RESEARCH ARTICLE

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Molecular Docking and Dynamic Studies of Chlorogenic Acid Isomers as Antagonists of p53 Transcription Factor for Potential Adjuvant Radiotherapy

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Abstract

Objective: Chlorogenic acids (CGAs) are among potential natural radioprotectant for inhibiting inappropriate p53 activation of adjacent normal tissues upon radiotherapy. However, previous studies are mainly focused on 5-O-caffeoylquinic acid (5CGA). In this study, the antagonist role of three CGAs isomers against p53 protein is assed for potential anti-apoptotic activity using molecular docking and dynamic experiments. **Methods:** The physicochemical and pharmacokinetic profile three CGA isomers (3-O-caffeoylquinic acid (3CGA), 4-O-caffeoylquinic acid (4CGA), and 5CGA) were predicted using SwissADME web. Subsequently, they were subjected to docking using AutoDock software against to p53's L1/S3 pocket. The best binding pose was advanced to molecular dynamic (MD) simulation spanning 5 ns to evaluate the time dependent stability using Visual Dynamic web. **Results:** The SwissADME prediction showed that the position of esterification on quinic moiety had no impact on the physicochemical and pharmacokinetic of CGA isomers. They only violated one out of five Lipinski's rules with the Abbot's bioavailability score of 0.11. The docking results revealed that the 4CGA has the highest binding energy (-5.41 kCal/mol) on L1/S3 pocket of p53 protein followed by 5CGA (-4.81 kCal/mol) and 3CGA (-4.62 kCal/mol). The MD simulation showed that the p53 complex with each CGA isomers had a root mean square deviation of less than 0.25 nm and a radius gyration that of close to reference apoprotein. Importantly, fluctuation of important residues at L1/S3 pocket was decrease through complex formation with 3CGA (at His155 and Ser121) and 4CGA (Lys120 and Ser121). **Conclusion:** The CGA isomers satisfy the drug-likeness for a potential oral medicine. They potentially play role as anti-apoptotic agent through binding with p53's pocket that involves in DNA transcriptional activity. Among them, the 4CGA possess the highest potential due to its highest free binding affinity and its ability to stabilize the residues fluctuation in L1/S3 pocket.

Keywords: Chlorogenic acid- isomerization- p53- molecular docking, molecular dynamic

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Introduction

Radiotherapy is one particularly potent cytotoxic treatment for localized solid tumors that can be used for both palliative and curative purposes. In spite of its effectiveness, it present threat by damaging or kill adjacent normal cells [1]. At present, amifostine is the only FDA-approved adjuvant radiotherapy being utilized to reduce the cytotoxic impact of radiation therapy in clinical settings. It is an organic thiophosphate prodrug which acts as a free radicals scavenger. The drug is typically administered intravenously before radiotherapy, with a short half-life requiring injection 15-30 minutes beforehand [2]. The short-half life and difficulty in administration procedure has led to investigation for natural product-based adjuvant radiotherapy as an alternative solution.

Chlorogenic acids (CGAs) have been reported as one amongst of natural products with potential radioprotection activity [3-5]. This is a group of water soluble polyphenols whose chemical structure consist of an aromatic ring and an alicyclic with one or more hydroxyl groups. They are widely distributed in plant materials, especially in high concentrations in coffee beans [6]. CGAs show antioxidant activity which could scavenge free radicals or reduce oxidative damage. Cinkilic et al. [3] showed that the pre-treatment with chlorogenic acid was an efficient radioprotective procedure protecting non-tumorigenic human lymphocytes from the damaging effects of X-ray irradiation. Yin et al. [4] reported that chlorogenic acid from coffee reduces radiation-induced apoptosis and DNA

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damage in hepatocellular carcinoma. While, Abedpour et al. reported [5] the protective effects of chlorogenic acid against ionizing radiation-induced testicular toxicity.

Previous studies [3-5] on CGAs as a potential radioprotectant are mainly focused on neochlorogenic acid/5-O-caffeoylquinic acid (5CGA). Indeed the 5CGA is a most abundant isomer among caffeoylquinic acid isomers. However, being part of the CGAs family, other chlorogenic acid isomers may also exhibit biological effects and potentially demonstrate different radioprotection activities. To our knowledge, there has been minimal research done to explore potential variations in biological activities among the isomers. While, the chlorogenic acid can undergo isomerization as a result of hydrolysis and the removal of ester groups during extraction using various methods [7, 8], which may result in the change of its bioactivity. Therefore, such comparisons are crucial for chlorogenic acid preparation and its utilization in medicine, in particular as the adjuvant radiotherapy.

