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Rutin Attenuates Oxidative Stress Associated with Aging: Molecular Docking Study

Ali H. El-Far[1, *], Shaimaa M. Saafan[2], Shymaa A. Mohamed[3], Fayza A. El Tedawy[2], and Abdelwahab A. Alsenosy[1]

[1]Department of Biochemistry, Faculty of Veterinary Medicine, Damanhour University, Damanhour 22511, Egypt; ali.elfar@damanhour.edu.eg; dr_alsenosy_2010@yahoo.com

[2]Department of Biochemistry, Animal Health Research Institute (AHRI), Damanhour Branch, Agriculture Research Centre (ARC), Damanhour 22511, Egypt; saafanshaimaa@gmail.com; Fayzaeltedawy@gmail.com

[3]Molecular Biology, Molecular biology unit, Medical Technology Centre, Medical Research Institute, Alexandria University, Egypt; shymaa.abdullah@alexu.edu.eg

Abstract: Aging is one of the major risk factors associated chronic diseases. Oxidative stress is one of the aging associated mechanisms induced by pro-oxidants. Oxidative stress is an imbalance between free radicals and antioxidants in body cells. In the current study, we investigated the molecular docking scores of rutin with aging associated biomarkers, including human *β*-galactosidase, caspase-8, caspase-9, caspase-3, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (PK3CD), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma (PK3CG), and RAC-alpha serine/threonine-protein kinase (AKT1). All proteins were retrieved from RCSB PDB database (https://www.rcsb.org/), while rutin three-dimensional structure was obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The docking process was achieved by InstaDock software (https://instadock.webs.com/) and visualized by BIOVIA Discovery Studio Visualizer software. Rutin exhibited binding affinity (p*Ki*) against AKT1, PK3CD, PK3CG, *β*-galactosidase, caspase-8, caspase-9, and caspase-3 of 7.85, 7.04, 6.89, 6.82, 5.94, 5.57, and 5.50, respectively. The obtained data revealed that rutin exhibited marked binding affinity to these biomarkers revealing its anti-aging potential.

Keywords: Molecular docking; Rutin; Aging; Apoptosis

*Correspondence: Ali H. El-Far
Department of Biochemistry, Faculty of Veterinary Medicine, Damanhour University, Damanhour 22511, Egypt
Email: ali.elfar@damanhour.edu.eg
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Prof Dr/Ali H. El-Far (ali.elfar@damanhour.edu.eg)

1. Introduction

Living organisms produce reactive oxygen species (ROS) because of normal cellular metabolism and environmental factors such as air pollutants or cigarette smoke. ROS are highly reactive molecules that can harm and change cell structures like carbohydrates, nucleic acids, lipids, and proteins. Free radicals derived from oxygen have a number of negative effects, including membrane lipid peroxidation, enzyme inactivation, DNA fragmentation, and apoptosis activation (Valko et al., 2007).

The shift in the balance of oxidants and antioxidants in favour of oxidants is referred to as "oxidative stress." (Birben et al., 2012). Oxidative stress is thought to be a major contributor to neurodegenerative diseases as well as the normal ageing process (Uttara et al., 2009). Aging is a degenerative process caused primarily by oxidative stress, which leads to a variety of oxidative stress-related diseases due to the accumulation of ROS and decreased antioxidant capacity (Chen et al., 2018).

There is currently an increase in the usage of natural compounds as potential neuroprotective and hepatoprotective agents. Recently, bioflavonoids have found use in the healthcare system owing to their wide range of biological activities, low cost, and significantly high safety margins (Sharma et al., 2013). Rutin is a polyphenolic bioflavonoid, largely extracted from natural sources such as oranges, lemons, grapes, limes, berries, and peaches (Huang et al., 2012). Chemically, it is a glycoside comprising of flavonol aglycone quercetin along with disaccharide rutinose (Ganeshpurkar & Saluja, 2017). Some studies suggest that rutin has a potential protective role in NDs due to its beneficial effects as a potent antioxidant (Park et al., 2014). Also,(Hou et al., 2020) found that rutin significantly decreased fibrosis markers, and TLR4, IRAK4, P2X7r/NLRP3 signalling pathway in activated HSCs, as well as functioning as TLR4 inhibitor.

