Indonesian Journal of Pharmaceutical Education (e-Journal) 2026; 6 (1): 168-189
ISSN: 2775- 3670 (electronic)
Journal Homepage: http://ejurnal.ung.ac.id/index.php/ijpe/index
DOI: 10.37311/ijpe.v6i1.33420

Natural ACE-Inhibitor Candidates for Hypertension: A Narrative Literature Review with In Silico Highlights

Rd Ajeng Tedjaningrum[1*], Regitha Ardhia Cahyani[2], Riska Amelia Putri[3], Salsabila[4], Sasqia Fitriyanti[5], Muhamad Iqbal Rhamadianto[6]

[1,2,3,4,5,6] *Department of Pharmacy, Faculty of Science and Technology, Muhammadiyah University of Bandung, Bandung, Indonesia.*
[*]*E-mail:* ajeng.tedjaningrum13@gmail.com

Article Information:
Received: 13 July 2025
in revised form: 16 January 2026
Accepted: 28 April 2026
Available Online: 30 April 2026

Keywords:
Angiotensin-converting enzyme;
Hypertension;
Natural bioactive compounds;
Molecular docking;
in silico study;
Flavonoids;
Bioactive peptides

Corresponding Author:
Rd Ajeng Tedjaningrum
Department of Pharmacy
Faculty of Science and Technology
Muhammadiyah University of Bandung
Bandung
Indonesia
E-mail:
ajeng.tedjaningrum13@gmail.com

ABSTRACT

Hypertension remains a major global health burden and is one of the leading risk factors for cardiovascular morbidity and mortality. The renin–angiotensin–aldosterone system, particularly angiotensin-converting enzyme (ACE), plays a central role in blood pressure regulation by catalysing the conversion of angiotensin I into angiotensin II, a potent vasoconstrictor. Therefore, ACE inhibition represents an important therapeutic strategy in hypertension management. This narrative literature review aimed to summarise and critically discuss the potential of natural bioactive compounds as ACE inhibitor candidates, with particular emphasis on evidence derived from *in silico* and molecular docking studies. Relevant peer-reviewed articles were reviewed by focusing on natural compounds, including flavonoids, phenolic compounds, bioactive peptides, chlorogenic acid, quercetin, luteolin derivatives, fucoidan, scopoletin, and folate. Several natural compounds demonstrated favourable binding affinity and interaction patterns with ACE active sites in computational studies. Chlorogenic acid, quercetin, luteolin derivatives, scopoletin, fucoidan, phenolic compounds, and selected bioactive peptides showed potential molecular interactions comparable to standard ACE inhibitors in several docking analyses. However, most available evidence remains predictive and should be interpreted as binding propensity rather than confirmed enzymatic inhibition or clinical antihypertensive efficacy. Natural bioactive compounds represent promising molecular scaffolds for the development of ACE inhibitor candidates in hypertension therapy. Nevertheless, further validation through *in vitro* enzymatic assays, kinetic inhibition studies, toxicity evaluation, and *in vivo* pharmacological assessment is required to confirm their biological relevance and therapeutic applicability.

How to cite (APA[6th]Style):

Tedjaningrum.R.A.,Cahyani.R.A,.Putri,R.A.,Salsabila.,Fitriyanti,S.,Rhamadianto.M.I.(2026). *Natural ACE-Inhibitor Candidates for Hypertension: A Narrative Literature Review with In Silico Highlights*. *Indonesian Journal of Pharmaceutical Education (e-Journal),* 6(1), 168-189.

ABSTRAK

Hipertensi masih menjadi beban kesehatan global dan merupakan salah satu faktor risiko utama morbiditas serta mortalitas kardiovaskular. Sistem renin–angiotensin–aldosteron, khususnya angiotensin-converting enzyme (ACE), berperan sentral dalam regulasi tekanan darah melalui katalisis konversi angiotensin I menjadi angiotensin II, yaitu peptida vasokonstriktor yang kuat. Oleh karena itu, penghambatan ACE menjadi salah satu strategi terapeutik penting dalam tata laksana hipertensi. Tinjauan pustaka naratif ini bertujuan untuk merangkum dan membahas secara kritis potensi senyawa bioaktif alami sebagai kandidat inhibitor ACE, dengan penekanan pada bukti yang diperoleh dari studi *in silico* dan analisis penambatan molekuler. Artikel ilmiah yang relevan ditinjau dengan fokus pada senyawa alami, meliputi flavonoid, senyawa fenolik, peptida bioaktif, asam klorogenat, kuersetin, turunan luteolin, fukoidan, skopoletin, dan folat. Beberapa senyawa alami menunjukkan afinitas pengikatan dan pola interaksi yang menguntungkan terhadap situs aktif ACE berdasarkan studi komputasional. Asam klorogenat, kuersetin, turunan luteolin, skopoletin, fukoidan, senyawa fenolik, dan beberapa peptida bioaktif menunjukkan potensi interaksi molekuler yang dalam beberapa analisis docking sebanding dengan inhibitor ACE standar. Namun, sebagian besar bukti yang tersedia masih bersifat prediktif sehingga perlu ditafsirkan sebagai kecenderungan pengikatan, bukan sebagai bukti pasti penghambatan enzimatik atau efikasi antihipertensi klinis. Senyawa bioaktif alami merupakan kerangka molekul yang menjanjikan untuk pengembangan kandidat inhibitor ACE dalam terapi hipertensi. Meskipun demikian, validasi lebih lanjut melalui uji enzimatik *in vitro*, studi kinetika inhibisi, evaluasi toksisitas, dan pengujian farmakologi *in vivo* diperlukan untuk memastikan relevansi biologis dan aplikabilitas terapeutiknya.

Kata Kunci: Angiotensin-converting enzyme; hipertensi; senyawa bioaktif alami; penambatan molekuler; studi *in silico*; flavonoid; peptida bioaktif.

1. Introduction

Hypertension is a chronic cardiovascular disorder characterised by persistently elevated blood pressure and structural or functional alterations in blood vessels that may progressively increase cardiovascular risk [1]. To date, hypertension remains one of the most important global health problems because of its high prevalence, long-term complications, and substantial contribution to cardiovascular morbidity and mortality. According to the World Health Organization, approximately 1.28 billion adults aged 30–79 years worldwide were living with hypertension in 2021, indicating that this condition continues to represent a major public health challenge requiring effective preventive and therapeutic strategies [2].

The development of hypertension is influenced by multiple risk factors that can be classified into modifiable and non-modifiable determinants. Modifiable risk factors include unhealthy dietary patterns, excessive intake of saturated and trans fats, inadequate consumption of fruits and vegetables, physical inactivity, smoking, alcohol consumption, and obesity. Meanwhile, non-modifiable risk factors include family

history, advanced age, and the presence of comorbid conditions such as diabetes mellitus or kidney disease [2]. The interaction between these factors may contribute to vascular dysfunction, increased peripheral resistance, impaired sodium balance, and dysregulation of neurohormonal pathways involved in blood pressure control.

One of the principal biological systems involved in blood pressure regulation is the renin–angiotensin–aldosterone system (RAAS). In this pathway, renin is released by the kidneys in response to decreased renal perfusion pressure, reduced intratubular sodium concentration, or sympathetic nervous system activation. Renin catalyses the conversion of angiotensinogen into angiotensin I, which is subsequently converted by angiotensin-converting enzyme (ACE) into angiotensin II [3]. Angiotensin II is a potent vasoconstrictor that binds primarily to type 1 angiotensin receptors located in vascular smooth muscle, the kidneys, adrenal glands, and the central nervous system. This interaction promotes vasoconstriction, aldosterone secretion, sodium and water retention, sympathetic activation, and ultimately elevation of blood pressure [4].

