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Biopeptides for Management of Chronic Non Communicable Diseases (A Review)

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Abstract: ***Chronic diseases have been on the increase due to modifications on lifestyle, inappropriate dietary habits, and certain disease conditions. Emphasis has been laid on the improvement of nutrition and the search for dietary compounds that could be beneficial in the prevention and management of chronic diseases. Favorable health effects have indeed been claimed for some peptides derived from dietary proteins, were able to positively affect cardiovascular, nervous, digestive, and immune systems. The activities of these peptides encompass antimicrobial properties, blood pressure-lowering effects, cholesterol-lowering ability, anti-tumor/anti-cancer, antioxidant activities and immunomodulatory effects. This review seeks to highlight the usefulness, efficacies, therapeutic applications, bio-properties and some mechanisms of action of selected peptides in management of chronic diseases. These may go in line of drawing the attention of researchers of developing countries to venture into areas of research especially on their verging wild portentous plants.***

Keywords: Biopeptides, Chronic Diseases, Dietary Proteins, Dietary Habits and Nutrition

1. Introduction

Chronic non-communicable diseases (NCDs) are usually of long duration, are generally slow progression and cannot be prevented by vaccines or completely cured by medication. The four main types' are cardiovascular diseases (like heart attacks and stroke), cancers, chronic respiratory diseases (such as chronic obstructed pulmonary disease and asthma) and diabetes [1]. Other chronic diseases include hypertension, arthritis, epilepsy, lipid disorders and chronic kidney disease. In middle and low income countries, deaths due to chronic diseases are greater than those associated with infectious diseases. Chronic diseases are by far the leading cause of mortality in the world, accounting for 60% of all deaths. Among Nigerian population, it accounts for approximately 24% of all deaths. In credibly, about 38 million people die every year from chronic diseases, Contrary to common perception 82% occur in low and middle income countries with the estimation of 52 million deaths by the year 2030 [2].

There is a complex relationship between nutrition and disease, insinuating that nutrient from food can aid in preventing and treating certain chronic diseases. A food can be considered as functional if, beyond its nutritional outcomes, it provides benefits upon one or more physiological functions, thus improving health while reducing the risk of illness. Bioactive peptides can be commercially sold as nutraceuticals and may exhibit more than one function, with the possibility that can be utilized in place of synthetic drugs in the treatment of chronic diseases. Bioactive peptides were demonstrated to ameliorates one form of chronic disease or the other [4]. However, the ability of bioactive peptides to exert a physiological effect *in vivo* is dependent on its bioavailability[5]. Unabsorbed one exerts their effects at GIT levels.

A database with more than 3000 bioactive peptides has been developed by Minkiewicz*et al.*[6] with antihypertensive peptides been the most occurring. A recent review article notes that digestion of milk proteins in the gastrointestinal tract results in the release of bioactive agents which may affect several physiological processes [7]. Microbial fermentation is one of the most promising strategies to generate bioactive peptides, hence genomic and proteomic characterization of new strains to predict their proteolytic profile is a challenging approach in view of obtaining functional food [8].

2. Effect of Chronic Disease on the Economy

Chronic diseases were assumed to be a difficulty affecting developed countries. Nevertheless, there has been interesting evidence to portend the fact that chronic diseases affect developing nations much more than developed nations [9]. The economic burden of chronic diseases in Nigeria reflects on the added cost of health care, complications leading to disability and even premature death [10]. The probability of dying between the ages of 30 and 70 years from the main four chronic diseases is 20%. [1]. Nigeria being a low-middle income country has an estimated population of 169,000, 000. Chronic diseases impede efforts to alleviate poverty and threaten the achievement of international development goals. The cost of treating diseases can be devastating, it weighs down on the individual and is a set back to the country's health system [1]. From 2011-2025, cumulative economic losses due to chronic diseases is estimated at US$ 7 trillion. WHO estimates the cost of reducing the global NCD burden is US$ 11.2 billion a year: an annual investment of US$ 1-3 per capita. High rates of death and disease, particularly in low- and middle-income countries, are a reflection of inadequate investment in cost-effective NCD (chronic diseases) interventions [1].

3. Biopeptides

Biopeptides ranged in size from 2 to 50 amino acid residues. Peptides/or proteins, control and direct all aspects of cellular function and coordinate most intercellular communication. Being the biological molecules with a wider range of

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chemical diversity, peptides and closely related analogues possess huge potential that can protect health and could reduce the risk of unforeseen side reactions [11]. Manufacture of bioactive peptides is usually carried out through hydrolysis using digestive, microbial, plant or animal enzymes, or by fermentation with lactic starter cultures. In some cases, a combination of these processes has proven crucial to obtain functional peptides of small size [12]. The type of bioactive peptides generated from a particular protein is dependent on two factors: (a) the primary sequence of the source protein and (b) the specificity of the enzyme(s) used to generate such peptides. Bioactivity of peptides depend on the structure [13].