The current experiment aims to investigate the binding affinity of rutin to human *β*-galactosidase, caspase-8, caspase-9, caspase-3, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (PK3CD), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma (PK3CG), and RAC-alpha serine/threonine-protein kinase (AKT1) for oxidative stress attenuation.

2. Materials and Methods

2.1. Receptor preparation

The three-dimensional structural of human *β*-galactosidase (PDB ID: 3WF2), caspase-8 (PDB ID: 1I4E), caspase-9 (PDB ID: 3V3K), caspase-3 (PDB ID: 1CP3), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (PK3CD; PDB ID: 6OCU), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma (PK3CG; PDB ID: 1HE8), and RAC-alpha serine/threonine-protein kinase (AKT1; PDB ID: 6HHF) proteins were retrieved from RCSB PDB

database (https://www.rcsb.org/). All co-crystallized ligand and co-crystallized hetero atoms, including water molecules, were removed by BIOVIA Discovery Studio Visualizer software (https://discover.3ds.com/discovery-studio-visualizer-download).

2.2. Ligand preparation

The three-dimensional structural of rutin was downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) with compound CID of 5280805.

2.3. Molecular docking scores and interaction

Molecular docking scores and interaction of rutin against human *β*-galactosidase, caspase-8, caspase-9, caspase-3, PK3CD, PK3CG, and AKT1 proteins were done using InstaDock software (https://instadock.webs.com/) (Mohammad et al., 2021). Visualization of molecular interactions were done using BIOVIA Discovery Studio Visualizer software.

3. Results and Discussion

Molecular docking scores of rutin represented in Table 1 and represented in Figures 1-7 revealed that rutin exhibited binding affinity against AKT1 (7.85), PK3CD (7.04), PK3CG (6.89), *β*-galactosidase (6.82), caspase-8 (5.94), caspase-9 (5.57), and caspase-3 (5.50).

β-galactosidase activity was detected in senescent cells and called senescence-associated β-galactosidase (SA-β-gal) is the most widely used biomarker for aging cells (Lee et al., 2006). Therefore, inhibition of *β*-galactosidase activity and its accumulation attenuate the aging features in the living cells (Cai et al., 2020). In the same context, (Al-Mustafa et al., 2021) stated that rutin revealed anti-β-galactosidase activity as a competitive inhibitor.

Aging is associated with ehancement in cellular apoptosis (Zheng et al., 2005). In apoptosis, caspase-8, caspase-9, and caspase-3 expression and activities were increased in response to aging (Aggarwal & Gupta, 1999). Rutin is potentially alleviated the apoptosis present in cardiomyocyte that induced by high glucose (Wang et al., 2021).

PI3K/AKT/mTOR signaling is significant activated in aging cells in comparison with the young cells (Tan et al., 2016). Rutin showed high affinity to PI3K and AKT enzymes, indication their ability to control PI3K/AKT/mTOR pathway in aging.

Table 1. Molecular docking scores of rutin against *β*-galactosidase, caspase-8, caspase-9, caspase-3, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (PK3CD), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma (PK3CG), and RAC-alpha serine/threonine-protein kinase (AKT1)

	Binding Free Energy (kcal/mol)	p*Ki*	Ligand Efficiency (kcal/mol/non-H atom)
***β*-galactosidase**	-9.3	6.82	0.2163
Caspase-8	-8.1	5.94	0.1884
Caspase-9	-7.6	5.57	0.1767
Caspase-3	-7.5	5.5	0.1744
PK3CD	-9.6	7.04	0.2233
PK3CG	-9.4	6.89	0.2186
AKT1	-10.7	7.85	0.2488