Because of its central role in the formation of angiotensin II, ACE represents an important molecular target in antihypertensive therapy. ACE inhibitors act by reducing the conversion of angiotensin I into angiotensin II and by preventing the degradation of bradykinin, a vasodilatory peptide. These mechanisms contribute to vasodilation, natriuresis, diuresis, reduced peripheral vascular resistance, and prevention of cardiovascular remodelling, including left ventricular hypertrophy [4]. Clinically used ACE inhibitors are commonly recognised by the suffix "-pril", such as captopril and lisinopril, and have become important agents in the pharmacological management of hypertension and related cardiovascular disorders [5].

In addition to synthetic ACE inhibitors, natural bioactive compounds have attracted increasing scientific interest as potential sources of antihypertensive agents. Several secondary metabolites, including flavonoids, phenolic compounds, catechins, and bioactive peptides, have been reported to exhibit potential ACE-inhibitory activity through interaction with the ACE active site or modulation of pathways associated with vascular function [5]. Among these compounds, flavonoids are particularly relevant because their molecular structure may influence their ability to interact with ACE. Previous literature has indicated that structural features such as the C2=C3 double bond, 4′-O-methoxylation, 3′-hydroxylation, and 3-O-glycosylation may contribute to ACE-inhibitory activity [6].

From a medicinal chemistry perspective, understanding the interaction between ACE and natural ligands is essential for identifying potential molecular scaffolds that may be developed into safer and more effective antihypertensive candidates. Computational approaches, especially *in silico* analysis and molecular docking, provide useful preliminary information regarding binding affinity, ligand–receptor interactions, and the possible orientation of natural compounds within the ACE active site. However, docking results should be interpreted carefully because they indicate predicted binding potential rather than definitive enzymatic inhibition or clinical efficacy. Therefore, this narrative literature review aims to summarise and critically discuss the potential of natural bioactive compounds as ACE inhibitor candidates for hypertension therapy, with emphasis on evidence from *in silico* studies and molecular interaction analyses.

2. Methods

Study Design

This study was conducted as a narrative literature review to summarise and critically discuss the potential of natural bioactive compounds as angiotensin-converting

enzyme (ACE) inhibitor candidates for hypertension therapy. The review focused on studies reporting the antihypertensive potential, ACE-inhibitory mechanisms, and molecular interaction profiles of natural compounds, particularly those evaluated using *in silico* approaches such as molecular docking, binding affinity prediction, and ligand–receptor interaction analysis.

A literature search was performed using several scientific databases, including PubMed, Scopus, ScienceDirect, and Google Scholar. The search covered articles published between 2013 and 2025. The keywords were arranged using Boolean operators as follows: "ACE inhibitor" OR "angiotensin-converting enzyme inhibitor" AND "hypertension" OR "high blood pressure" AND "bioactive compound". Additional relevant terms, including "natural compound", "flavonoid", "phenolic compound", "bioactive peptide", "molecular docking", and "in silico study", were also considered to broaden the literature coverage and identify studies directly related to natural ACE inhibitor candidates.

Eligibility Criteria and Study Selection

Articles were selected based on their relevance to the objective of this review. The inclusion criteria were original research articles discussing natural bioactive compounds with potential ACE-inhibitory activity, studies related to hypertension or blood pressure regulation, articles reporting molecular mechanisms or ligand–ACE interactions, and studies available in full-text form. Articles were excluded if they were review articles, conference abstracts, duplicate records, inaccessible full-text articles, or studies that did not directly discuss ACE inhibition, hypertension-related mechanisms, or natural bioactive compounds.

The article selection process was conducted in several stages. First, duplicate records were removed from the initial search results. Second, titles and abstracts were screened to identify articles relevant to ACE inhibition and natural antihypertensive compounds. Third, the full texts of potentially eligible articles were evaluated based on the inclusion and exclusion criteria. From the initial 150 records identified, 30 duplicate records were removed, leaving 120 articles for screening. After title and abstract screening, 65 articles were excluded because they were not directly relevant to the review topic. A total of 55 full-text articles were then assessed for eligibility, of which 45 articles were excluded because they did not specifically address natural ACE inhibitor candidates, molecular interaction mechanisms, or hypertension-related outcomes. Finally, 10 studies were included in the narrative synthesis. The article selection process is presented in **Figure 1**, which illustrates the flow of record identification, duplicate removal, screening, eligibility assessment, and final study inclusion.

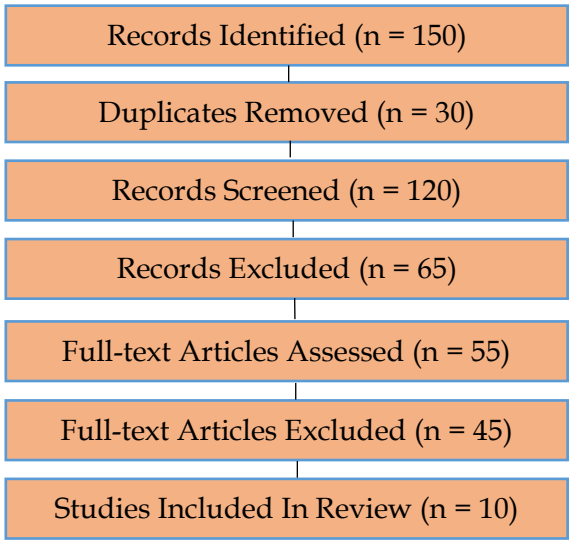

Figure 1. Flow diagram of the article selection process adapted from the PRISMA framework

Data Extraction and Narrative Synthesis

Data from the included studies were extracted and organised based on the type of natural compound, source or compound class, reported mechanism of action, molecular docking results when available, binding affinity or docking score, interaction with ACE active-site residues, and comparison with standard ACE inhibitors such as captopril or lisinopril. The findings were analysed using a qualitative descriptive synthesis approach. Particular attention was given to distinguishing computational predictions from experimentally confirmed ACE-inhibitory effects, because *in silico* findings indicate potential binding affinity and interaction patterns rather than definitive biological activity or clinical efficacy.

3. Results and Discussion

Overview of ACE as a Molecular Target in Hypertension

Hypertension is a chronic cardiovascular disorder characterised by persistent elevation of blood pressure and is closely associated with progressive vascular changes that may increase the risk of cardiovascular complications [1]. The global burden of hypertension remains substantial, as this condition affects a large proportion of the adult population and contributes significantly to morbidity and mortality related to cardiovascular disease [2]. Therefore, understanding the biological mechanisms that regulate blood pressure is essential for identifying effective therapeutic targets and developing antihypertensive agents with better efficacy and safety profiles.

One of the most important physiological pathways involved in blood pressure regulation is the renin–angiotensin–aldosterone system (RAAS). This system regulates vascular tone, sodium balance, fluid volume, and cardiovascular homeostasis. In the RAAS cascade, renin is released by the kidneys in response to decreased renal perfusion, reduced sodium delivery, or sympathetic nervous system stimulation. Renin then catalyses the conversion of angiotensinogen into angiotensin I, an inactive peptide precursor. Subsequently, angiotensin-converting enzyme (ACE) converts angiotensin I into angiotensin II, which is one of the principal effector molecules responsible for increasing blood pressure [3].

