Evaluation of the Effect of Gum Arabic on the Histological and Physiological Changes in the Liver of Albino Rats Exposed to Bisphenol A

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Bisphenol A, Gum Arabic, Hepatocytes, Glycoprotein, Congestion.

ABSTRACT:
We designed this work in order to study the protective effect of aqueous extract of gum arabic (GA) from oxidative damage induced by bisphenol A(BPA). This study was conducted on 35 male laboratory Albino rats of Sprague Dawley strain (165-210 grams) and divided into five groups. Each group included 7 rats. The experiment was performed at the animal house of Biology (College of Education for Pure Sciences).
The experiment continued for 90 days under conditions Standard laboratory, as follows: The first group was the control; the second group had GA taken orally; the third group had BPA taken orally; the fourth group had GA taken first, followed by BPS, and the fifth group had BPA taken first, followed by GA. According to the above results clearly, Serum levels of AST, ALT and Lipid profile (Cholesterol, Triglyceride) indicated a highly significant increase in these parameters at group 3, While the fourth and fifth groups show significant reductions in AST, ALT, cholesterol, triglycerides, and MDA, also significant increases in GSH levels, While the histological changes in the third group were represented by the presence of a state of blood congestion with depletion of glycoprotein and degeneration of some cells, in addition to the presence of a state of necrosis of liver cells, while it was not observed severe histological changes when compared to third group in both fourth and fifth groups. In Short, the above results indicated that GA treatment for BPA-induced liver injury had Therapeutic effect through anti-free radical formation and functional role as free scavenger.

1. Introduction

Bisphenol A is used extensively worldwide, with the goal of using it mainly for polycarbonate plastic and epoxy resin (Haitham et al., 2020). Because of its light weight, hard and thermally resistant properties it is widely used as intermediate in the manufacture of a variety of products, hardness, and temperature resistance (Rudawska, 2021). BPA is also widely used in the manufacture of some materials, including infant feeding bottles, tableware, food containers, and water bottles. Plastics made of polycarbonate have remarkable chemical and physical properties, such as excellent toughness and strength, thermal stability, and resistance to acids and oils (Yenil and Yemiş, 2020). It is frequently used in the coating and interior lining of other products due to its strong adhesion, high abrasion resistance, and viscous consistency (Mikołajewska et al., 2015). The liver has one of the body's most powerful antioxidant chemicals. It is locked in totally different organic forms, counting glycogen conservation, the decay of ruddy blood cells, plasma protein blend, detoxification, and others (Ozougwu, 2017). According to some reports, this tissue could be a noteworthy target for BPA and its metabolites (Arias et al., 2020).

Exposure to BPA in high concentrations causes cardiovascular abnormalities through the presence of BPA side effects in the brain and leads to the formation of multinucleated giant cells (Fonseca et al., 2022). Medicinal plants play an essential role as antioxidants in suppressing free radical scavengers (Rajab and Ali, 2020), reducing the effect of active oxygen species, and reducing the toxic side effects of the effectiveness of chemicals, which reduces the chemical effect throughout the treatment period and in different doses (Nwozo et al., 2023). Gum Arabic (GA) is an antioxidant that is used a lot. It is a natural resin that comes from the stems and parts of Acacia senegal trees (Dauqan and Abdullah, 2013). It is also an important commercial substance consisting of polysaccharides and containing calcium, magnesium and potassium. As a salt,(Said et al., 2019). GA is also used in traditional medicine to treat intestinal mucosal infections and to coat inflamed surfaces. Several studies have shown that GA has antioxidant and renal protective effects (Noha et al., 2022). It has other effects. Clinically, it has been tried in patients with chronic kidney failure. It also helps reduce the concentration of urea and reduces the concentration of nitrogen in the urine by excreting it into the blood (Noha

et al., 2022). The present study aimed to examine the efficacy of aqueous extract (GA) against the treatment's toxic effects of (BPA).

2. Materials and Methods

Animals used in the Study

We used 35 male Swiss white rats (Sprague Dawely), whose weight was between 165 and 210 grams. This study was conducted in the animal house of the Department of Life Sciences / College of Education for Pure Sciences / Anbar University, inside plastic cages with metal covers prepared for this purpose. Rats were placed in appropriate laboratory conditions, represented by a photoperiod (11 h light and 13 h dark) and a temperature set at 22±2°C. The cages were cleaned and disinfected with weekly sawdust change. Mice were allowed to acclimatize for two weeks and were fed a prepared diet, with food and water provided ad libitum throughout the study period.