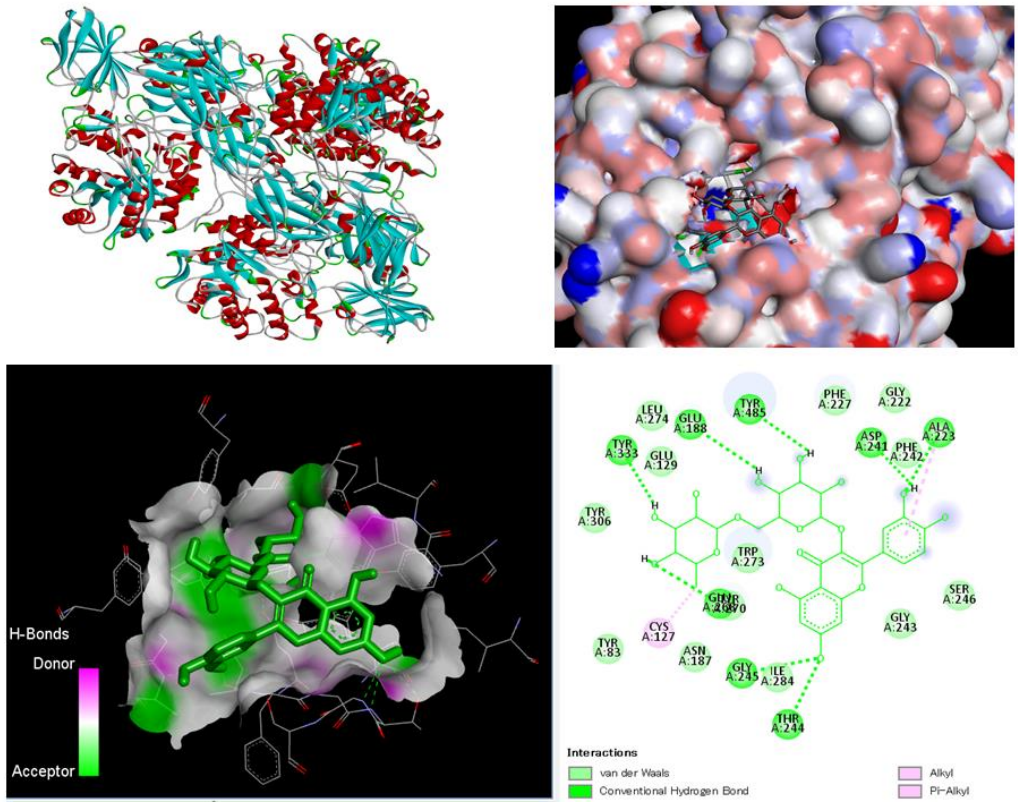

Figure 1. Molecular docking interaction of rutin against *β*-galactosidase

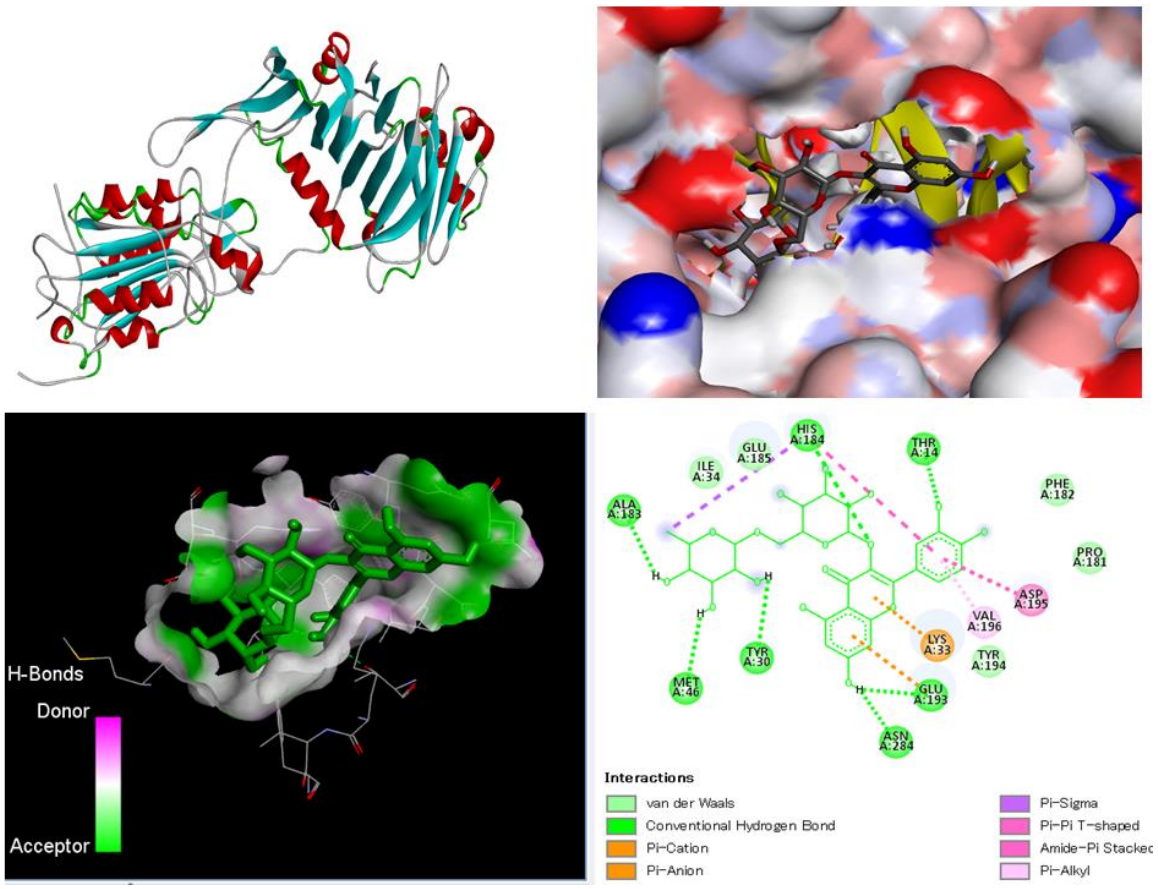