Angiotensin II plays a central role in hypertension pathophysiology because it induces vasoconstriction, stimulates aldosterone secretion, promotes sodium and water retention, enhances sympathetic activity, and contributes to vascular remodelling. Through these mechanisms, angiotensin II increases peripheral vascular resistance and intravascular volume, both of which are major determinants of elevated blood pressure. In addition, excessive RAAS activation may aggravate endothelial dysfunction, oxidative stress, and cardiovascular structural changes, thereby contributing to the progression of hypertensive complications [3], [4].

ACE is therefore regarded as a critical molecular target in antihypertensive therapy because it directly participates in the formation of angiotensin II. Pharmacological inhibition of ACE reduces angiotensin II production and prevents the degradation of bradykinin, a vasodilatory peptide that contributes to vascular relaxation. These combined effects result in vasodilation, natriuresis, diuresis, reduced peripheral resistance, and improved cardiovascular protection [4], [5]. Clinically used ACE inhibitors, such as captopril and lisinopril, have been widely applied in hypertension management due to their ability to modulate RAAS activity and reduce blood pressure through well-established molecular mechanisms [5].

In addition to synthetic ACE inhibitors, natural compounds and functional food-derived bioactive molecules have received increasing attention as potential ACE-inhibitory candidates. Several natural sources, including plant secondary metabolites and bioactive peptides from food materials, have been reported to interact with ACE or influence RAAS-related mechanisms. These compounds are of interest because they may provide alternative molecular scaffolds for antihypertensive development, particularly when supported by evidence from enzymatic assays, molecular docking, and functional food studies [5], [7]. Thus, ACE remains a rational and relevant molecular target for exploring natural bioactive compounds as potential antihypertensive agents.

Summary of Natural Bioactive Compounds Reported as ACE-Inhibitor Candidates

The reviewed literature indicates that natural bioactive compounds may serve as promising molecular scaffolds for the development of angiotensin-converting enzyme (ACE) inhibitor candidates. These compounds include phenolic acids, flavonoids, flavonoid derivatives, coumarins, polysaccharides, folate-related compounds, and bioactive peptides. Most of the included studies used *in silico* approaches, particularly molecular docking, to predict ligand–ACE interactions, binding affinity, and the possible occupation of ACE active sites. However, one study provided *in vitro* enzymatic evidence by reporting the inhibitory concentration of phenolic extracts against ACE activity. Therefore, the available evidence should be interpreted proportionally, because computational findings provide preliminary molecular predictions, whereas enzymatic assays provide more direct biological evidence of ACE inhibition. The main findings of the reviewed studies are summarised in **Table 1**.

Table 1. Results of Literature Review Analysis on Natural Bioactive Compounds as ACE-Inhibitor Candidates

No	Reference	Compound/Class	Source/Study Focus	Study Approach	Main Findings	Interpretation Related to ACE Inhibition
1	Yunita et al. [8]	Chlorogenic acid	Bioactive compounds from *Psidium guajava* leaves	*In silico* molecular docking	Chlorogenic acid showed favourable interaction with ACE, with a reported binding energy of approximately −7.09 kcal/mol.	Chlorogenic acid may interact with the ACE active site and has potential as a natural ACE-inhibitor candidate; however, enzymatic validation is required to confirm its inhibitory activity.
2	Mardianingrum et al. [10]	Luteolin derivative TL59	Luteolin derivatives from corn silk (*Zea mays* L.)	Molecular docking and MM-GBSA analysis	TL59 showed a lower total free energy value, with ΔGtotal of −44.65 kcal/mol, compared with the control compound at −29.25 kcal/mol.	TL59 is predicted to have stronger molecular affinity toward the ACE target than the comparator, suggesting potential as an antihypertensive candidate through ACE interaction.
3	Nissa et al. [11]	Isoflavones and quercetin	Natural flavonoid compounds with vasoprotective potential	*In silico* analysis	Isoflavones and quercetin were reported to have molecular properties that support interaction with ACE, particularly through phenolic structural components.	These compounds may bind to ACE and potentially interfere with angiotensin II formation, although their effects require further experimental confirmation.
4	Utari et al. [13]	Quercetin	Quercetin as a natural antihypertensive compound	Molecular docking against ACE	Quercetin showed a binding energy of −6.32	Quercetin demonstrated a more favourable predicted interaction than

					kcal/mol and formed hydrogen-bond interactions with ACE amino acid residues, including ALA356, HIS383, TYR523, and GLU411.	the reference ligand in the docking model, supporting its potential as an ACE-inhibitor candidate.
5	Abdullah [14]	Folate	Bioactive compound from lactic acid bacteria	Molecular docking against ACE2	Folate showed a binding score of approximately −8.4, close to lisinopril at −8.7, in docking analysis involving ACE2.	Folate may interact with proteins related to the angiotensin system; however, because the target was ACE2 rather than classical ACE, its interpretation as an ACE inhibitor should be made cautiously.
6	Oboh et al. [16]	Phenolic compounds	Phenolic extracts from garlic (*Allium sativum*)	*In vitro* ACE inhibition assay	Bound phenolic extracts showed stronger ACE inhibition with IC_{50} = 3.48 µg/mL compared with free phenolic extracts with IC_{50} = 14.81 µg/mL.	Garlic phenolic compounds provide direct enzymatic evidence of ACE inhibition, making this study biologically stronger than purely computational studies.
7	Widiasari [6]	Flavonoids	Structural features of flavonoids related to ACE inhibition	Mechanistic literature analysis	ACE-inhibitory activity of flavonoids was associated with structural features such as C2=C3 double bond, 4′-O-	Flavonoids may act as natural ACE inhibitors through structure-dependent molecular interactions with ACE, supporting their

					methoxylation, 3′-hydroxylation, and 3-O-glycosylation.	role as important scaffolds for antihypertensive compound development.
8	Kurniawan et al. [17]	Fucoidan	Fucoidan from brown seaweed	Molecular docking and toxicity prediction	Fucoidan showed MolDock and rerank scores of −82.311 kcal/mol and −70.872 kcal/mol, respectively, values relatively close to captopril. However, its RMSD value was higher than the ideal range.	Fucoidan may interact with ACE and zinc-related catalytic components, but its higher RMSD suggests that the predicted binding stability should be interpreted carefully.
9	Praja et al. [18]	Scopoletin	Scopoletin from *Morinda citrifolia* L.	Molecular docking against ACE	Scopoletin showed a docking score of −6.21 kcal/mol, slightly lower than captopril at −5.97 kcal/mol, and formed hydrogen-bond interactions within the ACE binding site.	Scopoletin may occupy a similar binding region to captopril, suggesting potential ACE-inhibitory activity based on docking prediction.
10	Fakih and Dewi [19]	Bioactive peptides CF, IF, and MF	Marine organism-derived peptides from shrimp and shark	Molecular docking against ACE	Bioactive peptides CF, IF, and MF showed favourable molecular interaction profiles and higher predicted affinity than captopril based on	Marine bioactive peptides may serve as natural ACE-inhibitory candidates, particularly due to their predicted capacity to bind ACE more favourably than the reference inhibitor.

	docking parameters.

Based on **Table 1**, the reviewed studies demonstrate that natural compounds may inhibit or interact with ACE through different molecular mechanisms. Flavonoids and phenolic compounds appear to be the most frequently reported groups because their hydroxyl groups, aromatic rings, and conjugated structures enable hydrogen bonding, hydrophobic interactions, and possible coordination within the ACE active site. Chlorogenic acid, quercetin, isoflavones, and phenolic extracts from garlic represent this group and show either computational or experimental support for ACE-inhibitory potential [6], [8], [11], [13], [16]. Among these studies, the work by Oboh et al. [16] provides stronger biological relevance because it reports *in vitro* ACE inhibition using IC_{50} values, whereas most other studies mainly report docking scores or binding energies.

