International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 1007-1023 www.ijprajournal.com ISSN: 2249-7781

Overview on Antihypertensive Effect of Modern Marine Drugs for Hypertensive Disorder

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Submitted: 05-02-2022 Accepted: 20-02-2022

ABSTRACT

An alternative option to overcome these side effect is marine drugs. Marine drugs exhibits various befinifical biological activities such as anticancer, antioxidant, antihypertensive. Hypertension, or high blood pressure is a serious health problem because it can lead stroke, heart attack, heart failure or kidney disease.

Angiotensin- I converting enzyme (ACE) plays on important physiological role in regulation of blood pressure by converting angiotensin-I to angiotensin-II a potent vasocontrictor. Therefore, the inhibition of ACE activity is a major target in the prerention of hypertension .Recently, the search for natural ACE inhibitors as alternatives to Synthetic drugs is great interest side to a prevent several side effect and a number of novel compounds such as bioactive peptides and phlorotannis have been derived from marine organisms as potential ACE inhibitors. These inhibitory derivatives can be developed as nutraceuticals and pharmaceutical with potential to prevent hypertension.Hence, the aim of this review is to discuss marine - derived ACE inhibitors and drugs candidates for treating hypertension.

Keywords: Antihypertensive, marine drugs, Hypertension, bioactive peptides, angiotensin-I-converting enzyme

I. INTRODUCTION

hypertension is a common serious chronic factor, which seriously affects about 25% adult population worldwide and is a causative factor of cardiovascular disease; stroke, renal diseases, among other[1]. Number of CVD cases have nearly doubled during the past 2 decades due to inappropriate dietary habits (a diet high in saturated fat and cholesterol) and lifestyle (overweight 1% billion and 312 million obese adult) [2].

Figure 1:-

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 1007-1023 www.ijprajournal.com ISSN: 2249-7781

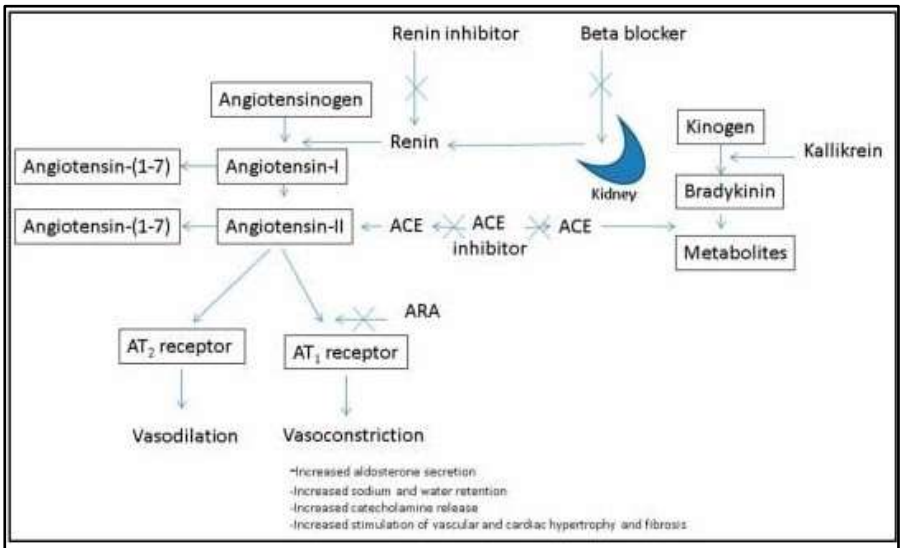

Figure 1. The Renin-Angiotensin-Aldosterone System (RAAS) can be inhibited by ACE-I inhibitors, angiotensin II type 1 receptor antagonists (ARA), renin inhibitors and beta blockers. ACE-I also plays a role in bradykinin metabolism and metabolism of angiotensin-(1-7)[3].

Renin -angiotensin system (RAS) is the important regulator of blood pressure homeostasis in mammals[4]. In renin-angiotensin system it inactivates the vasodilator bradykinin, which has a depressor action as well as promotes the conversion of ang-I to the potent vasoconstrictor ang-II [5]. 70% of earth's surface, nearly ocean cover and posses nearly three lakh deserted species of plants and animals from marine sources [6].

Captopril, Benzepril, enalpril, perindepril, zefenoprilare synthetic ACE inhibitors as associated with various side effects; such as cough & taste disturbances, allergic reaction and skin rashes [7, 8]. Therfore, safer alternatives are desirable. Recently, many peptides have been isolated from food-derived marine protein hydroxylates, such as cad, sea cucumbar, collagen, shrimp, salmon and squid skin,[9] jellyfish, collagen,actinopyga,Lecanora [10].

