Original Article

Influence of Infugem on the Histology, Biochemistry, and Hematology of Liver and Kidneys of Pregnant Albino Mice

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ABSTRACT

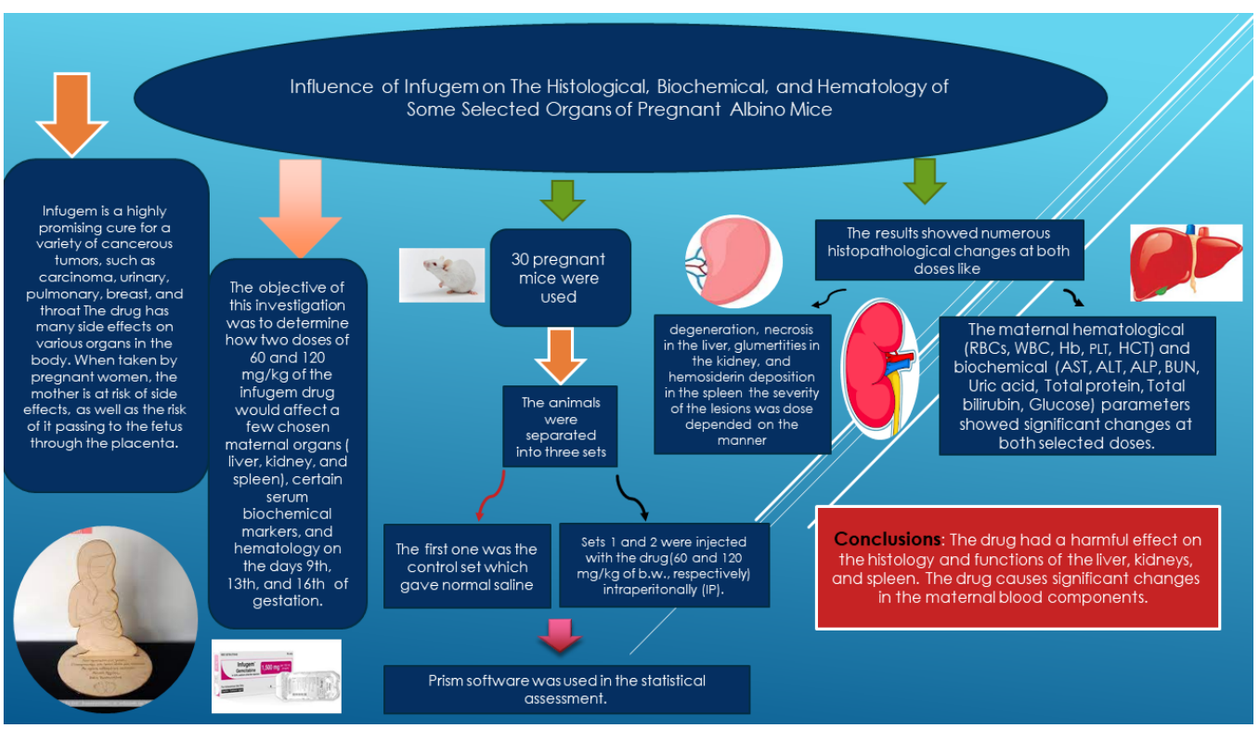
Introduction: Infugem is a highly promising cure for various cancerous tumors, such as urinary, pulmonary, breast, and throat carcinoma The drug has many side effects on various organs in the body.

Aim of the Study: The objective of this investigation was to determine how two doses 60 and 120 mg/kg of the infugem drug would affect some maternal organs (liver and kidney), certain serum biochemical markers, and hematology. The drug was given during the pregnancy period for three days) those days were 9th,13th, and 16th).

Materials and Methods: 30 pregnant mice were used. The animals were separated into three sets. The control (set I) was injected with normal saline. Sets II and III were injected intraperitonally (IP) with infugem (60 and 120 mg/kg of b.w., respectively) during pregnancy. The histopathological changes of the maternal liver, kidney, blood biochemistry, and hematology were conducted. Prism software was used in the statistical assessment.

Results: The results showed numerous apparent histopathological changes at both doses like degeneration, necrosis in the liver, (and glomerulitis in the kidney the severity of the lesions was a dose-dependent manner. The maternal hematological (RBCs, WBC, Hb, PLT, HCT) and biochemical (AST, ALT, ALP, BUN, Uric acid, Total protein, Total bilirubin, Glucose) parameters showed significant changes at both selected doses.

Conclusions: The drug harmed the histology and functions of the mice's maternal liver and kidneys, and the drug caused significant changes in the maternal blood components.



Graphical Abstract

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Key Words: Anticancer, blood toxicity, histopathology, infiltration.

