DFT AND MOLECULAR DOCKING STUDIES TO INVESTIGATE THE ANTIOXIDANT MECHANISMS OF QUERCETIN AND ITS METAL COMPLEX DERIVATIVES

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Abstract: The antioxidant activities of flavonoids have been found to occur through different mechanisms. In this study, the Density Functional Theory (DFT) method was employed to investigate the mechanisms for the antioxidant activities of a polyphenolic flavonoid, Quercetin and its three metal complex derivatives at the level B3LYP/6-31G (d) and B3LYP/LanL2DZ level of theories respectively. The bond dissociation enthalpies (BDEs), ionization potentials (IPs), proton dissociation enthalpies (PDEs), proton affinities (PAs), and electron transfer enthalpies (ETEs) connected to the H-atom transfer (HAT), single electron transfer-proton transfer (SET-PT) and sequential proton loss electron transfer (SPLET) mechanisms respectively were determined for quercetin, quercetin-cadmium complex1[Cd (Q) (Bpy) $(CH_3COO)_2$] , quercetin-cadmium complex2 [Cd (Q) (Phen) $(CH_3COO)_2$] and quercetin-vanadium complex $[VO(Que)_2]$. The IP values for most phenolic -OH positions of the three metal complex derivatives studied are lower in magnitude when compared with their corresponding BDE values but the natural flavonoid, quercetin shows a considerable higher IP values for the phenolic-OH positions. The results suggest that quercetin uses the HAT mechanism for its antioxidant activity, while its three metal complexes preferred the SET-PT mechanism. The Molecular docking experiment showed successful binding of studied compounds to the standard drug's binding pocket on the receptor with binding affinities -35.6 $kJmol^{-1}$, -38.5 $kJmol^{-1}$, -39.3 $kJmol^{-1}$ and -39.7 $kJmol^{-1}$ for quercetin, quercetin-Cd complex1, quercetin-V complex and quercetin-Cd complex2 respectively.

Keywords: DFT, Flavonoids, Ionization potentials, Phenolic-OH, Proton affinities, Quercetin.

Introduction

Flavonoids (from the Latin "flavus," yellow) are secondary plant metabolites naturally occurring in seeds, fruit skin, peel, and bark of plants (George *et al*., 2017). Flavonoids are important components of the human diet, the major sources of flavonoids being apples, red fruits, onions, citrus fruits, nuts, and beverages such as tea, beer, and wine. Although they are not considered nutrients, due to the variety of pharmacological activities in the mammalian body, flavonoids are more correctly referred to as "nutraceuticals" (Tapas *et al*., 2008).

Due to the presence of hydroxyl and oxo groups within flavonoids, they possess metal chelating abilities that can have profound effects on their pharmacokinetic and pharmacological properties. The flavonoid structure, type of chelating metal and the pH of the surrounding medium are determining factors of the preferred coordination site (Kasprza *et al*., 2015).

Quercetin is a polyphenolic flavonoid compound (Rauf *et al*., 2018) which is abundantly present in kales, onions, berries, apples, red grapes, broccoli, and cherries, as well as tea and red wine. Modern studies have shown that quercetin prevents various diseases, such as osteoporosis, some forms of cancer, tumours, and lung and cardiovascular diseases. The antioxidant effects of quercetin play a significant role in the prevention and treatment of such diseases (Boots *et al*., 2008). Moreover, owing to its high solubility and bioavailability, quercetin may also exhibit strong antioxidant activity after forming a complex or combining to form some novel preparations used for human health care. At the same time, according to the bibliometric analysis results based on the Web of Science database, the antioxidant property of quercetin has become a research hotspot (Xu *et al*., 2019). Due to the poor water solubility and low bioavailability (5.3%) of quercetin, several studies have been performed to modify its structure to increase its water solubility and bioavailability, and thus enhance its antioxidant activity (Chen *et al*., 2005).

