Jurnal Kesehatan Tropis Indonesia
Volume 04 Nomor 04 September 2026
e-ISSN: 2986-6332, Hal 1638-1651
Available online at: https://journal.larpainstitute.com/index.php/jkti

Sustainable In Silico Discovery Of Antihypertensive Agents From Papuan Red Fruit Compounds

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Abstract. Hypertension remains a leading cause of cardiovascular morbidity and mortality worldwide, while the long-term use of angiotensin-converting enzyme inhibitors (ACEIs) is often associated with adverse effects, drug resistance, and high treatment costs, highlighting the need for safe and affordable natural alternatives. Pandanus conoideus (red fruit), an endemic Papuan plant rich in carotenoids, tocopherols, unsaturated fatty acids, and phenolic compounds, has demonstrated antioxidant and vasoprotective properties that may inhibit ACE activity. This study aimed to evaluate the ACE inhibitory potential of major carotenoids from P. conoideus using an in silico approach. Molecular docking and pharmacokinetic analyses were performed using BIOVIA Discovery Studio, AutoDockTools, and AutoDock Vina to prepare molecular structures, simulate ligand–receptor interactions, and visualize binding conformations. The results showed that β-carotene, lutein, and capsanthin exhibited stronger binding affinities toward ACE (−8.4 to −8.7 kcal/mol) than the reference drug captopril (−5.7 kcal/mol). Whereas captopril primarily formed hydrogen bonds with Arg522, carotenoids were stabilized mainly through hydrophobic and van der Waals interactions within the ACE catalytic pocket. Capsanthin demonstrated the most favorable binding configuration by forming additional hydrogen bonds with Phe102 and Gln120, suggesting greater binding stability. These findings indicate that carotenoids from Pandanus conoideus, particularly capsanthin, have promising potential as natural ACE inhibitors and warrant further in vitro and in vivo investigations to validate their antihypertensive efficacy and safety.

Keywords: Antihypertensive agents; Angiotensin-converting enzyme (ACE); Carotenoids; In silico molecular docking; Papuan red fruit (Pandanus conoideus); Sustainable drug discovery

1. INTRODUCTION

Hypertension, defined as a systolic blood pressure (SBP) ≥130 mmHg and/or a diastolic blood pressure (DBP) ≥90 mmHg measured across repeated examinations (Jones et al., 2025; Iqbal et al., 2013), remains one of the leading global public health challenges. It contributes substantially to the growing morbidity and mortality from cardiovascular diseases and imposes a significant economic burden due to non-communicable diseases (Jones et al., 2025). According to the World Health Organization (2024), an estimated 1.4 billion people worldwide are affected by hypertension, predominantly among individuals aged 30 to 79 years (WHO, 2025). The control of non-communicable diseases, including hypertension, represents a key target of Sustainable Development Goal 3 (Good Health and Well-Being), which seeks to reduce premature mortality through prevention, management, and improved access to healthcare services (United Nations, 2015; WHO,2025). Consequently, strengthening health systems, increasing public awareness, and ensuring the availability of effective and affordable antihypertensive drugs remain global health priorities (Jones et al., 2025; Parati et al., 2022).

Pharmacological therapy for hypertension is generally initiated when patients with stage 1 hypertension fail to achieve optimal blood pressure control after at least six months of lifestyle modification, or immediately in cases of stage 2 hypertension and above (Perhimpunan Dokter Spesialis Kardiovaskular Indonesia, 2015; Carey et al., 2021; Jones et al., 2025). Current treatment guidelines recommend combination therapy for most patients to attain target blood pressure levels, with single-pill combinations (SPCs) preferred to enhance adherence (Rosas et al., 2025). The five major drug classes widely prescribed include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), and diuretics (Kementerian Kesehatan Republik Indonesia, 2021; Coca et al., 2024). Among these, ACE inhibitors such as captopril remain the mainstay of therapy. However, their use is often limited by adverse effects, potential drug resistance, high costs, and restricted accessibility in developing countries (Kementerian Kesehatan Republik Indonesia, 2021; Jones et al., 2025). This underscores the urgent need to discover safer, more affordable, and environmentally sustainable natural alternatives (Zhou et al., 2021).