Bisphenol A (BPA)

The 2,2 Bis-4-hydroxyl phenyl propane was obtained from Sigma Chemical Company and mixed with olive oil.

Preparation of Gum Arabic Extract

Gum Arabic is purchased in local markets in Ramadi city from apothecaries in the form of solid blocks or solid knots. It was ground finely and prepared at a concentration of 15% by weighing 15 g of GA. It was dissolved in an amount of distilled water and the volume was completed to 100 ml and stirred well to completely dissolve, and the rats were dosed with the glue with water instead of drinking water and placed in opaque glass bottles to prevent its oxidation by light(Ahmed et al., 2015).

The Experiment Design

The animals were divided into (5) groups and distributed randomly, and each group contains (7) animals:

The first group: Control: was given 0.5 ml of olive oil per rat. The second group received aqueous extract of GA 8 g / kg of rat weight. The third group: received BPA 50 mg/kg of rat weight (dissolved in olive oil).The fourth group: Preventive group: first dose received aqueous extract of GA, and after two hours dose received BPA Same concentration as above and Fifth group - Therapeutic group: received only BPA for six weeks, then left for three days, after received aqueous extract of GA.

The dosing period for all of the above groups is between one day and another for a period of 90 days.

Biochemical analysis

Rats were anesthetized through inhalation of diethyl ether. to immediately confirm the biomarkers of liver function include , Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured in serum by a modified kinetic method determined using assay kits (Randox Research facilities, UK) according to the manufacturer's instructions. Cholesterol (TC) was determined using an analysis kit according to the method (Allain et al., 1974), Triglycerides (TG) measured using colorimetric assay (Fossati and Prencipe, 1982) ,malondialdehyde (MDA) were measured using colorimetric assay (Kei, 1978). Finally, the procedure to estimate the glutathione (GSH) level followed the technique described by Griffith (Griffith, 1980)

Blood samples were collected and processed at −20°C. For the purpose of histopathological examination, a portion of each rat's liver was preserved in 10% neutral formalin.

Histological Examination

Liver samples were fixed in 10% formalin solution. Alternatively, liver sections were fixed as usual in paraffin blocks and prepared into 5–6 μm thick sections. To determine morphological differences, after being deparaffinized, the sections were rehydrated, stained with hematoxylin and eosin, and a light microscope was used to identify them (Gharban et al., 2019)

Statistical analysis

The collected data were subjected to one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test, using SPSS (version 20.0), and P≤0.05 was considered statistically significant (Gharban, 2024).

3. Results

Biochemical results

The results of the present study, shown in Figures (1) and (2), exhibited a significant increase (P≤0.05) in the activities of ALT and AST enzymes in the third group treated with BPA A in comparison to the control group, while the results showed no significant difference (P≤0.05) in the efficiency of ALT and AST enzymes in the second group treated with GA, as the results were similar to those of the control group, while the results showed a significant decrease (P≤0.05)in the above records in the 4th and 5th groups compared with the BPA group.

The results of our present study showed that the cholesterol and triglyceride levels were not significantly reduced in the second group given GA extract compared to the control group, while the results showed a significant increase (P≤0.05) for the above same indices in the third group that received BPA, i.e., compared to the control group. While there was a significant decrease (P≤0.05) in the fourth group and a very significant low in the fifth group compared to the bisphenol A group as shown in Figures (3 and 4). The results showed that the MDA level was significantly decreased (P≤0.05) and the glutathione GSH antioxidant level was high in the second group given GA extract, while the results showed a significant increase (P≤0.05). MDA and GSH levels were significantly decreased (P<0.05) in the third group receiving BPA, i.e. compared with the control group, while in the fourth and fifth groups, a significant decrease (P≤0.05) in MDA level and a significant increase (P≤0.05) in GSH level were observed compared with the third group, and the results of the fifth group were better than the fourth group as shown in Figures (5 and 6).

Histological changes in liver

In the human body, the liver is a large organ in the upper right part of the abdomen. Its primary function is to remove harmful substances and toxins from the blood.

Hepatocytes are arranged in radial rows around the central vein, and each cell has a polygonal shape with spherical nuclei centrally located in the cytoplasm - and between the rows of cells - in the current study's histological results for the control group, which are depicted in figure 1. These found blood sinusoids containing Kupffer cells with little numbers.

