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Theoretical Study of Electronic Properties of few Variants of Gingerol, a Group of Biologically Active Compounds

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Abstract

This work presents the first theoretical study of gingerol, an important biological extract from ginger oil, and its variants viz. 6-gingerol, 6-paradol, 6-shogaol, 8-gingerol, 10-gingerol and zingerone. Standard DFT calculations reveal some effect of side chains on properties such as optimized structures, electronic states, energy gaps, ionization potential, hardness, softness, electrophilicity and dipole moment. The predicted biological activity of the studied molecules are calculated also. The harmonic vibration frequencies and ^{1}H-NMR data for the molecules have also been calculated. Finally, docking studies of gingerol and its variants with the human protein leukotriene A-4 hydrolase (PDB ID: 1HS6) show stable binding of the molecules with the latter.

Keywords: DFT, optimization, electronic properties, vibration frequency, ^{1}H-NMR, Autodock, PASS

1. Introduction

Gingerol is a prime constituent of the rhizome, *Zingiber officinale*, used for cooking and in medicine, which gives the latter its characteristic pungent taste. Chemically, gingerol is a relative of capsaicin and piperine, the compounds which give chilli peppers and black pepper their respective spiciness (McGee, 2004). It is normally found as a pungent yellow oil, but also can form a low-melting crystalline solid. Gingerol seems to be effective in an animal model of rheumatoid arthritis (Funk et al., 2009). It may reduce nausea caused by motion sickness or pregnancy (Emst and Pittler, 2000) and may also relieve migraine (Mustafa and Srivastava, 1990). 6-Gingerol has been used to induce a hypothermic state in rats (Ueki et al., 2008). Gingerol has been investigated for its effect on cancerous tumors in the bowel (Jeong et al., 2009), in breast tissue (Lee et al., 2008) ovaries (Rhode et al., 2007), pancreas (Park et al., 2006) etc., with beneficial results. The reason behind choosing these six variants of gingerol are due to their anti-emetic properties, action on central nervous system, antitussive activity, action on endocrine system etc (Singh et al., 2010).

Much work has been done on gingerol, but we have not found any theoretical calculation so far. In the present work, we calculate some physical properties of the gingerol variants along with their IR stretching frequencies, proton NMR spectra and biological activity. We have also attempted docking of these variants with human protein leukotriene A-4 hydrolase. Among the molecules studied here, only binding of 6-gingerol with this protein is reported in the literature. We predict the binding pattern of the other variants with the same protein. We show possible modes of binding and also the lowest energy of the binding ligands with protein.

2. Computational Methods

We optimized all the structures of the studied molecules shown in Fig.1 in the DFT formalism using the Gaussian 09 suite of programs with 6-31g(d) basis sets (Ditchfield, Hehre and Pople, 1971, 1972; Francl et al., 1982) and B3LYP functional (Becke, 1988, 1993; Lee, Young and Parr, 1988) for calculating the molecular properties of the studied compounds. NMR shielding constants were calculated in the GIAO method (Wolinski, Hilton and Pulay, 1990; Osmilowski, Kolehmainen, and Gawinecki, 2001) with the same basis and functional, at the optimized geometry. Docking of the variants of gingerol with the protein was performed using Autodock 4.2 software (Trott and Wolson, 2010) and the docking structure was analyzed by Accelrys Discovery Studio client (version 3.5, free for academic use). ChemUltra3D software was also used in this regard.

Optimized structures of all molecules are shown in Fig. 1. Some relevant electronic properties such as ionization potential (IP), electron affinity (EA), electronegativity (χ), hardness (η), softness (S) and electrophilicity index (ω) were calculated at the optimized geometries of the molecules. These are displayed in Table 2. The (vertical) ionization potential (IP_V) is calculated as the difference in energy between the cation (E_{cation}) and the neutral molecule (E_n) i.e. $IP_v = E_{cation} - E_n$, and also by Koopmans' approximation as $IP_K = - \varepsilon_{HOMO}$ (Sadasivam and Kumaresan, 2011). Similarly, the electron affinity (EA_V) is calculated as the difference in energy between the neutral molecule and the anion (E_{anion}) as $EA_V = E_n - E_{anion}$ and also by Koopmans theorem as $EA_K = - \varepsilon_{LUMO}$ (Demetrio et al., 2007). Here, ε_{HOMO} and ε_{LUMO} are the energies of the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals (MOs) respectively.

