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Research Article

Effect Of Ribavirin in Causing Phenotypic Abnormalities and Histological Lesions in Albino Rat Fetuses and The Protective Role of Ginger Root Aqueous Extract.

Eidan khalaf Mohamed Hussein[1]
Department of Life Sciences - College of Education for Pure Sciences - Tikrit University/Iraq.
almhmdyedan@gmail.com

Rashid Khamees Shaban[2]
Department of Life Sciences - College of Education for Pure Sciences - Tikrit University/Iraq.

Abstract

The aim of this study recognition phenotypic abnormalities and histological changes in fetuses caused by Ribavirin and to detect the protective role of ginger root aqueous extract. The treatment with RBV at dose 16 mg/kg and for the period from 5 to 10 days of pregnant showed anomalies represented by the non-equal distribution of embryos on the two horns of the uterus and a small number of fetuses, and skeletal system abnormalities compared with the control group. As for the group treated with the aqueous ginger root extract at dose 200 mg/kg and for the same period , a distorted effect was observed on the fetuses, as the treatment with the extract showed a small number of fetuses and their non-equal distribution on the two horns of the uterus, as well as a small dorsum in the size of the fetus and appeared congestion in the abdominal area with torsion of the tail end compared to the control group, and it was possible to notice the irregularity of the hind limbs and dorsum Small size, mutated, deformed, incomplete and unclear rat fetus compared to the control group, and no fetus was obtained from the group treated with the drug and the extract despite repeating the experiment as a result of miscarriages that occurred during pregnancy. In the histological study of the liver of fetuses at the age of 19 days of gestation, the group treated with ribavirin showed degeneration of hepatocytes, increased numbers of macrophages, while the histological study of kidneys showed necrosis of the endothelium of the renal tubules and degeneration of renal tubule cells, while the group treated with ginger did not show any differences with the control group.

Keywords
Ribavirin, Ginger, Teratogenicity

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Introduction

Hepatitis C virus is a small, enveloped, single-stranded RNA virus of the family Flaviviridae of the genus hepacivirus [Kaito et al , 1994]This virus was discovered recently in 1988 and between 1990 and 20l3, viral hepatitis infection moved from the tenth to the seventh rank in the whole world as a daily cause of death and a higher death rate than HIV infection, malaria and tuberculosis [Stanaway et al , 2016] Hepatitis appears as the leading cause of death by infection in the world although its prevalence has decreased from 170 million carriers from 1999 [Cohen, 1999] 71 million in 2017 [Polaris, 2017] 1% in the world's population is considered to have viral hepatitis with more than 1750000 new infections in 2015 primarily related to intravenous drug use [WHO, 2017] Regional disparities It is significant in this spread, as the most exposed areas are Egypt and Mongolia, where the infection rate reached 15% of the population [Thursz and Fontant , 2014] In addition, the population of other regions such as West and Central Africa has reached the infection rate of 5-8% due to practices Certain folklore (such as scratching, circumcision, cupping and shaving).

Interferon has been used as a treatment for viral hepatitis for more than twenty years because of its Antiviral and immune stimulating properties [Hoofnagle and Seef, 2006;Mchutchison et al, 2009] , In 1997 the addition of ribavirin, a nucleoside analogue discovered in 1972 by Witkowski and his group[Witkowski et al , 1972] led to a significant increase in the efficacy of treatment [Maan , 1978] but what hindered treatment were some complications such as weak immunity, neurological disorders, hemolytic anemia, abnormalities caused by ribavirin, thrombocytopenia, or neutropenia caused by interferon [Hoofnagle and Seef, 2006].

Since the beginning of the twentieth century, some natural factors began to threaten the development of congenital anomalies in the offspring of humans and animals, as well as the susceptibility to interference and mutation of X-rays, radio rays, radioactive isotopes and some metals and inorganic elements in embryonic development. On the other hand , Many researchers pointed to effect of medical drugs on the genetic system of cells and the process of embryonic development in a cumulative manner, so that a comprehensive evaluation of the effect of drugs using laboratory animals will help reduce the possibility of the phenomenon of harmful effects of drugs in the fetus.[Khafizyanova et al , 2004]

In recent times, researchers have turned towards medicinal plants because of their important role in treating various diseases , Many traditional practitioners claimed that many medicinal plants and their formulations can be used effectively to relieve various types of diseases [Edoga et al , 2005] .Ginger (Zingiber officinale Roscoe) of the Zingiberaceae family Its roots contain polyphenol compounds (gingerol and shogaols) which have high antioxidant activity , Ginger has been used as a spice for more than a thousand years The antioxidant property of ginger has been suggested as one of the main possible mechanisms for the plant's protective effects against various diseases [Ramakrishna et al , 2016] .

Materials and methods

Plant collection used in the study:

The roots of the ginger plant were obtained from the local market, they were exposed to fresh air away from sunlight, dried, then crushed, and then kept in tightly closed plastic containers at room temperature until the preparation of the extract started [Ilyas et al , 2011]

Preparation of the aqueous extract of ginger

the dry ginger root was crushed and turned into a fine powder using an electric mill from AL-Araby Company.50 g were taken and placed in a 1000 ml glass beaker and 500 ml was added to it , then the material was mixed with a heater device and a hot plate with magnetic stirrer for 20 minutes at a temperature of 40°C, then the mixture was left for 24 hours on a shaker device. The mixture was filtered by several layers of gauze and separated by a centrifuge to get rid of the insoluble materials after that. The extract was placed in glass dishes with a capacity of 250 ml and placed in the electric oven at a temperature of 40°C to obtain the crude aqueous extract. The process was repeated several times to obtain a sufficient amount of the extract.[El-Demerdash et al , 2005]

Animals Used in Study

In this study, (12) female Sprague Dawley rats, bred for the purpose of obtaining homogeneous offspring in terms of age and healthy from pathological injuries, were used, and they were isolated from males until reaching puberty and starting the experiment. The approved laboratory conditions were taken into account, where the animals were placed in plastic cages of dimensions 30 cm x 40 cm x 40 cm at a temperature of 25 ± 2 ° C, a photoperiod of 12 hours light and 12 hours of darkness, and food and water were provided continuously. The study was conducted in the animal house of the College of Veterinary Medicine and in the laboratories of the Department of biology and the Central Laboratory of Tikrit University

Mating

After selecting healthy female rats aged between 10-12 weeks and weighing 200-150 g, they were placed with males of the same breed in a plastic cage throughout the night and the next morning were examined , as the vaginal plugs or the appearance of sperm in the vaginal fluid is evidence of the occurrence of insemination, and females are considered on the zero day of pregnancy .

