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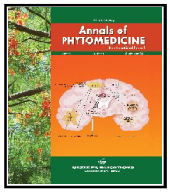

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Exploring antihypertensive effect of rutin through system based computational analysis

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Abstract

The continuous scientific engagement for developing new therapies is a top priority for treating both acute and chronic illnesses. Rutin, as a natural product, has been reported for having promising properties in dealing with variety of maladies. The potential of rutin as a valuable therapeutic agent for the management of hypertension and related complications was the objective of the present study through system based computational analysis by *in silco* examining the impact on several genomic expressions. We also assessed antioxidant potential through standard chemical assays.

The study analyzed rutin interaction with genes such as MR S810L (which causes severe hypertension) and ACE1 protein in relation to antihypertensive effects. We found that significant scavenging activity of rutin against free radicals such as DPPH, ABTS, and nitirc oxide scavenging and iron chelating activities. Additionally, rutin had shown a strong interaction with the MR S810L protein, underpinning the role of rutin as a potent antihypertensive agent. The hydrogen bonding of rutin was found to be more effective than that of captopril, a commonly used medication for hypertension.

This scientific delving underlines the multifaceted significance of the incumbent compound for its anti-radical potential and for an antihypertensive agent. By regulating genomic expression and interacting with critical proteins, rutin shows promise in combating hypertension and its complications ramified due to high blood pressure. By targeting genomic expression and interacting with specific proteins, rutin may offer a novel approach to controlling hypertension.

1. Introduction

Hypertension is a complex disorder and a significant threat to the general population's health because of its widespread occurrence across the world. Approximately 12.8% of all yearly fatalities worldwide are related to elevated hypertension. It is anticipated to reach 1.56 billion (Mills *et al*., 2020). The kidney has an essential regulatory function in numerous attributes of blood pressure, especially in the availability of chronic conditions including diabetes as well as prevailing cardiac disease, contributing hugely to hypertension progression as a supplementary situation (Chen *et al*., 2019). When renal function is affected, the capacity of the nephron to establish stability is reduced, and blood pressure could be lowered. For most people, an unmanaged or uncontrolled phase of high blood pressure results from a quiet, asymptomatic period, which makes treatment difficult (Fuchs and Whelton, 2020). Since ancient times, herbal medical formulations have been administered as medications to treat a variety of illnesses (Thakur *et al*., 2018). There is a growing need for investigation into the phytochemical composition of herbal medicines since it is important for understanding their clinically beneficial effects (Ekor, 2014; Bhadarka *et al*., 2018; Yasheshwar *et al*., 2022). Traditional medicine certainly contributes significantly to enhancing and sustaining wellness, and in numerous societies, it is an integral aspect of their legacy (Fokunang *et al*., 2011). Plants have a significant role in Mexican traditional medicine, and numerous of them are seen as being part of the country's cultural legacy. There are presently between 4,000 and 6,000 species of plants with medicinal properties utilized in Mexico; moreover, there are many issues related to the consumption of herbal supplements because, with the exception of conventional drugs, they are not completely regulated, and the majority of these species have not been confined to chemical, physiochemical, pharmacological, or clinical research (Heinrich *et al*., 1998).

The word 'rutin' comes from the plant *Ruta graveolens*, which also contains rutin. Pharmacologically, it is a glycoside made up of the disaccharide rutinose and the flavonolic aglycone quercetin. It has shown a variety of pharmacological properties, such as anti-inflammatory, anticancer, vasoprotective, neuroprotective, cytoprotective and hepatoprotective effects (Ganeshpurkar and

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Saluja, 2017). Rutin is one of the most common polyphenols of flavonoid glycoside compound that present in most of the plant species and novel antihypertensive flavanol might offer unbelievable advantages for the therapy of hypertension through inhibitory activity of the angiotensin transforming enzyme as well as the mineralocorticoid receptor (Khalil and Sulaiman, 2010). To explain the ligand-binding characteristics of rutin with the angiotensin-converting enzyme (ACE), the trial compound rutin was subjected to molecular docking research. These investigations serve as a computing tool to predict the probable connections between rutin and proteins. Swiss ADME conducted an *In silico* analysis of rutin to determine its pharmacokinetics, drug-likeness, and pharmaceutical application compatibility to aid in drug development (Daina *et al*., 2017). A variety of rutin formulations may enable this stimulating flavonoid to take the lead among nutraceuticals for the prevention and/or treatment of many chronic human illnesses.

2. Materials and Methods

2.1 Reagents and software

Griess reagent, sodium nitroprusside, ammonium per sulphate, potassium ferricyanide, ammonium molybdate, and phenanthroline iron (III) reagent were procured from SD Fine Chem Pvt. Ltd, Mumbai, India. 2,2-Diphenyl-1-picrylhydrazyl (DPPH), rutin and ascorbic acid were acquired from Sigma Aldrich (St. Luis, MO, USA). All solvent and chemicals used in the study were of analytical grades.

