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Cholesterol Metabolism and Its Regulation by Functional Foods

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Abstract— *Currently, obesity is considered an epidemic due to the disruptions it causes to health, highlighting the incensement in cardiovascular diseases associated with cholesterol and low-density lipoprotein (LDL) high concentrations. However, cholesterol is also involved in various metabolic and structural functions vital to human biology. This homeostasis can be modified by external factors such as medications or by internal factors such as diseases or metabolic changes generated by the type of diet at which each person is exposed.In this sense, the research points to the knowledge of functional foods, which provide beneficial health effects and prevent the risk of disease. It has been reported that hypocholesterolemic type bioactive peptides obtained by enzymatic hydrolysis of various seeds such as soybeans, rice and sunflower. A similar effect is observed with unsaturated fatty acids, which have antithrombotic and antiarrhythmic effects, prevent atherosclerosis, contribute to decrease blood pressure and reduce the concentration of triglycerides, total cholesterol and lipoproteins of very low-density lipoprotein (VLDL) in plasma. Therefore, these compounds incorporated in foods are considered functional, since its bioactive potential could be used to prevent cardiovascular disease.*

Keywords— cholesterol, functional foods, hypocholesterolemic.

I. INTRODUCTION

Obesity is a chronic disease originated by various causes and with numerous complications, characterized by body fat excess that threatens the health of the individual. Its growth isconsidered a risk worldwide, an epidemic. In 2013, the obesity in men was 36.9% and 38% in women[1]. In 2030, the number of obesity people will increase at 573 million[2]. Also, obesity carries high concentrations of total cholesterol and of the one found in the low-density lipoproteins (LDL), which are strongly associated with a risk increment in cardiovascular diseases, for this reason a reduction in total cholesterol and LDL in hypercholesterolemic individuals reduces the incidence of these diseases[3].

II. CHOLESTEROL AND ITSMETABOLISM

Cholesterol is involved in various metabolic and structural processes that are vital to human biology. Its homeostasis is strict and controlled differentially[4]. Under physiological conditions, the organism obtains cholesterol from the diet (daily intake), the absorption rate and cell synthesis. The average daily intake provides 300-500 mg, the bile of 800 to 1200 mg and the epithelium of the intestinal mucosa contributes with 300 mg per day. The average rate of absorption of cholesterol in the intestine, specifically in the duodenum and jejunum, individually varies between 30 and 70%[5]. At plasma level, cholesterol levels are regulated by the endogenous synthesis, secretion and catabolism of several plasma lipoproteins[6]. It is noteworthy that the liver contributes with 20% of the overall input of cholesterol and is the organ that maintains homeostasis by five mechanisms: a) By the 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGCoAR); b) The consumption through low-density lipoprotein receptors (LDLr), c) The release of lipoproteins in the blood, d) The esterification and storage, e) The degradation/conversion into bile salts[4,7].However, this homeostasis can be modified by external factors such as medications or by internal factors such as diseases and metabolic changes.

In the enterocyte, approximately half of the cholesterol molecules are introduced into the endoplasmic reticulum (ER), where this biomolecule is esterified by the corresponding acyltransferase (ACAT) before its incorporation into the nascent chylomicron[8].Chylomicrons release triglycerides to peripheral tissues by the hydrolysis of lipoprotein lipase (LPL) through vascular pathway and its abundant in cholesterol remnants are taken up by hepatocytes for the synthesis of bile acid or are incorporated into very low-density lipoproteins (VLDL), which are released into the systemic circulation. VLDL are also assembled in the

liver and they distribute triglyceridesand cholesterol to peripheral cells, where they become LDL after partial depletion has occurred in triglycerides, due to vascular LPL activity. LDL are considered "bad" cholesterol because it causes the release of cholesterol in peripheral tissues. In contrast, high-density lipoprotein (HDL) contains A1 and A2 apolipoproteins(APOA1 and APO2, respectively), which serve as acceptors and trap cholesterol from peripheral tissues effectively[8,9].VLDL are the primary cholesterol source for the peripheral tissues via the LDLr, which is the major regulatory step to adjust the importance of this biomolecule. Export from cells requires both the expression of ABC superfamily (belt conveyors coupled to ATP) and extracellular presence of apolipoproteins as free cholesterol acceptors. If cholesterol is in excess, the body accelerates its conversion into bile acids, allowing its elimination in the stool, which is the only route of excretion of this substance. On the other hand, if the supplement of cholesterol is low, the de novosynthesis iscarried out in the liver [3,10].

