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Research Article
Perindopril Alleviates Inflammation via Cyclooxygenase Inhibition: A Bioinformatics, *in vitro* and *in vivo* Evaluation

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Abstract

Background and Objective: Perindopril (PER), an angiotensin-converting enzyme (ACE) inhibitor with anti-apoptotic, antioxidant and anti-inflammatory characteristics, has long been used to treat cardiovascular illnesses. In this study, the enzyme inhibitory activity of PER against Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2) was determined. **Materials and Methods:** The PER's anti-inflammatory actions were estimated by *in vitro* COX-1 and COX-2 inhibition assays, the *in vivo* rat model of carrageenan-induced paw edema, histopathological examination, molecular modeling, docking and molecular dynamics studies. The data were analyzed using the Analysis of Variance (ANOVA) Test. **Results:** The PER IC_{50} values for COX-1 and COX-2 were calculated to be 8.3 and 0.1 μM, respectively, showing that PER has an 85.5-fold higher affinity for COX-2 than for COX-1. The PER was found to be a moderate inflammation suppressor in rat paw assay, comparable to celecoxib and indomethacin. Docking and molecular dynamics (MD) simulation supported the stable binding of PER with COX-2. **Conclusion:** Current findings revealed that PER can be used for local acute inflammation and utilized as a substitute for other topical anti-inflammatory medicines, particularly those containing steroids.

Key words: Perindopril, cyclooxygenase, inflammation, drug discovery, Cyclooxygenase-2 (COX-2)

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The complex renin-angiotensin endocrine system (RAS) regulates bodily fluids, electrolyte balance and blood pressure. Angiotensin II (Ang II), produced by the angiotensin-converting enzyme (ACE) from angiotensin I (Ang I), is a crucial component of this system. Aside from its role in blood pressure, the RAS is also responsible for various other processes, including inflammation and immunity and can even impact longevity[1].

Angiotensin-II promotes transcription of pro-inflammatory cytokines, adhesion molecules and nicotinamide adenine dinucleotide phosphate oxidase by activating Nuclear Factor-kappa B (NF-κB) and increasing oxidative stress. Tumor necrosis factor (TNF), interleukin-6 and the chemokine monocyte chemoattractant protein-1 are all highly upregulated by AngII, leading to an influx of inflammatory cells[2]. Furthermore, ACE was discovered to accumulate in sites of inflammation[3].

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are the most common pharmacotherapy for painful, inflammatory conditions. However, NSAIDs have been associated with adverse health outcomes like erosive gastritis, peptic ulcers, prolonged bleeding time, impaired renal function, hyperkalemia, an increased risk of stroke, osteoarthritis and myocardial infarction[4,5]. Hence, drugs providing additional anti-inflammatory effects can minimize the need for NSAIDs during treatment, thereby reducing the use of multiple drugs in combination and preventing multiple adverse reactions.

Perindopril (PER) is a long-acting, once-daily lipophilic antihypertensive drug. An ACE inhibitor, it demonstrates high tissue ACE affinity, reducing Ang II and potentiating bradykinin which has traditionally been used for treating cardiovascular disorders[6]. The PER is converted into perindopril after absorption, which reaches its maximum plasma concentration in 3-4 hrs, reduces Ang II production and has a half-life of 1-17 hrs before excretion in the urine[7]. Also, research shows that PER is a viable treatment option for heart failure that lowers blood pressure and relaxes blood vessels, thereby facilitating blood flow in addition to its antioxidant and anti-apoptotic properties[8-11]. Drug repositioning is a promising alternative approach to the traditional drug discovery process. Repurposing drugs involves finding new therapeutic uses for existing medications. The described strategy saves time and costs and minimizes failure risks, increasing a drug's success rate and maximizing its therapeutic value[12]. Minoxidil, aspirin, valproic acid, methotrexate and sildenafil are some of the best-known and most successful drugs to come out of the described approach[13]. Recently, FDA-approved drugs were repurposed for use against viruses and modulation of inflammation[14-16].

Cyclooxygenase-2 (COX-2) activates the renin system[17]. In addition, Ang II increases the activity of COX-2[18]. The PER has, therefore, great potential as an anti-inflammatory drug since it has high ACE affinity, thereby lowering Ang II levels.

The study assessed whether PER can counter inflammatory activity by COX inhibition. First, the enzyme inhibitory activity of PER against Cyclooxygenase-1 (COX-1) and COX-2 was determined *in vitro* and the results of the assay were compared to those of indomethacin and celecoxib, selective and non-selective inhibitors of COX[19,20]. In addition, PER's effectiveness in reducing acute carrageenan-induced edema *in vivo* on rat paws was determined.