Bioactive molecules containing functional foods or dietary supplements are come under nutraceuticals. In recent years, natural sources such as terrestrial and marine plants, animals or even microorganisms have become sustainable solution and get functional and bioactive compound that offers new molecules with strong biological activity[11].

Due to their high-value metabolites with specific activities and promising benefits, marine organisms like fish, shellfish, seaweeds, microalgae, molluscs, crustaceans and cephalopods are rich sources of bioactive compounds[12].

According to researches, it has proved that marine-derived bioactive peptides, chitooligosaccharide derivatives (COS) and Phlorotannins have potent ACE inhibitory activity. Peptides derived from fish protein hydrolysate have been shown antihypertensive effects by blocking the calcium channels.

As antioxidants, Anti-hypertensive ,antitumour, anticoagulant and antimicrobial components in functional foods or nutraceuticals and pharmaceutical due to their health benefits and therapeutic potentials marine bioactive compounds can be used[13,14].

II. PATHOPHYSIOLOGY OF HYPERTENSION:

A number of physiological mechanisms are involved in the maintainance of normal BP, and their derangement may play a part in the development of essential hypertension. Among the factors that have been intensively studied are salt intake, obesity and insulin resistance, the renin- angiotensin system, sympathetic nervous system, endothelial dysfunction (as manifested by changes in endothelin and nitric oxide) [15].

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Renin-Angiotensin system (RAS):

The RAAS is composed of a cascade of hormones initially triggered by the release of of renin from the kidney [16,17]. The production of renin is raised by a decrease in perfusion of the Juxtraglomerular apparatus. Renin is a proteolytic enzyme that has a local action in the kidney as well as in the circulation upon the substrate angiotensinogen, which is a protein precursor that is produced in and secreted by liver. Angiotensinogen is cleaved by renin to form the biologically inactive peptide angiotensin I (A-I). This circulating decapeptide is then efficiently converted to the active octapeptide angiotensin- II(A-II) by angiotensin-converting enzyme (ACE). ACE is a largely tissue - based zinc metalloprotease, mainly generated by the lungs, the cell membranes of the kidneys and the endothelial cells of the vasculature. Angiotensin-II is produced in a number of organs, largely locally from locally generated angiotensin-I.This local production of Angiotensin-I involves renal renin taken up at tissue sites,possibly involving e renin receptor. This allows the tissue renin levels to be higher than expected on the basis of simple diffusion from blood .Consequently, Angiotensin-II levels are often much higher in tissues than in the circulation. Two well-characterized subtypes of Angiotensin-II recetors mediate the major physiological action of Angiotensin-II in humans: these have been termed angiotensin type I(AT1) and angiotensin type 2 (AT2) receptors. Both receptors are G-coupled polypeptides, containing approximately 360 amino acids, and have 7 cell membrane- spanning regions [18-20].

In the human body, the AT1 receptor is more widely distributed and thus more important than the AT 2 receptor. Genetically, both receptor subtypes have a sequence homology of only 30%. There genes reside on different chromosomes: the AT1 receptor on chromosome 3 and the AT2 receptor on the x chromosome [21-23]. Stimulating either AT1 or the AT2 receptor results in activation of different signal transduction pathways, which results in antagonizing effects. For example, Angiotensin-II, stimulating the AT1 receptor, is a potent vasoconstrictor, whereas AT2 receptor stimulation by Angiotensin-II results in vasodilation.

In addition to its vasoconstricting and other effects, Angiotensin-II can activate AT1 receptors in the adrenal gland, which results in synthesis of the steroid hormone aldosterone. It is generally accepted that excessive stimulation of the AT1 receptor by Angiotensin-II results in unfavorable effects, whereas stimulation of AT2 receptor is responsible for beneficial, however in humans less important, effects of Angiotensin-II .The overall effect of activation of the RAAS is an increase in effective circulating volume, resulting in an increase in perfusion of the Juxtraglomerular apparatus. Through this phenomenone, the release of renin by the kidney is inhibited : a feedback mechanism [24].

Endothelial dysfunction:

