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Marine Organisms as Potential Sources of Inhibits ACE on Hypertension Patient

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Abstract: Hypertension is a condition of chronic high blood pressure in the systemic arteries which is a major risk factor for cardiovascular disease, kidney disorders and death. The conversion process of Angiotensinogen to Angiotensin I, then Angiotensin II by ACE can cause vasoconstriction and fluid retention which contributes to hypertension. Changes in circulation and blood vessel structure play a role in the risk of hypertension complications, including stroke. Therefore, bioactive peptides from marine organisms can be an efficient and safe natural alternative. This article carries out a search strategy on online databases, such as PubMed, Google Scholar, and Proquest for scientific journal articles published in the last 10 years related to the topic discussed. Research on protein hydrolysates from various sources found ACE inhibitory activity and several peptides such as Trp-Pro-Met-Gly-Phe (WPMGF) and APP, KPLL, and VYPPGPIPNSLPQNIPP were identified to have strong ACE inhibitory activity. Potential sources of ACE inhibitors in hypertension sufferers come from fish, jellyfish, sea shells and sea cucumbers. This fish contains anti-ACE biopeptide. Jellyfish produce two ACE-inhibiting peptides, sea mussels with sequences that further inhibit ACE, and sea cucumbers produce ACE-inhibiting peptides from Acaudina molpadioides. The potential source of marine organisms can be used as a natural alternative in the treatment and prevention of hypertension. Various marine animal organisms, such as fish, jellyfish, sea shells and sea cucumbers as sources of bioactive proteins and relevant peptides, some function with antihypertensive, anticoagulant, antithrombotic and hypercholesterolemic activities. This is used as a potential source of ACE inhibitors in hypertension patients.

Keywords: Hypertension marine organism, inhibit ACE, potential sources, treatment.

Introduction

Chronically high blood pressure in the systemic arteries is a hallmark of hypertension. Hypertension is the most common and preventable risk factor for coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation, peripheral arterial disease, chronic kidney disease, cognitive impairment, and a major cause of death and disability worldwide. Right now, around 3.5 billion grown-ups overall have sub-par systolic strain levels (more than 110-115 mmHg) and 874 million grown-ups have systolic tension ≥140 mmHg. As a result, approximately one in four adults have high blood pressure. Between 1990 and 2015, the number of years of life lost worldwide due to unhealthy blood pressure increased by 43%. Population growth, population aging, and an increase of 10% in the age-adjusted prevalence of hypertension are the root causes. The Worldwide Weight of Illness Study has demonstrated that sub-par circulatory strain keeps on being a significant gamble factor adding to the worldwide weight of sickness and mortality overall and causes

roughly 9.4 million passings every year (Oparil, 2019).

Hypertension is found in 34.1% of the 18 year old population in Indonesia (Riskesdas, 2018). South Kalimantan has the highest incidence rate at 44.1%, while Papua has the lowest incidence rate at 22.2%. Hypertension attacks occur in various age groups, including ages 31 to 44 years (31.6%), 45 to 54 years (45.3%), and 55 to 64 years (55.2%). The prevalence of hypertension in the elderly is still quite high, ranging from 60 - 80% of people over 65 years of age. Women were more likely to suffer from hypertension (36.9%) than men at 69.5%, compared to 31.3% for men. In 2017, the population of Central Java had their blood pressure measured, approximately 8 million people (36.53%) were at risk and were at least 18 years old, and approximately 1 million people (12.98%) suffered from hypertension (Soesanto and Zulino, 2021).

The mechanism of ACE in patient with Hypertension is started with produced of Angiotensinogen by RAAS. The RAAS is initiated by angiotensinogen which is created in the liver. The process of converting angiotensinogen to angiotensin I occurs through the action of Renin. Next, Angiotensin Converting Enzyme (ACE) transformed Angiotensin I into Angiotensin II. The sustained production of Angiotensin II can cause vasoconstriction, increased Aldosterone, and fluid retention which can ultimately contribute to hypertension (DEWI et al., 2019). Recently, More than 125 ACE inhibitory peptides have been identified from marine organisms. Bioactive peptides of marine origin appear to have higher levels of ACE inhibitory activity than peptides derived from terrestrial sources (Pujiastuti et al., 2019). Apart from conventional medicines, there are some concerns among the public about the side effects of conventional medicines. There has now been a lot of research on the use of natural ingredients to lower blood pressure.

