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Physiological and histological effects of apigenin and luteolin on Cytarabine injected rats

Omar N. Sultan ***Ghada A. Taqa****

Department of Dental Basic Sciences, College of Dentistry, University of Mosul, Mosul, Iraq.
*Corresponding author: ghadataqa@uomosul.edu.iq
E-mail address: omaralsultan@uomosul.edu.iq

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Abstract:

The present study was undertaken to study the effect of apigenin and luteolin on physiological and histological changes in rats treated with cytarabine drugs. Thirty-five albino healthy male adult rats with equal age weighing 250 -300g were enrolled. Rats were randomly divided into seven groups according to the treatment. Group "1" was treated with normal saline and served as the control group. Groups "2,3 and 4" received cytarabine, apigenin, and luteolin respectively, while groups 5, 6, and 7 received a combination of "apigenin + cytarabine", "luteolin + cytarabine", and "apigenin + luteolin + cytarabine", respectively. After one week of treatment, all seven groups of rats were sacrificed for histological finding, and blood samples were collected from each rat for biochemical parameters analysis. The results of this study showed that cytarabine increased the activity of GPT, GOT, and cholesterol levels in rats after one week of intraperitoneal injection in comparison to the control. There was no significant difference in GPT and GOT when apigenin and luteolin were administrated orally compared to the control group. When apigenin and luteolin are combined with cytarabine, they have a protective effect on leakage of liver enzymes GPT and GOT in serum. Apigenin and luteolin histologically protect liver cells from cytarabine damage when administered alone. These findings conclude that apigenin and luteolin have a protective effect on cytarabine side effects on the liver and its function in rats.

Keywords: Apigenin, Cholesterol, Cytarabine, Liver enzymes, Luteolin.

Introduction:

Apigenin and luteolin are natural flavonoids found in a variety of fruits and vegetables[1]. Apigenin, (chemically known as 4′,5,7-trihydroxyflavone), one of the popular dietary flavonoid plants, shows a range of biological activities in various cellular processes, including anticancer, antimicrobial, antiviral, anti-inflammatory, and antioxidant properties [2-5]. Apigenin has thus been used as conventional medicine for centuries due to its antioxidant and anti-inflammatory physiological functions [6,7]. Chemotherapy in many malignances is an effective treatment strategy, but this procedure also entails many issues, as it uses a combination of highly toxic chemicals. Possibly, the problem with this form of treatment is the high toxicity and poor specificity [8].

Some food-derived phytochemicals and derivatives provide a cornucopia of novel anticancer compounds. The flavonoid luteolin (3,4,5,7-tetrahydroxy flavone) can be found in many plants, including vegetables, herbs, and fruits. It is an anticancer drug against a variety of human cancers , including lung, breast, glioblastoma, prostate, colon, and pancreatic cancer [9]. Chemotherapeutic agents have devastating side effects: the majority of chemotherapeutic patients die as a result of pneumonia, common infections, or other cancer-related complications [10]. Cytarabine is primarily used to treat acute leukemia, especially acute non-lymphoblastic leukemia. It is an antimetabolic agent called 1-β arabinofuranosyl cytosine that is interfering with DNA synthesis [11]. Its mode of action is due to its rapid conversion into cytosine triphosphate arabinoside, which causes DNA damage when the cell holds in phase S (DNA synthesis). Cytosine also inhibits DNA and RNA polymerases , as well as the nucleotide reductase enzyme necessary for DNA synthesis[12]. This work aims to study the adverse effects of cytarabine by measuring some associated biochemical and histological changes after cytarabine administration

to rats, as well as to assess the protective effect of the flavonoids apigenin and luteolin on this adverse effect.

Materials and Methods:

Drugs: Apigenin and luteolin pure powder were purchased from Yanhuang Industrial Park (Guanxian, Liaocheng, Shandong, China)**.** Apigenin and luteolin solution were prepared by mixing pure powder of each one 50 mg with 1 mal of distilled water to prepared 50 mg\kg\ml. The drug cytarabine was purchased from Boston Biopharma, U.S.A. Each vial contains 10% of Cytarabine for injection. The dose of Cytarabine 100mg/kg was intraperitoneal injected.

Animals

Thirty-five healthy albino male adult rats with equal age weighing 250 -300 g were used in the current study. Rats were obtained from the animal care housed in the Veterinary Medicine Collage of Mosul University in Iraq. The animals were kept under standard condition housing at 23±2°C room temperature with 12h light\12h dark cycle and given a standard diet and tap water *ad libitium*. The rats were housed in the College of Dentistry, University of Mosul.