Figure 2. Molecular docking interaction of rutin against caspase-8

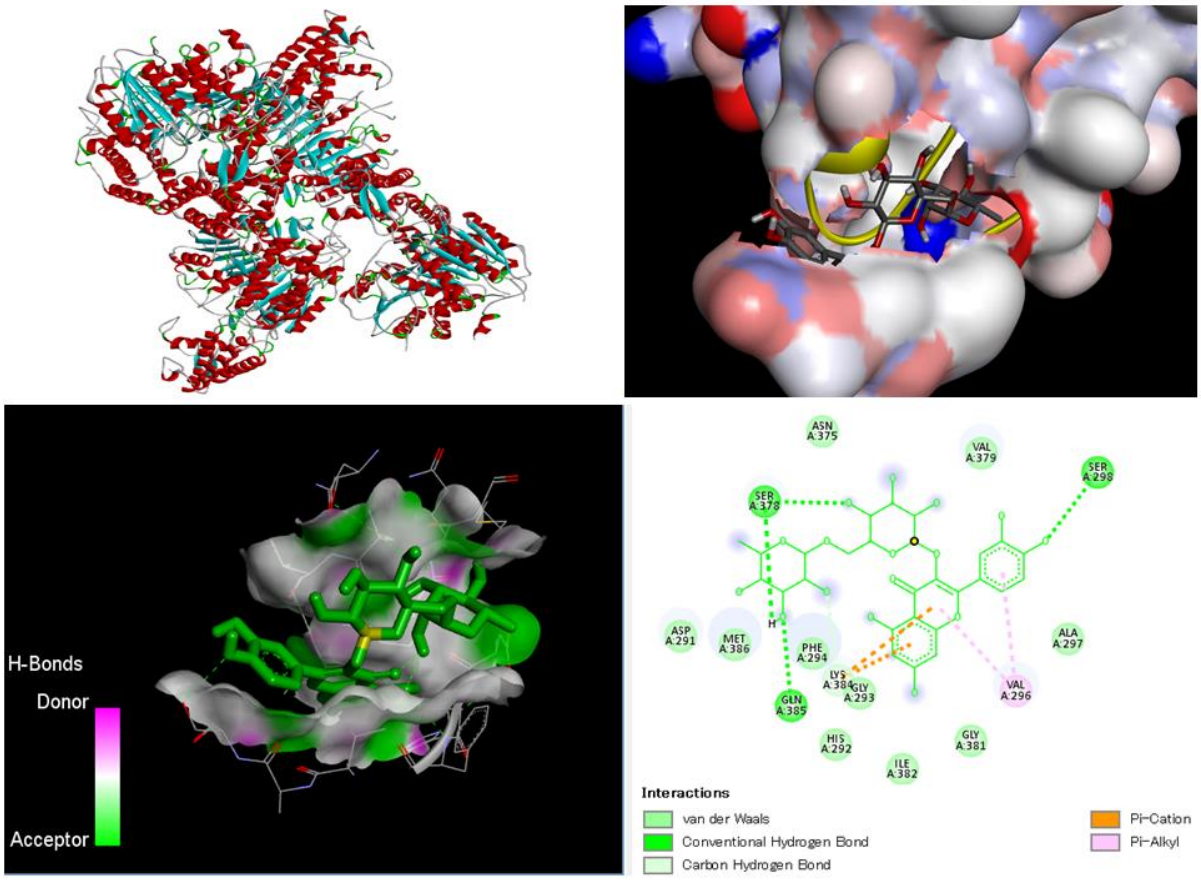

Figure 3. Molecular docking interaction