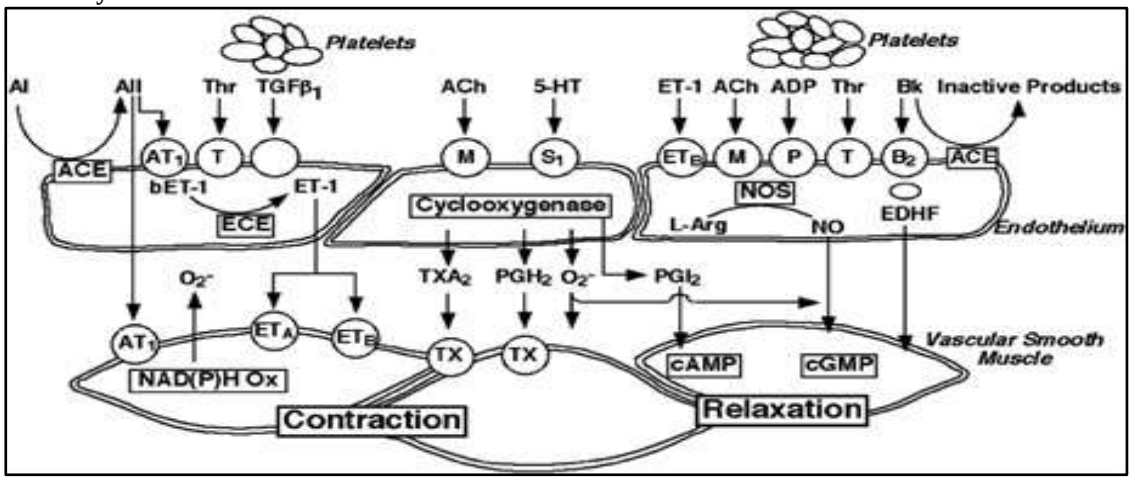

Figure No. 2:- Endothelial Dysfunction[25]

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Endothelium-derived vasoactive substance. NO is released from endothelial cells in response to shear stress and to activation of a variety of receptors. NO exerts vasodilating and antiproliferative effects on smoth muscle cells & inhibits thrombocyte aggregation and leukocyte adhesion. ET-1 exerts its major vascular effects - vasoconstriction and cell proliferation- through activation of specific ETA receptors on vascular smooth muscle cells. In contrast, endothelial ETB receptors mediate vasodilation via release of NO and prostacyclin.

Additionally, ETB receptors in the lung were shown to be a major pathway for the clearance of ET-1 from plasma. ACE denotes angiotensin-converting enzyme; Ach, acetylcholine; A-I, Angiotensin-I; A-II, Angiotensin-II; AT1, angiotensin 1 receptor; Bk, bradykinin; cox, cyclooxygenase ; ECE ,ET-converting enzyme ; EDHF, endothelium-derived hyperpolarizing factor; ETA and ETB ; endothelin A and B receptors; ET-I, endothelin-1; L-Arg ,L-arginine; PGH_2, prostaglandin H_2; PGI2, prostacyclin; S, serotoninergic receptor; T, thromboxane receptor ;Thr, thrombin; $TQFB_1$, transforming growth facto - B_1; TXA_2 ,thromboxane; 5-HT, 5-hydroxy-tryptamine (serotonine). Modified from Luscher &Noll [26].

