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The Effect of the Artemisinin on the Liver Functions in Iraqi Patients Infected by Ovarian Cancer

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Abstract :

This study aims to assess the effectiveness of artemisinin as a treatment for ovarian cancer disease. In this study, cases were divided into three groups, the first group contains thirty women with ovarian cancer from the third stage, the second group contains thirty women with ovarian cancer from the fourth stage and the third group contains thirty healthy women. During this study we detected the hematological Parameters include Red Blood Cells (RBCs) , White Blood Cells (WBCs) and Platelets (PLTs) . As well as detected the liver functions include Glutamic Oxaloacetic Transaminase(GOT) and Glutamate Pyruvate Transaminase (GPT). A significant increase in the RBC, WBC and PLT level in sera of Iraqi patients with ovarian cancer has been reported compared with the control. A significant increase in the GOT and GPT activities in sera of Iraqi patients with ovarian cancer has been reported compared with the control before add the artemisinin. A significant decrease in the activities of GOT and GPT after addition of artemisinin in sera of ovarian cancer patients has been reported compared to control

Key words: Artemisinin, RBCs, WBCs ,PLTs , GOT ,GPT , Ovarian cancer

Introduction

Artemisinin (ART), a sesquiterpene lactone endoperoxide isolated from traditional Chinese herb Artemisia annua , has been recognized as a novel class of antimalarial drugs. ART is termed as "Nobel medicine. (Rajabi & Mousa, 2017) (Muangphrom & Seki et al., 2016) . Malaria has long been an overwhelming , devastating, global and risky disease in human history . Artemisinin has saved millions of lives and made an important contribution to global health in China (Muangphrom et al., 2016) The molecular formula of artemisinin is C15H22O5 And that the molecular mass of artemisinin: 282.332 g / mole (Dayrit, 2018). Artemisinin (ART), which is an antimicrobial and anti-inflammatory and antioxidant, and against the effects of malaria, except that it restricts its use because of its low water solubility and poor oral availability (Ramazani & Keramati et al., 2018). The chemical synthesis of artemisinin is a lactone system with a bridging contact with endoperoxide . Artemisinin has anti-tumor activity over the past five years , and many new studies and research have shown that artemisinin and its derivatives can specifically kill various malignant growth cells, including leukemia (Hutterer et al., 2015) . Ovarian cancer (Bao, 2011). liver cancer (Deng et al., 2013). breast cancer (Tran et al., 2015) (Jabbarzadegan et al., 2017). gastric cancer (Zhang & Luo et al., 2015). B cell lymphoma (Yang & Zhang et al., 2017). cervical cancer (Chen et al., 2017). neck and

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head carcinoma (Lin et al., 2016). nasopharyngeal cancer (Eichhorn et al., 2012). Artemisinin is a sesquiterpene lactone with a peroxide component). The presence of the endoperoxide bridge is isolated from Artemisia herb. The main mechanisms of action of ART include: oxidative stress, angiogenesis inhibition and the arrest of the cell cycle at G0/G1 (Slezakova & Ruda-Kucerova, 2017) (Das, 2015). Artemisinin has several biological characteristics that include anticancer properties. Artemisinin has been shown to inhibit cell proliferation, inflammation, invasion and metastasis . Anatomy of Ovary The two ovaries are female gonads . Each ovary is whitey in color and located alongside the lateral wall of the uterus in area called the ovarian fossa. The ovarian fossa is the area that is bounded by the external iliac artery and the internal iliac artery. The size of this area is about 3 cm x 2 cm x 1 cm. It is enclosed by a container, and it has an outer shell and an internal marrow (Hadi, 2019). The ovaries lie in a parallel mass on both sides of the pelvis, lower pelvis (uterus), where they are attached to a fibrous tensile line called ovarian tendon (round, ovarian tendon). The ovaries perform two primary functions: Eggs formation and secretion of sex hormones (Thiyagarajan et al., 2019). Patients with ovarian cancer often present late and are diagnosed at an advanced stage. At the beginning of the disease, women create side effects of natural gynecological diseases, for example, exudate or vaginal bleeding . Urinary tract obstruction may result from compression of the rectum or bladder. Women with malignant ovarian growth at all stages of the disease may build up the disease with flatulence and pain. They link its symptoms to the symptoms of the digestive system, for example , abdominal bloating , it associates early satiety and loss of appetite with the arrangement of advanced diseases and with dropsy and peritoneal cancer (Scott, 2010) (Lurie & Thompson

