RESEARCH
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EFFECT REMDESIVIR ON PREGNANT RATS AND THEIR FETUSES AND THE PROTECTIVE ROLE OF ARTEMISIA SIEBERI.

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Abstract
Background: At the beginning of October 2020, a treatment for Covid-19, Remdesivir, was approved, which showed a high recovery rate.
Objective: To evaluate effect remdesivir on liver, kidney of pregnant rats and ability to cause phenotypic abnormalities in their fetuses and protective role of Artemisia sieberi.
Materials and Methods: 28 pregnant white rats, divided into 4 groups (Materials were given in day to day, from 5-19 of pregnancy).1st group: treated with distilled water ,2nd group: treated with remdesivir (5 mg/kg) ,3rd group: treatment with aqueous extract of A. sieberi leaves (200 mg/kg),4th group: treated with remdesivir (5 mg/kg) and aqueous extract of A. sieberi leaves (200 mg/kg). Animals were sacrificed 24 h after the last treated. Biochemical parameters like AST, ALT, ALP, urea and creatinine, histopathologic changes of liver and kidney were studied and embryos were extracted and examined.
Results: Giving remdesivir led to increase in levels of ALT, AST, ALP, urea and creatinine, In 3rd group there was a slight decrease in levels of ALT, AST, ALP, creatinine and urea. In 4th group, A.sieberi reduced levels of ALT, AST, ALP, urea, and creatinine, but they were still higher compared to the control group .Histological changes in 2nd group in liver were represented by congestion central vessel, bleeding, degeneration , infiltration of inflammatory cells, and necrosis .In kidneys, bleeding, infiltration, and glomerular atrophy with necrosis and shedding of lining of renal tubules. 3rd group, liver and kidneys tissue sections did not show significant changes. 4th group, A.sieberi decreased hepatic and renal necrosis induced by remdesivir. The embryos were malformed in 2nd group, while they were healthy in the remaining groups.
Conclusions: A.sieberi extract played a protective role in protecting liver and kidneys from effects of remdesivir.
Key words: Remdesivir, Artemisia sieberi, Liver, Kidney, preganent, Biochemical parameters, Histopathology.

Introduction

The new coronavirus is the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which was first identified in December 2019 as a cause of respiratory disease (**Co**rona **vi**rus **d**esease-**19**) and abbreviated as **Covid-19**[1].At global level, health systems have been subjected to great stress due to cases of Covid-19 infection, and since then the World Health Organization (WHO) declared it a pandemic on March 11, 2020[2].By early 2021, SARS-CoV-2 was responsible for more than 85 million cases of Covid-19 and nearly 2 million deaths globally[3] .Pregnancy while infected with Covid-19 exacerbates the disease. The incidence is more severe as the period of birth approaches[4]. A number of antiviral drugs have been used and repurposed and are being studied for Covid-19 although they are primarily intended to treat other diseases, these drugs have potential to prevent viral replication, reduce morbidity and relieve symptoms for patients with Covid-19[5].
At the beginning of October 2020, anti-Covid-19 treatments was approved, Remdesivir, which showed a high recovery rate and reduction in the length of patients' stay in the hospital[6].Remdesivir (GS- 5734) is an antiviral agent designed to target copies of pathogenic RNA viruses[7]. Pregnant and breastfeeding women were specifically excluded from all clinical trials evaluating the efficacy of remdesivir [6]. Therefore, the developmental toxicity of remdesivir, or side effect on embryogenesis, remains unclear [8].
Herbal treatment is a good option to treat various disorders caused by chemical drugs. The market for natural functional foods is expanding due to the increasing number of consumers who are concerned about side effects of various pharmaceutical drugs[9]. Among many plants, Artemisia an important medicinal herb that grows annually, or some of which grow for up to four years. It represents a genus belonging to the Asteraceae family and contains 500 species. It has been used to treat fever, gastric ulcers, and respiratory infections [10]. In addition to the low cytotoxicity of this herb, recent research has revealed that the essential oils extracted from Artemisia contain active agents that have antifungal, antibacterial, and antiviral properties and have fewer side effects[11]. Artemisia is considered one of the medicinal plants that is currently of interest to researchers due to the chemical diversity in its content of biologically active compounds[12]. *Artemisia sieberi* one of types of Artemisia, widespread in northwestern Iraq.
Aim of this study is to determine effect of remdesivir on liver, kidney of pregnant rats, fetus, and to evaluate preventive role of aqueous extract of *A.sieberi* leaves.

Materials and methods

Plant collection

A.sieberi leaves were collected from the wilds of Al-Alam City (Salah al-Din, Iraq) in March and April 2022.The plant specimens were identified in the Iraqi National Herbarium.

Picture (1) shows *A.sieberi* plant.