The results shown in figure (2) in the second group treated with gum arabic show that the appearance of the liver tissue is similar to that of the control group, as hepatocytes are observed to be arranged in rows distributed in many directions around the central vein, with limited atrophy of some veins. Blood sinusoids are also found in the form of a network of vascular channels with a large number of Kupffer cells, while figures (3) and (4) show histological changes represented by the presence of glycoprotein depletion in the hepatocytes, accompanied by degeneration of the hepatocytes, in addition to the dilation of the blood sinusoids between the hepatocytes, The changes also show the presence of congestion as well as necrosis of the hepatocytes. Simple histological changes, such as a slight depletion of intracellular matrix glycoprotein and the presence of blood congestion and a slight expansion of the blood sinusoids, were observed in the fourth group of the figures (5,6). The presence of inflammatory cell infiltration in addition to cell necrosis was also seen, but in a relatively small amount. In the third group, while the histological results in the figures (7,8) in the fifth group showed the presence of a slight blood congestion in the liver tissue, as well as a slight decrease in glycoproteins in the hepatocytes, in addition to the presence of a slight expansion of the blood sinusoids.

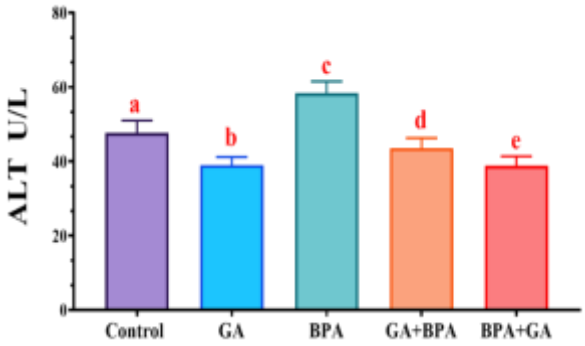

Figure (1): The effect of Arabic gum on the activity of ALT in the serum of male rats treated with bisphenol A

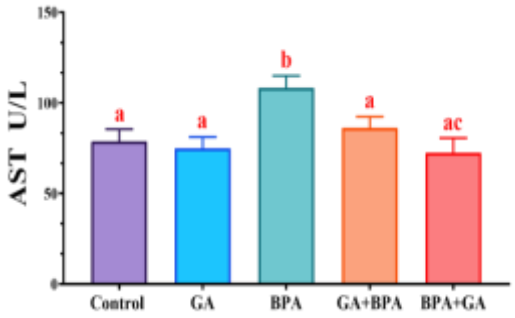

Figure (2): The effect of Arabic gum on the activity of AST in the serum of male rats treated with bisphenol A

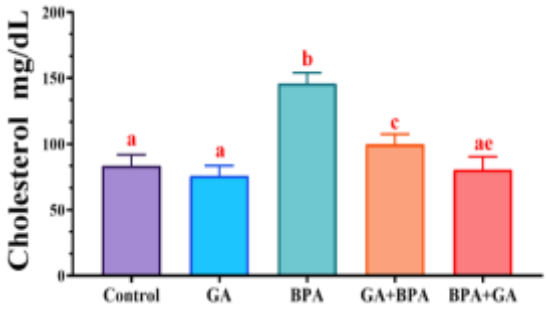

Figure (3) The effect of Arabic gum on the activity of Cholesterol in the serum of male rats treated with bisphenol A

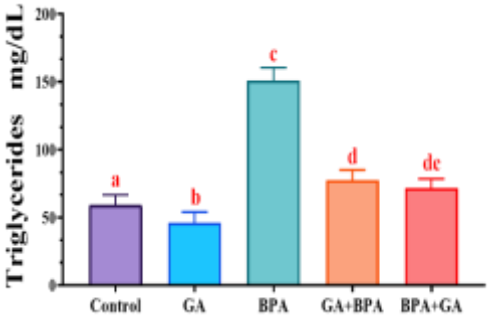

Figure (4) The effect of Arabic gum on the activity of Triglycerides in the serum of male rats treated with bisphenol A