Sympathetic Nervous system :-

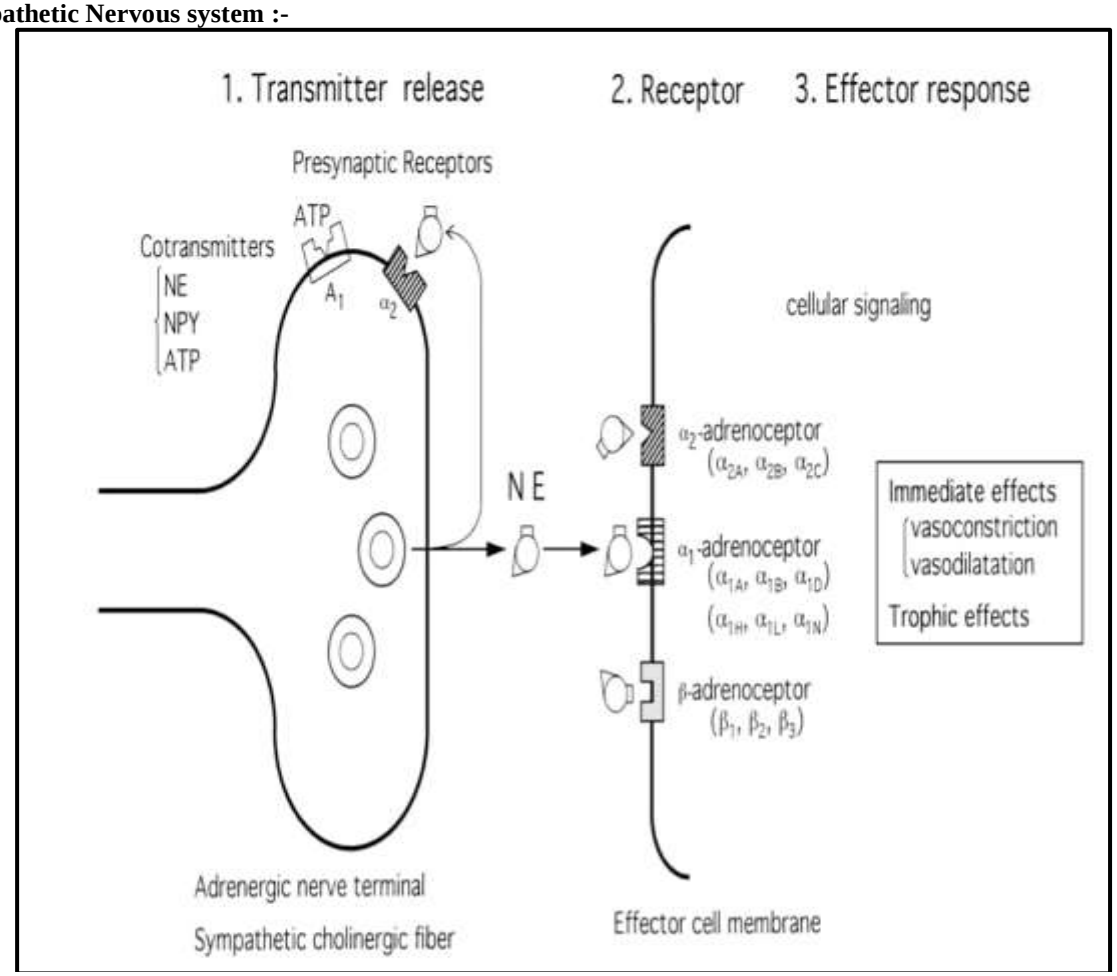

Figure No. 3- Sympathetic nervous system [27]

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Diagram of the sympathetic nerve and adrenergic neuroeffector mechanism 1. Transmitter release from the sympathetic nerve terminal : sympathetic nerve fibre may contain three cotransmitters , i.e. norepinephrine (NE),neuropeptide Y (NPY) and ATP. Release of main transmitter NE may be presynaptically modulated by α2-adrenoceptor, A1 adenosine receptor, etc. There may be dopaminergic as well as cholinergic fibers in the special organs. 2. Adrenoceptors on the effector cell membrane. There area α and β-adrenoceptors and subtypes: a1(α1A, α1B & α1D; α1H;α12 & α1n), α2(α2A,α2B &α2C) & β1,β2 & β3. There may be remarkable regional differences in the population of adrenoceptor subtypes. 3. Effector responses. Sympathetic nerves have both immediate effects-contraction and dilation, differing from vessel to vessel-as well as long term trophic effects on blood vessels [27].

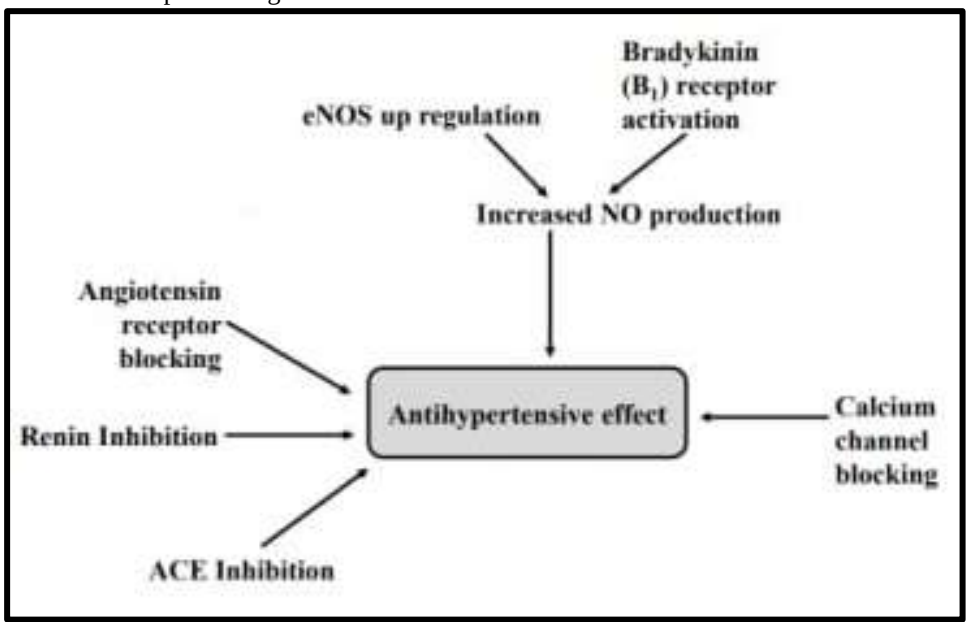

Figure No. 4- Various Vasodilatory mechanisms of different peptides are summarized[28].