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INTRODUCTION

In recent years the number of cancer patients has increased and broken this out. Several drugs have been developed against novel molecular targets, nonetheless, despite their amazing results, the majority of these medications' therapies have adverse effects and thus are hazardous to other parts of the body. Infugem is among the most efficient medications for treating a range of cancerous tumors, including malignancy, urinary, breast, pulmonary, and throat cancer[1,2]. Infugem is a substance that fights cancer (pyrimidine analog) when DNA replication occurs, the medication substitutes cytidine, which is one of the nucleic acid's basic components. Since new nucleosides cannot be linked to the wrong nucleoside, the mechanism stops tumor growth and causes cellular death " necrosis "[3,4]. The medicine can be catabolized by cytidine deaminase into an inert uracil derivative after already being transformed by nucleoside kinases into two active compounds, gemcitabine diphosphate, and gemcitabine triphosphate. Gender and age had an influence on infugem elimination. Females have lower clearance rates and longer half-lives than males[5]. The major toxicities caused by this drug are myelosuppression, paraesthesias, respiratory failure and death, and severe rash. gemcitabine administration remarkably raises the concentrations of the inflammatory cytokines IL-1α, IL-1β, and IL-17 in rodents (mouse) blood[3]. Clinical information dosages in male mice tend to result in mild to extreme hypospermatogenesis and fertility problems like reduction in sperm number and fertilization degradation in both mice males and females. While observations of cancer throughout gestation are uncommon, they have increased with the rise in maternal age and are still a global issue of concern, as well as the proportion of females diagnosed with cancer throughout gestation, is already growing, as the incidence of cancer increases with age[6]. A week of anticancer drug use throughout gestation can impair organogenesis and cause maternal toxicity, which corresponds to the properties of the alkylating infugem[7,1]. However, studies on individuals as well as animals have demonstrated that raising the therapeutic dose of chemotherapeutics causes a significant rise in the incidence of structural toxic effects[8]. Once administered to pregnant women, infugem and other relatives' drugs can cause physical and psychological harm, and these drugs have an adverse influence on the pregnant mother and unborn child's bodies[6]. Gemcitabine was found to be an embryotoxic and fetotoxic factor in mice and rabbit breeding studies. At 1.5 mg/kg/day, daily gemcitabine administration to pregnant mice raised the risk of fetal deformities (cleft palate, incomplete bone formation). Pregnant rabbits who received a daily dose of gemcitabine had fetotoxicity (lower embryonic survivability, smaller litters, and impaired cognitive development) as well as a rise in fetal abnormalities like disappearance of gall bladder). There isn't any documented remedy for infugem overdosing[9]. 90mg/kg of gemcitabine in combination with 6m/kg of cisplatin were given to the rats causing weight changes, renal toxicity, and a significant change in the serum antioxidant levels[10]. Unforeseen harmful influences of such drugs in the clinic seem to be difficult to anticipate and there is little data on the effect of infugem on the maternal body. Thus, the objective of this research was to determine how two doses of 60 and 120 mg/kg of the infugem drug would affect some maternal organs (liver and kidney), certain serum biochemical markers, and hematology during three days which were they 9th, 13th, and 16th of gestation.

MATERIALS AND METHODS

Ethical approve

The Animal Care and Use Committee of the University of Mosul's College of Veterinary Medicine looked at and confirmed each stage of the research's procedures.

Animals

Thirty pregnant mice aged 10-12 weeks, 29 ±31 GM weighted, were used during the current study. Experimental animals were obtained from the College of Veterinary Medicine, Mosul University. Mosul, Iraq. Animals were maintained in the animal house of the Department of Biology / College of Pure Science Education in compliance with standards and suitable conditions. They had been exposed to a normal day/night cycle, at 22±4 C[11], and. Animals have been treated with the care and use of experimental animal instructions.

Infugem

The drug that was used in the current research is infugem. The product Infugem is a sterilized, alcohol-free, and uncolored liquid of 10 mg/mL gemcitabine in 0.9% sodium chloride. The chemical formula is C9H11F2N3O4. The medication was Manufactured by: Sun Pharma Ind. Ltd. Gujarat, India.

Experimental Design

30 pregnant mice were employed. Three sets of the animals, each with ten pregnant mice, were used. Set I was regarded as the control group (all animals received normal saline). Sets II and III were regarded as test groups. Both sets received intraperitoneal (IP) injections of infugem at a concentration of 60 & 120 mg/kg[12] The drug was given for three days during pregnancy those days were 9th, 13th, and 16th. The weight of the pregnant mice determined the dose volume.