The marine organisms such as sea cucumbers, *Actinopyga lecanora* which contain the bioactive ingredient saponin, are believed to have the effect of lowering blood pressure in hypertension sufferers. In addition, various types of marine organisms have been identified as having the benefit of lowering blood pressure through different mechanisms. The one of which is the most commonly used, namely Angiotensin Converting Enzyme (ACE) receptor inhibitors. The use of angiotensin receptor blockers (ARBs) (losartan, olmesartan, valsartan, telmisartan) rarely causes mild or severe side effects, limited in the medical field (Festa M et al., 2020). However, pharmaceutical drugs can cause side effects such as changes in taste, coughing, and rashes. As a result, it is critical to discover new, safe, and effective natural alternatives to reduce chemical drug use (Li et al., 2018).

Materials and Methods

We carried out a search strategy on online databases, such as PubMed, Google Scholar, and Proquest for scientific journal articles published in the last 10 years related to the topic discussed. The keywords we used in the search were as follows: "Marine Organism", "Potential Sources", and "ACE Inhibits in Hypertension Patients".

Results and Discussion

Definition of hypertension

A chronic condition known as hypertension, or high blood pressure, is characterized by elevated blood pressure on the artery walls (Azizah et al., 2022). This increase of blood pressure can increases the heart's workload in circulating, and throughout the body by blood vessels. Hypertension is a significant gamble factor for a few different sicknesses, one of which is cardiovascular illnesses, incorporates stroke, myocardial dead tissue, cardiovascular breakdown, and atrial fibrillation which can bring about death (Gabb, 2020). Hypertension is nicknamed “the silent killer” because it has no specific signs and can attack anyone (Azizah et al., 2022). A person has hypertension if their diastolic and systolic blood pressures are greater than 90 mmHg and 140 mmHg, respectively (Kementerian Kesehatan RI, 2021).

Etiology of hypertension

Depending on the cause, there are two types of hypertension: primary hypertension and secondary hypertension. About 95% of people suffer from primary hypertension, which has no known cause. Individual characteristics that

influence the onset of hypertension include age (blood pressure increases, as age increases)gender (men are taller than women), race (blacks are more prevalent than whites), and habitual factors. Primary hypertension is thought to be caused by hereditary factors. a life of excessive salt intake, obesity or overeating, stress, smoking, alcohol consumption, and drug use (ephedrine, prednisone, and epinephrine) (Kartika et al., 2021).

Pathophysiology of hypertension

A chronic condition known as hypertension is characterized by elevated blood pressure in the arteries (Azizah et al., 2022). Hypertension can be caused by hereditary factors, individual characteristic, gender, race, habitual factors, obesity, overeating, stress, smoking, drinking alcohol, and taking drugs (Kartika et al., 2021). Angiotensin I Changing over Protein (Expert) which structures Angiotensin I to Angiotensin II which assumes a physiological part has a significant impact in controlling pulse and is the pathophysiology of hypertension. Blood contains angiotensinogen which is an amino corrosive created in the liver. Next, the hormone renin will be converted into angiotensin I. Then angiotensin I will be converted into angiotensin II as a result of ACE in the lungs. The renin that is combined and latent is called prorenin which will then, at that point, be put away in the juxtaglomerular cells (JG cells) in the kidney, where these JG cells are the consequence of alteration of smooth muscle cells situated in the walls of the afferent arterioles, exactly proximal to the glomerulus. If arterial pressure falls, there will be an intrinsic reaction in the kidneys that causes many JG cell protein molecules to break down and release renin (Harrison et al., 2021).

Apart from being a very powerful vasoconstrictor, angiotensin II also has other effects that also affect circulation. Angiotensin II has two main effects that can increase arteries as long as angiotensin II is in the blood. The first effect is that vasoconstriction appears quickly. The main point where vasoconstriction occurs is in the arteriole area and is slightly weaker in the veins. The second effect of angiotensin II in increasing arterial pressure is by reducing the excretion of salt and water in the kidneys. Vasopressin or also known as ADH (AntiDiuretic System) is considered stronger than angiotensin as a vasoconstrictor, and is thought to be the body's most powerful vasoconstrictor. This material is formed by the hypothalamus and transported down the nerve axon centers to the posterior pituitary gland, where it is then secreted into the blood (Harrison et al., 2021).

An important regulator of the renal tubules' sodium (Na+) reabsorption and potassium (K+) secretion is the adrenal cortex's zona glomerulosa cells' release of aldosterone. Aldosterone acts primarily in the cortical collecting tubules' principal cells. Aldosterone temporarily increases potassium secretion and sodium reabsorption by stimulating the sodium potassium ATPase pump on the basolateral side of the cortical collecting tubule membrane. Knowledge about the pathogenesis of primary hypertension will continue to develop because satisfactory answers about the causes of increased blood pressure have not yet been found. The things that influence blood pressure itself are cardiac output and peripheral resistance (Harrison et al., 2021).