III. REVIEW OF LITERATURE

Marine derived ACE inhibitors and their Anti-hypertensive activity:There are different categories of marine antihypertensive agent which are as shown in figure no.5-

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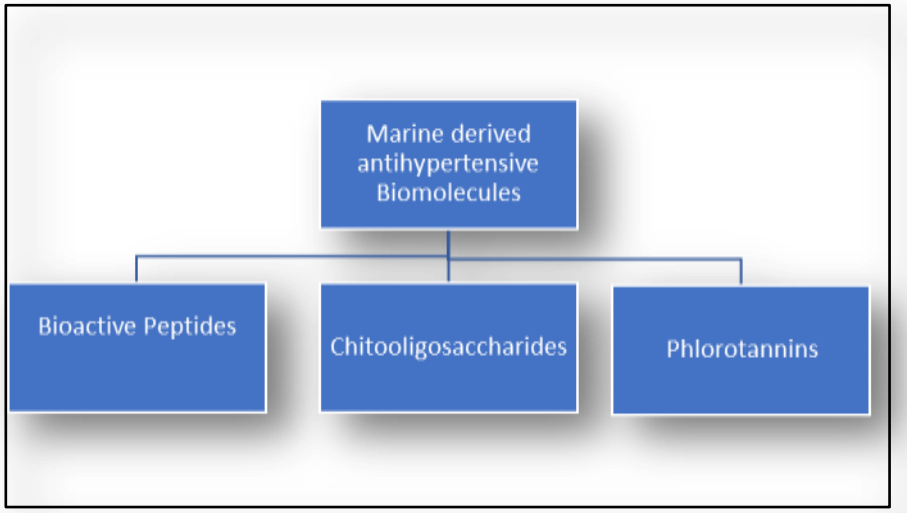
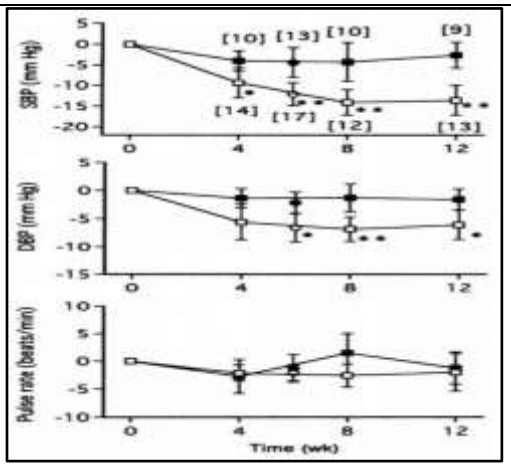


Figure No. 5 – Various classes of marine derived hypertensive

1.1. BIOACTIVE PEPTIDES:

Isolation of first ACE inhibitory peptide from snake venom .Many other ACE inhibitory peptides have been discovered in the enzymatic hydrolysates of various food proteins, including animal, plant & microorganism derived pepeptide[29]. These agents are described in table no. 1

Table No. 1- Bioactive peptides Antihypertensive Agents

Drug Name	Description	Effect on ECG	Reference
VPP and IPP:-	The milk casein derived tripeptide VPP and IPP, derived from Lactobacillus helveticus fermented milk or hydrolysate of milk casein were potent candidates , because they show antihypertensive effect in animals [30]. The blood pressure of subjects in the sour milk group who received ACE inhibitors tended to the lower than their baselines values		**[30-33]**

	by 26.5 mmHg and 20.5 mmHg at dose 0:33 mg VPP and 0.17 mg IPP. The tripeptides had an antihypertensive effect after a single oral administration in SHR. Recently, two meta-analysis on antihypertensive peptides derived from food sources have been performed. Pripp included 15 clinical trials in the analysis, of which 13 trials concerned milk-derived peptides; results was 4.6 & 2.2 mmHg. In SBP and DBP respectively. Xuetal had 12 trials in analyse& the intervention in all of them contained lactotripeptides significant decrease 4.8 mmHg in SBP and 2.2 mmHg in DBP were found in meta-analysis of Xuetal.		

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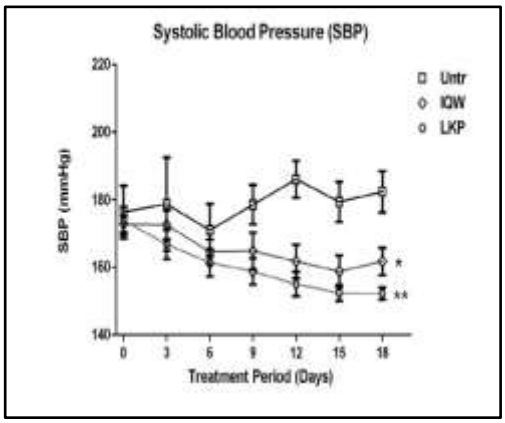
2)IQW and LKP :-	After 1-8 days of IQW and LKP treatment SBP was significantly decrease in both IQW and LKP groups to 161.40 ± 1.6 mmHg and 152.23 ±0.8 mmHg DBP with both IQW and LKP treatment also showed similar effects Angiotensin-II levels in untreated group were 23.96± 1.7 pglmL compared to 12.42± 0.7 pglmL and 12.62 ±1.04 in the IQW and LKP treated groups, respectively.		**[34]**