Indonesia's vast biodiversity offers a valuable reservoir of bioactive natural compounds with significant pharmaceutical potential. One notable example is *Pandanus conoideus* (red fruit), an endemic plant from Papua, which is rich in carotenoids (β-carotene, lutein, and capsanthin), tocopherols, unsaturated fatty acids, and phenolic compounds—recognized for their potent antioxidant and vasoprotective properties (Yantewo et al., 2024; Mufti et al., 2025). These antioxidants play a crucial role in neutralizing free radicals and reducing oxidative stress, a key contributor to endothelial dysfunction and vascular remodeling in the pathophysiology of hypertension (Xia et al., 2018; Sinha, 2015). Carotenoids have been shown to improve endothelial function, enhance nitric oxide (NO) bioavailability, and reduce inflammation, thereby exerting antihypertensive and cardioprotective effects (Abbasian et al., 2023; Sumalla-Cano et al., 2024). Dietary carotenoid intake, including β-carotene and lutein, has been inversely associated with blood pressure levels and cardiovascular mortality in hypertensive populations (Zhu et al., 2023; Behzadi et al., 2025). Moreover, antioxidants such as tocopherols and phenolic compounds from natural sources have been reported to modulate oxidative stress pathways and inhibit angiotensin-converting enzyme (ACE) activity, supporting their potential as alternative antihypertensive agents (Pari et al., 2024; Młynarska et al., 2024).

Experimental evidence further supports the therapeutic potential of *Pandanus conoideus*. A study in pregnant Wistar rats demonstrated that oral administration of red fruit oil at doses ranging from 0.15 to 0.6 mL per day effectively prevented oxidative stress–induced increases in blood pressure and proteinuria (Sugitritama, 2006). Furthermore, *in vitro* analyses revealed

that red fruit oil enhances endothelial nitric oxide synthase (eNOS) phosphorylation, increases nitric oxide (NO) production, promotes vasodilation, and reduces oxidative DNA damage in endothelial cells (Xia et al., 2018). These findings suggest that enhanced endothelial NO production and reduced oxidative stress may underlie the antihypertensive mechanisms of red fruit oil. Collectively, this evidence highlights *Pandanus conoideus* as a promising natural source of ACE, providing a potential complementary strategy for hypertension management within Indonesia's rich medicinal flora (Abbasian et al., 2023; Młynarska et al., 2024).

Despite these promising findings, limited research has explored the molecular interactions of *Pandanus conoideus* bioactive compounds through *in silico* approaches. Therefore, the present study aims to: (1) Identify carotenoid compounds in *Pandanus conoideus* with potential inhibitory activity against ACE using *in silico* methods; (2) evaluate their molecular interactions and binding affinities; and (3) provide a scientific foundation for developing sustainable, natural antihypertensive agents.

In summary, this study focuses on analyzing and comparing the molecular interactions of β-carotene, lutein, and capsanthin as potential inhibitors of angiotensin-converting enzyme (ACE) using *in silico* molecular docking approaches.

2. METHOD

a. Study Design

This research was designed as an experimental in silico study employing a computational drug discovery approach through molecular docking simulation. The study was conducted in November 2025 and utilized an Advan 1701 laptop powered by an Intel® Core™ i5-1035G7 processor (1.20 GHz), 4 GB RAM, and Windows 11 (64-bit) operating system. An exploratory bioinformatics workflow was implemented, encompassing structure preparation, docking simulation, and post-docking visualization. The primary software tools used included BIOVIA Discovery Studio, AutoDock Tools (ADT), and AutoDock Vina (Sakinah et al. 2023).