MATERIALS AND METHODS

Study area: The current study was performed at the College of Veterinary Medicine, King Faisal University in 2023.

Chemicals, reagents, instruments and software: Vernier calipers were purchased from Shanghai Machinery International Trading Corporation Ltd. (Shanghai, China). The top-quality chemicals were provided by Sigma-Aldrich, Inc. These include indomethacin, celecoxib, PER, λ-carrageenan, tris (hydroxymethyl) aminomethane, diclofenac sodium, carboxymethyl cellulose (NaCMC), EDTA, hematin, phenol and hydrochloric acid. The APExBIO (Houston, Texas, USA) provided the quercetin. Cayman Chemical (Ann Arbor, Michigan, USA) supplied the screening kits for COX or lipoxygenase (LOX) inhibition. Schrodinger Maestro release 2020.1 was used to prepare the modeling systems (Schrodinger, Inc., LLC, New York, USA). GraphPad Prism 7 software was obtained from GraphPad Software (San Diego, USA).

Drug structure retrieval and 3D optimization: To examine PER's structure, a 2D file was retrieved from the PubChem database and then saved as an SDF file. At physiological pH, the OPLS2005 force field was used in LigPrep to perform 3D optimization of the structures.

Formulating and optimizing the COX-2 structure: The structure for molecular docking was managed via the Maestro software suite and carried out energy minimization, protonation, missing-atom and residue corrections and a pH- and temperature-dependent isoelectric point adjustment on the protein with PDB ID 5IKQ using the OPLS2005 force field. To make the docking grid, a 20 Å cube was built over the attached ligand.

Molecular docking: Schrodinger Maestro's high precision (XP) glide docking module was used to perform molecular docking and the docking score was then used to rank the results. The reliability of the analysis was verified by comparing the positions of the bound ligand in the structure file to the PER docking data.

Estimation of COX-1, COX-2 and Lipoxygenase (5-LOX) inhibitory effects: To test PER's inhibitory functions on COX-1 and COX-2, used COX and LOX inhibitor screening kits according to the manufacturer's guidelines and by earlier described methods[21,22]. As a preliminary step, reactions were carried out in test tubes, including reaction buffer as previously described by Kandeel *et al.*[15]. To this end, COX-1 or COX-2 was added and subsequently incubated at 37°C for 10 min. A final incubation for 2 min at 37°C after adding arachidonic acid. After comparing the predetermined standard curve to the enzyme immunoassay results, the Prostaglandin F2α (PGF2α) concentration was calculated. A total of three experiments were carried out to determine the IC_{50}. The selectivity index was estimated by Eq. (1):

$$\text{Selectivity index} = \frac{\text{PER IC}_{50}\,\text{COX} - 1}{\text{PER IC}_{50}\,\text{COX} - 2} \quad (1)$$

A rat model of carrageenan-induced paw edema for anti-inflammatory activity assessment: As described by Morris[23] an *in vivo* rat paw edema inhibition test was performed. The Animal Breeding Center at the College of Veterinary Medicine, King Faisal University, provided 42 male adult albino rats weighing 180 to 220 g. Rats were randomly divided into six groups (n = 7 per group), including the control animals and the carrageenan group. Four groups received carrageenan combined with indomethacin, celecoxib, or PER (10 and 20 mg kg^{-1}). Rats were housed in 25°C-controlled rooms on a 12 hrs light/dark cycle and allowed free access to food and water. A suspension of PER, indomethacin and celecoxib was prepared using 1% NaCMC in normal saline. Rats were orally administered celecoxib or indomethacin at a dose rate of 10 mg kg^{-1} or PER at one of two dose levels (10 and 20 mg kg^{-1}). One hour after administration, a 1% carrageenan solution dissolved in normal saline was injected into the rats' right hind paws in the subplantar area. To avoid measurement bias, the paw thickness of all rats in all groups was measured blindly with a Vernier caliper at 0, 1, 2, 3 and 5 hrs following drug administration. As per King Faisal University Ethics Committee regulations, all rats were euthanized by pentobarbital (200 mg kg^{-1} IP) overdose and decapitation at the end of the experiment. The King Faisal University Ethics Committee (Ref. No. KFU-REC-2023-JAN-ETHICS497) provided regulatory approval for animal experiments.

Histopathological examination: To observe the nature of structural abnormalities associated with carrageenan injection, the entire paw tissue section (5 µm) was fixed in 10% formalin, embedded in paraffin and processed for sections and staining. The tissue sections were stained with Hematoxylin-Eosin (H&E), examined and photographed.