of rutin against caspase-9

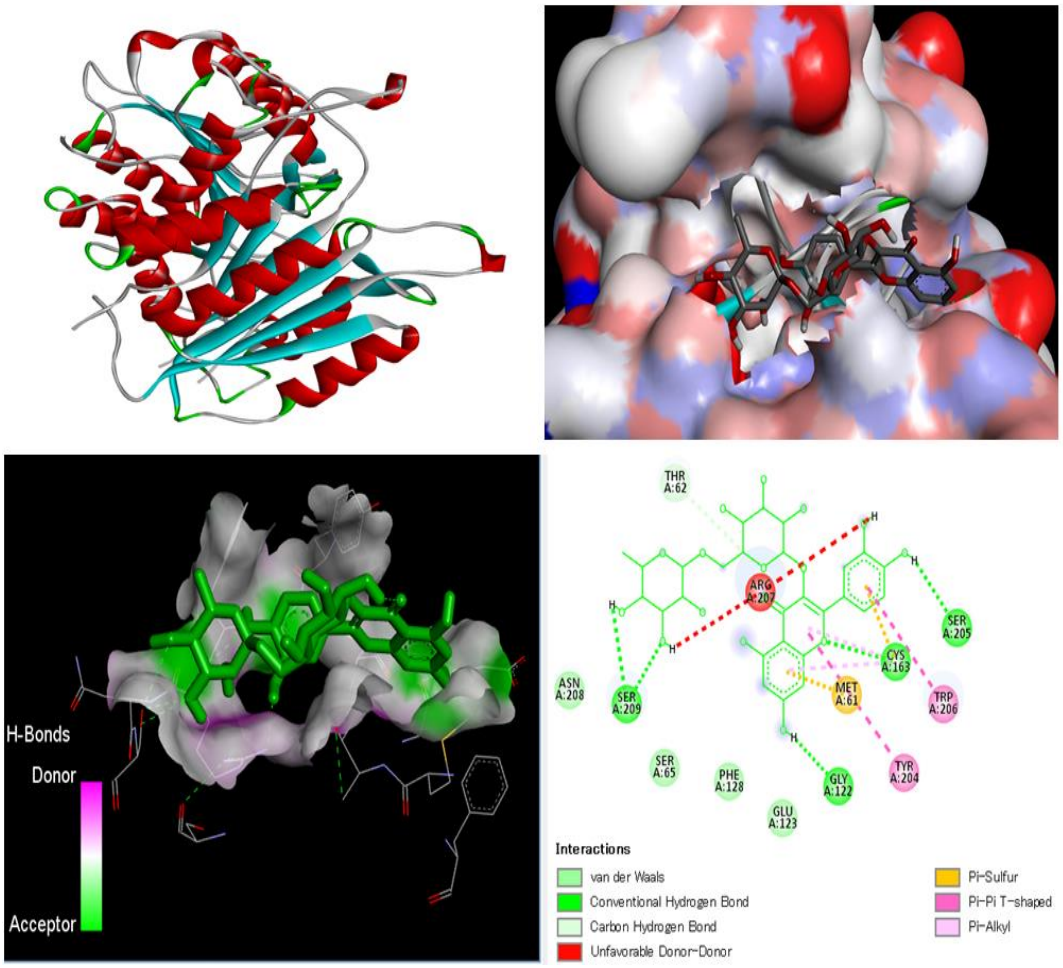

Figure 4. Molecular docking interaction of rutin against caspase-3