The cardiovascular system undergoes a series of changes that also include changes in cerebral circulation. Because hypertension has a significant impact on the structure of the cerebral vasculature, changes like vascular remodeling, inflammation, oxidative stress, baroreflex dysfunction, and others may contribute to the pathogenesis of stroke. Mechanical, nervous, and humoral factors also influence changes in the cerebrovascular wall's composition and structure (Husada et al., 2020). Oxidative stress is a condition in which the antioxidant defense system is overwhelmed by an imbalance in reactive oxygen species (ROS). This oxidative pressure happens because of overabundance responsive oxygen species (ROS), discouraged cell reinforcement limit, or is brought about by a mix of both. Damage to the antioxidant defense system is caused by persistent oxidative stress, which can result in the depletion of antioxidant molecules and the deactivation of antioxidant enzymes.

Oxidative pressure plays a significant part in the pathogenesis of hypertension and stroke as a drawn out complexity. Oxidative stress in the brain and cerebral blood vessels can cause hypertension, as evidenced by normal animal

hypertension caused by induced oxidative stress. Reactive oxygen species (ROS) become the primary mediator of angiotensin II-induced cerebrovascular dysfunction by activating NADPH oxidase in blood vessels. The cycle that happens next is irritation (Yonata et al., 2016)

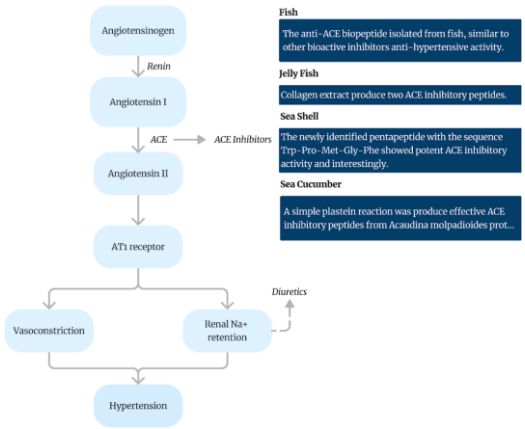
The blood vessel baroreflex is one of the main physiological components for controlling circulatory strain guideline. In many cardiovascular diseases, baroreflex sensitivity (BRS), a marker of arterial baroreflex function, plays a significant role. Due to changes in blood vessel distensibility and activity in brainstem reflex regions, the baroreflex is occasionally less sensitive to changes in blood pressure that are associated with hypertension. Vascular changes and arterial stiffness caused by a lack of baroreflex sensitivity contribute to the vicious cycle of hypertension and its complications.

Apart from being caused by hypertension, damage to the blood vessel baroreflex is also a determining factor in the occurrence of stroke. After ischemic or hemorrhagic stroke, baroreflex dysfunction and blood pressure variations can significantly alter cerebral perfusion and increase perihematomal edema. In addition, damage to the baroreflex can also fundamentally cause an increase in IL-1 and IL-6 levels and infarct volume (Yonata et al., 2016). In general, oxidative stress, inflammation, baroreflex dysfunction, and hypertension all contribute to stroke and can be linked together. Secondary morphological and functional changes in cerebral blood vessels are to blame for this (Yonata et al., 2016).

The Potential Sources of Marine Organisms in Inhibiting ACE in Hypertension

Bioactive proteins and peptides, some of which may have antihypertensive, anticoagulant, antithrombotic, and hypercholesterolemic properties, are found in a wide range of marine animal species, including fish, jellyfish, sea shells, and sea cucumbers (Liu Xin et al., 2013). At present, in excess of 125 Pro inhibitory peptides have been recognized and secluded from marine organic entities. Bioactive peptides from marine sources appear to have a higher ACE inhibitory activity than peptides from terrestrial sources (Pujiastuti et al., 2019). ACE inhibitory peptides of marine origin share short amino acid sequences characterized by low molecular weight and hydrophobic residues that confer enhanced anti-ACE activity (Wijesekara Isuru and Kim Se-Kwon, 2010).

The angiotensin converting enzyme (ACE) is very important in the blood pressure regulation system (Renin-Angiotensin-Aldosterone System) because it converts angiotensin I to angiotensin II, resulting in hypertension. Therefore, it is important to investigate ACE inhibition to avoid and treat hypertension. Chemically produced ACE inhibitor drugs, such as captopril, enalapril, and lisinopril, are currently frequently used in clinical applications (Li et al., 2018). In the medical field, the use of angiotensin receptor blockers (ARBs) like losartan, olmesartan, valsartan, and telmisartan rarely results in mild or severe side effects (Festa et al., 2020). However, adverse effects of pharmaceutical drugs include taste changes, coughing, and rashes. As a result, it is critical to discover new, safe, and effective natural alternatives to reduce chemical drug use (Li et al., 2018).