De novo synthesis requires that genes involved in cholesterol productionbe transcribed, such as LDLr and HMGR. These genes are transcribed in terms of the amount of sterols detected by some cellular transcription factors. The cholesterol reservation obtained from de novo synthesis by hepatocytes will subsequently be esterified by ACAT and incorporated into VLDL APO B-100, which will be secreted into blood and transported into tissues. Also, the peripheral tissues contribute to hepatic cholesterol reservation through itstransfer to the liver in a process mediated by HDL[9]. Cellular transport of this substance can change LDLr synthesis, which contributes to cell and blood cholesterol concentration. Hormones, such as estrogen, thyroid hormone and insulin, modulate this process. During aging, and mRNA increased LDLr, with decreasing exposure to cholesterol contributes to hypercholesterolemia and cardiovascular disorders[11].

When the human body is subjected to a diet high in cholesterol, serum and liver cholesterol concentration increases and lipoproteins (VLDL and LDL) concentration increases too, which is considered a cardiovascular risk factor[12]. Several studies have shown that the high cholesterol concentration in serum and liver, such as triglyceride, from diets rich in cholesterol, have a direct relationship between the amount administered and the period of the diet. However, some authors report an opposite effect on serum triglyceride levels. Hu y col, found that a 1% cholesterol diet in rats show a decrease of more than 50% of the serum triglyceride levels, but increases the hepatic levels of them, also the serum and liver figures of the molecule are maintained[13]. Other studies made, in laboratory animals, have tried also to establish the metabolic behavior of these diets: rats fed high cholesterol diets have an increment in serum and hepatic cholesterol concentration[14]. Rats show an increment in serum and hepatic triglyceride levels, which conditions a non-alcoholic liver disease (NAFLD).Given this evidence, it can be established a relationship between dietary cholesterol and triglyceride metabolism, which is evident mainly in the liver tissue. However, lipid homeostasis in vertebrates is mainly regulated by a family of membrane-bound transcription factors known as sterol regulatory element binding proteins (SREBP)[15].

2.1 Sterol regulatory element binding proteins

The SREBP are transcription factors with three regions: i) A N-terminal fragment, which is actually a family b/HLH/LZ (basic/helix-loop-helix/leucine zipper) transcription factor with a tyrosine residue in the basic region of the b/HLH motive that allows it to join to the SRE sequences of the erythrocyte membrane; ii) a central domain containing two transmembrane regions separated by 31 amino acids located in the endoplasmic reticulum; and (iii) a regulatory carboxyterminal domain. SREBP has 3 isoforms: SREBP-1a and 1c and SREBP-2. These proteins regulate the expression of over 30 genes involved in the metabolism and intake of cholesterol, fatty acids, triglycerides and phospholipids and in the reduced nicotinanide adeninedinucleotide (NADPH) metabolism, which is required for the synthesis of these molecules[15,16].

The SREBP-1 and SREBP-2 proteins share 47% homology. The SREBP-1a and 1c transcripts are produced to be used as an alternative start site of transcription and differ in the first exon (exon 1a and 1c). SREBP-1a is a more potent transcriptional activator that SREBP-1c due to its NH2-terminal higher transactivation domain. However, SREBP-1c isoform is predominantly expressed in most human and mice tissues, with high levels particularly in the liver, white adipose tissue, skeletal muscle, adrenal glands and brain. In contrast SREBP-1a is highly expressed in cell lines and tissues with high capacity for cell proliferation, such as the spleen and intestine[17,18].SREBP-1a is considered a potent activator of all SREBP-responsive genes, including those that mediate the cholesterol, fatty acids and triglycerides synthesis. SREBP1c preferentially power the genes required forfatty acids synthesis and SREBP-2 has a large transcription domain has, but it preferentially activates cholesterol synthesis (Fig. 1)[19,20].