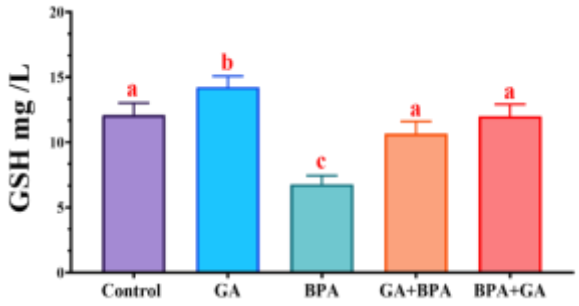

Figure (5) The effect of Arabic gum on the activity of GSH in the serum of male rats treated with bisphenol A

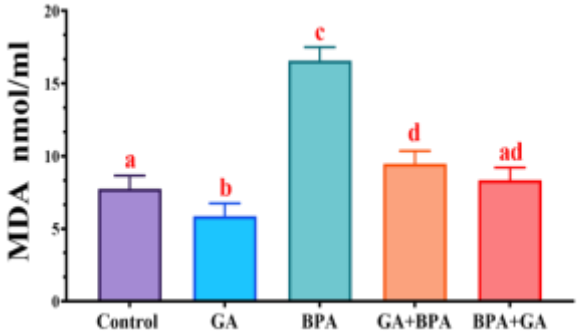

Figure (6) The effect of Arabic gum on the activity of MDA in the serum of male rats treated with bisphenol A.

4. Discussion

BPA can cause a number of common toxic effects in humans, such as alterations in human estrogen receptor activity, changes in DNA integrity, steatosis and obesity, and disruption of hormonal balance (Cimmino et al., 2020). Increased levels of liver enzymes, including (AST) and (ALT) as a result of exposure to bisphenol (BPA), are linked to multiple effects on the liver, including oxidative stress (Meli et al., 2020), as BPA can lead to the production of free radicals in the liver, causing oxidative stress that leads to damage to hepatocytes membranes, causing the release of these enzymes and increasing their level in blood serum (Hussen et al., 2024), It may be that bisphenol may stimulate an inflammatory response in the hepatocyes, which increases the activity of liver cells, which increases the release of these enzymes(Karabekir et al., 2024). Exposure to bisphenol can also cause direct toxicity to liver cells, leading to their damage and death, this damage cause's release liver enzymes into the blood (Aja et al., 2024). BPA also works similarly to estrogen (a female hormone) in the body, which can affect hormonal balance and liver function, Changes in hormonal activity can affect the production of liver enzymes (Zhang et al., 2014).

This study used gum arabic because it was found to have antioxidant properties (Hassanien, 2021) In addition, gum Arabic was viewed as safe for people 'utilization and doesn't change the food properties (Azouz and Hassanen, 2020). GA works to reduce the toxicity of bisphenol (BPA) and improve the analysis of liver enzymes, including ALT and AST, due to its rich composition of active substances that have multiple biological properties, including antioxidant properties(Hamid et al., 2021). Gum arabic contains compounds such as flavonoids, phenols, and alkaloids, which are antioxidants (Ayaz et al., 2017). A natural GA product that neutralizes free radicals and reduces oxidative stress in the liver, helping to protect liver cells from damage and reduce liver enzyme secretion to normal levels. Amino acids such as histidine, methionine, and tyrosine also appear to be responsible for AG's antioxidant properties against ROS (Al-Khatawi et al., 2025).

Gum arabic also contains anti-inflammatory compounds like gallic acid, salicylic acid, flavonoids, anthocyanins, quercetin, and others. These compounds reduce liver inflammation and can protect liver cells from damage., which reduces the levels of liver enzymes in the blood (Ali et al., 2020). Gum arabic is rich in soluble dietary fiber. Soluble fiber improves intestinal health and promotes beneficial bacteria, which enhances

the removal of toxins and improves liver function in general, as good intestinal health reduces toxic pressure on the liver(Abaker et al., 2021). Gum arabic also contains many sugars such as arabinose and galactose. Which may help strengthen the cell membrane and maintain the integrity of liver cells, reducing the leakage of liver enzymes into the blood (Musa et al., 2018).

One of the molecular mechanisms thought to be involved in the BPA-induced toxicity in experimental rats is lipid peroxidation. In the present study, BPA administration altered oxidative stress parameters as indicated by increased MDA and ROS levels and decreased GSH levels. Exposure of the body to high levels of BPA can lead to increased production of free radicals and increased lipid peroxidation, which increases pressure on the body's antioxidant defense system, leading to a change in antioxidant activity (Amjad et al., 2020).

