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Interpretation of Role of Both Perfluorooctane Sulfonateand Quercetin on Adult Liver

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Abstract
Perfluorooctane sulfonate (PFOS) is one of the most widely used PFAS. This substance contains a hydrophobic and lipophobic perfluoroalkyl chain and a sulfonic acid group that adds the polarity of this substance. These structural characteristics support their applications and usage as water and oil repellents, firefighting foams, lubricants, surfactant additives, and coating agents. Hepatotoxicity is chemical-driven liver injury.Exposure to PFOS can cause oxidative damage to hepatocytes. Quercetin (QE)has been reported to be beneficial to human healthsuch as osteoporosis, pulmonary and cardiovascular diseases, and aging.
Key words: Liver, Quercetin, Perfluorooctane sulfonate.

Anatomy of Human Liver

The human liver is the 2nd largest organ (second to the skin). It is the most unique metabolic center in the body. Its weight varies between 1.4–1.8 kg in adult men and 1.2–1.4 kg in adult women. It is about 2% of body weight (BW) **(1)**.

The liver is a wedge-shaped organ occupying a substantial portion of upper abdominal cavity. It is reddish brown in color, located immediately below the diaphragm, filling most of the right hypochondriac and part of the epigastric regions. It has a dense, irregular sub peritoneal fibrous capsule, Glisson's capsule, which is loosely attached over the entire circumference of the liver except at the porta hepatis. The liver is completely enveloped by visceral peritoneum except at sites of bare areas**(2,3and 4)**.

The liver is soft to firm in consistency; this depends partly on the volume of blood the liver contains and the fat content. The liver is usually described as having diaphragmatic and inferior (visceral) surfaces separated from each other by a distinct sharp inferior border. The diaphragmatic surface is directed superiorly, anteriorly and to the right with no definable borders separating them**(5).**

The liver is suspended from the diaphragm superiorly by the coronary ligaments, which continues outward to form the right and left triangular ligaments, anteriorly by the falciform ligament and at the porta hepatis by the gastrohepatic and hepatoduodenal ligaments. The hepatoduodenal ligament envelops the porta hepatis **(6).**

The porta hepatis or hilum of the liver is a deep, short, transverse fissure that passes across the left posterior aspect of the undersurface of the right lobe of the liver between the quadrate lobe in front and the caudate process behind. It contains hepatic ducts anteriorly, the portal vein and its branches posteriorly and hepatic artery with its branches in between them. Also, porta hepatis contains hepatic nervous plexuses as they ascend into the liver and some lymph vessels as they exit from the liver **(7)**.

Standring (5)stated that stabilization of liver in its position in the right upper quadrant of the abdomen is obtained by both static and dynamic factors that include the suspensory attachments at the posterior abdominal wall to the inferior vena cava, hepatic veins, coronary and triangular ligaments (primary factors); the support provided by the right kidney, right colic flexure and duodenopancreatic complex (secondary factors); and the attachment to the anterior abdominal wall and diaphragm by the falciform ligament (tertiary factors). The inferior vena cava (IVC) and the hepatic veins especially the right hepatic vein are the most important anatomical structures that support the liver. Other factors that affect the position of the liver within the abdominal cavity include movement of the diaphragm during respiration and positive intra-abdominal pressure.

The liver has two surfaces, diaphragmatic and visceral. The diaphragmatic surface is relatively convex and molded to the undersurface of the diaphragm; and is subdivided into four surfaces which are anterior, posterior, superior and right surfaces. The anterior surface is convex, triangular and covered by peritoneum expect at the site of attachment of falciform ligament, it is in contact with diaphragm which separates it from pleura and sixth to tenth ribs and cartilages on right side and separate it from seventh to ninth costal cartilages on left side. The right surface is enveloped by peritoneum and lies close to the right dome of the diaphragm that separates it from the right lung and pleura and the seventh to eleventh ribs. There is a sharp inferior border which separates the right and anterior surfaces from the

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visceral surface **(8).**

The superior surface is considered the largest surface and lies below the diaphragm, but separated from it by peritoneum except at the site where the two layers of the falciform ligament diverges. The majority of the superior surface lies beneath the right dome of diaphragm. The left side of the superior surface lies beneath part of the left dome of the diaphragm. On the center of superior surface, there is a shallow cardiac impression that corresponds to the position of the heart above the central tendon of the diaphragm **(5).**
Posterior surface of the liver is convex and much of it is attached to diaphragm by loose connective tissue, forming the triangular bare area. IVC is present in a tunnel or groove in the medial end of bare area. To the left of this caval groove, the posterior surface of the liver is formed by the caudate lobe, and covered by a layer of peritoneum that is continuous with that of the inferior layer of the coronary ligament and the layers of the lesser omentum. The fissure for the ligamentum venosum cuts deeply in front of the caudate lobe and contains the two layers of the lesser omentum. On posterior surface of left lobe, there is a shallow impression near the upper end of the fissure for the ligamentum venosum these related to the abdominal part of the esophagus. To the left of this impression the posterior surface of the left lobe is related to part of the fundus of the stomach. Together these posterior relations make up what is called the 'bed' of the liver **(5).**