Concerning the radiotherapy, the tumor suppressor p53 is a master regulator which plays a crucial role in managing cell fate following exposure to radiation. Exposure to ionizing radiation can lead to the activation of p53 signaling. The activation can promote cell survival through mediating cycle arrest and DNA repair, or lead to cell death through inducing the intrinsic pathway of apoptosis and cell senescence [9]. Counterintuitively, inappropriate p53 activation in normal tissues during cancer therapy can lead to excessive apoptosis or decreased proliferation, and resulting tissue-specific developmental defects [10]. Hence, blocking p53 activation has clinical therapeutic significance for the protection of normal tissue against radiotherapy treatment and the treatment of diseases with inappropriate p53 activation.

Thus the aim of the study is to compare the antagonist activity of three chlorogenic acid isomers against p53 transcription factor for potential anti-apoptotic activity using molecular docking experiments. Subsequently, molecular dynamics simulations were conducted to validate representative docking complexes.

Materials and Methods

Ligand preparation

The three CGA isomers were selected i.e. 3-O-caffeoylquinic acid/chlorogenic acid (3CGA), 4-O-caffeoylquinic acid/cryptochlorogenic acid (4CGA), and 5-O-caffeoylquinic acid/neochlorogenic acid (5CGA) (Table 1). The nomenclature in this paper conforms to the numbering scheme of carbon atom by the National Library of Medicine of the NIH in the United States [11]. The structures of these isomers were retrieved from PubChem database in sdf format, then subsequently were converted into pdb format using Open Babel software [12]. The obtained molecular structures (Figure 1) were then be subjected to different in silico screening.

Prediction of pharmacokinetic parameters

To estimate the relevant physicochemical and pharmacokinetic characteristics, the isomeric simplified molecular input line entry system (isomeric SMILES) of each isomer was entered to SwissADME web tools [13]. The drug-likeness of CGA isomers were assessed based on the rule of five criteria proposed by Lipinski et al. [13].

Molecular docking studies

The 3D structure of p53 protein receptor was obtained at resolution of 1.64 Å from the public domain in the Protein Data Bank under PDB ID 6ZNC. The necessary modification were made to the protein to facilitate docking using AutoDock tools [14]. The docking algorithms employed a rigid receptor/flexible ligand protocol. Each ligands was subsequently docked to the DNA binding domain between L1 loop and S3 sheet (L1/S3 pocket) on the surface of p53 protein (Figure 2). Based on Wu et al. [10], the grid center for docking was identified at coordinate X = 155.496, Y = -4.397, and Z = 35.680. The dimension of grid box was 40 x 4 x 40 Å3. Ligand tethering was performed by regulating Lamarckian Genetic Algorithm parameter using 15 numbers of run. Default setting were used for all other parameters. The 3D docking pose and 2D ligand-receptor interactions were investigated using PyMol [15] and LigPlot [16] softwares, respectively.

Molecular dynamic simulation

Molecular dynamic (MD) simulations was performed using web-based platform called Visual Dynamics in which the simulations performed in Gromacs [17]. The best-docking scored of each CGA isomer in complex with p53 protein were chosen as starting coordinates for 5 ns all-atom molecular dynamics. The molecular topology information file of ligands were generated using ACYPE web server [18], while the p53 protein was prepared using PlayMolecule ProteinPrepare web [19]. Each ligand–protein complex was solvated within a cubic box of the transferable intermolecular potential with a simple point charge (SPC) water model allowing a minimum of 0.2 nm marginal distance between protein and each side of the 3D box. The MD trajectories were evaluated by the plots of the root mean square deviation (RMSD), root mean square fluctuation (RMSF), and radius of gyration (Rg) using the QtGrace software.

Results

Pharmacokinetic profile

The CGAs are natural phenolic acids that are derived from esterification of one molecule of caffeic acid and one molecule of quinic acid. As depicted in Table 1 and Figure 1, the carboxyl group of caffeic acid may condensates with either 3-hydroxy, 4-hydroxy, or 5-hydroxy group of quinic acid, which is resulting 3CGA, 4CGA or 5CGA isomer, respectively. Consequently, these three CGA isomers shared similar physicochemical properties (Table 2).

In the context of oral bioavailability's prediction, physicochemical properties of these CGA isomers fulfilled the criteria for the molecular weight (MW ≤ 500 Da), the HBA (≤ 10), the MR (40 ≤ MR ≤ 130), the flexibility (rotatable bond < 9), and the saturation (fraction Csp3 >