Exposure to bisphenols may result in decreased GSH levels due to its widespread use to counteract bisphenol-induced oxidative stress, as glutathione is a potent antioxidant that plays an important role in protecting cells from oxidative damage (Ozaydın et al., 2018).

High levels of bisphenol can also increase the process of lipid peroxidation, leading to increased levels of MDA in the body, which is a by product of the lipid peroxidation process and is used as an indicator of oxidative stress and cellular damage(Meli et al., 2020). Therefore, high levels of bisphenol can lead to an increase in oxidative stress, which affects the reduction of levels and activity of antioxidants in the body (such as SOD and GSH) and increases the levels of biomarkers of oxidative stress such as (MDA)(Ola-Davies and Olukole, 2018). Since these phytocomponents have been widely reported to possess antioxidant and anti-lipoperoxidative activities, AG's constituent flavonoids, alkaloids, tannins, saponins, and other polyphenolics could be responsible for its antioxidant and antilipoperoxidative properties (Rady et al., 2023). AG may exert its effects directly by scavenging free radicals and this property may be due to the presence of several antioxidant compounds (Hassanien, 2019). Another possible mechanism of action is an increase in the synthesis of antioxidant compounds in the body. Furthermore, the mechanism of action that increases the antioxidant capacity of AG may contents of amino acid residues such as histidine, lysine and tyrosine. These amino acid residues are often considered antioxidants (Prasad et al., 2022). The increase in cholesterol levels may be due to oxidative stress caused by bisphenol A consumption, which in turn leads to disturbances in fat metabolism, resulting in increased breakdown of fats and fatty acids and increased blood levels..(Ozaydın et al., 2018). In addition, the increase in triglyceride concentration may be due to the inhibition of the activity of the enzyme lipoprotein lipase (LPL) in the circulation, which is responsible for the fragmentation of triglycerides under normal conditions, causing aggregation or inhibition of the enzyme activity, leading to the inhibition of cholesteryl ester transfer protein (CETP), the protein that transports TG to the HDL molecule. This disruption of lipid levels may be due to exposure of rat to doses of bisphenol A, which stimulates the activity of the enzyme HMG-CoA reductase, thereby stimulating the conversion of HMG-CoA to mevalonate and increasing blood cholesterol through the liver, while inhibiting the enzyme lipoprotein lipase (LPL). Lipase responsible for the breakdown of plasma lipids and the accumulation of C-VLDL and TG in the blood (Marmugi et al., 2012).

The fiber found in gum arabic can bind to bisphenol in the digestive system and prevent its absorption into the blood, This reduces the amount of BPA that reaches the liver and other organs (Eyibo et al., 2018). GA can also slow down the digestion process and extend it, which reduces the absorption of bisphenols and other harmful substances in the intestine, as dietary fats and bile acids are absorbed with these fibers and merge with them in the intestine, and then the bile acids are lost by being excreted with the feces, thus reducing the amount of recycled bile acids(Ahmed et al., 2016). absorption and to replace lost bile acids, the rate of conversion of cholesterol to bile acids in the liver increases, thereby on the one hand reducing the absorption of cholesterol from the intestine and reducing blood cholesterol levels when using it. on the other hand to produce bile acids, or gum arabic containing sapiens has the ability to decompose.(Ali et al., 2009). In the intestines, it turns into Sapogenins and Diosgenin and inhibits the absorption of cholesterol, or this is attributed to the ability of gum arabic to reduce cholesterol concentration by inhibiting the HMG-COA reductase enzyme and stimulating the formation of bile acids as a result of it containing multiple active compounds (Ayaz et al., 2017).

The exposure of various animals to oxidative stress resulting from the injection of doses of bisphenol A has led to destructive oxidative effects that increase the peroxidation of fat in tissues, which leads to the depletion of tissue glutathione and the occurrence of many changes in the antioxidant enzymatic system (Helal et al.,

