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The Protective Effect of Antioxidants in Alcohol Liver Damage

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1. Introduction

The term antioxidant was originally utilized to refer specifically to a chemical product that prevented the consumption of oxygen (Burneo, 2009); thus, antioxidants are defined as molecules whose function is to delay or prevent the oxygenation of other molecules. The importance of antioxidants lies in their mission to end oxidation reactions that are found in the process and to impede their generating new oxidation reactions on acting in a type of sacrifice on oxidating themselves. There are endogenous and exogenous antioxidants in nature. Some of the best-known exogenous antioxidant substances are the following: β -carotene (pro-vitamin A); retinol (vitamin A); ascorbic acid (vitamin C); α -tocopherol (vitamin E); oligoelements such as selenium; amino acids such as glycine, and flavonoids such as silymarin, among other organic compounds (Venereo, 2002).

Historically, it is known that the first investigations on the role that antioxidants play in Biology were centered on their intervention in preventing the oxidation of unsaturated fats, which is the main cause of rancidity in food (Wolf, 2005). However, it was the identification of vitamins A, C, and E as antioxidant substances that revolutionized the study area of antioxidants and that led to elucidating the importance of these substances in the defense system of live organisms (Jacob, 1996).

Due to their solubilizing nature, antioxidant compounds have been divided into hydrophilics (phenolic compounds and vitamin C) and lipophilics (carotenoids and vitamin E). The antioxidant capacity of phenolic compounds is due principally to their redox properties, which allow them to act as reducing agents, hydrogen and electron donors, and individual oxygen inhibitors, while vitamin C's antioxidant action is due to its possessing two free electrons that can be taken up by Free radicals (FR), as well as by other Reactive oxygen species (ROS), which lack an electron in their molecular structure. Carotenoids are deactivators of electronically excited sensitizing molecules, which are involved in the generation of radicals and individual oxygen, and the antioxidant activity of vitamin A is characterized by hydrogen donation, avoiding chain reactions (Burneo, 2009).

The antioxidant defense system is composed of a group of substances that, on being present at low concentrations with respect to the oxidizable substrate, delay or significantly prevent oxygenation of the latter. Given that FR such as ROS are inevitably produced constantly during metabolic processes, in general it may be considered as an oxidizable substrate to nearly all organic or inorganic molecules that are found in living cells, such as proteins, lipids, carbohydrates, and DNA molecules. Antioxidants impede other molecules from binding to oxygen on reacting or interacting more rapidly with FR and ROS than with the remainder of molecules that are present in the microenvironment in which they are found (plasma membrane, cytosol, the nucleus, or Extracellular fluid [ECF]). Antioxidant action is one of the sacrifices of its own molecular integrity in order to avoid alterations in the remainder of vitally functioning or more important molecules. In the case of the exogenic antioxidants, replacement through consumption in the diet is of highest importance, because these act as suicide molecules on encountering FR, as previously mentioned (Venereo, 2002).

This is the reason that, for several years, diverse researchers have been carrying out experimental studies that demonstrate the importance of the role of antioxidants in protection and/or hepatic regeneration in animals. Thus, in this chapter, the principal antioxidants will be described that play an important role in the regeneration of hepatic cells and in the prevention of damage deriving from alcohol (Burneo, 2009; Venereo 2002).

2. Retinol (Vitamin A)

Vitamin A, also called trans-retinol, is an isoprenoid alcohol that performs several important functions in the organism, is essential in vision, in addition to being necessary for epithelial tissue regulation and differentiation, as well as for bone growth, reproduction, and embryonic development. Together with some carotenoids, vitamin A increases the immunity function, reduces the consequences of infectious diseases (Goodman & Gilman, 1996), and, more recently, it has been observed that it provides certain protection against malignant diseases such as cancer (Morales-González 2009).

Vitamin A belongs to a family of similarly structured molecules that are generically denominated retinoids (low-molecular-weight molecules, derived from the hydrophobic molecules of vitamin A) (Mathews-Van Holde, 1998).

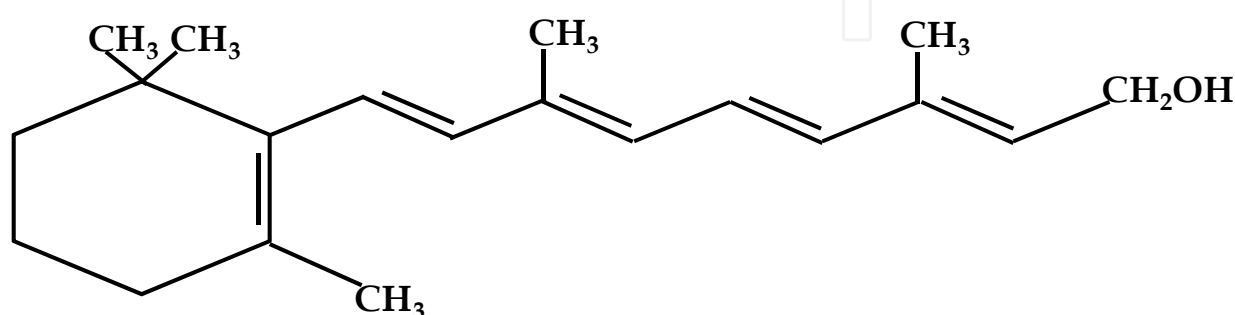
The activity of vitamin A in mammals is due not only to retinoids, but also to certain carotenes that are widely distributed in the majority of vegetables. Carotenes do not possess intrinsic vitamin A activity, but are converted into vitamin A by means of enzymatic actions that take place in the intestinal mucosa and in the liver (Morales-González 2009).

2.1 Structure

Vitamin A can present as a free alcohol, as a fatty acid ester, as an aldehyde, and as an acid (Figure 1). In this structure, on replacing the alcohol group, it obtained retinal, the principal functional form of rods and cones in the retina and, by an acid group, retinoic acid, the main functional form in cellular regulation and differentiation (Morales-González 2009; Mathews Van-Holde 1998).

2.2 Digestion, absorption, and metabolism

Because vitamin A is a liposoluble vitamin, retinol digestion and absorption is intimately linked to that of lipids. Retinol esters dissolved in fat from the diet arrive in the small intestine, forming micelles with the aid of bile salts. Later, hydrolysis is produced in which the pancreatic lipase enzyme participates, acting on formed micelles, causing the absorption of 90% of dietary fats. Vitamin A, together with the additional products of enzymatic hydrolysis, enter the enterocyte after passing through the cellular membrane, whether by facilitated diffusion or passively depending on the concentrations present (Morales-González 2009).



Retinol

Fig. 1. The chemical structure of vitamin A is made up of a 6-carbon-atom cyclic nucleus with an 11-carbon side-chain.

