Details

Density functional calculations are performed on curcumin-PLGA complexes to study their molecular structure, interactions, and antimicrobial activities. The molecular structure of SSC, AAT conformers of glycolic acid, Lactic acid (LA), PLGA, curcumin, and the curcumin-PLGA complexes such as Cur-SSC, Cur-AAT, Cur-LA, Cur-PLGA are optimized using dispersion corrected M06-2X functional with 6-31 + G* basis set. The reason for the selection of M06-2X functional is, in general, the dispersion forces play a vital part

in weakly interacting systems. These forces induce charge fluctuations in the system, so the precise calculation of binding energies can be obtained using the dispersion corrected functional [32, 33]. The reason for the selection of SSC and AAT is, these two Glycolic acid conformers are experimentally available [34, 35]. The reactivity parameters such as chemical hardness (η) [36] and chemical potential (μ) [37] are calculated using ionization energy and electron affinity. The computational details of the calculation of chemical hardness, chemical potential, condensed Fukui functions, the interaction energy between the molecules in Cur-PLGA complexes, Dual Descriptor (Δf), NBO, AIM, and RDG are given in the supporting information. To understand the reactivity of the sites in curcumin, condensed Fukui functions [38] are calculated using the NBO atomic charges. Quantum Theory of Atoms in Molecule (QTAIM) analysis is used to obtain electron density (ρ), Laplacian of electron density ($\nabla^2\rho$), and H-Bond energy [39–42]. The mass and volume of Cur-PLGA complexes are calculated using the M06-2X/6–31 + G* method. The second-order stabilization energy (E_2) is calculated using Natural Bond Orbital analysis [43]. RDG, NCI, ELF, and LOL topological analyses of curcumin and curcumin-PLGA complexes are performed using Multiwfn 3.6 software [44]. All the above-mentioned calculations are performed using the GAMESS-US program [45].

Results And Discussion

The molecular geometries of glycolic acid conformers (SSC, and AAT), LA, PLGA, and curcumin are optimized using the M06-2X/6–31 + G* method and are shown in Fig. 1. The selected (optimized) bond length values of SSC, LA, and curcumin molecule along with their experimental values are given in Table 1. That is, the bond length values which are significantly deviated from experimental values are given in Table 1. However, all the optimized bond length values of SSC conformer of glycolic acid, LA and curcumin, are given in Table S1 in supporting information. The selected bonds given in Table 1 are C–C, C = C, and C–O bonds. The bond length values of these bonds slightly deviate from the experimental values, the deviation is greater than 0.02 Å. The deviation is due to the artifact of the selected DFT functional. Because earlier Senthilkumar *et al.* have noted that the DFT functionals have difficulty determining the bonds with electronegative elements [46]. All other bond length values coincide well with the experimental values (Table S1). The calculated glycolic acid SSC conformer bond length values are compared with Blom *et al.*'s experimental data [47]. In the case of lactic acid, the calculated bond length values are compared with Borba *et al.*'s experimental data [48]. Earlier Tsonko *et al.* have synthesized curcumin crystals and compared their crystal structure with the theoretical values. [49]. Our calculated bond length values of curcumin are compared with Tsonko *et al.* study. From Table S1, it can be noted that in curcumin, all enol ring structures there are no large differences in the C–C bond in the skeleton and the C–O bonds in both experimental and our theoretical calculation values. Our calculations for the curcumin predict C22–O6 bond is a single bond (1.328 Å), and C21 = O5 is a double bond (1.251 Å), respectively. However, the experimental values are 1.316 for C22–O6 and 1.312 Å for C21 = O5, respectively (Table 1).

Table 1

Calculated bond length values of Glycolic acid (SSC) conformer, Lactic acid (LA) and Curcumin using M06-2X/6-31 + G*, and compared with the available experimental data.

SSC		
Bonds	M06-2X	Exp. ^a
C1–C2	1.512	1.495
C1–O6	1.398	1.406
C2 = O5	1.208	1.210
C2–O8	1.339	1.349
LA		
C4 – O1	1.404	1.425
C4 – C5	1.525	1.521
C4 – C6	1.518	1.519
C6 – O2	1.340	1.320
C6 – O3	1.209	1.208
C6 – C4	1.518	1.519
curcumin		
C19 = C23	1.343	1.348
C20 = C24	1.345	1.348
C21 – O5	1.251	1.312
C22 – O6	1.328	1.316
C21 – C23	1.476	1.450
C22 – C24	1.457	1.450
C21 – C25	1.444	1.392
C22 = C25	1.374	1.403
C21 – C23	1.476	1.450
C21 – C25	1.444	1.392
C22 – C25	1.374	1.403
C26 – O1	1.414	1.440

^aExperimental values are taken from Ref No:[47] for SSC, Ref No:[48] for LA, Ref No:[49] for curcumin.

SSC		
C27 – O2	1.415	1.440
^a Experimental values are taken from Ref No:[47] for SSC, Ref No:[48] for LA, Ref No:[49] for curcumin.		