The modification process of quercetin is generally divided into two types, namely, the derivation of quercetin or recombination with other active groups. The former changes the structure of quercetin and improves its solubility through derivation, while the latter produces a synergistic effect based on the properties of active groups and quercetin, such as metal complexes of quercetin. Moreover, the bioactivity and pharmacological action of quercetin are significantly enhanced after forming complexes with some metal or complex ions. Therefore, many researchers have attempted to improve the antioxidant activity of quercetin using the complex formation method (Xu *et al*., 2019). Recently, the development of metal-based compounds with flavonoids has been stimulated and the complexation of flavonoids like quercetin, rutin and luteolin with a large number of metal cations such as Cu(II), Zn(II), V(II), Mo(VI), Fe(II), Fe(III), Sn(II), Cr(III) and Cd(II) have already been reported (Dong *et al*., 2017). The complex formation between luteolin and vanadium (IV) oxide sulphate monohydrate was investigated by Roy *et al*., (2014) and it was observed that the free radical scavenging activity and ferric ion reducing potential of luteolin was increased after the formation of complex with vanadium oxide cation.

Phenolics scavenge free radicals usually via any of the following three mechanisms; Hydrogen atom transfer (HAT), Single electron transfer-proton transfer (SET-PT) and the Sequential proton loss-electron transfer (SPLET) mechanisms (Wright *et al*., 2001, Musialik *et al*., 2005, Vafiadis *et al*., 2005, Leopoldini *et al*., 2006, Platzer *et al*., 2021).

(i) Hydrogen atom transfer (HAT);

$ArOH + R^{\cdot} \rightarrow ArO^{\cdot} + RH$ ---------- (1)

In the HAT mechanism, the bond dissociation enthalpy (BDE) of the phenolic O–H bond is an important parameter in evaluating the antioxidant action. The BDE is evaluated from the enthalpy values of the species in equation (1) as:

$BDE = H_{(ArO^{\cdot})} + H_{(H^{+})} - H_{(ArOH)}$ ---------- (2)

(ii) Single electron transfer (SET) mechanisms;

$ArOH + R^{\cdot} \rightarrow ArOH^{\cdot +} + R^{-} \rightarrow ArO^{\cdot} + RH$ ---------- (3)

This mechanism is divided into two; Single electron transfer-proton transfer (SET-PT) and the Sequential proton loss-electron transfer (SPLET) mechanisms

In the SET-PT mechanism the ionization potential (IP) of the molecule and proton dissociation enthalpy (PDE) from $ArOH^{\cdot +}$ are important. The IP and PDE are respectively calculated from the enthalpies values as:

$IP = H_{(ArOH^{+\cdot})} + H_{(e^{-})} - H_{(ArOH)}$ (4) and

$PDE = H_{(ArO^{\cdot})} + H_{(H^{+})} - H_{(ArOH^{+\cdot})}$ (5)

The SPLET mechanism is also a two steps mechanism with the proton affinity (PA) of the anion, ArO^{-} connected to the first step (6) while the second step (7) is governed by the electron transfer enthalpy (ETE).

$ArOH \rightarrow ArO^{-} + H^{+}$ (6)

$ArO^{-} + R^{\cdot} \rightarrow ArO^{\cdot} + R^{-}$ (7)

$R^{-} + H^{+} \rightarrow RH$ (8)

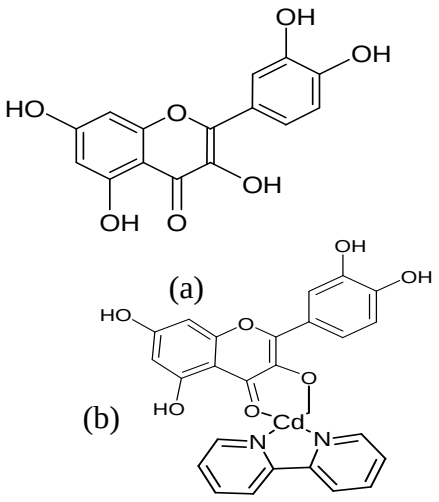
The PA and ETE are respectively calculated from the enthalpies values as:

$PA = H_{(ArO^{-})} + H_{(H^{+})} - H_{(ArOH)}$ (9) and

$ETE = H_{(ArO^{\cdot})} + H_{(e^{-})} - H_{(ArO^{-})}$ (10)

The enthalpies values of 6.19700 kJmol^{-1} and 3.1449998 kJmol^{-1} for the proton ($H_{(H^{+})}$) and electron ($H_{(e^{-})}$) respectively were taken from the literature (Bartmess *et al*., 1994).