Carotenes as such are absorbed passively, and once in the cytoplasm, are transformed into retinol. Within the intestinal cell, the greater part of the retinol is esterified with saturated fatty acids such as palmitic acid and is incorporated in lymphatic kilomicros, which enter into the bloodstream and are transported to the liver, where it is stored in parenchymatous cells and in the adiposites in the form of retinyl ester. The greater part of this is taken up by the hepatocytes of kilomicro fragments and is transferred in the form of light retinol to the Retinol binding protein (RBP) and toward the Kupffer cells, whose main function appears to be storage of these. When the tissues require retinol, this is transported by means of RBP and Transthyretin (TTR, prealbumin) for transport in the circulation of the target cells. The tissues are capable of taking this up through surface receptors, where the retinol is transferred to a retinol membrane binding protein and becomes a retinyl ester. Later, a hydrolase related with the membrane unfolds the latter. RBP exists in nearly all tissues; the exceptions comprise cardiac and skeletal muscle. In addition to its uptake of retinol, the RBP functions as a reservoir for cellular retinol and releases the vitamin to the appropriate sites for its conversion into active compounds. In the retina, retinol becomes 11-cis-retinal, which is incorporated into the rhodospin. In other target tissues, retinol apparently is oxidized into retinoic acid, which is transported to the nucleus. It is noteworthy that the RBP plasma concentration is crucial for regulation of the retinol in plasma and its transport to the tissues (Morales-González, 2009). In general, within the organism retinol can follow three processes; esterification and storage in the liver; conversion into active metabolites (retinal), and/or catabolism and excretion as retinoic acid (Allende-Martínez 1997).

2.3 Antioxidant action

Vitamin A is a natural antioxidant that prevents cellular aging, eliminates FR, and protects the DNA in its mutagenic action. β -carotene is also a powerful antioxidant. We must clarify that this antioxidant function is only obtained in foods that were submitted to cooking for at least 5 minutes. Some studies have demonstrated that β -carotene supplemented in the diet has shown some evidence of antitumor action (Allende-Martínez 1997).

On the other hand, in the case of its participation in the regeneration of hepatic cells in alcohol-induced damage, a positive result is obtained, because vitamin A has shown a lesser protector effect against the formation of FR in the reversion of the hepatic regeneration inhibition caused by ethanol consumption, due to that retinol is the principal component of vitamin A, that it is an alcohol, and that retinol as well as ethanol utilize the same enzymatic pathways; thus, storage of vitamin A and of ethanol in hepatic cells is altered. Therefore, an excess of vitamin A and its interaction with the alcohol increase the capacity to produce fibrous tissue that, in the long term, can cause a cirrhosis (Ramírez-Farías et al., 2008). Thus, it is considered that vitamin A can generate, instead of a benefit, a hepatotoxicity with subsequent inflammation, necrosis, and the increase of some serum enzymes (Morales-González, 2009).

3. Ascorbic acid (Vitamin C)

L-Ascorbic acid (AA), commonly known as vitamin C, is considered one of the organism's most powerful antioxidant agents due to its capacity to donate two electrons from its double link, that of positions two and three; thus, it interacts with the FR, blocking their harmful effect. The human body is not capable of obtaining vitamin C exogenously through foods; it is found concentrated in certain organs such as eye, liver, spleen, suprarenal glands, and thyroids. It is an essential vitamin, in that it participates in reactions such as the synthesis of molecules such as carnitine or thryisine acid, which are fundamental for good bodily function; it participates in iron absorption and presents immunological and anti-inflammatory actions such as the synthesis of neurotransmitters and hormones, playing an important role in collagen synthesis (Morales-González, 2009; Mathews-Van Holde 1998).

AA ($C_6H_8O_6$) is an essential vitamin that is chemically synthesized from glucose by a series of enzyme-catalyzed actions, the last enzyme involved in its synthesis being L-gulonogamma-lactone oxidase (GLO); it is hydrosoluble and possesses acidic and strongly reductive properties. These properties are due to its enediol structure and to the possibility of ionizing the hydroxyl situated on carbon 3, forming an anion that remains stabilized by resonance. Eventually, it can dissociate the carbon-2 hydroxyl, forming a dianion, although it does not acquire the same stability as that of carbon 3. In nature, two isomers are found with nutritive properties (Figure 1): the L- isomer (L-ascorbic acid), and the D-isomer (L-dehydroascorbic acid). The functions of vitamin C apparently reflect its redox capacity. Thus, it participates in some hydroxylation reactions in which it maintains optimal enzymatic activity by means of electron donation. Vitamin C also increases the absorption of no-heme iron and serves as an important mechanism for inactivating highly reactive radicals in tissue cells. Similarly, it delays the formation in the body of nitrosamines, which are possible carcinogens. The accumulated evidence links ascorbic acid with many elements of the immunity system (Morales-González, 2009).

3.1 Absorption

Vitamin C absorption is carried out in the small intestine by sodium-dependent active transport (faster and more efficient), or by passive transfusion through a glucose transporter (insulin). L-dehydroascorbic acid is more easily absorbed than L-ascorbic acid. This characteristic is attributed to that the oxidized form of the vitamin remains with ionization to the physiological pH and to that the molecule is slightly hydrophobic, which permits it to penetrate into the membranes. Once inside, it is reduced to ascorbate; in this manner, it circulates mainly in plasma and in suprarenal glands and hypophysis. The effectiveness of the absorption depends on the dose administered, because it has been observed that on increasing the dose, the effectiveness of the absorption diminishes (Morales-González, 2009).

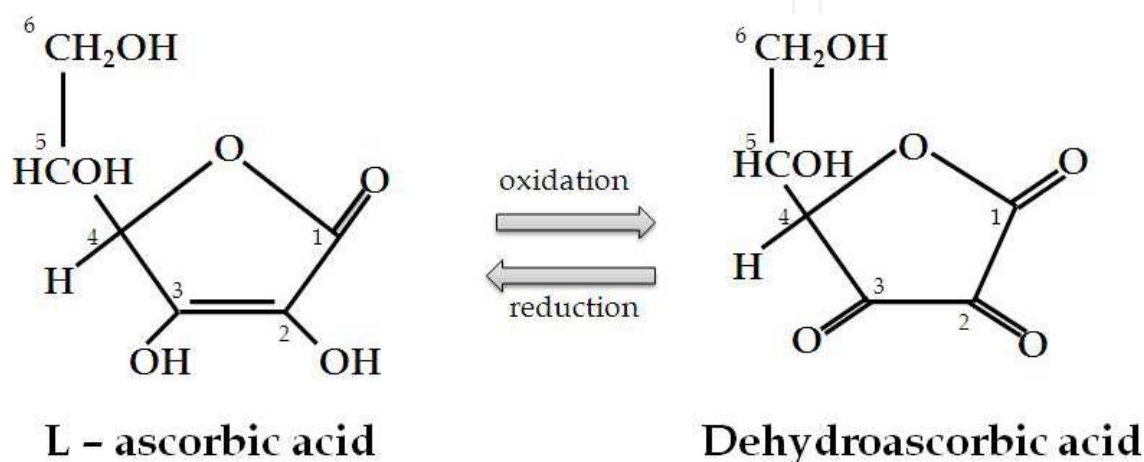


Fig. 2. The chemical structure of vitamin C corresponds to that of a lactone; L-ascorbic acid presents a double connection link between the 2 and 3 carbon; this characteristic allows the molecule to donate electrons from this double link, forming L-dehydroascorbic acid, or in a reversible reaction.