The visceral surface of the liver is also covered with visceral peritoneum except at the site of the fossa for the gallbladder rand the porta hepatis. In contrast to the smooth diaphragmatic surface, the visceral surface has multiple impressions and fissures from the contact with other organs. Two sagittal oriented fissures, linked centrally by the transverse porta hepatis, form the shape of letter H on the visceral surface. The right sagittal fissure is the continuous groove formed posteriorly by the groove for IVC and anteriorly by the fossa for the gallbladder. The left sagittal (umbilical) fissure is the continuous groove formed posteriorly by the fissure for the ligamentum venosum and anteriorly by the fissure for the round ligament. The quadrate lobe lies between the gallbladder and fissure for the ligamentum teres **(9).**

The liver is anatomically divided into a larger right and a smaller left lobe where the caudate lobe and the quadrate lobe were included as a part of the right lobe. This subdivision of the liver doesn't follow the arrangement of the vascular and biliary channels within the liver. On the other hand, the functional division of the liver into right and left halves is along an oblique plane that passes through the center of the bed of the gallbladder and the groove for the inferior vena cava. Thus, the quadrate and caudate lobes functionally belong to the left lobe of the liver **(8).**

Segments and sectors of the human liver
The functional anatomy of the liver is based on Chouinard's division of the liver into eight functional segments, based on the distribution of the intrahepatic biliary system and the portal venous branches in the parenchyma. The liver is divided into four portal sectors by the four main branches of the portal vein. These are right lateral, left lateral, left medial and right medial (sometimes, the term posterior is used instead of lateral and anterior instead of medial). The three main hepatic veins are present between these sectors as intersectoral veins **(Fig. 1)**. These intersectoral planes are also called portal fissures. Each sector is then subdivided into segments (usually two), this is based on their supply by tertiary divisions of the vascular biliary (Glissonian) sheaths **(5).**
The sectors of the liver are: right lateral sector (segments VI and VII); right medial sector (segments V and VIII); left medial sector (segments III and IV and part of I) and left lateral sector (segment II). Segments are numbered clockwise from below, starting with segment I and ending with segment VIII.

- **Segment (I):** corresponds to the anatomical caudate lobe and lies posterior to segment IV.
- **Segment (II):** lies posterolateral to the left portal fissure and is the only segment in the left lateral sector of the liver.
- **Segment (III):** lies between the umbilical fissure and the left portal fissure.
- **Segment (IV):** Lays between the umbilical fissure and the main portal fissure, immediately anterior to segment I.
- **Segment (V):** is the inferior segment of the right medial sector and lies between the middle and the right hepatic veins.
- **Segment (VI):** forms the inferior part of the right lateral sector posterior to the right portal fissure.
- **Segment (VII):** forms the superior part of the right lateral sector and lies behind the right hepatic vein.
- **Segment (VIII):** is the superior part of the right medial sector (**Fig.1**) **(5).**

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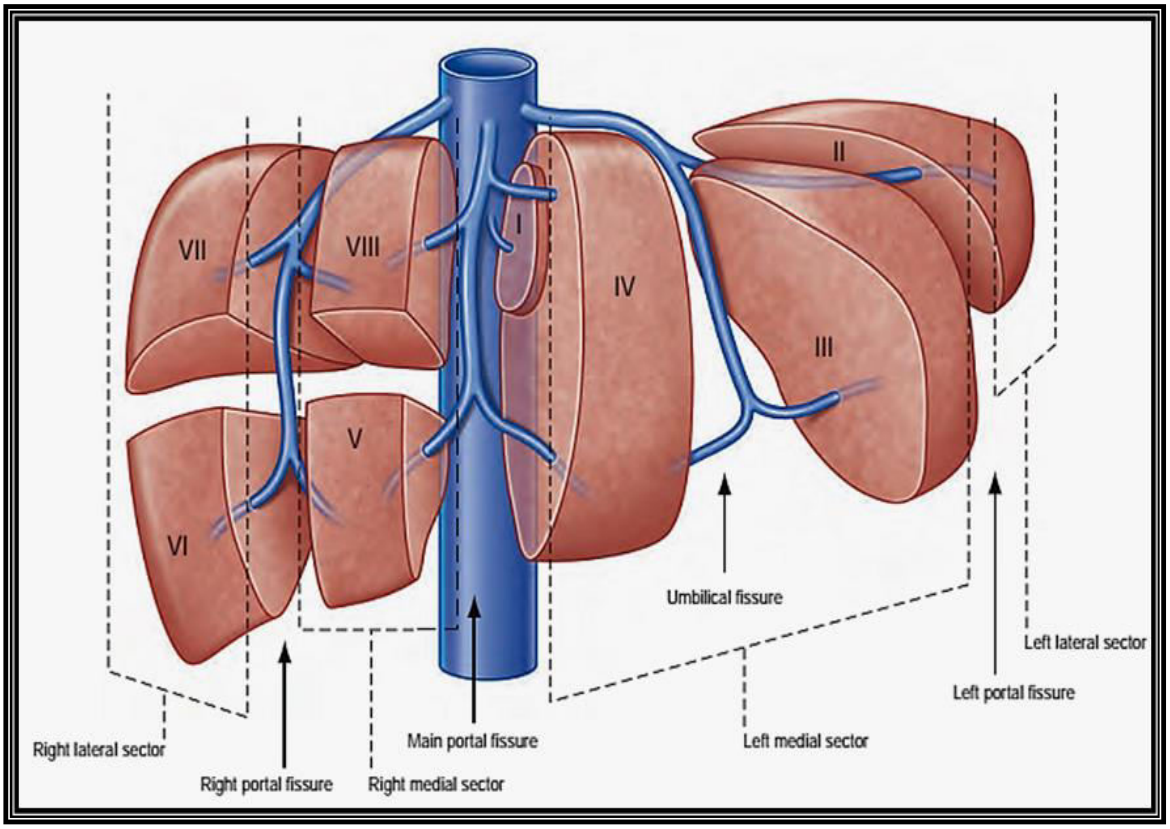