Experimental Design

Experimental animals were divided and homogeneously distributed in terms of weight into 4 groups with 3 animals for each group. The animals were treated with the special treatments from the fifth day of pregnancy to the tenth day, as follows:

1. The first group (control) (treated with distilled water) from day 5 to day 10 of pregnancy
2. The second group treated with ribavirin (RBV) (16 mg/kg twice daily orally by oral tube feeding) from day 5 to day 10 of pregnancy
3. The third group treated with aqueous extract of Zingiber officinale roots (200 mg/kg once daily orally by oral tube feeding) from day 5 to day 10 of pregnancy
4. The fourth Group treatment with aqueous extract of ginger root at 200 mg/kg once a day with ribavirin at 16 mg/kg twice a day orally by tube-oral feeding From all lambs fed from day 5 to day 10 Experiment with a standard formula

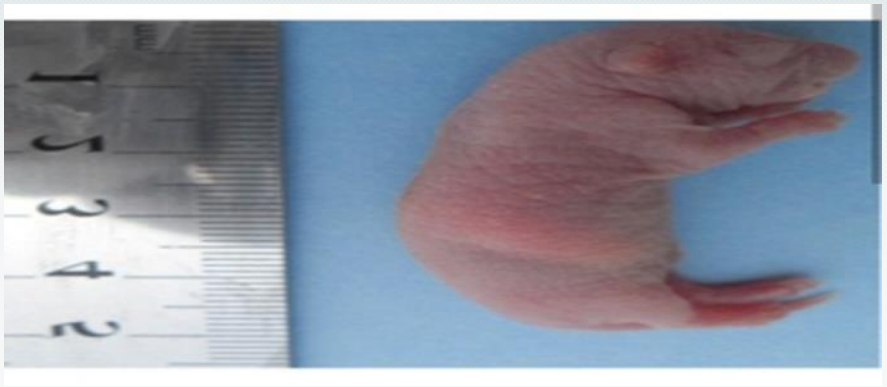
Results

Phenotypic results

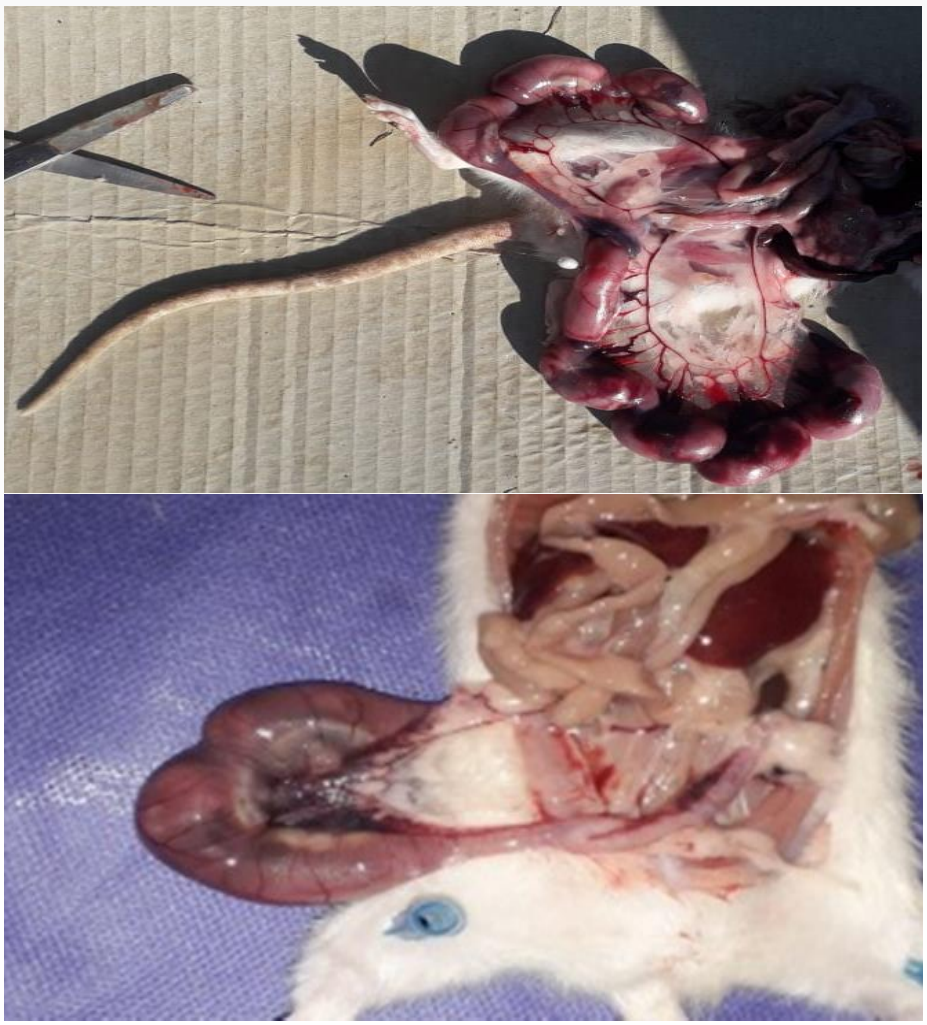
at control group embryo's appear in normal numbers distributed over the uterine horns and dorsum, about 6 cm in size, well-defined from the head, front and hind limbs, and moderate spine , picture (1,2) Many malformations appeared in the group treated with ribavirin, such as the non-equal distribution of fetuses on the two uterine horns, where the fetuses were found in one of the uterine horns and were absent in the other, in addition to the small number of fetuses compared to the control group. Other malformation appeared , the majority of which were malformation of skeletal system ,such us the outward curvature of the back area , torsion in the hind limbs, curvature of the tail upwards, some fetuses had a longer tail than normal. It was noted that there was congestion and the possibility of deformation in the pelvic girdle area and wrinkling of the skin in it. It was also noted that the small size of The fetus compared with the control group, and some fetuses showed inward curvature of the spine and deformation in both the front and hind limbs, , In addition shrinkage of the abdominal region, and wrinkling of the skin, picture (3,4,5)