2.2 Antioxidant activity of rutin

2.2.1 DPPH radical scavenging activity

The free radical scavenging activity of the rutin was evaluated using the stable free radical, *i.e*., DPPH. 1.0 ml of standard/extract solution at different concentrations was added to 1.0 ml of 0.1 mM DPPH solution in methanol and the absorbance of mixture recorded at 517 nm after 20 min of incubation (Polu *et al*., 2017). Ascorbic acid was used as positive control. DPPH radical scavenging activity was calculated using the formula:

$$\% \text{ Scavenging} = (Ao - At)/Ao) \times 100$$

where Ao = Absorbance of control (without extract) and At = Absorbance of sample. All samples and readings were prepared and measured in triplicate.

2.2.2 ABTS radical scavenging activity

By reacting, 7 mM ABTS solution with 2.45 mM potassium persulphate, ABTS free radical was generated and it was allowed to stand for 15 h in dark at room temperature. To obtain the absorbance of 0.7 ± 0.2 units at 750 nm, the overnight stored ABTS solution was diluted with methanol. The standard/extract solutions were prepared at various concentrations in methanol and 20 ml of test solutions were added to 180 µl of ABTS free radical solution. The absorbance was measured at 750 nm after 20 min incubation (Suseela *et al*., 2010). Ascorbic acid was used as positive control. The ABTS free radical scavenging activity was calculated using the formula:

$$\% \text{ Scavenging} = ((Ao - At)/Ao) \times 100$$

where Ao = Absorbance of control (without extract) and At = Absorbance of sample. All samples and readings were prepared and measured in triplicate.

2.2.3 Nitric oxide scavenging activity

Nitric oxide scavenging activity was estimated by using the Griess reagent assay. Briefly, 0.5 ml of standard/extract solutions at different concentrations were mixed with 2 ml of 10 mM sodium nitroprusside and 0.5 ml phosphate buffered saline (PBS). Then, the mixture was incubated for 150 min at 25°C. After the incubation, 0.5 ml of reaction mixture was incubated with 1ml sulphanilic acid reagent (0.33% sulphanilic acid in 20% glacial acetic acid) for 5 min, followed by addition of 1 ml 0.1% naphthyl ethylene diamine dihydrochloride. This incubation mixture was allowed to stand for 30 min and absorbance read at 540 nm. Curcumin was used as positive control (Patel *et al*., 2010). Percentage scavenging was calculated by the following formula:

$$\% \text{ of Scavenging} = (Ao - At)/Ao) \times 100$$

where Ao = Absorbance of control (without extract) and At =Absorbance of sample. All samples and readings were prepared and measured in triplicate.

2.2.4 Iron chelating activity

1, l0-phenanthroline-iron (III) reagent was prepared by mixing 2 ml of 1M hydrochloric acid, 0.16 g of ferric ammonium sulphate and 0.198 g of l, l0-phenanthroline monohydrate in 100 ml water. Briefly, 0.2 ml 1, l0-phenanthroline-iron (III) reagent, 0.6 ml methanol and 4 ml water were mixed with 0.2 ml standard/extracts and absorbance measured at 510 nm after the incubation period of 30 min at 50°C. Ascorbic acid was used as positive control. Higher iron chelating activity was indicated by higher absorbance (Polu *et al*., 2017). Percentage scavenging was calculated by using the following formula:

$$\% \text{ of Scavenging} = (Ao - At)/Ao) \times 100$$

where Ao = Absorbance of control (without extract) and At = Absorbance of sample. All samples and readings were prepared and measured in triplicate.

2.2.5 Total antioxidant capacity

With modest adjustments, the technique of Yu *et al*. (2006) was used to assess total antioxidant activity. B-carotene in the amount of 5 mg was diluted in 10 ml of chloroform, 250 ml of linoleic acid, and 1.5 g of Tween-20. The chloroform was eliminated by spinning on a vacuum evaporator at 50°C for 10 min. The semi-solid residual was then gently combined to with vigorous stirring in order to create an emulsion. In a tube with 1 ml of the antioxidant (rutin and ascorbic acid) solutions at 0.05 or 0.2 mg/ml, a 5 ml aliquot of the emulsion was mixed. A spectrophotometer (TU-1800) was used to test the absorbance immediately at 470 nm employing a blank that consisted of the emulsion without b-carotene. The tubes were put in a water bath set at 50°C, but until 150 min had passed, the absorbance was checked every 25 min. Applying the formula given, the antioxidant capacity of the samples and standard was evaluated by means of b-carotene bleaching:

$$AA = (1 - A_0 - A_t/A0_0 - A0_t) \times 100$$

where AA is the antioxidant activity, A0 the initial absorbance of sample, At the absorbance of sample after 150 min, A00 the initial absorbance of control, and A0t is the absorbance of control after time 150 min.