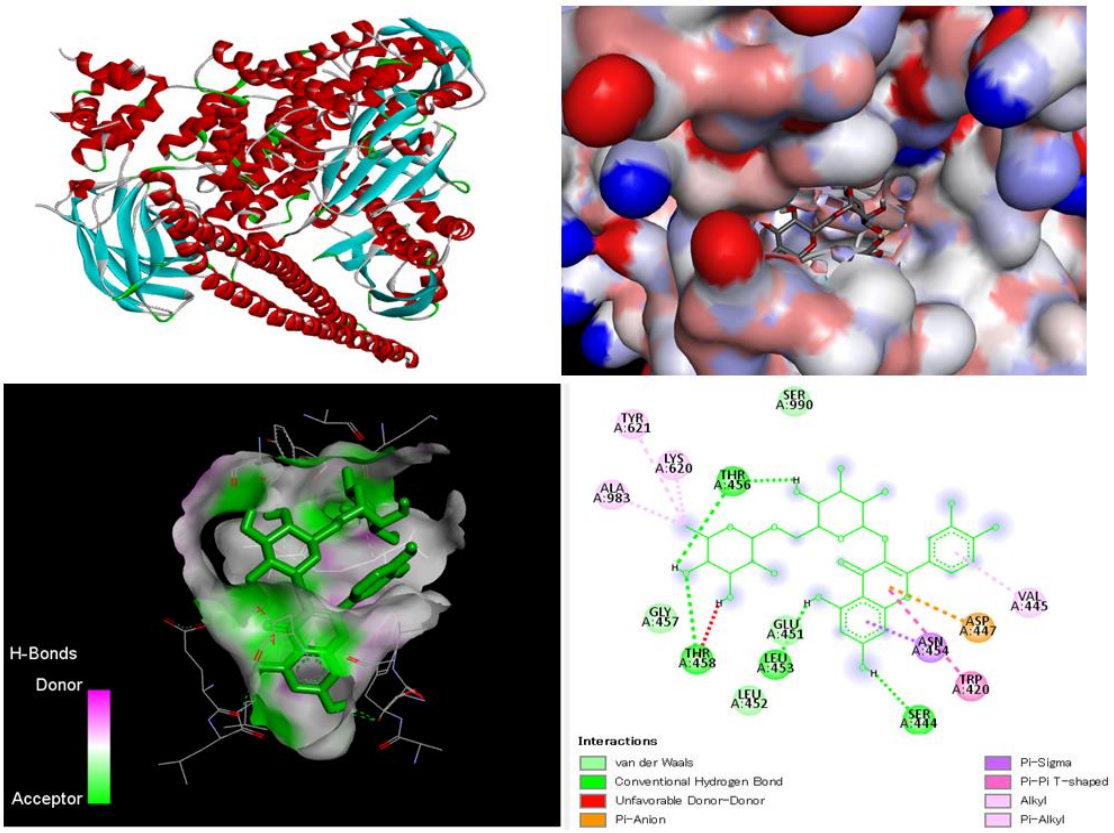

Figure 5. Molecular docking interaction of rutin against phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (PK3CD)

