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Hepatoprotective Potential of Apigenin versus Vitexin: A Comparative Study in an Acetaminophen-Induced Acute Liver Injury Rat's Model

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Abstract

Acetaminophen (Paracetamol) poisoning is a global issue that can result in severe liver failure and permanent liver damage, necessitating the need for liver transplantation. The aim of our study was to assess and compare the preventive effects of Apigenin and vitexin against acetaminophen-induced acute liver damage in rats. Twenty male rats were divided into four groups (5 per each) and treated for seven consecutive days. Group I (negative control group) received 5% DMSO, Group II received a single acetaminophen dose, Group III received 10 mg/kg Apigenin i.p, while Group IV received 40 mg/kg vitexin i.p. On the seventh day, all groups except Group I received a single oral dosage of 3000 mg/kg acetaminophen three hours after their final Apigenin or vitexin dose. After 24 hours of acetaminophen administration, the animals were sacrificed, and their blood and livers were taken for biochemical and histopathological examination. The results demonstrated that acetaminophen treatment led to notable increases ($p < 0.05$) in blood biochemical markers (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase), in contrast to the negative control group. However, rats who received Apigenin exhibited a notable decrease ($p < 0.05$) in the level of these biomarkers. For vitexin pretreatment, the levels of these enzymes were reduced, but this reduction was significant only for alkaline phosphatase levels compared to the acetaminophen group. Furthermore, Apigenin pretreatment was able to restore normal liver histopathology, while vitexin was not. In conclusion, our research validated the hepatoprotective properties of Apigenin against acetaminophen hepatotoxicity and provided insight into potential distinctions in the effects of a flavonoid versus its glycosylated form.

Keywords: Apigenin, Vitexin, Hepatoprotection, Acetaminophen, Paracetamol, Liver Damage

Introduction

Drug-induced liver injury (DILI) is still a major issue in clinical practice, necessitating the research for potential protective agents [(1)]. DILI ranges from asymptomatic rise in liver enzymes to acute liver failure (ALF). DILI remains the predominant cause of ALF in Western countries [(2)]. Acetaminophen-induced hepatotoxicity is an example of a dose-dependent and predictable DILI [(3).] In the United States, acetaminophen overdose causes roughly 40% of all cases of ALF, while idiosyncratic drug reactions account for approximately 13% of cases[(4)].

Acetaminophen was discovered in 1878 and became popular as an over-the-counter analgesic and antipyretic in the 1950s. Since then, multiple studies have found a dose-dependent link between acetaminophen use and liver injury. These consequences can be exacerbated in the presence of other risk factors such as alcohol misuse, starving ketosis, or concurrent illnesses [(5)]. When taken in therapeutic amounts, over 90% of acetaminophen is transformed into harmless byproducts by sulfation and glucuronidation processes and then excreted through the kidneys. However, when a dangerously high amount of acetaminophen is taken, the body's mechanisms for processing the medication get overwhelmed. This results in a higher proportion of the drug being eliminated without any changes (~10%) and being metabolized into a harmful substance called N-acetyl-p-benzoquinone imine (NAPQI) (>15%) by CYP450 enzymes [(6)]. After undergoing glutathione conjugation, NAPQI is ultimately removed since it is converted into innocuous metabolites [(6,7).] The effect of acetaminophen on glutathione levels depends on the dosage, with greater dosages leading to prolonged depletion of glutathione [(8).] When glutathione is depleted, oxidative stress triggers the activation of

mitochondria-permeability transition pores. This leads to the disruption of the membrane potential and the cessation of ATP generation [9]. Ultimately, this leads to the degradation of DNA and cell membranes, as well as the initiation of apoptosis, resulting in cell demise and intense inflammation [9].

N-acetyl cysteine (NAC) is a well-known anti-oxidant that is most commonly utilized to reduce acetaminophen-induced hepatotoxicity. NAC provides protection by reducing hepatic glutathione depletion, hence limiting the generation of reactive oxygen species in mitochondria [10]. N-acetyl cysteine is frequently poorly tolerated at the doses needed to treat acetaminophen overdose, resulting in adverse effects including fever, rash, chills, headache, tinnitus, urticarial rash, and anaphylactoid reactions (pseudoanaphylaxis) [11]. Another significant drawback of NAC is its lack of efficacy, especially when starting the treatment eight hours after poisoning [12]. This emphasizes the need for novel NAC replacement or supplement drugs and the utilization of natural anti-oxidants, particularly phytochemicals, in the treatment of oxidative stress-related liver disorders.