2.3 *In silico* docking

In silico docking analysis of rutin was performed to determine the effect and the binding strength or molecular interaction pattern with the genomes such as S810L mutation within the human mineralocorticoid receptor (MR S810L), induces severe hypertension and ACE1 protein. This analysis was performed for possible exploration of therapeutic role of rutin in hypertension.

For this analysis, three-dimensional structure (3D structure) of proteins (targeted protein MR S810L ID: 1ya3 and ACE1 ID: 1o8a) was found in RCSB Protein Data Bank (http://www.rcsb.org/pdb).

2.3.1 Ligand preparation

The ligands of rutin (https://pubchem.ncbi.nlm.nih.gov/compound/5280805) as well as captopril as standard compound (https://pubchem.ncbi.nlm.nih.gov/compound/44093) in 3D SDF format were transferred from the database of PubChem and formatted in PDB and PDBQT format using software (BIOVIA Discovery Studio Visualizer 2021) and further processed for Autodock for molecular docking by adjusting torsion, ionization, degree of freedom and stereo-chemical variation (Rahman *et al*., 2019).

2.3.2 Preparation of protein structure for docking

The Autodock was used to prepare and refine the selected protein structure (MR S810L and ACE 1). The protein structure in PDB format was downloaded with Resolution: 2.34 Å, R-Value Free: 0.284, R-Value Work: 0.237, R-Value Observed: 0.252 for 1YA3 protein of hypertension while Resolution: 2.00 Å, R-Value Free: 0.220, R-Value Work: 0.180, R-Value Observed: 0.180 for ACE1 protein. In autodock tool, the protein structure was refined via deleting the water atoms and adding polar hydrogen atoms. Molecular docking was performed by Autodock Vian and BIOVIA Discovery Studio Visualizer software. Further, the processing of the docking analysis was performed using command Prompt and prerequisite before the docking analysis.

2.4 Statistical analysis

Statistics interpretations of the data were presented as mean ± SD by Using Way ANOVA proceeded by Tukey test to analyse all the pairings of the section. The statistical significance variation was expressed as a p value and a conclusion. The normal groups were evaluated against the toxic control group, whereas the other treatment groups were matched to the toxic control group. The $p<0.05$ were indicated as statistical significance.

3. Results

3.1 *In vitro* antioxidant activity of rutin

3.1.1 DPPH radical scavenging activity

The impact of antioxidant properties on DPPH radical scavenging is considered to be due to their hydroxyl radical potential. A stable form of free radical called DPPH may take an electron or even a hydrogen ion to transform into a strong diamagnetic structure. The decreasing potential of Dpph was determined by the reduction in its absorbance at 517 nm probably caused by antioxidants. Technically, it appears as a discoloration that changes from purple to yellow. Hence, DPPH is generally utilized as a substrate to assess the antioxidative activity of rutin (Figure 1A) demonstrates a considerable reduction in the concentration of DPPH radicals due to the scavenging potential of rutin as well as ascorbic acid. We used ascorbic acid as a benchmark for radical scavengers. The antioxidative effect of rutin and ascorbic acid on the DPPH radical was reduced in the sequence of ascorbic< rutin, while at a concentration of 500 µg/ml, the subsequent inhibition was 87.8% and 92.2%, respectively. Correlating to this (Yang *et al*., 2008) revealed that rutin had a high level of DPPH radical scavenging effectiveness, whereas ascorbic acid had levels equivalent to rutin. These findings suggested that rutin significantly reduces the number of free radicals in the body. These findings unambiguously show that rutin is a potent free radical scavenger and inhibitor.

3.1.2 ABTS radical scavenging activity

A chemical substance called ABTS (2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)) is employed to monitor the reaction rate of certain enzymes. Its usage makes it possible to monitor the peroxidases' own reaction rate. This method may also be used to measure the quantity of hydrogen peroxide in a specimen or to estimate the reaction rate of any enzyme that produces hydrogen peroxide (Ilyasov *et al*., 2020). Figure 1B shows the ABTS capability of rutin compared to ascorbic acid as standards. Higher absorbance of the reaction mixture indicated greater ABTS. The ABTS of rutin was in a concentration-dependent manner. At all the concentrations, ABTS capability of rutin was similar to ascorbic acid. These results suggest that rutin and the ascorbic acid have a remarkable potency to monitor the peroxidases' own reaction rate. While at a concentration of 500 µg/ml, the subsequent inhibition was 81.8% and 86.6%, respectively. Similar result has been obtained by (Habu and Ibeh, 2015) *in vitro* antioxidant scavenging activity of bioactive compound present in leaf extract of *Newbouldia laevis*.