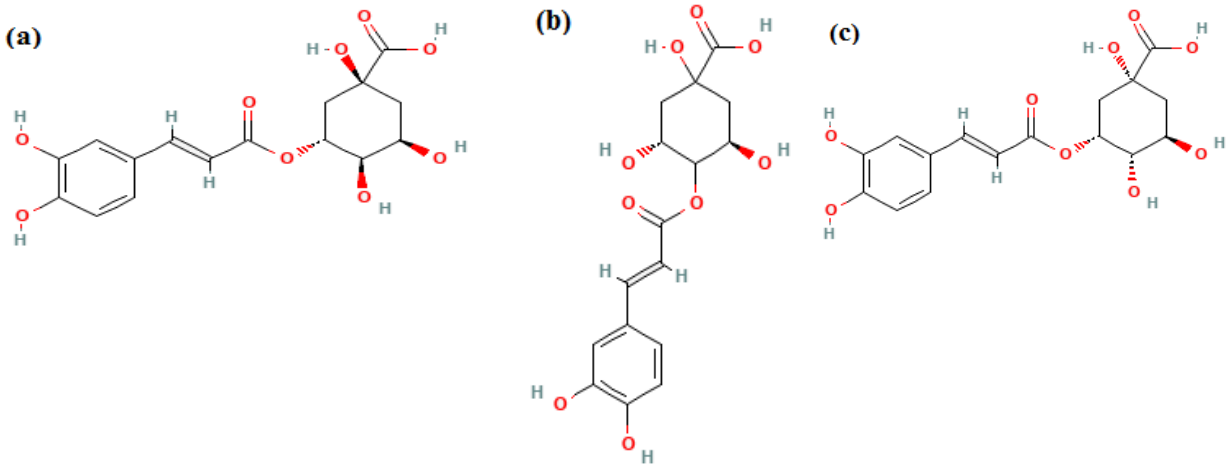

Figure 1. Molecular Structure of (a) 3-CGA, (b) 4-CGA, and (c) 5-CGA.

Table 1. Descriptors for CGA Isomers

Molecule	Pubchem CID	Formula	Isomeric SMILES
3CGA	1794427	C16H18O9	C1[C@H]([C@H]([C@@H](C[C@@]1(C(=O)O)O)OC(=O)/C=C/C2=CC(=C(C=C2)O)O)O)O
4CGA	9798666	C16H18O9	C1[C@H](C([C@@H](CC1(C(=O)O)O)O)OC(=O)/C=C/C2=CC(=C(C=C2)O)O)O
5CGA	5280633	C16H18O9	C1[C@H]([C@@H]([C@@H](C[C@]1(C(=O)O)O)OC(=O)/C=C/C2=CC(=C(C=C2)O)O)O)O

0.25). However, their properties violated the criterion for the polarity in which HBD should be > 5, while TPSA should be between 20 and 130 Å2. Furthermore, the lipophilicity Log Po/w score of each CGA isomers shows a negative values which indicates a higher affinity for the aqueous phase (Table 3). While, their water solubility score are categorized as very soluble (-2 < Log S < 0) with predicted solubility at 8.50 mg/ml or 2.40 x 10-2 mol/L. The Abbot bioavailability of the CGA isomers are at 0.11 (cut-off value of at least 0.10) which meet the requirement for a good oral medicine. Overall, the CGA isomers satisfy the drug-likeness, thus they can be considered as good orally active drug candidates.

The pharmacokinetic findings (Table 4) reveal that the CGA isomers are low-absorbed in GI tract, and are not transported across the BBB. These results related to their

Table 2. Physicochemical Properties of CGA Isomers

Molecule	MW (g/mol)	HBA	HBD	MR	Rotatable bond	TPSA (Å2)	Fraction Csp3
3CGA	354.31	9	6	83.5	5	164.75	0.38
4CGA	354.31	9	6	83.5	5	164.75	0.38
5CGA	354.31	9	6	83.5	5	164.75	0.38

Note: MW refers to molecular weight; HBA refers to number of H-bond acceptor; HBD refers to number of H-bond donor; MR refers to molar refractivity; TPSA refers to topological polar surface area; Fraction Csp3 refers to ratio of sp3 hybridized carbons over the total carbon count of the molecule.

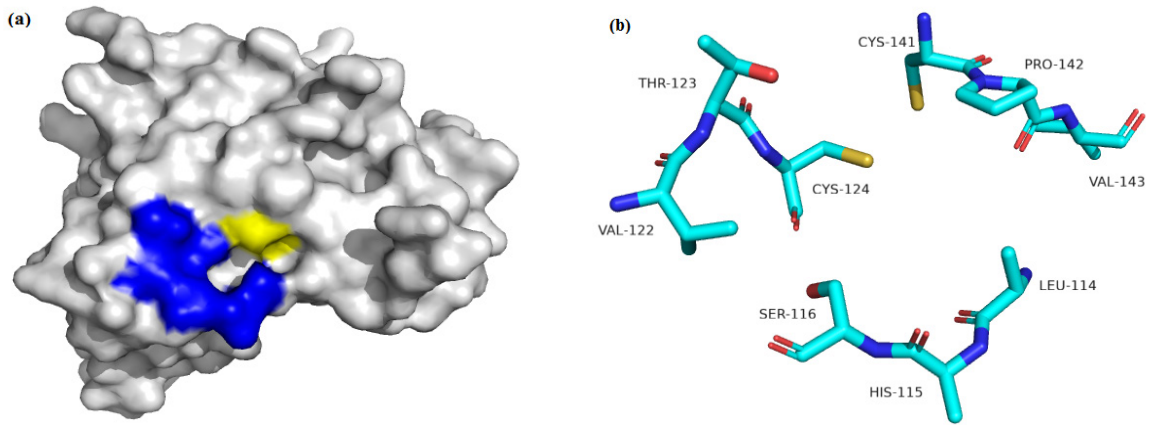

Figure 2. (a) The drugable pocket between L1 loop (blue) and S3 sheet (yellow) on the surface of p53 protein (grey) and (b) the corresponding important residues.