4. Mechanism and Bioactivities of Biopeptides

With regard to the mechanisms underlying the physiological roles of bioactive peptides, a few involve action only upon certain receptors, whereas others are enzyme inhibitors; they may also regulate intestinal absorption, and exhibit antimicrobial or antioxidant activities. Food derived bioactive peptides unlike endogenous ones they show multifunctional features which can useful in management of chronic diseases [14]. The native structure has on C-terminal or N-terminal either aromatic or branched side chain. The presence of Prolin with certain amino acids possessing aliphatic structures is favored in the both ultimate positions (C-terminal and N-terminal amino acid residues).

The presence of amino acid with positive charge like "Arg" on the N-terminal and also the amino acid with negative charge like "Met" on the C-terminal of peptide chain contributed significantly to the ACE-inhibitory activity. Meanwhile, the immunomodulatory activity, Phe, Tyr and Pro are the most preferred amino acid residues, where the hydrophobic characteristic of Phe and hydrophilic affinity of Tyr on the N-terminal amino acid residues causes pronounced results towards immune response including stimulation of lymphocytes and modulating the cells growth. The biological function of peptide is determine by factors such as; size and sequence, hydrophobicity, and nature of amino acid located on the variable and constant sides of peptide fragment [15]. Various studies have indicated that these peptides are inhibitors of lipid peroxidation, scavengers of free radicals and chelators of transition metal ions [16]. In addition, it has been reported that ant oxidative peptides keep cells safe from damage by ROS through the induction of genes [17], it could be due to presence of Tyr, Trp, Met, Lys, Cys, and His are examples of amino acids that cause antioxidant activity. Amino acids with aromatic residues can donate protons to electron deficient radicals [18]. It is proposed that the antioxidative activity of His containing peptides is in relation with the hydrogen donating, lipid peroxyl radical trapping and/or the metal ion chelating ability of the imidazole group [16]. On the other hand, SH group in Cys has an independently crucial antioxidant action due to its direct interaction with radicals [19].

5. Common Dietary Plant and Animal Biopeptides

There has been increasing attention focused on identifying dietary compounds, from plants and animals, for promotion of specific health benefits [20]. Peptides from both plant and animal sources are usually not active within their parent protein, but becomes active after been released by enzymatic hydrolysis either during gastrointestinal digestion or during food processing. Of all the animal derived peptides, peptides derived from milk are the most studied and extensively researched [12]. Dietary peptides could be targeted for development of functional food products for infants, elderly and immune-compromised people as well as to improve performance and prevent diet-related chronic diseases [21].

Table 1: Plant and Animal Bioactive Peptides and their Effects

Plant Sources	*Biopeptides*	*Effects*
Soybean	Lunasin, Bowman Birk Inhibitor, Glycine Max, Glycinin, β-Conglycinin, Globulin	Anticancer [22]/ Antihypertensive/ Anti-Obesity, hypocholesterolemic[23][24]
Wheat	Gluten, Lunasin, Gliadin, B-conglycinin, Wheat albumin	Anti-diabetic/Immunomodulatory[25][26]/ antioxidant/ anticancinogenic[27]. Obesity [17] Antihypertensive [28]/Anti-Diabetics [29]
Rice Bran	Oryzatensin	Immunomodulatory/ Anticarcinogenic[30], Anti-Diabetic [31]
Peas cowpea, chickpea, Black eyed pea	Vicilin, Legumin, Hydrolysate	Antihyperpensive /Anticarcinogenic[32].
Corn	A-ZeinHydrolysate	Antihypertensive [33].
Barley	Lunasin	Anticarcinogenic[34]
Sunflower	Helianthininhydrolysate	Antihypertensive [35]
Rapeseed	Protein Isolate	Antihypertensive [36]
Winged Bean	Protein Isolate	Antihypertensive/ antioxidant [37]
Yam	Protein Isolate	Antihypertensive [38]
Rye	Lunasin	Anticarcinogenic[39]
Potato	Patain	Antihypertensive [40]
Garlic	Protein Isolate	Antihypertensive [41]
ANIMAL SOURCES	**BIOPEPTIDES**	**EFFECT**
Milk	α-Lactorphin, β-Lactorphin, α-Lactalbumin, β-Lactoglobulin, Lactoferin, Lactoferricin, β-Casomorphin 7 and β-Casomorphin 5.	Anti-diabetic [42]/ Antihypertensive [43]/ Immunomodulatoty/ Cytomodulatory / Opioid Agonist /Antagonist/ Antithrombotic/ Mineral Binding/ Anticarcinogenic/ Antioxidant/ Immunomodulatory[41]
Egg	Egg Yolk hydrolysates, Lysozyme, Ovumucin,	Antioxidative /Antihypertensive / Immunomodulatory/ Antimicrobial/Anticarcinogenic[44]

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Chicken	Chicken Connectin (Titin), fragment (Gallus gallus). Chicken Collagen	Antioxidative/Antihypertensive [45]
Fish and sea foods (Oyster, Chum salmon, Atlantic cod, Marine sponge) Giant Squid, AplidiumAlbicans, Red Sea Mosses Sole	Fish Protein Hydrolysates, Oyster Hydrolysates, Oligopeptide Preparation, Hemiasterlin, EsperaseHydrolysate, AplidinePardaxin	Antihypertensive/ Antioxidant/Cytostatic/ Immunomodulatory/Anti-Cancer/Cytotoxic/Anti-Cancer/Cytotoxic [46]
Meat	Carnosine, Anserine	Antihypertensive [47]