In this study, the radical scavenging activity of quercetin, quercetin-Cd Complex1, quercetin-Cd Complex2 and quercetin-V complex (Fig. 1) were investigated in terms of some key parameters such as BDE, IP, PDE, PA, and ETE using the density functional theory. The binding affinities and the nature of interactions of these compounds with xanthine oxidase receptor were studied with molecular docking.



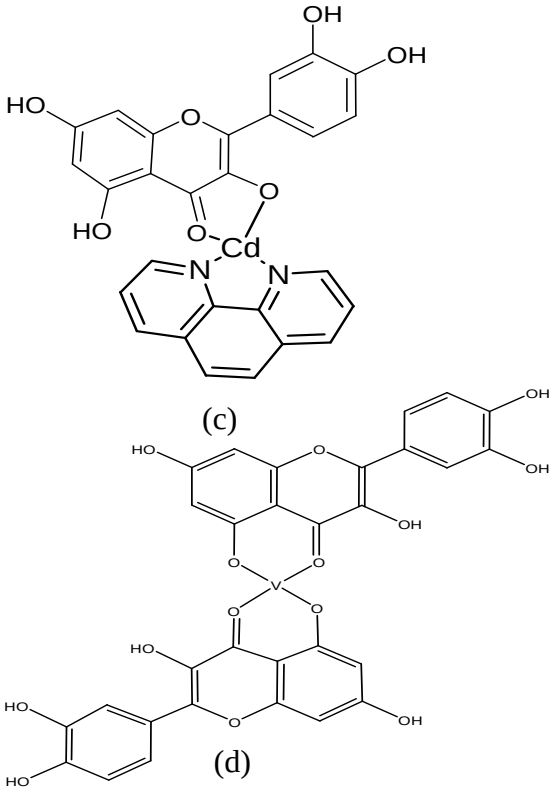


Fig. 1: *Structure of (a) Quercetin, (b) Quercetin-Cd Complex1, (c) Quercetin-Cd complex2 (d) Quercetin-V complex.*

Methodology

All the density functional theory (DFT) calculations were carried out with the General Atomic and Molecular Electronic Structure System (GAMESS) software (Schmidt *et al*., 1993, Gordon and Schmidt, 2005). The molecular and vibrational properties of the compounds were computed at the B3LYP level of theory with the standard 6-31G (d) and LanL2DZ basis sets. In the ground state, the parent molecules were optimized at the B3LYP level of theory and with the 6-31G (d) basis set for the natural flavonoid Quercetin and LanL2DZ basis set for the metal complexes. The optimizations of the corresponding cations, anions and neutral radicals were also carried out at the same level of theory and basis sets

The harmonic vibrational frequency calculations on the optimized structures of the parent molecules and radicals were carried out to characterize the electronic transitions using the time-dependent density functional theory (TD-DFT) at both B3LYP/6-31G(d) and B3LYP/LanL2DZ for quercetin and the metal complexes respectively.

Molecular Docking Studies

Crystal structure of Hypoxanthine–Xanthine oxidase complex (PDB ID: 3NRZ) (Cao *et al.*, 2010) was downloaded from Protein Data Bank (http://www.rcsb.org/pdb). Co-crystal ligands, water and ions were removed and hydrogen were added. Energy minimization using steepest descent algorithms was employed to obtain a stable conformation of the Xanthine oxidase (XO) receptor. Following this initial preparation of the receptor, molecular docking experiment were successfully performed with the AutoDock Vina and AutoDock version 4.2.5.1 docking program (Morris *et*

al., 2009). The Lamarkian Genetic Algorithm stochastic search method (Morris *et al.*, 1998) was implemented with the semi-empirical free-energy force field scoring function used to represent the potential energy surface of the ligand−protein interaction. The structures of two standard drugs for xanthine oxidase inhibition, allopurinol and febuxostat (Love *et al.*, 2010) were downloaded from the PubChem repository (Kim *et al.*, 2019) with Pubchem CIDs 135401907 and 134018, respectively. The optimized structures of the four studied compounds and the two standard drugs, were docked to the xanthine oxidase receptor as a target using the reported binding sites in the hypoxanthine-xanthine oxidase complex (Cao *et al.*, 2010) to detect the native ligand-receptor conformations in accordance with the AutoDock4 docking protocol (Morris *et al.*, 2009).