Fig. (1): The fissures and sectors of the liver according to Couinaud's division **(5).**

Blood supply of the human liver:

The liver is a very vascular organ. The afferent blood supply of the liver has dual origin. The portal vein (formed by the union of superior mesenteric and splenic veins) brings 75–80% of the blood to the liver. It carries mixed blood (40% oxygenated) and nutrients absorbed from the alimentary tract to the hepatic sinusoids. The remaining 20–25% from the hepatic artery (originates from the coeliac trunk of the abdominal aorta) supplying the non-parenchymal structures, mainly the intrahepatic bile ducts **(9).**

Both portal vein and hepatic artery divide initially to form right and left portal veins and hepatic arteries, respectively, supplying the right and the left lobes of liver. Within each lobe they subdivide further into secondary and tertiary branches supplying the hepatic segments. The arterial and portal blood mixes within the hepatic sinusoids before draining into the systemic circulation. The hepatic sinusoids drain into intralobular veins, which unite to form sub lobular veins that eventually unite to form hepatic veins that drain into the inferior vena cava. There are three hepatic veins: right, intermediate (middle) and left that provide the venous outflow **(10)**.

The right lobe of liver receives the first large branch of the portal vein stem, called right portal vein and present on the right side. The second branch, called caudate portal vein, is situated on the left side and supports the caudate lobe. In addition, other very small veins, originating directly from the main portal vein and its right and left branches enter the paracaval portion (caudate process) **(11)**.

The blood sinusoids drain into intralobular veins, which usually unite to from sub lobular veins that are ultimately unite to form hepatic vein (**Fig. 2)(12and 10).**

The liver drains by three major hepatic veins (left, intermediate or middle and right) into the suprahepatic part of IVC and via numerous minor hepatic veins that drain into the retro hepatic inferior vena cava. The three major veins are located between the four sectors of the liver Thus, the right hepatic vein lies between the right medial and lateral sectors, the middle hepatic vein lies between the right and left hemi livers, and the left hepatic vein lies between the left medial and lateral sectors **(5).**

There is some anastomosis between portal venous channels in the liver and the azygos system of veins above the diaphragm across the bare area of the liver **(8).**

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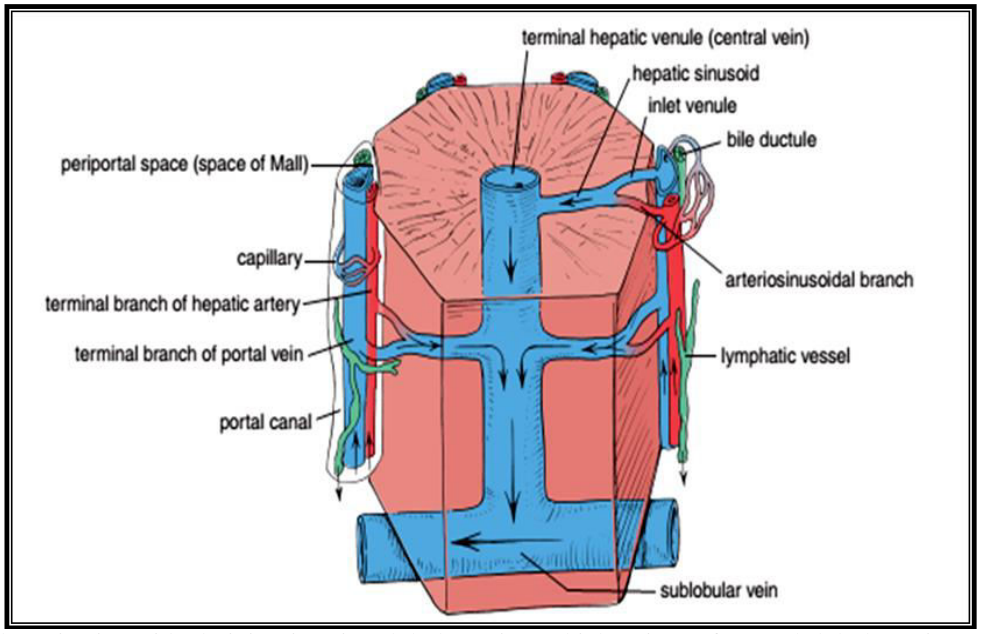