The result showed that the water extract of ginger root had a distorting effect on the embryos, whether it was from the numerical, phenotypic or volume side, where the treatment with the extract showed a small number of embryos compared to the control group and non-equal distributed over the two horns of the uterus, as well as a small appearance in the size of the fetus in relation to the control group. And congestion appeared in the abdominal area with torsion of the tail end, and it was possible to notice irregularity of the hind limbs and the dorsum of a small, misshapen, deformed, incomplete and unclear rat fetus (8,7,6)No fetus was obtained from the group wich treted with the drug (RBV) and the extract despite repeating the experiment as a result of miscarriages that occurred during pregnancy

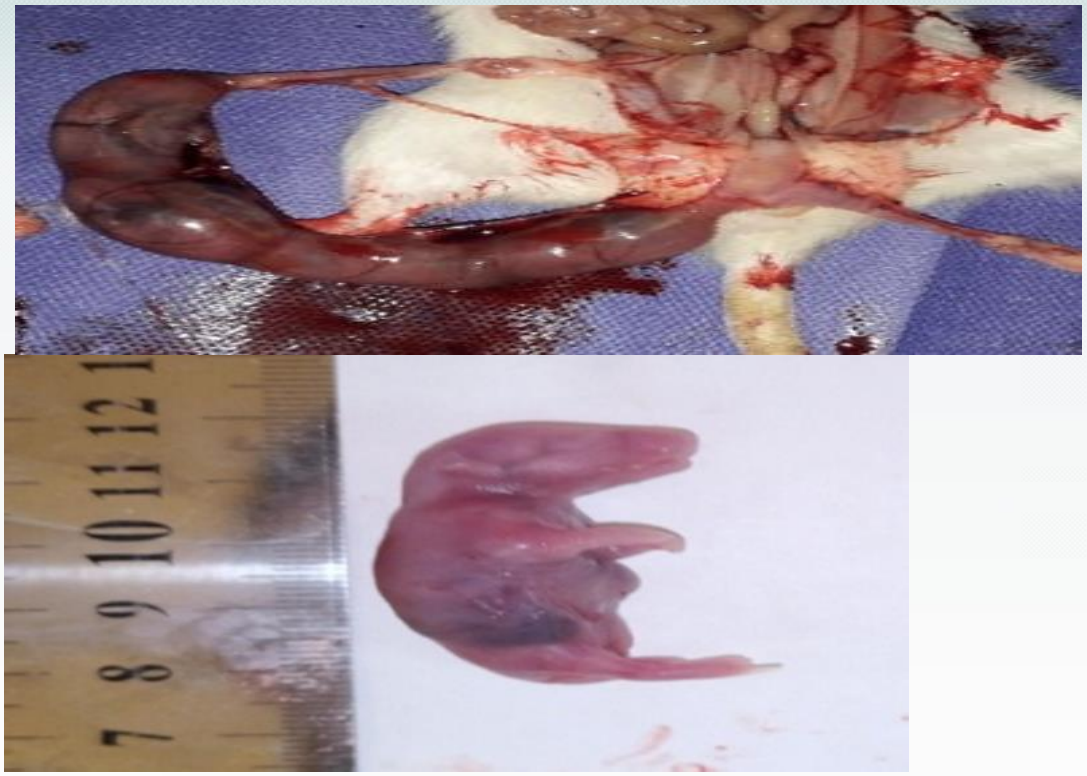
Picture (1) Two horns of the uterus of a female rat. The control group contains eight embryos distributed over the two horns of the uterus.



Picture (2) rat fetus 19 days of gestation, control group, about(6)cm size.



Picture (3) of the Ribavirin group on the 19 day of pregnancy, showing an uneven distribution of fetuses, their small number and wrinkled skin.



Picture (4) of the group treated with RBV drug for a 19-day-old fetus showing shrinkage and congestion in the abdominal area, wrinkling of the skin, and deformation of the pelvic girdle and congenital limbs.

Picture (5) of a rat fetus treated with RBV at the age of 19 days of gestation showing inward curvature of the spine, deformation of the front and rear limbs, and abdominal congestion.

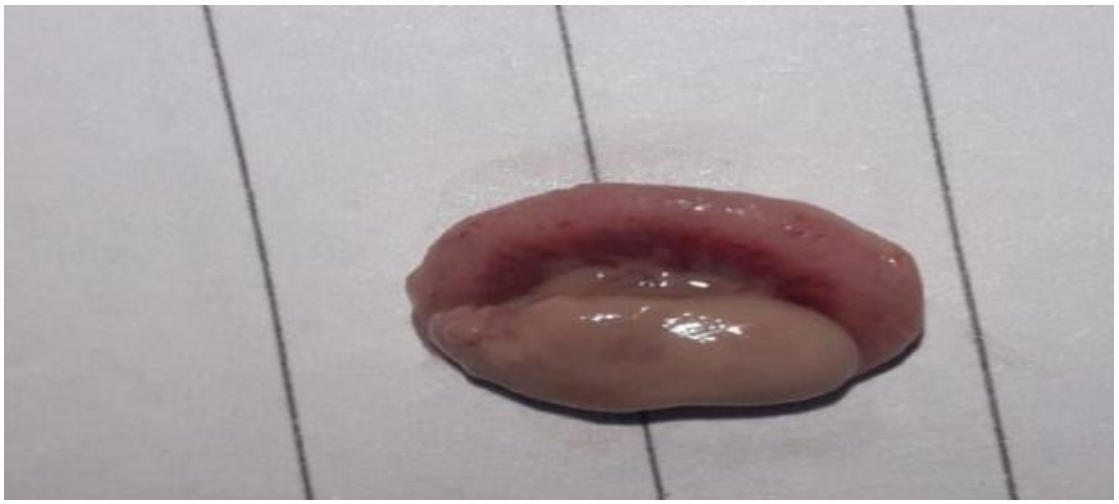
Picture (6) shows the two uterine horns of rats female on the 19th day of pregnancy, the extract group, where the embryos were formed in one of the two uterine regions and did not appear in the other, noting the small number.