Results and Discussion

Optimized Geometries of Molecules and their Radicals

The most stable geometries of the compounds under study were obtained from optimizing the initial structures at the level B3LYP/6-31G(d) for the natural polyphenols and B3LYP/LanL2DZ for the metal-complex derivatives. The most stable optimized geometries are presented in Fig. 2.

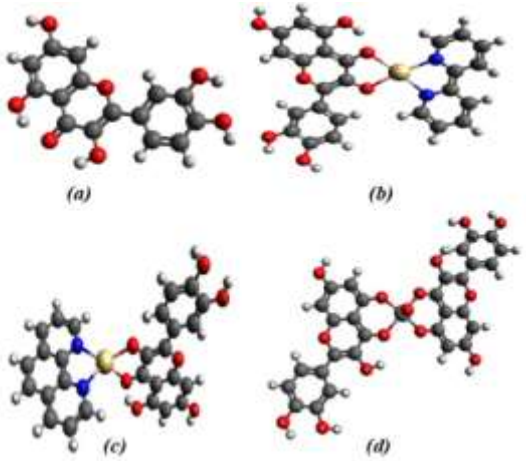


Fig. 2: *Optimized geometries of the most stable structures of the compounds (a) Quercetin (b) Quercetin-Cd complex1[Cd (Q)(Bpy)($CH_3COO)_2$] (c) Quercetin-Cd complex2 [Cd(Q)(Phen)($CH_3COO)_2$] (d) Quercetin-V complex [$VO(Que)_2$].*

The Mechanisms of Antioxidant Activity

The HAT Mechanism

The BDEs values calculated for the natural quercetin and the metal derivatives in gas phase and aqueous solvent are as presented in Table 1. From the computed BDE values for quercetin and the three metal complex derivatives shown in Table 1. The lowest BDE values in gas-phase are 1594.73 $kJmol^{-1}$ at 4'–OH, 1540.92 $kJmol^{-1}$ at 7–OH, 1634.98 $kJmol^{-1}$ at 3–OH and 1721.79 $kJmol^{-1}$ at 7–OH for quercetin-Cd complex1, quercetin-Cd complex2, quercetin and quercetin-V complex respectively. Thus, the BDE values in the gas phase of quercetin follows the sequence 3-OH < 4′–OH < 7–OH < 5– OH < 3′–OH, quercetin-Cd metal complex1 follows the similar order. However, quercetin-Cd metal complex2 and quercetin-V complex follows a slightly different order.

Table 1: Bond Dissociation Enthalpies of Quercetin and the metal complex derivatives in Aqueous and gas phase

	Quercetin BDE ($kJmol^{-1}$)		**Quercetin-Cd complex 1 BDE ($kJmol^{-1}$)**		**Quercetin-Cd complex 2 BDE ($kJmol^{-1}$)**		**Quercetin-V complex BDE ($kJmol^{-1}$)**	
Radical position	Gas Phase	Aqueous phase	Gas Phase	Aqueous phase	Gas Phase	Aqueous phase	Gas Phase	Aqueous phase
3-OH	1634.98	1623.76	1524.94	1423.10	1596.73	1554.60	1725.52	1683.68
5-OH	1777.40	1760.16	1641.17	1602.59	1636.02	1520.38	1724.01	1680.96
7-OH	1754.30	1728.11	1628.28	1475.36	1540.92	1477.41	1721.79	1675.18
3′-OH	2095.22	1738.95	1692.38	1646.52	1686.65	1521.88	1780.25	1727.11
4′-OH	1700.62	1678.50	1594.73	1518.54	1634.81	1497.91	1786.19	1700.37

In the aqueous phase the BDE of quercetin and its metal complex derivatives have lower values compared to the corresponding gaseous phase species. This implies that the HAT mechanism of their antioxidant activities is more favoured in aqueous media. The lowest BDE values in aqeous-phase are 1475.36 $kJmol^{-1}$ at 7–OH, 1477.41 $kJmol^{-1}$ at 7–OH, 1678.50 $kJmol^{-1}$ at 4'–OH and 1683.68 $kJmol^{-1}$ at 3–OH for quercetin-Cd complex1, quercetin-Cd complex2, quercetin and quercetin-V complex respectively.