Fig. (2): The hepatic sinusoids draining into intralobular veins, which unite to form sub lobular veins, the portal triad and the periportal space (space of Mall)**(12).**

Nerve supply of the liver:

The liver has a dual innervation. The parenchymal supply arises from the hepatic plexus (the largest derivative of the celiac plexus) and contain parasympathetic (vagal) and sympathetic fibers. They reach the liver through the porta hepatis and mostly accompany the bile ducts and hepatic arteries but very few fibers may run directly within the liver parenchyma. The lower intercostal nerves supply the capsule by some fine branches, particularly in the 'bare area' and superior surface; thus, distension or disruption of the liver capsule causes quite well localized sharp pain**(5).**

Lymphatic drainage of the liver:

The liver is the most important lymph producing organ. Between one quarter to one half of the lymph entering the thoracic duct comes from the liver. The lymphatic vessels of the liver are classified into superficial lymphatic in sub-peritoneal fibrous capsule of the liver (Glisson's capsule) which forms its outer surface, and deep lymphatic in the connective tissue, which accompany the ramifications of hepatic vein and the portal triad. Most lymph is formed in the perisinusoidal spaces (space of Disse) and drain into the deep lymphatics in the surrounding intralobular portal triads **(9).**

The superficial lymphatic drains into the hepatic lymph nodes which scattered along the hepatic ducts and vessels in the lesser omentum. Lymphatic vessels which come from the hepatic nodes drain into celiac lymph nodes, which in turn drain into the cisterna chili; while lymphatic vessels come from right triangular, and the coronary ligaments may directly enter the thoracic duct without any intervening node **(9).**

In addition, deep lymphatics from upper portion of the liver (majority of posterior surface, the posterior part of the inferior surface of the right lobe and the surface of the caudate lobe) form ascending trunks which pass in the diaphragm through the caval opening to drain into nodes around the end of the inferior vena cava. While lymphatic vessels from the lower portion of the liver emerge from the porta hepatis form descending trunks and drain into the hepatic nodes **(5).**

Histological structure of the liver

Histologically, the liver includes four components which are parenchyma, hepatic sinusoids, perisinusoidal spaces (spaces of Disse) and connective tissue stroma. Parenchyma consists of 1- parenchymal cells, organized plates of hepatocytes. 2- non-parenchymal cells include Pit cells, the Kupffer cells, Ito stellate cells and endothelial cells. Sinusoids are channels which lie between the plates of hepatocytes, while perisinusoidal spaces are spaces which lie between the sinusoidal endothelium and the hepatocytes. Connective tissue stroma is continuous with the Glisson's capsule (a thin layer of moderately dense connective tissue) a thin connective tissue septa arise from it and enter the substance of the liver at the porta hepatis and divides it into lobes and ensheath most of the blood vessels, bile ducts, nerves, and lymphatics (**13,14).**

Three ways are used to describe the structure of the liver: the classic lobule, the liver acinus and the portal lobule**(12).**

The classical liver lobule was the first to be defined histologically as the portal areas are connected by relatively thick layers of connective tissue in some species (e.g., the pig.) however, in humans, there is normally very little interlobular connective tissue. The classical hepatic lobule is roughly hexagonal in shape measuring about 2.0 X 0.7 mm. The central vein occupies the center of the lobule and the hepatocyte plates and sinusoids radiate from it to the periphery of

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the lobule. At the angles of the lobule, the portal tracts and loose stromal connective tissue are present. Where three classical lobules are in contact with each other, the connective tissue elements are increased, and these regions are known as portal areas (triads) that contain branches of the hepatic artery, tributaries of portal vein and interlobular bile ducts**(15)**.

Portal areas are isolated from the liver parenchyma by the limiting plate, a sleeve of modified hepatocyte. In addition, a narrow space, the space of Möll, separates the limiting plate from the connective tissue of the portal area. This space is thought to be one of the sites where lymph originates in the liver. According to this concept, blood flows from the periphery to the center of the lobule into the central vein. Bile, manufactured by liver cells, enters into small intercellular spaces, bile canaliculi, located between hepatocytes, and flows to the periphery of the lobule to the interlobular bile ducts of the portal areas **(15)**.