Picture 1. Intervention marine sources in pathophysiology of Hypertension (ACE Inhibitors Pathways)

Fish

As to peptide from the pal salmon Oncorhynchus keta (Walbaum, 1792), it was shown that its movement is similar to that of the drug captopril (Lee et al., 2014). One more wellspring of Expert inhibitors and cancer prevention agent peptides might result from the hydrolysis of dietary proteins by trypsin and chymotrypsin. Trypsin and chymotrypsin hydrolysates from the ascomycetous yeast Kluyveromyces marxianus (EC Hansen, Van der

Walt) appear to require further purification in order to yield compounds with ACE inhibitory activity. These compounds have an IC50 range of 15.20 mM to 22.88 mM, which is approximately 1.76 times to three times higher than the original peptide fractio (Li et al., 2018). The ACE counter biopeptide derived from fish, like other bioactive inhibitors, has an antihypertensive effect, without secondary effects related to cytotoxicity, thus indicating that the biopeptide is an elective competitor for drugs produced and anticipated hypertension so it has been proven to lower blood pressure (Wijesekara Isuru and Kim Se-Kwon, 2010).

Jellyfish

It has been determined that portions and subfractions of the chemical hydrolyzate of the jellyfish Rhopilema esculentum prevent Pro movement at IC50s ranging from 1.28 mg mL-1 to 0.16 mg mL-1 (Liu Xin, et al., 2013). Alcalase hydrolyzes collagen extract from the jellyfish Rhopilema esculentum to produce ACE inhibitor peptide (Zhuang et al., 2010). Alcalase was used to hydrolyze jellyfish (Rhopilema esculentum) to produce two ACE inhibitory peptides. The antioxidant activity was then purified using ultrafiltration and chromatography, and the resulting peptides were identified as VKP (342 Da) and VKCFR (651 Da) using spectrometry electrospray ionization tandem mass (Li et al., 2014).

One kilogram of a wet Rhopilema esculentum sample, containing approximately 91% water and 5% protein, respectively. To get rid of salt, the samples were cut into small pieces, boiled twice in water for 30 minutes, and washed three times. The sample was boiled, then cooled to room temperature (25 °C) and sieved to separate the soluble fraction from the insoluble mass. After that, the insoluble residue was hydrolyzed by incubating it with alcalase for two hours at 45 °C in 0.1 M sodium phosphate buffer (PBS, pH 8.0) with an enzyme-to-substrate ratio of 2%. The mixture was inactivated by 10 minutes of incubation at 85 °C following incubation (Li et al., 2014).

Sea Shells

Trypsinized hydrolyzate of Chinese venus, or Cyclina sinensis, obtained through a series of chromatographic separation and purification steps (Gmelin, 1791), displayed increased ACE inhibitory activity. The Trp-Pro-Met-Gly-Phe pentapeptide, which was recently discovered (WPMGF; WPMGF maintained its potent ACE inhibitory activity (IC50 value 0.789 mM) at pH values between 2 and 8 (simulation of gastrointestinal environmental conditions)—MW = 636.75 Da). Trypsin was used to hydrolyze Cyclina sinensis to various peptides as well as peptides with the highest inhibitory activity that had been purified via ultrafiltration, rapid protein liquid chromatography, and reversed-phase high-performance liquid chromatography (Yu F et al., 2018).

Sea cucumber (*Cucumaria frondosa*)

Sea cucumbers' chemical defense is generally based on saponins, which are their primary secondary metabolites. According to studies (Fagbohun et al.,), saponins extracted from sea cucumbers have biological properties that include modulating the immune system, antitumor, anti-obesity, anti-fungal, anti-bacterial, and anti-hyperuricemia. 2023). One of sea cucumbers' most significant secondary metabolites and bioactive components are saponins (Meng et al., 2018). Compared to other sea cucumber components like polysaccharides, collagen peptides, dregs, or non-saponin residues, saponin from Cucumaria frondosa has superior lipid-lowering properties in mice. The system basic the activity is connected with the concealment of pancreatic lipase action, which is answerable for the breakdown of dietary fats in the small digestive tract (Lin et al., 2022). The body wall was separated from all internal organs and stored separately in a plastic zip-lock bag for this sample. locks were frozen, then moved to the lab and put away at −20 C.