The table also shows that several non-flavonoid compounds, including luteolin derivatives, scopoletin, and fucoidan, have been evaluated using molecular docking and related computational methods. TL59, a luteolin derivative from corn silk, demonstrated favourable free-energy values in MM-GBSA analysis, suggesting stable interaction with the ACE target [10]. Scopoletin also showed a docking score slightly more favourable than captopril, indicating that this coumarin derivative may occupy the ACE binding site and form stabilising interactions [18]. Fucoidan demonstrated docking scores relatively close to captopril and may interact with zinc-related catalytic components of ACE; however, its higher RMSD value indicates that the predicted binding conformation may be less stable and should be interpreted cautiously [17].

Bioactive peptides represent another important category of natural ACE-inhibitory candidates. Peptides derived from marine organisms, such as CF, IF, and MF, showed favourable docking interactions with ACE and were predicted to have better affinity than captopril in the reported model [19]. This finding is relevant because many food-derived peptides are known to exert biological activity through specific amino acid sequences that allow interaction with enzymatic targets. In this context, functional food sources and peptide-rich materials may offer potential for antihypertensive development, particularly when supported by enzymatic and pharmacological validation [7], [19].

A critical point in interpreting the reviewed data is the distinction between ACE and ACE2. The folate-related study by Abdullah [14] reported docking against ACE2, not classical ACE. Although ACE and ACE2 are both associated with the angiotensin system, they have different biological functions and should not be interpreted interchangeably. Therefore, folate may be discussed as a compound with possible interaction with an angiotensin-system-related protein, but its role as a classical ACE inhibitor remains uncertain and requires further clarification through specific ACE inhibition assays.

Overall, **Table 1** indicates that natural bioactive compounds provide a broad chemical diversity for ACE-inhibitor exploration. Nevertheless, most evidence remains preliminary because it is predominantly derived from *in silico* prediction. Docking score, binding energy, and molecular interaction patterns are useful for early screening, but they cannot independently confirm enzymatic inhibition, pharmacological efficacy, bioavailability, toxicity, or clinical relevance. Therefore, compounds identified as promising through computational studies should be further evaluated using *in vitro*

ACE inhibition assays, kinetic studies, *in vivo* antihypertensive models, and pharmacokinetic-toxicological assessment.

Flavonoids and Phenolic Compounds as Natural ACE-Inhibitor Scaffolds

Flavonoids and phenolic compounds are among the most frequently reported natural scaffolds with potential relevance to ACE inhibition. Their biological activity is closely related to the presence of hydroxyl groups, aromatic rings, conjugated double bonds, and other substituent patterns that may facilitate hydrogen bonding, hydrophobic interactions, and electrostatic interactions with amino acid residues in the ACE active site. From a medicinal chemistry perspective, these structural characteristics are important because ACE is a zinc-dependent metallopeptidase, and ligand binding within its catalytic region may interfere with the conversion of angiotensin I into angiotensin II. Therefore, flavonoids and phenolic compounds provide a rational chemical basis for the development of natural ACE-inhibitor candidates [6], [9].

The potential of flavonoids as ACE inhibitors has been discussed through structure–activity relationship perspectives. Several structural features, including the C2=C3 double bond, 4′-O-methoxylation, 3′-hydroxylation, and 3-O-glycosylation, have been associated with ACE-inhibitory activity [6]. These molecular features may influence the spatial orientation, polarity, and binding capacity of flavonoids within the ACE binding pocket. The presence of hydroxyl groups may support hydrogen bond formation, whereas conjugated aromatic systems may contribute to ligand stability through hydrophobic and π-related interactions. Thus, the ACE-inhibitory potential of flavonoids is not only determined by their general antioxidant properties but also by specific structural arrangements that affect ligand–enzyme interaction.

Chlorogenic acid, a phenolic acid identified in *Psidium guajava* leaves, has been reported as one of the promising natural compounds targeting ACE. Yunita et al. [8] reported that chlorogenic acid demonstrated favourable interaction with ACE in an *in silico* study, with a binding energy of approximately −7.09 kcal/mol. This value suggests that chlorogenic acid may possess sufficient affinity to interact with the ACE active site. Mechanistically, such interaction may reduce the catalytic conversion of angiotensin I into angiotensin II, thereby potentially contributing to antihypertensive activity. However, because this finding was generated through molecular docking, it should be interpreted as a prediction of binding propensity rather than definitive evidence of enzymatic inhibition. The relevance of *Psidium guajava* as a potential antihypertensive source is further supported by experimental evidence showing that *Psidium guajava* leaf extract may contribute to blood pressure control and modulation of inflammatory mediators in salt-dependent hypertensive rats [12].

Quercetin is another flavonoid that has received considerable attention as a potential ACE-inhibitory compound. Nissa et al. [11] reported that quercetin and isoflavones possess molecular characteristics that support interaction with ACE, particularly due to their phenolic structures. Quercetin is considered more vasoprotective than isoflavones because its polyhydroxylated structure may enhance interaction with vascular and enzymatic targets. In computational terms, its molecular weight and lipophilicity are compatible with drug-likeness criteria, supporting the possibility of receptor or enzyme binding. However, these properties only indicate molecular suitability and cannot independently confirm pharmacological activity.

Further support for quercetin as an ACE-inhibitor candidate was provided by Utari et al. [13], who reported that quercetin showed a binding energy of −6.32 kcal/mol in molecular docking against ACE. The docking visualisation demonstrated hydrogen-bond interactions between quercetin and several ACE amino acid residues, including

ALA356, HIS383, TYR523, and GLU411. A more negative binding energy suggests a more favourable predicted ligand–enzyme interaction, while hydrogen bonding with active-site residues may stabilise the ligand within the ACE binding pocket. These findings indicate that quercetin may interfere with ACE activity by occupying or interacting with residues involved in substrate binding or catalytic function. Nevertheless, this conclusion remains predictive and requires validation through ACE inhibition assays, dose–response analysis, and biological models of hypertension.

Isoflavones also represent an important subgroup of phenolic compounds with possible ACE-inhibitory relevance. As reported by Nissa et al. [11], isoflavones possess molecular weight and lipophilicity characteristics that may support interaction with ACE. Isoflavones are commonly found in soy-based foods, including tempeh and tofu, and their phenolic components may contribute to vascular protection. Although their predicted interaction with ACE is less extensively discussed than quercetin, their presence in functional foods makes them relevant for antihypertensive research, particularly in the context of dietary prevention and nutraceutical development. In this regard, evidence from flavanol-rich foods also supports the concept that dietary phenolic compounds may contribute to ACE inhibition and vascular regulation [9].

Phenolic compounds from garlic provide comparatively stronger biological support because they have been evaluated using an *in vitro* ACE inhibition assay. Oboh et al. [16] demonstrated that phenolic extracts from *Allium sativum* inhibited ACE activity in a dose-dependent manner. Bound phenolic extracts showed stronger inhibitory activity, with an IC_{50} value of 3.48 µg/mL, compared with free phenolic extracts, which had an IC_{50} value of 14.81 µg/mL. This finding is important because IC_{50} values represent direct enzymatic evidence of inhibitory activity, unlike docking scores that only predict molecular interaction. The stronger activity of bound phenolic extracts suggests that phenolic composition, matrix association, and structural configuration may influence ACE-inhibitory potency.