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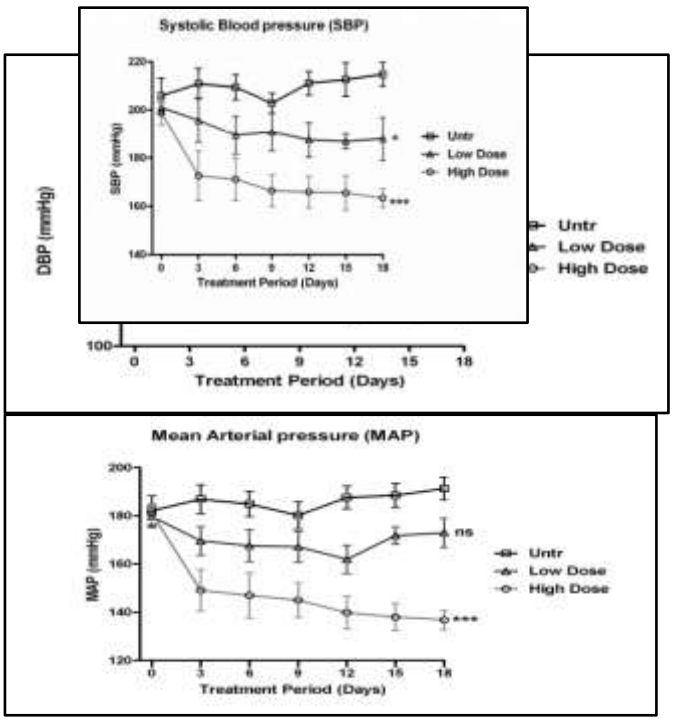
3)IRW :- Source- Eggwhite protein ovotransferrin .	IRW treatment decreased Ang III level from 35.3 ± 5.4 pglmL in untreated group to 14.2 ±2.1 pglmL in high dose treated group. The treatment also increased circulating levels of bradykinin which increases from 1.5± 0.2 mg/mL in untreated group to 3.10 ± 0.6 mg/mL in high dose treated group.These results suggest that IRW can act as an ACE inhibitor and thus decrease the production of Ang II as well as inhibit the degradation of bradykinin. After 18 days of IRW treatment, SBP was significantly decrease in both low and high dose groups to 191.4 ± 2.0 mmHg and 172.1 ± 4.7 mmHg respectively. Similar effects were observed in BBP with high dose treatment.		**[35]**

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1.2. CHITOOLIGOSACCHARIDEDERIVATIVE (COS):

Chitin is most abundant natural amino polysaccharide and is estimated to be produced annually almost as much as cellulose [36]. Researchers on chitosan and its oligomers have identified their potential to inhibit ACE activity [37]. further, studied ACE inhibitor activity of different COS and identified that chitosan trimer is more effective in lowering BP compared to other oligomers Luscher TF, Noll G. studied,among these hetero-COS, 50%. deacetylated and medium molecular weight (l,000 - 5,000) hetero-COS has exhibited highest ACE inhibitory activity with IC50 value of 1.22 mm/mL and the inhibition pattern is competitive according to the Lineweduer- Burk plots. chitosan trimer:

When the single oral dose (2.14 mm/kg similar to dose level of captopril known as strong ACE inhibitors) of chitosan trimer was given to 8 or 21 week aged SHRs, the BP reduction of both SHRs, in 4hrs were 27± 4.8 mmHg and 364.3 mmHg respectively. Therefore, it was suggested that chitosan trimer could be applicable as natural ACE inhibitor related to antihypertension[38].

1.3. PHLOROTONNINS:

Brown algal phenols attracts considerable attention due to the wide variety of biological activities and potential beneficial health effects of these so called phloratannins [39]. Phloroglucinol polymerization gives a family of important natural compounds the Phlorotannins which are highly hydrophilic and have a wide range of molecular sizes ranging between 126 Da and 650kDa[40]. The monomeric unit of phlorotanninsphloroglucinal, is assumed to be formed through the acetate malonate [Polyketide Pathway]. Their occurrence in brown seaweeds is very common, mainly in Ecklonia species and their various beneficial biological activities such as anticancer, antidiabetic, antiallergic, antioxidant and antihypertensive activities are also recognized.Inhibition of ACE is considered to be a useful therapeutic approach in the treatment of hypertension. Therefore, in the development of drugs to control high blood pressure, ACE inhibition has become an important activity. Assumed that phlorotannins in E. Cava might form some type of complex associated with proteins or glycoproteins and then inhibit the ACE activity [41-44].