Apigenin (4′, 5, 7-trihydroxyflavone) is an aglycone flavonoid. It is extracted from Matricaria chamomilla. Additionally, large amounts of Apigenin are present in a variety of fruits and vegetables, including propolis, honey, thyme, garlic, onions, celery, parsley, and chamomile [13].

It possesses a multitude of medicinal properties, such as anti-inflammatory, anti-tumor, and anti-oxidant properties. Previous studies showed that Apigenin was effective against several models of chemically induced liver injury [13,14].

Vitexin, or apigenin-8-C-glucoside, is found in several plants, including Pennisetum millet, Vitex agnus-castus, and bamboo leaves. It exhibits a diverse range of pharmacological activities, including anti-inflammatory, neuroprotective, and anti-cancer properties [15]. According to earlier research, administering vitexin to mice with liver damage resulted in a reduction in hepatic enzyme levels and a decrease in the release of inflammatory cytokines TNF-α, IL-1β, and IL-6 when exposed to 4% dextran sodium sulfate [16]. Furthermore, prior research found that vitexin could be employed as a therapeutic drug to counteract Cd-induced liver damage in rats due to its anti-oxidant, anti-inflammatory, and anti-apoptotic characteristics [17].

These researches provide empirical backing for the traditional application of naturally derived compounds in treating jaundice and other hepatic disorders.

The aim of this study was to compare the protective effects of Apigenin against its glycosylated form, vitexin, in rats with acetaminophen-induced acute hepatotoxicity

Materials and Methods

Chemicals

Apigenin and vitexin pure powders (purity >98%) were purchased from Chengdu Biopurify Phytochemicals Co., Ltd, China. Acetaminophen was obtained from Pioneer, Iraq.

Apigenin and vitexin were dissolved in 5% dimethyl sulfoxide (DMSO), while acetaminophen was dissolved in 0.9% normal saline.

Experimental design

Twenty Male Sprague-Dawley rats weighing between 180 and 250 g were purchased from the University of Basrah/ College of Medicine's Animal House. Animals were provided standard feed and a free supply of water. The NIH's Guide for the Care and Use of Laboratory Animals was adhered to throughout the research. The research was approved by the ethical committee of the College of Medicine, University of Basrah (No. 1 at 12/10/2023, research no. 030406-005-2023)

Four groups of rats (5 per Group) had 24-hours of fasting before the initiation of therapy. The animals were then treated once daily for seven consecutive days. Group I (negative control) received vehicle (5% DMSO i.p), Group II (induction group) received a single dose of acetaminophen (3000 mg/kg orally), Group III was pre-administered with 10 mg/kg Apigenin i.p, while Group IV was given 40 mg vitexin i.p. Except for the negative control group, all other groups were given a single oral dose of 3000 mg/kg acetaminophen 3 hours after their last dosage of vitexin or Apigenin on the 7th day. Following acetaminophen administration, all animals fasted for 24 hours. Subsequently, the animals were given mild anesthesia (ketamine 80 mg/kg + xylazine 10 mg/kg), and their blood was extracted via heart puncture for biochemical tests. The animals' livers were then removed for histopathological study after they were mercifully sacrificed by cervical dislocation.

Assessment of serum biochemical markers

Blood samples were placed in gel separator vacuum tubes. The serum was separated by blood-centrifugation at 5000 rpm for 5 minutes. The biochemical markers examined were alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). The automated chemistry analyzer (ARCHETIC c40000, Abbott core laboratory, USA) was utilized for all analyses by using commercial kits (Randox veterinary kits, Randox Laboratories Ltd, Antrim, United Kingdom) and according to the provided manuals.

Histopathological examination

To assess the pathological alterations in the liver tissues, Hematoxylin and eosin (H&E) staining was utilized. For 48 hours, the liver tissues were incubated in 4% paraformaldehyde. Following dehydration, the tissues were fixed in paraffin and cut into sections that were 4-5 µm thick. Hematoxylin and eosin stains were used to stain the sections after they had been dewaxed and rehydrated. Hepatic morphological changes were seen using an optical microscope (Olympus, Tokyo, Japan), and histopathological analysis was done blindly by an independent histopathologist.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) application was used to conduct statistical analysis. All data were provided as means ± standard errors of the means. The data were compared between the groups using one-way ANOVA and post-hoc LSD testing. A P-value of 0.05 or lower was judged statistically significant

Results

Effects of Apigenin and vitexin on serum ALT, AST and ALP levels

Compared to the negative control groups, the administration of acetaminophen led to substantial increases ($p < 0.05$) in the activities of blood biochemical markers such as ALT, AST, and ALP. However, rats who received Apigenin exhibited a substantial ($p<0.05$) decrease in the levels of ALT, AST, and ALP.