3.2 Antioxidant action

Similar to vitamin A, vitamin C is a natural antioxidant characterized by the capacity to donate two electrons from its double link at positions two and three, in such a way that it interacts with FR, blocking their harmful effect; consequently, it is oxidized. In addition to exerting an effect on FR, it also acts by regenerating oxidized antioxidants such as α -tocopherol and β -carotene. In a study published by Ramírez-Farías et al., in 2008, the author concluded that administration of vitamins C and E provided a protector effect against liver damage; they attenuate lipid peroxidation, and both vitamins present a significantly greater effect than vitamin A against ethanol-mediated toxic effects during hepatic regeneration.

4. Vitamin E

Vitamin E ($C_{29}H_{50}O_2$) is known as the generic of a derived set of tocopherols, with α -tocopherol the most active form for humans. Tocopherols possess a functional phenolic group in a chromanol ring and an isoprenoid side-chain of 16 carbons; it is saturated with three double links. There are two groups of compounds with vitamin E activity, and the tocopherols (with a 16-carbon isoprenoid side-chain) and the tocotrienols (with the same 16-carbon chain, but with three double links); both groups present vitameres that differ in the number

and position of the methyl groups in the chromanol ring, designated as α , β , γ , and δ (Figure 3) (Morales-González, 2009).

This vitamin forms part of the essential vitamins; thus, it should be acquired by means of its consumption in the daily diet. The distinct forms of vitamin E are not interchangeable among themselves in humans; in addition, they present distinct metabolic behaviors; therefore, other existing forms do not convert into α -tocopherol at any time and do not contribute to covering the vitamin E requirement. One of the main functions of α -tocopherol is that of its being a lipid antioxidant; on the other hand, it diminishes the production of thromboxanes and prostaglandins, is capable of inducing apoptosis directly or indirectly in tumor cells, modulates microsomal enzyme activity, inhibits protein kinase C activity, functions as a genetic regulator at the messenger RNA (mRNA) level, modulates the immunitary response during oxidative stress, and intervenes in the processes of fetal development and gestation, as well as in the processes of the formation of elastic and collagen fibers of the connective tissues, and in addition promotes the normal formation of erythrocytes; thus, the importance of this vitamin (Morales-González, 2009; Sayago, 2007).

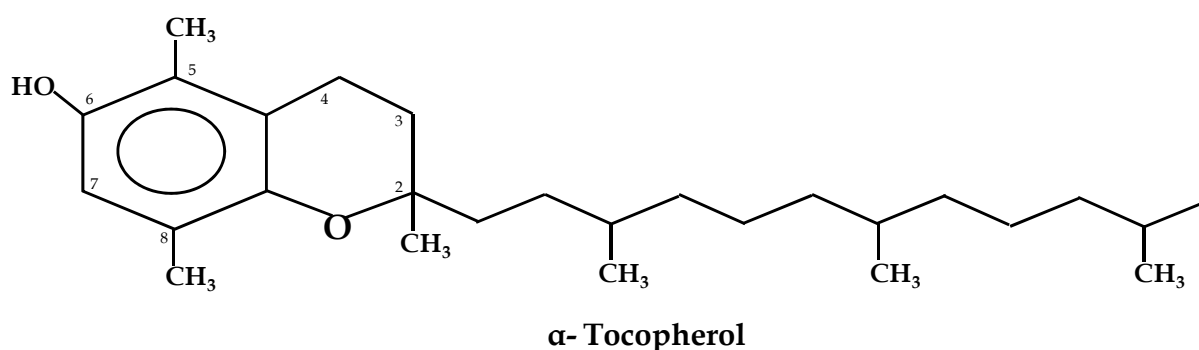


Fig. 3. In tocopherol structure, the alpha (α) homologue possesses four methyl groups in positions 2, 5, and 7.

4.1 Absorption and metabolism

Vitamin E is principally absorbed in the small intestine, with biliary secretion and micelle solubilization as indispensable. The bile acids, proceeding from the liver and segregated in the small intestine, favor the formation of micelles and facilitate the action of pancreatic lipases on lipids. Absorption of vitamin E within the erythrocyte is a passive process; α -tocopherol and non-esterized δ -tocopherol are incorporated into the kilomicons and for transport to the liver, in which the alpha-Tocopherol transfer protein (α -TTP) binds to the natural α -tocopherol stereoisomer or to the Golgi apparatus to incorporate it into Very-low-density lipoproteins (VLDL), from which is transferred to other circulating lipoproteins such as High-density (HDL) and Low-density lipoproteins (LDL) during their catabolism by the Lipoprotein lipase (LPL). LPL can also act on HDL and LDL in order for vitamin E to be able to accede to the peripheral tissues (Morales-González, 2009; Sayago, 2007).

4.2 Antioxidant activity

α -Tocopherol inhibits lipid oxidation by means of two mechanisms. On the one hand, it eliminates the FR produced during peroxidation, thus inhibiting the oxidation chain reaction and, on the other hand, it acts as a singlet oxygen chelator. Polyunsaturated fatty

acids (PUFA) have methylene groups localized between two double links; this renders PUFA sensitive to auto-oxidation; the initial reaction produces the lipid radical, a conjugated diene radical (L●), which reacts rapidly with the oxygen molecule, giving rise to a peroxy free radical L-OO. In turn, this FR can act upon another PUFA, which will re-initiate the entire process and which would give rise to the peroxidation chain. The FR chain reaction is broken when α -tocopherol, present in the membrane, transfers a hydrogen to a peroxy FR, transforming it into a hydroperoxide and giving rise to a tocopherol radical. The latter can react with different electron donors, among which ascorbate (vitamin C) is highlighted, for regenerating the tocopherol. In general, each α -tocopherol molecule can react with two peroxy radicals (Morales-González, 2009; Sayago, 2007).

5. Oligoelements

Oligoelements comprise nine micronutrients that are found in the organism in amounts of <0.01% of body weight, and are the following: iron; zinc; selenium; manganese; iodine; chromium; fluorine; copper, and molybdenum. Oligoelements are very important for the organism because they perform functions such as serving as co-factors in enzymatic systems or as vital molecular components (Morales-González, 2009).

5.1 Selenium (Se)

Selenium is localized within the group of micronutrients constituting a trace element or an essential micronutrient for all mammals. Selenium is defined as a non-volatile micromineral that fulfills numerous biological functions; thus, its best known function is its role as part of the glutathione peroxidase enzyme that protects cells from oxidative damage. Its presence in tissues such as liver, heart, lung, and pancreas is essential because it promotes the breakdown of toxic peroxides formed during metabolism, impeding cell membrane damage. Selenium protects against toxicity by means of mercury, cadmium, and silver (Morales-González, 2009; Manzanares-Castro, 2007).