Molecular dynamics (MD) simulation: Protein preparation and all simulation steps were performed by Desmond software. The MD conditions and steps were performed as described by Shinu *et al.*[24]. The purpose of the molecular simulation dynamics was to verify the docking results. The protocol of the runs was as described by Barton[25].

Statistical analysis: The PER was compared with a control group and standard NSAID treatment for its effects on alleviating rat paw edema. An ANOVA with Tukey's *post hoc* test was used to determine significant differences. The results were concluded to be significant if $p<0.05$. GraphPad Prism software version 7 (GraphPad Software, La Jolla, California, USA) was used to perform all analyses.

RESULTS

***In vitro* enzyme inhibition assays of cyclooxygenases and lipoxygenases:** The PER was tested for its inhibitory efficacy versus COX-1, COX-2 and 5-LOX and then compared to the traditional inhibitors of these enzymes. According to data from the IC_{50} measurements, PER hindered COX-1, COX-2 and 5-LOX with IC_{50} values of 8.33±0.15, 0.1±0.006 and 3.83±0.12 µM, respectively. The PER had an 85.5-fold higher selectivity index than indomethacin and diclofenac. Celecoxib, on the other hand, had a 326-fold higher index. The PER showed a slightly higher IC_{50} value than quercetin for 5-LOX inhibition (Table 1).

Table 1: Inhibitory properties of celecoxib, indomethacin, quercetin, diclofenac sodium and perindopril against COX-1, COX-2 and 5-LOX

	IC_{50} (µM)			
Drugs	COX-1	COX-2	5-LOX	Selectivity index
Celecoxib	14.7	0.044	ND	334.1
Indomethacin	0.1	0.07	ND	1.4
Quercetin	ND	ND	3.33	-
Diclofenac sodium	3.77	0.7	ND	5.4
Perindopril	8.83	0.10	3.83	85.5

COX-1: Cyclooxygenase-1, COX-2: Cyclooxygenase- 2 and 5-LOX: Lipoxygenase

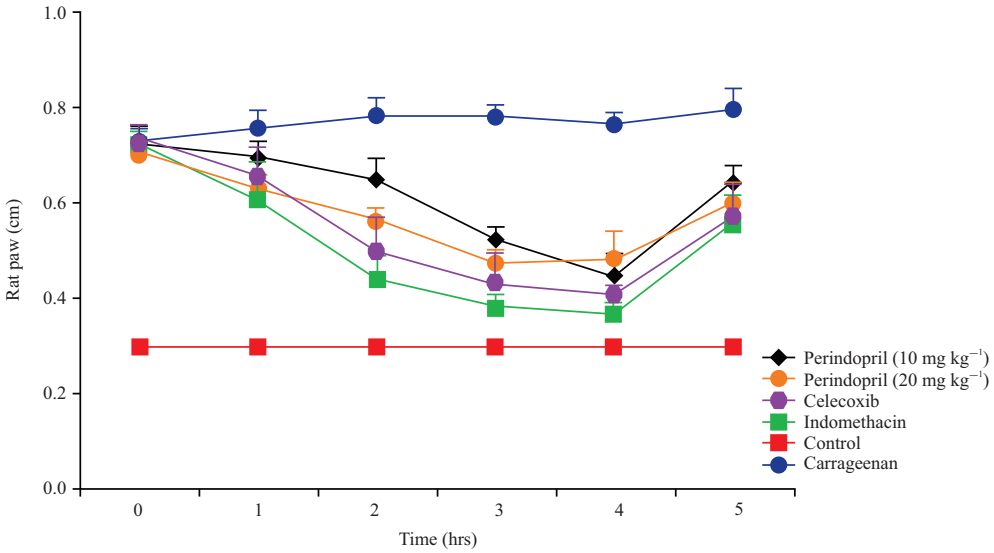

Fig. 1: Findings of an anti-inflammatory activity test for perindopril in rats' paws

X-axis: Calculating the size of a rat's paw in (hrs), Y-axis: Rat's paw length in (cm), when compared to the untreated carrageenan group and all treatments significantly decreased paw edema in rats ($p<0.0001$)