Moreover, Athukoralo& Jeon have been reported the Flavourzyme enzymatic digest of E. cava is a potent ACE inhibitor, exhibited an IC50 of 0.3 ug/ml in-vitro and captopril a commercial antihypertensive exhibited an IC50 of 0.5ug/ml . Phenolic compounds inhibit ACE activity through sequestration of the enzyme metal factor, Zn^{2+}[45,46] .

Furthermore, the in-vitro ACE inhibitory activity of ten Korean seaweeds including, five phaeophyta [E.Cava, E. stolonifera, PelvetiaSiliqousa, HizikiaFusiforme, and Undaria pinnatifida] Four Rhodophyta (Gigartina tenella, Gelidiumamansii, chondriacrassicaulis, and Porphyratenera), and one chlorophyta (capsosiphonFulvescens) have been reported [47-49]. The ethanol extracts of E. Stolonifera, E.cava, P. Siliquosa. U pinnatifida. and G. tenella exhibited significant inhibitory properties against ACE at more than 50% inhibition of a concentration of 163.93 ug/ml [50,51].

Moreover, they have found that phlorotannins such as eckol, phlorofucofuroeckol A and dieckol which derived from E. stolonifera , have shown considerable inhibitory activity against ACE. Among them ,Phlorofucofuroeckol-A is the strongest ACE inhibitor with an ICso value of 12.74 µM [52-56}.

Table 2:- Phlorotannin Antihypertensive agents

Marine drug	Source	IC50value	Structure	Reference
Peptide Iy	Pyropiayezoensis , Porphyrayezoensis	2.96 uM	–	[57,58]

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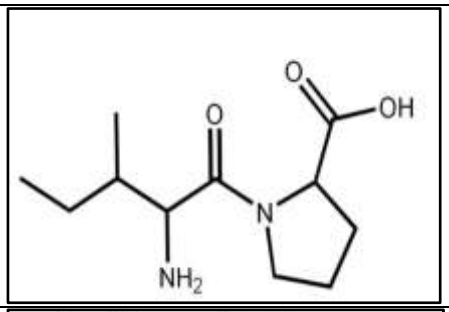
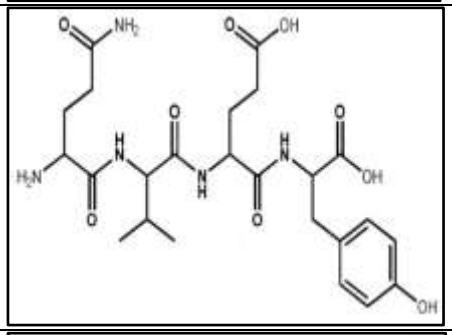
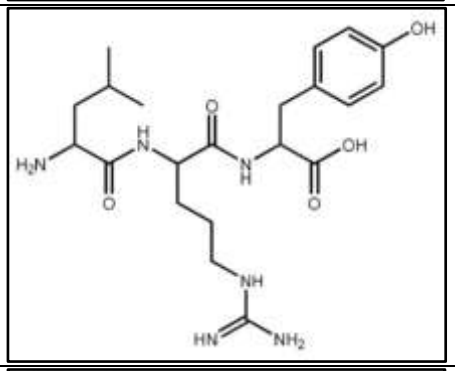
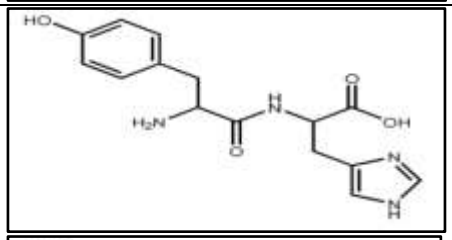
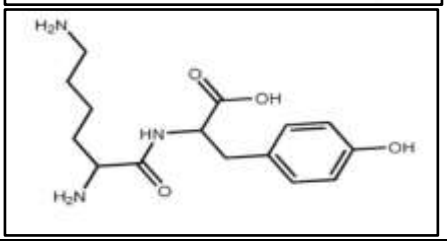
Peptide IP	Macroalgaundaria Pinnatifida (Marvey suringar) (ulva rigida C. Agardh protein)	2.96 uM		[59]
Peptide QVEY	GracilariopsisLemaneiformis	474.36 uM		[60]
PeptideLRY (furuta-et-al)	Dulse (palmariaPlanata)	5.06 uM		[61]
Peptide YH Peptide KY	Undaria, UndariaPinnatifida	5.1 uM 7.7 uM	 	[62,63]