6. Antihypertensive Peptides

Hypertension defined by a blood pressure measurement of 90/140 mmHg or above is a major public health issue worldwide that affects nearly one fourth of the population. Hypertension is a major risk factor concomitant with cardiovascular disease (CVD) states such as coronary heart disease, peripheral artery disease and stroke, and kidney disease [48]. Hypertension can be improved with lifestyle choices such as regular exercise, heart-healthy eating, non-smoking, reducing sodium intake and reducing the level of stress [49]. For these reasons it is defined as a controllable risk factor of CVD. Its specific treatment will likely reduce the risk of incidence of cardiovascular diseases [50]. Using nutraceuticals with proven antihypertensive activity in humans, in association with a coherent improvement in diet and lifestyle, could represent a good compromise for the treatment of prehypertensive patients and an excellent adjuvant, together with the pharmacological treatment, for hypertensive patients [51] Experimental evidence – including spontaneous hypertensive rats and human studies, claimed that oxidative stress is one of the causes of hypertension and several vascular diseases, via increase production of reactive oxygen species and reduction of NO synthesis and bioavailability of antioxidants [52]. ACE (i.e. a dipeptidylcarboxypeptidase) is an ubiquitous enzyme that plays a basic role in regulation of peripheral blood pressure via the renin-angiotensin system (RAS) and the kinin-nitric oxide system (KNOS). ACE inhibition causes dilation of the arterial walls (vasodilation) which leads to lowering of Blood Pressure (BP). However, it is not yet known whether this is the main mechanism followed *in vivo* or whether there are a number of other BP control mechanisms involved [53]. There are several synthetic ACE inhibitors such as captopril, Lisinopril, and enalapril that are currently being used for management of hypertension. However, their use is associated with a range of side effects including cough, skin rashes, hypotension, loss of taste, angioedema reduced renal function and fetal abnormalities [53]. Many biopeptides have been found to have antihypertensive properties *in vivo*. Food proteins such as the casein and whey protein components of milk, meat, egg, marine and meat proteins have all been found to contain peptides with potential antihypertensive properties within their primary sequences. These peptides may become active when released through enzymatic/bacterial hydrolysis [35]. It has been proposed that bioactive peptides may have higher tissue affinities and may be subjected to a slower elimination than captopril [45]. There are other regulatory pathways of BP control, independent of ACE that are also potential targets for the action of antihypertensive peptides [47].

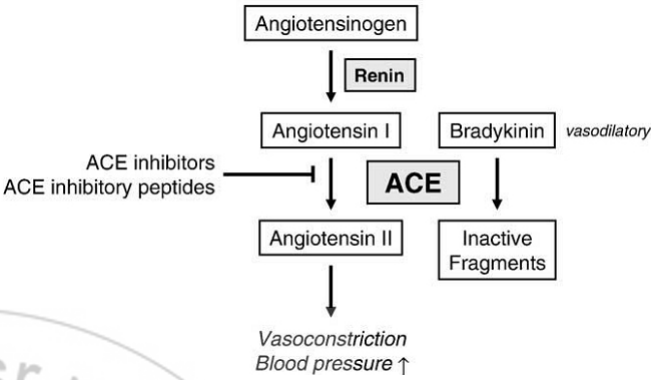

Figure 1: The renin-angiotensin system [16]

Calcium Channel Blocking Effects

It has been shown that peptides can act as calcium channel blockers as Trp-His induced the most potent vasodilation among 67 synthetic di-and tripeptides. It was also shown that His-Arg-Trp, at a concentration of 100 μM, caused a significant reduction in intracellular Ca2+ concentration [54]. Another study reported a similar result with Trp-His which was also found to block L-type Ca2+ channels. Trp-His at 300 μM elicited an intracellular Ca2+ reduction of 23 % in 8 week-old male Wistar rat thoracic aortae smooth muscle cells [55].

Opioid Peptide Vasorelaxive Effects

Food-derived peptides have also been found to be sources of opioid like-activities. These peptides bind to opioid receptors to produce morphine-like effects. Nurmine*et al.* [56] found an antihypertensive effect on oral administration of the tetrapeptide, α-lactorphin (Tyr-Gly-Leu-Phe), to SHR and to normotensive. The casein-derived peptide casoxin D (Tyr-Val-Pro-Phe-Pro-Pro-Phe) has also been reported to have normotensive effect via opioid receptors. Anti-opioid and vasorelaxing effects were mediated by the opioid μ-receptor and BK B1-receptor, respectively [57].

Endothelin-1 and Endothelin Converting Enzyme (ECE) Inhibition

It has been found that food proteins have the ability to act as inhibitors of ECE. Okitsu*et al.* [58] found ECE inhibitory peptides up to 45 and 40 % of ECE activity could be inhibited with the beef and bonito peptides, respectively. A second study showed that the ACE-inhibitory peptide Ala-Leu-Pro-Met-His-Ile-Arg, released through tryptic digestion of bovine β-lactoglobulin, can inhibit the release of ET-1 in cultured porcine aortic endothelial cells (PAECs) by 20%. The study concluded that the ET-1 reduction may be due to indirect reduction of ET-release by ACE inhibition through the BK pathway, rather than direct action on ET-1 by the peptide [59].