The energetical parameters of SSC, AAT, LA, PLGA, and curcumin are given in Table 2. Among the SSC and AAT conformers, SSC is energetically more stable than AAT conformers. However, AAT is highly polar i.e. AAT has a larger dipole moment than SSC conformer. Further, the chemical hardness, chemical potential, of curcumin are comparably lower than other studied systems. The condensed Fukui functions of selected atoms *i.e.* most favorable sites of curcumin are given in Table 3. The condensed Fukui functions of all the atoms of curcumin are given in Table S2. In general, the condensed Fukui function is used to explain the reactivity of the particular site of any chemical system. Earlier the molecular selectivity of the site was first analyzed by Parr and Yang [50] using local reactivity descriptors, in particular, Fukui functions. More recently, Mohamed *et al.* have performed docking studies of Dihydrothiouracil-Indenopyridopyrimidines with Human-DNA Topoisomerase II using theoretical methods [51]. They have determined the electrophilic as well as nucleophilic sites using condensed Fukui functions. Therefore, condensed Fukui functions can be used to predict the favorable reactive sites of any given molecule. In the present study, the Fukui function indices and Dual descriptor [52] are calculated using M06-2X/6–31 + G* and are given in Table 3. From Table 3, it can be noted that the C21 and C22 site is the most electrophilic active site in curcumin. Similarly, the active nucleophilic sites are O5 and O6 in curcumin. This is because the presence of O5 and O6 are attached to the C21 and C22 atoms respectively, Similarly, the same conclusion is derived from Dual descriptor Δf regarding electrophilic and nucleophilic attacks respectively.

Table 2
Calculated Total energy (E, hartree), dipole moment (μ_m , Debye), chemical hardness (η , eV), and chemical potential (μ , eV) of glycolic acid (SSC and AAT), LA, PLGA and curcumin using the M06-2X/6–31 + G* method.

	E	μ_m	η	μ
SSC	-304.17966	2.45	5.01	-4.91
AAT	-304.17420	4.65	4.69	-4.87
LA	-343.47905	2.42	4.95	-4.81
PLGA	-571.26298	2.19	5.03	-4.90
curcumin	-1263.09165	2.19	2.62	-4.25

Table 3
Calculated condensed Fukui functions values
of selected atoms of curcumin using the M06-
2X/6–31 + G* method.

	f^+	f^0	f^-	Δf
O5	-0.215	-0.732	-0.841	0.626
O6	-0.703	-0.827	-0.876	0.172
C21	0.743	0.554	0.726	-0.162
C22	0.728	-0.453	0.505	-0.069

The energetical parameters of Cur-SSC, Cur-AAT, Cur-LA, and Cur-PLGA complexes are calculated using the M06-2X/6–31 + G* method. The energetical parameters such as total energy, interaction energy, and energy gap (HOMO-LUMO gap) and reactivity parameters such as chemical hardness and chemical potential are calculated and are given in Table 4. The sum of NBO charges of each molecule in Cur-PLGA complexes is given in Table 5. The detailed NBO charges of Cur-PLGA complexes are given in Table S3. From Table 5, it can be seen that among the studied complexes, large charge transfer is noted in Cur-AAT and Cur-LA complexes. For example, after the interaction, curcumin becomes slightly positive (0.029 e) and AAT becomes negative (-0.029e). That is more negative charges are localized in AAT. A similar trend is observed in the Cur-LA complex. The optimized structures of Cur-SSC, Cur-AAT, Cur-LA, and Cur-PLGA complexes are given in Fig. 2 using the M06-2X/6–31 + G* method. The total energy and dipole moment values of each complex are mentioned in Table 4. From Fig. 2 and Table 4 it can be seen that Cur-AAT is energetically more stable than the Cur-SSC complex. This is due to the formation of inter-and intramolecular H–bond interactions in curcumin as well as the AAT conformer of glycolic acid. In the case of dipole moment values, all the complexes predict similar values except Cur-AAT and Cur-PLGA complexes. The dipole moment values increases in the order of Cur-SSC > Cur-LA > Cur-PLGA > Cur-AAT. This indicates that Cur-AAT and Cur-PLGA complexes are highly polar than the other two studied complexes. That is, Cur-AAT and Cur-PLGA complexes could be highly stable in the liquid phase because of the larger dipole moment. The chemical hardness, chemical potential, and HL gap values predict a similar result in all the complexes considered in this study. Further, a large interaction energy value is noted for the Cur-AAT complex (-17.83 kcal/mol). The interaction energy value increases in the order of Cur-LA > Cur-SSC > Cur-PLGA > Cur-AAT. This trend is in agreement with dipole moment order. However, there is a slight change in the order between Cur-LA and Cur-SSC in the case of dipole moment and interaction energy. The large dipole moment and interaction energy value of the Cur-AAT complex is due to the presence of strong intra- and intermolecular H-bond interactions. Earlier Karataş *et al.* have concluded that curcumin has a stronger interaction with PLGA, and PLGA can be used as a carrier for drug delivery systems [26]. In the present study, it can be noted that glycolic acid conformers have strong interaction with curcumin, because of this reason glycolic acid is in a polymeric form, and its copolymers for ex. PLGA is used as a carrier for drug delivery systems. In addition to this, polyglycolic acid and its copolymers are also used as a material for synthesizing absorbable sutures in the biomedical field.

Table 4
Calculated Total energy (E, in hartree), dipole moment (μ_m , in Debye), chemical hardness (η , in eV) chemical potential (μ , in eV and Interaction energy (E_{int} , in kcal/mol) of glycolic acid (GA-SSC and GA-AAT), LA, PLGA and curcumin using M06-2X/6-31 + G* level of theory.