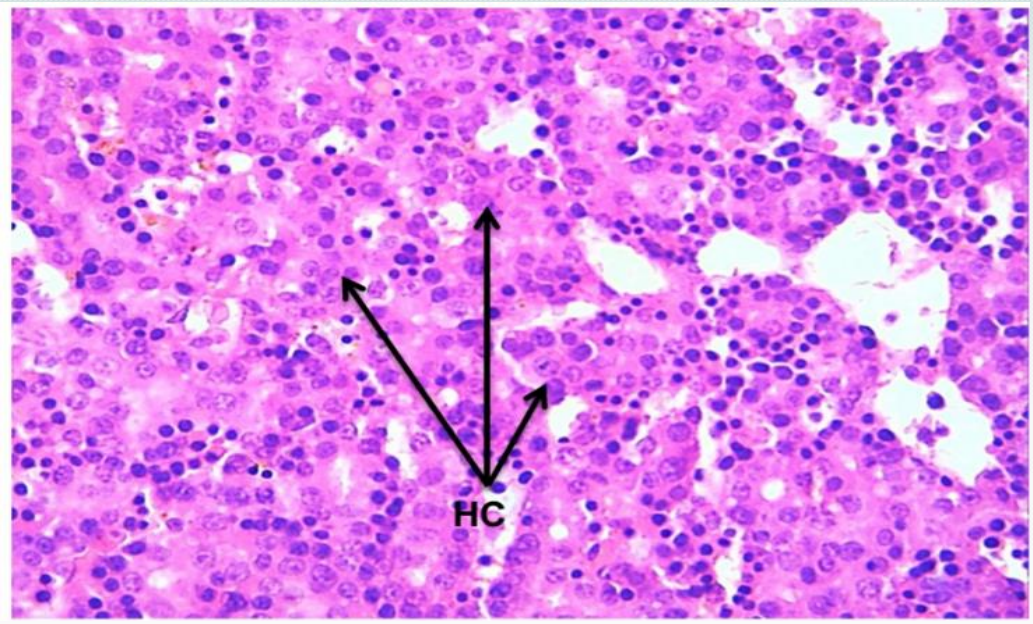
Picture (7) of the group treated with the extract of a rat fetus at the age of 19 days of gestation showing the curvature of the tail, congestion in the abdominal area and the small size of the fetus.

Picture (8) of the extract group shows the fetus of a rat at the age of 19 days of gestation that is small in size, mutated, distorted, incomplete and undefined.

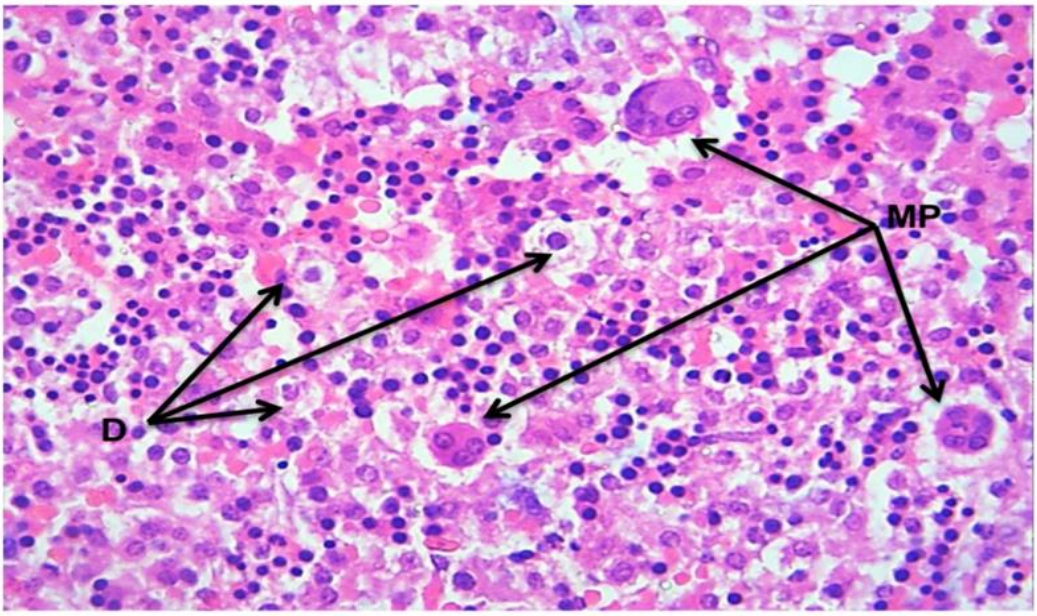
Histological results

Through the microscopic examination of the liver sections of the 19-day-old fetuses from the pregnant of the group treated with ribavirin (16 mg/kg) from day 5 to day 10 of pregnancy, it was noticed that there is presence of various histological lesions represented by the obvious degeneration of some liver cell and un increase in the number of macrophages, picture (9) . while in kidney it was observed rupture of the renal tubule lining and degeneration of renal tubule cells, picture (10). As for the liver and kidneys of the group treated with aqueous extract of ginger roots at a concentration of 200 mg / kg, it was found that there was no histological change compared to the control group,