The portal hepatic lobule is considered as the triangular area of the liver parenchyma that delivers its bile to a particular interlobular bile duct. The center of the portal lobule is the portal area and the periphery is bounded by imaginary straight lines connecting the three surrounding central veins that form the three apices of the triangle**(3).**

Gartner&Hiatt (3)and Ross&Pawlina (12). stated that bile secretion is the major exocrine function of the liver. Thus, the morphological axis of the portal lobule is the interlobular bile duct of the portal triad. Its outer margins are imaginary lines drawn between the three surrounding central veins that are closest to that portal triad. These lines define a roughly triangular block of tissue that includes portions of three classic lobules that secrete the bile draining into its axial bile duct. This concept allows a description of hepatic parenchymal structure comparable to that of other exocrine glands.

The hepatic acinus is the third concept of hepatic lobules which is based on blood flow from the distributing arteriole and consequently, on the order in which hepatocytes degenerate subsequent to toxic or hypoxic insults. It is considered the structural unit that provides the best correlation between blood perfusion, metabolic activity, and liver pathology. The hepatic acinus is diamond shaped representing the smallest functional unit of the hepatic parenchyma. It extends from two portal triads to the two closest central veins)**(3).**
The hepatocytes are arranged in each liver acinus in the form of three concentric elliptical zones: zone 1 is the closest to the short axis and the blood supply from the penetrating branches of hepatic artery and portal vein, zone 3 which is farthest from the short axis and the closest to the terminal hepatic vein (central vein) and zone 2 which lies in between zones 1and 3 but has no sharp boundaries **(16).**
Furthermore, the cells in zone 1 are the first to receive nutrients, oxygen and toxins from the sinusoidal blood and also, they are the last to die if circulation is impaired and the first to regenerate. On the other hand, cells in zone 3 are the first to suffer from ischemic necrosis (centrilobular necrosis) if there is reduction in perfusion and the first to show fat accumulation**.** Normal variations in the number and size of cytoplasmic organelles, enzyme activity and the size of cytoplasmic glycogen deposits are also seen between zones 1 and 3 **(15)**.

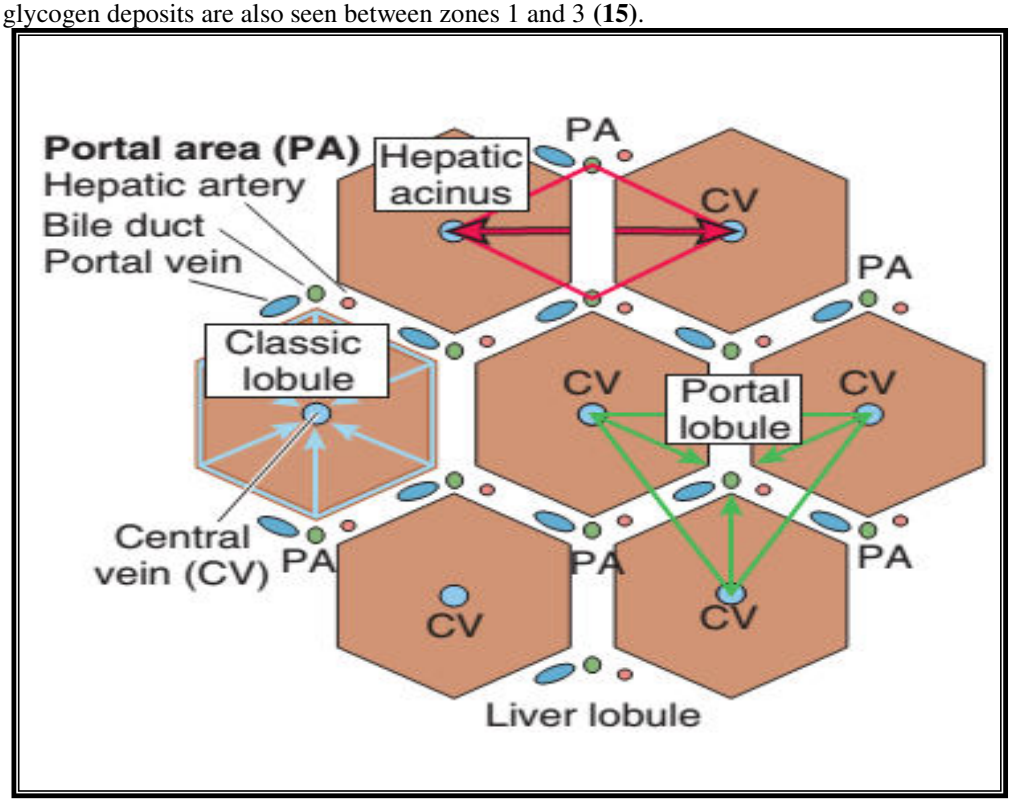

Fig. (3): Schematic diagram of the three concepts of the liver lobule: classic lobule, portal lobule and the hepatic acinus **(3).**