Electronegativity (χ), hardness (η), softness (S) and electrophilicity (ω) can all be calculated from the orbital energies as

follows (Chattaraj, Sarkar and Roy, 2006): $\chi = (\varepsilon_{HOMO} + \varepsilon_{LUMO})/2$, $\eta = 1/S = \varepsilon_{LUMO} - \varepsilon_{HOMO}$, $\omega = \chi^2/2\eta$. These properties for each variants are computed by two different ways. The ΔSCF method is based on the differences of total electronic energies when an electron is added or removed with respect to the neutral molecule. The second method is based on the differences between the HOMO and the LUMO orbital energies of the neutral molecule and is known as the Koopmans' method ("Koop" in Table 2 below). These methods have also been referred to as Energy-Vertical and Orbital-Vertical methods respectively (Hasan, 2013). In other words, IP_V is the same as IP(ΔSCF) and IP_K is identical with IP(Koop/Koopmans), and so on for the other parameters.

3. Results and Discussion

Total energy, orbital energies of HOMO and LUMO, and dipole moments of all molecules, calculated at their optimized structures, are shown in Table 1 below. While total energy and orbital energies are in atomic units (or a.u.), dipole moments are in Debye units.

Other physical properties of the molecules are displayed in Table 2. Here, all parameters e.g. ionization potential (IP), electron affinity (EA), electronegativity (χ), hardness (η) and electrophilicity (ω) are all in atomic units.

It would be interesting to try to make sense of the data in some fashion. We try the simplest approach. An idea of the size of each molecule can be obtained from the largest end-to-end distance or from the radius of gyration.

3.1 IR vibration frequencies

The theoretical IR spectra, calculated from the vibration frequencies at the optimized geometries, of all the gingerol variants are given in Fig. 2. The C-H stretching vibration for aromatic molecules falls in the region 2900-3250 cm^{-1} which is characteristic and used for ready identification, particularly the region 3250-3100 cm^{-1} for asymmetric stretching and 3100-2900 cm^{-1} for symmetric stretching modes of vibrations of aromatic C-H bonds (Fozard and Mwaluko, 1976). Again for sp^3 carbon, the C-H stretching frequency is expected in the region 2850-3000 cm^{-1}. For the free phenolic O-H, the stretching vibration is 3580-3650 cm^{-1}. For saturated ketones, the IR stretching vibration appears in the region 1710-1720 cm^{-1}. See, for example (Coates, 2000). Some major bands from our calculations are reported in Table 3 below.

The IR bands of the studied molecules given above seems satisfactory. Theoretical IR spectra of the molecules which are compared with the experimental values are given in Fig 2. In these figures, some vibrational spectral lines other than the major ones given above, are also seen. These may arise due to the various vibrational modes of C-H bonds like scissoring, rocking, waging and their interactions. Bending vibrations are also responsible for the IR peaks and bands in the low frequency region. Again both the values have satisfactory results. The slight deviation arise due to use of different medium.

3.2 ^1H NMR spectral data

The ^{1}H-NMR spectra of all the gingerol variants are given in Fig. 3. We must note that in all the variants of gingerol, mainly four types of protons are present. One is aromatic, another is etherial, the other is 2^0-aliphatic and the last one is 1^0 aliphatic type. Only for 6-shogaol two vinylic protons are present. Now for the aromatic protons the peak is expected at 6.5-8 ppm, for 2^0-aliphatic groups the peak may appear at or near 1.3 ppm, for the etherial group the peak may be seen at 3.2-4 ppm and for the conjugated vinylic group, it will be in the region 5.5-7.5 ppm.

Our theoretical NMR data are tabulated below (Table 4) for all the gingerol variants. And compared with the experimental value for 6-gingerol. These are in good agreement with the experimental values, and also with key results of other workers (Stuart, 2004; Halling et al., 2010). Other experimental values are not found. The slight difference in two values arise due to different solvents used.

The slight deviation from actual data of ^{1}H-NMR spectra are due to the presence of various groups like carbonyl, alcoholic etc. i.e. due to shielding and deshielding arises for these groups and due to absence of solvent.