The administration of vitexin resulted in a moderate decrease in the activity of ALT, AST, and ALP. However, this decrease was statistically significant only for the ALP level compared to the acetaminophen group. ($p<0.5$), Figures 1, 2, 3.

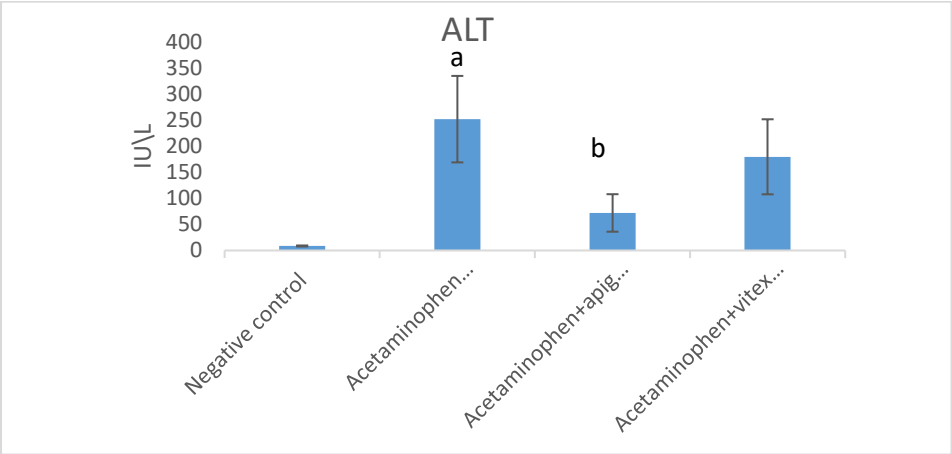


Figure 1. Effects of Apigenin and vitexin on serum ALT in an acetaminophen-induced hepatotoxicity in male rats. (a) Significant from negative control group, (b) significant from acetaminophen- treated Group (induction group)

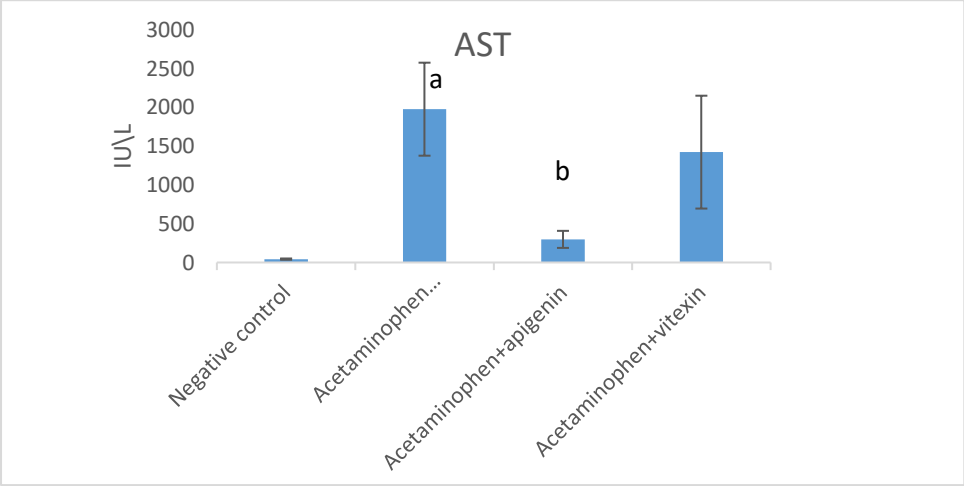


Figure 2. Effects of Apigenin and vitexin on serum AST in an acetaminophen-induced hepatotoxicity in male rats. (a) Significant from negative control group, (b) significant from acetaminophen- treated Group (induction group)