	E	μ_m	η	μ	E_{int}
Cur-SSC	-1567.28644	1.94	2.59	-4.19	-9.49
Cur-AAT	-1567.29426	5.86	2.44	-4.53	-17.83
Cur-LA	-1606.58540	2.27	2.55	-4.37	-9.23
Cur-PLGA	-1834.37838	4.51	2.58	-4.31	-14.91

Table 5
Natural bond orbital (NBO) charges (in e) of Cur-complexes calculated at M06-2X/6-31 + G* method.

Cur-complexes		q
Cur-SSC	SSC	0.001
	Cur	-0.001
Cur-AAT	AAT	-0.021
	Cur	0.021
Cur-LA	LA	-0.029
	Cur	0.029
Cur-PLGA	PLGA	0.008
	Cur	-0.008

To get more detailed information about the covalent and noncovalent interactions on the stability of Cur-PLGA complex as well as Cur-SSC, Cur-AAT, and Cur-LA complexes, NBO and QTAIM analysis are performed. The QTAIM theory is one of the useful methods to get an insight into a region of the system. It is used to predict the strength of the covalent and noncovalent interactions in the given system. The Bond Critical Points (BCP) are used to recognize the chemical bonds and strength between atoms.. The AIM analysis of curcumin and Cur-PLGA complexes are performed by using the M06-2X/6-31 + G* method. The topological, and energy parameters for Cur-PLGA complexes are listed in Table 6. The electron density (ρ) and Laplacian of electron density ($\nabla^2\rho$) values from our AIM analysis is confirmed that the formation of intramolecular H-bond in AAT conformer between O53...H56-O55 (Table 4). Apart from O53...H56-O55, all other interactions mentioned in Table 6 are van der Waals interactions. The H-bond

energy value for the Cur-AAT complex is -9.29 kcal/mol. Earlier studies have shown that the moderate H-bond energy is ~ -10 kcal/mol [53]. This indicates that the Cur-AAT complex possesses strong intermolecular and intramolecular interactions. This is the reason behind the higher stability of the Cur-AAT complex. There are three intramolecular H-bond interactions were present in the curcumin molecule namely O1 $\cdots$ H28–O3, O2 $\cdots$ H29–O4, and O5 $\cdots$ H30 respectively. From Table 6 we can justify that the intramolecular H-bond energy (O5 $\cdots$ H30) of pure curcumin (-6.045 kcal/mol) is reduced in Cur-SSC (-5.819 kcal/mol), Cur-AAT (-5.868 kcal/mol)), Cur-LA (-5.849 kcal/mol) and Cur-PLGA (-5.867 kcal/mol) respectively. This is reduced due to the formation of curcumin with SSC, AAT, LA, and PLGA complexes.

Table 6

Calculated bond length (R_v , in Å), topological parameters: the electron density (ρ_{BCP} , in a.u.) and Laplacian electron density ($\nabla^2\rho_{BCP}$, in a.u.), energetic parameters: electron kinetic energy density (G_{BCP} , in a.u.), electron potential energy density (V_{BCP} , in a.u.), total electron energy density (H_{BCP} , in a.u.) of the Bond critical point (BCPs), hydrogen bond energy (E_{HB} , in eV) and reduced gradient density (RDG or $s(r)$, in a.u.) of the Cur and Cur-complexes using M06-2X/6-31 + G* method.

Complex	Interaction	R_v	ρ_{BCP}	$\nabla^2\rho_{BC}$	G_{BCP}	V_{BCP}	H_{BCP}	E_{HB}	$s(r)$
Cur	O1...H28 – O3	2.079	0.548	1.752	0.475	-0.511	-0.037	-16.041	0.100
	O2...H29 – O4	2.083	0.202	0.893	0.207	-0.191	0.016	-5.992	0.103
	O5...H30	1.636	0.203	0.897	0.208	-0.193	0.016	-6.045	0.198
Cur-SSC	O1...H28 – O3	2.096	0.020	0.088	0.020	-0.019	0.002	-5.854	0.040
	O2...H29 – O4	2.088	0.020	0.089	0.021	-0.019	0.002	-5.963	0.041
	O5...H30	1.645	0.054	0.172	0.047	-0.050	-0.004	-15.727	0.185
	O6...H56 – O55	3.020	0.005	0.018	0.004	-0.004	0.000	-1.153	0.011
Cur-AAT	O1...H28 – O3	2.095	0.516	1.676	0.449	-0.480	-0.030	-15.054	0.100
	O2...H29 – O4	2.099	0.196	0.874	0.202	-0.185	0.017	-5.809	0.250
	O5...H30	1.661	0.198	0.879	0.203	-0.187	0.016	-5.868	0.124
	O53...H56 – O55	1.908	0.316	1.134	0.290	-0.296	-0.006	-9.289	0.064
	O5...H54 – O53	1.750	0.368	1.362	0.339	-0.338	0.001	-10.608	0.048
	O52...H31 – C13	2.475	0.099	0.359	0.080	-0.070	0.010	-2.193	0.037
	O55...H31 – C13	2.505	0.091	0.359	0.079	-0.068	0.011	-2.125	0.039
Cur-LA	O1...H28 – O3	2.096	0.489	1.613	0.428	-0.452	-0.024	-14.191	0.028
	O2...H29 – O4	2.097	0.197	0.882	0.203	-0.186	0.017	-5.838	0.144
	O5...H30	1.683	0.197	0.882	0.203	-0.186	0.017	-5.849	0.124