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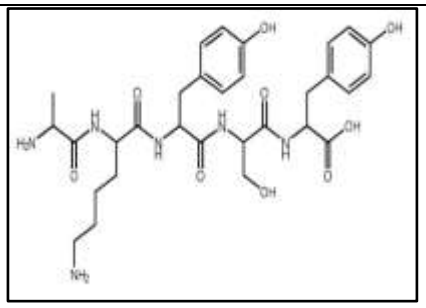
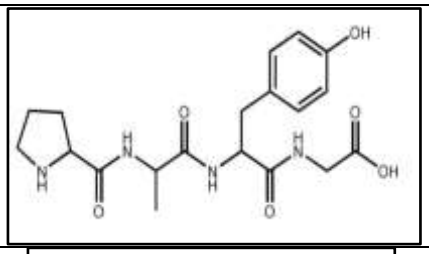
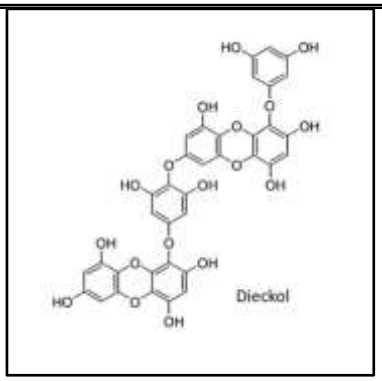
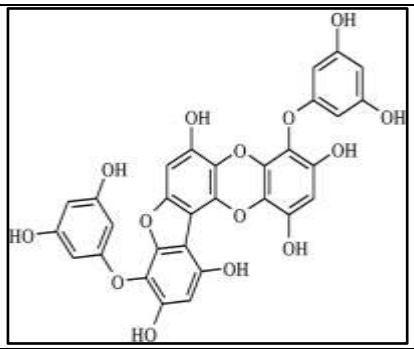
Peptide AKSY	PorphyraYezoensis	1.52 uM		[64-66]
Peptide PAFG	Enteromorpha clathrata	35.9 uM		[67]
Phlorotanins Dieckol	E.cava	1470 uM		[68,72]
PhloroFucoFuroeckol-A	E-cava E-stolinifera E-Kurome	12.74 uM		[68-74]

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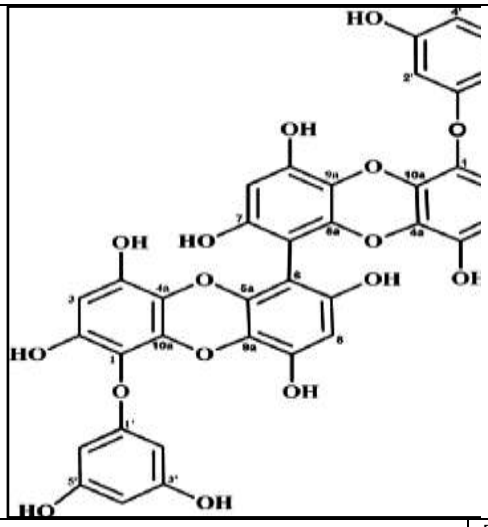
6,6'- Bieckol	E-cava Ishigeakamurae	0.42 uM		
COS chitosan Trimer	_	0.9 uM	_	[75]

IV. DISCUSSION:

The ultimate goal of this study was to investigate ACE inhibitory properties of proteolysatederived from marine sources,which can be used as alternative therapy for prevention and treatment of hypertension [54].

Recenty, much attention has been paid by consumers towards natural bioactive compounds as functional ingredients and hence it can be suggested that, marine derived ACE inhibitors are alternative tools that can be contribute consumer's well being, by being a part of novel neutraceuticals or pharmaceuticals replacing synthetic drugs [25]. Bioactive peptides derived from marine resources have potential ACE inhibitory activity and are considered as therapeutic agents to combat hypertension [55].

E. cava is a very Interesting research due to unique Phlorotannin derivatives with special bioactivities, including ACE inhibitory activity. It can be suggested that due to valuable biological functions with health beneficial effects, phlorotannins are much potential as active ingredients for preparation of neutraceuticals, cosmeceuticals and pharmaceuticals [56].

V. CONCLUSIONS :

This brief review on the marine drugs for hypertension here by concludes with a note that marine drugs play an important role by being a part of novel pharmaceuticals replacing synthetic drugs.

Marine Anti-hypertensive drugs are important weapons to fight against hypertension. The identification & design of new functional molecules, nutraceuticals and pharmaceuticals and bioactive compounds of marine source represent a big a promising approach in both intervention & prevention of inflammatory cardiovascular disease, hypertension .

This revision will provide inspiration for such detailed research, which can result in preclinical and clinical trials of specific seaweed compounds and boost their value as a resource of potential antihypertensive drugs.

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