Study design

The rats were randomly divided into seven experimental groups. Each group consisted of five animals treated as follows:

1- Control group (G1) (n=5): Rats were orally administered normal saline daily for seventh days as a negative control but on day four the rats were treated with normal saline intraperitoneal as well as orally to encounter same conditions of other groups.

2- Group G2 (n=5): Apigenin 50 mg\kg was given orally to rats for seventh days, but on day four, the rats were given normal saline intraperitoneally for three days.

3- Group G3 (n=5): Luteolin 50 mg\kg daily was given orally to rats for seventh days, but on day four, the rats were given normal saline intraperitoneally for three days.

4- Group G4 (n=5): Rats were orally administered normal saline daily for seventh days, but on day four, rats were injected intraperitoneal cytarabine at a dose 100 daily for three days.

5- Group G5 (n=5): Rats were orally administered apigenin at 50 mg\kg daily for the seventh days, but on day four the rats were treated with cytarabine 100 mg\kg intraperitoneal.

6- Group G6 (n=5): Rats were orally administered luteolin at 50 mg\kg daily for the seventh days, but on day four, the rats were treated with cytarabine 100 mg\kg intraperitonial for three days .

7- Group G7 : (n=5): Rats were orally administered apigenin at 50 mg\kg and luteolin at 50 mg\kg daily for seventh days, but in day four, the rats were treated with cytarabine at 100 mg\kg intraperitonial for three days.

The rats in all seven groups were sacrificed after one week of treatment under chloroform general anesthesia inhalation. Their livers were collected from each one for evaluating histological changes. Blood samples were collected from each rat after the animals were sacrificed for the analysis of biochemical parameters. Before inhaling chloroform, blood samples (5ml) were collected from all rats via the orbital eye angle vein. Blood was placed in plain tubes and allowed to coagulate for thirty min at room temperature, before being centrifuged for 10 minutes at 3000 rpm. Serum samples were separated and kept at –20°C until analysis by using spectrophotometer kits (GPT and GOT (Randox Laboratories, UK)) to measure liver enzyme activities, as well as bilirubin, and cholesterol concentrations.

Statistical Analysis:

All of the data have been analyzed using the statistical software SPSS ver. 18. The ANOVA test followed by post-hoc Duncan's test were used to compare mean differences between groups. The data was presented as a mean ± standard deviation. Statistical significance was defined as p-value ≤0.05.

Result:

GPT and GOT:

GPT enzyme activity increased significantly in cytarabine treated animals 45.0±2.0 in comparison to the control 28.66±3.0 and others treated groups. Apigenin and luteolin administration alone had no significant effect on GPT activity 32.6 ±2.5 and 33.6 ±4.1, respectively in comparison to the control 28.66±3.0 , whereas apigenin or luteolin combined with cytarabine had a significant decrease in GPT activity 38.0±2.0 and 38.0±2.0 , respectively in comparison to the group treated with cytarabine only. There was a significant decrease in GPT level 36.3±1.5 in the group treated with “apigenin+ luteolin+ cytarabine together compared to the group treated with cytarabine only 45.0±2.0 ,but there was no difference when compared to the control group (Table 1).

Table 1. Comparison of changes in GPT and GOT activities between control and other groups

Groups	Median (range; IU/L)	
	Activity of GPT	Activity of GOT .
Control	28.7±3.0 a	34.0±1.0 a
Cytarabine	45.0±2.0 b	65.0±3.0 b
Apigenin	32.6 ±2.5 a	37.0±2.0 a
Luteolin	33.6 ±4.1 a	36.8±0.07 a
Apigenin + cytarabine	38.0±2.0 c	35.0±2.0 a
Luteolin+ cytarabine	38.0±2.0 c	42.0 ±2.0 c
Apigenin+ luteolin+ Cytarabine	36.3±1.5 a c	37.1 ±1.0 a

GPT: alanine Aminotransferase; GOT: aspartate aminotransferase, , *p*-value ANOVA followed by Duncan multiple tests.
-Data were describe (Mean + SD)
-Different small letters mean there are significant different in the same Colum at $p \leq 0.05$.