5.1.1 Absorption and metabolism

Absorption is mainly carried out in the duodenum. This element enters into the body in two principal ways depending on its source: selenocysteine (in animals), and selenomethionine (in plants); once in the organism, sulfur replacement takes place in cysteine and methionine for the formation of amino acids and selenoproteins. It is excreted through the urine and when consumed in high quantities, it also can be eliminated through the breath (Manzanares-Castro, 2007).

5.1.2 Antioxidant action

Selenium (Se) possesses a potent antioxidant power, which is associated with the so-called selenoenzymes. To date, approximately 35 selenoenzymes have been described; these are proteins contain a selenocysteine residue in their active site and in which Se constitutes their enzymatic co-factor. Among the selenoenzymes, the best characterized and studied are Glutathione peroxidase (GPx) and Selenoprotein P (SePP). Another two very important enzymes are thioredoxin reductase, whose function is to reduce nucleotides during DNA synthesis, and iodothyronine deiodinase, which is responsible for the peripheral conversion

of T_4 in active T_3 . Selenium, together with vitamin E, protects cells from peroxidation because the former destroys peroxides through the cytoplasm, while the latter prevents peroxide formation (Manzanares-Castro, 2007).

The biological role that selenium presents is based on two fundamental properties: the antioxidant protector function from oxidative damage, and immunomodulation; in this case, it had the antecedent of a study carried out in rats in whom oxidative damage was induced and by means of Selenium (Se); a significant diminution of the enzymes aspartate aminotransferase (AST), Alkaline phosphatase (ALT), and Alanine aminotransferase (ALP) was observed, as well as an improvement in the antioxidant state. The results suggested that administration of Se to hepatic tissue protects against intoxication due to its antioxidant properties (Mahfoud et al., 2010).

6. Amino acids

Amino acids are nutrients that function as raw material for protein formation. According to their classification due to their requirement in the diet, they are classified as essential, non-essential, and semi-essential. Their most important function is the formation of peptides, structural proteins, enzymes, transporter proteins, immunoproteins, and hormones. However, each has special chemical functions in which they are exchanged or cede methyl or sulfhydroxyl groups in choline synthesis or substance detoxification. Some of these, such as glycine, cysteine, glutamic acid, or taurine, assume the role of antioxidants, and under extreme conditions when other energy sources are insufficient, these are utilized to produce energy through glyconeogenesis; each amino acid possesses different specific and concrete functions (Morales-González, 2009).

6.1 Glycine (Gli)

This is the simplest amino acid of all, and it is one of the so-called non-essential amino acids; thus, no minimal nutritional contribution is required, given that there are substances available in the organism for its synthesis. Glycine ($C_2H_5NO_2$) is produced in hepatocyte mitochondria from 3-D-phosphoglycerate, giving rise to serine, and in the presence of pyridoxal phosphate, serine hydroxymethyltransferase removes one carbon atom, thus producing glycine. It can also be constituted from carbon dioxide, ammonium, and from N5N10-methylenoTetrahydrofolate (TFH) in the same manner as in the mitochondria (Morales-González, 2009; Mathews-Van Holde, 1998).

Glycine is found at high concentrations in the organism, functioning as an important carbon donor for the formation of numerous essential compounds. It also functions in the biosynthesis of multiple compounds, such as the heme group, purines, proteins, nucleotides, nucleic acids, creatinine, conjugated bile salts, and porphyrins, or it can be degraded and converted into serine. In the brain, it functions as a neurotransmitter inhibitor; in addition, it serves as an extracellular communications molecule; therefore, it possesses different antioxidant protector effects (Morales-González, 2009).

6.1.1 Antioxidant activity

Glycine possess a protector effect due to that it prevents due to that it prevents the decrease of antioxidant hepatic enzyme activity after hemorrhagic processes; this effect can be due to

that glycine blocks the activation of Kupffer cells, which produce FR. Likewise, glycine exercises an ascorbate oxidation protector effect by means of cupric ions; consequently, it diminishes hydroxyl radical generation. In addition to this, glycine forms part of glutathione, tripeptidic and intracellular, that combats FR and maintains some essential biological molecules in a reduced chemical state (Morales-González, 2009).

A group of researchers demonstrated the hepatoprotector effect of glycine and vitamin E in a study conducted in rats in which Partial hepatectomy (PH) was practiced with subsequent administration of these antioxidants; finally, it was observed that treatment with either of the two antioxidants causes an increase in the peroxidase dismutase enzyme; it diminishes Thiobarbituric acid (TBARS) levels, exhibiting the protector effect in hepatic regeneration (Parra-Vizuet et al., 2009).

7. Flavonoids

Flavonoids are compounds that make up part of the polyphenols and are also considered essentials nutrients. Their basic chemical structure consists of two benzene rings bound by means of a three-atom heterocyclic carbon chain. Oxidation of the structure gives rise to several families of flavonoids (flavons, flavonols, flavanons, anthocyanins, flavanols, and isoflavons), and the chemical modifications that each family can undergo give rise to >5,000 compounds identified by their particular properties (Morales-González, 2009).

Flavonoid digestion, absorption, and metabolism have common pathways with small differences, such as, for example, unconjugated/non-conjugated flavonoids can be absorbed at the stomach level, while conjugated flavonoids are digested and absorbed at the intestinal level by extracellular enzymes on the enterocyte brush border. After absorption, flavonoids are conjugated by methylation, sulfonation, and glucuronidation reactions due to their biological activity, such as facilitating their excretion by biliary or urinary route. The conjugation type the site where this occurs determine that metabolite's biological action, together with the protein binding for its circulation and interaction with cellular membranes and lipoproteins. Flavonoid metabolites (conjugated or not) penetrate the tissues in which they possess some function (mainly antioxidant), or are metabolized (Morales-González, 2009).

7.1 Silymarin

Silymarin is a compound of natural origin extracted from the *Silybum marianum* plant, popularly known as St. Mary's thistle, whose active ingredients are flavonoids such as silybin, silydianin, and silycristin. This compound has attracted attention because of its possessing antifibrogenic properties, which have permitted it to be studied for its very promising actions in experimental hepatic damage. In general, it possesses functions such as its antioxidant one, and it can diminish hepatic damage because of its cytoprotection as well as due to its inhibition of Kupffer cell function (Sandoval, 2008).