Biopsies Preparation and Microscopic Evaluation

All animals were killed on the 17th day of gestation after being provided by neck dislocation. The kidney, and liver of the mother were taken. They were rinsed using normal saline. Over two days, all of the chosen organs were preserved in 10% formalin. The organs were then rinsed for 120 minutes in distilled water. The samples were handled according to standard histopathological methodology. Hematoxylin and eosin by Delafield were employed to stain histologic slides. A suitable medium (D.P.X) for mounting was used[13]. The microscopic examination and

photography were done with a light microscope and a digital camera conducted the optical lens of it[13].

Blood Collection

Retro-orbital hemorrhage was used for obtaining blood samples before dissection. The amount of blood that was drawn was 1.5 to 2 ml. Two portions of the blood were separated. For biochemical estimation, portion one was placed in anticoagulant mini tubes. Portion 2 was placed into mini tubes without anticoagulants for hematology estimation (manual procedure). The traditional method adopted in biochemical laboratories was adopted in the preparation of blood serum[11].

Biochemistry and Hematology

The function of the liver was measured by the assessment of the serum glutamic-oxaloacetic transaminase (AST / SGOT), orthophosphoric monoester phosphohydrolase (ALP), and serum glutamic-pyruvic transaminase (ALT/ SGPT) levels by employing Biomerieux-France a set of equipment (kits) . The function of the kidney was estimated by measuring the creatinine, urea, BUN (BUN blood urea nitrogen), Uric acid, Total protein, Total bilirubin, and Glucose by using Biolabo, France kits. The blood variables that were measured in the current study were: RBCs(Red blood corpuscles count), WBCs (the total count of white blood corpuscles), HCT(the number of platelets and Blood cell volume), and Hb (Hemoglobin concentration)[14].

Statistical Evaluation

GraphPad Software Inc. was employed in data analysis. All values were expressed mean ±Std. *P-value* considered meaningful $P<0.05$, highly meaningful $P<0.01$, and very highly meaningful $P<0.001$. sub-test called Dunnetts (only used as a follow-up examination to ANOVA) was estimated in data analysis.

RSEULTS

The microscopical analysis of the hepatic tissue of set I (control group) showed normal histological structure (Figure 1). In both groups II & and III, the affection of liver tissue was moderate and focal, in which hepatic configuration of hepatic lobules was more or less preserved.

In group II, the affection was mild, some hepatic lobules showed apparent dilatation and congestion of their central veins as well as dilatation of blood sinusoids with the presence of minimal cellular infiltration. Also, some hepatocytes were seen with apparent cytoplasmic vacuolations and faintly stained nuclei (Figure 2). In group III, the affection was moderate, some hepatic lobules showed hepatocytes with vacuolations, with faintly stained nuclei, and others appeared with shrunken darkly stained nuclei. Congestion and dilatation of central veins and blood sinusoids were apparent with a moderate increase in cellular infiltration (Figure 3).The microscopic assessment of group I (control) kidney showed normal histological pattern of renal tubules and glomerului (Figure 4).Examination of renal sections of group II, affection was mostly detected all over kidney tissues, In group II, affection appeared variable, in which proximal and distal tubules appeared dilated in which some were seen with vacuolated cytoplasm and pyknotic nuclei, others appeared with faintly stained nuclei and shrunken cytoplasm. Collecting tubules appeared dilated with disorganization of their lining epithelium in which some cells appeared detached within their lumena and others were vacuolated with pyknotic nuclei. Some glomeruli showed vacuolations and darkly stained nuclei (Figure 5) In group III, affection was more marked and prominent as compared to that of groups I and II, renal tubules appeared more disorganized and more dilated, in which almost all of their cells appeared with pyknotic nuclei and excessive vacuolation and some lining cells appeared detached within renal tubules lumena. Also, cellular infiltration was more apparent in group III as compared to groups I and II. Haemohrage was detected in the renal interstitial space as well (Figures 6,7).

Impact of Infugem on The Blood Components

The findings of the maternal blood assessments confirmed that the medication at the concentration of 60 mg/kg caused a highly meaningful decrease of $P<0.01$ in the red blood cell count, a meaningful decrease of $P<0.5$ in WBCs numbers, insignificant change in the Hb amount, a significant raise $P<0.01$ in the PLT count, and insignificant reduction in the HCT compared to the set I. At the concentration of 120 mg/kg, the effect of the drug becomes more noticeable and represented by a very highly meaningful reduction ($P<0.001$)in the RBCs and WBCs counts, as well as a highly meaningful reduction ($P<0.01$) in the Hb concentration, a very meaningful raise $P<0.001$ in the PLT count, and highly meaningful increase ($P<0.01$) in the HCT compared to the set 1 (Figure 8).

Impact of Infugem on Maternal Blood Biochemistry

The biochemical analysis of the mother's serum showed that the concentration of 60 mg/kg revealed an insignificant rise in the levels of SGOT, and SGPT as well as an insignificant reduction in the ALP in comparison to set I, respectively. There was a highly meaningful rise of $P<0.01$ in the amount of SGOT, SGPT, and ALP at the dose of 120 mg/kg (Figure 9).