Cutting the sample into small pieces, lyophilized and ground with a blonde tool and extracted with 70% EtOH liquid on a shaker followed by filtration through Whatman funnel paper. Overnight at room temperature After that, the hydromethanol phase's water content was reduced to 20% and then to 40%, respectively, and the solution was divided into CH2Cl2 and CHCl3. The water extract was then eluted sequentially with MeOH, acetone, and water before being subjected to Amberlite XAD-4 column chromatography, thoroughly washed to remove salts and impurities. After that, the eluate

was concentrated, redissolved, and dried in 5 milliliters of MilliQ water (Bahrami et al., 2018). Additionally, these findings suggest that saponins like echinoside A may aid in the reduction of hyperlipidemia by promoting the conversion of cholesterol to bile acids and the elimination of lipids. By suppressing SREBP-1c and increasing the expression of PPAR and acyl-CoA oxidase 1 (ACOX1), respectively, sea cucumber saponin also decreased lipogenesis and increased FA oxidation in SD rats and C57BL/6 mice (Lin et al., 2022).

Sea cucumber saponin decreased liver TG partly through increasing PPARα expression when combined with EPA-enriched phospholipids. This combination has a better effect in reducing insulin sensitivity and systematic glucose intolerance (Han et al., 2019). Testing of sea cucumbers (*Actinopyga lecanora*) was carried out by drying and mashing using a Waring blender then sieving (tissue size 600 micrometers). Before use, the powder samples were stored at 80 C. Following previous research procedures, hydrolysis was carried out. On a dialysis tube with a sub-atomic weight limit of 12–14 kDa (MWCO) (Dialysis Tubing-Visking, width 28.6 mm), test powder (10 g) was dialyzed with 50 mL of distilled water. After dialysis, the samples were hatched in a water shower to reach the ideal temperature for bromelain catalyst response. The cylinder was tightly sealed at both ends and submerged for 24 hours at 4 C in a buffer setting that was within acceptable limits (50 mM).

In the test vessel, the bromelain is thoroughly mixed with the dialysis sample and dissolved in the appropriate buffer solution. Enzymatic hydrolysis can be used to produce *A. lecanora* hydrolyzate with ACE inhibition and anti-oxidative bioactivity. The findings demonstrate that the hydrolysis time and type of catalyst have a significant impact on the formation of amino corrosive precipitates and their subsequent inhibitory and anti-oxidant activities. Among different proteases attempted, alcalase was viewed as the most fit for creating a hydrolyzate with the most noteworthy expert hindrance and balancing oxidative movement. Heart-related conditions can benefit from A. lecanora hydrolyzate's dual bioactivity as a rich source of bioactive peptides (Vishkaei et al., 2016)

Sea cucumber (*Acaudina molpadioides)*

A simple plastein reaction was recently described to produce effective ACE inhibitory peptides from *Acaudina molpadioides* protein hydrolysates. When Danilevski introduced the enzyme chymotrypsin to protein hydrolysates in 1902, he discovered the reverse enzymatic process, which led to the first discovery of the Plastein reaction. Since then, the plastein reaction has been used for a lot of different things, like changing some protein hydrolysates to make them have more antioxidant activity or stop ACE from working. Examination of design action connections has uncovered that peptides like Application, KPLL, and VYPFPGPIPNSLPQNIPP have significant Pro inhibitory movement, demonstrating the importance of proline in regulating Expert inhibitory action. By adding proline to casein hydrolyzate, the Pro inhibitory action can be expanded from 27.8% to 76.4%. Acaudina molpadioides modified hydrolyzate with 40% proline (w/w, free proline/amino groups) which was proven to have a stronger ACE inhibitory action than the original hydrolyzate (Li et al., 2018).

Conclusion

Chronically high blood pressure in the systemic arteries is a hallmark of hypertension. The significance of forestalling and treating hypertension in diminishing the weight of sickness and expanding future across the total populace is huge. Antihypertensives like calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) and lifestyle modifications are currently the most common treatment for people with hypertension. Bioactive peptides derived from the sea appear to have a higher level of ACE inhibitory activity than peptides derived from land sources. Through several studies on marine natural ingredients that have been carried out, compounds can be found that have the potential to be used as alternative treatments for hypertension that are safer and have minimal side effects. Some of them are natural marine ingredients that are easily found in Indonesia, namely jellyfish, sea cucumbers, fish and sea

shells. It is hoped that further development and processing of compounds that have been discovered can be carried out as forms of medicine that can be accepted by the public.

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