Data Sources

The three-dimensional (3D) structures of the carotenoid ligands—β-carotene, lutein, and capsanthin—and the control drug captopril were retrieved from the PubChem database. The crystal structure of the target protein, angiotensin-converting enzyme (ACE), was obtained from the Protein Data Bank (PDB ID: 1O86); receptor structure was also accessed from the same database. Protein structures were downloaded in .pdb format, and ligand structures in .sdf format. Receptor and ligand preparation was carried out using BIOVIA Discovery Studio, which included removal of water molecules and heteroatoms, addition of

polar hydrogens, and energy minimization. Subsequently, all files were converted into PDBQT format using AutoDock Tools, with Gasteiger charges assigned and rotatable bonds defined (Sakinah et al. 2023). The active site of ACE was identified based on the coordinates of its co-crystallized native ligand and further validated through literature, encompassing the key catalytic residues Ala354, Glu384, Tyr523, Glu162, Gln281, His353, Lys511, His513, Tyr520, Ser355, and Pro519 (Tahir et al., 2020).

b. Docking Procedure

Ligand and receptor optimization was performed using AutoDock Tools, ensuring correct geometry, charge distribution, and torsional flexibility. A grid box was carefully configured to cover the ACE catalytic pocket, and all docking parameters including grid dimensions, center coordinates, and exhaustiveness were specified in a configuration file (.config.txt) created using Notepad. The molecular docking simulations were executed using AutoDock Vina, with all necessary files (ligand .pdbqt, receptor .pdbqt, and configuration .txt) stored in the same directory and processed via the command-line interface. The docking results generated multiple ligand conformations ranked by binding affinity (ΔG, kcal/mol). The lowest ΔG value was selected as the optimal conformation, representing the most stable ligand–receptor complex. Post-docking analysis was conducted using BIOVIA Discovery Studio to examine hydrogen bonds, hydrophobic contacts, and electrostatic interactions between each ligand and key active-site residues of ACE. The binding affinity values and interaction patterns were used to assess ligand potency, where more negative ΔG values indicate stronger and more stable binding, suggesting higher inhibitory potential (Sakinah et al. 2023; Pinzi & Rastelli, 2019).

c. Comparative Control

To validate the docking protocol and provide a reference for comparative analysis, captopril a clinically established angiotensin-converting enzyme (ACE) inhibitor was employed as the standard control compound. Captopril was selected due to its well-characterized binding mechanism and therapeutic relevance in hypertension management. The docking parameters and evaluation criteria applied to captopril were identical to those used for the carotenoid ligands (β-carotene, lutein, and capsanthin) to ensure methodological consistency. Comparative assessment was performed to determine whether the natural carotenoid compounds exhibited comparable or superior binding affinity and interaction stability relative to captopril.

d. Data Analysis

Docking outcomes were analyzed through both quantitative and qualitative

approaches. Quantitatively, the binding affinity (ΔG, kcal/mol) values for each ligand–receptor complex were tabulated and compared to identify the most stable binding configuration. Qualitatively, the 2D and 3D interaction profiles were examined using BIOVIA Discovery Studio, highlighting the hydrogen bonds, hydrophobic interactions, and electrostatic contacts formed with the active-site residues of ACE receptors. All results were compiled into comparative tables and interaction maps, allowing visual interpretation of key binding features. Descriptive analysis was employed to interpret the relative affinity strength and interaction patterns among the ligands. Ligands demonstrating the lowest binding energy and most favorable interaction networks were considered to possess the highest inhibitory potential against ACE activity.