The assessment of the kidney function revealed a highly meaningful rise of $P<0.01$ in the creatinine and a significant increase ($P > <0.05$) in the levels of urea, BUN, total protein, serum total bilirubin, and glucose at the concentration of 60 mg/ kg. An insignificant increase in uric acid level was observed at the previous dose in comparison to set I. At the dose of 120 mg/kg (Set III) there was a very greatly meaningful raise $P<0.001$ in the amount of total bilirubin, but the amounts of the urea, uric acid, BUN, total protein, and glucose confirmed a highly meaningful rise in $P<0.01$ compared to the set I, respectively (Figure 10).

Additionally, the assessment of the lipid profile revealed at the concentration of 60 mg/kg an insignificant reduction in the amounts of cholesterol and a non-significant increase

in TG, but a meaningful depletion $P > 0.05$ in the level of HDL was observed. LDL showed an insignificant rise compared to set I. A highly meaningful decrease $P > 0.01$ in the amounts of cholesterol and HDL at the concentration of 120 mg/kg was noticed. TG revealed a very highly meaningful rise of $P<0.001$. An insignificant reduction in the amount of LDL was indicated at the previous dose compared to set I (Figure 11).

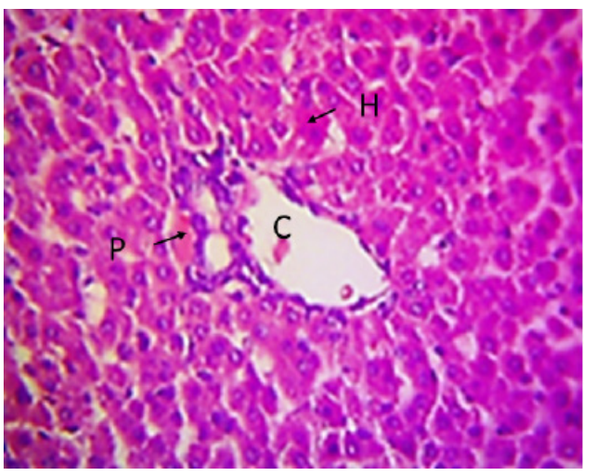

Fig. 1: A photomicrograph of a pregnant mouse liver of set I represented by central vein (C), portal area (P), and hepatocytes (H). (Hematoxylin & Eosin stain, 400X).

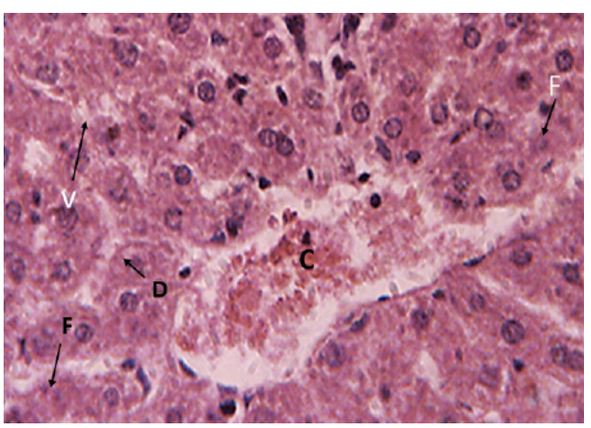

Fig. 2: A photomicrograph of the liver of set II which was injected (IP) with 60 mg/kg of infugem drug on the 9th and 13th, 16th days of pregnancy showing congestion and dilatation of the central vein (C), dilated congested sinusoids (D), and Faint nuclei (F). (Hematoxylin &Eosin stain,400X).

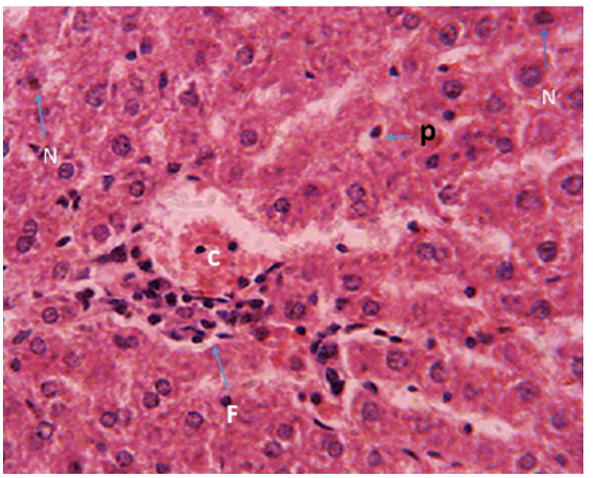

Fig. 3: A photomicrograph section of the liver of set III which was injected (IP) with 60 mg/kg of infugem drug on the 9th and 13th, 16th days of pregnancy showing congestion of the central vein(C) , pyknosis (P), and infiltration of the inflammatory cells (F), and Darkly stained shrunken nuclei (D) , Necrosis (N). (Hematoxylin &Eosin stain,400X)