Collectively, flavonoids and phenolic compounds appear to be promising natural scaffolds for ACE-inhibitor development because they combine structural diversity, potential vascular benefits, and molecular compatibility with ACE binding sites. Chlorogenic acid and quercetin provide supportive *in silico* evidence, garlic phenolics provide direct *in vitro* enzymatic evidence, and isoflavones and flavanol-rich foods strengthen the broader concept that dietary phenolics may influence ACE-related blood pressure regulation [8], [9], [11], [13], [16]. Nevertheless, the strength of evidence varies across studies. Compounds supported only by docking analysis should be considered preliminary candidates, whereas compounds with enzymatic IC_{50} data provide stronger biological plausibility. Therefore, future studies should integrate molecular docking, ACE inhibition assays, kinetic studies, bioavailability evaluation, and *in vivo* antihypertensive assessment to determine whether these compounds can be translated into clinically meaningful antihypertensive agents.

Luteolin Derivatives, Scopoletin, and Fucoidan: *In Silico* Evidence and Molecular Interaction Profiles

In addition to flavonoids and phenolic compounds, several structurally distinct natural compounds have been investigated as potential ACE-inhibitor candidates using *in silico* approaches. Among these, luteolin derivatives, scopoletin, and fucoidan are of particular interest because they represent different chemical classes with different predicted modes of interaction toward ACE. Luteolin derivatives are flavone-based compounds, scopoletin is a coumarin derivative, whereas fucoidan is a sulfated polysaccharide commonly derived from brown seaweed. Although these compounds

differ markedly in molecular size, polarity, and functional groups, all have been reported to show potential interaction with ACE based on molecular docking or related computational analyses [10], [17], [18].

Mardianingrum et al. [10] investigated luteolin derivatives from corn silk (*Zea mays* L.) as potential antihypertensive agents through an *in silico* approach. Among the evaluated compounds, TL59 was reported as the most promising luteolin derivative because it demonstrated a lower total free energy value compared with the reference compound. The MM-GBSA analysis showed that TL59 had a ΔGtotal value of −44.65 kcal/mol, whereas the control compound showed a value of −29.25 kcal/mol [10]. A more negative free energy value generally indicates a more favourable ligand–receptor interaction, suggesting that TL59 may form a more stable complex with the ACE target. This finding supports the potential of luteolin derivatives as molecular scaffolds for antihypertensive compound development.

The predicted interaction of TL59 with ACE may be explained by the structural properties of luteolin derivatives, particularly the presence of aromatic rings and hydroxyl groups that may support hydrogen bonding and hydrophobic interactions within the enzyme binding pocket. These interactions can theoretically interfere with the positioning of angiotensin I or affect the catalytic environment required for angiotensin II formation. However, the interpretation of TL59 as an ACE-inhibitor candidate should remain cautious because the available evidence is computational. Molecular docking and MM-GBSA analysis provide useful estimates of binding affinity and complex stability, but they do not directly measure enzymatic inhibition, dose–response activity, metabolic stability, or antihypertensive efficacy in biological systems.

Scopoletin, a coumarin derivative identified from *Morinda citrifolia* L., has also been evaluated for its potential ACE-inhibitory activity. Praja et al. [18] reported that scopoletin showed a docking score of −6.21 kcal/mol, which was slightly more favourable than captopril with a docking score of −5.97 kcal/mol. This result suggests that scopoletin may have a comparable or slightly stronger predicted binding affinity toward ACE than the reference inhibitor in the docking model. The study also reported that scopoletin occupied a similar binding region to captopril and formed hydrogen-bond interactions with amino acid residues in the ACE binding site, including interaction involving the oxygen atom of scopoletin and the nitrogen atom of the GLN residue [18].

The similarity of the binding site between scopoletin and captopril is pharmacologically relevant because it suggests that scopoletin may interact with residues involved in ACE catalytic or substrate-binding functions. Hydrogen bonding may stabilise scopoletin within the ACE binding pocket, while its coumarin ring system may contribute to hydrophobic or π-related interactions. Nevertheless, the difference between the docking score of scopoletin and captopril is relatively small, and therefore should not be overinterpreted as definitive superiority. Docking score differences can be influenced by the software, scoring function, grid parameters, receptor preparation, ligand conformation, and assumptions used in the computational protocol. Consequently, scopoletin should be considered a promising preliminary candidate, but its ACE-inhibitory effect must be confirmed through enzymatic assays and pharmacological studies.

Fucoidan represents another interesting natural compound because, unlike luteolin derivatives and scopoletin, it is a sulfated polysaccharide with high polarity and structural complexity. Kurniawan et al. [17] reported that fucoidan showed potential interaction with ACE based on molecular docking analysis. The MolDock score and

rerank score of fucoidan were reported as −82.311 kcal/mol and −70.872 kcal/mol, respectively, whereas captopril showed values of −84.816 kcal/mol and −74.758 kcal/mol. These relatively close values suggest that fucoidan may interact with ACE in a manner that is computationally comparable to captopril. In addition, fucoidan was reported to form hydrogen bonds with amino acid residues, including Glu384 and Tyr523, which were also involved in captopril interaction [17].

The possible interaction of fucoidan with zinc ions is particularly important because ACE is a zinc-dependent metallopeptidase. Interaction with the zinc-associated catalytic environment may theoretically affect ACE catalytic activity and reduce the conversion of angiotensin I into angiotensin II. However, the docking interpretation for fucoidan requires special caution because polysaccharides are structurally flexible and may present challenges in computational modelling. Kurniawan et al. [17] reported that fucoidan had an RMSD value of 3.726 Å, which was higher than that of captopril at 1.352 Å. Because lower RMSD values generally indicate better reproducibility or stability of the docking pose, the higher RMSD of fucoidan suggests that its predicted binding conformation may be less optimal or less stable than that of captopril.

Overall, the *in silico* findings on TL59, scopoletin, and fucoidan indicate that structurally diverse natural compounds may interact with ACE through different molecular features, including hydrogen bonding, hydrophobic interactions, electrostatic interactions, and possible zinc-related interactions [10], [17], [18]. TL59 showed favourable free-energy prediction, scopoletin demonstrated a docking score slightly better than captopril, and fucoidan showed docking scores close to captopril with potential zinc-related interaction. However, these findings should be interpreted as early-stage computational evidence rather than confirmed pharmacological activity. Further studies involving *in vitro* ACE inhibition assays, enzyme kinetic evaluation, molecular dynamics simulation, toxicity assessment, and *in vivo* antihypertensive models are needed to determine whether these compounds have biologically meaningful ACE-inhibitory activity and therapeutic relevance.

Bioactive Peptides and Functional Food-Derived ACE-Inhibitory Candidates

Bioactive peptides represent an important group of natural ACE-inhibitory candidates because their biological activity is closely related to specific amino acid sequences, molecular size, hydrophobicity, and ability to interact with the catalytic or substrate-binding region of ACE. Unlike small phenolic compounds or flavonoids, bioactive peptides are generally produced through protein hydrolysis, fermentation, enzymatic digestion, or food processing. Their antihypertensive potential is particularly relevant in the development of functional foods, nutraceuticals, and peptide-based natural therapeutic candidates. In this context, marine organisms and fermented food products have attracted attention as potential sources of ACE-inhibitory peptides [7], [19].