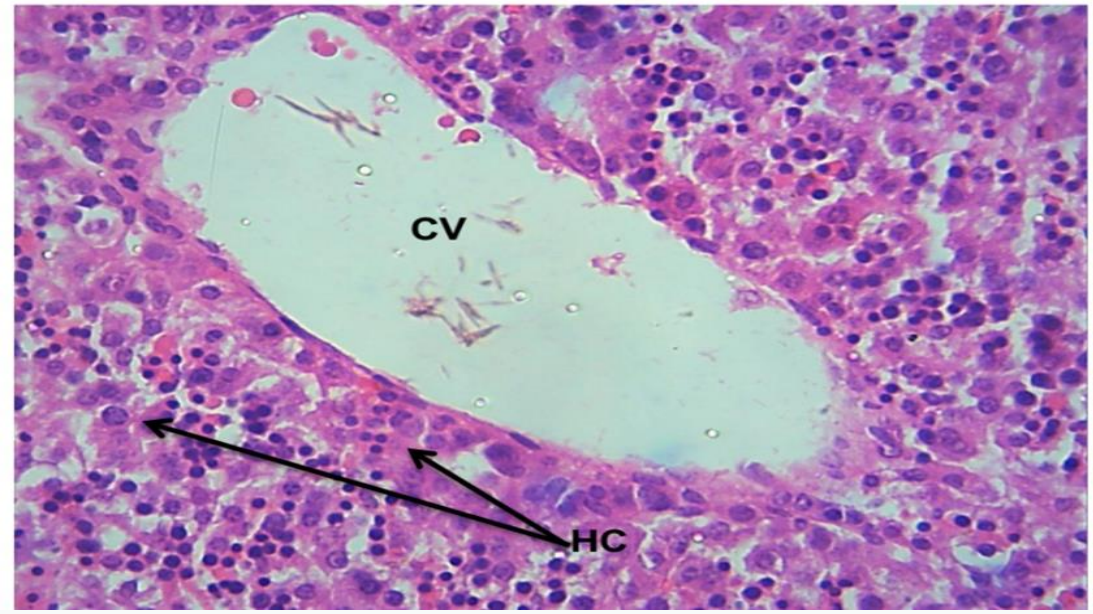




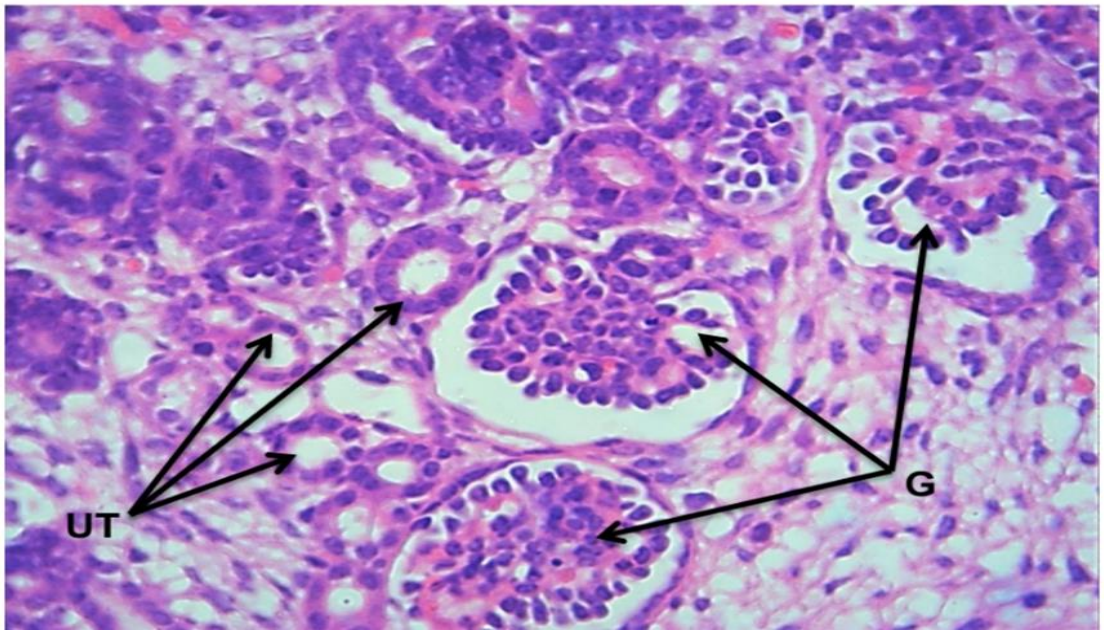
Picture (9) a section of the liver of a 19-day-old rat fetus, the control group, showing the formation of hepatocytes.