Preparation of plant extract

The dry leaves of *A.sieberi* were crushed in an electric grinder until powder was obtained. 50 grams of it were used with 1000 ml of boiling distilled water, and the mixture was placed in an electric blender, and the mixture was mixed for 15 minutes, then the solution was left for 24 hours at room temperature after covering it, then the mixture was filtered using several layers of medical gauze to get rid of plankton. After that, a centrifuge was used at a speed of 3000 rpm for 10 minutes to separate the solution and take the filtrate and leave the sediment. Then the filtrate was placed in clean, sterile metal dishes and the extract was dried. Using an electric oven at a temperature of 40°C to obtain the raw aqueous extract, it is then scraped off and collected from the dishes**.** Then store it in dark containers and keep it in the refrigerator until the experiment is conducted [13].

Determine doses

After obtaining the drug remdesivir(BDR pharmaceuticals ,India) from pharmacy , the rats were given dose of 5 mg/kg body weight [14].As for the aqueous extract *A. sieberi* leaves, the dose was determined after conducting an experiment in which four groups of rats were used, each group consisting of three rats weighing 200-225 grams.1st group was considered a control group and was dosed with distilled water, 2nd was given extract at a concentration of 50 mg/kg, 3rd group at a concentration of 100 mg/kg, and 4th group at a concentration of 200 mg/kg of body weight, after 24 hours, samples were taken. The blood was then separated by a centrifuge at 3000 rpm for 10 minutes, after which the level of sugar and cholesterol in serum was measured. After conducting two tests, it was found that the dose (200 mg/kg) is the most effective in reducing level of glucose and cholesterol in blood when compared with control group. It was adopted as a dose to evaluate the effect of plant extract used in the current study.

Animals used in the study

(28) female white rats, *Rattus norvegicus*, were used in this study, obtained from the animal house of College of Veterinary Medicine / Tikrit University. Approximately 12-14 weeks old and weighing between 225-275 grams and in good health. The females were placed with males of the same breed at a rate of one male and two females in each cage during the night hours. The next morning, the females were examined, as the vaginal plug, or the appearance of sperm in the vaginal fluid, is evidence of the insemination process. Females on day zero are considered Pregnancy [15].

Experimental Design

In current study, 28 pregnant female rats were used. The experiment began on May 1, 2022 and lasted for three weeks. The animals were treated with the treatments specific to the experiment from 5-19 day of pregnancy in day to day, and on 20 day, an autopsy was performed. Pregnant rats, and their fetuses were examined through morphological, histopathological examinations, and biochemical analysis. Rats divided into 4 groups, 7 animals for each group,1st group: treated with distilled water, 2nd group: it was injected with remdesivir (5 mg/kg) ,3rd group: treatment with aqueous extract of *A. sieberi* leaves (200 mg/kg), 4th group: treated with injections of remdesivir (5 mg/kg) and oral administration of aqueous extract of *A. sieberi* leaves (200 mg/kg).

Animals were sacrificed on day 20 of pregnancy under mild anesthesia with chloroform 10%. The blood, liver, kidney of each animal was collected, and the embryos were extracted and examined.

Biochemical tests

After separating the blood serum by centrifuge, a test was performed alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), Urea and Creatinine[16]. AST, ALT and ALP levels determined liver functions while urea and creatinine, renal functions.

Preparation of histological sections

Histological sections of liver and kidney were prepared from pregnant females. Fixation was done directly in 10% formalin solution for 24 hours, after which histological sections were prepared. The samples were washed, then passed through increasing concentrations of ethyl alcohol, then stained with xylene, then the samples were embedded in paraffin wax, then the samples were trimmed and cut, then the sections were placed on a glass slide to be stained with hematoxylin-eosin, then D.P.X was used for the purpose of mounting, after which the slides were covered with a glass cover [17].

Statistical analysis

Statistical analysis of the results was conducted using Analysis of Variance test, and significant differences were determined according to Duncan's multiple ranges test with a significance level ($P \leq 0.05$).

Results and Discussion

Biochemical parameters

It is noted from Table (1), in 2nd group a significant increase ($P \leq 0.05$) in levels of ALT, AST, ALP, Urea and Creatinine compared with 1st group. In 3rd group was a slight, non-significant decrease in all parameters compared with 1st group. As for 4th group, there was a significant decrease in levels of ALT, AST, ALP, urea, and creatinine compared to 2nd group, but they were still higher compared to the 1st group.