3.3 Predicted biological activity of the molecules

The biological activity spectra for the studied compounds were done by using the web- based program PASS (Prediction of Activity Spectra for Substances, see www.chemspider.com) which predicts the probability of biological activity and inactivity of the studied compounds. For calculation of biological activity we use the files of the studied compounds in .SMILES format as given in the website referred above. There are two probabilities which are calculated for each activity, one is Pa, termed as probability of activity and another is Pi, termed as probability of inactivity. The sum of Pa and Pi varies from 0.000 to 1.000, and in general Pa+Pi < 1, since these probabilities are calculated independently (Vladimir et al., 2003)

According to data it is seen that all studied molecules (except 6-shogaol) have more than 90% (Pa=0.9) of activity in

5-Hydroxytryptamine release stimulant whether 6-shogaol has about 87% of activity in 5-Hydroxytryptamine release stimulant. This 5-Hydroxytryptamine inhibits the stimulant effect on cardiac sympathetic nerves of rabit (Vladimir et al., 2003). Other biological activity (more than 80%) which are commonly present in these studied molecules are listed in Table 5.

3.4 Docking information

Finally, we investigated the binding pattern of these molecules with the human protein leukotriene-A-4-hydrolase (LTA4H). Among these six variants, the binding of only 6-gingerol with this protein has been reported. However, we studied the binding with all other variants of gingerol as well. The molecules were docked into the cavities inside the protein cavity in various patterns. Only the strongest (i.e. energetically most favourable) binding mode is reported here.

From our theoretical data, it is seen that 6-gingerol binds with the protein in the strongest manner vis-a-vis the other variants. Most stable binding modes of all gingerol variants with this protein is shown, in 2D fashion, in Fig. 4. Energetics of binding are presented in Table 6.

5. Conclusion

Density functional (DFT) study has been carried out on gingerol and its variants. The calculated electronic properties such as ionization potential, electron affinity, electronegativity, hardness, softness, electrophilic index were calculated by two different ways viz. energy-vertical and orbital-vertical methods. From PASS we predict the biological activity of these compounds. Theoretical vibrational (IR) spectra of the molecules have also been calculated, which give results near expected regions. Therefore, the structures of the molecules can also be theoretically established. Theoretical proton NMR spectra of the molecules were also computed in gas phase, again giving results close to our expectations. Finally, docking of all the molecules with a protein leukotriene-A-4-hydrolase was studied, and most stable binding modes obtained.

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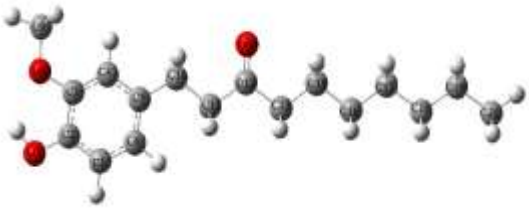
6-gingerol