et al., 2009). There are four stages of the Ovarian Cancer Stage The first stage of ovarian cancer is limited to one or both ovaries .Second stage Cancer cells are also spread from one or the two ovaries, and they has moved to the point that another sibling's tissue exists in the AlHawd locale Furthermore, the cells are there cancer in the fallopian cylinders, uterus, or different tissues in the Basin zone .Third stage Cancer cells are spread to tissue outside. Malignancy cells may show up in the external piece of the liver . fourth stage Cancer cells are spread to the tissue outside the abdominal zone and pelvis . That is, the tumor spread to other organs such as the liver and lungs . Ovarian cancer is a type of cancer that begins in the ovaries. The female reproductive system contains two ovaries, one on each side of the uterus. Ovarian cancer often goes undetected until it has spread within the pelvis and abdomen. At this late stage, ovarian cancer is more difficult to treat. In women ages 35-74, ovarian cancer is the fifth leading cause of cancer-related deaths. An estimated one woman in 78 will develop ovarian cancer during her lifetime The American Cancer Society estimates that there will be over 22,280 new cases of ovarian cancer diagnosed this year and that more than 14,240 women will die from ovarian cancer this year . This study is aim of detect the Hematological parameters include (RBCs , WBCs and PLTs and detect the liver functions test before and after add the artemisinin to serum for patients of ovarian cancer .

MATERALS AND METHODS:

This study is include 60 patients have selected additionally 30 healthy individuals

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were also enrolled. In addition, blood samples were collected from patients who undergo ovarian cancer Samples collection was performed in Baghdad Teaching Hospital / Medical City National Hope Hospital, and Al-Kadhimiya Teaching Hospital / Al-Jawed Center for Oncology. The patients are divided into three groups as follows :

1. Ovarian cancer patients group of stage 3 : It includes (30) patients

with the age ranged from 40 to 70 years old .

2. Ovarian cancer patients group of stage 4 : It includes (30) patients

with the age ranged from 40 to 70 years old . All patients were newly diagnosed and they do not undergo from any chemotherapy.

3. Control group: It includes (30) healthy female individuals with the age ranged from 25 to 65 years old .

Specimen Collection and Preparation :

5 ml of blood was controlled and withdrawn from both patients and healthy people. Blood samples were divided into two groups: the first group of blood samples was tested for the performance of RBC, WBC and Platlate . This was done by taking 2 ml of blood in a purple tube containing EDTA. On the other hand, the second group was transported directly to tubes that contain an amount of gel that support the coagulation of the blood at room temperature for 20 -30 minutes. The serum was obtained by centrifugation after 15 minutes. The serum from all samples were transferred to Eppendorf tubes by using a small pipette, and all tubes were stored at -20 ° C for doing liver functions tests . Each serum was divided in to two parts to measure the variables without and with the addition of Artemisinin .

Detect the Hematological parameters :

The Enumeration of Red Blood Cells (RBCs) (Erythrocyte count): The RBCs were calculated by a (Hemocytometer slide). Red blood cells were counted by using a diluted solution to dilute a certain amount of blood . This diluted solution is called (Hymens fluid). Its components are (sodium chloride 0.5mg, sodium sulfate, mercury chloride 0.25mg , distilled water 100ml) . Hymens fluid components prevent coagulation of the blood . This method is very necessary in order to reduce the density of the cells seen under the microscope and to see the individual cells clearly.

Total Counting of Leukocyte (WBCs) : White blood cells were basically counted in a similar way to the method of calculating erythrocytes with exception for the dilution solution and the sucking tool . The diluting sucking tool of WBCs were divided into 0.5, 1, and 11, and it contains a white bead. It can give a dilution ratio of(1:20) The dilution solution is a (Turkeys fluid) that consists of : Glacial acetic acid (1.5) ml , Gentian violet tincture or methyl violet tincture (1) ml and Distilled water (100) ml. This solution, which includes glacial acetic acid, leads to the deterioration of the RBCs and prevents the growth of the germs that makes them easily differentiated and counted .

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Platelets Count Thrombocyte Count (PLTs) : Platelets are small cells with a diameter between 3-2 microns that are irregular in shape. They give prominent, soft, and light blue elongations, in which there are two types of small granules usually accumulated in their center, and they do not have a nucleus, as they are part of the megakaryocyte cytoplasm . Platelets were quickly being tight or compact with each other. So you often see together in clumps . Their age was estimated between 8-10 days. The platelets have a vital role in the coagulation of the blood . ammonium oxalate was prepared at 1% which is special in counting the platelets.1% of ammonium oxalate was dissolved in 100 ml of distilled water, after which it was filtered and stored at 4 ° C in the refrigerator. It is possible to add 0.5% formula to it, and there is no need to put it in the refrigerator(Harrison, Briggs, & Machin, 2001).