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Table 2: ACE Inhibitory Peptides With In Vivo Antihypertensive Effects [17]

Origin	*Sequence/name*	*IC50 (µmol/L)*	*Subjects*	*Reference*
Milk (β-casein)	VPP	9.0	SHR, humans	[60]
	IPP	5.0		
Milk (β-lactoglobulin)	PA (β-lactosin A)	141.0	SHR	[61]
	ALPM (β-lactosin B)	928.0		
Fish (sardine muscle)	VY	26.0	SHR, humans	[62]
Fish (bonito muscle)	LKPNM	2.4	SHR	[46]
	LKP	0.32		
Meat (chicken muscle)	LKP	0.32	SHR	[44]
	IKW	0.21		
	LAP	3.5		
Meat (porcine muscle)	MNPPK	945.5	SHR	[47]
	ITTNP	549.0		
Egg (ovalbumin)	LW	6.8	SHR	[44]
Soy (glycinin)	NWGPLV	21	SHR	[63]
Wheat (gliadin)	IAP	2.7	SHR	[28]

7. Cardiovascular Protective Peptides

Bioactive peptides have been shown to possess properties that may be advantageous to cardiovascular health. These effects include the lowering of blood pressure and lipid levels as well as reducing free radical formation. The most frequent cardiovascular diseases are coronary heart disease, peripheral artery disease and stroke. The World Health Organization estimates that by 2020, heart disease and stroke will have surpassed infectious diseases to become the leading cause of death and disability worldwide [64]. Life style and diet improvement has been the present area of concentration with regards to reduction of cardiovascular disease and risks associated with it. There is an assertion that increased consumption of protein, particularly plant protein, may further lower the risk of hypertension and CVD [65]. In blood vessels, oxidant stress has deleterious consequences for basal vascular function. Then, the cellular mechanisms that result in vascular redox imbalance leading to an increase in oxidant stress are implicated in the pathogenesis of vascular disease ([66]. In pathological conditions, ROS attack nucleic acids (DNA or RNA), proteins, and unsaturated fatty acids and aggravate cellular damage [67]. Bioactive peptides are an attractive option for treating and managing endothelial dysfunction and its complications, based on potential modulation of oxidative stress, inflammation and RAS over activity [68].

A novel fish protein extracted from marine fish (Limandaaspera) was found to have anticoagulant and antiplatelet properties, inhibited the activated coagulation factor XII (FXIIa) by forming an inactive complex regardless of Zn2+ mediation, and arrest platelet aggregation which indicates that it is able to inhibit thrombosis in vitro [16]. A positive correlation between raised plasma lipids with atherosclerosis on one hand and coronary heart disease on the other has been established. More specifically, LDL-cholesterol is positively correlated whereas HDL-cholesterol is negatively correlated with cardiovascular diseases. Atherosclerosis is characterized by deposition of cholesteryl esters and other lipids in the intima of the arterial walls often leading to hardening of coronary arteries and cerebral blood vessels. Two bioactive peptides with sequence (LDAVNR; 686Da) and (MMLDF; 655Da) purified from gastric enzymatic hydrolysate of Spirulina maxima were found to have protective effects against early atherosclerotic responses induced by histamine (a potent inflammatory mediator, known to cause the pathogenesis of atherosclerosis) in endothelial cells suggesting that peptides are effective to suppress histamine-induced endothelial cell activation that may contribute to the prevention of early atherosclerosis [69]. Liu *et al.* [70] found that purified patatin exert antioxidant or antiradical activity in various *in vitro* tests, such as radical, scavenging activity assay and protection against hydroxyl radical-induced calf thymus DNA damage. Potato protein hydrolysates showed antioxidant activity [71]

8. Antioxidant Activity

Continuous generation of free radicals (ROS) can lead to serious damage to biological macromolecules and severe tissue injury. Intervention of endogenous antioxidant defense mechanisms helps to fight and reduce the damage caused by oxidative stress. Dietary consumption of antioxidants appears to provide further benefits to the endogenous antioxidant defense strategies in the fight against oxidative stress [72]. Caseins and casein-derived peptides were found to inhibit lipoxygenase, an enzyme which catalyzes the peroxidation of unsaturated fatty acids such as linoleic acid [73]. The antioxidant properties of these peptides have been suggested to be due to metal ion chelation, free radical scavenging and singulet oxygen quenching [74]. The antioxidant activity of whey-derived peptides and whey itself has been linked with the presence of cysteine-rich proteins which promote the synthesis of glutathione, a potent intracellular antioxidant [75]. Glutathione is involved in the detoxification process as toxic amounts of peroxides and free radicals produced in the cells are scavenged by glutathione peroxidase.