6-paradol

6-shogaol

8-gingerol

10-gingerol

zingerone

Fig. 1. : Optimized structures of all gingerol variants

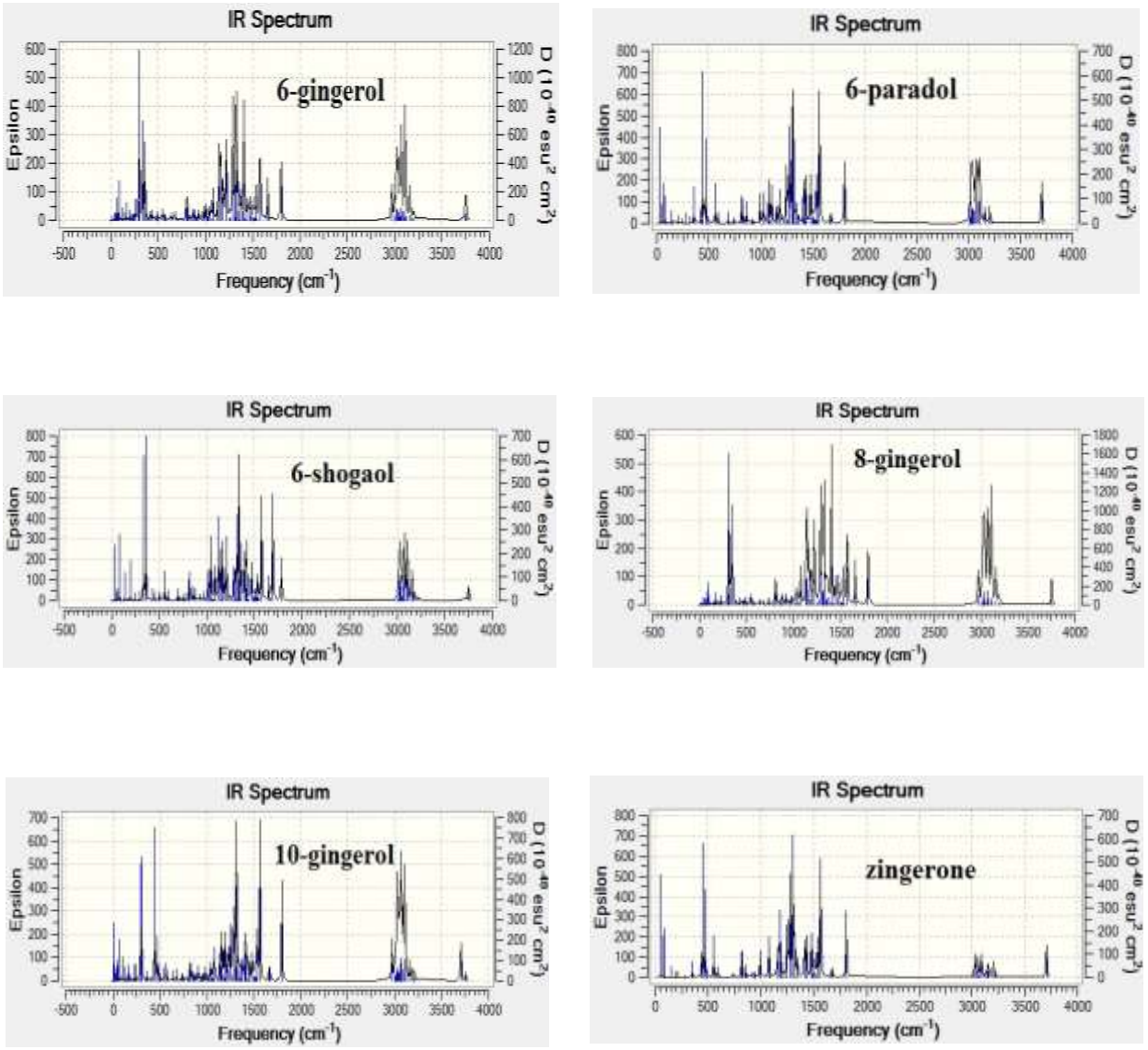