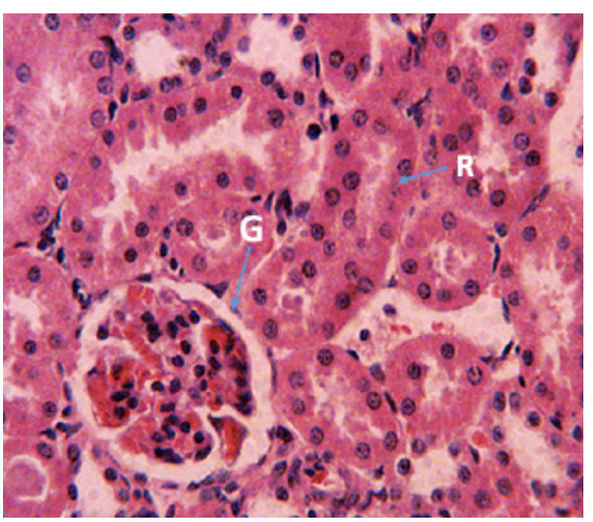

Fig. 4: A photomicrograph of a pregnant mouse kidney of the set I showing the normal architecture of the renal tissue: Glomerulus (G)and renal tubules (R). (Hematoxylin & Eosin, 400 X).

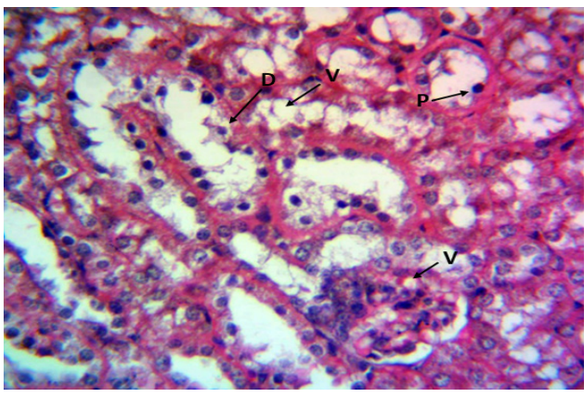

Fig.5: A photomicrograph of the kidney of set II which was injected (IP) with 60 mg/kg of the drug on the 9th, 13th, and 16th days of pregnancy showing dilated proximal and distal tubules (D) with vacuolated cytoplasm (V) and pyknotic nuclei (P), some tubules appeared with faintly stained nuclei and shrunken cytoplasm. Notice dilatation of Collecting tubules with disorganization of their lining epithelium, some cells are seen detached within the lumen and others are vacuolated with pyknotic nuclei. Some glomeruli show vacuolation (G),and darkly stained nuclei. (Hematoxylin & Eosin stain, 400X)

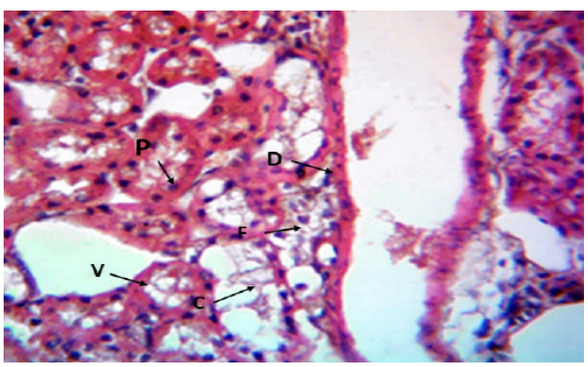

Fig. 6: A photomicrograph of the kidney of set III which was injected (IP)with 120 mg/kg of infugem drug on the 9th, 13th, and 16th days of pregnancy showing, renal tubules more disorganized and more dilated (D) , in which almost all of their cells are seen with pyknotic nuclei(P) and excessive vacuolation (V) and some lining cells appear detached within renal tubules lumena (C). Notice cellular infiltration is apparent (F).

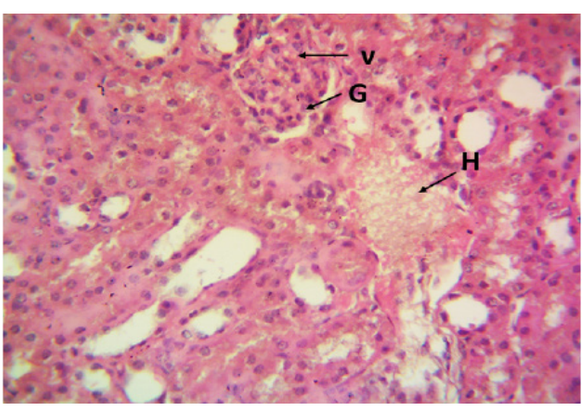

Fig . 7: A photomicrograph of the kidney of set III which injected (IP) with 120 mg/kg of infugem drug on the 9th, 13th, and 16th days of pregnancy showing glumertitis (G) and Haemorrhage in renal interstitial (H)), and more vacuoles in the glomerular cells (V). Hematoxylin & Eosin stain, 100X).