The Sequential Electron Transfer Proton Transfer (SET-PT) Mechanism

The calculated IPs and PDEs are presented in Table 2. Lower IP values imply the molecules are more prone to ionization and easier in electron-transfer rate between free radicals and antioxidants. Quercetin-Cd complex2 has the lowest IP value (460.49 kJmol^{-1}) compared to quercetin, quercetin-Cd complex1 and quercetin-V complex with low IP values of 2263.63 kJmol^{-1}, 453.42 kJmol^{-1} and 648.23 kJmol^{-1} respectively. The IP values have the following sequence, quercetin-Cd complex2 < quercetin-Cd complex1 < quercetin V complex < quercetin. This order reveals that quercetin-Cd complex2 is the most active antioxidant when considering SET-PT mechanism. The result obtained is in agreement with experimental results and reported by Srivastavaa *et al.* in 2020 and Khater *et al.* in 2019.

Table 2: The calculated IPs and PDEs of the Quercetin and the metal complex derivatives in aqueous and gas phase

	Compound	**Radical Position**	**IP (kJmol^{-1})**		**PDE (kJmol^{-1})**	
			Gas Phase	Aqueous Phase	Gas Phase	Aqueous Phase
1	Quercetin	3-OH	2273.79	2117.22	-635.67	-490.32
		5-OH	2456.34	2273.71	-675.79	-510.40
		7-OH	2374.83	2214.08	-617.39	-482.83
		3′-OH	2337.34	2174.42	-238.99	-432.33
		4′-OH	2263.63	2121.41	-559.86	-439.78
2	Quercetin-Cd complex-1	5-OH	460.49	386.60	1183.82	1235.45
		7-OH	460.52	284.38	1170.89	1194.11
		3′-OH	460.57	283.42	1234.94	1240.72
		4′-OH	460.61	286.60	1137.25	1235.07
3	Quercetin-Cd complex-2	5-OH	452.79	2078.69	1186.37	-555.17
		7-OH	452.79	287.69	1174.95	1192.85
		3′-OH	453.42	287.31	1236.37	1237.71
		4′-OH	479.36	298.36	1158.59	1203.31
4	Quercetin-V complex	3-OH	649.48	529.52	1079.17	1157.29
		7-OH	649.48	551.20	1075.45	1156.41
		3′-OH	648.23	551.24	1135.16	1179.00
		4′-OH	683.74	551.24	1105.91	1152.27

In the second step of the SET mechanism, the important parameter, PDE, measures the tendency of deprotonation of radical cations formed in the first step. Although the IP trend appears to be slightly different from that of BDE, the PDE value and the sum of these two steps energies; IP + PDE (Table 3) follows the same trend as BDE (Table 1).

The IP values for most of the compounds studied are lower in magnitude when compared with the corresponding BDE values with the exception of quercetin which shows a considerable higher IP value. This implies that the Sequential Electron Transfer Proton Transfer mechanism is the preferred mechanism for the antioxidant activities of the compounds except quercetin.

Table 3: The SET-PT Mechanism (IP + PDE) of the Quercetin and the metal complex derivatives in gas phase and aqueous

	Quercetin		**Quercetin-Cd complex 1**		**Quercetin-Cd complex 2**		**Quercetin-V complex**	
Radical position	Gas Phase	Aqueous phase	Gas Phase	Aqueous phase	Gas Phase	Aqueous phase	Gas Phase	Aqueous phase
3-OH	1638.11	1626.90	1559.00	1530.67	1554.39	1542.80	1728.66	1686.82
5-OH	1780.54	1763.30	1644.31	1522.05	1639.16	1523.51	1693.43	1667.57
7-OH	1757.44	1731.25	1631.42	1478.50	1627.74	1480.55	1724.93	1707.61
3'-OH	2098.35	1742.09	1695.52	1524.14	1689.79	1525.02	1783.38	1730.25
4'-OH	1703.76	1681.63	1597.86	1521.67	1637.95	1501.05	1789.66	1703.51

The Sequential Proton Loss Electron Transfer Mechanism

The sequential proton loss electron transfer (SPLET) path has been suggested as a possible route to trap radical particularly in polar environments. The values obtained for proton affinity (PA) and electron transfer enthalpy (ETEs) for the different phenolic-OH positions (Table 4) show that the first step of the SPLET mechanism (PA) requires much more energy than the second step (ETE). This indicates that the first step is the slowest and the rate-determining step. For all the studied compounds, the PA values of the solvated species decrease drastically, this can be attributed to the relatively high enthalpies of proton and anion solvation

The antioxidant activity of the studied compounds can be arranged according to the lowest PA values in the following sequence: quercetin-Cd complex2 > quercetin-Cd complex1 > quercetin > quercetin-V complex.