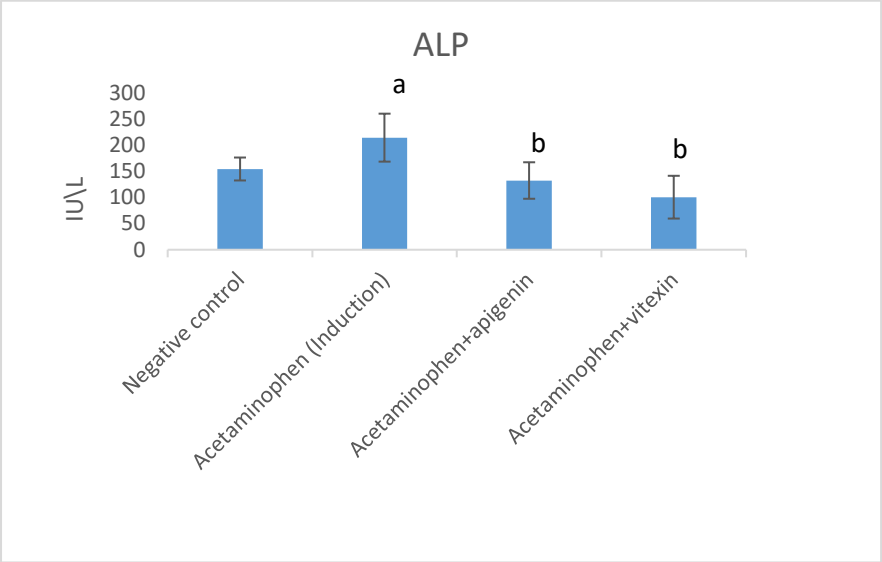


Figure 3. Effects of Apigenin and vitexin on serum ALP in an acetaminophen-induced hepatotoxicity in male rats. (a) Significant from negative control group, (b) significant from acetaminophen- treated Group (induction group)

Histopathological study

The control group's liver appeared within normal bounds, with hepatocytes arranged in rows around the central vein and into the portal area. Sinusoids displayed minimal congestion and were typical within the context. The portal vein and the central vein were both normal (Figure 4). In the induction (acetaminophen) group, the liver displayed several foci of hepatocellular necrosis scattered throughout the hepatic parenchyma, including the sub-capsular location. The liver also displayed substantial hepatocellular necrosis in the centrilobular area, with clear congestion in the sinusoids, central vein, and portal vein. (Figure 5)

All of the alterations brought on by acetaminophen toxicity that were observed in the induction group were absent in the Group that received Apigenin. There was no congestion in the portal or central veins, and the hepatocytes were normal. The sinusoids amidst the hepatocyte rows exhibit typical architecture, as illustrated in Figure 6, A These views were noticed in all hepatic parenchyma.

In the Group treated with vitexin, there was noticeable hepatocellular necrosis accompanied by hepatic sinusoidal rupture and hepatic parenchymal bleeding. (Figure 6, B)

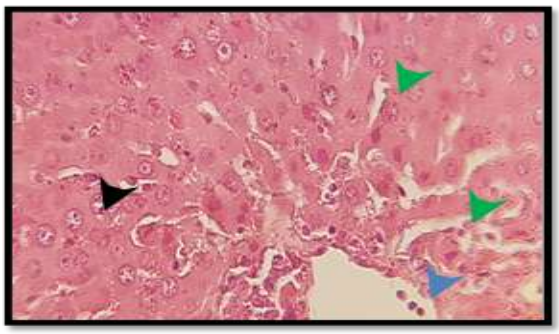


Figure 4. Liver section of control group shows normal hepatocytes in the centrilobular area (black arrow), normal central vein (blue arrow), normal hepatic sinusoids (green arrow). H&E, 40 X

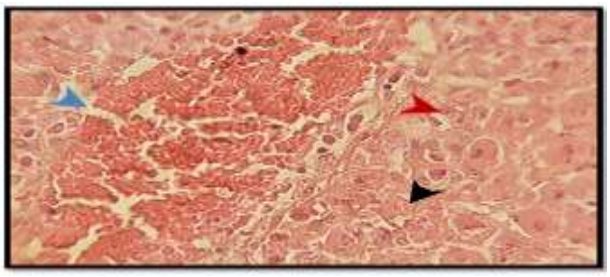
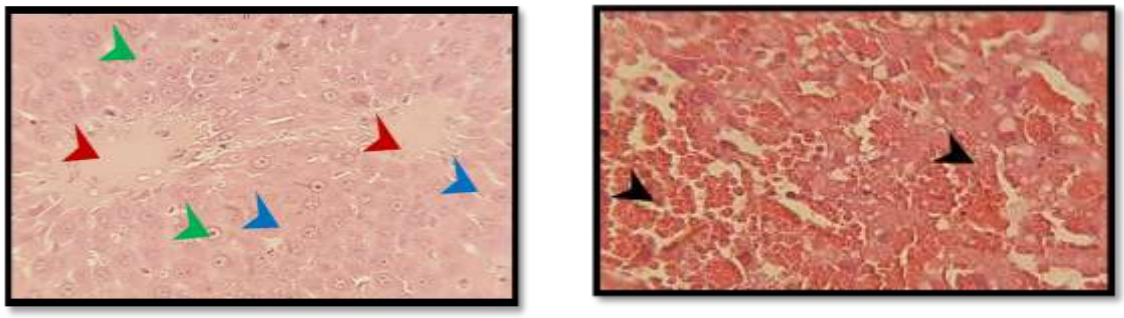