Detect the liver functions test

Assay of Activity Glutamate Pyruvate transaminase (GPT) : The activity of (GPT) was measured in the serum by depending on the method called colorimetric as applied by (Mohun & Cook, 1957) . Alanine aminotransferase of the serum was determined by a readymade utilized kit . Measuring Glutamate-pyruvic transaminase was accomplished by controlling pyruvate hydrazone concentration which was formulated with 2, 4-dinitrophenyl-hydrazine .

Assay of Activity Glutamate Oxaloacetate Transaminase (GOT) : The activity of (GOT) was measured in the serum by using the method that called colorimetric as emphasized in (Mohun & Cook, 1957). by the applications of a kit which is ready made and can determine aspartate aminotransferase in the serum. Glutomic-Oxaloocetate transaminase could be measured by controlling Oxaloacetate hydrazone concentration which is formulated with 2, 4- dinitrophenyl-hydrazine .

Statistical analysis :

The data resulted from present study could be represented by the means standard deviation. Furthermore, the t-test was used when, P value lesser than or equal to 0.05 it means the difference is statistically significant with the benefit of the comparison between two groups that differ in mean values and noting the importance of that difference. The office program (Excel 2010) was used to perform all the values of the results in all groups enrolled in the present study .

Results and Discussion :

Table (1): which shows WBCs , RBCs and PLTs values for control and patients groups ovarian cancer stage 3 and stage 4 respectively.

Parameters	**Control Mean ±SD**	**Stage 3 Mean± SD**	**T – test Stage 3/control**	**Stage 4 Mean ±SD**	**T –test stage 4/control**
WBCs	**6.86±2.47**	**11.11±2.25**	**H.S**	**11.9±1.99**	**2.59×10^{-12}**
RBCs	**4.63±0.55**	**5.18±2.56**	**N.S**	**4.47±0.94**	**0.42****
PLTs	**244±74.85**	**252.86±65.64**	**N.S**	**63.7±219.6**	**0.18****

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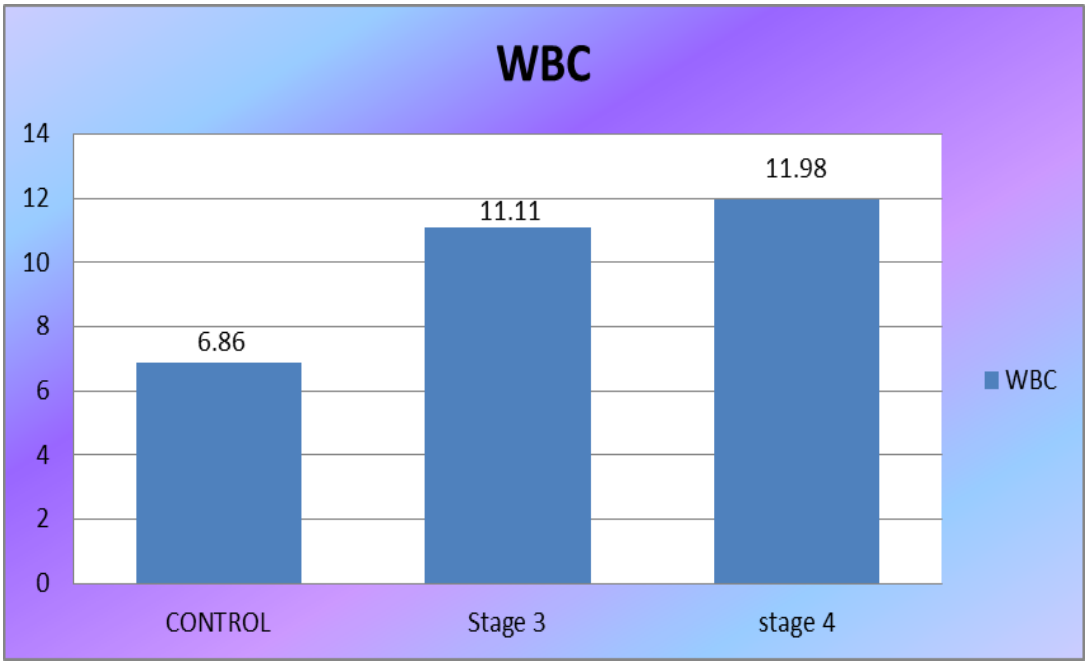

Figure (1): WBC levels in blood of the three studied groups .