7.1.1 Antioxidant and hepatoprotector action

Silymarin is an active principle that possesses hepatoprotector and regenerative action; its mechanism of action derives from its capacity to counterarrest the action of FR, which are formed due to the action of toxins that damage the cell membranes (lipid peroxidation), competitive inhibition through external cell membrane modification of hepatocytes; it forms

a complex that impedes the entrance of toxins into the interior of liver cells and, on the other hand, metabolically stimulates hepatic cells, in addition to activating RNA biosynthesis of the ribosomes, stimulating protein formation. In a study published by Sandoval et al., in 2008, the authors observed that silymarin's protector effect on hepatic cells in rats when they employed this as a comparison factor on measuring liver weight/animal weight % (hepatomegaly), their values always being less than those of other groups administered with other possibly antioxidant substances; no significant difference was observed between the silymarin group and the silymarin-alcohol group, thus demonstrating the protection of silymarin. On the other hand, silymarin diminishes Kupffer cell activity and the production of glutathione, also inhibiting its oxidation. Participation has also been shown in the increase of protein synthesis in the hepatocyte on stimulating polymerase I RNA activity. Silymarin reduces collagen accumulation by 30% in biliary fibrosis induced in rat (Boigk, 1997). An assay in humans reported a slight increase in the survival of persons with cirrhotic alcoholism compared with untreated controls (Ferenci, 1989).

8. Ethanol metabolism

Ethanol is absorbed rapidly in the gastrointestinal tract; the surface of greatest adsorption is the first portion of the small intestine with 70%; 20% is absorbed in the stomach, and the remainder, in the colon. Diverse factors can cause the increase in absorption speed, such as gastric emptying, ingestion without food, ethanol dilution (maximum absorption occurs at a 20% concentration), and carbonation. Under optimal conditions, 80–90% of the ingested dose is completely absorbed within 60 minutes. Similarly, there are factors that can delay ethanol absorption (from 2–6 hours), including high concentrations of the latter, the presence of food, the co-existence of gastrointestinal diseases, the administration of drugs, and individual variations (Goldfrank et al., 2002).

Once ethanol is absorbed, it is distributed to all of the tissues, being concentrated in greatest proportion in brain, blood, eye, and cerebrospinal fluid, crossing the feto-placental and hematocephalic barrier (Téllez & Cote, 2006). Gender difference is a factor that modifies the distributed ethanol volume; this is due to its hydrosolubility and to that it is not distributed in body fats, which explains why in females this parameter is found diminished compared with males.

Ethanol is eliminated mainly (> 90%) by the liver through the enzymatic oxidation pathway; 5–10% is excreted without changes by the kidneys, lungs, and in sweat (Goldfrank et al., 2002). The liver is the primary site of ethanol metabolism through the following three different enzymatic systems:

8.1 Alcohol dehydrogenases (ADH)

Alcohol dehydrogenases (ADH) are cytoplasmic enzymes with numerous isoforms in the liver of humans, with high specificity for ethanol as substrate; these are codified by three separate genes designated as *ADH1*, *ADH2*, and *ADH3*; these genes translate into peptide subunits denominated alpha, beta, and gamma. Variations in ADH isoforms can explain the significance in alcohol elimination levels among ethnic groups (Feldman et al., 2000).

This enzyme utilizes Nicotinamide adenine dinucleotide (NAD⁺) as a Hydrogen (H⁺) receiver for oxidizing ethanol into acetaldehyde. In this process, H⁺ is transferred from the

substrate (ethanol) to the co-factor (NAD^+), converting it into its reduced form, NADH; likewise, H^+ acetaldehyde is transferred from acetaldehyde to NAD^+ . Later, the acetaldehyde oxidizes into acetate by means of the reduced Aldehyde-dehydrogenase enzyme (ALDH). Under normal conditions, acetate is converted into acetyl coenzyme A (acetyl-CoA), which enters the Krebs cycle and is metabolized into carbon dioxide and water (Goldfrank et al., 2002).

8.2 Microsomal ethanol oxidation system (MEOS)

This system is localized at hepatocyte smooth reticulum cisterns; this cytochrome P-450 2E1-dependent enzymatic system contributes to 5–10% of ethanol oxidation in moderate drinkers, but its activity increases significantly in chronic drinkers by up to 25% (Roldán et al., 2003).

A critical component of MEOS is Cytochrome P-450 2E1 (CYP2E1); this enzyme catalyzes not only ethanol oxidation, but also the metabolism of other substances such as paracetamol, the barbiturates, the haloalkalines, and the nitrosamines, among others (Feldman et al., 2000).

CYP2E1 utilizes Nicotinamide adenin dinucleotide phosphate (NADP^+) as a (H^+) receiver for oxidizing ethanol into acetaldehyde. In this process, H^+ is transferred from the substrate (ethanol) to the co-factor (NADP^+), converting this into its reduced form, NADH; Similarly, the acetaldehyde is as the H^+ transfers from acetaldehyde to NADP^+ (Goldfrank et al., 2002).

While MEOS participation is more active in the ethanol metabolism of chronic than in occasional drinkers and its relative contribution in comparison with ADH is difficult to determine, notwithstanding this, MEOS is important in the pathogeny of ethanol consumption-associated hepatic lesions because oxidation of this CYP2E1-mediated substance produces reactive oxygen intermediaries as subproducts (Feldman et al., 2000).

8.3 Catalase system

This presents in the peroxisomes and utilizes Hydrogen peroxide (H_2O_2) for ethanol oxidation; its contribution is minimal (Roldán et al., 2003). This system exists in a tight relationship with the reduced-oxidase-glutathione system and, like MEOS, is induced by chronic ethanol consumption. Ethanol oxidizes into acetaldehyde, utilizing H_2O_2 as co-enzyme; this metabolite continues the same course as for converting into acetate through the ALDH enzyme (Morales-González et al., 2001; Morales-González et al., 1998).

Any of the three ethanol pathways transforms it into acetaldehyde, which afterward is oxidized into acetate by the Aldehyde-dehydrogenase (ALDH) enzyme. Aldehyde is a highly reactive compound and is potentially toxic for the hepatocyte.

9. Hepatic regeneration

Hepatic regeneration (HR) is a process arising throughout evolution to protect animals from the catastrophic results of hepatic necrosis caused by the effect of the toxins of plants that serve them as food; this extraordinary process has been the object of the curiosity of scientists of all times. In ancient Greece, the myth of the chained Prometheus in Caucasus mountains of the Caucasus while an eagle daily devoured his entrails, which regenerated

during the night, is based on the recognition from those times of hepatic regeneration (Michalopoulos & DeFrances, 1997).

Several terms such as replacement of lost parts, restitution, or repair have been employed to designate “regeneration”, which is indicative of the active cell proliferation that invariably precedes differentiation. After partial liver extraction, cell proliferation does not occur at the level of the incision, new lobules do not develop instead of the removed part; ascribing to cell migration and differentiation results in the formation of new lobules, and the liver’s preoperative weight is rapidly restored (Higgins & Anderson, 1931).

The liver in humans as well as in rodents possess a noteworthy capacity of regenerative response to several stimuli, including massive destruction of hepatic tissue by toxins, viral agents, or by surgical desertion; liver regeneration depends on the ability of the hepatocytes to be submitted to cell division, which is strictly controlled by intra- and extrahepatic factors (Gutiérrez-Salinas et al., 1999).