3.1.3 Nitric oxide scavenging activity

Nitric oxide is crucial in the inflammation reaction but is potentially hazardous to cells at high levels, leading to vascular damage and other illnesses. Its toxic effects are increased when the peroxynitrite anion (ONOO), a secondary reactive molecule, reacts with the superoxide radical. By engaging in close conflict with oxygen, rutin prevents nitrite production during the generation of the radical (N). Moreover, peroxynitrous acid (ONOOH), a risky and extremely reactive molecule, is created when peroxynitrite (ONOO) is protonated (Pacher *et al*., 2007). Rutin blocks the action by removing peroxynitrite. When combined with ascorbic acid, rutin had a similar action. There is no discernible change when compared to the ascorbic acid standard. The total nitric oxide (NO) at 500 µg/ml was 72.83 ± 1.01% comparable to those of ascorbic acid 92 ± 2.0% (Figure. 1D). Similar result has been obtained by (Yang *et al*., 2008) by the investigation on antioxidant properties of rutin.

3.1.4 Iron chelating acitivity

As excess free irons have been implicated in the induction and formation of free radicals in biological systems, we tested rutin in a metal chelating assay. Tested in the concentration range in descending order 500 to 9.370 µg/ml, rutin and ascorbic acid demonstrated strong chelating activities in concentration-dependent manner (Figure. 1C). Compared at the concentration of 500 µg/ml rutin and *ascorbic acid* demonstrated the strongest activities. The Iron chelating (IC) activity of rutin at 500 µg/ml was 78.32 ± 1.01% comparable to those of ascorbic acid 75.01 ± 2.0%. By the dissolution of the heme prosthetic group, hypochlorous acid (HOCl)

denatures catalase. Catalase inhibition by the plant extract demonstrated its HOCl scavenging ability. There is no considerable change with respect to values of ascorbic acid standard. Iron chelating action, which can promote lipid peroxidation, and also singlet oxygen, which causes hyperoxidation and oxygen toxicity, are all inhibited by the rutin in a concentration-dependent way. Similar result has been obtained by (Habu and Ibeh, 2015) *in vitro* antioxidant scavenging activity of bioactive compound present in leaf extract of *Newbouldia laevis* which contain rutin as a major bioactive metabolite.

3.1.5 Total antioxidant capacity

Employing the β-carotene-linoleic acid coupled oxidation model system, the antioxidant activity of rutin were assessed between 500-9.370 µg/ml. Figure 1E depicts the decline in β-carotene absorbance in the presence of rutin and ascorbic acid at a concentration of 500-9.370 µg/ml. ascorbic acid shown diverse antioxidation abilities. Rutin concentrations dropped at a pace that was significantly faster than those of ascorbic acid. B-carotene bleaching is an oxygen radicals process brought on by the hydroperoxides produced by linoleic acid. In this method, b-carotene quickly turns discolored in the lack of antioxidants. By oxidizing α -carotene monomers, the product lost its chromophore and distinctive reddish orange, which may be seen UV-visible spectrophotometer. We found that by scavenging the linoleate-free radicals as well as other free radicals generated in the process, antioxidants might reduce the degree of b-carotene bleach. The antioxidant properties were considerably ($p \leq 0.05$) enhanced when rutin and ascorbic acid concentrations were increased to 500 µg/ml. The maximal activity of the rutin was 83.03% at 500 µg/ml and standard antioxidant ascorbic acid was 72.8% activity at a concentration of 500 µg/ml. Rutin action in this experiment is lower than that of other flavonoids like quercetin, which found to have a 70% reduction in activity (Chen *et al*., 2020).