At cellular level, to monitor the sterols level in the erythrocyte membrane, the cell uses two proteins: The SREBP cut activating enzyme (SCAP) and the HMG-CoAR. These proteins share an intramembranal sequence called Sterol Screening Domain (SSD). Through this domain, sterols cause that SCAP and HMG-CoAR bind to

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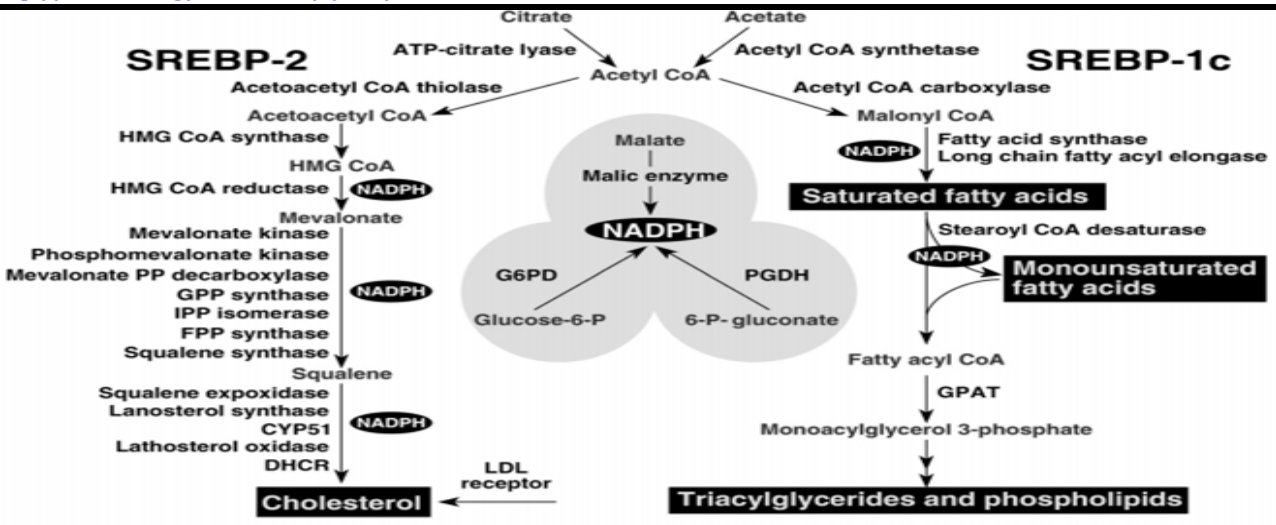

Fig.1: Genes regulated by SERBP and the metabolic intermediates in the pathways for the synthesis of cholesterol, fatty acids and triglycerides[21].

amembrane protein of the erythrocyte, which is an insulin inductor (INSIG). The INSIG protein produces a crossroad between the transcriptional and post-transcriptional regulatory mechanisms that ensure cholesterol metabolism[10]. In presence of this molecule, the SREBP are retained in the erythrocyte; in its absence they are released by proteolysis that allows the activation of target genes that control lipid metabolism[18]. Molecularly it occurs as follows: after the translation of the mRNA, SREBP precursors are retained in the erythrocyte membrane through an association with the SCAP. Under low cholesterol conditions, the SCAP accompanies the SREBP precursors from the erythrocyte to the Golgi apparatus where two functionally different proteases, site 1 of protease (S1P) and site 2 of protease (S2P), hydrolyzed sequentially the precursor protein releasing nuclear SREBP (nSREBP) in the cytoplasm[22]. In contrast, when cells have abundant cholesterol SCAP binds to INSING, stabilizing the protein and allowing the accumulation of a stable complex INSIG/SCAP/SREBP. In consequence, the content of SREBP and INSING decrease, serving as a reservoir for SREBP. When cells are lacking cholesterol, SCAP/SREBP of INSING dissociates and then it is degraded in proteasomes. The free SCAP/SREBP complex binds proteins from the rough endoplasmic reticulum and migrates to the Golgi apparatus where SREBP is processed into nSREBP. This activates the transactivation genes of the cholesterol biosynthetic enzymes and LDLR. At the same time, nSREBP activates genes for INSING, for this reason it relates to the carbohydrates metabolism[15,10].