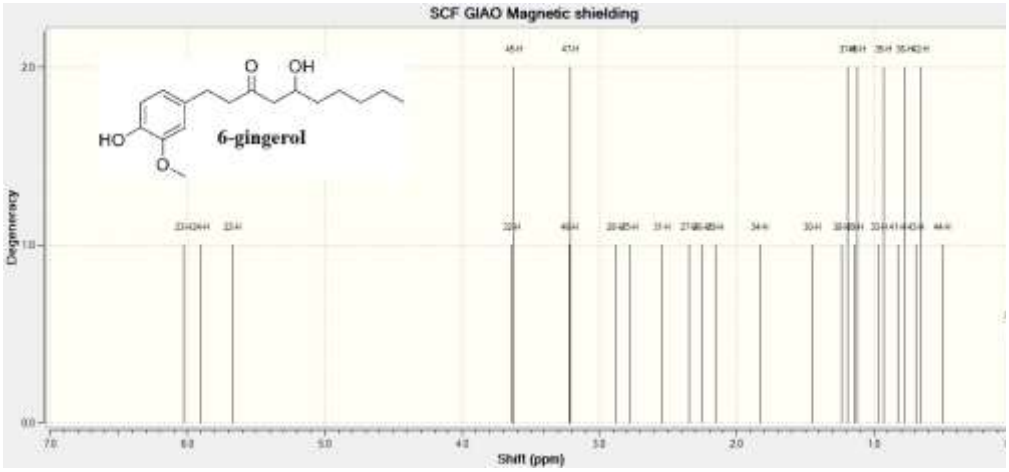
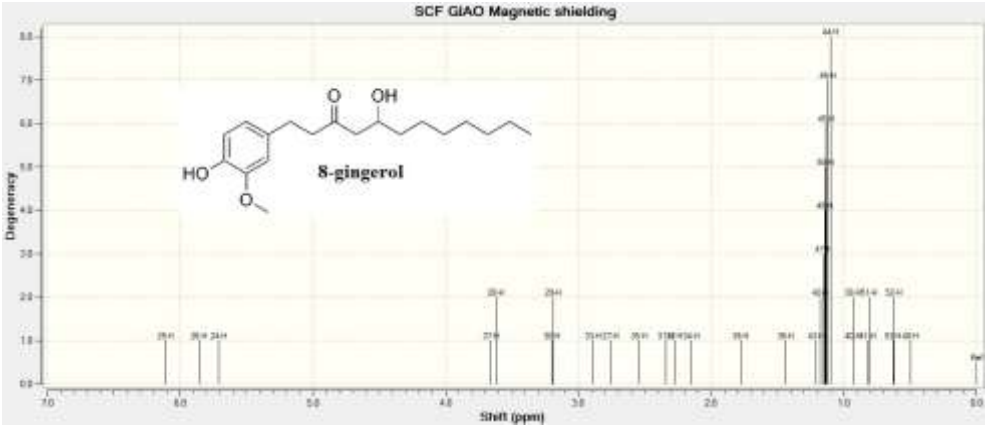
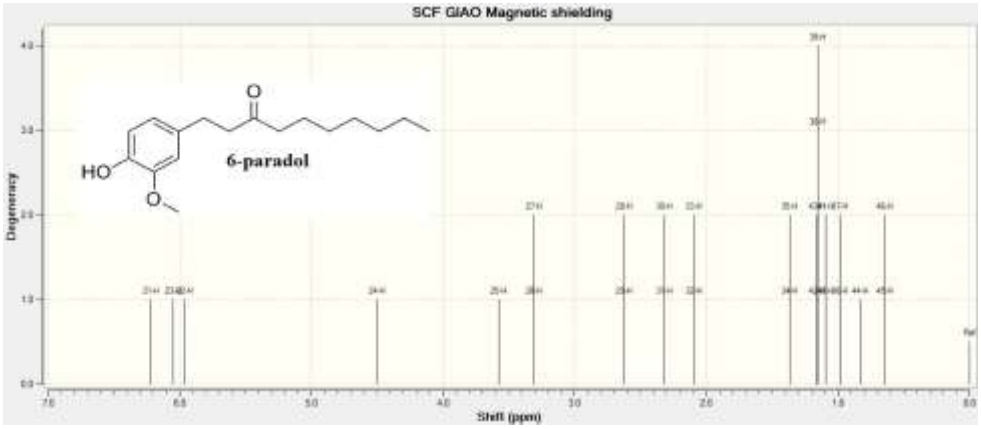
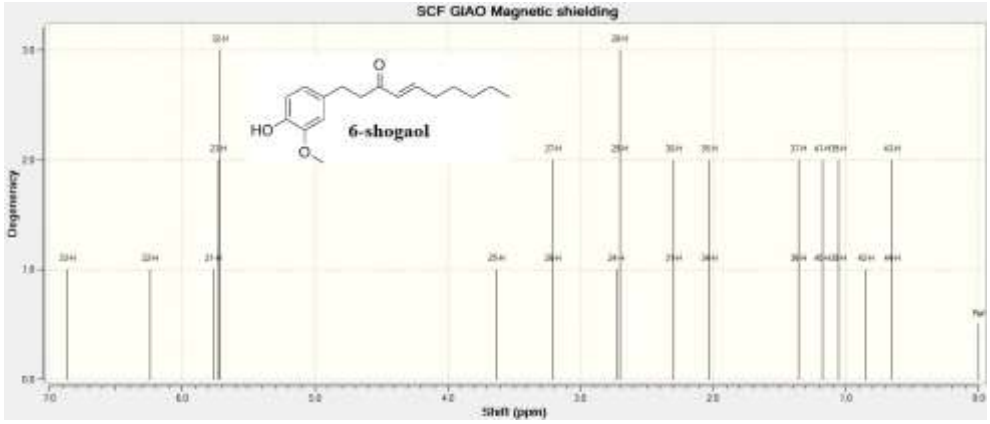