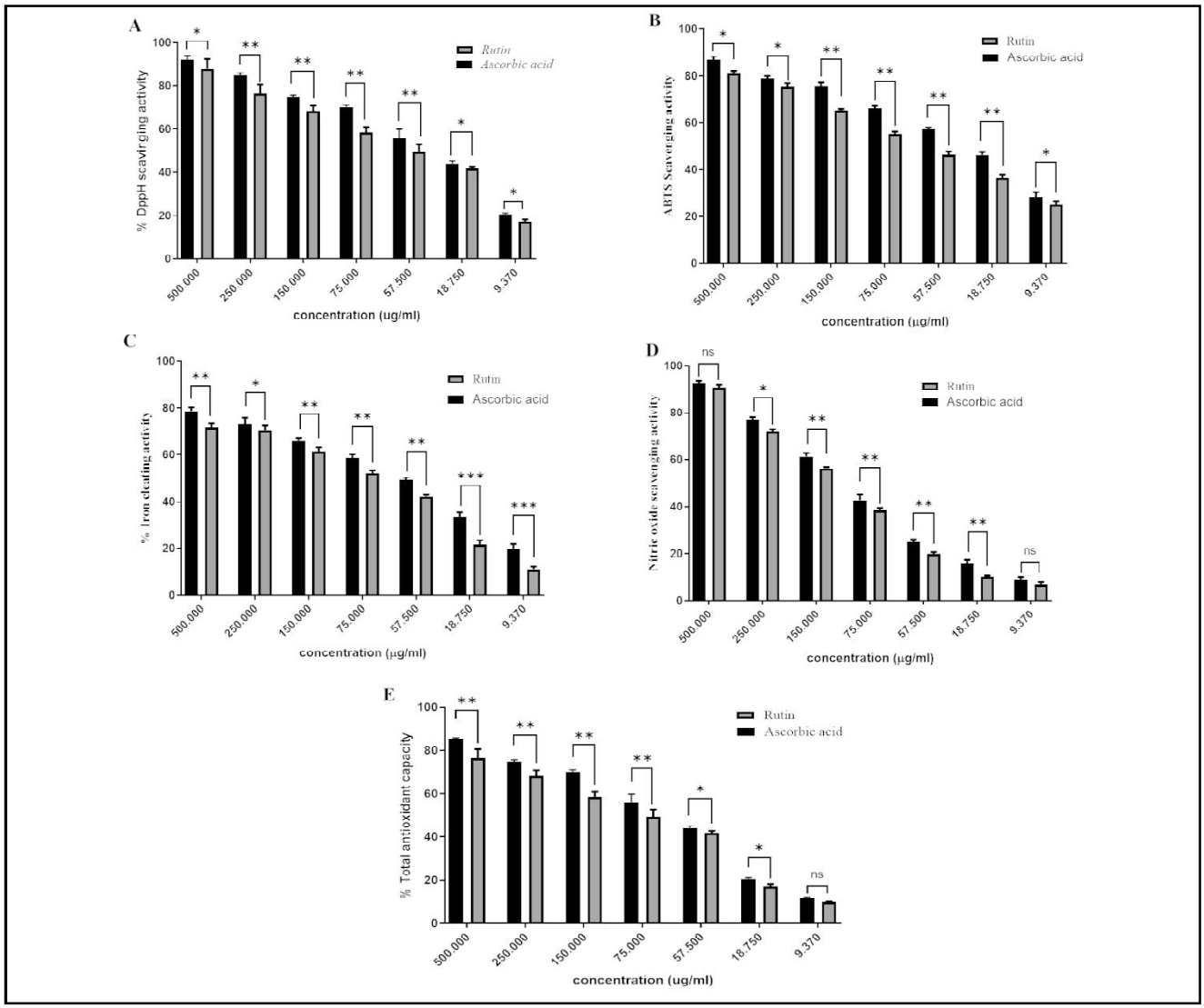

Figure 1: ***In vitro*** **antioxidant activity of rutin with reference to ascorbic acid as standard using different scavenging methods. Figures A-E represent DPPH, ABTS, iron chelating, nitric oxide and total antioxidant activity, respectively.**

3.2 *In silico* docking analysis

In silico docking analysis of rutin was performed *via* assessing its interaction profile with the proteins such as S810L mutation within the human mineralocorticoid receptor (MR S810L), induces severe hypertension and ACE1 protein. The interaction of each protein was considered as the development of conventional hydrogen bonding with different amino acid bundle pockets. The outcome of the study showed that rutin significantly interact with both the protein and showed several hydrogen bonding then captopril used as reference drug against rutin. The conventional hydrogen bonding of each protein with rutin was found such as VAL C: 830 intreact with diphenyl group of flavone ring while GLC C: 779 and TRP C 816 found interacted with hydroxyl group of sugar and non-sugar moiety of rutin. However, ARG C: 817 gives interaction with ketone group of captopril.

In ACE interaction profile of ritin and captopril, it was found that rutin interact with GLU A: 411, ARG A: 522, ASN A:66 ASN A: 70 gives the strong interaction with hydroxyl and ketone group of rutin. Moreover, captopril gives interaction with ARG A: 522 and GLU A: 411.