There are three factors that selectively regulate the SREBP-1c transcription: the liver X activated receptor (LXR), insulin and glucagon. Studies in animals fed with a high cholesterol diet and the use of oxysterols synthetic agonists have shown that LXRα and LXRβ nuclear receptors form heterodimers with the retinoid X receptor (RXR), which are activated by a variety of sterols including oxysterolsintermediaries and produce an expression of lipogenic genes and high speed of lipogenesis[23]. Thus, LXR functions as a sensor for cholesterol levels and promotes its excretion and clearance. Therefore, when a rich cholesterol diet is consumed, SREBP-1c is activated by LXR to induce oleate synthesis, which participates in the synthesis of cholesterol esters, required for transport and storage[24].Also, another function of the liver is to convert carbohydrates excess to fatty acids for storage as triglycerides. Insulin stimulates the synthesis of fatty acids in response to carbohydrates excess. SREBP-1c mediates the lipogenic effect of insulin in the liver. Insulin increases the mRNA levels of SREBP-1c and regulates the expression of their target genes. In liver, both SREBP-1c and SREBP-2 transcription is stimulated by the SREBP by a feedback mechanism that requires sterol regulatory elements (SRE) sequences in the promoters of these genes[17].The SREBP-1c expression to normal levels, promotes the biosynthetic pathway of fatty acids, while SREBP-2 promotes the synthesis of cholesterol. Genes who respond to the SREBP-1c activation include ATP citrate lyase (which produces acetyl CoA), the acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS)[9]. FAS protein is a cytosolic protein and a major lipogenic enzyme in mammals. It catalyzes the reactions that contribute to the conversion of acetyl-CoA andmalonyl-CoA to palmitate (C16:0). FAS gene transcription is under strict nutritional and hormonal control in lipogenic tissues strict, such as the liver and adipose tissue[22].Other SREBP-1c target genes encode fatty acids elongation complex limiting enzymes, which

convert palmitate into stearate (C18:0);the stearoyl CoA desaturase, which converts stearate intooleate (C18:1) and the glycerol 3-phosphate acyltransferase, enzyme that participates in the synthesis of phospholipids and triglycerides. Also, SREBP-1c and SREBP-2 activate three genes: the malic enzyme (ME) gene, glucose 6 phosphate dehydrogenase (G6PD) gene and 6-phosphogluconate dehydrogenase gene, required to generate NADPH, which is consumed throughout the lipids biosynthetic pathway[19,16]. Malic enzyme presents in cytosolic (ME1) and mitochondrial (ME2) form. The ME1 catalyzes reversibly the oxidative decarboxylation of malate to pyruvate, carbon dioxide and NADPH, and then contributes to the de novo synthesis of fatty acids via FAS. It has been found that mutations in ME eliminate the function of this gene to generate a predisposition to obesity and diabetes type 2[25].

The SREBP-1c total amount in liver and adipose tissue is reduced during fasting, by decreasing insulin levels and increasing glucagon levels. This relationship is reversed during feeding[25]. SREBP-1c overexpression in the liver of transgenic mice produces a rich in triglycerides fatty liver without increasing cholesterol, whereas SREBP-2 over expression in transgenic mice results in a 28% increment in cholesterol synthesis. In rat hepatocytes, insulin treatments increase the total amount of SREBP-1c[14]. SREBP-1a over expression in mouse liver markedly increases the expression of genes involved in cholesterol synthesis (such as HMGCoA, HMGCoAR, squalenesynthetase) and fatty acid synthesis (such as ACC, and FAS) causing the accumulation of such molecules[10]. Studies in rats using orotic acid, a compound known for the ability to produce nonalcoholic fatty liver disease (NAFDL) showed an increment in de novo lipogenesis from elevated FAS, ME and G6PDH activity in rat liver[26]. Other studies shown that the activity of FAS, G6PDH and MEin the liver is increased in presence of hepatic steatosis[27]. Even Tang y col, established that inhibition of the SREBP pathway can be used as a therapeutic strategy for treating diseases of lipid metabolism including type II diabetes and atherosclerosis[28].