Fig. 2. The IR spectra of molecules under study, Epsilon ≡ Intensity (Km/mol)




SCF GIAO Magnetic shielding
O
OH
HO
O
8-gingerol
Degeneracy
Shift (ppm)


SCF GIAO Magnetic shielding
O
HO
O
6-paradol
Degeneracy
Shift (ppm)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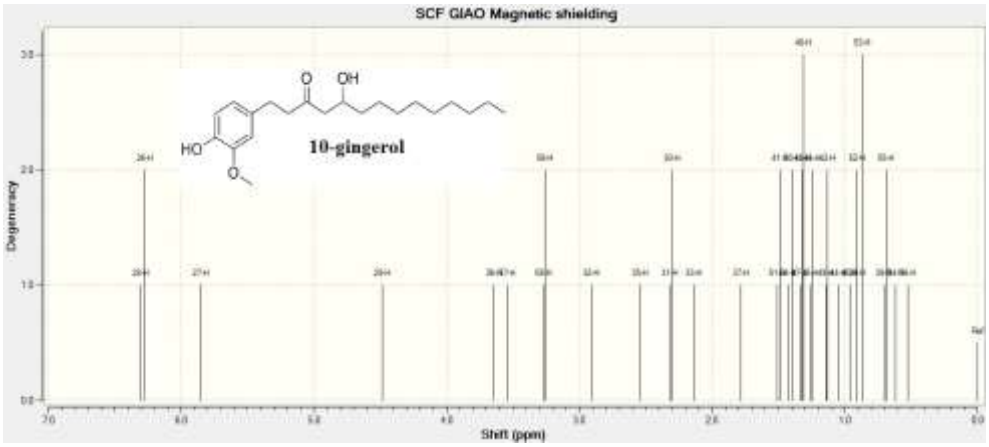
HO
O
6-shogaol
Degeneracy
Shift (ppm)


SCF GIAO Magnetic shielding
O
OH
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10-gingerol
Degeneracy
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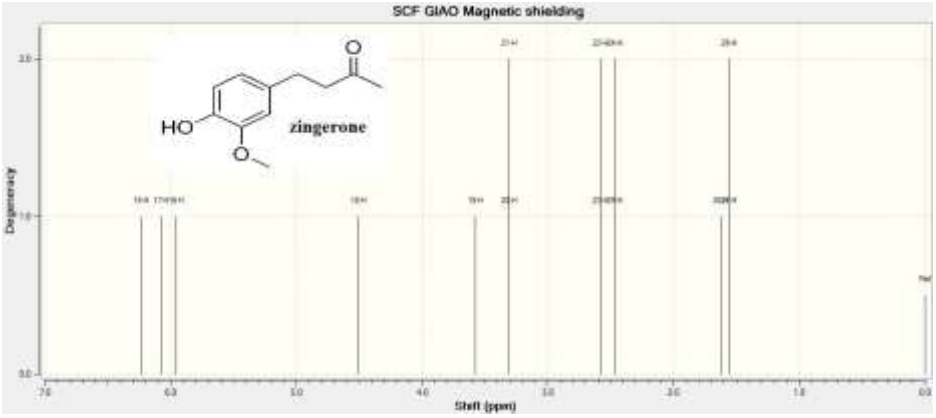
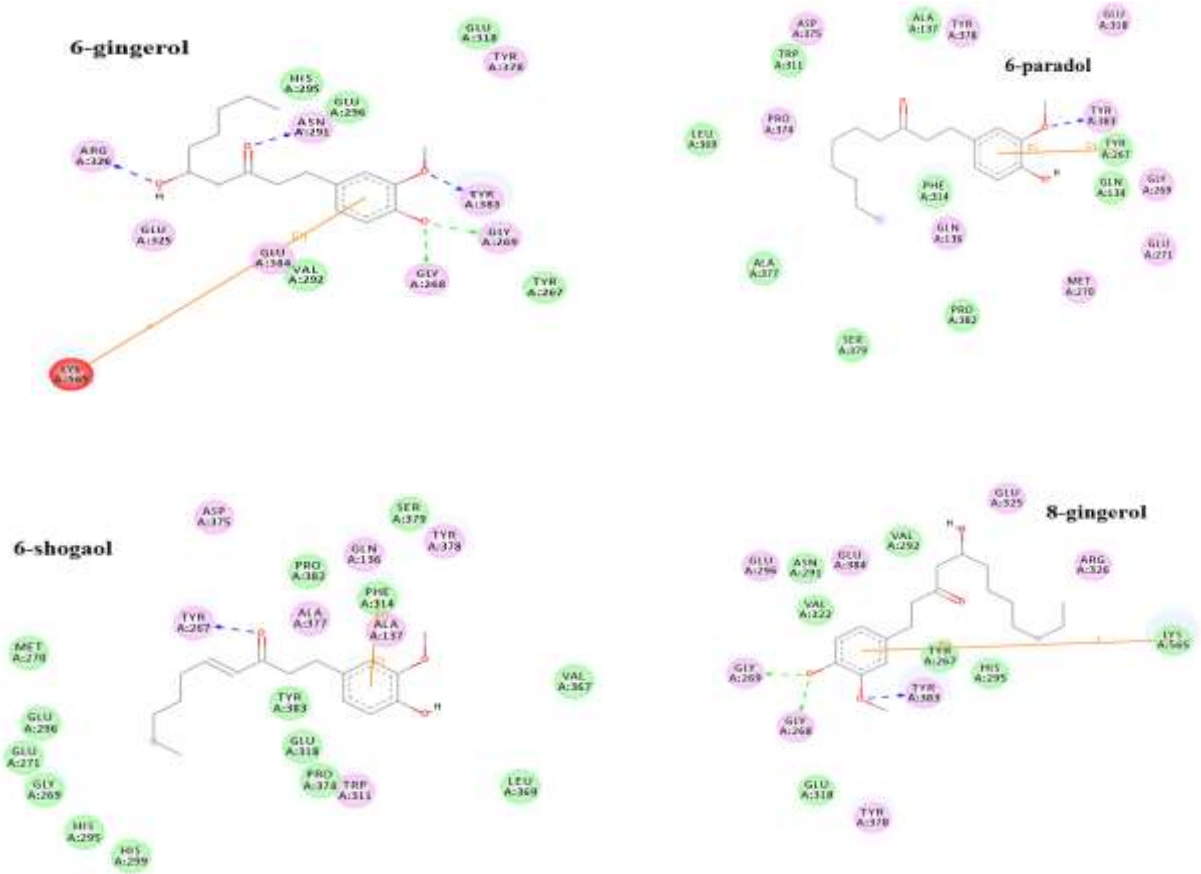