Figure 5. Liver section of induction group shows necrotic hepatocytes in the centrilobular area (black arrow) hepatic vascular congestion (blue arrow), subcapsular hepatocellular necrosis (red arrow). H&E, 40 X



A **B**

Figure 6. (A) Liver section of Apigenin group shows normal hepatocytes (blue arrow) normal central vein (red arrow) and normal hepatic sinusoids (green arrow) in the centrilobular area.(B) liver section of vitexin group shows area of hemorrhagic necrosis (black arrow). H&E, 40 X

Discussion

One of the most common over-the-counter drugs for treating pain and pyrexia is acetaminophen. When taken over the recommended therapeutic dose, it has been reported to produce liver toxicity[18]. N-acetyl-para-benzoquinone immine (NAPQI) is the harmful metabolite that is formed when the hepatic cytochrome P450 break down acetaminophen. Elevated NAPQI levels lead to reactive oxygen species buildup, which damages hepatocyte membranes, triggers lipid peroxidation, and results in liver necrosis [10].

Given that oxidative stress plays a significant role in the pathology of liver injury [10], it might be inferred that any agent with anti-oxidative properties is likely to protect against liver damage. Based on this assumption, numerous natural compounds have been identified as having the potential to treat acetaminophen-induced liver damage via anti-oxidant pathways[19]. In the same context, it is possible to conclude that Apigenin and its glycosylated flavone; vitexin may have in vivo anti-oxidant and hepatoprotective characteristics, necessitating further investigation of these effects.

Excessive consumption of acetaminophen leads to the formation of reactive substances that harm liver cells, resulting in elevated levels of liver enzymes in the bloodstream. One important indicator of hepatotoxicity is ALT. This enzyme is more concentrated in the liver than in other tissues. Meanwhile, AST has lesser specificity for liver injury because it is also present in other organs, yet its importance in hepatotoxicity should not be ignored. Consequently, when the liver is under stress, these enzymes are released into the bloodstream in direct correlation to the degree of liver injury [20]. Therefore, it is crucial to measure ALT and AST levels, especially when evaluating acetaminophen toxicity. In this investigation, acetaminophen administration significantly increased serum ALT and AST levels (Figure 1, A, B). These findings were consistent with the results published in prior studies that utilized animal models to examine acetaminophen-induced liver damage [19, 21]. Our study found that pretreatment with Apigenin considerably decreased the levels of AST and ALT in rats. This finding aligns with prior studies conducted by Rašković et al and Zhao et al [22, 23]. It is noteworthy that in the present study, Apigenin protected the liver against harm caused by a comparatively greater dose of acetaminophen (3000mg/kg), whereas smaller doses (400-600 mg/kg) were used in the two prior studies. This confirms the hepatoprotective effect of Apigenin against a broad range of doses.

Alkaline phosphatase (ALP) is another liver enzyme that merits more study. ALP is produced in the membranes of the bile duct and canaliculi. When there is hepatobiliary damage, a substantial quantity of it is discharged into the bloodstream [24]. Biliary congestion, which accompanies hepatic damage, leads to the body's inability to eliminate ALP, resulting in its increase, as demonstrated in the acetaminophen group. Nevertheless, the animals' ALP levels returned to normal after receiving Apigenin. This shows that Apigenin displayed hepatoprotective effects, presumably through a decrease in bile duct blockage.