Peroxidase

$$2\ GSH + H_2O_2 \text{ ---------- } G - s - s - G + 2\ H_2O$$

Antioxidant activity has been found specifically in whey proteins, probably via scavenging of such radicals via Tyr and Cys amino acid residues – which is predominantly based on proton-coupled single electron or hydrogen atom transfer mechanisms; or else chelation of transition metals [76]. Studies have revealed that some peptides with antioxidant properties are released from food sources such as milk casein [77] whey protein [43], egg [78] and soy protein [79]. One study revealed than certain amino acid

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sequences are responsible for the antioxidant activity of peptides [77]. High amounts of histidine and some hydrophobic amino acids are related to the antioxidant potency [80]. One study demonstrated that salmon myofibrillar and sarcoplasmic protein fractions as potential sources of antioxidant peptides that could be released in the gastrointestinal tract but their amino acid sequence and quantification vary [81]**.** Many peptide hormones contain carboxyl terminal amide which is derived from terminal glycine. Hydroxylation of glycine is carried out by peptidylglycine hydroxylase which requires vitamin C. Antioxidants prevents and reduces the risk of chronic diseases such as cancer, cataract, and coronary heart diseases. Chen *et al.*,[79] designed 28 synthetic peptides following the structure of an antioxidative peptide (Leu-Leu-Pro-His-His) from digestion of soybean protein conglycinin. According to the results, Pro-His-His sequence displayed the greatest antioxidative activity among all tested peptides. It has been shown that certain amino acids can exert higher antioxidativeproperties when they are incorporated in dipeptides [82] and some peptide bond or its structural conformation can reduce the antioxidant activity of the constituent amino acids [43]. Amino acids with aromatic residues can donate protons to electron deficient radicals. On the other hand, SH group in Cys has an independently crucial antioxidant action due to its direct interaction with radicals [19]. In addition to the amino acid composition, their correct position in peptide sequence plays an important role in antioxidative properties of peptides. The antioxidant activity of a peptide was more dependent on His-His segment in the Leu-Leu-Pro-His-His-domain and its activity was decreased by removing a His residue from the C-terminus. Moreover, substitution of L-His by D-His in a peptide leads reduction of activity [79]. They concluded that the correct position of imidazole group is the key factor influencing the antioxidant activity. [83]studiedantioxidative activity of peptides created in two tripeptide libraries. According to their results, for the 114 peptides containing either His or Tyr residues, tripeptides containing two Tyr residues showed higher activity in the linoleic acid peroxidation system than tripeptides containing two His residues. Further, Tyr-His-Tyr showed strong synergistic effects with phenolic antioxidants.

Table 3: Some Antioxidative Peptides And Amino Acid Sequence from Biopep Database [6]

Peptides	*Seq.*	*Activity*	*ID*	*No. of aa*	*References*	*Peptides*	*Seq.*	*Activity*	*ID*	*No. of aa*	*references*
A.ox. P.	YHH	A. OX.	3297	3	[79]	A ox. P.	HHLP	A. OX.	3308	4	[79]
A.ox. P.	HHPL	A. OX.	3298	4	[79]	A ox. P.	LPYY	A. OX.	3309	4	[79]
A.ox. P.	LHPH	A. OX.	3299	4	[79]	A ox. P.	LYPY	A. OX.	3310	4	[79]
A.ox. P.	PHH	A. OX.	3300	3	[79]	A ox. P.	LANAK	A. OX.	8994	5	[84]
A.ox. P.	HLH	A. OX.	3301	3	[79]	A.ox. P.	PSLVGRPP VGKLTL	A. OX.	8995	14	[84]
A.ox. P.	LHH	A. OX.	3302	3	[79]	A.ox. P.	VKVLLEHPVL	A. OX.	8996	10	[84]
A.ox. P.	HPLH	A. OX.	3303	4	[79]	A.ox. P.	LLPF	A. OX.	8997	4	[84]
A.ox. P.	LH	A. OX.	3305	2	[79]	A.ox. P.	FLPE	A. OX.	8998	4	[84]
A.ox. P.	HPHL	A. OX.	3306	4	[79]	A.ox. P.	AWFS	A. OX.	8999	4	[84]
A ox. P.	PYY	A. OX.	3307	3	[79]	A.ox. P.	YGIKVGYAIP	A. OX.	9000	10	[84]

Abbreviations: A ox P. - Antioxidative Peptides, A. OX. - Antioxidant, Seq. - Sequence, aa – Amino Acid

9. Antihyperlipidemic Peptides

Hypercholesterolemia is associated with atherosclerosis and coronary heart disease. A study conducted to elucidate the mechanism underlying the inhibition of cholesterol and bile acid absorption following fish protein intake on rats for 4 weeks found that fish protein consumption decreased serum and liver cholesterol content and increased fecal cholesterol and bile acid excretion and simultaneously increased fecal nitrogen excretion though the mechanism underlying this effect is not yet fully understood. [85]. In addition, fish protein hydrolyzate prepared by in vitro digestion had lower micellar solubility of cholesterol and higher binding capacity for bile acids compared with casein hydrolyzate. These results suggest that the hypocholesterolemic effect of fish protein is mediated by increased fecal cholesterol and bile acid excretion, which is due to the digestion products of fish protein having reduced micellar solubility of cholesterol and increased bile acid binding capacity [85]. The majority of studies that have evaluated the hypocholesterolemic effects of legume consumption examined soybeans [86]. Elevation in plasma cholesterol is observed in people with smoking, abdominal obesity, Lack of exercise, stress, high blood pressure, consumption of soft water etc. Therefore, adequate changes in the lifestyles will bring down plasma cholesterol. Vitamin E, an essential membrane structure antioxidant prevents the peroxidation of polyunsaturated fatty acids (PUFA) in various tissues and membrane. Vitamin E being lipophilic is found in association with lipoproteins, fat deposits, cellular membranes and acts as a scavenger and gets itself oxidized (to quinone form) by free radicals (R) and spares PUFA. Some peptides derived from hydrolyzed food proteins exert antioxidant activities against enzymatic (lipoxygenase- mediated) and nonenzymatic peroxidation of lipids and essential fatty acids [79]. In addition, a meta-analysis conducted on dietary proteins showed that diet rich in legumes, such as a variety of beans, peas, and some seeds other than soy decreases total and low-density lipoprotein (LDL) cholesterol [87].