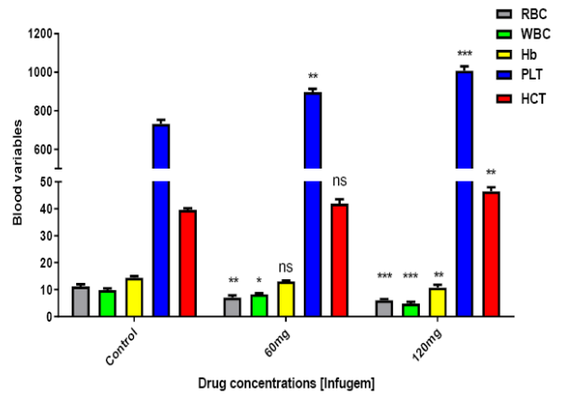

Fig. 8: The influence of Infugem drug administration (60 and 120 mg/kg of b.w.) on the maternal blood parameters: RBCs, WBCs, PLT, HCT, and Hb. The drug was injected IP on the days 9th, 13th, and 16th of gestation. All values were regarded as ns: insignificant, meaningful **P*<0.05, a significant ***P*<0.01, and a very greatly significant ***P*<0.001. The Dunnetts test was used in the data analysis.

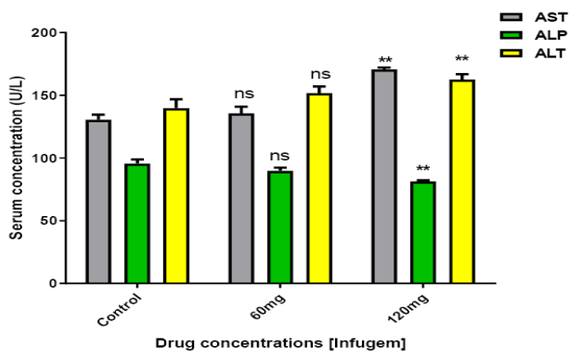

Fig. 9: The effect of Infugem drug administration (60 and 120 mg/kg of b.w.) on the maternal blood serum levels of AST/ SGOT, ALP/ SGPT, and ALT to evaluate liver function. The drug was injected IP on the days 9th, 13th, and 16th of pregnancy. All values were regarded as ns: insignificant, meaningful **P*<0.05, a significant **P<0.01, and a very greatly meaningful ****P*<0.001 in comparison to the control group. The Dennetts test was used in data analysis.

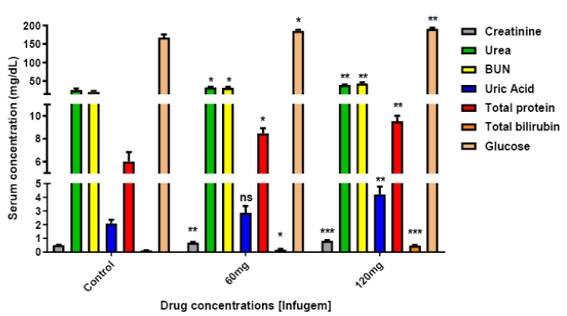

Fig. 10: The effect of Infugem drug administration (60and 120 mg/kg) on the mother's blood serum amounts of creatinine, urea, BUN, Uric acid, Total protein, and Total bilirubin, to evaluate the kidney function and Glucose level. The drug was injected IP on the days 9th, 13th, and 16th of pregnancy. All values were regarded as ns: insignificant, meaningful **P*<0.05, a greatly meaningful***P*<0. 01, and a very greatly meaningful***P*<0.001 in comparison to the control group. The Dunnetts test was used in data analysis.