Histopathological abnormalities in liver tissues verified the changes in liver enzyme levels that occurred after acetaminophen administration. Acetaminophen overdose resulted in pathological alterations in the liver, including hepatocyte degradation, hemorrhagic necrosis, and congested sinusoids, which are similar to previous observations [19, 25]. Apigenin treatment reversed this impact. The hepatoprotective effect of Apigenin is probably attributed to its well-known anti-oxidant potential [22]. Addition mechanism may include Apigenin' inhibitory effect on CYP450 isozyme

particularly CYP3A4[26] which might lead to inhibition of NAPQI formation

Apigenin and vitexin indeed share the same basic chemical structures; however, being a glycosylated form of Apigenin, vitexin's endogenous anti-oxidant potential and protective effects might essentially vary. The results of our study showed that vitexin possesses minimal protective effects against acetaminophen hepatotoxicity as indicated by mild reduction in liver enzymes with failure to restore the histopathological changes. Nevertheless, previous studies revealed that vitexin provided protection against chemically induced and colitis-induced liver injury[16,17]. This might be attributed to the difference in the injurious agent, dosage, and duration of treatment

Conclusion

In summary, our research validated the hepatoprotective properties of Apigenin against hepatotoxicity induced by acetaminophen and provided insight into potential distinctions in the effects of a flavonoid and its glycosylated form.

Acknowledgment

None

Conflicts of Interest

All authors declare that they have no conflicts of interest.

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Ethics Statements

The research was approved by the ethical committee of College of Medicine, University of Basrah.

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: SFA, SAH, RSL; data collection: RSL; analysis and interpretation of results: SFA; draft manuscript preparation: SFA, SAH. All authors reviewed the results and approved the final version of the manuscript

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الامكانية الوقائية الكبدية المحتملة للابجنين مقابل الفيتكسين: دراسة مقارنة في نموذج إصابة الكبد الحاد الناجم عن الاسيتامينوفين في الجرذان

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الخلاصة

يمثل التسمم بالباراسيتامول مشكلة عالمية تؤدي إلى فشل كبدي حاد وتلف دائم في الكبد، مما يستلزم الحاجة إلى زراعة الكبد. كان الهدف من دراستنا هو تقييم ومقارنة الآثار الوقائية للابيجنين وفيتكسين ضد تلف الكبد الحاد الناجم عن الباراسيتامول في الجرذان، شملت الدراسة عشرين جرذ من الذكور تم تقسيمهم إلى أربع مجموعات (خمس جرذان في كل مجموعة) وعولجت لمدة سبعة أيام متتالية. تلقت المجموعة الأولى (مجموعة السيطرة السلبية) ٠,٥٪ DMSO، وتلقت المجموعة الثانية جرعة واحدة من الباراسيتامول، وتلقت المجموعة الثالثة ١٠ مغ / كغ من الابجنين بينما تلقت المجموعة الرابعة ٤٠ مغ / كغ من الفيتكسين عن طريق الحقن داخل الصفاق لمدة ٧ أيام. في اليوم السابع، تلقت جميع المجموعات باستثناء المجموعة الأولى جرعة فموية واحدة من ٣٠٠٠ ملغم / كغم من الباراسيتامول بعد ثلاث ساعات من اخر جرعة أبيجينين أو فيتكسين. وقد تم التضحية بالحيوانات بعد ٢٤ ساعة من إعطاء الباراسيتامول، وأخذ دمها وكبدها للفحص الكيميائي الحيوي والنسيجي. وقد أظهرت النتائج أن العلاج بالباراسيتامول أدى إلى زيادات ملحوظة ($p < 0.05$) في علامات الكيمياء الحيوية في الدم (انزيم ناقلة امين الالانين، انزيم ناقلة امين الاسبارتات، انزيم الفوسفاتاز القلوي)، على عكس مجموعات التحكم السلبية. ومع ذلك، بعد تلقي الابجنين، أظهرت الجرذان انخفاضا ملحوظا ($p<0.05$) في مستوى هذه المؤشرات الحيوية. بعد المعالجة المسبقة بالفيتكسين، تم تقليل مستويات هذه الإنزيمات، ولكن هذا الانخفاض كان ذا دلالة إحصائية فقط لمستوى انزيم الفوسفاتاز القلوي عند مقارنته بمجموعة الباراسيتامول. علاوة على ذلك، كانت المعالجة المسبقة بالابجنين قادرة على استعادة شكل الأنسجة الطبيعية للكبد، في حين أن فيتكسين لم يكن كذلك. وقد أكد البحث الخصائص الوقائية للابجنين ضد السمية الكبدية للباراسيتامول وقدم نظرة ثاقبة على الفروق المحتملة في تأثيرات الفلافونويد وشكله الغليكوزيلاتي.

الكلمات المفتاحية: الابجنين, الفيتكسين, الحماية الكبدية ,الاسيتامينوفين, الباراسيتامول, تلف الكبد.