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Physiology of the liver

The liver is one of the most complex and important organs. Its main function is to control the flow and safety of substances that are absorbed from the digestive system before they become distributed to the systemic circulatory system. Death occurs within minutes if liver function is completely lost, this refers to the liver's importance **(17).**

The liver may have many different functions, most of which are performed by the hepatocytes. The hepatocytes have endocrine-like actions as they can modify the action of hormones released by other organs, this involves: conversion of vitamin D to the predominant form (25-hydroxycholecalciferol), conversion of thyroxine to the biologically active form, (T3) and GHRH production and they are also involved with the kidney in insulin and glucagon degradation. Moreover, they metabolize the end products of absorption from the alimentary canal, store them as inclusion products, and release them in response to hormonal and nervous signals **(12).**

In addition, hepatocytes are considered as a massive detoxification center for degrading alcohol, toxins and drugs (protecting the body from their deleterious effects). These toxic substances can be inactivated by oxidation, methylation, or conjugation mainly in the smooth endothelial reticulum (SER) of hepatocytes. This explains the increase in the hepatocyte's SER to improve the detoxification capacity under the effect of certain drugs that are inactivated in the liver. Occasionally, detoxification occurs in peroxisomes rather than in the SER. Hepatocytes also transfer secretory IgA from the space of Disse into bile **(3).**

Hepatocytes can store fat, vitamins (A, B12, D, E, and K) and minerals (copper, and iron). This storage function is usually short term, and the amount of stored material in the hepatocytes and the cell size fluctuate during a given day. Vitamin A is stored in the greatest amount in the liver, but vitamins D and B12 are also present in substantial quantities. The liver contains enough vitamin stores to prevent deficiency of vitamin A for about 10 months, vitamin D for about 4 months, and vitamin B12 for more than 12 months **(3).**

The liver is responsible for the synthesis of coagulation factorsI (fibrinogen), II (prothrombin), V, VII, IX, XI, XIII), anticoagulant proteins (protein S, protein C , antithrombin III , heparin cofactor II and antiplasmin) and fibrinolytic factor (plasminogen). The liver is a major site for production of thrombopoietin, a glycoprotein hormone that regulates the production of platelets by the bone marrow. So, the liver has a major role in hemostasis **(18)**.

Albumins and all globulins (except gamma (γ) globulins) are synthesized by the liver. They are important to maintain the plasma osmotic pressure. Also, liver synthesizes glycoproteins (including proteins involved in iron transport as haptoglobin, transferrin, and hemopexin), proteins required for the complement reactions and all of the nonessential amino acids that the body requires **(12).**

The liver has a vital role in carbohydrate metabolism. In glucose metabolism, the liver phosphorylates absorbed glucose to glucose-6- phosphate. Depending on energy requirements, glucose-6-phosphate is either stored in the liver in the form of glycogen or used in the glycolytic pathways. During fasting, glycogenolysis occurs and glucose is released into the bloodstream. The liver is also responsible for gluconeogenesis, which involves the synthesis of glucose from other sugars (such as fructose and galactose) or from non-carbohydrate sources (such as certain amino acids, lactate or glycerol) **(12).**
The liver is responsible for a great part of the lipid metabolism as: degradation of fatty acids with formation of ketone bodies (acidoacetic acid, β-hydroxybutyric acid, and acetone) that are used as a fuel by organs (except the liver) and synthesis of large quantities of phospholipids and cholesterol, which are utilized by the cells to form membranes, organelles and many chemical substances that are important for cellular function. About 80 percent of the cholesterol manufactured in the liver is converted into bile salts **(3).**

Liver is part of reticuloendothelial system (RES) as much of 10 % of its weight is derived from the Kupffer cell mass. This is very important in the ability of the liver to phagocytose antigens absorbed from the gastrointestinal tract to act as a filter for the systemic circulation **(19).**

Perfluorooctane Sulfonate (PFOS)
Chemical structure and uses of PFOS
Per- and polyfluoroalkyl substances (PFAS) comprise a diverse family of compounds used in a wide variety of industrial processes and the production of consumer goods **(20).** They all consist of a hydrophobic fluorinated carbon chain of varying length (typically C4 to C16) and a hydrophilic end group, i.e. sulfonate or carboxylate. If the hydrophobic carbon chain is fully fluorinated, it is called per-fluorinated compounds (PFCs). PFCs have specific properties due to the fluorine atoms. A carbon-fluorine bond (C-F) is extremely strong, which causes PFCs to be very stable. This stability makes them hydro- and oleophobic, and therefore water-, oil- and stain resistant. This is resulting in a high degree of environmental persistence and bioaccumulation of PFCs and their derivatives **(21).**