3. RESULTS AND DISCUSSION

a. Visual Output and Binding Interactions

1) Captopril and ACE

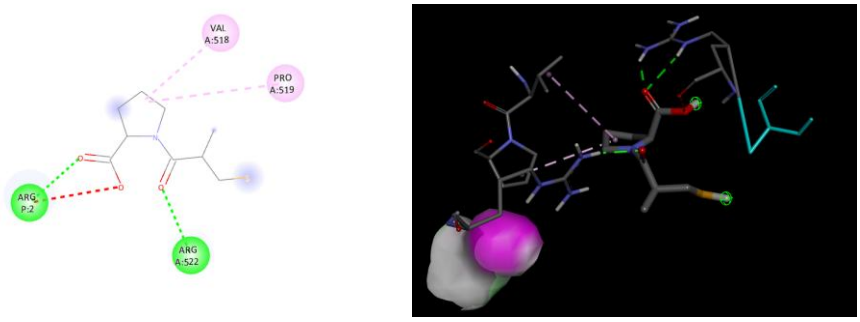

Figure 1. Bond interaction model between Captopril and ACE

Illustrates the two-dimensional (2D) interaction profile of captopril bound to the angiotensin-converting enzyme (ACE) active site. The docking analysis revealed that captopril interacts with several key amino acid residues that contribute to its inhibitory activity. Specifically, hydrogen bond interactions were formed with Arg522 and Arg2, while hydrophobic contacts were observed with Val518 and Pro519 residues. These interactions collectively stabilize the ligand within the catalytic pocket of ACE. The carbonyl oxygen of captopril acts as a hydrogen bond acceptor, whereas the thiol (–SH) group participates in electrostatic interactions that enhance complex stability. Such bonding patterns are consistent with previously reported captopril ACE binding mechanisms, indicating accurate docking validation. The presence of multiple arginine-mediated hydrogen bonds supports the strong inhibitory potential of captopril through stable anchoring within the ACE catalytic site.

2) β-carotene and ACE

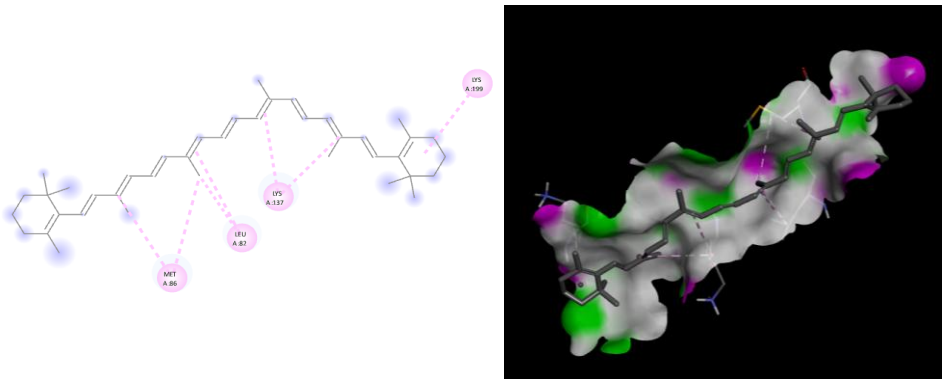

Figure 2. Bond interaction model between β-carotene and ACE

Illustrates the two-dimensional (2D) interaction diagram of β-carotene docked into the angiotensin-converting enzyme (ACE) active site. The docking analysis revealed that β-carotene was stabilized mainly through hydrophobic interactions, particularly Alkyl and Pi-Alkyl contacts, with residues Met86, Leu82, Lys137, and Lys199. These non-polar contacts suggest that the elongated polyene chain of β-carotene fits well within the hydrophobic pocket of ACE, promoting van der Waals stabilization rather than hydrogen-bonding interactions. The absence of conventional hydrogen bonds is consistent with the non-polar nature of β-carotene, whose interaction relies on dispersion and π-alkyl forces. Such binding characteristics imply that β-carotene may inhibit ACE activity through hydrophobic anchoring and steric hindrance mechanisms rather than electrostatic or hydrogen-bond-mediated interactions.