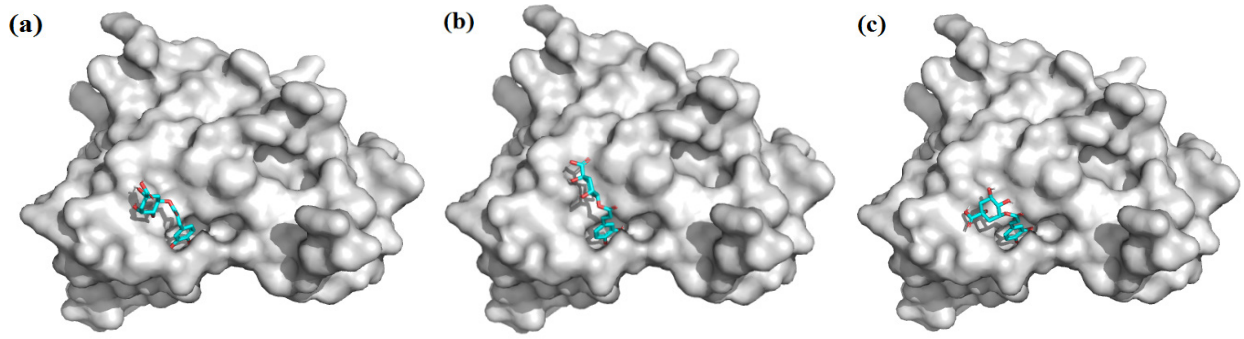

Figure 3. The 3D Representation of Docking Pose of (a) 3CGA, (b) 4CGA, and (c) 5CGA in the L1/S3 Pocket of p53 Protein.

Table 3. Lipophilicity, Water Solubility, Bioavailability, and Lipinski's Drug-Likeness of CGA Isomers

Molecule	Lipophilicity Log Po/w (XLogP3)	Water solubility Log S (ESOL)	Bioavailability score	Lipinski's Drug-Likeness
3CGA	-0.42	-1.62	0.11	Yes; 1 violation: NHorOH>5
4CGA	-0.42	-1.62	0.11	Yes; 1 violation: NHorOH>5
5CGA	-0.42	-1.62	0.11	Yes; 1 violation: NHorOH>5