Table (1): Biochemical parameters.

parameters / group	AST (IU/L)	ALT (IU/L)	AL P (IU/L)	Urea (mg/dl)	Creatinine (mg/dl)
G1	116.832±3.9322 C	31.6571±0.40406 c	41.1271±0.399 c	40.4457±1.26537 c	0.8171±0.0363 c
G2	219.428±14.101 A	57.2857±1.12788 a	69.0129±1.517 a	61.1414±0.93555 a	2.2557±0.08056 a
G3	112.714±5.2902 C	29.8714±0.64944 c	39.8186±0.553 c	39.5571±2.84053 c	0.7426±0.04538 c
G4	148.571±2.20235 B	45.1429±1.03345 b	51.2543±0.4149 b	50.0100±0.79933 b	1.4729±0.03393 b

*Values represent arithmetic mean ± standard error. Different letters vertically mean there is a significant difference at a significance level ($P \leq 0.05$). The number of animals is 7 in each group.

The significant increase in levels of three enzymes ALT, AST, and ALP in 2nd group compared to 1st group, supports what Ahmed (2022)[18] indicated that there was an increase in level of these enzymes as a result of treatment with remdesivir, as it can examples of drug-induced liver injury include acute hepatitis, biliary breakdown, or mixed liver injury. The enzymes ALT, AST, and ALP are located in liver cells and are released into the bloodstream if liver cells are damaged [19].Ghosh (2020)[20] also reported that patients treated with remdesivir showed significantly higher levels of transamines and ALP levels compared to patients who were not treated with it .It is believed that the exact mechanism by which remdesivir causes liver injury may be direct hepatocyte toxicity due to inhibition of hepatocyte mitochondrial RNA polymerase .These enzymes rise above the normal level in the event of a viral disease or other liver disease, in addition to the effects of taking some chemical medications. The main indicator for evaluating liver function is measuring the levels of these enzymes[21]. An increase in the level of the three liver enzymes can also be attributed to the effect of free radicals, as an increase in liver enzymes is an indicator of cell damage, loss of plasma membrane function, and release of enzymes into the interstitial fluid and then into the blood[22]. Oxidative stress causes an increase in liver enzyme values [23].

In 3rd group was a slight, non-significant decrease ($P \leq 0.05$) in levels of ALT, AST, and ALP compared to 1st group. These results are consistent with findings of Shahraki (2017)[24] where they used *A. dracunculus*, Mirghaed (2020)[25], and Park (2020)[26] where they used *A. annua*. The activities of AST, ALT and ALP in blood decreased as a result of the effectiveness of Artemisia extracts compared to 1st group. The reason for this may be due to reducing the role of the active compounds found in Artemisia extract, such as phenols, flavonoids, alkaloids, tannins, and coumarins, which may contribute to reducing liver cell damage through a decrease in the level of the enzymes ALT, AST, and ALP in the blood plasma[27] .

The results of 4th group showed a significant decrease in ALT, AST, and ALP compared to 2nd group, but they were still significantly higher compared to 1st group. Various antioxidants represent compounds capable of destroying free radicals in the body [28], as Cordova's (2002)[29] study showed that multiple phenols, and flavonoids in particular, initially have an inhibitory effect on the cytochrome P450 system and prevent further damage from metabolism of toxic compounds, which ultimately leads to reducing the production of free radicals. Artemisia extract, because it contains antioxidants, is able to neutralize free radicals present in the cell environment and prevent their harmful effects[30]. Many studies have shown that medicinal plants in which phenolic compounds are present can prevent toxic effects on liver and reduce damage to its cells, which leads to a decrease in level of ALT, AST, and ALP enzymes in the plasma [31].