A comparison of the result obtained for the three mechanisms from the studied compounds revealed that only quercetin, the natural flavonoid, uses the HAT mechanism for its antioxidant activity, because the BDE values for the phenolic-OH positions are lower compared to the IP and PA values. The three metal complex derivatives of quercetin preferred the SET-PT mechanism as evident from their lower IP values compared to the BDE and PA values.

Table 4 The computed PA and ETE of the Quercetin and the metal complex derivatives in gas and Aqueous phase

	Compound	Radical position	**PA (kJmol^{-1})**		**ETE (kJmol^{-1})**	
			Gas Phase	Aqueous Phase	Gas Phase	Aqueous Phase
1	Quercetin	3-OH	1634.98	1248.96	207.06	377.94
		5-OH	1777.40	1261.68	323.84	501.61
		7-OH	1754.30	1224.78	359.99	506.47
		3'-OH	2095.22	1268.50	640.40	473.58
		4'-OH	1700.62	1211.30	344.51	470.32
2	Quercetin-Cd complex-1	5-OH	1641.17	1219.55	227.40	302.50
		7-OH	1628.28	1191.72	278.40	286.77
		3'-OH	1692.38	1235.53	255.85	288.61
		4'-OH	1594.73	1187.96	265.51	330.53
3	Quercetin-Cd complex-2	5-OH	1636.02	1240.55	222.46	282.96
		7-OH	1624.60	1193.40	274.80	287.14
		3'-OH	1686.65	2512.07	253.71	-987.04
		4'-OH	1634.81	1217.46	258.40	283.59
4	Quercetin-V Complex	3-OH	1725.52	1170.05	361.53	516.76
		7-OH	1721.79	1185.91	392.91	521.70
		3'-OH	1780.25	1189.76	406.47	540.48
		4'-OH	1786.52	1172.90	431.57	530.61

Molecular Docking

Molecular docking results showed that studied compounds formed stable complexes with the receptor and interacted well with the active sites of the receptor binding at one of the experimental binding pockets (inhibition zone II) of the xanthine oxidase where febuxostat, the non-purine based drug binds (Fig. 3). This shows that the mechanism for the antioxidant activities of quercetin and its metal complexes is similar to that of non-purine based drug since none of the studied compounds binds to the purine based drug binding pocket (inhibition zone I).

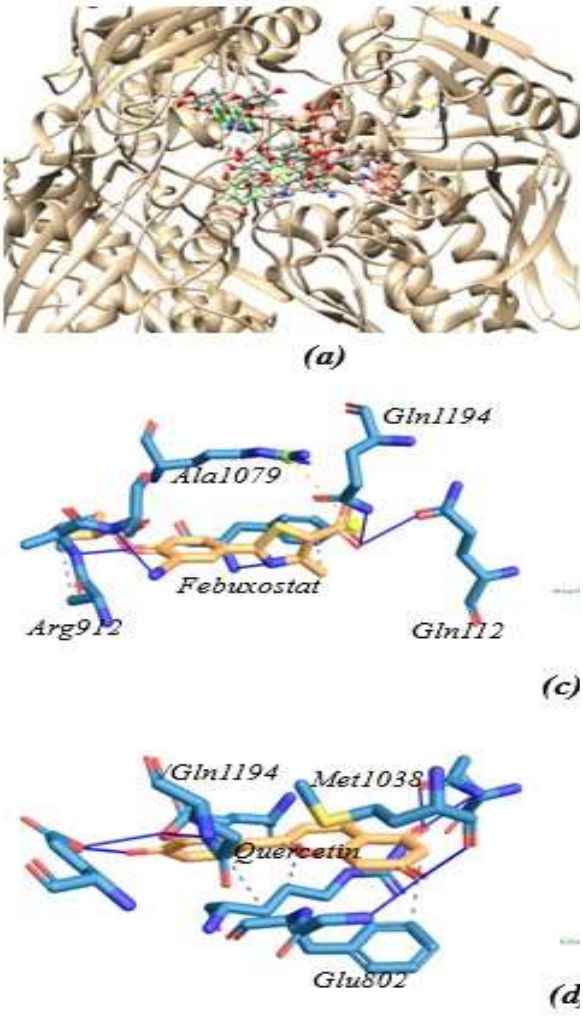


Fig. 3: Ligand binding and interactions with xanthine oxidase receptor

Table 5: The binding affinity and molecular interactions of the docked ligands with xanthine oxidase