10. Obesity and Diabetes Mellitus

Obesity is an abnormal increase in the body weight due to excessive fat deposition. Obesity is associated with many health complications such as type ll diabetes, CHD, hypertension, stroke, arthritis, gall bladder disease. Hence, treatment of obesity assumes a lot of significance in the prevention of these diseases. One study showed that rice bran peptides could be useful as natural alternatives to aid in the management of chronic disease states like obesity [88]. Over 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. Overweight and obesity,

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together with physical inactivity, are estimated to cause a large proportion of the global diabetes increase. Diabetes can damage the heart, blood vessels, eyes, kidneys and nerves, leading to disability and premature death. Over the past decade, diabetes prevalence has risen faster in low- and middle-income countries than in high income countries [2]. The use of peptides and proteins for treating autoimmune diseases, including Type 1 Diabetes, has been increasing steadily. Antigenic peptides and bifunctional peptide inhibitors (BPI) have been explored for altering the differentiation and proliferation of T cells to regulatory cells to prevent the development of diabetes. These molecules are developed to affect immune cells in an antigenic-specific manner; thus, they do not suppress the general immune response for fighting infections [89]. One study conducted by [90] found that treatment with oligopeptides from marine salmon skin significantly reduced Fasting blood glucose in diabetic rats and concluded that the antidiabetic activity may be mediated by down-regulating T2DM-related oxidative stress and inflammation, protecting the pancreatic β-cells from apoptosis. Alpha-glucosidase and dipeptidyl peptidase IV (DPP-IV) enzymes play a significant role in development of T2D. Hence, reduction or inhibition of their activity can be one of the important strategies in management of T2D. Studies in the field of bioactive peptides have shown that dietary proteins could be natural source of alpha-glucosidase and DPP-IV inhibitory peptides [91]. Exogenous GLP-1 has considerable insulinotropic potency in Type 2 diabetes. Besides being an insulin secretagogue, this hormone combines several antidiabetic effects including suppression of glucagon secretion, delay of gastric emptying and decrease in food intake. Furthermore, evidence from animal models suggests that GLP-1, unlike other insulin secretagogues that are currently used for the treatment of Type 2 diabetes, also increases β-cell mass. This effect might be particularly helpful to prevent the diabetic islet cells from early decompensation[92]. GLP-1 (Glucagon-like peptide-1 (7-36) amide (GLP-1))-based therapy possesses a number of potential advantages over existing agents for the treatment of Type 2 diabetes, particularly in terms of the effects on pancreatic B-cell growth, potential weight loss and hypoglycaemic risk. Available data shows that DPP-IV-resistant GLP-1 analogues and DPP-IV inhibitors are remarkably efficacious and are well tolerated, with transient nausea and vomiting being the commonest reported side-effect [93]. Emerging peptide technologies such as multifunctional peptides, cell penetrating peptides and peptide drug conjugates, will help broaden the applicability of peptides as therapeutics. Peptides offer enormous growth potential as future therapeutics for the treatment of unmet medical conditions [94] such as diabetes. Milk protein-derived peptides with alpha-glucosidase and DPP-IV inhibitory traits potentially regulate the post-prandial hyperglycemia in healthy and T2D subjects by inhibiting both the inactivation of the incretin hormones and the carbohydrate hydrolyzing enzymes [91].

Gastric inhibitory polypeptide /glucose -dependent insulinotropic polypeptide (GIP) plays a key role in glucose-stimulated insulin secretion and the regulation of post-prandial nutrient homeostasis. GIP, like GLP-1, is rapidly degraded in the blood by dipeptidyl peptidase 4 (DPPIV) to the inactive N-terminally truncated GIP (3-42). Like GLP-1, N-terminal modification of GIP prevents degradation by DPPIV and prolongs biological activity, facilitating the use of such stable analogues for treatment of diabetes, obesity and related metabolic disorders. Although GIP agonists promote glucose lowering by acute actions on beta cells, there is now increasing awareness of a beneficial effect of GIP antagonism in diet-induced obesity, leading to amelioration of insulin resistance, body weight loss and preferential burning of fat. One study found that treatment with Marine Collagen Peptides (MCP) from fish hydrolysates improved glucose and lipid metabolism and may help control hyperglycemia in T2DM patients and concluded such hyperglycemia may be mediated by activating PPARs, leading to down-regulation of chronic inflammation and up-regulation of bradykinin and adiponectin production. These findings suggest that MCPs, which are relatively safe, may be used in addition to regular antihyperglycemic therapy for intervention in T2DM patients [95].