Fig. 3. [1]H-NMR spectra of studied molecules in gas phase using TMS as reference.



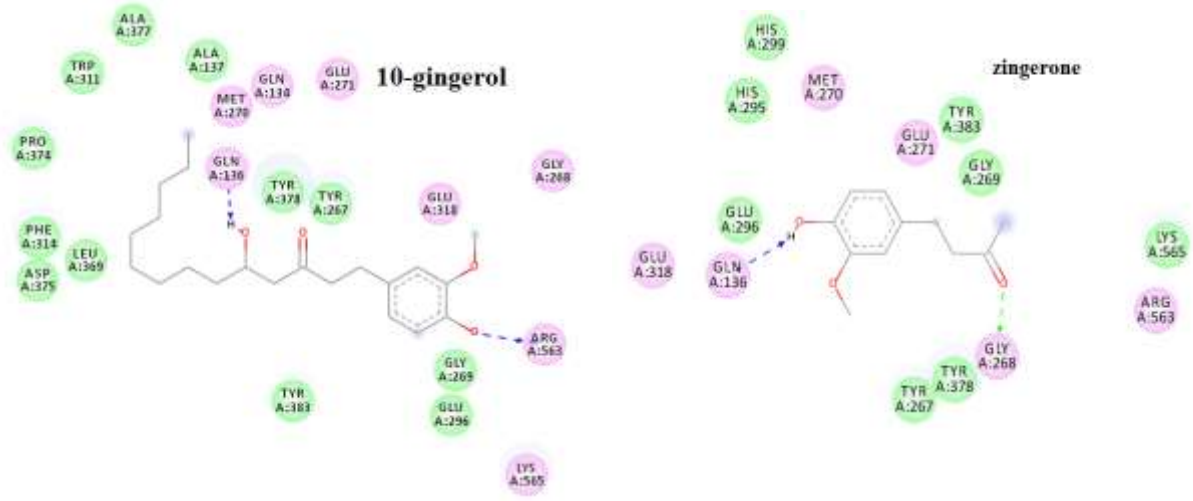


Fig. 4: Binding of gingerol variants with LTA4H protein

Molecule	Energy (a.u.)	Orbital energy (a.u.)		Dipole moment (debye)
		HOMO	LUMO	
6-gingerol (1)	-964.34414	-0.19452	-0.00972	2.8083
6-paradol (2)	-889.14119	-0.20005	-0.01093	0.4961
6-shogoal (3)	-887.90343	-0.19411	-0.04828	2.7074
8-gingerol (4)	-1042.97136	-0.19412	-0.00966	3.0764
10-gingerol (5)	-1121.59948	-0.19589	-0.00985	3.0085
Zingerone (6)	-653.25731	-0.20044	-0.01330	0.3694