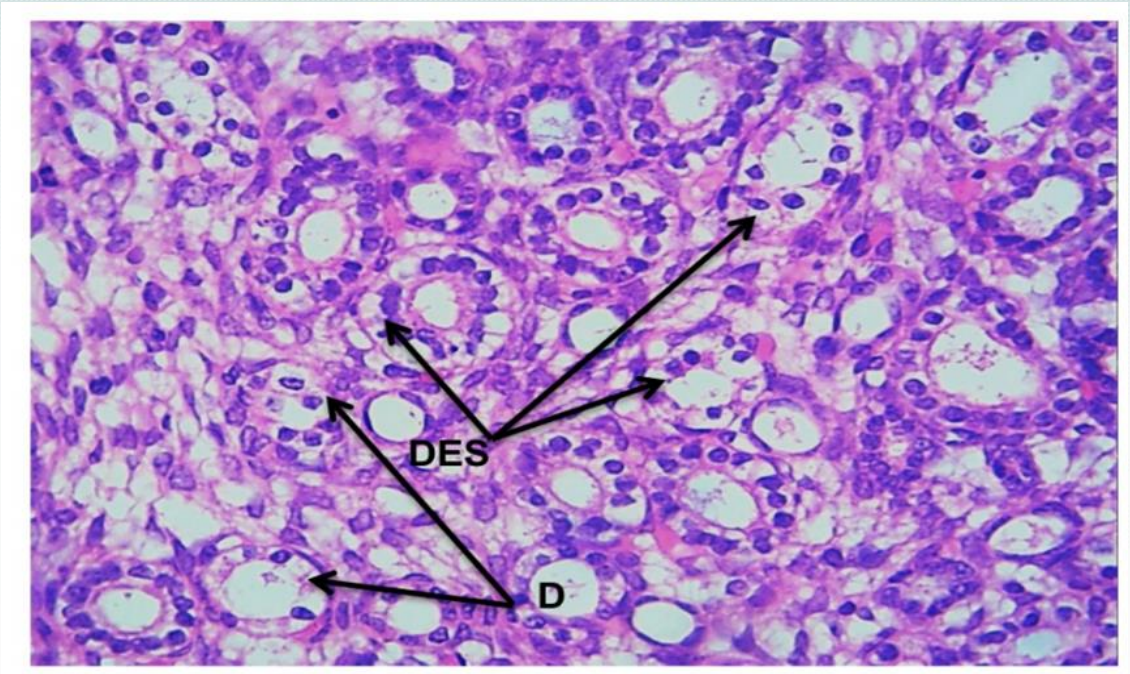
Picture (10), a section of the liver at a 19-day of gestation of rat fetus. The group treated with ribavirin showed obvious degeneration of some hepatocytes and an increase in the number of macrophages, H & E 400X.



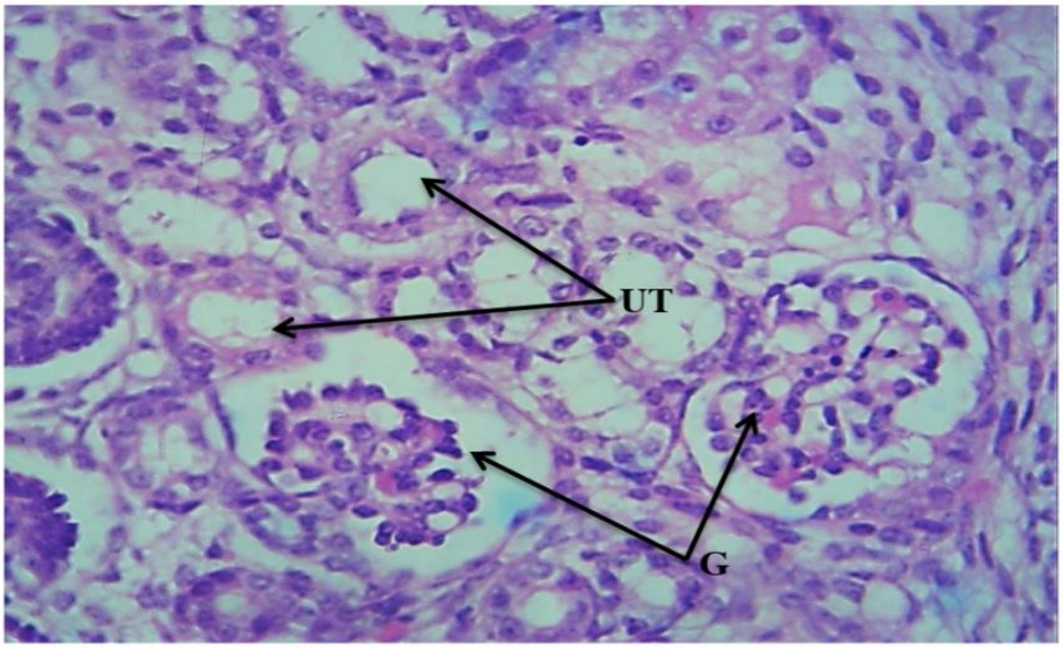
Picture (11) of a fetal liver section at 19 days of gestation. The group treated with the extract showed hepatocytes and central vein.



Picture (12) a section of the kidney of a rat fetus at the age of 19 days of gestation, the control group, showing the renal glomeruli and renal tubules.



Picture (13), a section of the kidneys at a 19- days of gestation of rat fetus. The group treated with ribavirin shows necrosis of the renal tubule lining and degeneration of renal tubule cells, H & E 400X.



Picture (14) a section of the kidney of a rat fetus at the age of 19 days of gestation. The group treated with the extract develops normal glomeruli and renal tubules.

Discussion

The effect of ribavirin on the fetus can be in two ways, the first is indirect, which is the effect of the drug on the environment in which the fetus lives. In this area, it has a significant effect, as ribavirin leads to hemolytic anemia in pregnant females, in addition to its effect on the number of blood cells through its effect on the bone marrow [Musser et al , 2015] and consequently a lack of oxygen supply and ischemia in the placental tissues, which in turn affects the shape and size of the fetus [Pavlova et al , 2007] .As for the direct way in which ribavirin affects the fetus, it is by crossing the placenta, where Kochhar and his group [Kochhar et al , 1980]demonstrated the possibility of

crossing 1-5 micrograms to the fetus for every 100-50 mg/kg of ribavirin given to pregnant female mice, and since ribavirin is nucleoside analogue therefore, it can be expressed across the placenta by Equilibrative nucleoside transporters (ENTs) [Karbanova et al , 2019]and it is a family of Integral protein that is often present in the plasma membranes of living cells and serves to transport nucleosides and nitrogenous bases essential in DNA and RNA synthesis where ENTs participate in the uptake of ribavirin by a placental cell line that has the ability to absorb a range of nutrients such as glucose, amino acids and this line is called BeWo [Orendi et al , 2010].