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Polyfluoroalkyl substances (PFASs) are man-made compounds, which belong to a kind of persistent organic pollutants (POPs)**.** PFASs are known for their antiwetting and surfactant properties and used in nonstick cookware, waterproof, breathable textiles, firefighting foams, and protective coatings for paper, food packing materials production. PFASs are discovered ubiquitously in various environmental matrices as well as in wildlife and human samples **(22).**
Per-fluorinated compounds (PFCs) have been manufactured and used for various industrial applications for over 50 years **(21).**

Route of PFC exposure to PFOS

Humans are exposed to PFAS through a variety of pathways, including drinking water, air, diet, dust, through maternal to fetal transfer in utero, and through breastfeeding as neonates (Sunderland et al., 2019). For adults, diet and drinking water are the main sources of exposure; however, this may vary depending on lifestyle, diet, proximity to point and nonpoint sources, and local drinking water contamination levels. Formula-fed infants are thought to be the most highly exposed members of the human population due to their high-water intake to body weight ratio. Wildlife and human beings are widely exposed to PFASs during the production, usage, and disposal of the related products **(23).** Because of the bioaccumulation, PFASs can be accumulated into higher trophic levels by food chains **(24).**
These chemicals have been detected in indoor and outdoor air, in rivers, lakes and groundwater, in wastewater treatment effluent, in landfills and in the marine environment. It is highly resistant to environmental degradation and has been detected in drinking water sources impacted by releases from industrial facilities and wastewater treatment plants **(25).**

The increased manufacture and use are helping PFOS get an easy entry into the human body through the skin **(26),**respiratory tract **(27) and** digestive tract **(28).** Possible exposure sources for the general population include airborne exposures, drinking water, dust in homes, food and food packaging, fabrics, and carpeting **(29).** PFOS is the stable and persistent end-product that has been measured at part per billion concentrations in biological samples from humans and wildlife **(30,21).** PFOS, PFOA chemicals have been found to be widespread in the serum of wildlife and humans, including fluorochemical production workers**,** and in the general population **(31).** In humans, the long plasma half-lives of PFOA and PFOS are (3–5years) **(31**), 30 to 50 days in rats **(46).**

Occupational exposure to PFOS has been limited to personnel engaged in the production of PFOS and its derivatives. In a retrospective cohort mortality study of 2083 workers with at least one year of exposure in a plant producing, PFOS 145 deaths were identified **(26).**
Occupationally, the exposed people have much higher serum PFOS levels than general population **(31).** An investigation in China from 2008 to 2012 showed that the median serum PFOS concentration reached 5544 ng/mL (range, 416 to 118,000 ng/mL) in workers from sulfonation department of a fluorochemical plant **(32).**

It is of a particular concern because this indicates that they can accumulate, which may result in higher body burdens on repeated exposures which might, in turn, increase the risk of potential adverse health effects. However, there is evidence that the serum levels of these chemicals in the US have been declining since 2000 **(33).**

Quercetin (QE)

Quercetin chemistry

QE, (3,5,7,3',4'-pentahydroxyflavone) a typical flavanol-type flavonoid, is frequently present in regular diets and exhibits a wide range of beneficial effects, including antioxidative, anti-inflammation and anti-apoptotic properties. This flavonoid has demonstrated constructive effects against oxidative stress induced by xenobiotics. Various experimental studies have demonstrated that dietary QE supplementation exerts beneficial effects against a wide range of hepatic ailments **(34).**
Plant flavonoid compounds are a gifted class of so-called “nutraceuticals” that include the ability to amend the harshness of hepatic damage. Numerous studies have revealed the affirmative functions of flavonoids, especially quercetin (QE), in defending against hepatic dysfunctions **(35).**

Flavonoids are a group of natural antioxidants found in several vascular plants and include more than 8000 individual bioactive compounds with the ability to sequester free radicals **(36).**
In plants, flavonoids act as antioxidants, antimicrobials, photoreceptors, auxin transport and feeding repellents, and are also responsible for the flowers' colors which are known to be visual signals for attracting pollinators **(37).** In food, such as fruits and vegetables, flavonoids are responsible for bitterness, astringency, color, flavor, odor, and oxidative stability **(37).** QE has received considerable attention due to its overwhelming presence in foods **(38).**

Flavonoids are chemically based upon a fifteen-carbon skeleton containing two hydroxylated aromatic rings, A and B linked by a three-carbon fragment forming an oxygenated heterocycle (ring C). Structurally, flavonoids can be divided into 6 categories consisting of flavanols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols such as catechins and proanthocyanidins which are determined by the linkage of aromatic rings, the oxidation state of the central pyran ring and the presence of functional groups. Individual compounds are identified and characterized by the hydroxylation and conjugation patterns of the A and B rings. As such, the flavanols possess a 3-hydroxyflavone skeleton. Moreover, polyphenolic compounds can be associated with different carbohydrates and organic acids **(39).**
QE belongs to the flavanol subclass, which contain a double bond between positions 2 and 3 and anoxygen (i.e., a ketone group) in position 4 of the heterocyclic C ring**.** However, there are some differences between flavanols with the