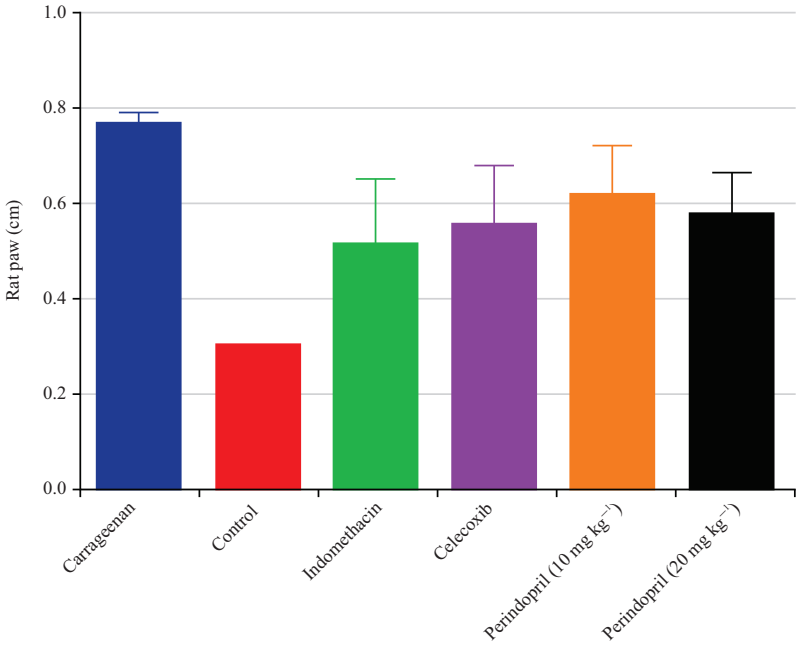

Fig. 2: Rat paw size after treatment with indomethacin, celecoxib and perindopril at 10 and 20 mg kg^{-1} b.wt.

Red: Control negative did not receive any treatments, Blue: Positive control received carrageenan without any treatments, when compared to the untreated carrageenan group and all treatments significantly decreased paw edema in rats ($p<0.05$)

Carrageenan-induced rat paw edema: Carrageenan-injected rat paws grew 0.3-0.75 cm in size after injection. Notably, 2-5 hrs after PER administration, rat paw edema significantly decreased with 10 and 20 mg kg^{-1} PER treatments (Fig. 1). Moreover, a dose-dependent reduction in edema was seen in paw sizes at 3, 4 and 5 hrs after treatment (Fig. 2), consistent

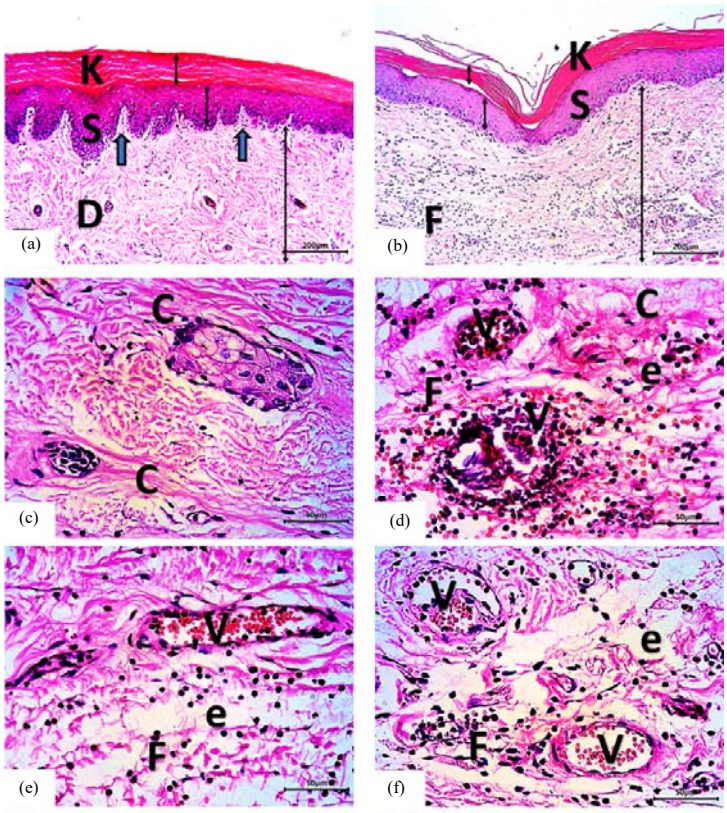

Fig. 3(a-f): Histopathological tissue sections stained with H&E from rat paws, (a) Histological analysis of the normal control group (×100) revealed an intact epidermis, (b) Control positive group displaying massive infiltration, (c) Normal control group (×400), (d) Control positive group displaying massive infiltration, (e) Histological examination of animals that received carrageenan and were treated with indomethacin showed lower cell infiltration, compared with the control carrageenan group and (f) Histological examination of animals that received carrageenan and were treated with perindopril showed lower cell infiltration, compared with the control carrageenan group