Complex	Interaction	R _v	ρ_{BCP}	$\nabla^2\rho_{BC}$	G _{BCP}	V _{BCP}	H _{BCP}	E _{HB}	s(r)
	O48 – H58...O5	2.019	0.218	0.796	0.198	-0.197	0.001	-6.166	0.078
	C19 – H37...O48	2.322	0.137	0.460	0.111	-0.108	0.004	-3.379	0.099
Cur-PLGA	O1...H28 – O3	2.094	0.550	1.745	0.474	-0.511	-0.038	-16.048	0.100
	O2...H29 – O4	2.099	0.197	0.881	0.203	-0.186	0.017	-5.828	0.119
	O5...H30	1.636	0.198	0.883	0.204	-0.187	0.017	-5.867	0.076
	O50...H33 – C15	2.337	0.124	0.430	0.102	-0.097	0.005	-3.058	0.067

Bonding and nonbonding interactions interplay in the Cur-PLGA complexes. Hence it is difficult to understand the functionality of these complexes. The bonding and nonbonding interactions in Cur-PLGA complexes are described by combining Bader's QTAIM analysis with the noncovalent interaction (NCI) index [54]. The 2D NCI scatter plots of RDG for curcumin are shown in Fig. 3. Figures 4 (a), 4 (b), 5 (a), and 5(b) show that the 2D NCI scatter plots of RDG for Cur-SSC, Cur-AAT, Cur-LA, and Cur-PLGA complexes respectively. In general, the 2D NCI scatter plots of RDG will give a clear picture of the noncovalent interactions in the Cur-PLGA complexes. From Fig. 4(b) it is seen that the Cur-AAT complex is having intramolecular H-bonds in both curcumin as well as in AAT. The peaks at $\text{sign}(\lambda^2)\rho(r) \approx -0.03$ a.u. in each scatter plot indicates that the presence of conventional H-bonds in curcumin (O5...H30) and in Cu-AAT (O5...H54–O53) complex. There are no intramolecular H-bonds that exist in all other studied systems, *i.e* curcumin with SSC, LA, and PLGA complexes. Recently, Nkungli *et al.* have studied the interaction between iron(III) protoporphyrin IX and 4-methoxyacetophenone thiosemicarbazone theoretical studies [55]. Their NCI index values indicate that the formation of van der Waals interaction in the studied system.

The natural bond orbital (NBO) analysis is one of the best quantum chemical tools to determine the strength of non-covalent interactions as well as the stabilization energy of the interaction between donor and acceptor region [56]. In particular, the stabilization energy predicts the delocalization of electron density in donor-acceptor interaction. In the present study, the stabilization energy $E_{(2)}$ is calculated by using the second-order perturbation theory. The $E_{(2)}$ values for the Cur-SSC, Cur-AAT, Cur-LA, and Cur-PLGA are given in Table 7. The H-bond stabilization energy value for Cur-AAT (LP (1) O53 → BD* (1) O55 – H56) is 4.08 kcal/mol. The new H-bond is formed between Cur-AAT complexes with the highest stabilization energy value. The H-bond stabilization energy value for Cur-AAT (LP (1) O5 → BD* (1) H54–O53) is 14.36 kcal/mol. From Table 4 in all complexes LP (1) O5 → LP* (1) H30 having a higher stabilization value. This clearly explains that the curcumin is having strong intramolecular H-bonding interactions. In Cur-LA complexes the H-bond stabilization energy value (LP (1) O5 → LP* (1) H30) is

11.79 kcal/mol. From the NBO analysis, it is noted that there is a transfer of electrons from curcumin to AAT, curcumin to LA, and curcumin to PLGA takes place. That is electrons are transferred from the lone pair orbital of curcumin to the anti-lone pair orbital of AAT, LA, and PLGA respectively. In summary, from AIM and NBO studies, it is concluded that the interaction in curcumin and Cur-SSC, Cur-AAT, Cur-LA, Cur-PLGA complexes are found to be van der Waals in nature.

Table 7

Calculated van der Waals bond length (R_v , in Å), Donor–Acceptor Interactions in the NBO Basis, and Their Second-Order Perturbation Stabilization Energies ($E_{(2)}$, in kcal/mol) of Cur and Cur-complexes using M06-2X/6–31 + G* method.