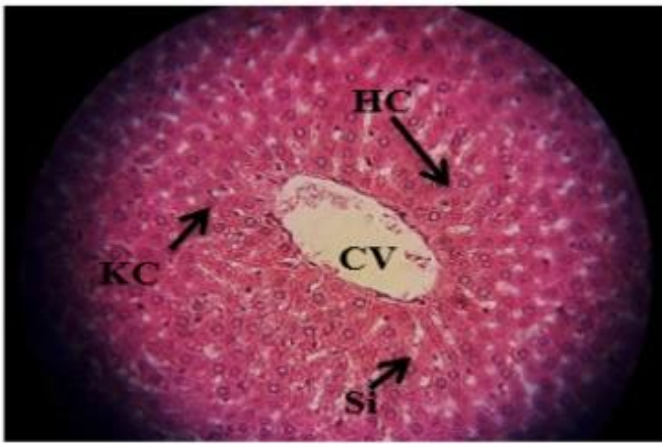
In the results of the kidney function test, represented by the creatinine and urea tests, for 2nd group, it was noted that there was a significant increase ($P \leq 0.05$) in them compared to 1st group .El-Haroun (2021)[32] indicated an increase in creatinine and urea levels in blood of rats treated with this drug .It is think that kidney injury and high urea and creatinine levels are associated with downregulation of sirtuin-1 ,which works to improve kidney functions and protect them from ischemic injuries or toxic substances [33] .There have also been concerns raised about potentially toxic accumulation of the carrier compound sulfobutylether β-cyclodextrin sodium (SBECD) and its metabolite GS-441524 in patients with renal insufficiency [34].In 3rd group, there was no significant change in the levels of creatine and urea compared to 1st group. Aldraji and Al-Ali (2023)[35] stated that the group treated with Artemisia extract did not have a significant change in the values of urea and creatine compared to the control group. This result is also similar to the results of the study Conducted by Yazdani (2013)[36] which showed no significant differences in urea and creatine levels in mice treated intraperitoneally with *A. deserti* extract at a concentration of 100 and 200 mg/kg, respectively, for 6 days .The reason may be due to the presence of phenols, alkaloids, flavonoids, sterols, tannins, volatile oils, anthraquinones, and other effective chemical compounds in the aerial parts of different Artemisia species, which have an effective role in removing toxins from the organs [37].The levels of creatinine and urea decreased significantly in 4th group compared to 2nd group, but they are still significantly high compared to the concentrations of 1st group .The phytochemicals of Artemisia may protect against remdesivir-induced nephrotoxicity because it contains flavonoids such as quercetin, flavonoid glycosides and phenolic acids that contribute to free radical scavenging mechanism [38].

Histological changes

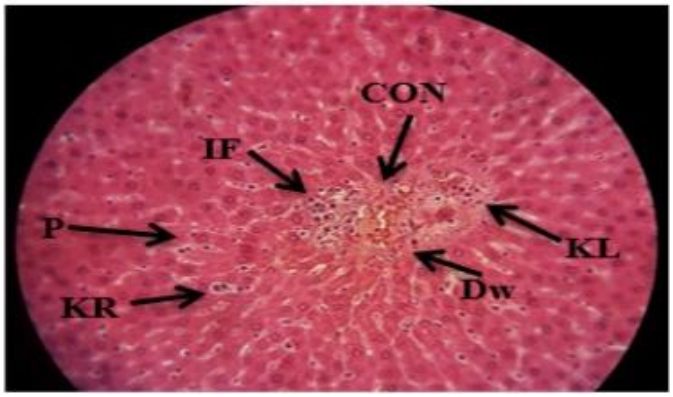
Liver:

Microscopic examination of liver tissue in 1st group showed normal shape of central vein (Cv) surrounded by rows of hepatocytes (Hc), which are arranged around central vein in form of ropes radiographically, separated by sinusoids (Si) that appeared normal in size with the proliferation of Kupffer cells (Kc) during the sinusoids, as indicated in the picture (2). It was

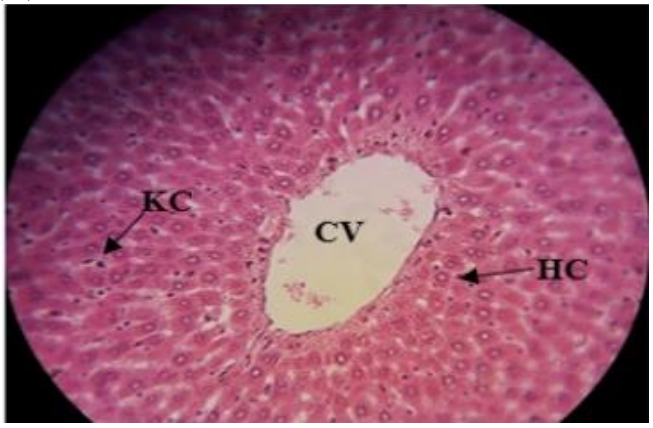
observed in 2nd group that there was congestion (C) in central vein with thickening of pyknosis(P), karyorrhexis (Kr), and karyolysis (Kl) of the nuclei of some hepatic cells, and infiltration of inflammatory cells (If) with damage wall (Dw) blood vessel (3). Liver tissue sections in 3rd group showed no significant changes, picture (4). As for histological sections of 4th group, it appears that there is congestion and Hemolysis of blood cells, and infiltration of inflammatory cells, picture (5).



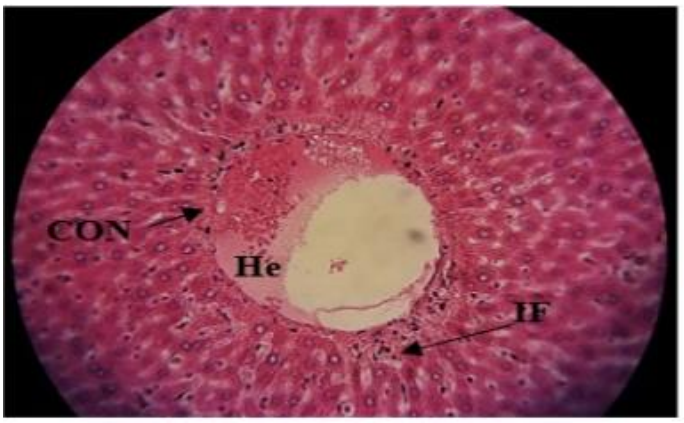
Picture (2): liver of a pregnant rat of 1st group showing central vein (CV), hepatic cells (HC), hepatic sinusoids (SI), and Kupffer cells (KC), stain : H&E, 400X.