This amount of the drug that has crossed the placenta is transferred into to ribavirin-5-phosphate in the cells of the fetus, which affects the function of Inosin monophosphate dehydrogenase (IMPDH) which has a role in the synthesis of the nitrogenous base guanosine monophosphate and thus ribavirin affects the synthesis of DNA inside the fetus [Kochhar et al , 1980]. Ribavirin affects cells with high activity, and this explains the teratogenicity effect of ribavirin on embryos, since the cells are in permanent and continuous division, which means that they have to create new genetic material and therefore by inhibition DNA synthesis by effect on IMPDH , accumulative effect that appears in the form teratogens in various embryonic regions[Ferm et al , 1978]

This result agreed with [Salman et al , 2016] as they studied the effect of a dose of 10, 20, 50 mg / kg of ribavirin on rat embryos and their skeletons. The researchers noted that treatment with RBV has many side effects, including teratogenicity, as it causes birth defects in the fetus in addition to it causes mutations. While other studies have shown that this drug does not have any toxicity [Joksic et al , 2000] As for the number of embryos when a drug was affected by RBV, significant differences were observed in the number of embryos of the groups treated with the drug (RBV) when compared to the control sample, as well as the appearance of fatalities in them. From this we conclude that the drug RBV has severe effects, as it was proved that the drug RBV, like the rest of the analogw necleoside They are often teratogenic and mutagenic, and our findings regarding the relationship of RBV to congenital malformations confirm the assumption made by [Narayana et al , 2002] that ribavirin is among the cytotoxic and genotoxic substances.

The results showed current that the group treated with ginger extract had many abnormalities on the fetuses,It is possible that the numerical distortions that occurred in the group treated with ginger extract is the effect of the ginger plant on the corpus luteum because of its active substances. [Abdalhadi and Khaled, 2015] indicated the possibility of the corpus luteum being affected when treated with ginger extract, which lead to have a case of necrosis in which its severity increases with the increase in concentration in addition to the decomposition of the nuclei , a decline in growth and a decrease in the diameter of the corpus luteum, which leads to a decrease in the rate of production of the Progesterone hormone [Halio et al , 2010;Rendi et al , 2012] lead to miscarriages and failure to implant the fetus in the uterus, in addition to weakening the function of the inner lining of the uterus. Some researchers explained that the presence of active substances such as alkaloids and phenols in plant extracts contribute to Abortion [Yakubu and Bimbo, 2009]

Many researchers indicated the need for a balance between the estrogen and progesterone hormones in order to ensure the occurrence of implantation and pregnancy, and any imbalance in the concentration of these hormones leads to the failure of the embryo to implant in the uterus.[Patil and Saraswat, 2012]. It is possible that the miscarriages that occurred in the group treated with ribavirin and ginger extract were due to the synergistic action between the drug and the extract, which led to miscarriages during the early stages of pregnancy. As we have previously shown that the drugs are toxic and distorted, and the extract of the ginger plant had a great effect on the corpus luteum, and since the corpus luteum is the only source of progesterone in rats, it is possible that all of these reasons led to these miscarriages. Through the microscopic examination of the liver sections of the 19-day-old fetuses of the group treated with ribavirin and a concentration of 16 mg/kg from day 5 to day 10 of pregnancy, it was found that there was a different sputum symbol, eye twitching in some hepatocytes and an increase in the number of macrophages, picture (32) It was observed shedding of the renal tubule lining and degeneration of renal tubule cells, picture (35). As for the liver and kidneys of the group treated with aqueous touch of the roots of ginger plant at a concentration of 200 mg / kg, it was found that there was no histological change compared to the group group,

The reason for the effect of the drug on the liver and kidneys in the fetus may be due to the effect of oxidative stress and free radicals caused by ribavirin, as this affects the pancreatic tissue of pregnant females, and the production of pancreatic lipase decreases, which leads to a decrease in the absorption of fatty substances and thus a decrease in the absorption of fat-soluble vitamins, including (A). K, D, E, K) which leads to a decrease in its concentration in the mother's blood and

not reaching it in sufficient quantities to the fetus, which it needs during the process of fetal development, which led to the small size of the fetuses and the emergence of some tissue lesions in the organs [2018 :شعبان وعزيز]

The reason can also be attributed to the fact that ribavirin is a base analogue, it directly affects the mitochondrial DNA Polymerase enzyme, and this enzyme is essential for cellular respiration and homeostasis.Thus, ribavirin causes a decrease in ATP and an increase in free radicals, thus destroying cell membranes, an increase in MDA, and a deficiency in SOD enzyme leads to an increase in hydrogen peroxide H_2O_2, which leads to the depletion of thyrodoxin enzyme from endothelial cells, which leads to apoptosis of endothelial cells [Vicentini et al ,2012]. The histological effects of RBV can be explained by the hypoxia that occurred as a result of anemia, which led to the failure of mitochondria to provide the active cells with energy, and thus after depletion of ATP, which leads to a failure in the work of the calcium pump to the cytoplasmic membrane and free entry of calcium into the cytoplasm, activation of the lipid-digestive phosphorylation process and the destruction of the cell membrane leading to necrosis [Kumar et al , 2007]

Refrences

Kaito M, Watanabe S, Tsukiyama-Kohara K, Yamaguchi K, Kobayashi Y, Konishi M,(1994). Hepatitis C virus letected by immunoelectron microscopic study. *J Gen Virol* 17(55) 60- 75

Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, et al.(2016)The global burden of viral hepatitis from 1990 to 2013: *findings from the Global Burden of Disease Study.Lancet*.:388(10)81-88.

Cohen J. The scientific challenge of hepatitis C. Science. 1999:285:2630

Polaris (2017) Observatory, HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection : a modeling study. *Lancet Gastroenterol Hepatol.* (2)161-176.

World Health Organization. Global hepatitis report. http://www. Who.int/news-room/detail/27-07-2017-eliminate-hepatitis-who Organization WH. Geneva. 2017.

Thursz M, Fontanet A. (2014) HCV transmission in industrialized countries and resource-constrained areas. *Nat Rev Gastroenterol Hepatol* 11:28-35.