As it was mentioned before, cholesterol metabolism is under strict genetic regulation and different routes are used for absorption, synthesis and secretion. Knowing the metabolic pathways activated during the intake of high cholesterol diets opens strategies that could potentially counteract the effects caused by this type of food.Another protein called Peroxisome Proliferation Activated Receptor (PPAR) is also involved in the regulation expressed in hepatocytes and cardiomyocytes. This protein is required for the fatty acids to express its function in the genetic processes and participates in a large network of genes that regulate the metabolism of lipids and glucose, and the differentiation of adipocytes. There are several types of PPAR: α, β and γ. PPAR α is associated with fatty acid metabolism in the liver, kidney, heart, skeletal muscle and brown adipose tissue. PPAR γ is associated more with other adipose tissue. Some medications such as fibrates and thiazolidinediones act by activation of PPAR. The effects of these receptors in metabolism range from peroxisomal proliferation, increment in fatty acid oxidation, reduction in plasma triglyceride levels, and improvement in glucose tolerance. It is important to remember that the fatty acids are energy elements of the body, and they modulate its metabolism, synthesis and oxidation through an allosteric enzyme action. In this way, omega fatty acids regulate lipogenic, mitochondrial oxidative and gluconeogenic enzymes. Long chain polyunsaturated fatty acids reduce hepatic lipogenesis and consequently reduce the amount of enzymes involved in lipid synthesis; they also modulate adipogenesis[29]. Another regulatory mechanism that refers to triglycerides adipose tissue is the storage of a wide range of fatty acids, which differ in their molecular structure. The output of fatty acids from adipose tissue of a subject is selective; it dependson the size of the chain and the degree of unsaturation. This has been observed in vitro in human and animal adipocytes[30].

As remarkable progress,genes related to the different metabolic pathways of lipids provide insight into the effects and responses to various diets, which generates changes in health from the nutritional status of the individual[31]. Therefore, there will be a beneficial effect to consume diets that include functional foods and their bioactive components.

III. FUNCTIONAL FOODS

Functional foods are defined as specific food substances that promote health as part of a varied diet. In general, they provide beneficial effects in contributing to the maintenance of health status and reducing the risk of illness. They are natural or processed foods that, in addition to its nutritional components, contain additional components, nutritious or not, to help maintain or improve health and promote physical fitness and mental state of the person who consumes them. There are flavonoids that neutralize free radicals focusing on lower the risk to develop cancer; caroteniodes that contribute to eye health; fiber that reduces the risk of colon cancer and various bioactive peptides with antioxidant, antimicrobial and antihypertensive effects, among others. Some of the components forming part of functional food are shown in TABLE 1. However, there are specific components such as hypocholesterolemic unsaturated fatty acids and bioactive peptides capable of reducing the levels of triglycerides and cholesterol[32, 33, 34].

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Table.1: Chemical components with functional potential present in many foods[33, 34].

Component	Food	Potentialbenefit
Flavonoids(Catechins and flavonols)	Green tea and citrus	Neutralize free radicals and reduce risk of cancer
Carotenoids(β-carotene and lutein)	Carrots and green vegetables	Improvevision
Fiber	Shell grains	Reduces the risk of colon cancer
Unsaturated fatty acids(ω-3 y ω-6)	Fish oils and some grasses	Reduce levels of cholesterol and triglyceride
Bioactive peptides (antioxidants, ACE inhibitors, hypocholesterolemic)	Eggs, meat, chickpea, soy, milk, rice, sunflower, and others.	Reduce the risk of cardiovascular disease and degenerative

3.1 Unsaturated fatty acid

Among ordinaryfats and oils, waxes and related compounds found in foods and in the human body are included. These lipids are composed of triglycerides containing a glycerol molecule (an alcohol) and three fatty acids. From the chemical standpoint, fatty acids are hydrocarbon straight chains terminating in a carboxyl group at one end and a methyl group at the other. The most common way to classify them is: a) For their degree of saturation, they are divided into saturated and unsaturated. Aldo,may be classified in monounsaturated and polyunsaturated. b) For their length of the chain they can be classified as short (4-6 carbons), medium (8-12 carbons), long (14-18 carbons) or very long (20 or more carbons) chain.According to the position of the first double bond in the chain, called omega, counting from the methyl end, there are three families of polyunsaturated fatty acids: ω-3, ω-6 and ω-9. Some are classified as essential because the human body cannot synthesize them and they are needed for vital functions, these are the ω-3 and ω-6 families commonly known as omega 3 and omega 6[35,36].

Unsaturated fatty acids have antithrombotic and antiarrhythmic effects, increase bleeding time preventing the adhesion of platelets in the arteries, prevent atherosclerosis by lowering cholesterol levels in plasma, they are useful in hypertensive patients, because they help to lower blood pressure and reduce the concentration of plasma triglyceride, and they decrease the total cholesterol and VLDL[37].In the nervous system, unsaturated fatty acids are necessary for proper development and functioning of the brain and nervous system. They are concentrated in the retina and cerebral cortex, and have the ability to correct visual and brain problems in patients with deficiencies[38].Unsaturated fatty are hormonal precursors compounds also, such as prostaglandins and thromboxanes, which facilitate the transmission of messages in the central nervous system[37].