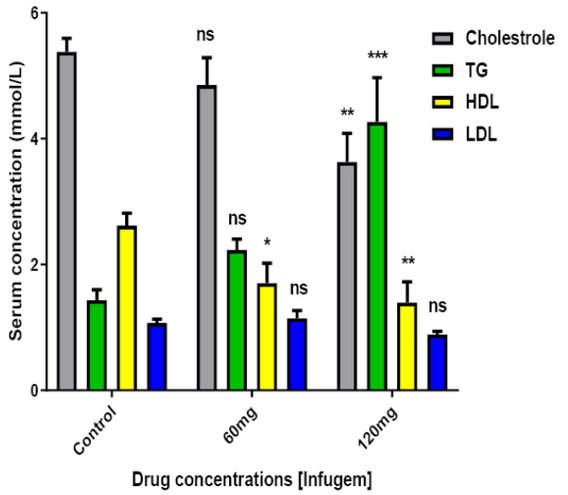

Fig. 11: The effect of Infugem drug administration (60 and 120 mg/kg of) on the mother's blood serum amounts of cholesterol, TG, HDL, and LDL. The drug was injected IP on the days of the 9th, 13th, and 16th of pregnancy. All values were regarded as ns: insignificant, meaningful *P<0.05, a greatly meaningful ** P<0.01, and a very greatly meaningful ***P<0.001 in comparison to set 1. The Dunnetts test was used in data analysis.

DISCUSSION

The recent findings showed various lesions with both used doses in the liver and kidney. As regards the liver tissue results, they appeared mild and focal, The most common lesions were congestion, dilatation of the central vein, and moderate dilatation and congestion of the sinusoids at a concentration of 60 mg/kg (Set II) which could be due to the relaxation of the walls blood vessels. The lesions became more marked and prominent at a concentration of 120 mg/kg(Set III) with an apparent increase of cellular infiltration which is most probably inflammatory cellular infiltration. The recent findings were partly consistent with other study findings[15] who found that the administration of gemcitabine to an adult male rat with the dose of 25 mg/kg b.w. for 4 weeks caused congestion in the portal area, inflammatory cell infiltration, and condensation of the nucleic material of the hepatocytes, also the findings were similar to those of[12] Who indicated that gemcitabine causes severe hepatic impairment. The results were similar to those of[16] who found that the gemcitabine administration to the mice at the dose of 415 mg/kg caused apoptosis, toxicity to cells, and injury to the liver, they further proposes that mechanism by which this medicine causes damage in the animal body may be restriction or modification of DNA production in tissues. Despite the drug's ability to trigger mitochondrial malfunction, cell damage via oxygen and nitrogen species that are reactive, or its potential to alter mitochondrial DNA and impair mitochondrial respiration may all contribute to liver damage. Stimulation of the mitochondria can lead to tissue injuries via adenosine triphosphate consumption or caspase-dependent fatal injury if ATP damage is imperfect, which is another process that encourages mitochondrial dysfunction. Liver injury continues to be a major cause of medication removal from pharmacological research and clinical usage[17]. As regards renal tissue affection, it was more apparent all over renal tissue, The results revealed dilatation of some proximal and distal renal tubules, as well as collecting tubules vacuolation, and pyknosis of nuclei at the of 60mg/kg(Set II). Furthermore, glomerular cells revealed vacuolations and pyknotic nuclei. Affection was more marked in group III in which hemorrhage was more apparent within the renal tissue at 120mg/kg (Set III). The results of the present study were similar to the results of[18] who found that using a combination of gemcitabine and cisplatin medications in humans for treating cancers like biliary cancer increases the risk of oxidative stress which in a role leads to damage of various vital organs like liver and kidney, they also similar to the results of[19] who indicated that giving a combination of gemcitabine and cisplatin to the male mice C5743Ll/6 caused renal tissue defects, reduction in the testis weight, and elevation in the reproductive hormones. The abnormal changes in the renal tissue were usually associated with the abuse of a lot of medications like anticancer[20]. The results of the current study were comparable to the results of[10] who found that injecting (IP) a combination of gemcitabine and cisplatin in rats caused inflammation, tubular epithelial cell death, and nuclear changes. Injecting (IP) gemcitabine (50mg/kg) into the rats showed significant tubular deterioration, mild destruction, and outflow of mononuclear inflammatory cells in the kidney interstitium[1].

The results of the present study were not similar to those of[15] who found that giving male adult rats gemcitabine intraperitoneally at the dose of 25 mg/kg for 4 weeks caused thrombosis, vascular degeneration, and renal epithelial cell swellings. The recent findings also were not comparable to the results of[21] who found that giving a combination of cisplatin (10 mg/kg) and gemcitabine (100 mg/kg) to the mice induced fibrosis. The most recent findings could be explained by the fact that renal injuries appear after the anterior interaction with drug or their metabolic products, transport of medication and their metabolites from the anterior surface, and secretion of drugs from the basolateral surface into the lumen of the renal tubule[22] or may be due to that the drug may induce internal vasoconstriction, direct tubular damage, and intratubular lesions[23].