	Interaction	Donor (i)	Acceptor (j)	R_v	$E_{(2)}$	$E_{(j)}-E_{(i)}$	$F_{(i,j)}$
Cur	O1...H28 – O3	LP (1) O1	BD* (1) O3 – H28	2.079	3.52	1.17	0.058
	O2...H29 – O4	LP (1) O2	BD* (1) O4 – H29	2.083	3.48	1.16	0.057
	O5...H30	LP (1) O5	LP* (1) H30	1.636	6.55	0.95	0.079
Cur-SSC	O1...H28 – O3	LP (1) O1	BD* (1) O3 – H28	2.096	3.1	1.23	0.056
	O2...H29 – O4	LP (1) O2	BD* (1) O4 – H29	2.088	4.550	0.84	0.056
	O5...H30	LP (1) O5	LP* (1) H30	1.645	6.56	0.94	0.079
Cur-AAT	O1...H28 – O3	LP (1) O1	BD* (1) O3 – H28	2.095	3.37	1.16	0.056
	O2...H29 – O4	LP (1) O2	BD* (1) O4 – H29	2.099	2.79	1.18	0.052
	O5...H30	LP (1) O5	LP* (1) H30	1.661	7.58	0.99	0.086
	O5...H54 – O53	LP (1) O5	BD* (1) O53 – H54	1.750	14.36	0.77	0.094
	O53...H56 – O55	LP (1) O53	BD* (1) O55 – H56	1.912	4.08	1.00	0.057
	O52...H31 – C13	LP (1) O52	BD* (1) C13 – H31	2.475	0.16	1.36	0.013
	O55...H31 – C13	LP (2) O55	BD* (1) C13 – H31	2.505	0.53	0.99	0.021
Cur-LA	O1...H28 – O3	LP (1) O1	BD* (1) O3 – H28	2.096	2.2	1.14	0.045
	O5...H30	LP (1) O5	LP* (1) H30	1.683	11.79	1.02	0.109
Cur-PLGA	O1...H28 – O3	LP (1) O1	BD* (1) O3 – H28	2.094	3.33	1.16	0.056
	O2...H29 – O4	LP (1) O2	BD* (1) O4 – H29	2.099	3.26	1.16	0.055
	O5...H30	LP (1) O5	LP* (1) H30	1.636	6.31	0.96	0.078
	O50...H33 – C15	LP (1) O50	BD* (1) C15 – H33	2.337	0.61	1.29	0.025

The antimicrobial activity of any molecule depends on the LUMO energy and density of the molecule. Molecules with lower LUMO orbitals (energy) can accept more electrons than the molecules with higher

LUMO orbitals (energy). This indicates higher antimicrobial activity. The molecular density is the molecular mass per unit volume. The activity of the molecule depends upon the molecular density only. If it is negative the molecule is compact and it will reduce the density of the molecule [57]. The LUMO energy and molecular density values are given in Table 8. From Table 8 and Fig. 6, it can be seen that the energy of the LUMO corresponding to the Cur-SSC, Cur-AAT, Cur-LA, and Cur-PLGA complexes is found to be increased in the range of 0.09–0.45 eV. Whereas, the density of the Cur-SSC, Cur-AAT, and Cur-PLGA complexes is increased in the range of 0.04–0.30 amu/A³ respectively. But in the case of the Cur-LA complex, the density is found to be decreased by 0.07 amu/A³. The volume of the Cur-LA is somewhat high (375.92 A³) compared with the other Cur-PLGA complexes. The Cur-PLGA complex shows lower LUMO energy and density values than the other studied systems. This indicates that the Cur-PLGA complex shows higher antimicrobial activity than the other complexes studied. The Cur-LA complex gives a major contribution to increasing the antimicrobial activity of the Cur-PLGA complex. A similar trend is observed in an earlier study also. Recently, Mary *et al.* have studied the antimicrobial properties of the chalcone-based Schiff bases using the theoretical method [31]. They found that the HL(1–3)-Cu²⁺ complexes have lower LUMO energy and density. They concluded that the HL(1–3)-Cu²⁺ complex shows higher antimicrobial activity than the other studied complexes.

Table 8
LUMO energy (in eV) and density (mass/volume, in amu/A³) of Cur and Cur-PLGA complexes calculated at M06-2X/6–31 + G* method.

	LUMO	mass	volume	Density
Cur	-1.64	368.13	286.11	1.29
Cur-SSC	-1.74	444.14	334.73	1.33
Cur-AAT	-2.09	444.14	315.69	1.41
Cur-LA	-1.81	458.16	375.92	1.22
Cur-PLGA	-1.72	516.16	324.57	1.59

Conclusion

In the present investigation, we have studied the molecular structure, interactions, and antimicrobial activity of Cur-SSC, Cur-AAT, Cur-LA and Cur-PLGA complexes at M062X/6–31 + G* method. The condensed Fukui functions predict the favorable reactive sites in curcumin. The noncovalent interactions in the Cur-SSC, Cur-AAT, Cur-LA, and Cur-PLGA complexes are investigated using QTAIM and RDG. From the above topological analysis, it is confirmed that the van der Waals interaction exists in curcumin and Cur-SSC, Cur-AAT, Cur-LA, and Cur-PLGA complexes. This can be confirmed from our NBO analysis also. Further, the intramolecular H-bond interaction also plays a crucial role in the curcumin and Cur-AAT complexes. That is the stability of Cur-AAT complexes increases due to the presence of strong

intramolecular (H–bond) interactions. Our NBO analysis indicates that interactions such as LP-LP* and LP-BD* orbitals are more crucial for studying the Cur-PLGA complexes. The antimicrobial activity of Cur-PLGA complexes is studied using the M06-2X/6–31 + G* method. Our study reveals that the Cur-PLGA complex shows higher antimicrobial activity than the other studied complexes.

We hope that our modeling study of curcumin with PLGA and other derivatives will be helpful to future experimental and theoretical studies on the design and development of new antimicrobial agents as well as the development of new drug carriers.