HG is a physiological process that includes hypertrophy (increase in cell size or in protein content in the replicative phase) and hyperplasia (increase in cell number), the latter governed to a greater degree by functional than by anatomical needs (Palmes & Spiegel, 2004). Studies with hepatic resections in large animals (dogs and primates) and in humans have established that the regenerative response is proportional to the amount of the liver removed (Michalopoulos & DeFrances, 1997).

Partial hepatectomy (PH) is the best studied animal hepatic regeneration model and was proposed in 1931 by Higgins and Anderson and consists of the surgical extraction of 70% of hepatic mass; hepatic regeneration is induced at an important stage when all of the hepatocytes are virtually found in phase G₀ of the cell cycle. Stimulated by PH, all of the hepatocytes in synchronized fashion enter into the cell cycle; initiation of maximum Deoxyribonucleic acid (DNA) synthesis takes place 24 hours after PH and 7–14 days after the removed hepatic mass is restored (Palmes & Spiegel, 2004).

In contrast with other regenerating tissues (bone marrow and skin) hepatic regeneration does not depend on a small population of progenitor cells; liver regeneration after PH is carried out by the proliferation of all of the existing mature cell populations that comprise the intact organ; this includes the hepatocytes, biliary endothelial cells, fenestrated endothelial cells, Kupffer cells and Ito cells; all of these cells divide during hepatic proliferation, hepatocytes the first to do this. Cell proliferation kinetics differs slightly from one species to another; the first DNA synthesis peak in hepatocytes occurs at 24 hours, with a second peak between 36 and 48 hours; when three quarters of the hepatic tissue is removed, restoration of the original number of hepatocytes theoretically requires 1.66 cell cycles per residual hepatocyte (Michalopoulos & DeFrances, 1997).

10. Ethanol-derived hepatic damage

The liver is the main target organ of ethanol toxicity; it has been demonstrated experimentally that chronic ethanol ingestion leads to an increase of lipid peroxidation products and a decrease of antioxidant factors such as glutathione (GSH) and derived enzymes. Likewise, oxidative stress has been related as the main factor implicated in

alterations derived from its chronic consumption, from the Central nervous system (CNS) as well as from the peripheral nervous system (Díaz et al., 2002).

There are several mechanisms involved in ethanol consumption-related liver damage; the former results from the effects of alcohol dehydrogenase (ADH) mediated by the excessive generation of NADH and acetaldehyde, which generates the formation of FR (Lieber, 2004). Acetaldehyde increases the production of alkanes and causes an imbalance in potential cytosolic redox on altering the NAD^+/NADH relationship, as occurs in the mitochondria; this redox alteration favors the production of lipoperoxides, which increase damage to the cell (Gutiérrez-Salinas & Morales-González, 2004).

Acetaldehyde inactivates the enzymes, diminishing DNA repair, antibody production, and glutathione depletion, and increasing mitochondrial toxicity, endangering oxygen utilization, and increasing collagen synthesis (Lieber, 2000).

Another probable mechanism of hepatic damage associated with chronic ethanol consumption is the increase in the synthesis of fatty acids and triglycerides and a decrease of the oxidation of the former, generating hyperlipidemias that leads to the development of fatty liver, in addition to inhibiting fatty acids utilization and the availability of precursors, which stimulate the hepatic synthesis of triglycerides (Téllez & Cote, 2006).

Previous studies have suggested that Kupffer cells are involved in hepatic damage caused by ethanol consumption; this is due to that there are reports that ethanol alters the functions of these cells, such as phagocytosis, bactericide activity, and the production of inflammatory cytokines such as Tumor growth factor alpha (TNF)- α , Interleukin 1 (IL-1), and IL-6, among others, which result in hepatic cell toxicity (Thurman et al., 1998). It has been reported that TNF- α and IL-1 inhibit protein synthesis in hepatocytes in rat, in addition to stimulating neutrophil migration and activation, as well as protease induction and FR release (Thurman, 1998).

Cytokines and chemokines originated by the Kupffer cells employ autocrine as well as paracrine effects that initiate the defensive response in the liver, but that also promote the infiltration of inflammatory leukocytes and activate the oxidative attack response, accompanied by strong damage originating from degrading cytokines and proteins. Cellular infiltration of activated neutrophils produces oxygen FR and secretes other toxic mediators; additionally, these can increase the inflammatory response, causing damage and cell death (Thurman, 1998).

Ethanol consumption induces changes in the mitochondrial membrane, such as Mitochondrial permeability transition (MPT), which is associated with loss of mitochondrial energy, mitochondrial matrix inflammation, and external membrane rupture; this is accompanied by the release of numerous proapoptotic factors; in addition, TNF- α activates different hepatic cell cascades, resulting in the stimulation of mitotic genes such as *p38* of Mitogen-activated protein kinases (MAPK) and the Jun N-terminal kinase (JNK), which affect mitochondrial sensitivity to the proapoptotic stimulus as follows: JNK by the phosphorylation of proapoptotic proteins such as Bcl-2 and Bcl-X_L, and *p38* MAPK by reinforcing the effects of the Bcl-2 proapoptotic Bax Protein family.

Acute ethanol consumption can produce a hypermetabolic state in the liver that is characterized by increase in mitochondrial respiration, which is driven by the great demand

for NADH reoxidation produced during ethanol metabolism by cytosolic ADH (Adachi & Ishii, 2002); in addition, it alters hepatic microcirculation by stimulating endothelial-1 production (Thurman, 1998); similarly, the acetaldehyde generated by ethanol metabolism causes hypoxia on chemically reacting with free sulfate groups such as glutathione, in such a way as to alter the reaction of this metabolite, which activates the xanthine oxidase and xanthine dehydrogenase enzymes, in order to finally diminish the NAD^+/NADH equilibrium (Gutiérrez-Salinas & Morales-González, 2004).

Depletion of antioxidant levels, above all that of hepatic glutathione, caused by acute as well as by chronic ethanol consumption, increases oxidative stress, which induces changes in the mitochondrial membrane, such as diminution of the mitochondrial membrane potential in hepatocytes and MPT, both inhibited by the antioxidants or by an ADH inhibitor (Adachi & Ishii 2002).

11. Inhibition of hepatic regeneration by ethanol

When there is an important, functional hepatic mass loss, such as occurs in PH, the remnant tissue undergoes a regeneration process in which the removed tissue is replaced in its totality; during this process, DNA synthesis increases notably, reaching a maximal peak of 23 at 25 hours postsurgery. After PH, hepatic tissue becomes more vulnerable to the damage caused by consumption of xenobiotics, particularly ethanol administration, which causes damage to HR, above all in the early regenerative process phase (Morales-González et al., 2001; Morales-González et al., 1999).