Picture (3): liver of a pregnant rat of 2nd group shows damage central vein wall (Dw), Congestion (CON), occurrence of pyknosis (P), karyorrhexis (KR) of some hepatic cell nuclei and their karyolysis (KL) with infiltration of inflammatory cells (IF). stain: H&E, 400X.



Picture (4): shows liver of 3rd group of pregnant rats appearing normal H&E stain: 400X.



Picture (5): is the liver of a pregnant rat 4th group, showing occurrence of congestion (CON) with hemolysis (He) and infiltration (IF) of inflammatory cells H&F stain: 400X.

As a major organ involved in metabolism and detoxification, the liver is vulnerable to damage caused by many chemical substances [39]. The result of the histological change in the liver of pregnant rats treated with remdesivir was consistent with increased levels of liver enzymes, ALT, AST and ALP [40]. The rate of remdesivir flow out of liver cells may be reduced by glycoprotein inhibitors, leading to if its concentration in liver cells is near the toxic threshold [41] , remdesivir causes mitochondrial toxicity and liver cell injury, leading to the accumulation of free radicals and oxidative damage, which leads to degeneration and necrosis of hepatocytes [42] .Liver toxicity may be due to damage of the lysosomal membrane caused by remdesivir to release hydrolase enzymes that promote cell death and degradation [43].

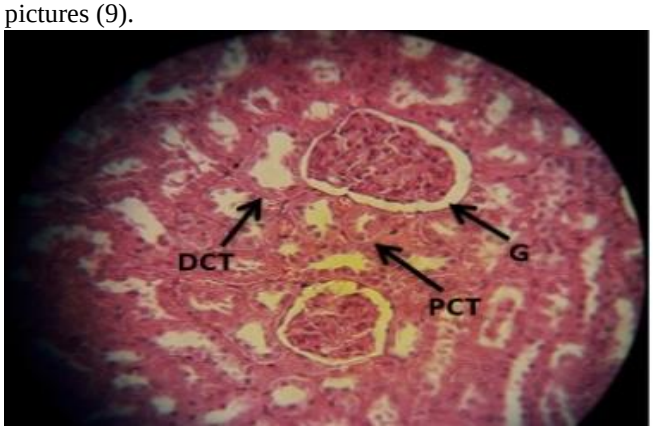
No significant histological changes occurred in livers of animals in 3rd group , this may be due to the non-toxic nature and the protective activity of Artemisia extract in protecting liver, or to the small dose of the extract used in the study, or as a result of the nutritional substances and active compounds that this plant contains with a chemical content that made it one of the important medicinal plants that it supports the organism's immunity and supports the work of some important organs in the body, such as the liver, bile, and kidneys [44].

In 4th group, histological sections showed the protective role of Artemisia extract and its protection of liver tissue in reducing the effect of harmful drug remdesivir by reducing the severity of deformities and histological changes occurring in it. This may be due to the various active compounds present in the plant extract in addition to the high ability to scavenge free radicals that it possesses this extract, this histological result is consistent with the restoration of the activities of the three liver enzymes to almost normal levels in the rats after treatment with the extract, as an indication of preventing the leakage of enzymes inside the cells to the outside by maintaining the integrity of the liver cell membrane. This result is consistent with what Cordova (2002)[45] indicated that polyphenols, especially flavonoids, have an inhibitory effect on the cytochrome p-450 system, which prevents the metabolism of drug compounds, thus reducing the formation of free radicals.