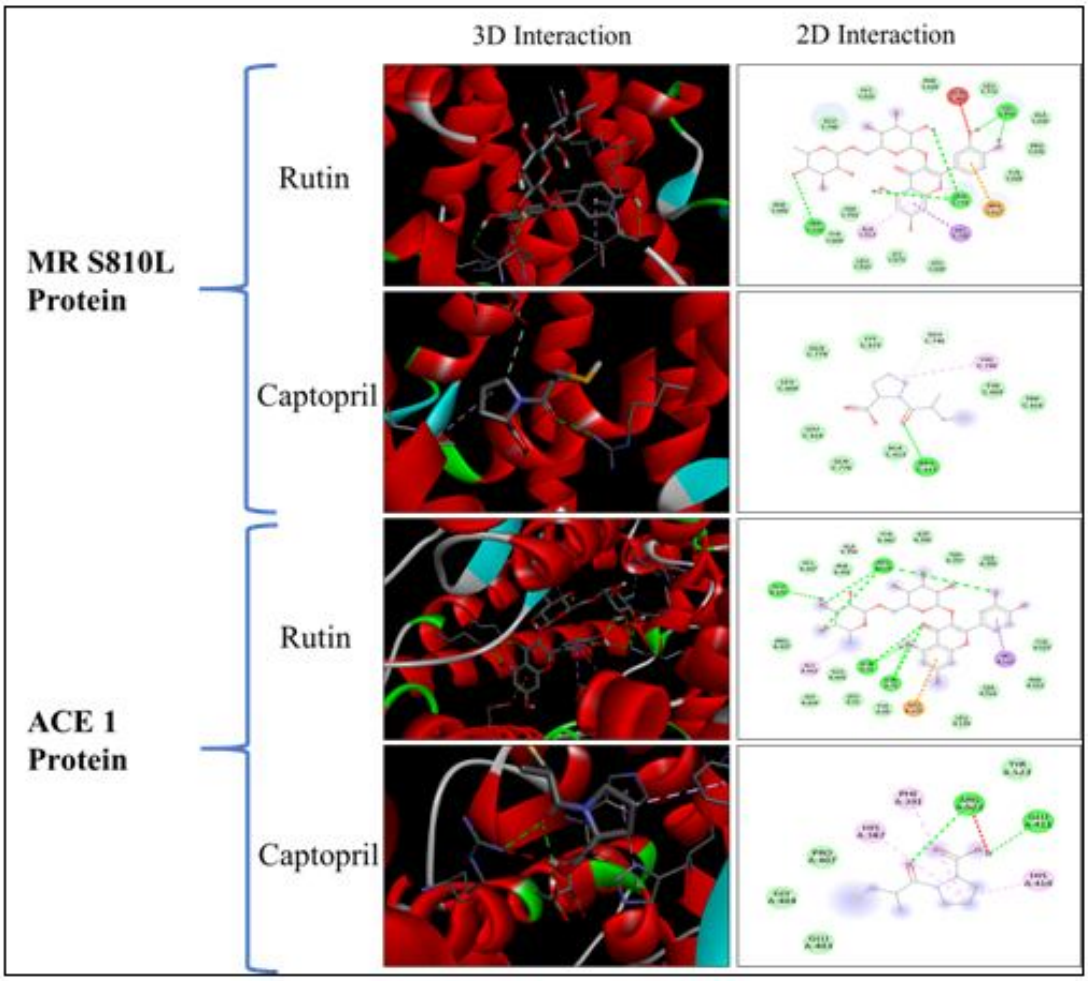

Figure 2: ***In silico*** **docking interaction profile of rutin and captopril with S810L mutation within the human mineralocorticoid receptor (MR S810L) that induces severe hypertension and ACE1 protein. Column 1 represent the 3D interaction of ligand with protein while column 2 represents 2D interaction of protein with compound such as rutin and captopril, respectively.**

4. Discussion

Rutin is one of the most common components belongs to the glycoside category and due to its antioxidant and anti-inflammatory activity with reduction of vascular rigidity, the present study was associated to determine the antihypertensive potential of rutin *via* determination of interaction with protein that is regulates the physiology of hypertension (Pyo *et al*., 2016; [a]enocak *et al*., 2022, 2020; Yang *et al*., 2008; Falguni *et al*., 2019). In this study, antioxidant activity of rutin exhibited the significant interaction with the free radicals of DPPH, ABTS ferrous ions, *etc*., and played a significant role in quenching the oxidants thus showing antioxidant activity. The reported literatures showed that rutin play a potent antioxidant agent and significantly suppress the oxidative stress induced by pathophysiological alterations (Enogieru *et al*., 2018; Rusmana *et al*., 2017; Yang *et al*., 2008). Furthermore, *In silico* docking studies

were conducted to determine the effect of rutin in hypertension. The protein such as S810L mutation within the human mineralocorticoid receptor (MR S810L) that induces severe hypertension and ACE1 protein and the effect of rutin as well as the reference compound against the protein was found significantly and regulation genomic expression and thus exhibiting their role as antihypertensive agents. However, with the so far of this study, the effect of rutin is far better than the effect of captopril that was found based on the interaction of conventional hydrogen bonding (Girsang *et al*., 2020).