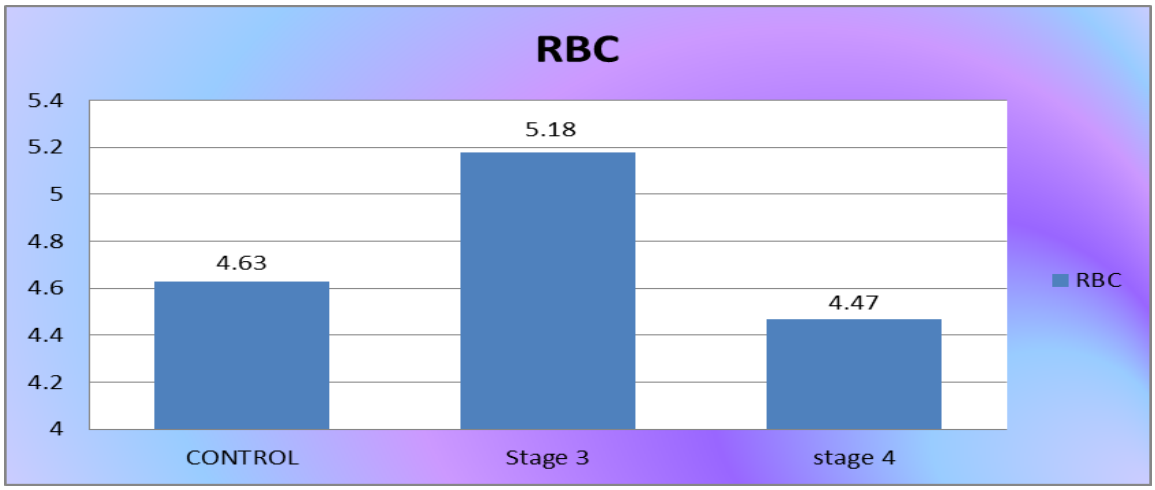

Figure (2): RBC levels in blood of the three studied groups

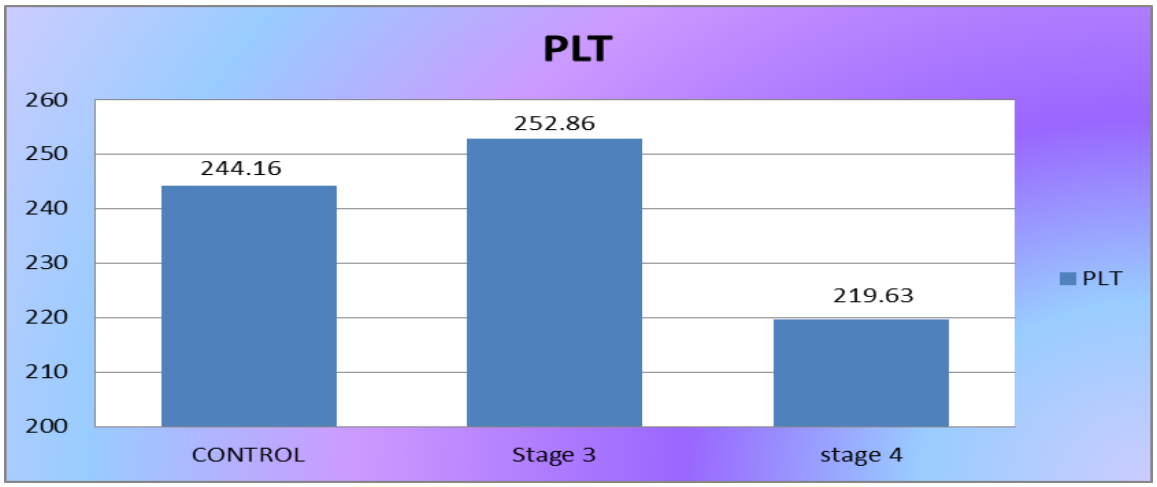

Figure (3): PLT levels in blood of the three studied groups

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From the table 1 and figures 1,2 and figure 3 show there is a significant increase of WBC level was found for stage 3, 4 ovarian cancer patient group compared to control group with ($P \leq 0.001$). It is noted that the high level of urea is often attributed to cancer patients with renal impairment (the loss of college function) due to physiological changes associated with aging and factors associated with the disease (Weinstein & Anderson, 2010). No significant difference was found in the creatinine level in the patient's group compared to the control group, and the reason could be attributed to the reason to the fact that the patients did not take chemotherapy and therefore the results were close to normal. And that these results are consistent with previous studies. Studies have proven that high white blood cells are due to a tumor and considered a very sensitive indicator, regardless of the size of the tumor . (Boonsongserm et al., 2019). It is observed that there is a decrease in the number of red blood cells (RBC) given that many patients (especially in advanced stages of the disease) are already suffering from anemia before the onset of chemotherapy (Madeddu et al., 2018) . Where the "degree of malnutrition and inflammation" has shown a strong association with anemia (Rattanasompattikul et al., 2013) . Megakaryocyte-derived (Bone Marrow) platelets play