Table 1: Total energy, energies of HOMO and LUMO, and dipole moments of the molecules

Mol.	IP (a.u.)		EA (a.u.)		χ (a.u.)		η (a.u.)		S (a.u.)		ω (a.u.)	
	ΔSCF	Koop	ΔSCF	Koop	ΔSCF	Koop	ΔSCF	Koop	ΔSCF	Koop	ΔSCF	Koop
1	0.3473	0.1945	0.1795	0.0097	0.2634	0.1021	0.1678	0.1848	5.9591	5.4112	0.2067	0.0282
2	0.3619	0.2001	0.1783	0.0109	0.2701	0.1055	0.1836	0.1891	5.4454	5.2876	0.1986	0.0294
3	0.3418	0.1941	0.1857	0.0483	0.2638	0.1212	0.1561	0.1458	6.4082	6.8573	0.2229	0.0504
4	0.3445	0.1941	0.1811	0.0097	0.2628	0.1019	0.1635	0.1845	6.1173	5.4213	0.2112	0.0281
5	0.3554	0.1959	0.1723	0.0098	0.2639	0.1029	0.1832	0.1860	5.4588	5.3752	0.1900	0.0284
6	0.3735	0.2004	0.1844	0.0133	0.2789	0.1069	0.1892	0.1871	5.2865	5.3436	0.2057	0.0305

Table 2: Some electronic properties of the molecules

Molecule	IR vibration frequency (cm^{-1})		
	C=O	C—H	O—H
Zingerone	1812 (1726)	3020-3219 (2931, 3024)	3705 (3580)
6-paradol	1805	3010-3218	3706
6-shogoal	1783	3012-3228	3752
6-gingerol	1798 (1708.8)	2970-3210 (2858.3, 2927.7)	3760 (3435)
8-gingerol	1798	2970-3210	3759
10-gingerol	1798	2969-3213	3705

Table 3: IR stretching vibration frequencies (in cm^{-1}) for all the studied molecules. Some available experimental values are given in parentheses.

	1^0-aliphatic proton	2^0-aliphatic proton	Etherial proton	Aromatic proton
Zingerone	1.56-1.62	2.46-2.57	3.3-3.57	5.95-6.2
6-paradol	0.64-0.83	0.98-2.62	3.3-3.6	5.9-6.2
6-shogoal	0.64-0.84	1.17-2.3	3.2-3.6	5.7-6.2
6-gingerol	0.50-0.69 (0.85)	0.7-1.8 (1.2-2.8)	3.2-3.4 (3.85)	5.6-6 (6.61-6.80)
8-gingerol	0.62-0.80	0.82-2.88	3.19-3.6	5.7-6.1
10-gingerol	0.52-0.68	0.65-3.64	3.25-3.54	5.85-6.3

Table 4: ^{1}H-NMR spectral data for all the studied molecules. Experimental values for 6-gingerol are given in brackets. Such values are not available for other molecules.

	MMP9 expression inhibitor		Linoleate diol synthase inhibitor		Ubiquinol-cytochrome-c reductase inhibitor	
	(Pa) (%)	(Pi) (%)	(Pa) (%)	(Pi) (%)	(Pa) (%)	(Pi) (%)
Zingerone	82.2	0.3	90.6	0.3	82.8	2.3
6-Paradol	85.5	0.2	89.7	0.4	85.1	1.7
6-Shogoal	86.3	0.2	92.7	0.3	81.9	2.7
6-Gingerol	91.3	0.1	91.9	0.3	81.7	2.7
8-Gingerol	91.3	0.1	91.1	0.3	81.7	2.7
10-gingerol	91.3	0.1	91.1	0.3	81.7	2.7

Table 5: Common biological activity of all studied molecules.

Molecules	Lowest energy of the molecules after docking with LTA4H (kcal/mol)
6-GINGEROL	-6.7
6-PARADOL	-8.8
6-SHOGAOL	-9.1
8-GINGEROL	-7.2
10-GINGEROL	-8.0
ZINGERONE	-6.5

Table 6: Lowest Energy of different variants after docking with the protein LTA4H