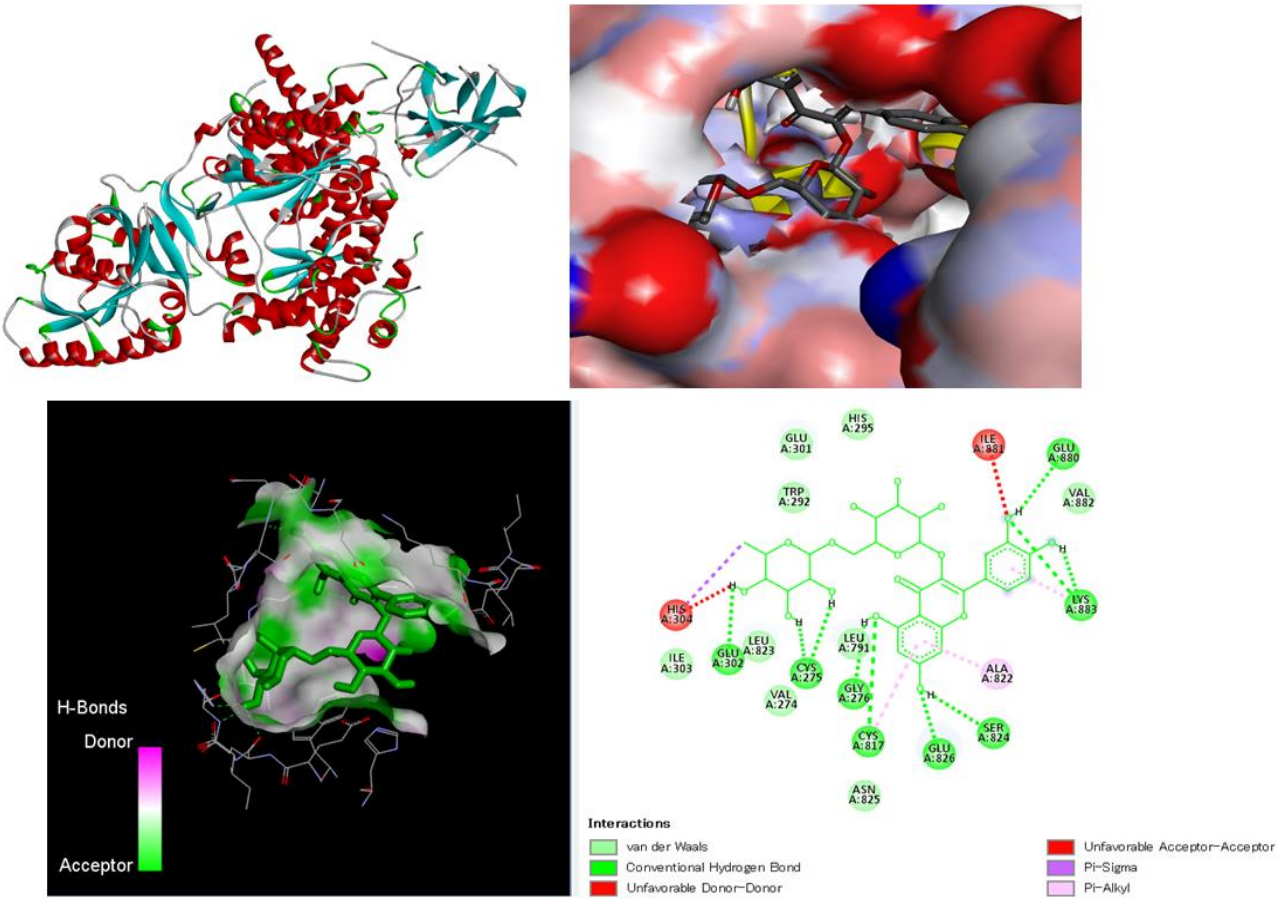

Figure 6. Molecular docking interaction of rutin against phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma (PK3CG)