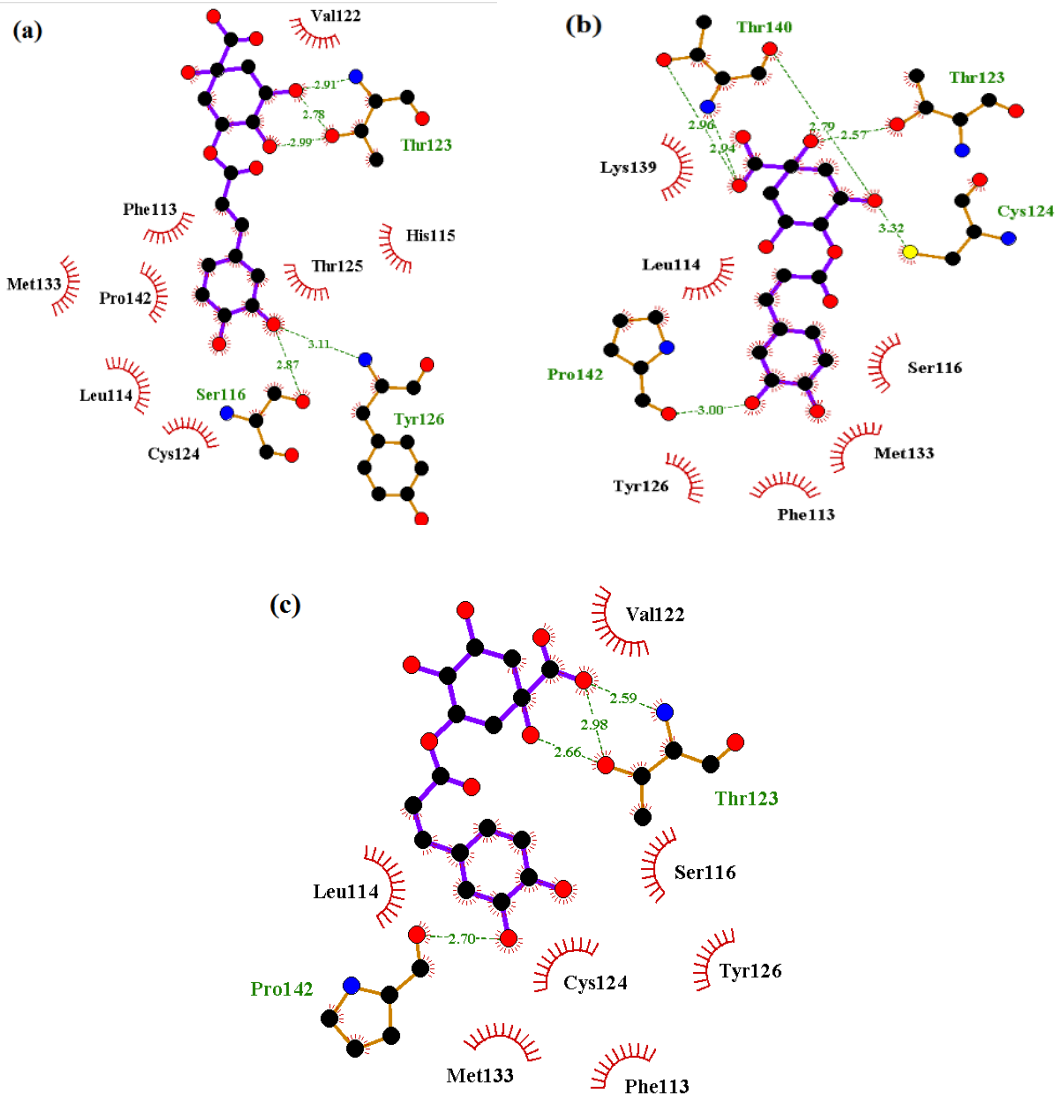

Figure 4. The 2D Representation of Interaction between L1/S3 Pocket's Key Residues of p53 protein with (a) 3CGA, (b) 4CGA, and (c) 5CGA. Note: Hydrophobic bonded residue name is in black-colored label, hydrogen bonded residue name is in blue-colored label.

Table 4. Pharmacokinetics Parameters of CGA Isomers

Molecule	GI absorp.	BBB perm.	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
3CGA	Low	No	No	No	No	No	No	No
4CGA	Low	No	No	No	No	No	No	No
5CGA	Low	No	No	No	No	No	No	No

Note: GI absorp, refers to gastrointestinal absorption; BBB perm, refers to blood brain barrier permeation; P-gp, refers to P-glycoprotein; CYP, refers to cytochrome P450.

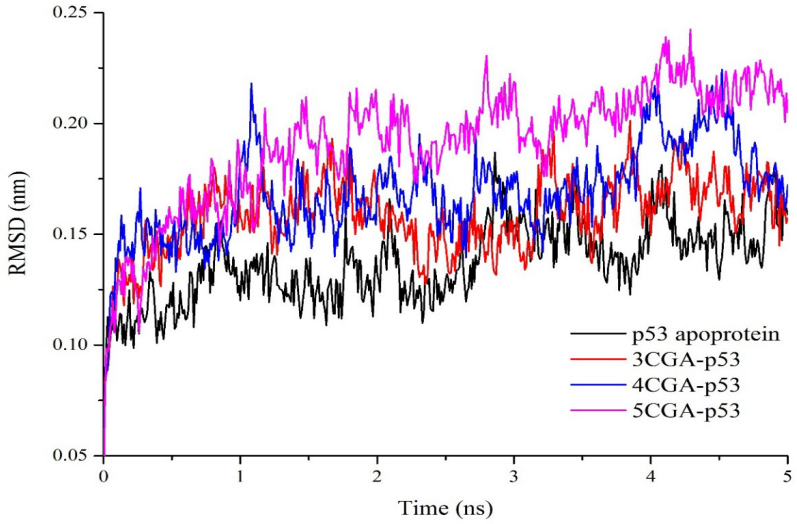

Figure 5. RMSD Values of p53 Apoprotein (Black Line), and Complexes of p53-3CGA (Red Line), p53-4CGA (Green Line), and p53-5CGA (Blue Line) Across the Entire Simulation Duration.

high polarity nature as previously described. Importantly, the CGA isomers are not a substrate of p-glycoprotein, thus they are not actively effluxed by this membrane protein transporter. Furthermore, they are not inhibit the activity of five isoforms of major cytochrome P450 enzymes.

Docking with p53 protein

Molecular docking has been applied to compares the binding affinity and interaction of different CGA isomers with residues in the L1/S3 pocket on the surface of p53 protein. The L1/S3 pocket is a shallow depression centered at Cys124 which flanked by residues 141-143 of β-strand S3 as well as N-termini's residues 113-116 and C-termini's residues 122-123 of the L1 loop (Figure 1). It is a transcriptionally active DNA-binding site for human p53 protein complexes. However, the L1 is highly flexible, thus stabilizing this segment by a small molecule would improve the p53 activity. Results shows that the CGA isomers were well adapted to the p53 binding pocket, in which the quinic acid moiety (tetrahydroxy-cyclohexane carboxylic acid) is located inside the L1/S3 pocket (Figure 3).