Fakih and Dewi [19] reported that bioactive peptides derived from marine organisms showed promising molecular interaction with ACE based on *in silico* analysis. In their study, the peptides CF and IF derived from shrimp, as well as the peptide MF derived from shark, demonstrated favourable predicted affinity toward ACE. These peptides were reported to have better molecular interaction profiles than captopril based on docking parameters, indicating that short peptide sequences may interact effectively with ACE. This finding suggests that marine-derived peptides may serve as potential natural ACE-inhibitory candidates, particularly because marine organisms are rich in bioactive proteins and peptides with diverse pharmacological properties.

The ACE-inhibitory potential of bioactive peptides is strongly influenced by their amino acid composition and sequence. Peptides containing hydrophobic, aromatic, or positively charged residues may interact more effectively with ACE because these residues can contribute to hydrogen bonding, hydrophobic interactions, and electrostatic stabilisation within the enzyme binding pocket. Inhibition of ACE by bioactive peptides may reduce the conversion of angiotensin I into angiotensin II, thereby decreasing vasoconstrictive signalling and contributing to blood pressure regulation. However, as with other docking-based findings, predicted peptide–ACE interaction does not necessarily indicate confirmed enzymatic inhibition. Therefore, marine peptides such as CF, IF, and MF require further validation using ACE inhibition assays, IC_{50} determination, stability testing, and biological evaluation in hypertensive models [19].

Functional food-derived peptides also provide an important perspective in antihypertensive research. Rizkaprilisa and Hapsari [7] discussed the potential of ACE inhibitors from koro-koroan tempeh as a functional antihypertensive food. Tempeh and other fermented legume-based products may generate bioactive peptides during fermentation and protein degradation. These peptides may contribute to blood pressure regulation by inhibiting ACE activity, supporting endothelial function, or modulating vascular homeostasis. The relevance of koro-koroan tempeh is particularly important because it reflects the possibility of developing locally available food materials into functional products with potential cardiovascular benefits.

The functional food approach differs from conventional drug development because it emphasises dietary intake, long-term prevention, and health-supporting effects rather than immediate pharmacological intervention. In the case of ACE-inhibitory peptides, fermented foods may act as sources of naturally generated peptide fragments that contribute to antihypertensive potential. Nevertheless, several factors must be considered, including peptide concentration, digestibility, gastrointestinal stability, absorption, bioavailability, and consistency of peptide production during fermentation. Without these evaluations, the antihypertensive effect of functional food-derived peptides remains difficult to translate into predictable therapeutic outcomes [7].

Overall, bioactive peptides from marine organisms and fermented functional foods represent promising natural ACE-inhibitory candidates. Marine-derived peptides such as CF, IF, and MF provide molecular evidence of potential ACE interaction, while koro-koroan tempeh illustrates the broader relevance of fermented food products as functional antihypertensive sources [7], [19]. However, the evidence remains preliminary and should be strengthened through integrated experimental approaches, including enzymatic ACE inhibition assays, peptide sequencing, molecular stability evaluation, simulated gastrointestinal digestion, *in vivo* antihypertensive testing, and safety assessment. Such validation is essential to determine whether these peptides can be developed into functional foods, nutraceuticals, or natural antihypertensive agents with measurable biological efficacy.

Folate, Probiotic-Derived Compounds, and Antioxidant-Related Support for Blood Pressure Regulation

Folate and probiotic-derived bioactive compounds represent a different category of natural candidates in the context of blood pressure regulation. Unlike flavonoids, phenolic compounds, or bioactive peptides that are commonly discussed as direct ACE-inhibitory candidates, folate and compounds produced by lactic acid bacteria (LAB) should be interpreted more cautiously because their relationship with the renin–angiotensin–aldosterone system (RAAS) may involve indirect or supportive

mechanisms. In hypertension pathophysiology, RAAS activation contributes to angiotensin II formation, vasoconstriction, sodium and water retention, and vascular remodelling; therefore, compounds that interact with RAAS-related proteins or reduce oxidative stress may have potential relevance to vascular regulation [3]–[5].

Abdullah [14] reported that folate, as a bioactive compound associated with lactic acid bacteria, showed a favourable binding score in molecular docking analysis. Folate had a binding score of approximately −8.4, which was close to lisinopril at approximately −8.7. At first glance, this result may suggest that folate has potential interaction with a protein related to the angiotensin system. However, this finding must be interpreted carefully because the docking target reported in the study was ACE2, not classical angiotensin-converting enzyme (ACE). Although ACE and ACE2 are both components of the broader angiotensin system, they have different biological roles and should not be used interchangeably when discussing ACE-inhibitory mechanisms.

Classical ACE catalyses the conversion of angiotensin I into angiotensin II, a potent vasoconstrictor involved in blood pressure elevation. Therefore, inhibition of ACE reduces angiotensin II formation and supports vasodilation, natriuresis, and reduction of peripheral vascular resistance [3]–[5]. In contrast, ACE2 is generally recognised as a distinct enzyme within the RAAS axis and is functionally different from ACE. Consequently, a compound showing predicted binding to ACE2 cannot automatically be classified as a classical ACE inhibitor. For this reason, folate should be discussed as a probiotic-associated compound with possible interaction toward an angiotensin-system-related protein, rather than as a confirmed ACE-inhibitor candidate.

The relevance of folate and probiotic-derived compounds may also be explained through antioxidant-related mechanisms. Wang et al. [15] reported that probiotic bacteria possess antioxidant properties, including the ability to reduce oxidative stress through several mechanisms. This is relevant to hypertension because oxidative stress contributes to endothelial dysfunction, reduced nitric oxide bioavailability, vascular inflammation, and increased vascular resistance. Therefore, probiotic-derived antioxidant activity may support vascular health and blood pressure regulation indirectly, even when direct ACE inhibition has not been clearly demonstrated. In this context, folate and LAB-derived compounds may contribute to antihypertensive potential through antioxidant and vascular-protective pathways rather than through a confirmed ACE-blocking mechanism.

This distinction is important for maintaining scientific accuracy in interpreting the reviewed literature. While synthetic ACE inhibitors such as captopril and lisinopril have well-established mechanisms through suppression of angiotensin II formation and preservation of bradykinin activity, probiotic-derived compounds may act through broader biological pathways, including modulation of oxidative stress, inflammation, endothelial function, or possibly interaction with RAAS-related proteins [3]–[5], [14], [15]. Therefore, the evidence for folate should not be overstated. Its docking affinity toward ACE2 provides preliminary computational information, but it does not confirm ACE inhibition, antihypertensive efficacy, or clinical relevance.

Overall, folate and probiotic-derived compounds may have supportive relevance in blood pressure regulation, particularly through antioxidant-related mechanisms and possible interaction with proteins within the angiotensin system. However, because the available docking evidence involves ACE2 rather than classical ACE, folate cannot be directly concluded as an ACE inhibitor based on the current evidence. Further studies are required to evaluate whether folate or LAB-derived compounds can inhibit classical ACE activity using specific enzymatic assays, influence angiotensin II formation,

improve endothelial function, and reduce blood pressure in appropriate *in vivo* hypertension models. This cautious interpretation strengthens the scientific validity of the review and prevents overgeneralisation of ACE2 docking findings as evidence of ACE inhibition.

Critical Interpretation of *In Silico* Findings and Experimental Validation Needs

The reviewed studies indicate that *in silico* approaches, particularly molecular docking, are widely used as preliminary tools to identify natural bioactive compounds with potential interaction toward ACE or RAAS-related proteins. Molecular docking is useful in early-stage screening because it can predict ligand orientation, binding affinity, interaction with amino acid residues, and possible occupation of the enzyme active site. In the context of natural ACE-inhibitor candidates, docking studies have identified several promising compounds, including chlorogenic acid, luteolin derivative TL59, quercetin, scopoletin, fucoidan, folate-related compounds, and marine bioactive peptides [8],[10],[17]–[19]. However, these findings should be interpreted as computational predictions rather than direct evidence of pharmacological activity.