GOT

GOT enzyme activity in cytarabine treated animals 65.0±3.0, increased significantly in comparison to the control 34.0±1.0 and others treated groups. Administration of apigenin 37.0±2.0, and luteolin 36.8±0.07 each one alone had no significant effect on GOT activity in comparison to the control group 34.0±1.0 . However, there was a significant decrease in GOT activity when apigenin and cytarabine 35.0±2.0 combined together in comparison to the group treated with cytarabine alone 65.0±3.0 .

The combination of luteolin and cytarabine reduced the GOT levels 42.0 ±2.0 compared to the cytarabine group alone 65.0±3.0, but they GOT level was significantly higher than the level of others groups. There was a significant decrease in GOT level 37.1±1.0, in the group treated with "apigenin+ luteolin+ Cytarabine" together compared to the group treated with cytarabine alone 65.0±3.0, but a non-significant difference was observed when compared with the control group (Table 1).

Bilirubin and cholesterol

Bilirubin concentrations increased significantly 1.7±0.15 in cytarabine-treated animals compared to control 1.1±0.17 and others treated groups. Administration of apigenin and luteolin (separately or together) decreased significantly bilirubin concentrations in the cytarabine-treated group (Table 2).

Administration of cytarabine significantly increases cholesterol levels 91.7±2.0 in comparison to the control 77.0±2.0 and other treated groups. Administration of apigenin alone decreased cholesterol level 70.0±2.0 in comparison to the control 77.0±2.0 and all other treated groups, but with non-significant effect with luteolin alone 75.0±5.0 (Table 2).

The combination of apigenin and luteolin with cytarabine significantly reduces cholesterol levels(81.0±2.0, 80.6 ±3.0, and 80.3 ±1.0, respectively when compared to cytarabine alone 91.7±2.0 (Table 2).

Table 2. Comparison of changes in bilirubin and cholesterol concentration between groups.

Groups	Median (range; mg/ml)	
	Concentration of Bili	Concentration of Chol
Control	1.1±0.17 a	77.0±2.0 a
Cytarabine	1.7±0.15 b	91.7±2.0 b
Apigenin	0.72 ±0.2 a	70.0±2.0 c
Luteolin	0.73 ±0.2 a	75.0±5.0 a c
Apigenin + cytarabine	0.96±0.15 a	81.0±2.0 a
Luteolin+ cytarabine	1.0±0.25 a	80.6 ±3.0 a
Apigenin+ luteolin+ Cytarabine	1.1±0.4 a	80.3 ±1.0 a

Bili: Bilirubin; Choles: Cholesterol, , *p*-value ANOVA followed by Duncan multiple tests.
Data were describe (Mean + SD)
-The similar letters among groups mean there is no significant difference in the same column at $p \leq 0.05$
-The different letters among groups mean there is a significant difference in the same column at $p \leq 0.05$

Histological results

Histological analysis investigation of a liver sample of control group G1 revealed the normal architecture of liver tissue and hepatocyte pattern (Fig.1, G1).

Histological sections of the G2 liver treated with cytarabine revealed variable histological changes, including an abnormal pattern of hepatocytes, vacuolar degeneration (cell swelling), congestion of the central vein with evidence of endothelial cells desquamation , and fibrosis, whereas other sections showed pyknotic nuclei, necrosis, and infiltration of inflammatory cells (Fig. 1: G2).

The results of the current study showed that the number of kupffer cells and diploid hepatocytes was slightly increased in the livers of G3 and G4 that were subjected to apigenin and luteolin, respectively, when compared to the control group; however, other histological features of the liver were nearly similar to those of the control group (Fig. 1: G3 and G4).