3) Lutein and ACE

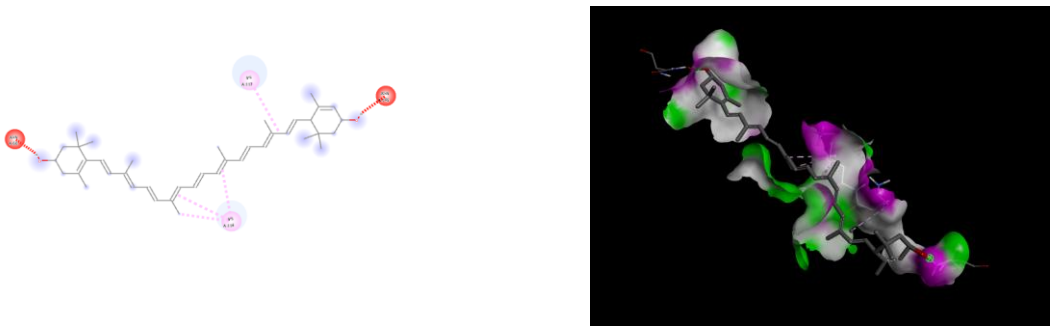

Figure 3. Bond interaction model between Lutein and ACE

Two-dimensional (2D) interaction diagram of lutein docked within the angiotensin-converting enzyme (ACE) binding site. The docking analysis revealed predominantly hydrophobic Alkyl and Pi-Alkyl interactions with key residues Lys117 and Lys118, accompanied by unfavorable positive–positive electrostatic interactions with Arg522 and

Arg105. These observations indicate that lutein is mainly stabilized by non-polar contacts, while the repulsive interactions at both terminal regions suggest limited electrostatic compatibility with the ACE catalytic pocket. The elongated conjugated structure of lutein aligns well within the hydrophobic region of ACE, similar to other carotenoids such as β-carotene and capsanthin. However, the presence of positive–positive repulsion with Arg522 and Arg105 may reduce the overall binding stability compared to β-carotene or capsanthin, which exhibit more balanced hydrophobic–polar interactions. Taken together, the interaction pattern suggests that lutein binds through hydrophobic anchoring, but with slightly weaker stabilization energy due to electrostatic repulsion near charged residues.

4) Capsanthin and ACE

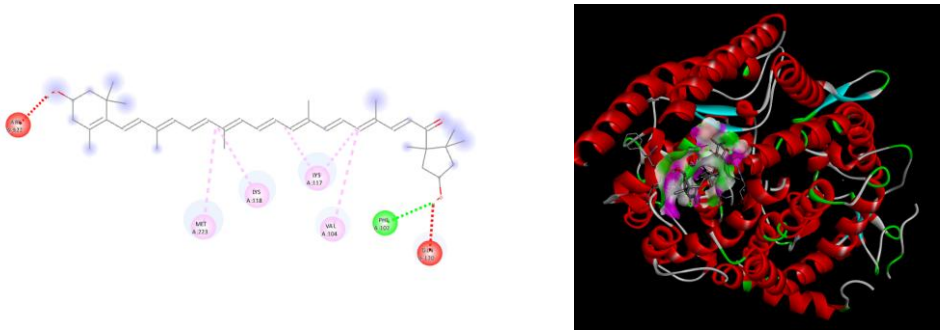

Figure 4. Bond interaction model between Capsanthin and AC

Two-dimensional (2D) interaction profile of capsanthin within the angiotensin-converting enzyme (ACE) active site. The docking visualization revealed a combination of hydrophobic and polar interactions, suggesting a moderately stable ligand–receptor complex. Capsanthin formed conventional hydrogen bonds (green lines) with Phe102, while a carbon–oxygen contact representing an additional hydrogen bonding interaction was observed with Gln120. Meanwhile, hydrophobic Alkyl and Pi–Alkyl interactions (pink lines) were detected with Val104, Lys117, Lys118, and Met223, contributing to non-polar stabilization within the receptor cavity. However, an unfavorable positive–positive interaction (red line) appeared with Arg522, indicating a mild electrostatic repulsion between charged centers. Overall, the molecular docking pattern indicates that capsanthin interacts with both polar and non-polar residues at the ACE active site. Despite the minor repulsion observed with Arg522, the coexistence of multiple stabilizing interactions—especially hydrogen bonds with Phe102 and Gln120—supports the potential inhibitory activity of capsanthin toward ACE through a mixed hydrophobic–hydrogen bonding mechanism**.**

5) Descriptive Summary

Table 1. Comparison of the binding interactions between β-carotene, lutein, capsanthin, and captopril with the ACE receptor