Declarations

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Availability of data and material: The calculation of chemical hardness, chemical potential, condensed Fukui functions, the interaction energy between the molecules in Cur-PLGA complexes, Dual Descriptor (Δf), NBO, AIM, and RDG are given in the supporting information. Also, the optimized bond length values of SSC conformer of glycolic acid, LA and curcumin, are given in Table S1, the condensed Fukui functions of all the atoms of curcumin are given in Table S2 and the detailed NBO charges of Cur-PLGA complexes are given in Table S3 are given in the supporting information file.

Code availability: GAMESS-US program is used for this study.

Authors' contributions: Conceptualization: Selvarengan Paranthaman; Methodology: Selvarengan Paranthaman; Formal analysis and investigation: Mahendiraprabu Ganesan; Writing - original draft preparation: Mahendiraprabu Ganesan; Writing - review and editing: Selvarengan Paranthaman; Supervision: Selvarengan Paranthaman, All authors read and approved the final manuscript.

References

1. Govindarajan VS, Stahl WH (1980) Turmeric – chemistry, technology, and quality. C R C Crit Rev Food Sci Nutr 12:199–301. <https://doi.org/10.1080/10408398009527278>
2. Food WHO (2004) Safety evaluation of certain food additives and contaminants WHO Library Cataloguing-in-Publication Data. World Heal Organ

3. Goel A, Kunnumakkara AB, Aggarwal BB (2008) Curcumin as “Curecumin”: From kitchen to clinic. *Biochem Pharmacol* 75:787–809. <https://doi.org/10.1016/j.bcp.2007.08.016>
4. Anand P, Sundaram C, Jhurani S, et al (2008) Curcumin and cancer: an “old-age” disease with an “age-old” solution. *Cancer Lett* 267:133–164
5. Ruby AJ, Kuttan G, Dinesh Babu K, et al (1995) Anti-tumour and antioxidant activity of natural curcuminoids. *Cancer Lett* 94:79–83. [https://doi.org/10.1016/0304-3835\(95\)03827-J](https://doi.org/10.1016/0304-3835(95)03827-J)
6. Kim M-K, Choi G-J, Lee H-S (2003) Fungicidal property of *Curcuma longa* L. rhizome-derived curcumin against phytopathogenic fungi in a greenhouse. *J Agric Food Chem* 51:1578–1581
7. Ono K, Hasegawa K, Naiki H, Yamada M (2004) Curcumin has potent anti-amyloidogenic effects for Alzheimer’s β -amyloid fibrils in vitro. *J Neurosci Res* 75:742–750
8. Shukla PK, Khanna VK, Ali MM, et al (2008) Anti-ischemic effect of curcumin in rat brain. *Neurochem Res* 33:1036–1043
9. Srimal RC, Dhawan BN (1973) Pharmacology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent. *J Pharm Pharmacol* 25:447–452. <https://doi.org/10.1111/j.2042-7158.1973.tb09131.x>
10. Allen TM, Cullis PR (2004) Drug Delivery Systems: Entering the Mainstream. *Science* (80-) 303:1818–1822. <https://doi.org/10.1126/science.1095833>
11. Liechty WB, Kryscio DR, Slaughter B V, Peppas NA (2010) Polymers for drug delivery systems. *Annu Rev Chem Biomol Eng* 1:149–173
12. Liu Z, Jiao Y, Wang Y, et al (2008) Polysaccharides-based nanoparticles as drug delivery systems. *Adv Drug Deliv Rev* 60:1650–1662
13. Singh R, Lillard Jr JW (2009) Nanoparticle-based targeted drug delivery. *Exp Mol Pathol* 86:215–223
14. Chan JM, Zhang L, Yuet KP, et al (2009) PLGA–lecithin–PEG core–shell nanoparticles for controlled drug delivery. *Biomaterials* 30:1627–1634
15. Kumari A, Yadav SK, Yadav SC (2010) Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids Surfaces B Biointerfaces* 75:1–18. <https://doi.org/10.1016/j.colsurfb.2009.09.001>
16. Zhang L, Chan JM, Gu FX, et al (2008) Self-assembled lipid– polymer hybrid nanoparticles: a robust drug delivery platform. *ACS Nano* 2:1696–1702
17. Mukerjee A, Vishwanatha JK (2009) Formulation, characterization and evaluation of curcumin-loaded PLGA nanospheres for cancer therapy. *Anticancer Res* 29:3867–3875
18. Song Z, Feng R, Sun M, et al (2011) Curcumin-loaded PLGA-PEG-PLGA triblock copolymeric micelles: Preparation, pharmacokinetics and distribution in vivo. *J Colloid Interface Sci* 354:116–123. <https://doi.org/10.1016/j.jcis.2010.10.024>
19. Chereddy KK, Coco R, Memvanga PB, et al (2013) Combined effect of PLGA and curcumin on wound healing activity. *J Control Release* 171:208–215. <https://doi.org/10.1016/j.jconrel.2013.07.015>
20. Khalil NM, Nascimento TCF do, Casa DM, et al (2013) Pharmacokinetics of curcumin-loaded PLGA and PLGA-PEG blend nanoparticles after oral administration in rats. *Colloids Surfaces B*