Table 4: Some Antidiabetic Peptide and their Amino Acid Sequence from Biopep Database [6]

Peptide	*Seq.*	*Effect*	*ID*	*No of aa*	*References*	*Peptide*	*Seq.*	*Effect*	*ID*	*No of aa*	*References*
DPP IV in	GP	A. D	3169	2	[96]	DPP IV in	LL	A. D	3182	2	[98]
DPP IV in	PP	A. D	3170	2	[31]	DPP IV in	W	A. D	3183	1	[98]
DPP IV in	MP	A. D	3171	2	[31]	DPP IV in	HA	A. D	3183	2	[98]
DPP IV in	VA	A. D	3172	2	[97]	DPP IV in	WD	A. D	8930	2	[99]
DPP IV in	KA	A. D	3174	2	[96]	DPP IV in	WH	A. D	8931	2	[99]
DPP IV in	AP	A. D	3177	2	[31]	DPP IV in	YA	A. D	8932	2	[99]
DPP IV in	GPPPPGPPPI	A.D	3178	10	[42]	DPP IV in	VQ	A. D	8925	2	[99]
DPP IV in	PA	A. D	3179	2	[98]	DPP IV in	VS	A. D	8926	2	[99]
DPP IV in	LP	A.D.	3180	2	[31]	DPP IV in	VT	A. D	8927	2	[99]
DPP IV in	VP	A. D	3181	2	[31]	DPP IV in	VW	A. D	8928	2	[99]

Abbreviations: DPP IV in. - Dipeptidyl Peptidase IV Inhibitor, A.D. - Anti-diabetic, Seq – Sequence. No. of aa- number of amino acids

11. Cancer

Cancer is characterized by uncontrolled division of cells and the ability of these cells to invade other tissues leading to the formation of tumor mass, vascularization, and metastasis [100]. Combination therapy is an important strategy to fight cancer as just one method may not be efficient enough to cure the disease completely or prevent recurrence [101]. New advances in using peptides to treat different types of cancer, indicating that peptides could be used as an ideal immunotherapy method in treating cancer due to the novel advantages of peptides, such as specifically targeting tumor cells, decreased toxicity and efficient immunoreaction. The development of identifying and synthesizing novel peptides

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could provide a promising choice to patients with cancer [102]. Features of tumors that could facilitate the targeting and uptake of peptides include the increased negative charge of the plasma membrane of tumor cells and the leakiness of the tumor vasculature. Taking advantage of tumor-specific membrane differences, AMPs (Anti-microbial peptides) are proving to be effective anti-cancer agents that cause cell lysis and induce apoptosis, with a lower risk of developing resistance. Similarly, pore-forming cytotoxic peptides based on transmembrane sequences from apoptosis-inducing Bcl-2 (B-Cell Lymphoma 2) proteins or BH3 (B-Cell Lymphoma Homology domain 3) peptides/mimetics, which interfere with the binding of anti- and pro-apoptotic Bcl-2 proteins, can promote mitochondrial-mediated apoptosis of tumor cells, specifically those overexpressing pro-survival proteins. However, neither AMPs nor Bcl-2 family-derived peptides can directly target tumors *via* tumor-specific markers. Such targeting is mediated by TTPs (Tumor Targeting Peptides) that in most part do not have inherent cytotoxic activity but can deliver drugs or cytotoxic peptides directly to tumors. Among the most effective TTPs are those bearing RGD (Arginine/Glycine/Aspartic Acid or NGR (Asparagine/ Glycine/ Arginine) motifs that bind to receptors overexpressed on endothelial cells of tumor vasculature. Modifications of these TTPs can elicit changes in the tumor environment to promote the accumulation of higher concentrations of anti-cancer agents or drugs within tumors. The combinations of TTPs with cytotoxic peptides or drugs in nanoparticles or as part of a self-assembled complex could produce the "magic bullet" that specifically targets and eradicates tumor cells [103]. The promising results obtained in preclinical studies indicate that Cell-Penetrating Peptides (CPPs) may have a significant role in the development of novel anticancer therapeutics. CPP effectiveness in penetrating tissues and the cell membrane, particularly in combination with established drug delivery technologies, could offer a framework to enable the development of CPP-based therapeutics, their implementation in clinical studies, and optimism for their eventual application in the cancer clinic [104].