Ligand	Binding affinity score (Kkal mol)	Type of binding to the active site of ACE		
		Hydrogen bond	van der Waals (v) / Hydrophobic (h)	Pi-anion / Electrostatic
Captopril	-5.7	Arg522	Val518 (h), Pro519 (h)	Arg2 (positive–positive repulsion)
β-Carotene	-8.4	–	Met86 (h), Leu82 (h), Lys137 (h), Lys199 (h)	–
Lutein	-8.7	–	Lys117 (h), Lys118 (h)	Arg522 (+/+), Arg105 (+/+)
Capsanthin	-8.7	Phe102, Gln120	Val104 (h), Lys117 (h), Lys118 (h), Met223 (h)	Arg522 (+/+)

The docking results presented in Table 1 summarize the binding affinity values (ΔG, kcal/mol) and the types of molecular interactions formed between ACE and the four ligands: captopril, β-carotene, lutein, and capsanthin. Captopril, the reference ACE inhibitor, exhibited a binding affinity of −5.7 kcal/mol. Its stabilization within the ACE catalytic site is primarily mediated by a hydrogen bond with Arg522, along with hydrophobic interactions involving Val518 and Pro519. A minor electrostatic repulsion was observed with Arg2, which corresponds to the positive–positive charge interaction. In contrast, the natural carotenoids demonstrated stronger binding affinities, with β-carotene (−8.4 kcal/mol), lutein (−8.7 kcal/mol), and capsanthin (−8.7 kcal/mol).

β-Carotene interacts mainly via hydrophobic contacts with residues Met86, Leu82, Lys137, and Lys199, reflecting its non-polar and van der Waals–driven binding behavior. Lutein also relied on hydrophobic interactions (Lys117 and Lys118), yet displayed electrostatic repulsion with Arg522 and Arg105, suggesting limited compatibility with ACE's charged regions. Capsanthin formed the most balanced profile, exhibiting hydrogen bonding with Phe102 and Gln120, along with extensive hydrophobic stabilization involving Val104, Lys117, Lys118, and Met223. A mild electrostatic clash with Arg522 was also noted but did not significantly affect complex stability.

Overall, the results suggest that capsanthin and lutein possess higher binding affinities than the reference drug captopril, primarily due to extensive hydrophobic and van der Waals interactions that enhance ligand anchoring within the ACE active site. These

findings support the potential of natural carotenoids as ACE inhibitory candidates through mechanisms dominated by non-polar stabilization rather than classical hydrogen bonding.

6) Comparative Analysis

The comparative docking analysis revealed distinct interaction mechanisms and binding affinities between captopril and the natural carotenoid ligands β-carotene, lutein, and capsanthin in relation to the angiotensin-converting enzyme (ACE). Overall, all carotenoid compounds exhibited stronger binding affinities, ranging from −8.4 to −8.7 kcal/mol, compared to the reference drug captopril (−5.7 kcal/mol), indicating a more stable ligand–receptor interaction. Captopril, as the control inhibitor, primarily established hydrogen bonding with Arg522 and additional hydrophobic contacts with Val518 and Pro519, which are characteristic of polar interactions that stabilize the ligand within the ACE catalytic pocket. In contrast, β-carotene, lutein, and capsanthin demonstrated predominantly non-polar binding mechanisms involving extensive hydrophobic (Alkyl and Pi–Alkyl) and van der Waals interactions, reflecting their conjugated and lipophilic molecular structures.

Among the three carotenoids, capsanthin and lutein displayed the highest binding affinity values (−8.7 kcal/mol), suggesting strong stabilization within the ACE active site. Capsanthin formed dual hydrogen bonds with Phe102 and Gln120, complemented by multiple hydrophobic interactions with Val104, Lys117, Lys118, and Met223, resulting in a well-balanced polar and non-polar interaction profile. Lutein, while also exhibiting strong hydrophobic anchoring with Lys117 and Lys118, showed electrostatic repulsion with Arg522 and Arg105, which may slightly reduce its overall stability. Meanwhile, β-carotene is bound exclusively through hydrophobic residues such as Met86, Leu82, Lys137, and Lys199, consistent with its highly non-polar nature and extensive van der Waals stabilization.