(a) Stratified squamous "S" keratinized "K" epithelium and dermis layer "D" with numerous capillaries and connective tissue cells, while dermal papillae, which are little projections of connective tissue on the skin that generate bumpy appearances (blue arrow), are plainly apparent, (b) Inflammatory cells "F", vasodilatation and edema, (d) Inflammatory cells "F", dispersed collagen fibers "C", Vasodilatation "V" with edema "e" as well as extravasated RBCs. H&E: Hematoxylin-Eosin

with that observed using indomethacin and celecoxib (Fig. 2). According to the results of statistical analysis of the treated groups, 10 and 20 mg kg^{-1} PER significantly reduced edema ($p<0.05$) in rats' paws compared to the controls. And noted 5 hrs after treatment that the 20 mg kg^{-1} PER group results were comparable to indomethacin and celecoxib and significantly differed from the other 10 mg kg^{-1}, therefore, 20 mg kg^{-1} was the only dose capable of reducing paw edema significantly.

Pathological examination of rat paw: Histologically, skin sections from the control group had a normal stratified squamous epidermis and dermis layer with ample capillaries, connective tissue cells and visible dermal papillae (Fig. 3). Compared to the control group, the histopathological images of paw tissues in the model group demonstrated flattening of epidermal-dermal junctions, a significant inflammatory reaction in the deep dermis, dilated blood vessels with subcutaneous edema and neutrophil migration. Treatment with indomethacin and PER decreased the cellular infiltration, implying a lower inflammatory response (Fig. 3e and f).

Molecular docking: The docking of PER into the active site of COX-2 was provided in Fig. 4. Both PER and meclofenamic acid (the co-crystalized ligand) showed similar hydrogen profiles as TYR355, SER530 and TYR385. The PER's docking score was

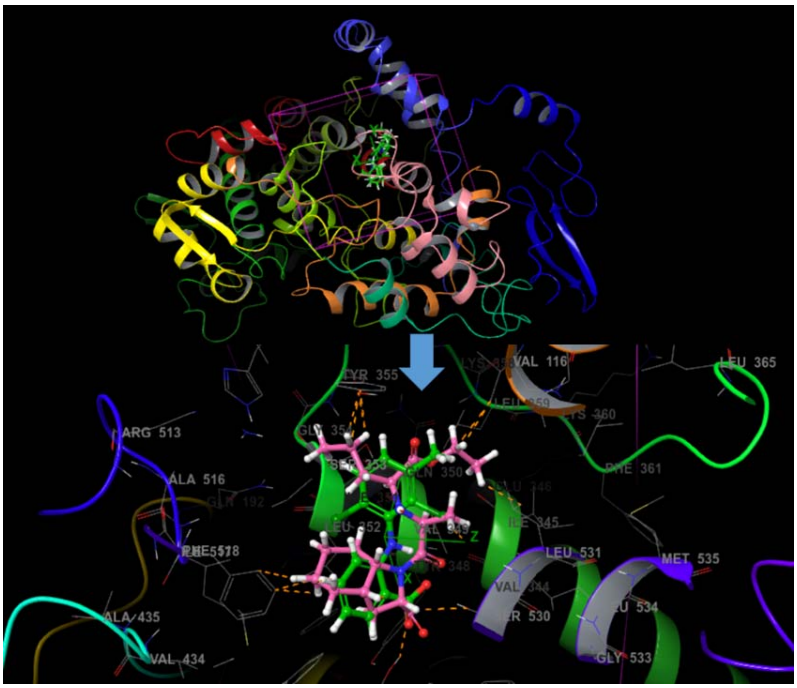

Fig. 4: Molecular docking of perindopril and meclofenamic acid

Docking site of meclofenamic acid (green) and perindopril (pink) in COX-2, hydrogen bonds in orange. COX2: Cyclooxygenase 2

Table 2: Docking results of perindopril against COX-2

Drugs	Docking score	Ligand efficiency	hbond	Glide Lipo
Meclofenamic acid	-9.86	-0.52	-0.32	-4.63
Celecoxib	-9.62	-0.37	-0.30	-4.37
Perindopril	-7.43	-0.29	-0.33	-3.71

Binding parameters were compared with the co-crystalized ligand meclofenamic acid and the standard COX-2 inhibitor celecoxib. COX-2: Cyclooxygenase-2