Unsaturated fatty are precursors of other fatty acids such as arachidonic, eicosapentaenoic (EPA) and docosahexaenoic acid (DHA). DHA is part of the membranes of retinal photoreceptors[38].

It is also important to remember that all cell membranes contain lipid bilayers and are impermeable to charged molecules, for communication between cellsand compartments, which require from protein transporters or receptors that are embedded in this double layer, occur. Furthermore, a flow mechanism that causes the lateral movement of proteins and invagination, that allows endocytosis and exocytosis, is observed. This fluidity requires long chain unsaturatedfatty acids, because saturated fatty acids decrease this vital characteristic, even more when proteins have to collide with other molecules in various biochemical processes. For example, the role of insulin to communicate its signal during glucose metabolism in rats is damaged when food provides more than 10% of dietary calories from saturated fatty acids, which can be improved with the intake of omega-3 fatty acids[39].

It has been shown that the antiarrhythmic effect of omega fatty acids may be associated with functional balance between the vague and sympathetic systems whose modulation is involved with the cardiac response[40]. In particular EPA and DHA could compare its effect with some medications used in the treatment of these cardiac problems, which has been observed when fish oil is supplied to rats in treatment, due to adrenoceptor involved in arrhythmias. These receptors are membrane proteins that transmit the catecholamines neuroendocrine message in the pace and strength of cardiac contraction. In this processDHA hasa similar activity to the one presented by theβ-blocking molecules. In relation to atherosclerosis, it is the product of a long period of artery inflammation and endothelial dysfunction plays an important role on it, because the flow associated with this function is mediated by nitric oxide and aggravated by atheroma. Omega fatty acids provide more fluidity to membranes of endothelial

cells promoting the synthesis or output of nitric oxide. To prevent atheroma, it is suggested the intake of omega fatty acids from fish sources. It has been observed in neutrophils and monocytes that fish oil reduces the formation of oxygen-derived free radicals and increased nitric oxide production in cultured human endothelial cells, which is beneficial to avoid atheromas[41]. As it has been already mentioned, another factor associated with heart problems is the concentration of HDL-cholesterol that may be a predictive factor to avoid the risk of coronary heart disease. Although, the current recommendations for the treatment of dyslipidemia do not include specific HDL-cholesterol values, the acceptable range was 35 mg/dL and it has been modified to 40 mg/dL. Statins, which are 3-hydroxy-3-methyl-CoA reductaseinhibitory molecules, are drugs used for reducing cholesterol and increase the HDL at moderate levels.Other resources for this purpose are, omega fatty acids, which are obtained from the oil of various animals and plants[42].Vegetable fats and oils are usually obtained from seeds or the outer layer of the fruit. The percentage of this oil reserves widely vary from about 5% in cereals to 68% in coconut. In plants and therefore in vegetable oils, factors such as the type of crop, agricultural land and climatic conditions have a strong influence on the content of fatty acids. Mediterranean populations consume large quantities of olive oil (rich in oleic acid, which helps in the formation of ω-9 acids), vegetables and fish; it was found that consumption of fish and olive oil over the life of these populations might provide independent protective effect on the development of many diseases[43]. Currently, there is interest in the oil obtained from Chia seed (Salvia hispanica), due to its high content of unsaturated fatty acids[44].

3.2. Bioactive peptides

Currently the study of dietary proteins as functional andbeneficial components has received much attention because the generation of bioactive peptides is under investigation[45]. The term bioactive is used to describe components with various types of biological activity, such as antimicrobial, immunomodulatory, regulating intestinal transit, antioxidants, ACE inhibitory, hypocholesterolemic and antithrombotic. Bioactive peptides are defined as amino acid sequences of between 2 and 20 residues withoutactivity in the original protein and presenting biological activity when released by hydrolysis. They cross the intestinal epithelium and reach peripheral tissues via systemic circulation, exerting specific functions locally, gastrointestinal and systemic[46]. These peptides may alter cellular metabolism and present these functions. Its activity is similar to a hormone or drug that modulates a physiological role through its interaction with a specific receptor triggering a physiological response[47]. Typically, the bioactive peptides are hydrophobic and absorbed between 70 and 80% faster compared to free amino acids[48].