a key function in a number of physiological and pathological processes, hemostasis, wound repair, inflammatory reactions and thrombosis involved Past researches showed a high PLT associated with tumorigenesis, metastasis and angiogenesis, metastasis, Is a common occurrence in solid-cancer patients (Qian et al., 2019) (Yan & Jurasz, 2016) (Heijnen & van der Sluijs, 2015).

Table (2): GOT activities before and after the addition of ART with concentration (3ppm) for control and ovarian cancer patients stage 3 and stage 4 groups respectively.

Parameters	**Control Mean ± SD**	**Stage 3 Mean ± SD**	**t-test**	**Stage 4 Mean ± SD**	**t-test**
GOT (U/L) Before addition ART	**3.71±29.59**	**13.67±60.03**	**5.35×10^{-17}**	**12.53±45.82**	**6.30×10^{-9} *****
GOT (U/L) After addition ART (3ppm)	**1.71±14.35**	**35.1±8.49**	**5.28×10^{-19}**	**24.97±3.27**	**1.40×10^{-22} *****

Table (3): GPT activities before and after the addition of ART (3ppm) for control and ovarian cancer patients stage 3 and stage 4 groups respectively

Parameters	**Control Mean ± SD**	**Stage 3 Mean ± SD**	**t-test**	**Stage 4 Mean ± SD**	**t-test**
GPT (U/L) Before addition	**4,36±27.52**	**19.38±67.05**	**1.17×10^{-15}*****	**18.47±61.5**	**6.48×10^{-14}*****

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 479 - 489
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ART					
GPT (U/L) After addition ART (3ppm)	**2.43±15.02**	**9.19±43.62**	**1.56×10^{-23}*****	**3.67±29.34**	**3.77×10^{-25}*****

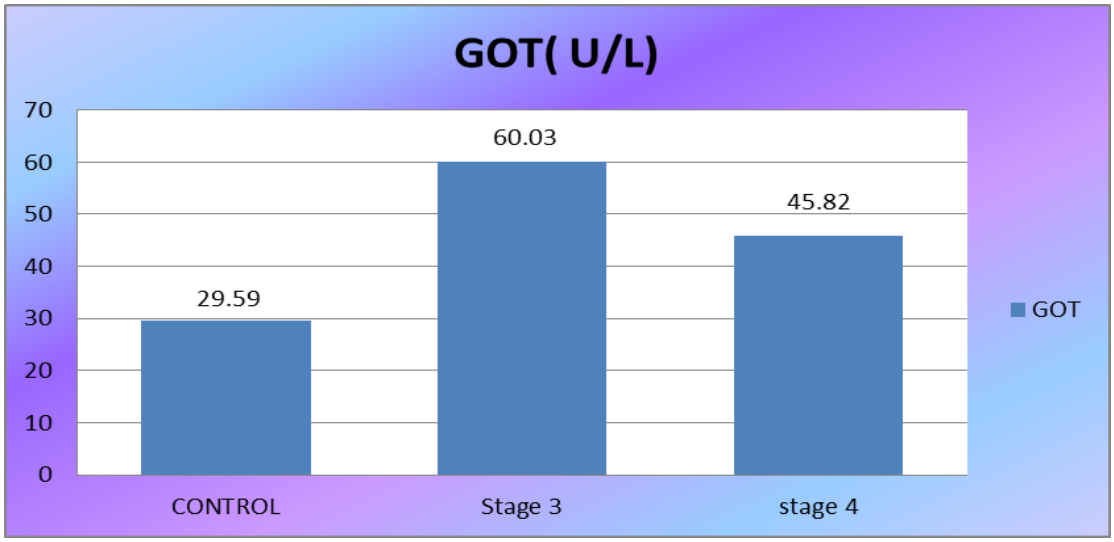

Figure (4): GOT activity in the sera of the three studied groups before addition the artemisinin .