All CGA isomers are able to forming hydrogen bond and hydrophobic contacts in protein–ligand complexes (Figure 4). However, esterification formed on the hydroxyl group at different carbon atom of quinic acid influences the best docking pose and molecular interaction (Figure 5 and 6). Inside the L1/S3 pocket, the quinic acid moety of 4CGA forms hydrogen bonding with Thr123 (1 bond), Cys124 (1 bond), and Thr140 (3 bonds) residues. Meanwhile, the 3CGA and 5CGA only interact with Thr123 (3 bonds) residue. Outside the pocket, hydrogen bonding is formed between the caffeolyl residue with Pro142 (1 bond) residue for 4CGA and 5CGA, while with Ser116 (1 bond) and Tyr126 (1 bond) for 3CGA.

Afterall, the 4-CGA shows the lowest binding energy of -5.26 kcal/mol for its best docking pose, followed by 5CGA and 3CGA at -4.81 and -4.62 kcal/mol, respectively (Table 5). Consequently, the 4-CGA shows the lowest inhibition constant of 108.52 μM. It is lower about one-third and one-fourth as compared to 3CGA and 5CGA, respectively. Eventhough 3CGA forms more hydrogen bondings than 5CGA, binding energy of 3CGA is lower than 5CGA. This results may influenced by that the length

Table 5. Molecular Docking Parameters of CGA Isomer-p53 Complex

Molecule	Binding Affinity (kCal/mol)	Ligand Efficiency	Ki (μM)	No. Hydrogen Bonding
3CGA	-4.62	0.18	409	5 (1 with Ser116, 3 with Thr123, 1 with Tyr126)
4CGA	-5.41	0.22	108.52	6 (1 with Thr123, 1 with Cys124, 3 with Thr140, 1 with Pro142)
5CGA	-4.81	0.19	299.94	4 (3 with Thr123, 1 with Pro142)

Note: Ki refers to inhibition constant.

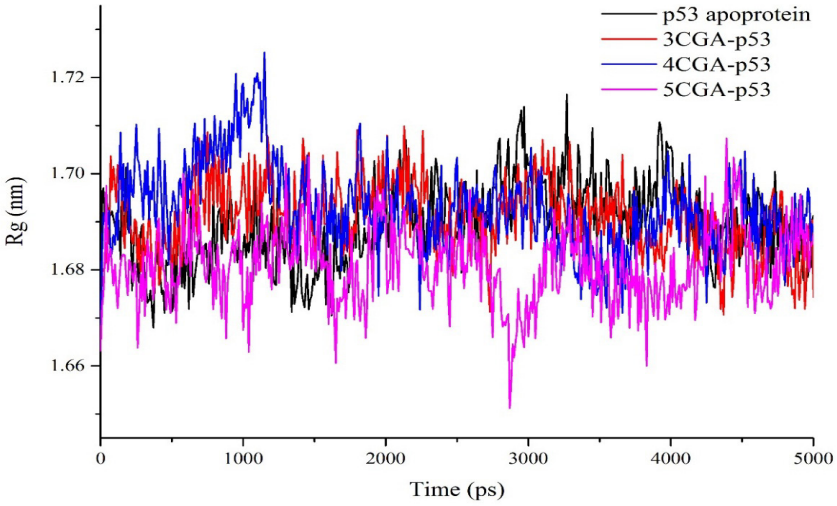

Figure 6. The Radius of Gyration Values of p53 Apoprotein and Its Complexes with CGA Isomers Calculated during MD Simulations.