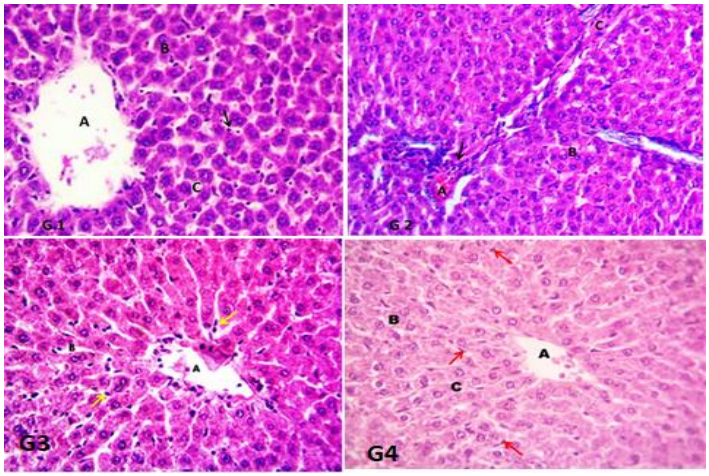

Figure 1. G1: photomicrograph of liver in control group G1 showing the normal architecture of liver tissue characterized by central vein (A), sinusoids (B) , normal hepatic cords (C), and kupffer cell (arrows). H&E stain, 400×.
G2: Photomicrograph of liver in G2 (cytarabine only) showing congestion of portal vein (A), vacuolar degeneration (B) , fibrosis (C), and infiltration of inflammatory cells (arrow). H&E stain, 100×.
G3: Photomicrograph of liver in G3 (apigenin only) showing the normal architecture of liver tissue characterized by central vein (A), sinusoids (B), and kupffer cell (arrows). H&E stain, 400×.
G4: Photomicrograph of liver in G4 (luteolin only) showing the normal architecture of liver tissue characterized by central vein (A), sinusoids (B) , normal hepatic cords (C) and kupffer cell (arrows). H&E stain, 400×.

The ameliorative effect of apigenin in G5 and luteolin in G6 against the effect of cytarabine was at minimum levels, anyway, the severity of lesions in these two groups was decreased in comparison to cytarabine group.

Apigenin or luteolin administration increased in the number of kupffer cells and apoptotic cells in damaged liver tissue, as well as sinusoid dilatation and a few necrotic and degenerated hepatocytes, with infiltration of polymorph nuclear cells (Table 3: G5 and G6).

When apigenin and luteolin were combined with cytarabine in G7, the ameliorative effect was greater than that in G5 and G6. Where the severity of lesions decreased markedly with a significant elevation in the number of kupffer cells. Some liver sections in this group showed mild to moderate vacuolar degeneration in hepatocytes (Table 3: G7).

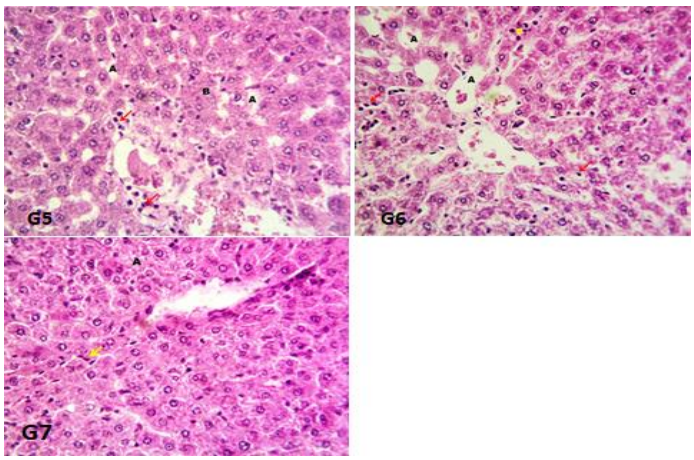

Figure 2. G5: photomicrograph of liver in group G5 (cytarabine+apigenin) showing sinusoid dilatation (A), as well as a few necrotic and degenerated hepatocytes (B) with infiltration of polymorph nuclear cells (arrow). H&E stain, 400×
G6: Photomicrograph of liver in group G6 (cytarabine+luteolin) showing congestion and dilation of sinusoids, (A) increased number of kupffer cells (arrow) and apoptotic cells (B), and necrotic hepatocytes (C). H&E stain, 400×.
G7:Photomicrograph of liver in group G7 (cytarabine+apigenin+luteolin) showing elevation in the number of kupffer cells (arrow) mild to moderate vacuolar degeneration of hepatocytes (A).H&E stain, 400×.

Table 3. Diameter in millimeter of Sinusoid and number of Kupffer cell.

Groups	Median (range; mm)	
	sinusoid diameter mm	Number of Kupffer cell
Control	4.60±0.83 a	21.8±3.34 a
Cytarabine	17.88 ± 2.99 b	23.00± 2.91 b
Apigenin	5.08± 0.84 a	21.60± 3.04 a
Luteolin	10.18± 1.17 c	20.6± 2.07 a
Apigenin + cytarabine	13.32± 2.11 d	35.60± 3.43 c
Luteolin+ cytarabine	7.78 ± 1.09 c	24.4 ± 3.64 b
Apigenin+ luteolin+ Cytarabine	7.96± 0.52 c	28.0 ± 2.0 b