Studies performed in animals in which PH was carried out suggest that the acute ethanol administration rapidly inhibits the result of the HR after surgery; this has been assessed by a frank diminution of the cell proliferation parameters in the remnant liver. Although the exact mechanism by which ethanol inhibits HR, it is reasonable to assume that this hepatotoxicity could alter the total metabolism of the regenerating liver, which includes ethanol oxidation into acetaldehyde, catalyzed by ADH, and the later conversion of this into acetate by means of the mitochondrial ALDH (Gutiérrez-Salinas, 1999).

Acute ethanol administration produces structural and biochemical changes such as partial inhibition of protein and DNA synthesis, which indicates the diminution of the mitotic index, transitory accumulation of fat, the presence of inflammation, modifications in hepatocellular organization, diminution of weight gain in the regenerating liver, and inhibition of hepatic regeneration (Morales-González et al., 2001).

Some physiological processes that are altered by ethanol are metabolite levels in serum (glucose, triglycerides, albumin, and bilirubin), in addition to causing modification of the serum activity of enzymes that reflect liver integrity (alanine and aspartate aminotransferase, lactate dehydrogenase, ornithine carbamoyltransferase, and glutamate dehydrogenase); also, on inhibiting DNA synthesis and the activity of enzymes intimately related with this process, such as Thymidine synthetase (TS) and Thymidine kinase (TK), in addition to diminution of the mitotic index (Morales-González et al., 2001).

A sole dose of ethanol is capable of significantly inhibiting the synthesis of the protein ornithine decarboxylase, in addition to causing tyrosine aminotransferase degradation, which suggests that acute ethanol consumption inhibits protein synthesis and regenerating

liver activity on transcriptional levels, interfering with RNA synthesis in the nucleus (Morales-González et al., 2001; Morales-González et al., 1999).

Investigations that have been conducted have demonstrated that the acute as well as the chronic ethanol administration jeopardize the incorporation of thymidine into the DNA of hepatocytes of rats on which PH had been performed with or without diminution of the DNA contents, in addition to reporting that chronic consumption of this substance inhibits regeneration 24 hours after the PH due to delay in the induction of ornithine carbamoyltransferase activity (Yoshida et al., 1997).

It has been suggested that damage cause by FR as the product of ethanol consumption occurs at the early phase of HR; on the other hand, a transcending increase has been reported in mitochondrial lipoperoxidation of the liver in rats after PH. In the same study, a diminution was also observed in the early HR phase of mitochondrial glutathione levels (Guerrieri et al., 1998).

12. Ethanol and free radicals

One factor that suggested that ethanol causes cell damage due to its hepatic metabolism is the excessive generation of FR, which can be the result of a state denominated oxidative stress; this is because any of ethanol's metabolic pathways, principally MEOS, is made up of chemicals oxido-reduction reactions, which produce highly unstable molecules called Reactive oxygen species (ROS), such as the superoxide anion (O_2^-), Hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH^\bullet) (Nanji & French, 2003).

FR can perform four main reactions (Wu & Cederbaum, 2003):

1. Hydrogen abstraction, in which FR interact with another molecule that acts as the donor of an atom of H^\bullet . As a result, FR bind to H^\bullet and become more stable, while the donor is converted into a FR.
2. Addition. Because the FR binds to a more stable molecule, which converts a receiver molecule into a FR.
3. Termination. In this, two FR react between themselves to form a more stable compound.
4. Disproportion. This consists of two LR that are identical to each other react between themselves. In this reaction, one FR acts as an electron donor and the other, as an electron receiver. In this manner, they become two more stable molecules.

Free radicals are chemical species that possess an unpaired electron in their last layer, which allows these to react with a high number of molecules of all types, first oxidizing these and afterward attacking their structures. If lipids (polyunsaturated fatty acids) are involved, they damage the structures rich in the latter, such as cell membranes and lipoproteins (Rodríguez et al., 2001). Within this generic concept, the partially reduced forms of oxygen are denominated Reactive oxygen species (ROS). This is a collective term that includes not only oxygen free radicals, but also some reactive non-radical oxygen derivatives.

The oxidating mechanism of FR is intimately linked to their origin, which follows a sequence of chain reactions; in these reactions, a very reactive molecule is capable of reacting with another, non-reactive molecule, inducing in the latter the formation of a FR ready to initiate a new neutrophilic attack, and so on successively.

The greatest source of ROS production in the cell is the mitochondrial respiratory chain, which utilizes approximately 80-90% of the O_2 that a person consumes; another important source of ROS, especially in the liver, is a group of Mixed function oxidase (MFO) Cytochrome P-450 enzymes. In addition to the ROS generation that takes place naturally in the organism, humans are constantly exposed to environmental FR including ROS in the form of radiation, Ultraviolet (UV) light, smoke, tobacco smoke, pesticides, and drugs utilized in the treatment of cancer (Wu & Cederbaum, 2003).

The increase in O_2^- and H_2O_2 formation is justified with the finding that in aging, electron flow conditions are modified in the transport chain of these, which is the last stage of high energy proton production, and whose passage through the internal mitochondrial membrane generates an electrical gradient that provides the energy necessary for forming ATP (5-Adenosin triphosphate). Researchers postulate that the ROS generated can produce damage to the internal mitochondrial membrane as well as to electron transport chain components or to mitochondrial DNA, which further increases ROS production and consequently, more damage to the mitochondria and an increase of oxidative stress due to increased oxidant production. FR produced during aerobic stress cause oxidative damage that accumulates and results in a gradual loss of the homeostatic mechanisms, in an interference of genetic expression patterns, and loss of cell functional capacity, which leads to aging and death.

ROS generation promotes the decrease of intracellular glutathione, elevation of cytoplasmic calcium, lipid peroxidation of the membranes, and a series of chain reactions that are accompanied by the disappearance of glycogen, decrease of ATP, and the descent of the energy state of hepatic cells; these events are the origin of membrane destruction and cell death (Thurman et al., 1999). Sustained elevation of cytoplasmic calcium is associated with activation of calcium-dependent enzymes such as phospholipase A_2 , glycogen phosphorylase, and the endonucleases, which cause plasmatic membrane ruptures and DNA molecule fragmentation. On the other hand, the transitory elevation of intracellular calcium intervenes in the progression of cell division in G_1 -to-S transitions and in those of the G_2 -to-M phase. Immediately after cell death, hepatocellular proliferation begins in order to re-establish cell populations that have been destroyed, thus restoring hepatic function (Andrés & Cascales, 2002).

The OH^- radical is highly toxic for the hepatocytes, which do not possess a direct system for its elimination; this FR is produced intracellularly by two reactions that occur spontaneously and that are catalyzed by a transition metal, generally iron (Fe), which are termed the Fenton reaction and the Haber-Weiss reaction (Boveris et al., 2000).

In this reaction, Hydrogen peroxide (H_2O_2) in the presence of Fe as catalyzer produce the hydroxyl radical (OH^\bullet).