Table 3: Binding free energy (MM/GBSA) of perindopril with COX-2

Drugs	MM/GBSA
Meclofenamic acid	-65.16
Celecoxib	-74.57
Perindopril	-15.05

Binding energy was compared with the co-crystalized ligand meclofenamic acid and the standard COX-2 inhibitor celecoxib, MM/GBSA: Binding free energy and COX-2: Cyclooxygenase- 2

approximately 76.7 and 77.2% of meclofenamic acid and celecoxib, respectively (Table 2). The ligand efficiency and Lipo parameters indicate that the observed relative efficiency of the COX-2 ligands was meclofenamic acid> celecoxib>PER. All drugs showed a similar hydrogen bond score. Furthermore, the binding energy shown in Table 3 was remarkably equivalent to the estimated docking model based on the MM/GBSA. However, the free energy of the binding of PER to COX-2 was found to be lower than that of meclofenamic and celecoxib. Therefore, PER can bind to COX-2, albeit at a lower strength than meclofenamic acid and celecoxib.

MD simulation: Figure 5 depicts the RMSD of the COX2-PER complex during the course of the MD simulation. The average Root Means Square Deviation (RMSD) for protein residues was found to be between 1 and 3.5 Å, suggesting that the majority of residues maintain their original positions when complexing with ligand molecules (Fig. 5a). In spite of individual residues fluctuating to reach their most stabilized conformation during the simulation process, the complex's macromolecular backbone remains remarkably stable throughout 50 ns of MD simulation. During the first part of the simulation, when the ligand is making specific adjustments to reach the stable conformation, its distance from the protein core swings between a range of 2.8-3.4 Å, later on, it fluctuates slightly within the range of 1.8-2.2 Å. Thus, the early oscillations in the RMSD value of the ligand from these continuous vibrations while conducting precise manoeuvres within the binding cavity of the human COX2 receptor. At the end of the 50 ns simulation, the RMSD of PER was almost similar or slightly lower than the RMSD of protein, indicating stable binding (Fig. 5b). Rout mean square fluctuation (RMSF) implied more stability of the complexed enzyme, compared with Apo COX-2.