- Biointerfaces 101:353–360. <https://doi.org/10.1016/j.colsurfb.2012.06.024>
21. Krausz AE, Adler BL, Cabral V, et al (2015) Curcumin-encapsulated nanoparticles as innovative antimicrobial and wound healing agent. *Nanomedicine Nanotechnology, Biol Med* 11:195–206. <https://doi.org/10.1016/j.nano.2014.09.004>
 22. Hussain Z, Thu HE, Amjad MW, et al (2017) Exploring recent developments to improve antioxidant, anti-inflammatory and antimicrobial efficacy of curcumin: A review of new trends and future perspectives. *Mater Sci Eng C* 77:1316–1326. <https://doi.org/10.1016/j.msec.2017.03.226>
 23. Akl MA, Kartal-Hodzic A, Suutari T, et al (2019) Real-Time Label-Free Targeting Assessment and in Vitro Characterization of Curcumin-Loaded Poly-lactic-co-glycolic Acid Nanoparticles for Oral Colon Targeting. *ACS Omega* 4:16878–16890. <https://doi.org/10.1021/acsomega.9b02086>
 24. Preis E, Baghdan E, Agel MR, et al (2019) Spray dried curcumin loaded nanoparticles for antimicrobial photodynamic therapy. *Eur J Pharm Biopharm* 142:531–539. <https://doi.org/10.1016/j.ejpb.2019.07.023>
 25. Dutta A, Boruah B, Saikia PM, Dutta RK (2013) Stabilization of diketo tautomer of curcumin by premicellar cationic surfactants: A spectroscopic, tensiometric and TD-DFT study. *J Mol Liq* 187:350–358. <https://doi.org/10.1016/j.molliq.2013.09.005>
 26. Karataş D, Tekin A, Bahadori F, Çelik MS (2017) Interaction of curcumin in a drug delivery system including a composite with poly(lactic- Co -glycolic acid) and montmorillonite: A density functional theory and molecular dynamics study. *J Mater Chem B* 5:8070–8082. <https://doi.org/10.1039/c7tb01964e>
 27. Pitchumani Violet Mary C, Vijayakumar S, Shankar R (2019) Inhibition mechanism of cathepsin B by curcumin molecule: a DFT study. *Theor Chem Acc* 138:. <https://doi.org/10.1007/s00214-018-2410-1>
 28. Ravichandran M, Hettiarachchy NS, Ganesh V, et al (2011) Enhancement of antimicrobial activities of naturally occurring phenolic compounds by nanoscale delivery against listeria monocytogenes, escherichia coli o157:H7 and salmonella typhimurium in broth and chicken meat system. *J Food Saf* 31:462–471. <https://doi.org/10.1111/j.1745-4565.2011.00322.x>
 29. des Rieux A, Fievez V, Garinot M, et al (2006) Nanoparticles as potential oral delivery systems of proteins and vaccines: A mechanistic approach. *J Control Release* 116:1–27. <https://doi.org/10.1016/j.jconrel.2006.08.013>
 30. Fu Y, Kao WJ (2010) Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. *Expert Opin Drug Deliv* 7:429–444. <https://doi.org/10.1517/17425241003602259>
 31. Pitchumani Violet Mary C, Shankar R, Vijayakumar S (2019) Theoretical insights into the metal chelating and antimicrobial properties of the chalcone based Schiff bases. *Mol Simul* 45:636–645. <https://doi.org/10.1080/08927022.2019.1573370>
 32. Zhao Y, Truhlar DG (2008) The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new

functionals and systematic testing of four M06-class functionals and 12 other function. *Theor Chem Acc* 120:215–241

33. Mardirossian N, Head-Gordon M (2016) How accurate are the Minnesota density functionals for noncovalent interactions, isomerization energies, thermochemistry, and barrier heights involving molecules composed of main-group elements? *J Chem Theory Comput* 12:4303–4325
34. Reva ID, Jarmelo S, Lapinski L, Fausto R (2004) First experimental evidence of the third conformer of glycolic acid: Combined matrix isolation, FTIR and theoretical study. *Chem Phys Lett* 389:68–74. <https://doi.org/10.1016/j.cplett.2004.03.062>
35. Godfrey PD, Rodgers FM, Brown RD (1997) Theory versus experiment in jet spectroscopy: Glycolic acid. *J Am Chem Soc* 119:2232–2239. <https://doi.org/10.1021/ja9616793>
36. Parr RG, Pearson RG (1983) Absolute Hardness: Companion Parameter to Absolute Electronegativity. *J Am Chem Soc* 105:7512–7516. <https://doi.org/10.1021/ja00364a005>
37. Parr RG, Donnelly RA, Levy M, Palke WE (2003) Electronegativity: The density functional viewpoint. *J Chem Phys* 68:3801–3807. <https://doi.org/10.1063/1.436185>
38. Yang W, Mortier WJ (1986) The Use of Global and Local Molecular Parameters for the Analysis of the Gas-Phase Basicity of Amines. *J Am Chem Soc* 108:5708–5711. <https://doi.org/10.1021/ja00279a008>
39. RFW B (1990) *Atoms in molecules: a quantum theory*. Clarendon Press Oxford A E Reed, LA Curtiss F Weinhold, *Chem Rev* 88:899
40. Popelier PLA, Bader RFW (1992) The existence of an intramolecular C–H···O hydrogen bond in creatine and carbamoyl sarcosine. *Chem Phys Lett* 189:542–548
41. Cheeseman JR, Carroll MT, Bader RFW (1988) The mechanics of hydrogen bond formation in conjugated systems. *Chem Phys Lett* 143:450–458
42. Koch U, Popelier PLA (1995) Characterization of C-H···O Hydrogen Bonds on the Basis of the Charge Density. *J Phys Chem* 99:9747–9754. <https://doi.org/10.1021/j100024a016>
43. Koopmans T (1934) Über die Zuordnung von Wellenfunktionen und Eigenwerten zu den Einzelnen Elektronen Eines Atoms. *Physica* 1:104–113. [https://doi.org/10.1016/S0031-8914\(34\)90011-2](https://doi.org/10.1016/S0031-8914(34)90011-2)
44. Lu T, Chen F (2012) Multiwfn: A multifunctional wavefunction analyzer. *J Comput Chem* 33:580–592. <https://doi.org/10.1002/jcc.22885>
45. Schmidt MW, Baldridge KK, Boatz JA, et al (1993) General atomic and molecular electronic structure system. *J Comput Chem* 14:1347–1363
46. Kolandaivel P, Senthilkumar K (2001) Ab initio and DFT studies on structure and stability of aliphatic aldoxime molecules. *J Mol Struct THEOCHEM* 535:61–70. [https://doi.org/10.1016/S0166-1280\(00\)00571-6](https://doi.org/10.1016/S0166-1280(00)00571-6)
47. Blom CE, Bauder A (1982) Structure of glycolic acid determined by microwave spectroscopy. *J Am Chem Soc* 104:2993–2996