The findings of this investigation unambiguously show that rutin had strong antioxidant activity *in vitro* against several antioxidant defense mechanisms, as well as that this ability was concentration-dependent. Rutin has been shown by some writers to greatly lessen the stomach local inflammation brought by the intragastric administration of the necrotizing drug and to boost GSHPx activation. Others mixed rutin with other antioxidants, which results in a combinatorial prevention of LDL against degradation of the lipid component as well as of the protein component (La Casa *et al*., 2000). These findings may be related to rutin potent antioxidant properties, but more study is required. Rutin is a typical dietary flavonoid found in vegetables, fruits, even in drinks made from plants like wine and grape juice (Girsang *et al*., 2020). Although, gut bacteria convert rutin to a number of chemicals that can be ingested, very little or no dietary rutin is actually absorbed intact (Ullah *et al*., 2020). After oral treatment of rutin, rutin's aglycone, flavonoid, as well as the monophenols 3,4-DHT, 3,4-DHPAA, m-HPAA, and HVA have all been found in the blood of animals (Ganeshpurkar and Saluja, 2017). Quercetin, 3,4-DHPAA, and 3,4-DHT are vicinyl dihydroxyl compounds found in rutin as well as its metabolites. Others have demonstrated that the capacity of phenols to prevent the generation of starting radical species *via* metallic catalysts is affected by the availability of vicinyl dihydroxyl radicals.

5. Conclusion

The study concludes that rutin exhibits as a potent antioxidant activity as well as antihypertensive activity *via* regulation of genomic expression of mineralocorticoid receptor (MR S810L) that induces severe hypertension and ACE1 protein. However, further experimental based examinations are necessary to validate even enhance the credibility of the present findings.

Conflict of interest

The authors declare no conflicts of interest relevant to this article..

References

Bhadarka, D.H.; Patel , U.D.; Ahmed, R., Patel , H.B.; Modi, C.M. and Fefar, D.T. (2018). Biochemical and histologic evaluation following multiple dose administration of paracetamol and along with polyherbal extract mixture in rats. Ann. Phytomed., **7**(2):114-123.

Chen, T.K.; Knicely, D.H. and Grams, M.E. (2019). Chronic kidney disease diagnosis and management: A review. JAMA - J. Am. Med. Assoc., **322**(13):1294-1304

Chen, W.; Wang, S.; Wu, Y.; Shen, X.; Xu, S.; Guo, Z.; Zhang, R. and Xing, D. (2020). The physiologic activity and mechanism of quercetin-like natural plant flavonoids. Curr. Pharm. Biotechnol., **21**(8):654-658. doi:10.2174/1389201021666200212093130.

Daina, A.; Michielin, O. and Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci. Rep., pp:1-2. doi:10.1038/srep42717.

Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring Safety. Front. Neurol., **4**(177):1-10

Enogieru, A.B.; Haylett, W.; Hiss, D.C.; Bardien, S. and Ekpo, O.E. (2018). Rutin as a potent antioxidant: Implications for neurodegenerative disorders. Oxid. Med. Cell. Longev., **2**(1):1-17.

Falguni, D.; Modi, Shailesh. K.; Bhavsar, Patel, J.H.; Varia, Rasesh. D.; Modi, L.C.; Modi, M. and Kale, N. (2019). Pharmacokinetic profile of rutin after intramuscular administration in rats favours its *in vivo* antiinflammatory activity in carrageenan-induced rodent model of inflammation. Ann. Phytomed., **8**(1):185-192.

Fokunang, C.N.; Ndikum, V.; Tabi, O.Y.; Jiofack, R.B.; Ngameni, B.; Guedje, N.M.; Tembe- Fokunang, E.A.; Tomkins, P.; Barkwan, S. and Kechia, F. (2011). Traditional medicine: Past, present and future research and development prospects and integration in the national health system of Cameroon. African J. Tradit. Complement. Altern. Med., **8**(3):284-29.doi:10.4314/ajtcam.v8i3.65276.

Fuchs, F.D. and Whelton, P.K. (2020). High blood pressure and cardiovascular disease. Hypertension, **75**(2):285-292.

Ganeshpurkar, A. and Saluja, A.K. (2017). The pharmacological potential of rutin. Saudi Pharm. J., **25**(2):149-164

Girsang, E.; Lister, I.N.E.; Ginting, C.N.; Sholihah, I.A.; Raif, M.A.; Kunardi, S.; Million, H. and Widowati, W. (2020). Antioxidant and antiaging activity of rutin and caffeic acid. Pharmaciana, **10**(2):147-156. doi:10.12928/pharmaciana.v10i2.13010.

Habu, J.B. and Ibeh, B.O. (2015). *In vitro* antioxidant capacity and free radical scavenging evaluation of active metabolite constituents of *Newbouldia laevis* ethanolic leaf extract. Biol. Res., **48**(16):1-10 doi:10.1186/s40659-015-0007-x.

Heinrich, M.; Ankli, A.; Frei, B.; Weimann, C. and Sticher, O. (1998). Medicinal plants in Mexico: Healers' consensus and cultural importance. Soc. Sci. Med., **47**(11):1859-1871. doi:10.1016/S0277-9536(98) 00181-6.