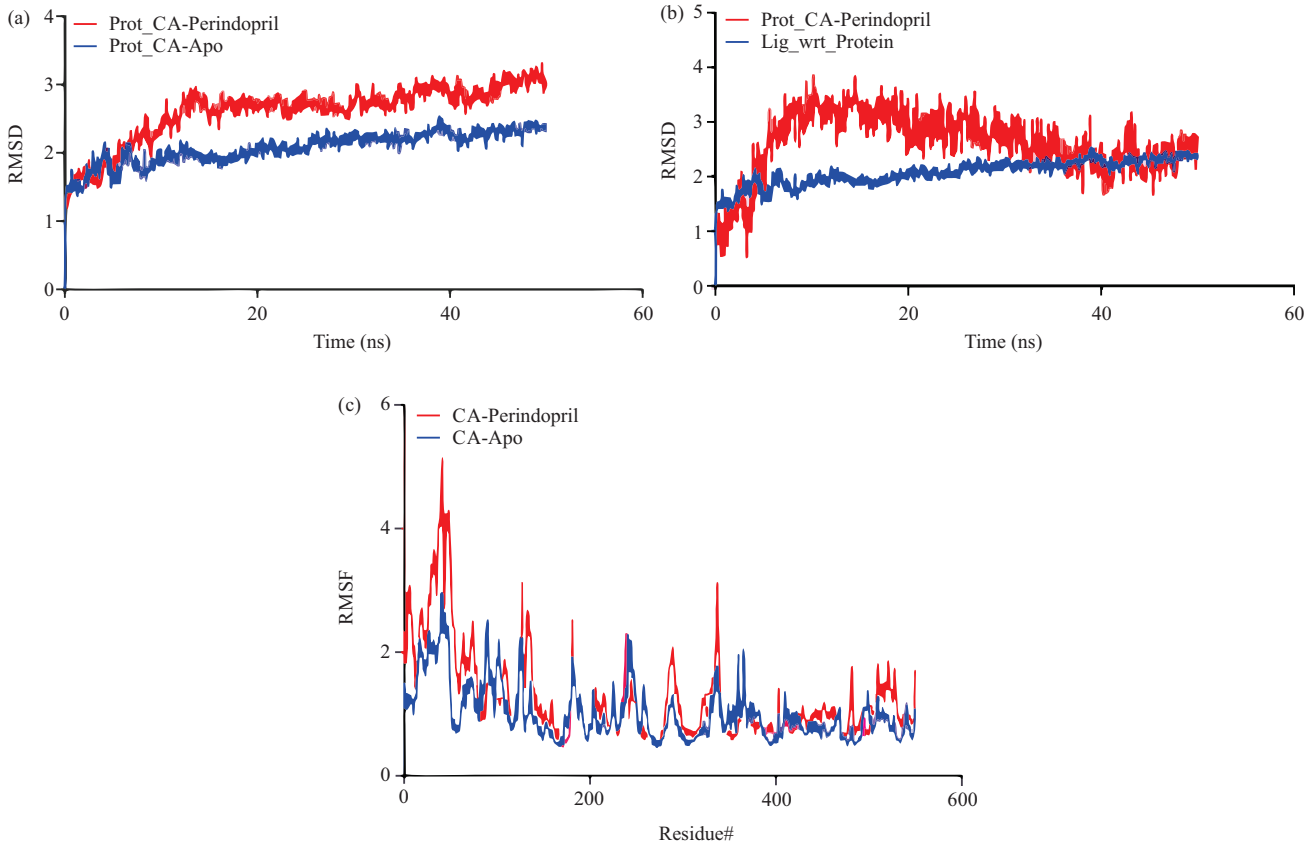

Fig. 5: MD simulation of the interactions of PER with COX-2, (a) RMSD of the Cα backbone of Apo human COX2 or bound with PER, (b) Protein and ligand RMSD and (c) RMSF

MD: Molecular docking, PER: perindopril, COX2: Cyclooxygenase 2 and RMSD: Average root means square deviation

DISCUSSION

The PER's anti-inflammatory effects were assessed by comparison with non-selective and selective COX inhibitors. When the inhibitory properties of PER, indomethacin, diclofenac and celecoxib were investigated, PER was shown to be less potent than indomethacin and diclofenac but more potent than celecoxib. The PER was a less effective COX-2 inhibitor than indomethacin and celecoxib but more effective than diclofenac. Celecoxib was shown to be the most specific of the drugs studied, inhibiting COX-2 at low doses and PER was the second most specific. The PER's medium selectivity score was lower than celecoxib but higher than non-selective drugs such as indomethacin and diclofenac. Consequently, PER administration would result in lower cardiovascular side effects.

Because carrageenan causes exudate to be produced and swelling to occur by upregulating COX-2 expression, the carrageenan-induced rat paw swelling experiment was ideal for testing COX-2 inhibitors. In the carrageenan-induced edema model, various molecules bind to their receptors, activating specific signaling pathways. This leads to transient changes in focal discontinuities between adjacent endothelial cells, increasing vascular permeability and causing edema to develop. The results showed that carrageenan injection induced a massive influx of inflammatory cells, resulting in significant sub-epidermal edema, which was not observed in control rats, whose paws had normal layers, including keratin, sub-epidermal and subcutaneous layers.

The inflammation process is a tightly controlled immune-protective response that helps eliminate offending factors and restores tissue structure and physiological function[25,26]. Inflammatory mediators engaged in various pathological processes, COX and its downstream effectors, particularly COX-1 and COX-2, are upregulated during inflammatory processes and are required in inflammatory signaling pathways[27]. By regulating COX-2 activity, inflammation can be controlled, essential to avoid excessive prostaglandin E2

(PGE2) production, which in turn might cause inflammatory-mediated diseases including cancer[28,29], Alzheimer's[30] and renal failure[31]. The NSAIDs have been commonly prescribed for decades to suppress PGE2 production associated with COX-2[32]. Although NSAIDs are widely used, long-term use of NSAIDs can cause serious and sometimes even fatal side effects[33,34]. Therefore, it is essential to develop alternative therapeutic regimens that offer similar efficacy but that also have fewer side effects.

The ACE inhibitors are associated with excessive buildup of bradykinins, which induce vasodilation. During the inflammatory process, bradykinin induces an increase in vasodilation, permeability and pain[35]. Thus, PER could be associated with higher expression of renal vasodilators comprising higher renal vasodilator prostanoids. In rats, PER lowered the risk of sepsis-induced acute kidney injury, possibly by lowering cell damage, decreasing inflammation and preventing apoptosis[36]. Given the complexity of interactions and many mediators involved in inflammation, it might be that PER modulates inflammation by decreasing the expression levels of inflammatory mediators, such as NF-κB/p65 and TNF-α[37]. Higher NF-κB/p65 and TNF-α expression levels have been associated with a corresponding up-regulation of COX-2 expression[37].

The acute carrageenan-induced inflammation in the rat paw supports the *in vitro* enzyme assay findings. When the rats' paw edema was treated with PER, indomethacin and celecoxib, the edema in their feet was considerably relieved. In terms of lowering rat paw edema, the highest PER concentration exhibited no advantage over indomethacin. Even at the highest PER dose, there was no statistically significant difference between indomethacin and PER.