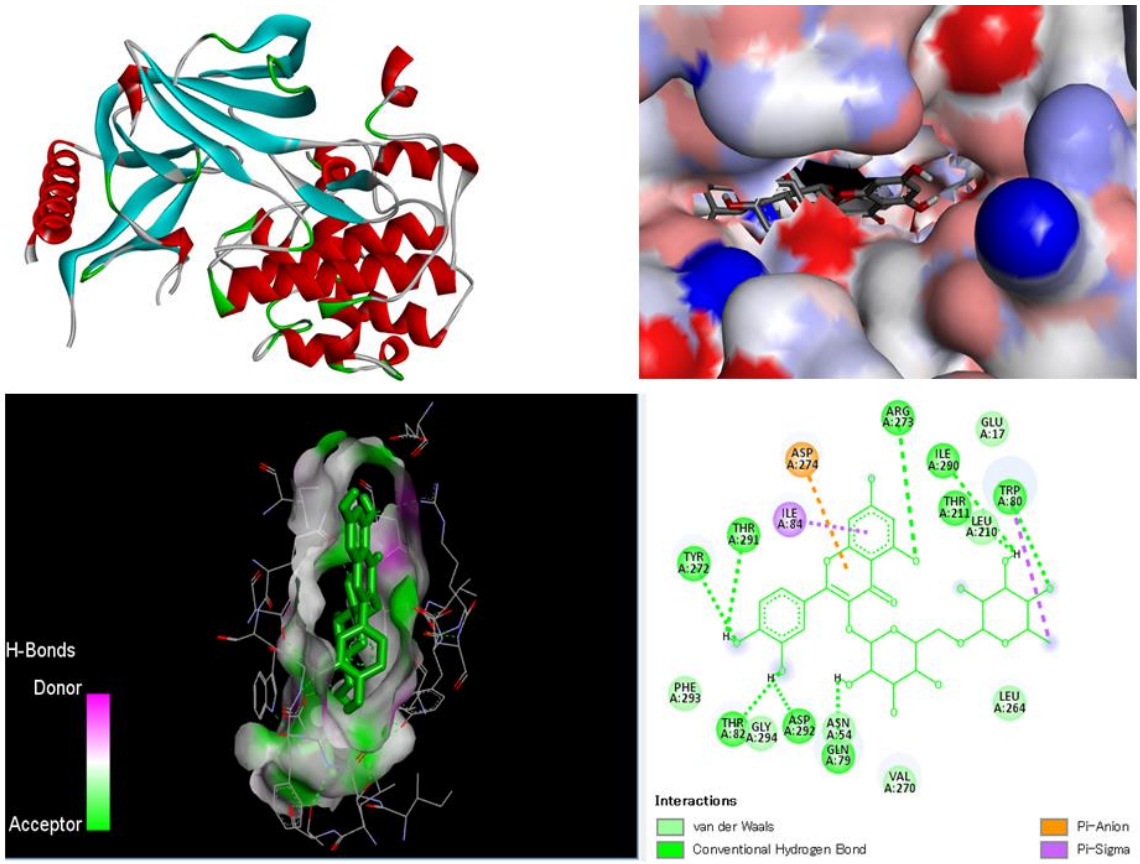

Figure 7. Molecular docking interaction of rutin against RAC-alpha serine/threonine-protein kinase (AKT1)

4. Conclusion

Aging is a process associated with accumulation of *β*-galactosidase, oxidative stress, and apoptosis. In the current computational study, rutin exhibited marked binding affinity to caspase-8, caspase-9, caspase-3, PK3CD, PK3CG, and AKT1. Further, *in vitro* and *in vivo* studies have been recommended to support the role of rutin as anti-aging drug.

Conflict of interest: The authors declare no conflict of interest.

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