The method for obtaining these molecules is by the hydrolysis of proteins; this is accomplished by chemical processes (acids or bases) or by biological processes (using enzymes). Biological processes are the most recommended if the products will be used in the food field[49].According to Guadix y col, the proteases or proteolytic enzymes are commercial grade enzyme mixtures, liquid or solid and are classified in various ways[50] (TABLE 2).

However, it should be considered the temperature, pH, hydrolysis time and degree of hydrolysis (DH) to obtain hydrolyzed with specific characteristics, such as the proper distribution of molecular masses of the peptides formed, the amino acids released, and the amount of residual undigested protein[45]. The temperature is selected to optimize the kinetics of the enzyme or mixture of them, using a range from 32 to 50 ºC. The pH is determined according to the range where the enzyme activity is at its highest. The hydrolysis time is related in direct proportion with the DH[51]. This is a measure of the proteins hydrolytic degradation ability. It is defined as the percentage of broken peptide bonds in relation to the total of them in the original protein. DH is considered practical and convenient to control the hydrolytic processes and as the largest indicator used for the comparison of different protein hydrolysates[52]. In response to DH, hydrolysatescan be classified as: a) Limited hydrolysates (DH <10%). They are used to improve the functional and technological properties, because an increase in solubility occurs. It also improves the emulsifying power, foaming and absorption of water or oil, which can be used in baked goods and mayonnaise[33]. b) Extensive hydrolysates (DH ≥ 10%). Used in specialized feeding, either as a protein supplement or medical diets. These hydrolysates include the ones that seek to exploit or improve the nutritional characteristics of the protein source, because the peptides obtained have higher thermal stability and reduced allergenicity. Its size can be more effectively absorbed in the gastrointestinal tract as compared to the intact proteins. Its high solubility allows their use in liquid foods[33].

Table.2: Classification of proteases according to source, action and catalytic site[50].

Classification	Diversity	Description
Source	Animals Vegetables Bacterial Fungal	They are extracted from animal tissues, plants, bacteria or fungus and its metabolites or its metabolites
Catalyticaction	Endoprotease	Hydrolyze peptide bonds along the protein chain.
	Exopeptidase	Hydrolyzed amino terminals (aminopeptidase) orcarboxylterminals (carboxypeptidase).
Catalyticsite	Serineproteinase Cisteinproteinase Metalloproteinase Aspartatoproteinase	Endoprotease able to hydrolyze amino acid linked to specific substrates
	Aminopeptidase Carboxipeptidase Dipeptidase	Exopeptidase able to hydrolyze amino, carboxyl or both

However, it should be considered the temperature, pH, hydrolysis time and degree ofhydrolysis (DH) to obtain hydrolyzed with specific characteristics, such as the proper distribution of molecular masses of the peptides formed, the amino acids released, and the amount of residual undigested protein[45]. The temperature is selected to optimize the kinetics of the enzyme or mixture of them, using a range from 32 to 50 ºC. The pH is determined according to the range where the enzyme activity is at its highest. The hydrolysis time is related in direct proportion with the DH[51]. This is a measure of the proteins hydrolytic degradation ability. It is defined as the percentage of broken peptide bonds in relation to the total of them in the original protein. DH is considered practical and convenient to control the hydrolytic processes and as the largest indicator used for the comparison of different protein hydrolysates[52].In response to DH, hydrolysatescan be classified as:a) Limited hydrolysates (DH<10%). They are used to improve the functional and technological properties, because an increase in solubility occurs. It also improves the emulsifying power, foaming and absorption of water or oil, which can be used in baked goods and mayonnaise[33].b) Extensive hydrolysates (DH ≥ 10%). Used in specialized feeding,either as a protein supplement or medical diets. These hydrolysates include the ones that seek to exploit or improve the nutritional characteristics of the protein source, because the peptides obtained have higher thermal stability and reduced allergenicity. Its size can be more effectively absorbed in the gastrointestinal tract as compared to the intact proteins. Its high solubility allows their use in liquid foods[33].