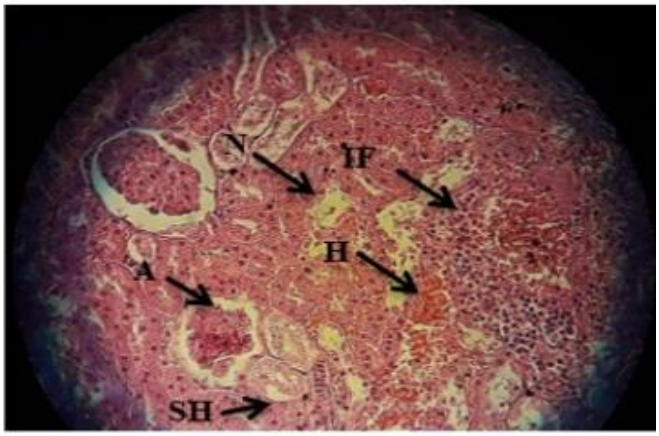
Kidney:

Microscopic examination of prepared histological sections shows the glomerulus (G) in its normal size, the proximal convoluted tubule (PCT), and the distal convoluted tubule

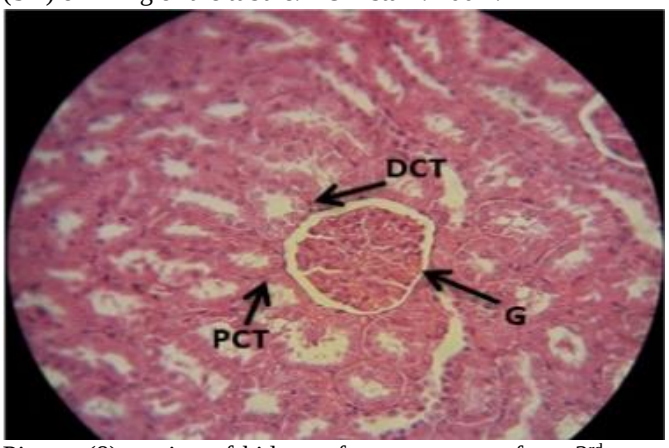
(DCT) in the picture(6). In 2nd group, microscopic examination shows occurrence of hemorrhage (H), infiltration of inflammatory cells (IF), atrophy (A) in glomerular, necrosis (N) and shedding (SH) of lining of the renal tubules, pictures (7). In 3rd group did not show significant changes in kidney tissues, pictures (8). In tissue sections of 4th group, hemorrhage, hemolysis, and infiltration of inflammatory cells occurred, pictures (9).



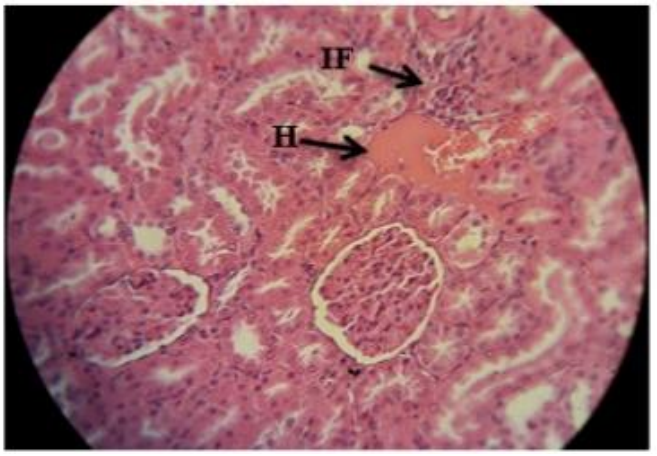
Picture (6) section of kidney of a pregnant rat from 1st group, showing normal size of glomerulus (G), proximal convoluted tubule (PCT), and distal convoluted tubule (DCT). Stain, H&E: 400X.



Picture (7) section of kidney of a pregnant rat from 2nd group, showing hemorrhage (H), severe infiltration of inflammatory cells (IF), atrophy of glomerular (A), necrosis (N) and shedding (SH) of lining of the tubule. H&E stain: 400X.



Picture (8) section of kidney of a pregnant rat from 3rd group, showing normal size of glomerulus (G), proximal convoluted tubule (PCT), and distal convoluted tubule (DCT). stain, H&E: 400X.



Picture (9) section of kidney of a pregnant rat 4th group, showing occurrence of hemorrhage (H) and infiltration of inflammatory cells (IF). Stain; H&E: 400X.

The results of treating kidney of pregnant rats with remdesivir in 1st group are consistent with the results of the study conducted by Van Laar (2021)[46], where it was found that giving remdesivir led to nephrotoxicity. Ahmad and Al-Sammak (2023)[47] indicated that remdesivir led to focal glomerular necrosis with lumen expansion of Bowman's capsule, congestion of capillaries in the glomeruli, and sheeding(sloughing) of the lining of tubule epithelium, after the drug was used for 5 days at a concentration of 10 mg/kg in rats. The cause of damage to these tissues may be due to the accumulation of free radicals as a result of the toxic effect of this drug.