Taken together, the visual and tabulated docking results indicate that hydrogen-bond-dependent interactions dominate in captopril, whereas hydrophobic and van der Waals forces govern the binding of carotenoid ligands. The extensive non-polar surface of carotenoids enables them to fit snugly within the lipophilic cavity of ACE, providing strong binding stabilization even in the absence of classical hydrogen bonds. Capsanthin, which combines both hydrogen bonding and hydrophobic interactions, exhibited the most balanced and stable configuration among all ligands. These findings collectively highlight that natural carotenoids, particularly capsanthin and lutein, have the potential to inhibit ACE through mechanisms distinct from conventional drugs like captopril primarily via

hydrophobic anchoring and steric complementarity within the catalytic site. This suggests that carotenoids could serve as promising bioactive molecules for natural ACE inhibition and cardioprotective modulation.

b. DISCUSSION

The molecular docking simulations performed in this study provided robust, quantifiable evidence for a novel class of ACE inhibitors derived from the phytochemical profile of Papuan red fruit (*Pandanus conoideus*). The core finding indicates that three primary carotenoids as β -Carotene, capsanthin, and lutein exhibit a significantly superior binding affinity (-8,4 to -8.7 kcal/mol) to the ACE receptor compared to the widely utilized conventional inhibitor, captopril (-5.7 kcal/mol). This thermodynamic stability strongly supports the hypothesis that these compounds are highly effective ligands for the ACE receptor *in silico*.

More critically, the study reveals a fundamental difference in the stabilization mechanism, presenting a novel mechanistic insight. While captopril relies on polar interactions (i.e., hydrogen bonds) with key residues such as Arg522, the carotenoids given their highly non-polar, polyene structure are stabilized predominantly through extensive hydrophobic contacts and strong van der Waals forces within the enzyme's catalytic pocket. This mechanism suggests a potential for non-competitive or allosteric inhibition facilitated by robust hydrophobic anchoring rather than the typical polar coordination, providing a clear molecular picture of their antihypertensive potential (See Figure. 5).

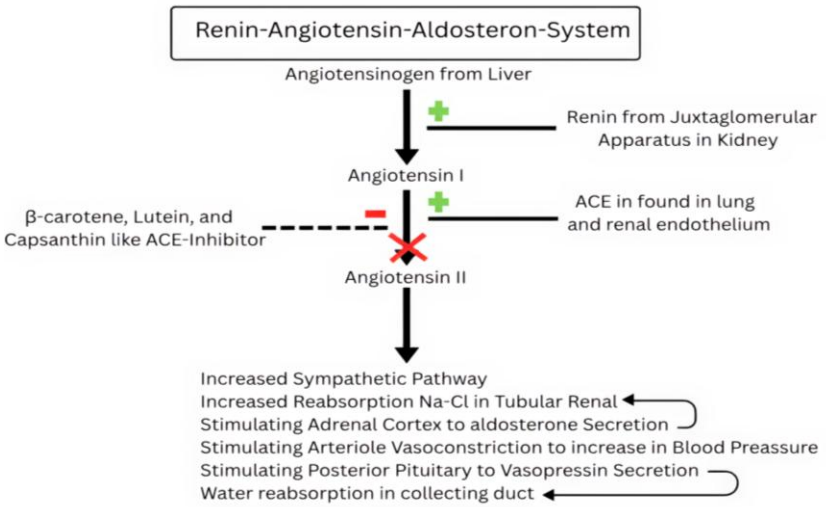

Figure 5. Mechanisme of β-Carotene, capsanthin and lutein like Ace-Inhibitor to prevent increasing blood preassure.

The genesis of this research lies in observing the traditional uses of red fruit by the indigenous Papuan population. This ethnopharmacological approach serves as a core

strength and unique differentiator, transforming centuries-old local wisdom into a modern, testable scientific hypothesis. Our selection of β-carotene, lutein, and capsanthin was deliberately based on the endemic phytochemical profile of *P. conoideus*, distinguishing our findings from research focused on other common carotenoids like lycopene.