Data were describe (Mean + SD)
-The similar letters among groups mean there is no significant difference in the same column at $p \leq 0.05$
-The different letters among groups mean there is a significant difference in the same column at $p \leq 0.05$

Discussion:

Cytarabine is a chemotherapeutic drug used to treat leukemias such as acute myeloid leukemia, chronic myelogenous leukemia, and acute lymphocytic leukemia [13]. Bone marrow suppression, vomiting, diarrhea, mouth ulcer development, rash, bleeding, liver difficulties, lung illness, and allergic responses are the most common side effects of this medicine [14]. In the present study, the injection of cytarabine to rats raised the activities of GOT and GPT enzymes in serum, as well as bilirubin and cholesterol. This finding is consistent with prior research that showed cytarabine treatment increased liver enzyme levels [15]. However, when bodily tissue or an organ such as the liver, becomes ill or damaged, more GOT and GPT are released into the circulation, raising the enzyme's levels [16]. As a result, the amount of GOT and GPT in the blood is proportional to the severity of tissue injury. After severe injury, GOT levels can rise 10 to 20 times higher than usual, and GPT levels can climb much higher (up to 50 times greater than normal) [17,18].
The administration of apigenin or luteolin to rats treated previously with cytarabine was shown to significantly lower cholesterol in rats [19]. They also reduced bilirubin and cholesterol levels , as well as glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) activities (the enzymes found mainly in the liver); therefore, is mainly affected by oxidative stress produced by administration of cytarabine [15].

In this study, the use of cytarabine resulted in an increase in cholesterol levels. This could be a return to oxidative damage caused by the liver's high levels of reactive oxygen species , which cause lipid peroxidation and the formation of reactive lipid dicarbonyls. These lipid oxidation products may be the most prominent mediators of oxidative injury , because they adduct to proteins, lipids, and DNA, causing cellular and organ dysfunction . As a result, alternative strategies for preventing oxidative injury are used [20]. In this study, administration of cytarabine and (apigenin or luteolin) were found to protect the liver from cytarabine- induced injury by decreasing serum levels of GOT and GPT. Apigenin and luteolin are natural flavonoid compounds found in many vegetables, medicinal plants and health foods [21].

The degree of liver damage was decreased by reducing serum alanine aminotransferase and aspartate aminotransferase levels after 7 days of oral treatment of apigenin and luteolin 50, 50 mg/kg, respectively. If the level of this enzyme decreases, it indicates that the drug is protecting the organ [19]. This might signal a return to Apigenin pretreatment. Apigenin has also been demonstrated to protect mice from agents induced liver injury, and its mechanisms are thought to be connected to increased Nrf-2- (mediated antioxidative enzymes and anti-inflammatory action)[22].

Because most chemotherapeutic medications are lipophilic substances and easily absorbed by the

liver, they can cause a variety of histological changes in the liver [23]. Higher susceptibility to chemotherapy, which causes irreversible hepatocellular injury by recruiting inflammatory cells and altering the cellular structure of the liver, and multiple foci of apoptotic cells is due to the liver's rich blood supply and increased lipid content in hepatic cells [24]. The results of this study on the cytarabine treated group revealed variable histological changes, including an abnormal pattern of hepatocytes, vacuolar degeneration, congestion of the central vein with evidence of desquamation of its endothelial cells, and fibrosis, whereas other sections showed pyknotic nuclei, necrosis, and inflammatory cells infiltration. The histological finding could be explained by oxidative damage, which causes mitochondrial DNA damage. These alterations have been linked to DNA fragmentation and the start of apoptosis. Tissue injury generates sinusoidal congestion in the liver, and hepatocyte damage causes hepatic fibrogenesis, which induces inflammatory cell recruitment, activation of von Kupffer cells, and cytokines production [25].