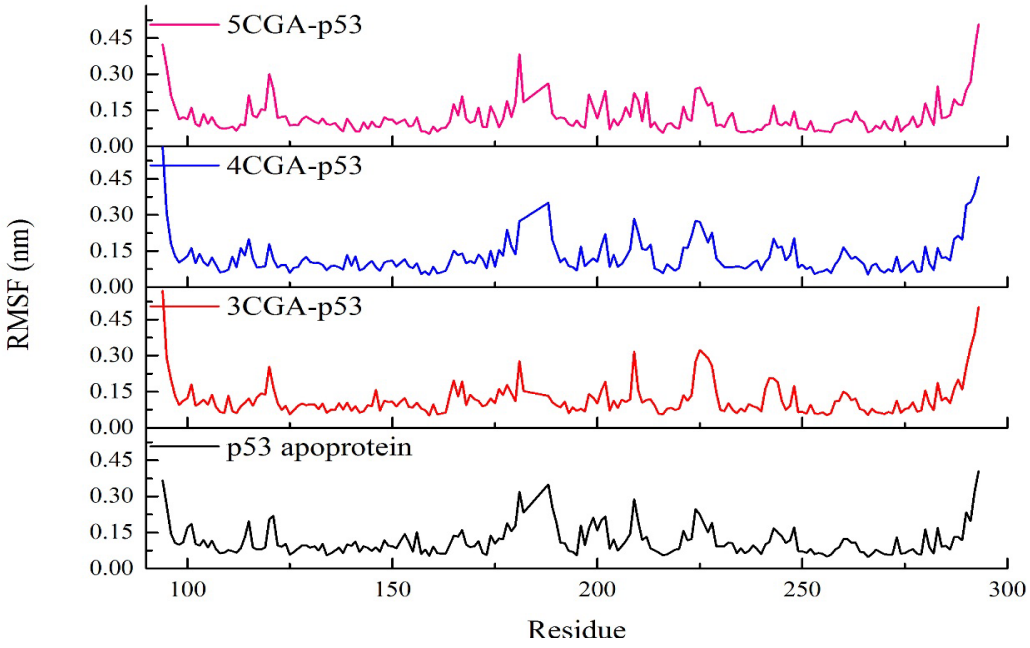

Figure 7. The Variation of RMSF of the Cα Atoms of within p53 Protein as Apoprotein (Black Line) and Complexes with CGA Isomers

of hydrogen bonding in which 5CGA formed shorter distance in compare to 3CGA.

Molecular dynamics

The simulations spanning 5 ns were conducted for p53 apoprotein and complexes of p53 with 3CGA, 4CGA, and 5CGA. The result shows that the median RMSD for p53 apoporotein is at 0.14 (range of range of 2.1 x 10-6 – 0.19) nm. While, the median RMSD are noted at 0.16 (range of range of 2.30 x 10-6 – 0.20), 0.17 (range of range of 2.40 x 10-6 – 0.22), and 0.20 (range of range of 2.40 x 10-6 – 0.24) nm for complexes of 3CGA-p53, 4CGA-p53, and 5CGA-p53, respectively. Even the complexes display lower stability, RMSD of less than 0.25nm is considered a very close to the reference structure.

The median Rg for p53 apoporotein is at 1.69 (range of range of 1.66 – 0.72) nm. While, the median Rg for complexes with 3CGA-p53, 4CGA-p53, and 5CGA-p53 are fluctuated at 1.69 (range of range of 1.67 – 1.71), 1.69 (range of range of 1.66 – 1.73), and 1.68 (range of range of 1.65 – 1.71) nm, respectively. Afterall, the Rg of complexes are considered a very close to the reference p53 structure. These results suggest that the regular secondary structures still compactly packed in to 3D structure of p53 protein post-binding with CGAs isomers.

The RMSF metric indicates the dynamics and flexibility of a protein structure in which regions with high RMSF values are typically more flexible, while regions with low RMSF values are typically more rigid. The median RMSF value for p53 apoporotein is at 0.09 (range of range of 0.05 – 0.41) nm. While, the median RMSF value for complexes of 3CGA-p53, 4CGA-p53, and 5CGA-p53 are fluctuated at 0.10 (range of range of 0.05 – 0.57), 0.10 (range of range of 0.05 – 0.58), and 0.10

(range of range of 0.05 – 0.51) nm, respectively.

Furthermore, the p53 apoprotein and its complexes exhibit the RMSF fluctuation at the same region (Figure 7). For p53 apoprotein, obvious fluctuations are observed for some residues in loop L1 (His115, Lys120, and Ser121), loop L2 (residues 181-190), S5-S6 loop (residues 198-202), S6-S7 loop (residues 208-210), s7-S8 loop (residues 224-228), and Loops L3 (residue 243-245 and Arg248). Concerning on the residues in L1/S3 pocket, the binding with 3CGA lead to reduction on the fluctuation in His115 (at 0.12 nm) and Ser121 (at 0.17 nm) residues, while the 4CGA

in residue Lys120 (at 0.18 nm) and Ser121 (at 0.12 nm) as compared to p53 apoprotein (at 0.20, 0.21, and 0.22 nm for His115, Lys120, and Ser 121, respectively). Meanwhile, binding with 5CGA increases the fluctuation in these three residue (at 0.21, 0.30, and 0.24 nm, respectively), but still within the range of ideal value of RMSF at less than 0.3 nm.

Discussion

Previous studies [4, 20-22], demonstrated that the CGA isomers are widely present in diverse plant family, but occurs in different proportion., Also, the proportion of CGA isomers undergo a change during extraction due to reversible isomerization induced by process conditions, such as temperature, pH, light exposure, and type of solvent [23, 7]. Nevertheless, this study shows that the position of esterification on the quinic moiety has no influence on the physicochemical and pharmacokinetics performance of CGA isomers.

Firstly, their physicochemical properties meet four out of Lipinski's five rules, except for the polarity-related criteria. Their high polarity underline their excellent solubility in water, but are poorly absorbed in GI tract and are not permeable in BBB [24]. While quinic acid (TPSA = 118 Å2) is noticeably more polar than caffeic acid (TPSA = 77.8 Å2), polarity of monoCGA may decrease with further esterification with caffeic acid into diCGA or triCGA isomers [8]. Nevertheless, the CGA isomer are still predicted as a good orally active drug with their Abbot's bioavailability value and one violation of Lipinski's five rules.