The superoxide radical (O_2^-) leads to the formation of Hydrogen peroxide (H_2O_2) and both products of the partial reduction of oxygen (O_2) produce the hydroxyl radical (OH^\bullet).

13. Effect of glycine in hepatic regeneration in the presence of ethanol damage

Recent studies have reported the beneficial effects of glycine, including protection against toxicity induced by anoxia and oxidative stress caused by several toxic agents for the cell,

including ethanol. These investigations have demonstrated that glycine blocks the increase of Calcium (Ca^{2+}) in hepatocytes, caused by agonists released during stress, such as Prostaglandin E_2 (PGE_2) and the adrenergic hormones (Qu et al., 2002).

It is known that the early, ethanol consumption-related hepatic-damage phase is characterized by steatosis, inflammation, and necrosis, which are principally mediated by resident Kupffer cells in liver macrophages (Yin et al., 1998). Senthilkumar and colleagues (2004) in a model of ethanol-intoxicated rats administered with glycine, observed a significant diminution of total free fatty acid levels in the liver, in addition to a decrease in steatosis and necrosis after glycine administration (Senthilkumar & Nalini, 2004). In another study conducted by the same researchers, the latter demonstrate that treatment with glycine offers protection against FR-mediated oxidative stress in the membrane of erythrocytes, plasma, and hepatocytes of rats with ethanol-induced hepatic damage (Senthilkumar et al., 2004).

It has been reported that glycine inhibits macrophage activation and $\text{TNF-}\alpha$ release; this amino acid prevents liver damage after chronic exposure to ethanol and attenuates the lipoperoxidation and glutathione depletion induced by diverse xenobiotics (Mauriz et al., 2001). Kupffer cells in liver constitute 80% of the resident macrophages in the organism. Glycine blocks the systemic inflammatory process arising in a broad variety of pathological states, due to the activation of macrophages that release potent inflammatory mediators such as toxic cytokines and eicosanoids, which perform an important role in the progressive inflammatory response (Matilla et al., 2002).

Prior studies have demonstrated that glycine administration prevents several forms of hepatic lesions; because it prevents the necrosis and the inflammation developed in the early phase during chronic ethanol administration, glycine's mechanism of protection against damage involves the Kupffer cells (Ishizaki et al., 2004). As mentioned previously, Kupffer cell activation releases active substances such as NO, $\text{TNF-}\alpha$, ROS, Interleukin β ($\text{IL-}\beta$), IL-6, and TGF, which cause potential damage to the liver; in particular, $\text{TNF-}\alpha$, as a product of Lipopolysaccharide (LPS), plays an important role in the induction of hepatic damage on activating gene transcription factors of nuclear regulator cytokines such as $\text{NF-}\kappa\text{B}$, which is related with the inflammatory response and which plays an important role in the activation of hepatic stellate cells (Mauriz et al., 2001).

One probable hepatoprotector mechanism of glycine is due to that this amino acid activates the chloride channels, causing a diminution of intracellular Calcium, (Ca^{2+}) concentration in the Kupffer cells, which hyperpolarize the cell membrane, rendering the opening of voltage-dependent Ca^{2+} channels difficult; in addition to inhibiting macrophage activation and $\text{TNF-}\alpha$ release, glycine prevents liver damage after chronic exposure to ethanol and attenuates lipoperoxidation and hepatotoxin-induced glutathione depletion (Senthilkumar & Nalini, 2004). It is well known that intracellular Ca^{2+} is important for activation and release of inflammatory cytokines. $\text{TNF-}\alpha$ production by Kupffer cells has been associated with an increase of Ca^{2+} (Ishizaki et al., 2004).

14. Effect of vitamin E on liver regeneration in the presence of ethanol-derived damage

Vitamin E is well known for its antioxidant properties; these function as rupturing the antioxidant chain that prevents the propagation of FR reactions; this protects cells from

oxidative stress. Vitamin E is particularly important, protecting cells against lipoperoxidation, during which FR attack the fatty acids, causing structural damage to the membrane, resulting in the formation of secondary cytotoxic products such as MDA, among others (Jervis & Robaire, 2004).

Since its discovery, α -tocopherol has shown to possess two important functions in the membrane: the first as a liposoluble antioxidant that acts to prevent FR damage to polyunsaturated acids, and the second, as a membrane stabilizing agent, which aids in preventing phospholipid-caused lesions. It has also shown to inhibit protein kinase C (Bradford et al., 2003).

Studies *in vitro* in animals and in artificial membranes have demonstrated that tocopherols interact with polyunsaturated-lipid acyl groups, stabilizing the membranes and eliminating ROS and the subproducts of oxidative stress (Sattler et al., 2004).

In vivo, vitamin E acts by rupturing the antioxidant chain and in this manner preventing propagation of damage to cell membranes that cause FR. This vitamin protects polyunsaturated fatty acids from biological membrane phospholipids and lipoproteins in plasma. When lipid peroxides oxidize and are converted into peroxy radicals (ROO^\bullet), the phenolic OH^- tocopherol group reacts with an organic ROO^\bullet radical to form the corresponding organic hydroperoxide and the tocopheroxyl radical (Vit E-O^\bullet) (Shils et al., 1999).

α -Tocopherol inhibits the activity of monocyte protein kinase C, followed by inhibition of phosphorylation and translocation of the p47 cytosolic factor, damaging the NADPH-oxidase assembly and O_2^- production; α -tocopherol exerts an important biological effect on inhibiting the release of proinflammatory cytokines, interleukin 1β , and inhibition of the 5-lipoxygenase pathway.

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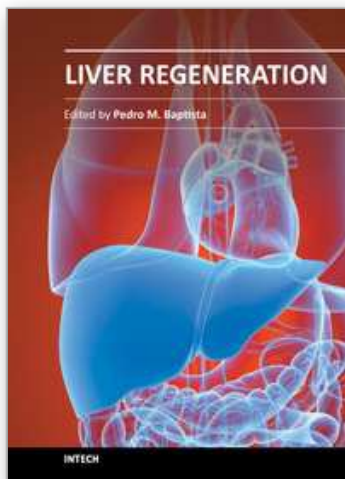
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Liver Regeneration

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Doctors and scientists have been aware of the "phenomenon" of liver regeneration since the time of the ancient Greeks, illustrated by the mythic tale of Prometheus' punishment. Nevertheless, true insight into its intricate mechanisms have only become available in the 20th century. Since then, the pathways and mechanisms involved in restoring the liver to its normal function after injury have been resolutely described and characterized, from the hepatic stem/progenitor cell activation and expansion to the more systemic mechanisms involving other tissues and organs like bone-marrow progenitor cell mobilization. This book describes some of the complex mechanisms involved in liver regeneration and provides examples of the most up-to-date strategies used to induce liver regeneration, both in the clinic and in the laboratory. The information presented will hopefully benefit not only professionals in the liver field, but also people in other areas of science (pharmacology, toxicology, etc) that wish to expand their knowledge of the fundamental biology that orchestrates liver injury and regeneration.

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