A local acute inflammatory response to carrageenan is a suitable criterion for evaluating anti-inflammatory agents[38]. Biphasic curves are common in the carrageenan-induced edema model in rats. The first phase involves histamine and serotonin lasting for one hour, followed by inflammation, production of enzymes such as COXs and cell infiltration lasting several hours[39]. Thus, PER's observed effect after 3-5 hrs of inflammation appears to fit with the observed effect on COXs. Moreover, previously published findings of drug-induced edema in rat paws were also consistent with these results[40,41]. Because it inhibits COX-2 activity, indomethacin is an ideal positive control for carrageenan-induced rat paw edema[42]. With PER administration, rat paw edema was significantly reduced, with paw sizes comparable to those of indomethacin-treated rats. One limitation of this study is using rat paw size instead of volume, which may better reflect drug response variations. A second limitation is tracing the paw size for only 5 hrs. However, as rat paw size declined after the 5th hr, the experiment was terminated.

For patients with arterial hypertension and type 2 diabetes mellitus, oral PER 4 mg daily for 4-6 weeks demonstrated organic protective and anti-inflammatory effects[43,44]. Also, PER is analgesic in albino mice exposed to thermal, chemical and mechanical pain models[45].

In this context, it appears that topical PER as an analgesic and anti-inflammatory agent could be well tolerated and a potential clinical topical drug. The IC_{50} values against both COX-1 and COX-2 can be obtained following the topical application of a high dose of PER. A dose of 20 mg kg^{-1} of PER was found to be the most effective in treating rat paw edema, but such a dose cannot be translated directly to human applications and needs further study. Furthermore, PER concentrations above the stated IC_{50} may be effective in inhibiting COXs at sufficiently high levels. Furthermore, because of its cardiovascular effects, there may be limitations in the systemic application, but topical uses may be possible. The clinical pharmacokinetic estimates of PER maximal serum concentration (C_{max}) were approximately 30.40-45.20 ng mL^{-1} underfed and fasting conditions, respectively[46]. Taking these observations into account, the C_{max} values for PER are much lower than PERIC_{50}-COX-1 and approximately equal to PERCOX-2-IC_{50} values. In ovariectomized rats, PER helped promote healing in fractures after local administration (0.4 mg/kg/day) for 7 days[47].

Transdermal patches have recently been developed as an effective method of administering the ACE2 inhibitor trandolapril. These patches increase drug penetration, lengthen the duration of drug exposure and avoid the significant hepatic first-pass metabolism[48]. Using such a delivery method, PER could be delivered at high concentrations above the estimated IC_{50} levels, enhancing PER's anti-inflammatory activity.

When it comes to inhibiting COXs, PER is a fairly selective inhibitor. It has the potential to be repurposed for use in anti-inflammatory topical therapies. The discovery of COXs inhibition expands our understanding of PER's complete spectrum of pharmacological activity and interactions. More research into the production of other inflammatory mediators is needed to gain a complete knowledge of the molecular mechanisms at work when PER is inflamed. Further research is warranted to explore the precise mechanisms underlying PER's anti-inflammatory effects and evaluate its efficacy in various inflammatory conditions. The utilization of PER as an anti-inflammatory agent through COXs inhibition could extend the treatment landscape, offering new possibilities for improving patient outcomes.

CONCLUSION

The current study concluded that PER appears to possess considerable anti-inflammatory effects according to *in-silico*, *in vitro* and *in vivo* studies. Regarding docking, binding profiles and MD simulations, PER shows a significant binding pattern with COX-2 with stable binding and low RMSD. The PER's pharmacological properties have also been identified at the micromolar level. The PER's paw foot edema reduction was likewise found to be dose-dependent. While these studies are still in their infancy, they appear to have much potential.

SIGNIFICANCE STATEMENT

The significance of using PER as an anti-inflammatory through COXs inhibition lies in its potential to provide a novel therapeutic approach for managing inflammatory conditions. The PER, ACE inhibitor, has traditionally been used for treating hypertension and cardiovascular disorders. However, the research outcomes suggest that PER may also exert anti-inflammatory effects by inhibiting COXs. These findings hold significant implications for various inflammatory conditions. By targeting COX-mediated inflammation, PER could potentially offer an alternative or adjunct treatment option for patients who do not respond adequately to existing therapies. Repurposing existing drugs like PER for new indications can expedite the drug development process, potentially reducing costs and improving patient access to effective treatments.

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