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presence of a hydroxyl moiety at position 3 **(40).**

QE is the aglycone form of several other flavonoid glycosides with at least one O-glycosidic bond **(40).** Glycosylation is important in plant biology, since aglycones have a lipophilic character whereas their glycosidic derivatives are hydrophilic and cytosol-soluble and therefore can easily be transported to different parts of the plant and stored in vacuoles **(38).**

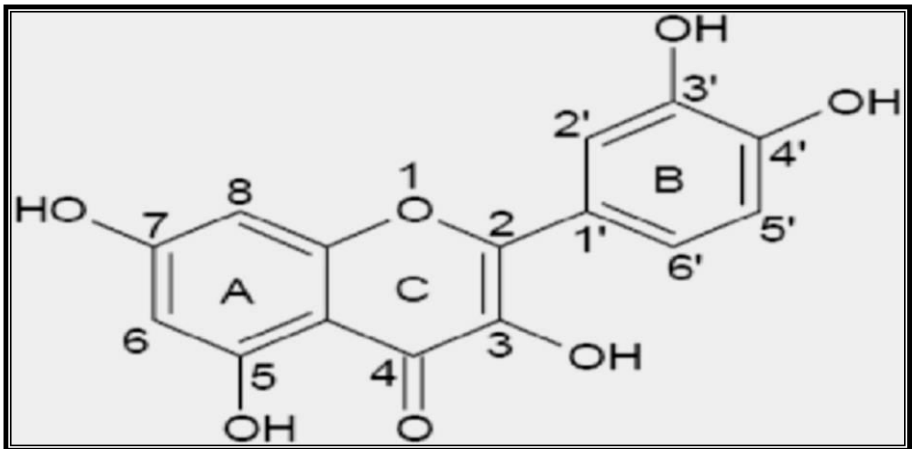

Fig. (4): Quercetin aglycone **(40).**

Quercetin biosynthesis

Flavonoids are synthesized through phenylpropanoid metabolism, involving phenylalanine ammonialyase, cinnamate 4-hydroxylase, and 4-coumarate: CoA ligase leads to the biosynthesis of 4-coumaroyl-CoA, which triggers the flavonoid biosynthesis pathways. Successive reactions catalyzed by structural enzymes, including isomerases, reductases, hydroxylases, and some Fe2þ/2-oxoglutarate-dependent dioxygenases, modify the basic flavonoid structure forming many products and giving rise to different flavonoid subclasses **(11).**

Dihydrflavanols are known to be common precursors of the biosynthesis of flavanols, anthocyanins, and proanthocyanidins, which are oxidized by flavanol synthase and lead to the generation of some flavanols such as QE **(41).**

Several organs contribute to QE metabolism, including the small intestine, the kidneys, the large intestine, and the liver, giving rise to glucuronidated, methylated, and sulfated forms of QE; moreover, free QE (such as its aglycone) is also found in plasma **(42).**

Sources and effects of quercetin

QE is a major flavonoid extensively found in fruits, leafy and pod vegetables and red wine and happens to be an indispensable component of the human diet **(Table 1).**

Table (1): Amount of quercetin in selected foods. (Adapted from USDA database. Nutrient Data Laboratory, Food Composition Laboratory. USDA database for the flavonoid content of selected foods. Beltsville, MD: Beltsville. Human Nutrition Research Center, Agriculture Research Service, USDA; January 2007).

Quercetin Content (mg/100 g)	Food source
233	Capers
46.9	Mango
22	Onions
20	Cocoa powder
14	Cranberries
7.40	Lingon berries
7.61	Asparagus, cooked
5.05	Blue berries
4.70	Apple, Red Delicious
2.64	Cherries
2.51	Broccoli, raw
2.02	Apple, Fuji
2.69	Green tea
1.99	Black tea
1.38	Red grapes

QE is now largely utilized as a nutritional supplement and as a phytochemical remedy for a variety of hepatic diseases like hepatitis, cirrhosis, acute liver failure, non-alcoholic fatty liver disease, alcoholic liver disease, fibrosis, steatosis,

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hepatoma, and hepatic portal inflammation **(42).**

QE displays antioxidant properties against various ailments, including cardiovascular disorders, atherosclerosis, liver fibrosis, cirrhosis, renal injury, and biliary obstruction, among others. Recently, QE has gained consideration for its outstanding range of health benefits, which establish it as an important compound for the development of novel and efficient functional foods and medicines **(43).**

QE has been reported as possessing a broad array of biological effects, including anti-oxidative, anti-inflammatory, anti-apoptotic, hepatoprotective, renoprotective, neuroprotective and cardioprotective effects **(44).**

Hepatic diseases represent a severe health concern around the globe, and both modern medicine and traditional herbal formulations offer few effective remedies **(45).**

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