Lunasin a 43-amino acid peptide with a sequence SKWQHQQDSCRKQLQGVNLTPCEKHIMEKIQGRGD DDDDDDDD, has been found to be useful for cancer prevention and therapy. Bioavailability studies carried out with animals have confirmed that 35% of ingested lunasin reaches the target tissues and organs in an intact and active form [27]. Similarly, lactoferricin has been demonstrated, by cell culture and animal models, to exert anticarcinogenic properties against different types of cancer, such as leukemia, colon, breast, and lung cancer, among others [105]. The high Cys and Met content can boost the body's antioxidant levels, potentially stabilizing DNA during cell division and reducing risk of certain forms of colon cancer [106]. *In vitro* studies have reported the potential of Bowman Birk Inhibitor (BBI) as chemopreventive agents in breast cancer. Soybean BBI has been shown to inhibit, specifically and potently, the chymotrypsin-like proteasomal activity in MCF7 breast cancer cells *in vitro* and *in vivo* [107]. BBI from black-eye pea (*Vignaunguiculata*) induced apoptotic cell death in MCF7 breast cancer cells associated with severe cell morphological alterations, including the alteration of the nuclear morphology, plasma membrane fragmentation, cytoplasm disorganization, presence of double-membrane vesicles, mitochondrial swelling and lysosome membrane permeabilization[32]. Milk contains a number of proteins and peptides exhibiting chemopreventive properties. Lactoferrin has shown inhibitory action on cancer cells proliferation, as well as antimicrobial, anti-inflammatory and antioxidant abilities [108].

Epidemiological studies have shown an inverse association between soy intake and the risk of developing prostate cancer [109]. Preclinical and clinical studies have shown the potential chemopreventive properties of BBI in prostate cancer and to decrease the growth, invasion and clonogenic survival of several human prostate cancer cells [110]. The protective effect of BBI from soybean or those from perennial horsegram (*Macrotymolaaxillare*) against inflammation and development of pre-neoplastic lesions induced in the dimethylhydrazine (DMH) mouse model has been reported [111]. Due to lack of toxicity as well as the reported anti-inflammatory properties in animals, the potential for BBIC to benefit patients with ulcerative colitis has been evaluated. BBI have been linked to a possible protective effect against both inflammatory disorders and cancer development Soybean BBI have been reported to be effective at concentrations as low as 10 mg/100 g diet, in reducing the incidence and frequency of colorectal tumors, in studies based on the DMH rat model, where no adverse effect of BBI was documented for animal growth or organ physiology [112].

Table 5: Some Anticancer Peptides and their Amino Acid Sequences From Biopep Data Base [6]

Peptides	*Sequence*	*Activity*	*ID*	*No of Amino Acid Sequence*	*Reference*
Citropin 1.1 From Australian Frog	GLFDVIKKVASVIGGL~	Anticancer	3910	17	[113]
Citropin 1.1 From Australian Frog	GLFDVIKKVASVIGGLG	Anticancer	3911	17	[113]
Uperin 3.6	GVIDAAKKVVNVLKNLF~	Anticancer	3912	18	[113]
Uperin 3.6	GVIDAAKKVVNVLKNLFG	Anticancer	3913	18	[113]
Aurein 1.2	GLFDIIKKIAESF	Anticancer	5455	13	[113]
Aurein 2.4	GLFDIVKKVVGTIAGL	Anticancer	5460	16	[113]
Aurein 3.2	GLFDIVKKIAGHIASSI	Anticancer	5463	17	[113]
Aurein 3.3.1	GLFDIVKKIAGHIVSSI	Anticancer	5464	17	[113]
Aurein 2.5	GLFDIVKKVVGAFGSL	Anticancer	7045	16	[113]
Aurein 2.6	GLFDIAKKVIGVIGSL	Anticancer	7046	16	[113]
Anticancer Peptide	EQRPR	Anticancer	8252	5	[30]
Anticancer Peptide	PMDYMVT	Anticancer	8276	7	[114]
Anticancer Peptide	LPTSEAAKY	Anticancer	8277	9	[114]
Anticancer Peptide	FFVAPFPEVFGK	Anticancer	8311	12	[115]

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Anticancer Peptide	ENLLRFFVAPFPEVFG	Anticancer	8312	16	[115]
Anticancer Peptide	NENLLRFFVAPFPEVFG	Anticancer	8313	13	[115]
Anticancer Peptide	LNENLLRFFVAPFPEVFG	Anticancer	8314	18	[115]
Anticancer Peptide	NLHLPLPLL	Anticancer	8315	9	[115]
Anticancer Peptide	ENLHLPLPLL	Anticancer	8316	10	[115]
Anticancer Peptide	VENLHLPLPLL	Anticancer	8317	11	[115]

12. Conclusion

The bioactive capabilities of most bioactive peptides have mainly been studied by invitro assay methods and by logical inference, this insinuates that invivo studies is necessary to determine the complex mechanism involve in the biologically plausible benefits of bioactive peptides. With vast knowledge about food-encrypted peptides and the potential health benefits they can offer, biopeptides can serve as valuable therapies for the management of chronic diseases. Availability of more sophisticated and modern research facilities together with homology-based identification of potential bioactive peptide domains on protein sequences open a broader way for the discovery of encrypted peptides that may be essential for targeting the right proteins. There is a great potential in the application and utilization of bioactive peptides in the suppression, management and treatment of chronic diseases and also boosting the immune system against other types of diseases. Food related diseases, such as cardiovascular disease, diabetes, cancer and obesity is increasing with more complications leading to disability and death, there is need for more research on food derived products that offer nutritional value as well as functional and health benefits. There is the requisition for more clinical trials and more research involving cell lines to access the efficacy and safety in clinical practice.

13. Conflict of Interest

The authors declare no conflict of interest

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