48. Borba A, Gómez-Zavaglia A, Lapinski L, Fausto R (2004) Rotational isomers of lactic acid: First experimental observation of higher energy forms. *Phys Chem Chem Phys* 6:2101–2108. <https://doi.org/10.1039/b316642b>
49. Kolev TM, Velcheva EA, Stamboliyska BA, Spiteller M (2005) DFT and experimental studies of the structure and vibrational spectra of curcumin. *Int J Quantum Chem* 102:1069–1079. <https://doi.org/10.1002/qua.20469>
50. Parr RG, Yang W (1984) Density functional approach to the frontier-electron theory of chemical reactivity. *J Am Chem Soc* 106:4049–4050
51. Elshakre ME, Noamaan MA, Moustafa H, Butt H (2020) Density functional theory, chemical reactivity, pharmacological potential and molecular docking of dihydrothiouracil-indenopyridopyrimidines with human-DNA topoisomerase II. *Int J Mol Sci* 21:1–27. <https://doi.org/10.3390/ijms21041253>
52. Morell C, Grand A, Toro-Labbe A (2005) New dual descriptor for chemical reactivity. *J Phys Chem A* 109:205–212
53. Rozas I, Alkorta I, Elguero J (2000) Behavior of Ylides Containing N, O, and C Atoms as Hydrogen Bond Acceptors. *J Am Chem Soc* 122:11154–11161. <https://doi.org/10.1021/ja0017864>
54. Contreras-García J, Boto RA, Izquierdo-Ruiz F, et al (2016) A benchmark for the non-covalent interaction (NCI) index or... is it really all in the geometry? *Theor Chem Acc* 135:. <https://doi.org/10.1007/s00214-016-1977-7>
55. Nkungli NK, Ghogomu JN (2017) Theoretical analysis of the binding of iron(III) protoporphyrin IX to 4-methoxyacetophenone thiosemicarbazone via DFT-D3, MEP, QTAIM, NCI, ELF, and LOL studies. *J Mol Model* 23:. <https://doi.org/10.1007/s00894-017-3370-4>
56. Tsipis AC, Tsipis CA, Valla V (2003) Quantum chemical study of the coordination of glycolic acid conformers and their conjugate bases to $[Ca(OH_2)_n]^{2+}$ ($n = 0-4$) ions. *J Mol Struct THEOCHEM* 630:81–100. [https://doi.org/10.1016/S0166-1280\(03\)00148-9](https://doi.org/10.1016/S0166-1280(03)00148-9)
57. Asiri AM, Khan SA, Marwani HM, Sharma K (2013) Synthesis, spectroscopic and physicochemical investigations of environmentally benign heterocyclic Schiff base derivatives as antibacterial agents on the bases of in vitro and density functional theory. *J Photochem Photobiol B Biol* 120:82–89

Figures

Figure 1

Optimized structures with atom numbering of SSC, AAT, LA, PLGA, and curcumin using the M06-2X/6-31+G* method.

Figure 2

Optimized structures of Cur-PLGA complexes using the M06-2X/6-31+G* method.

Figure 3

Plots of reduced density gradient (RDG) against electron density multiplied by the sign of the second Hessian eigenvalue ($\text{sign}(\lambda_2)\rho$ (in a.u.)) for curcumin.

Figure 4

Plots of reduced density gradient (RDG) against electron density multiplied by the sign of the second Hessian eigenvalue ($\text{sign}(\lambda_2)\rho$ (in a.u.)) for (a) Cur-SSC and (b) Cur-AAT complexes.

Figure 5

Plots of reduced density gradient (RDG) against electron density multiplied by the sign of the second Hessian eigenvalue ($\text{sign}(\lambda_2)\rho$ (in a.u.)) for (a) Cur-LA and (b) Cur-PLGA complexes.

Figure 6

HOMO-LUMO orbital energy plot (in eV) and its energy gap of Cur-PLGA Complexes calculated at M06-2X/6-31+G* method.

Supplementary Files

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