The computational results are not isolated, but rather provide a mechanistic underpinning for previously reported empirical observations. For instance, Sugiritama et al. (2006) demonstrated that red fruit oil prevents increases in blood pressure in a pre-eclampsia rat model. Furthermore, studies by Xia et al. (2018) proved that the oil stimulates endothelial nitric oxide synthase (eNOS) phosphorylation, leading to vasodilation. Our finding of the stable interaction between carotenoids and ACE therefore offers the necessary rational, molecular, evidence-based explanation for the observed antihypertensive activity, effectively bridging the gap between traditional use and modern molecular pharmacology.

While lutein and capsanthin shared an identical high affinity (-8.7 kcal/mol), a rigorous qualitative interpretation was necessary to determine the superior inhibitor. Our detailed analysis confirms that the stability of the capsanthin complex is qualitatively superior. Capsanthin achieved stability through a more balanced interaction profile, forming conventional hydrogen bonds with Phe102 and carbon-hydrogen interactions with Gln120. These polar contacts act as crucial "anchor points," supplementing the dominant hydrophobic forces to effectively reduce ligand mobility within the active site. In stark contrast, lutein lacked these specific stabilizing polar interactions and instead exhibited distinct electrostatic repulsion involving Arg522 and Arg105. This repulsion could potentially compromise the overall stability of the lutein-ACE complex *in vivo*, establishing capsanthin as the most promising lead candidate from the red fruit carotenoids.

From a public health perspective, the development of affordable, locally sourced anti-hypertensives from red fruit has significant strategic implications. This approach aligns with Sustainable Development Goal 3 (Good Health and Well-Being) by promoting health equity and utilizing renewable local biological resources. Consequently, our recommendations are translational and pragmatic: favoring the development of standardized functional foods or health supplements from red fruit extracts over the costly and complex isolation of single compounds. This strategy is more feasible for immediate public health intervention and respects the origin of the local wisdom that guided this research.

4. CONCLUSION

This study demonstrated that the carotenoid compounds β-carotene, lutein, and capsanthin found in the red fruit *Pandanus conoideus* exhibit strong binding affinities toward

the angiotensin-converting enzyme (ACE) based on *in silico* simulations. The binding energy values ranged from −8.4 to −8.7 kcal/mol, which are lower than that of the standard drug captopril (−5.7 kcal/mol), indicating greater ligand–receptor complex stability. Among these compounds, capsanthin showed the most stable interaction profile through a combination of hydrogen bonds with residues Phe102 and Gln120, as well as hydrophobic interactions with Val104, Lys117, Lys118, and Met223 effective natural ACE inhibitor candidates.

From a scientific perspective, this research provides a strong foundation for developing natural antihypertensive agents derived from Indonesia's endemic biodiversity, particularly the red fruit *Pandanus conoideus* of Papua, by integrating traditional knowledge with modern biotechnological approaches. In terms of global public health, the findings align with the *Sustainable Development Goal (SDG) 3* "Good Health and Well-Being," promoting sustainable, affordable, and locally sourced antihypertensive therapies. Future studies are recommended to isolate and identify active compounds, perform *in vitro* and *in vivo* biological and safety tests, and develop functional food or supplement formulations based on red fruit as a practical and sustainable public health intervention.

ETHICAL CONSIDERATIONS

This study did not require ethical approval because it was conducted entirely using computational and bioinformatics approaches. All procedures were performed in silico, including molecular docking and pharmacokinetic analyses, utilizing publicly available protein and compound databases. No human participants, animals, or biological specimens were involved in this research. Therefore, ethical clearance was not required in accordance with standard guidelines for computer-based studies.

AUTHOR'S CONTRIBUTION STATEMENT

Dr. Mitsla Chusnica Aulia As'ar was responsible for the research concept and methodology; Dr. Siti Syahral contributed to manuscript writing and content strengthening; Dr. Wisnu Gandhi Triwibowo analyzed and interpreted the results; Dr. Nabil Athoillah provided supervisory assistance and overall support throughout the research process.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

SOURCE OF FUNDING STATEMENTS

This study was self-funded by the authors, with no external financial support or sponsor involvement.

ACKNOWLEDGMENTS

The authors thank Universitas Papua for providing technical support, research facilities,

and administrative assistance during the study.

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