It may also cause mitochondrial toxicity and injury to renal tubular epithelial cells, leading to the accumulation of free radicals and oxidative stress, which leads to degeneration and necrosis of kidney tissues [42]. Kidney toxicity may be due to the damage of the lysosomal membrane caused by the drug, thus releasing hydrolytic enzymes that promote cell death and lysis [43]. Abnormalities in histological structure of liver and kidney may be due to mediators secreted by inflammatory cells, causing vascular dilatation and congestion [48]. Treatment of pregnant rats in 3rd group did not show any apparent malformities or significant histological changes. This may be due to the extract being a natural, non-toxic substance rich in active compounds, or to the amount of dose used in this study. This result is consistent with what Sekiou (2021)[49] indicated in his study to evaluate the role of the aqueous extract of *A. herba* at dose of 400 mg/kg in rats, the histopathological results showed that the aqueous extract did not show any morphological or histological changes in kidney, and had no toxic effect.

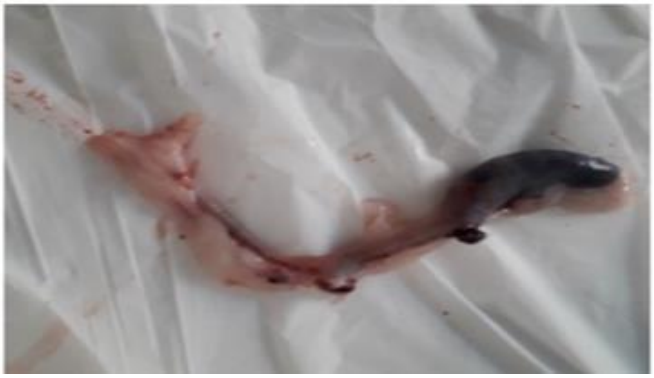
In 4th group, the plant extracts reduced effect of remdesivir on kidney, and this corresponds to a decrease level of creatinine and urea and thus a reduction in renal oxidative damage[50]. Several studies have reported that Artemisia has protective effects on kidney [51]. These studies confirmed that multiple phenols and flavonoids reduce uric acid levels, suppress oxidative stress and protect kidney tissue from damage [52].

Embryos variations

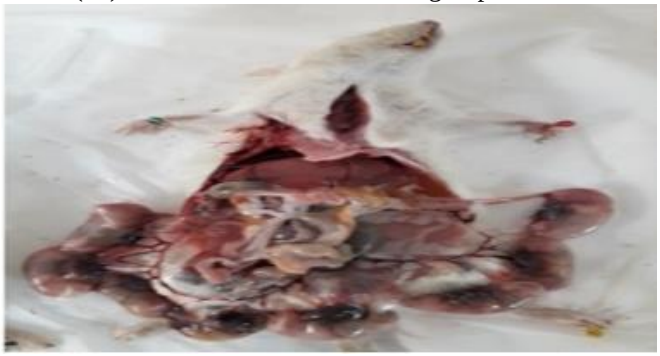
The results of current study showed that few cases of abortion occurred. The reason for this may be that the dose concentrations of the treatment used are a normal dose. Whole

abortion occurred in 2nd group of rats, pictures (11), while no abortion occurred in pregnant rats in 3rd group, and the embryos appeared distributed naturally and evenly on the horns of the uterus, picture (12). As for the rats of 4th group, a partial abortion occurred, picture (13) compared to the healthy pregnancy condition in 1st group, which shows the distribution of the embryos on the uterine horns regularly, picture (10). The fetuses in 1stgroup appeared in normal shapes and sizes, it was approximately 4 cm long, with clearly defined basic parts such as the head, front limbs, torso, and hind limbs, with a straight spine, picture (14). In 2nd group, it was noted that there were cases of uneven distribution of the embryos on the horns of the uterus with reabsoribtion, the fetus appeared with malformed upper limbs, picture (15). The embryos in 3rd group appeared homogeneously distributed over the uterine horns and were in normal shapes and sizes, pictures (16), while 4th group of rats showed a consistent number of embryos on the uterine horns with almost normal sizes and lengths for the embryo, pictures. (17).

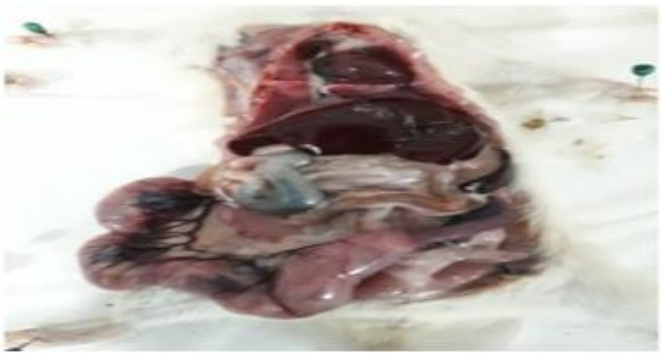
Picture (10): of a pregnant rat of 1st group shows the equal distribution of fetuses on the uterine horns.



Picture (11): whole abortion of rat in 2nd group.