Quercetin and the metal complexes under study bind to the xanthine oxidase receptor with binding affinities that are comparable to the binding affinity of febuxostat , the standard drug for xanthine oxidase inhibition. Febuxostat and the studied compounds interacted favourably with the inhibition zone II of xanthine oxidase receptor via

No.	Compound	Binding Affinity ($kJmol^{-1}$)	Interaction Type	Amino Acid Involved in Interaction
1	Allopurinol	-22.2	Hydrogen bonding	GLU428, GLY502, GLY503, HIS1212, TYR1213, HIS1220, SER1214
2	Febuxostat	-33.5	Hydrogen bonding	GLN112, PHE798, ALA1079, SER1080, GLN1194
			Salt Bridges	ARG912
			π-Cation Interactions	ARG880, ARG912
3	Quercetin	-35.6	Hydrogen bonding	GLY 797, GLU 802, MET1038, GLN 1194
4	Quercetin-Cd Complex1	-38.5	Hydrogen bonding	ALA1079, SER1080, THR1083
5	Quercetin-Cd Complex2	-39.7	Hydrogen bonding	PHE911, GLY913, GLN104, ALA107, ALA1079, SER1080, VAL1081, GLU 1261
6	Quercetin-V Complex	-39.3	Hydrogen bonding	CYS113, PHE798, GLU802, ARG880, GLY913, THR1010, VAL1011, MET1038, ALA1079, SER1080, GLN1194, VAL1259, GLY1260, GLU1261, ARG912

several non-bonded interactions, which were mainly hydrogen-bonding and hydrophobic interactions (Table 5). The binding affinity of quercetin is -35.6 $kJmol^{-1}$, this is better and compares reasonably well with the binding affinity of the standard drug, febuxostat which is -33.5 $kJmol^{-1}$. The binding affinities of -38.5 $kJmol^{-1}$, -39.3 $kJmol^{-1}$ and -39.7 $kJmol^{-1}$ for quercetin-Cd complex1, quercetin-V complex and quercetin-Cd complex2 respectively implies that the three quercetin-metal complexes have lower binding affinities than quercetin and this further confirm the experimental study's findings that the formation of metal complexes derivatives of polyphenolic compounds result in improved antioxidant activities of these compounds (Roy *et al*., 2014, Dong *et al*., 2017, Xu *et al*., 2019).
quercetin binds via hydrogen-bonding interactions with GLY 797, GLU 802, MET 1038 and GLN 1194, quercetin-Cd complex1 binds via hydrogen-bonding interactions with ALA1079, SER1080 and THR1083. quercetin-Cd complex2 binds via hydrogen-bonding interactions with PHE911, GLY913, GLN104, ALA107, ALA1079, SER1080, VAL1081 and GLU 1261. While quercetin-V complex binds via hydrogen-bonding interactions with CYS113, PHE798, GLU802, ARG880, GLY913, THR1010, VAL1011, MET1038, ALA1079, SER1080, GLN1194, VAL1259, GLY1260, GLU1261, ARG912. Finally, the reference compound, febuxostat, which is a known xanthine oxidase inhibitor, displays conventional hydrogen- bonding interactions with GLN112, PHE798, ALA1079, SER1080 and GLN1194; and Salt Bridge with ARG912. These results regarding hypoxanthine and febuxostat are in agreement with those found in the literature **(**Yusuff *et al.*, 2019). This result indeed further supports and explains the antioxidant activity of the quercetin and its metal complexes derivatives.

Conclusion

The results obtained from our DFT calculations revealed that quercetin and the three metal complexes successfully binds to the same active binding site of xanthine oxidase (inhibition zone II) where the standard drug febuxostat binds confirming their potency as antioxidant. It is also evident from this study that quercetin follows the hydrogen atom transfer (HAT) mechanism for its antioxidant activity, due to its lower BDE values compared to the IP and PA values while its metal complex derivatives preferred the Single electron transfer-proton transfer (SET-PT) mechanism as evident from their lower IP values compared to the BDE and PA values.

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Declarations
Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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