Hoofnagle JH, Seeff LB. (2006) Peginterferon and ribavirin for chronic hepatitis C. N *Engl J Med*. 355:2444-2451.

McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J(2009) Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N *Engl J Med* 361:580-93.

Witkuswski , J. T .. Robins , R K , Sidwell , R. W. and Simon . L. N. (1972) . Design synthesis and broad spectrum antiviral activity of 1- 5- D- Rihofuranosy 1- 1 , 2 , 4 - triazole - 3 - carlsoxamide and related nucleusides . *J. Med . Cherr* 15 : 1150 1154 .

Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, (2001). Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treat- ment of chronic hepatitis C: *a randomized trial. Lancet*. :358:958

Khafizyanova , R. KH . , Burykin , I.M. , Aleva , G. N. and Kiyasov , A.P. (2004) . Effect of Dineptusphone (Munuphosphonate) on the Course of Pregnancy and fetal Development in Rats . *Bulletin of Experimental Biology and Medicine* , 137 : 375-378 .

Edoga, H. ., Okwu, D. E. and Mbaebie, B.O. 2005. Phytochemicals constituents of some Nigerian medicinal plants. Afr. *J Biotechnol*. 4(7): 685-688.

Ramakrishna Pai Jakribettu, Rekha Boloor, Harshith P Bhat, Andrew Thaliath, Raghavendran Haniadka, Manoj P Rai, Manjeshwar Shrinath Baliga .(2016) Ginger (Zingiber officinale Roscoe) oil :Medicinal properties of Herbal plants (pp.447-454)

Ilyas, N., Sadiq, M., & Jehangir, A. (2011). Hepatoprotective effect of garlic (Allium sativum) and milk thistel (silymarin) in isoniazid induced hepatotoxicity in rats. In *Biomedica* (Vol. 27).

El-Demerdash, F. M., Yousef, M. I., & El-Naga, N. I. A. (2005). Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats. *Food and Chemical Toxicology*, 43(1), 57–63. https://doi.org/10.1016/j.fct.2004.08.012

Musser, J. M. B., Heatley, J. J., Koinis, A. V., Suchodolski, P. F., Guo, J., Escandon, P., & Tizard, I. R. (2015). Ribavirin inhibits parrot bornavirus 4 replication in cell culture. *PLoS ONE*, 10(7). https://doi.org/10.1371/journal.pone.0134080.

Pavlova TV, Petrukhin VA, Zhiliaeva OD, Nadezhdin SV. (2007) Placental morphology in pregnancy complicated with iron-deficiency anemia . *Arkh Patol*. Mar-Apr;69(2):31-2..

Kochhar DM, Penner JD, and Knudsen TB. (1980). Embryotoxic teratogenic and metabolic effects of ribavirin in mice. *Toxicol. Appl. Pharmacol*, 52 (1) 99–112. https://doi.org/10.1016/0041-008X(80)90252-5

Karbanova S, Cerveny L, Jiraskova L, Karahoda R., Ceckova M, Ptackova Z, and Staud F (2019). Transport of ribavirin across the rat and human placental barrier : Roles of nucleoside and ATP-binding cassette drug e flux transporters. *Biochemical Pharmacology*, 163: 60–70.

Orendi K, Gauster M, Moser G, Meiri H, and Huppertz B (2010). The choriocarcinoma cell line BeWo: *Syncytial fusion and expression of syncytium-specific proteins. Reproduction*, 140(5), 759–766.

Ferm VH, Willhite C, and Kilham H (1978). Teratogenic effects of ribavirin on hamster and rat embryos. *Teratology* 17: 93–102.

Salman SS, Shihab AF and Nada SM (2016) Sid Effect of Ribavirin Drug on Mice Embryos and their Skeleton .*Center of Research and Biotechnology* 10 (1) 5-10

Joksic G, Stankovic M, Vasic V, Cakar M and Jokanovic, M. (2000). Influence of ribavirin on the micronucleus formation and in vitro proliferation of human lymphocytes. Neoplasma, 47, 283–287.

Narayana KD ,Souza UJ and Seethangao KP (2002) Ribavirin - induced sperm shape abnormalities in Wistar *rul* . *Mutat* . *Res* . 513 :190- 196 .

Abdalhadi MG, Khaled R.M (2015). Effect of raw aqueous extract of ginger on the histology of the corpus luteum and the concentration of the hormones progesterone and estrogen in pregnant rat. *Baghdad Altitude Journal* . v(12). 638-644.

Halio AK, Kalita E and Kalita JC (2010). Effect of methanolic root extract of Careya arborea Roxb. On ovarian histology of albino mice. *Ne Bio* 1: 14–17.

Rendi MH, Atis M, RochelleL G, and Kelli LB (2012). Comparative anatomy and histology. 1st Ed , United States Of America ., 253–255.

Yakubu MT and Bimbo BB. (2009). Abortifacient potential of aqueous extract of Bambusa vulgaris leaves in pregnant Dutch rabbits. *elsevier Inc*. Contraception, 80, 308–313.

Patil SJ and Saraswat BP (2012) Effect of Oxalis corniculata whole plant extracts on fertility regulation in female albino rats. *J. of Adv. Sci. Res*, 3 (1)

Vicentini J, DuarteM and Emanuelli T (2012) Imbalance in superoxide dismutase/ thioredoxin reductase activities in hypercholesterolemic subjects: Relationship with low density lipoprotein oxidation. *Lipids. Heal Dis* 11: 79- 90.

Kumar V, Abul KA, Nelson F and Richard M (2007) Robbins basic pathology. 8 ed. 8th *Elisevier Inc*. Canada P 10- 1758–61.

شعبان , راشد خميس حميد, عزيز خالد .(2018) دراسة تأثير السمنة في اكباد وكلى أجنة الجرذان البيض وامكانية معالجة هذه التأثيرات باستخدام زيت بذور العنب (دراسة مظهرية ونسجية). مجلة تكريت للعلوم الصرفة .المجلد 22 العد