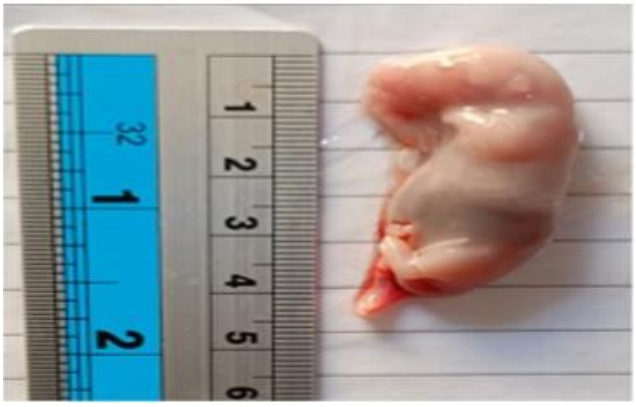


Picture (12): of a pregnant rat of 3rd group shows equal distribution of fetuses on the uterine horns.

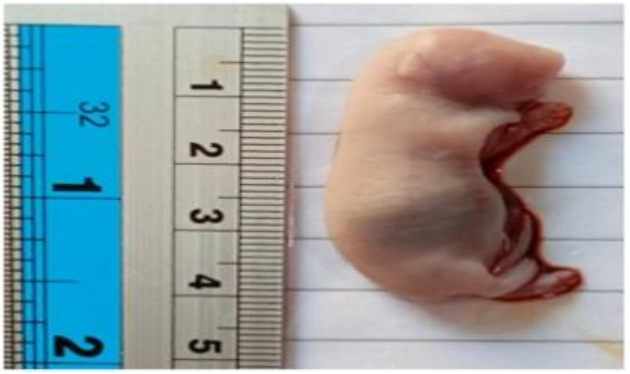


Picture (13): of 4th group on day 20 of pregnancy shows uneven distribution of embryos on uterine horns with their resorption.

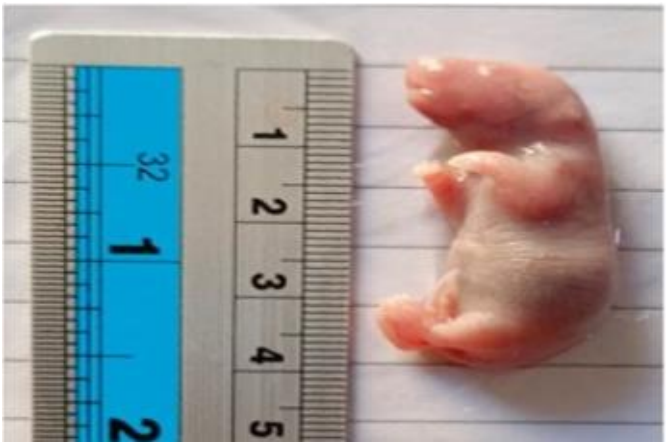
Picture (14) shows a rat embryo at 20 days of gestation, in 1st group, with a length of approximately 4 cm.



Picture (15) shows a rat fetus at 20 days of gestation, in 2nd group shows malformity of the upper limbs.



Picture (16) rat fetus at 20 days of gestation, in 3rd group, shows normal size and shape.



Picture (17) A rat embryo at 20 days of gestation, in 4th group, appears normal.

The current results of the effect of remdesivir on causing abortion and changes in rat fetuses are consistent with the evaluation of the effect of remdesivir on rat fertility and prenatal and postnatal studies, in addition to studies of fetal growth in mice and rabbits. In a prenatal study on mice, females were exposed to the drug at a dose of 10 mg/kg/day. This resulted in a decrease in the average number of corpous luteum, and thus a decrease in the average numbers of implantation sites and viable embryos, accompanied by a decrease in the average weights of the ovary and uterus, cervix and ovarian duct [53]. The absence of abortion and the appearance of rat fetuses of normal size and shape in 3rd group may seem normal because the dose of the extract used was moderate. This result is consistent with what Abolaji (2012)[54] observed in a study they conducted to evaluate the toxicity of *A. annua* on pregnant rats and their fetuses from 8th -19th day of pregnancy . On 20th day, the pregnant rat was sacrificed. The fetuses were in a normal condition at the dose of 100 And 200 mg/kg, but it was not viable at 300 mg/kg with fetal malformities. Fetal toxicity can occur when using Artemisia in high concentration. Finally, in 4th group, the fetuses appeared in normal shapes and sizes, not distorted .This may be due to the fact that the treatment used to treat pregnant rats was at a moderate concentration and did not cause malformations, in addition to the role of the preventive Artemisia extract. However, this did not prevent the occurrence of some cases of partial abortion that may occur as a result of the effect of the treatment used.

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