2018). Unsaturated fatty acids, the most critical components of cellular membranes, are known to be intolerant of the effects of active oxygen species. Active oxygen species are responsible for cell protein damage and reduce the effectiveness of antioxidant system(Recknagel et al., 2020). Therefore, they are toxic to cells and cause pathological histological changes in the cells and tissues of the body, including liver tissue, thus causing cell destruction and death (Chaudhary et al., 2023). The increase in oxidative stress resulting from the intake of BPA led to interaction with phosphorylated fats, resulting in lipid peroxidation, which stimulates a series of membrane-lytic reactions with a decrease in the vitality of the mitochondrial membrane, and the destruction of the membranes of lysosomes, and then the cell reaches the stage of necrosis (Faheem et al., 2021). A study demonstrated that liver damage is associated with an increase in MDA as a marker for lipid peroxidation, whereas an increase in hepatic GSH was accompanied by a decrease in MDA, which is the first antioxidant responsible for protecting cells from oxidative stress, as the depletion of GSH in the mitochondria of liver cells is a result of exposure to BPA, which led to the emergence of pathological conditions, including liver tissue damage, because GSH reduces the toxic effects through its association with the toxic substance and prevents its metabolism and transformation into free radicals(Apaydin et al., 2019). While in the second group, we did not notice any histological changes when compared with the group dosed with bisphenol, and this was confirmed by previous studies, the therapeutic role of GA extract as it contains many effective compounds, especially phenolic components and flavonoids, which are antioxidants that work to curb oxidative damage by scavenger free radicals (Kandeal et al., 2022). It prevents lipid peroxidation, and this in turn leads us to the conclusion that these components played a major role in maintaining cellular membranes by stimulating the activity of Glutathione-S-Transferase (G-S-T), which is the first antioxidant that has the ability to remove the toxic effect of its ability to bind, It is transported with it through sulfur groups (-SH) present in glutathione, which leads to its excretion to the outside during urinary excretion(Rady et al., 2023). In addition, it has the ability to restore liver enzymes to their normal activity, and enhances the body's immunity (Abaker et al., 2021).

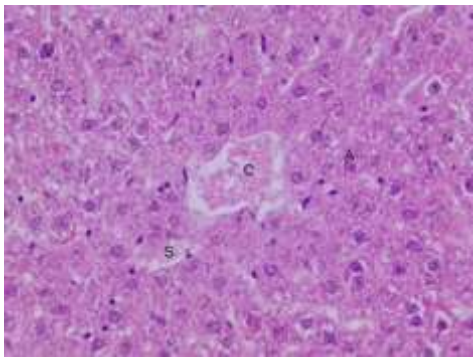

Figure (1) a cross-section of the liver of the control group showing a normal shape consisting of a central blood vein (C) surrounded by hepatic bands, including the presence of sinusoids (S) (X 40) (H&E)

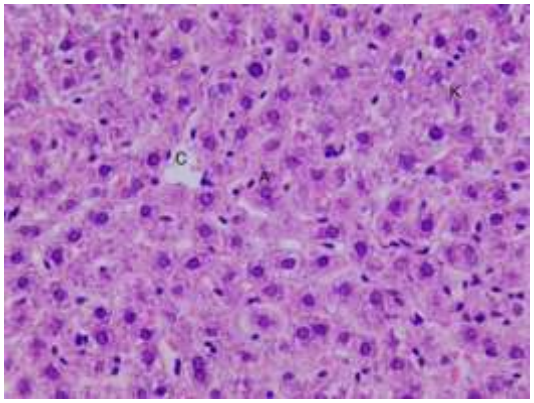

Figure (2) a cross-section of the liver of the second group treated with GA extract, showing the normal appearance of the liver tissue close to the control group and the presence of cohesive cells with an increase in Kupffer cells (K) (X 40) (H&E)

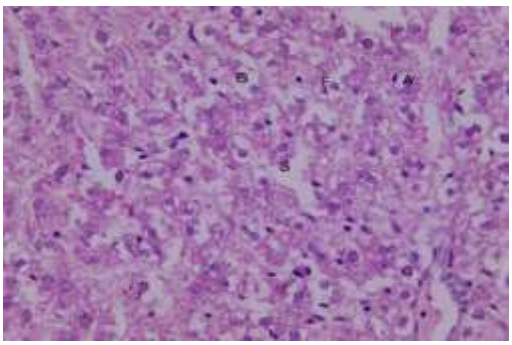

Figure (3) A cross-section of the liver of the group treated with BPA shows the presence of depletion of glycoprotein within the hepatic cells (A) with degeneration (F) of the hepatic cells (A) with expansion of the hepatic sinusoids (S) (X 40) (H&E)