A central limitation of molecular docking is that binding affinity does not necessarily indicate enzymatic inhibition. A compound may show favourable binding energy or docking score, but this does not automatically mean that it can effectively inhibit ACE catalytic activity under biological conditions. Docking scores are influenced by receptor preparation, ligand conformation, grid parameters, scoring algorithms, solvent assumptions, and the flexibility of the binding site. Therefore, values such as binding energy, MolDock score, rerank score, or MM-GBSA free energy should be considered comparative indicators rather than absolute measures of inhibitory potency [8], [10], [13], [17], [18]. This is especially important when comparing natural compounds with standard ACE inhibitors such as captopril or lisinopril, because computational superiority does not always translate into stronger biological or clinical effects.

The distinction between predicted ligand binding and confirmed enzyme inhibition is particularly relevant for compounds such as chlorogenic acid, quercetin, TL59, scopoletin, fucoidan, and marine bioactive peptides. Chlorogenic acid showed favourable binding energy against ACE, TL59 demonstrated a lower predicted free energy value, quercetin formed hydrogen-bond interactions with ACE residues, scopoletin showed a docking score slightly more favourable than captopril, fucoidan showed docking scores relatively close to captopril, and marine peptides were predicted to interact favourably with ACE [17]–[19]. Although these findings suggest molecular compatibility with ACE, they remain insufficient to establish true inhibitory activity unless supported by *in vitro* ACE inhibition assays, enzyme kinetic analysis, and dose–response evaluation.

Among the included studies, the work by Oboh et al. [16] provides stronger biological evidence because it evaluated ACE inhibition using an *in vitro* enzymatic assay and reported IC_{50} values for garlic phenolic extracts. The bound phenolic extract showed an IC_{50} of 3.48 µg/mL, while the free phenolic extract showed an IC_{50} of 14.81 µg/mL [16]. These data provide more direct evidence of ACE inhibition than docking scores alone because IC_{50} reflects the concentration required to inhibit enzymatic activity by 50%. Therefore, future studies on compounds identified through docking should proceed toward similar enzymatic validation to determine whether predicted binding translates into measurable ACE inhibition.

Another important limitation concerns the interpretation of ACE and ACE2-related findings. Abdullah [14] reported docking of folate against ACE2 rather than classical ACE. Although ACE2 is part of the broader RAAS network, it differs from ACE

in biological function and catalytic role. Therefore, predicted binding to ACE2 should not be interpreted as direct evidence of ACE inhibition. This distinction is essential because classical ACE inhibitors reduce angiotensin II formation by inhibiting the conversion of angiotensin I into angiotensin II, whereas ACE2 has a different role within angiotensin peptide metabolism. Consequently, folate may be discussed as a compound with potential interaction toward an angiotensin-system-related protein, but its classification as an ACE inhibitor requires direct testing against classical ACE [14].

The reviewed docking studies also demonstrate that molecular interaction profiles should be evaluated beyond docking score alone. Important parameters include interaction with key ACE residues, hydrogen bonding, hydrophobic contacts, electrostatic interactions, zinc-related interactions, RMSD value, and stability of the ligand–protein complex. For example, fucoidan showed MolDock and rerank scores close to captopril, but its RMSD value was higher than the ideal range, suggesting that its binding pose may be less stable or less reliable [17]. Similarly, small differences between the docking scores of scopoletin and captopril should not be overinterpreted without additional confirmation [18]. These examples show that docking results require integrated interpretation rather than simple ranking based on the most negative binding energy.

Experimental validation is therefore essential to strengthen the translational relevance of natural ACE-inhibitor candidates. The first step should involve *in vitro* ACE inhibition assays to determine IC_{50} values and compare inhibitory potency with established ACE inhibitors. Enzyme kinetic studies are also needed to identify whether the compound acts as a competitive, non-competitive, uncompetitive, or mixed inhibitor. This information is important because compounds that bind near the ACE active site may not always inhibit substrate conversion through the same mechanism as captopril or lisinopril. In addition, molecular dynamics simulations may be used to complement docking by evaluating complex stability, ligand flexibility, and binding persistence over time.

Beyond enzymatic validation, pharmacological evaluation in biological systems is required. Promising compounds should be tested in cellular or animal models relevant to hypertension to determine whether ACE inhibition is accompanied by reduced angiotensin II formation, improved endothelial function, decreased vascular resistance, or measurable blood pressure reduction. Toxicity assessment is equally important because natural origin does not guarantee safety. Compounds such as flavonoids, phenolics, polysaccharides, and peptides may differ in absorption, metabolism, bioavailability, tissue distribution, and elimination. Therefore, pharmacokinetic studies are needed to evaluate whether effective concentrations can be achieved in vivo after oral or other routes of administration.

Clinical validation remains the final and most critical stage before these compounds can be considered therapeutically relevant. Although several natural compounds show promising *in silico* or *in vitro* activity, clinical efficacy requires evidence from controlled studies involving appropriate dosage, safety monitoring, pharmacodynamic outcomes, and blood pressure endpoints. Without such evidence, natural compounds should be described as ACE-inhibitor candidates rather than confirmed antihypertensive agents. Thus, the current body of literature provides a valuable foundation for natural product-based antihypertensive research, but further experimental and clinical studies are required to determine whether these candidates can be translated into safe, effective, and clinically meaningful ACE-inhibitory interventions [16]–[19].

Limitations of the Study

This review has several limitations that should be acknowledged. First, most of the included studies were based on *in silico* approaches, particularly molecular docking, which provide useful preliminary information regarding ligand–target interactions but cannot independently confirm enzymatic inhibition or antihypertensive efficacy. Binding energy, docking score, and molecular interaction patterns should therefore be interpreted as predictive indicators rather than definitive evidence of ACE-inhibitory activity. Second, only a limited number of studies provided direct experimental evidence, such as *in vitro* ACE inhibition assays and IC_{50} values. This limits the ability to compare the biological potency of different natural compounds across studies.

Third, the reviewed studies varied in terms of docking software, receptor preparation, ligand optimisation, scoring functions, validation parameters, and comparator drugs, which may affect the consistency and comparability of the reported results. Fourth, not all studies evaluated the same molecular target. For example, the folate-related study involved ACE2 rather than classical ACE, and therefore its findings cannot be directly interpreted as evidence of ACE inhibition. Fifth, this article was designed as a narrative literature review; therefore, it did not include formal risk-of-bias assessment, meta-analysis, or quantitative synthesis of effect sizes. Finally, the clinical relevance of the reviewed compounds remains uncertain because most candidates have not been validated through *in vivo* antihypertensive models, pharmacokinetic studies, toxicity evaluation, or clinical trials. These limitations indicate that further experimental and translational studies are required before natural bioactive compounds can be considered reliable ACE-inhibitory agents for hypertension therapy.

4. Conclusion

Natural bioactive compounds represent promising candidates for the development of angiotensin-converting enzyme (ACE) inhibitors in hypertension therapy. The reviewed evidence indicates that compounds such as chlorogenic acid, quercetin, isoflavones, luteolin derivatives, scopoletin, fucoidan, garlic-derived phenolic compounds, folate-related probiotic compounds, and marine bioactive peptides may interact with ACE or related molecular pathways through favourable binding affinity, hydrogen-bond formation, and predicted molecular stability. However, most findings are still dominated by *in silico* evidence, so they should be interpreted as predicted binding potential rather than definitive proof of enzymatic inhibition or clinical antihypertensive efficacy. Therefore, further validation through *in vitro* ACE inhibition assays, enzyme kinetic studies, toxicity evaluation, pharmacokinetic assessment, *in vivo* antihypertensive models, and clinical studies is required to confirm their biological relevance, safety, and therapeutic applicability.