About the drug's effects on blood components, results have shown a highly meaningful depletion ($P > 0.01$) In the RBCs numbers, a meaningful depletion ($P > 0.5$) in WBCs numbers, non-significant change in the Hb concentration, a highly meaningful rise ($P > 0.01$)in the PLT numbers and a non-significant reduction in the HCT at the concentration of 60 mg/kg. Moreover, at the concentration of 120 mg/kg, the outcomes revealed a very high meaningful reduction ($P > 0.001$) in the RBCs and WBCs counts, a highly meaningful depletion ($P > 0.01$) in the Hb concentration, a very highly meaningful improvement ($P > 0.001$) in the PLT numbers, and highly meaningful improvement ($P > 0.01$) in the HCT. The findings were similar to the results

of the[20]. The findings also were comparable with[24]. The recent outcomes may be due to the drug dose and duration of treatment or may be due to the tumor's malignant cells splitting off and spreading to the bone marrow and other tissues. Your bone marrow may become displaced by the malignant cells, which will make it more challenging for it to produce the blood cells that the body requires.

The biochemical findings showed that at the concentration of 60 mg/kg a non-significant increase in the levels of AST, ALT, and a non- meaningful decrease in the ALP compared to set I, respectively. The levels of AST, ALT, and ALP revealed a highly meaningful rise ($P > 0.01$) at the concentration of 120 mg/kg. The outcomes were not comparable to the results of the[21,22]. The findings were similar to the results of[23].

The findings also indicated that the drug had a toxic effect on the kidney profile of both used doses. The findings showed a highly meaningful rise ($P > 0.01$) in the creatinine, a meaningful increase ($P > 0.05$) in the amounts of urea, BUN, albumin and globulin(total protein), total bilirubin, and glucose, and an anon meaningful arise in the amount of uric acid at the concentration of 60 mg /kg (Set II). At the concentration of 120 mg/kg (Set III), the levels of urea, uric acid, BUN, total protein, and glucose showed a highly significant increase ($P >0.01$). There was a very highly meaningful increase ($P >0.001$) in the total bilirubin level. The outcomes were in agreement with the results of many research's[10,9,21]. The previous results may be due to the administration of infugem-induced lipid peroxidation[10]. The study found considerable alterations in the lipid profile, particularly at high doses, and that the degree of these variations appeared dose-dependent. The recent outcomes were similar to some research[24]. These alterations in the present investigation may be brought about by the drug's potential to impact the expression of ABCA1 genes and 27-hydroxylase enzymes, which would then affect cholesterol, TG, LDL, and HDL levels[25].

CONCLUSIONS

One of the most frequently prescribed medications for the treatment of malignancies is the infugem . Using medications during pregnancy at specific gestational stages has harmful consequences on the histological structure of the mother's key organs (liver and kidneys). The drug affects maternal blood biochemistry and hematology. Pregnant mothers should be careful of this drug, and the treatment process must be carried out under the supervision of a specialist doctor.

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CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

تأثير الانفيوجيم على النسيج، الكيمياء الحيوية، والدم لكبد وكلى الفئران المهق الحامل

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المقدمة: Infugem هو علاج واعد للغاية لمجموعة متنوعة من الأورام السرطانية، مثل سرطان المسالك البولية والرئة والثدي والحنجرة.
الهدف من العمل: في الدراسة الحالية، دراسة تاثير عقار الانفيوجيم على الفئران البيض الحوامل (الامهات) Mus musculus خلال فترة الحمل ولمدة ثلاث أيام (حيث جرعت الحيوانات بالعقار في الأيام ٩، ١٣، ١٦ من الحمل) . ودراسة التغيرات النسجية المرضية لأعضاء الكبد والكلية والتغيرات الكيموحيوية والدموية كليهما.
المواد وطرائق العمل: استخدمت ٣٠ فأر حامل في الدراسة الحالية. قسمت الحيوانات الى ثلاث مجاميع الأولى كانت مجموعة السيطرة والتي أعطيت محلول ملحي. المجموعتين ١و٢ حقنت بالعقار (٦٠ و١٢٠ ملغم /كغم من وزن الجسم على التوالي) في البريتون وتم التشريح في يوم ١٧ من الحمل .
النتائج: أظهرت النتائج تغيرات مرضية متعددة عن التركيزين مثل احتقان الوريد المركزي وتمدده و ارتشاح الخلايا الالتهابية في نسيج الكبد ، الالتهاب الكلوي وتغلظ النوى في ظهارة النبيبات الكلوية وكانت شدة الافات تعتمد على مقدار الجرعة. أظهرت القياسات الدموية (RBCs، WBC، Hb، PLT ، HCT) والبايوكيميائية (AST، ALT ، Glucose ، Total bilirubin ، Total protein ، Uric acid ، BUN، ALP ،) تغيرا معنويا عند الجرعتين قيد الدراسة .
الخلاصة : كان للدواء تأثير ضار على أنسجة ووظائف الكبد والكلى حيث تسبب الدواء بتغيرات كبيرة في مكونات دم الأم.