Regarding the hypocholesterolemic effect, it has been reported more incidence of this activity in plant sources compared to animals. Specifically, the case of soybeansis mentioned, both recommended by the Food and Drug Administration (FDA) and the American Heart Association (AHA),because by consuming 25 g/day of this protein as part of a diet low in saturated fat there is a decrease in cholesterol levels. An estimated consumption amount of protein decrease lipoprotein LDL up to 8% in patients with high cholesterol levels, while it has no adverse effects in people with normal cholesterol levels[53]. By reducing serum cholesterol and LDL concentration there is a positive effect as the atherogenic index (LDL/HDL) decreases in rats, mice and humans[54, 55]. However, when taken orally these proteins are target of gastrointestinal proteases, which originate bioactive peptides and contribute to the effects mentioned before. It has been reported that soy peptides minimize serum cholesterol levels compared to the intact protein. Compared with casein, these hydrolysates also reduce serum cholesterol because the excretion is promoted through feces, because it cannot be absorbed. Similarly, it decreases the oxidation of LDL and triglyceride levels and enhance the vascular activity[56].One possible explanation for these events is given by the reduced levels of hepatic lipogenic enzymes such as G6PDH and stimulation of adiponectin, a hormone involved in adipocyte differentiation, and insulin and fatty acids sensitivity[51]. Based on these facts, Nagaokay col found that cholesterolmicellar solubility was significantly lower during the intake compared to hydrolyze soy protein. The same result was observed in serum, liver and intestines of rats, indicating inhibition of cholesterol absorption due to the inability of the micelles to solubilize the molecule[57]. It has also been found thehypocholesterolemic effect in glycinin, specifically in theLeu-Pro-Tyr-Pro-Argpentapeptide, obtained from soy protein, as mentioned

before. This pentapeptide reduced serum cholesterol in mice when administered orally in doses of 50 mg/kg and has a homologous enterostatin (Val-Pro-Asp-Pro-Arg) structure[58]. It has been shown that sunflower hydrolysates generated when using pepsin or alcalaseproteases and undergo to intestinal digestion in vitro, inhibit cholesterol incorporation into the micellar suspensions of bile salts. A similar effect was obtained with rice bran hydrolysates, which managed to reduce total serum cholesterol and increase HDL in male Wistar rats[59].

Concerning triglycerides, Ascencio y col reported that consumption of soy protein isolates maintained at a low level liver stores of these esters[60]. It is also reported that the isolated protein maintains in a low levelplasma triglycerides, increases adiponectin, accelerates lipid metabolism and decreases the body fat of obese rats and mice[61,62].

IV. CONCLUSIONS

Lipids we eat in the diet are important for the growth and development of human beings, both for its energy function, and for the supply of essential fatty acids. However, consumption of saturated fatty acids is harmful to the body, as it promotes the formation of cholesterol associated with low-density lipoproteins (LDL) and increases the rigidity of cell membranes, compromising their biological functions. Therefore, controlled fat intake may be beneficial to health, to prevent certain cardiovascular diseases. Unsaturated fatty acids protect at cardiovascular level, because they modulate serum cholesterol levels and reduce susceptibility to oxidation of LDL. The ω-3 and ω-6 acids prevent chronic inflammation, some carcinogenic processes and degenerative diseases, because they are precursors of eicosanoids or affect the transcription of some genes involved in the development of these diseases. These ω-3 and ω-6 acids exist in foods such as cold-water fish. But their presence has been reported in various vegetables like amaranth and olive, although chia has stood outdue to its high content of these acids. It is known that plant foods provide some metabolites with different biological properties, being the hypocholesterolemic activity, due to enzyme peptides origin, one that has received attention in recent years. When these peptides are ingested as part of the diet they have a role in reducing the risk of cardiovascular diseases, which have been guaranteed by in vitro and in vivo studies.

However, knowledge of how these ingredients work on the body is not sufficiently consolidated. This is due to the complexity of the multiple interactions between the constituents of the food during the digestive process and the impact on the metabolism of the same. The different lifestyles, age, health status and dietary habits among populations, even within the same society, make it difficult to generalize the results of studies and indicate that a bioactive ingredient is not necessarily effective for all consumers. Therefore, there are still many aspects of food/health relationship at different stages of life and to individuals in different metabolic situations that require research. For this it is necessary to demonstrate the biological activity of each specific food, this by performing clinical studies and evaluating the potential health risks of these functional foods to meet the risk-benefit balance that their consumption entails for the population.

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