Acknowledgements:

The authors would like to express their sincere gratitude to the Department of Pharmacy, Faculty of Science and Technology, Muhammadiyah University of Bandung, for providing academic support during the preparation of this narrative literature review.

Conflict of Interest:

The authors declare that there is no conflict of interest regarding the publication of this article.

References

[1] A. Wulandari, S. A. Sari, and Ludiana, "Implementation of Benson relaxation on blood pressure in hypertension patients at Ahmad Yani General Hospital, Metro City (2022)," *Jurnal Cendekia Muda*, vol. 3, no. 2, pp. 163–171, 2023. [Online]. Available: https://www.jurnal.akperdharmawacana.ac.id/index.php/JWC/article/view/453/0

[2] World Health Organization, "Hypertension," 2021. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/hypertension

[3] A. V. Purwaningtyas and M. I. Barliana, "Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers as cardioprotective agents against cardiovascular events: A review," *Farmaka Supplement*, vol. 19, no. 4, pp. 76–87, 2021. [Online]. Available: https://doi.org/10.24198/farmaka.v19i4.34939.g16846

[4] A. Utamayasa, M. A. Rahman, T. Ontoseno, and Budiono, "Comparison of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for heart failure treatment in congenital heart disease with left-to-right shunt," *Indonesian Biomedical Journal*, vol. 12, no. 1, pp. 62–68, 2020. [Online]. Available: https://doi.org/10.18585/inabj.v12i1.997

[5] J. Malau, M. N. Mulki, N. K. Fitri, N. Y. Wahyudi, P. C. Debora, Mulidini, N. O. E. Megrian, and N. K. Hanum, "Molecular mechanism review of antihypertensive drug classes in inhibiting angiotensin-converting enzyme (ACE)," *Wahana Pendidikan Scientific Journal*, vol. 9, no. 2, pp. 259–269, 2023. [Online]. Available: https://doi.org/10.5281/zenodo.7571470

[6] S. Widiasari, "Mechanism of angiotensin-converting enzyme inhibition by flavonoids in hypertension," *Collaborative Medical Journal*, vol. 1, no. 2, pp. 30–44, 2018. [Online]. Available: https://jurnal.univrab.ac.id/index.php/cmj/issue/view/65

[7] W. Rizkaprilisa and M. W. Hapsari, "The potential of angiotensin-I converting enzyme inhibitors from koro-koroan tempeh as functional antihypertensive food," *Science, Technology and Management Journal*, vol. 2, no. 1, pp. 20–25, 2022. [Online]. Available: https://doi.org/10.53416/stmj.v2i1.51

[8] A. Yunita, S. Z. Ramadhani, R. N. Andhryanti, N. Zhafirah, F. O. Muljono, F. M. Fardhan, and D. Novitasari, "In silico study of bioactive compounds from guava leaves (*Psidium guajava* L.) targeting angiotensin-converting enzyme for hypertension therapy," *Indonesian Journal of Chemical Science*, vol. 13, no. 3, pp. 208–219, 2024. [Online]. Available: https://doi.org/10.15294/ijcs.v13i3.8648

[9] L. Actis-Goretta, J. I. Ottaviani, and C. G. Fraga, "Inhibition of angiotensin-converting enzyme activity by flavanol-rich foods," *J. Agric. Food Chem.*, vol. 54, no. 1, pp. 229–234, 2006. [Online]. Available: https://doi.org/10.1021/jf052263o

[10] R. Mardianingrum, Y. Firiani, S. R. N. Endah, and R. Ruswanto, "In silico study of corn silk luteolin derivatives (*Zea mays* L.) as potential antihypertensive agents," *Journal of Chemistry, Science and Application*, vol. 28, no. 3, pp. 155–167, 2025. [Online]. Available: https://doi.org/10.14710/jksa.28.3.155-167

[11] C. Nissa, G. I. Sukma, I. J. Madjid, N. M. Sidin, and M. Musyarrofah, "In silico identification of isoflavone and quercetin binding interactions with angiotensin-converting enzyme," *Journal of Nutrition College*, vol. 11, no. 1, pp. 1–5, 2022. [Online]. Available: https://doi.org/10.14710/jnc.v11i1.29500

[12] D. C. A. Braga, P. M. Gomes, M. A. C. Batista, J. A. de Souza, J. C. S. A. Bastos, R. G. Rodrigues-das-Dores, A. C. Alzamora, G. H. B. de Souza, S. A. L. de Moura, A.

Talvani, V. R. Antunes, and L. M. Cardoso, "Effects of *Psidium guajava* L. leaves extract on blood pressure control and IL-10 production in salt-dependent hypertensive rats," *Biomedicine & Pharmacotherapy*, vol. 155, art. no. 113796, 2022. [Online]. Available: https://doi.org/10.1016/j.biopha.2022.113796

[13] D. A. P. Utari, N. P. R. Anggreni, P. R. J. Putri, and N. P. L. Laksmiani, "In silico antihypertensive activity of quercetin targeting angiotensin-converting enzyme," *Medicamento Scientific Journal*, vol. 7, no. 1, pp. 71–76, 2021. [Online]. Available: https://doi.org/10.36733/medicamento.v7i1.1504

[14] D. Abdullah, "Docking simulation of lab-active compounds as angiotensin-converting human enzyme chain A (ACE2)," *Jurnal Kesehatan Medika Saintika*, vol. 12, no. 1, pp. 159–166, 2021. [Online]. Available: https://doi.org/10.30633/jkms.v12i1.773

[15] Y. Wang, Y. Wu, Y. Wang, H. Xu, X. Mei, D. Yu, Y. Wang, and W. Li, "Antioxidant properties of probiotic bacteria," *Nutrients*, vol. 9, no. 5, art. no. 521, 2017. [Online]. Available: https://www.mdpi.com/2072-6643/9/5/521

[16] G. Oboh, A. J. Akinyemi, and A. O. Ademiluyi, "Inhibitory effects of phenolic extracts from garlic on angiotensin-I converting enzyme and lipid peroxidation," *Int. J. Biomed. Sci.*, vol. 9, no. 2, pp. 98–106, 2013. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/23847460/

[17] A. Kurniawan, E. M. Siswandono, and S. Abdillah, "Molecular docking and toxicity prediction of fucoidan compounds from brown seaweed as potential antihypertensive agents," *Pharmacon: Indonesian Journal of Pharmacy*, vol. 19, no. 1, pp. 1–9, 2022. [Online]. Available: https://doi.org/10.23917/pharmacon.v19i1.15933

[18] A. R. Praja, D. Pratiwi, and Nuraini, "Molecular docking study of scopoletin from *Morinda citrifolia* L. targeting angiotensin-converting enzyme," *Pharmacy Journal*, vol. 5, no. 1, pp. 40–47, 2018. [Online]. Available: https://doi.org/10.47653/farm.v5i1.91

[19] T. M. Fakih and M. L. Dewi, "In silico identification of bioactive peptides from marine organisms as natural angiotensin-I converting enzyme inhibitors," *Jurnal Sains Farmasi & Klinis*, vol. 7, no. 1, pp. 76–82, 2020. [Online]. Available: https://doi.org/10.25077/jsfk.7.1.76-82.2020