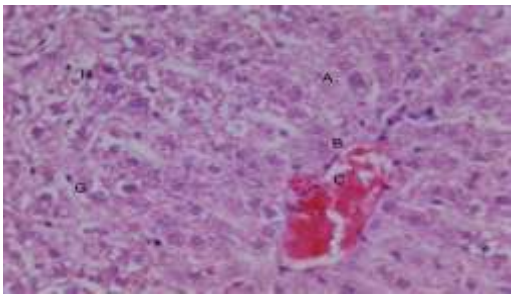

Figure (4): A cross-section of the liver of the third group, showing blood congestion(C) in the middle vessel, the presence of depletion of glycoprotein (G) inside the liver cells (A), with the presence of necrosis (H) in some hepatic cells (A), and an expansion of the hepatic sinusoids (40)(E&H)

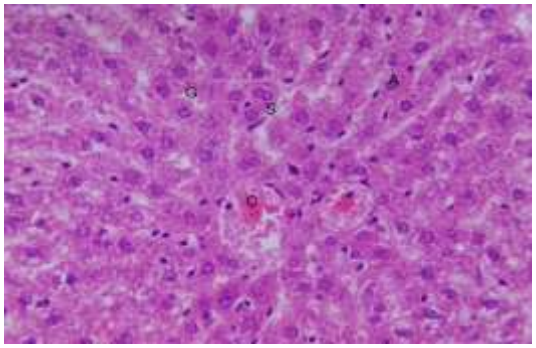

Figure (5) of a cross-section of the liver of the fourth group, which contains gum arabic extract I. + bisphenol A shows the presence of a slight depletion of intracellular Glycoprotein (G), blood congestion (B), and slight expansion of the sinusoids (S) (X 40) (H&E)

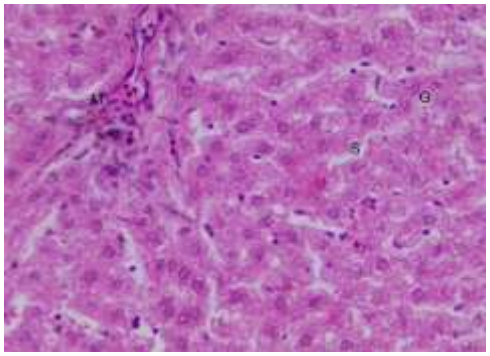

Figure (6): A cross-section in the fourth group treated with the extract + bisphenol A, showing the presence of a very small depletion of glycoprotein (G), expansion of the sinusoids (S), with slight infiltration of inflammatory cells (M), and necrosis of cells in very small numbers in the area (H). (40X)(E&H)

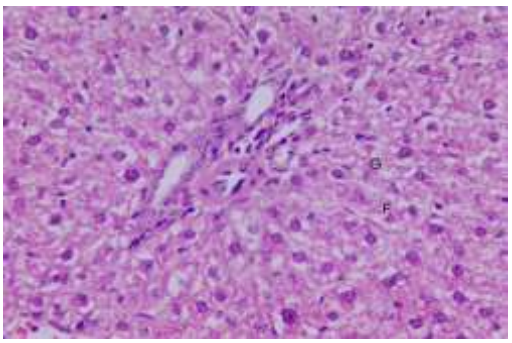

Figure (7): A cross-section of the liver of the fifth group that was given bisphenol A and then + gum arabic, showing a slight depletion of glycoprotein (G) in the hepatocytes, with degeneration in some liver cells (F), and blood congestion (C).40X)(E&H)

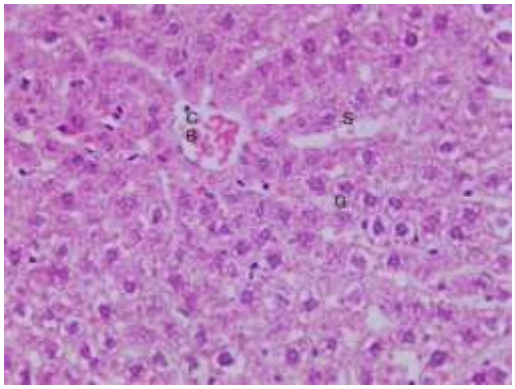

Figure (8) A cross-section of a liver in the fifth group with bisphenol A + gum arabic extract showing the presence of slight congestion (B) with a little depletion of glycoprotein (G) inside the hepatic cells (A) and a slight expansion of the sinusoids (S) (X 40) (H&E)

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