Secondly, the pharmacokinetic parameters prediction showed that the CGA isomers are not substrate for p-glycoprotein so the CGA isomers are not use the p-glycoprotein transporter for absorption, excretion and various activity of the compounds. This result infers that their efficacy are not depend on the expression of p-glycoprotein transporter in specific organ [13]. Also, the CGA isomers are not inhibitor of five major cytochrome P450 enzymes. Note that cytochrome P450 is a superfamily of membrane-bound hemoprotein isozymes that responsible in metabolize xenobiotic and clearance of potentially toxic compound [25]. Therefore, the CGA may not alters the metabolism of certain drugs by inhibiting the activity of the P450 enzymes.

Further, the anti-apoptotic activity of CGA have been demonstrated against chemically-induced oxidative stress in several *in vitro* [26-28] and in vivo [29-32] studies. The potential mechanisms are proposed through the up-regulation of *Bcl-2* expression [29, 26, 32] and *PI3K/Akt*-mediated activation of Nrf2/HO-1 pathway[26, 27, 30], and the down-regulation Bax [29, 28], dityrosine [30], NF-κB and caspase-3 [31]. While, there is a limited number of studies [3-5] about the protective effect of GCA against radiation-induced oxidative stress. The protection is through the prevention of DNA damage [3, 4], activation of Nrf2 antioxidant system [4], and decreasing the ratio of *Bax/Bcl-2* [5]. The CGA is also able to restoring the malonaldehyde level to normal level, increasing the level of anti-oxidant biomarkers (glutathione, total antioxidant capacity, and superoxide dismutase) [5]. In this study, the molecular docking and MD simulation reveals that anti-apoptotic activity of the CGA isomers might also through inhibition of p53 DNA translation activity. Considering that p53 is the master regulator in managing cell fate following exposure to radiation[9], the anti-apoptotic activity may subjected as adjuvant radiotherapy.

Among CGA isomers, the 4CGA shows the lowest binding energy (-5.41 kCal/mol). Even, this value is lower than the binding energy of PQ1 (at -5.0 kCal/mol), the most potent antagonist of p53 transcriptional activity from 3-phenylquinoline derivative[10]. Note that the antagonist activity of PQ1 against p53 transcriptional activityhad been demonstrated *in vitro*. Its transcription profiles overlapped on 32 genes with pifithrin-α, one of among four p53 inhibitors have been developed[10]. Therefore, further research on the potential of 4CGA as antagonist of p53 transcriptional activity need to be explore. In addition, the MD simulation indicates the 4CGA is able to improve the stability of residue L1 loop in L1/S3 pocket by minimizing fluctuation of atom at Lys120 residue.

In the context of cancer treatment, this study may also reveals the mechanism of anticancer activity of CGAs via binding at L1/S3 pocket of p53 protein. Previous studies [33-35] highlighted that the tumor suppressor p53 is the most frequently mutated protein in human cancer, while the L1/S3 pocket as a target for pharmaceutical reactivation of p53 mutants for cancer therapy. Indeed that CGAs can overcome cancer resistance to conventional chemotherapeutics and alleviate chemotherapy-induced toxicity by scavenging free radicals [6]. However, in the context of adjuvant radiotherapy, the anti-apoptotic activity of CGA may also reduce the efficacy from radiotherapy treatment. Yin et al. [4]reported that CGA might be a potential tumor-protective compound upon irradiation and reduce the efficacy of radiotherapy by decreasing tumor apoptosis.

Conclusively, the CGA isomers is predicted as an orally-active drug with p-glicoprotein independent transport and may not interfere the metabolism of other drug. All CGA isomer show good binding affinity upon binding with L1/S3 pocket of p53 which indicates their potential as antagonist of p53 transcription activity. The position of esterification on the quinic moiety shows influence on the molecular interaction. Among them, the 4CGA shows the lowest binding energy combined with stabilization of residue Lys120 in L1/S3 pocket. The anti-apoptotic activity may protect adjacent normal cell upon ionizing radiation therapy, but may also reduce the

tumor apotosis. Therefore, further exploration is critical to optimize the radioprotection effect while maintain the radiotherapy efficacy through *in vitro* and in vivo study.

Author Contribution Statement

DPP, DD, TP, and IS designed the model and the computational framework and analyzed the data. DPP, MFS, TP, and SI carried out the implementation. DPP, DD, TP, and IS wrote the manuscript. DPP and DD conceived the study and were in charge of the overall direction, planning, and approval of the final version of the manuscript.

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General

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Approval

This work has not been approved by any scientific body nor has been approved as student thesis.

Ethical Declaration

Authors declared that no experiment on human or animal was performed for the present study, thus this research did not go through a research ethics committee.

Data Availability

The model simulations are too extensive to archive. Instead, we provide information needed to replicate the simulations. Details of the data are available from the corresponding authors.

Study Registration

The study is not registered in any registering dataset.

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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