Ilyasov, I.R.; Beloborodov, V.L.; Selivanova, I.A. and Terekhov, R.P. (2020). ABTS/PP decolorization assay of antioxidant capacity reaction Pathways. Int. J. Mol. Sci., **21**:1-27

Khalil, M.I. and Sulaiman, S.A. (2010). The potential role of honey and its polyphenols in preventing heart diseases: A review. African J. Tradit. Complement. Altern. Med., **7**(4):315-321 doi:10.4314/ajtcam.v7i4.56693.

La Casa, C.; Villegas, I.; Alarcón De La Lastra, C.; Motilva, V. and Martín Calero, M.J. (2000). Evidence for protective and antioxidant properties of rutin, a natural flavone, against ethanol induced gastric lesions. J. Ethnopharmacol., **71**(1-2): 45-53. doi:10.1016/S0378-8741(99)00174-9.

Mills, K.T.; Stefanescu, A. and He, J. (2020). The global epidemiology of hypertension. Nat. Rev. Nephrol., **16**(4):223-237.

Pacher, P.; Beckman, J.S. and Liaudet, L. (2007). Nitric oxide and peroxynitrite in health and disease. Physiol. Rev., **87**:315-424.

Patel, A.; Patel, A. and Patel, N.M. (2010). Determination of polyphenols and free radical scavenging activity of *Tephrosia purpurea* Linn leaves (Leguminosae). Pharmacognosy Res., **2**(3):152-158. doi:10.4103/0974-8490.65509.

Polu, P.R.; Nayanbhirama, U.; Khan, S. and Maheswari, R. (2017). Assessment of free radical scavenging and antiproliferative activities of *Tinospora cordifolia* miers (Willd). BMC complement. Altern. Med., **17**(457):1-12. doi:10.1186/s12906-017-1953-3.

Pyo, S.M.; Meinke, M.; Keck, C.M. and Müller, R.H. (2016). Rutin- increased antioxidant activity and skin Penetration by nanocrystal technology (SmartCrystals). Cosmetics, **3**(9):1-10.

Rahman, N.; Muhammad, I.; Nayab, G.E.; Khan, H.; Aschner, M.; Filosa, R. and Daglia, M. (2019). Molecular docking of isolated alkaloids for possible α-glucosidase inhibition. Biomolecules, **9**:1-16. doi:10.3390/biom9100544.

Rusmana, D.; Wahyudianingsih, R.; Elisabeth, M.; Balqis; Maesaroh and Widowati, W. (2017). Antioxidant activity of *Phyllanthus niruri* extract, rutin and quercetin. Indones. Biomed. J., **9**(2):84-90. doi:10.18585/inabj.v9i2.281.

Senocak, A.; Khataee, A.; Demirbas, E. and Doustkhah, E. (2020). Ultrasensitive detection of rutin antioxidant through a magnetic micro-mesoporous graphitized carbon wrappe d Co nanoarchitecture. Sensors Actuators, B Chem., **321**:1-9. doi:10.1016/j.snb.2020.127939.

Senocak, A.; Sanko, V.; Tümay, S.O.; Orooji, Y.; Demirbas, E.; Yoon, Y. and Khataee, A. (2022). Ultrasensitive electrochemical sensor for detection of rutin antioxidant by layered Ti3Al0. 5Cu0.5C2 MAX Phase. Food Chem. Toxicol., **164**:113016. doi:10.1016/j.fct.2022.113 016.

Suseela, V.; Gopalakrishnan, V.K. and Varghese, S. (2010). *In vitro* antioxidant studies of fruits of *Artemisia nilagirica* (Clarke) Pamp. Indian J. Pharm. Sci., **72**(5):644-649. doi:10.4103/0250- 474X.78538.

Thakur, K.; Anchal, N; Jaswal, S. and Bhatt, A. (2018). Evaluation of antimicrobial potential of root extract of *Asparagus racemosus* Willd. and bark extract of *Juglans regia* L. against pathogenic bacterial isolates. Ann. Phytomed., **7**(2):64-69.

Ullah, A.; Munir, S.; Badshah, S.L.; Khan, N.; Ghani, L.; Poulson, B.G.; Emwas, A.H. and Jaremko, M. (2020). Important flavonoids and their role as a therapeutic agent. Molecules, **25**:1-39.

Yang, J.; Guo, J and Yuan, J. (2008). *In vitro* antioxidant properties of rutin. LWT., **41**:1060-1066 doi:10.1016/j.lwt.2007.06.010.

Yasheshwar; Singh, N; Gaurav and Parveen, R. (2022). Network pharmacology based mapping of potential pharmacological mechanism of metabolic profiles of *Tagetes erecta* L. against oxidative and inflammatory stress including associated complication. Ann. Phytomed., **11**(2):438-446. http://dx.doi.org/10.54085/ap.2022.11.2.53.

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