Similar to the result obtained by [26] , who looked at the histopathological effects of anticancer drugs cisplatin, doxorubicin, and 5-flu cancer therapy on the hepatic of rats and found ultrastructural abnormalities in the liver including marked disruption of hepatic cords and dilated blood sinusoids, inflammatory infiltration, periportal fibrosis, hyperplasia, and many hepatocytes showed karyomegaly and pyknotic nuclei representing apoptosis. Cancer treatment works by generating direct DNA damage, after which triggers an inflammatory cascade when cytokines reach the circulation [27]. Administration of cytarabine alone produces significant histopathological changes in liver sections of mice due to oxidative stress caused by the use of this anticancer drug [28], Lipid peroxidation is induced by high levels of reactive oxygen species, resulting in reactive lipid dicarbonyls. These lipid oxidation products may be the most important mediators of oxidative injury, as they cause cellular and organ dysfunction by adducting to proteins, lipids, and DNA [20]. Because apigenin and luteolin have antioxidant activity, histology of liver sections in the apigenin and luteolin showed normal views similar to the control group [19,6]. This result is in line with [29], who mentioned that antioxidant CoQ10 reduced hepatic histopathological damage in doxorubicin-treated mice via antioxidant and anti-inflammatory effects. Apigenin and luteolin protect against cytarabine toxicity by boosting antioxidants, preventing mitochondrial DNA damage, promoting replication, and inhibiting membrane-active lipases [30]. The antioxidant protective effect of apigenin and luteolin found in this study against anticancer therapy agreement with the previous study of Brassica vegetable that has the restraining effects of free radicals and antioxidants in that protect against the serious effects of free radicals by reducing and stopping oxidative reactions [31].

Conclusion:

The administration of apigenin and luteolin reduced the histological changes caused by cytarabine in the liver, and a combination of apigenin and luteolin with cytarabine produces more protection for the liver and a significant reduction in the severity of lesions, with a significant elevation in the number of kupffer cells.

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Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Besides, the Figures and images, which are not ours, have been given the permission for re-publication attached with the manuscript.
- The author has signed an animal welfare statement.
- Ethical Clearance: The project was approved by the local ethical committee in University of Mosul.

Authors' contribution statement:

G A. T conceived of the presented idea. O N. developed the theory and performed the computations and verified the analytical methods. All authors discussed the results and contributed to the final manuscript

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التأثيرات الفسيولوجية والنسجية للأبيجينين و اللوتولين على الجرذان المحقونة بالسيتارابين

عمر نجم سلطان غادة عبد الرحمن طاقة

فرع العلوم الأساسية، كلية طب الأسنان، جامعة الموصل، الموصل، العراق.

الخلاصة:
اجريت الدراسة الحالية لمعرفة تأثير الأبيجينين و اللوتولين على التغيرات الفسيولوجية والنسيجية في الجرذان المعاملة بعقار السيتارابين. تم استخدام خمسة وثلاثون من ذكور الجرذان البالغين ويتمتعون بصحة جيدة . تراوحت اوزانها بين 250 و 300 غرام. تم تقسيم الجرذان عشوائياً إلى سبع مجاميع حسب المعاملة. المجموعة " 1" التي عوملت بمحلول ملحي فسيولوجي وتعمل كمجموعة ضابطة عوملت المجموعة "2 و 3 و 4" بسيتارابين ، أبجينين ، ولوتولين على التوالي . بينما عوملت المجموعة 5 و 6 و 7 بمزيج من "أبيجينين + سيتارابين" و "لوتولين + سيتارابين" و "أبجينين + لوتولين + سيتارابين", على التوالى. بعد أسبوع واحد من المعاملة ، تم التضحية بالجرذان في المجموعات السبع من أجل الكشف النسيجي، وتم جمع عينات الدم من كل جرذ لتحليل المعلمات البيوكيميائية. أظهرت نتائج هذه الدراسة أن السيتارابين يزيد من نشاط الإنزيمات الناقلة لمجموعة الأمين "GP و GOT" ومستوى الكوليسترول في دم الجرذان بعد أسبوع واحد من الحقن داخل الصفاق مقارنة بالمجموعة الضابطة. لم يكن هناك فرق معنوي في نشاط الإنزيمات الناقلة لمجموعة الأمين "GPT و GOT" عندما تم إعطاء الأبيجينين واللوتولين بالفم مقارنة بالمجموعة الضابطة. والجمع بين الأبيجينين واللوتولين مع السيتارابين كان له تأثير وقائي على تسرب إنزيمات الكبد GPT و GOT إلى مصل الدم. اعطى الأبيجينين و اللوتولين تاثيرا وقائيا ومنع التلف لخلايا الكبد في الجرذان المعاملة بالسيتارابين .نستنتج من هذه النتائج ان اعطاء الأبيجينين و اللوتولين لهما تأثير وقائي على الآثار الجانبية للسيتارابين على الكبد ووظائفه في الجرذان.

الكلمات المفتاحية : ابجنين , كوليسترول , سيتارابين , انزيمات الكبد , لوتولين.