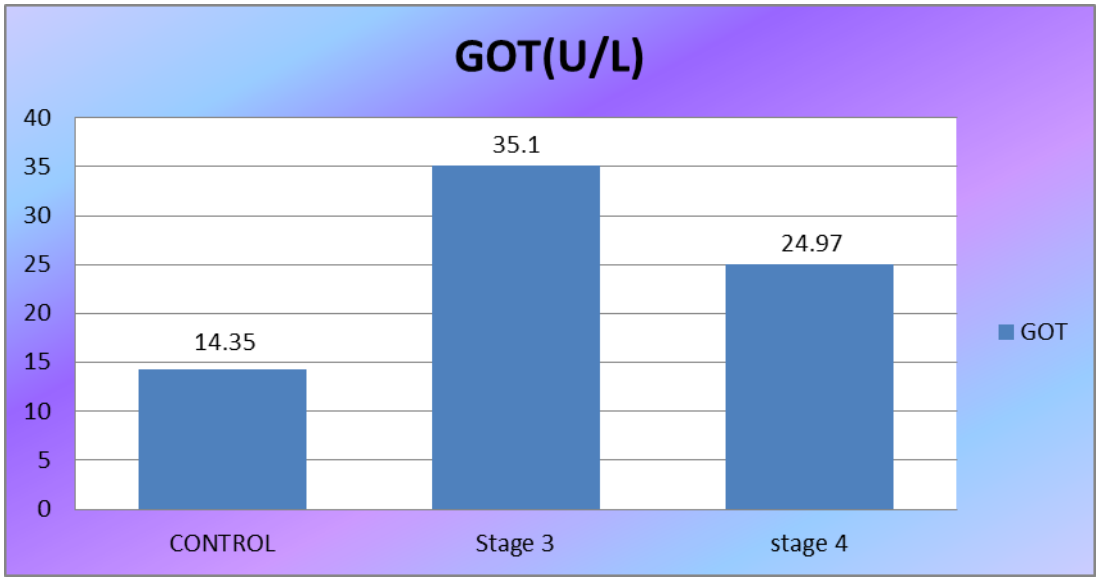

Figure (5): GOT activity in sera of the three studied groups after addition the artemisinin .

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 479 - 489
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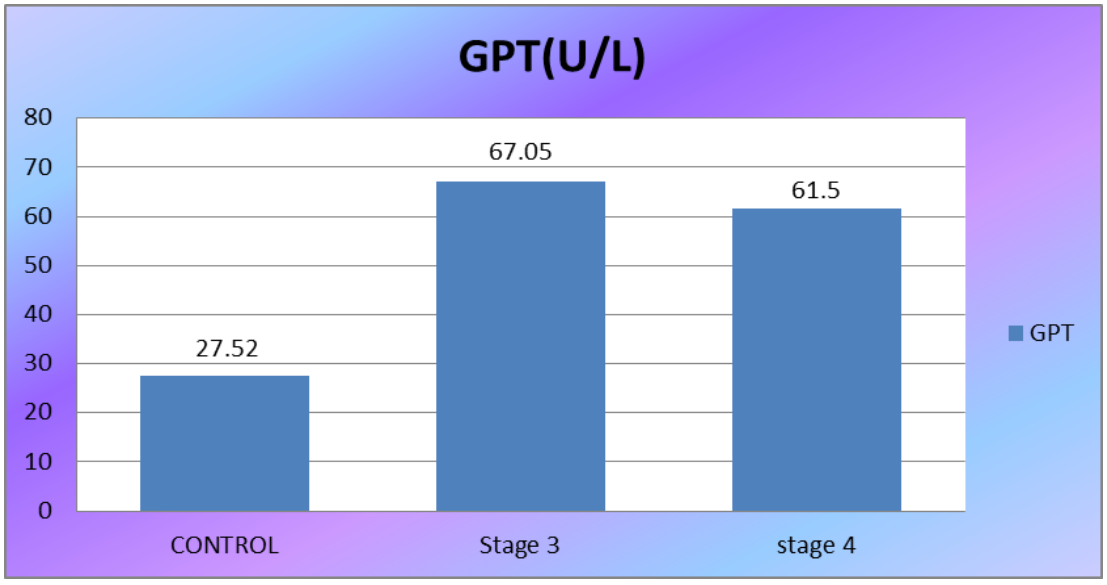

Figure (6): GPT activity in sera of the three studied groups before addition the artemisinin .

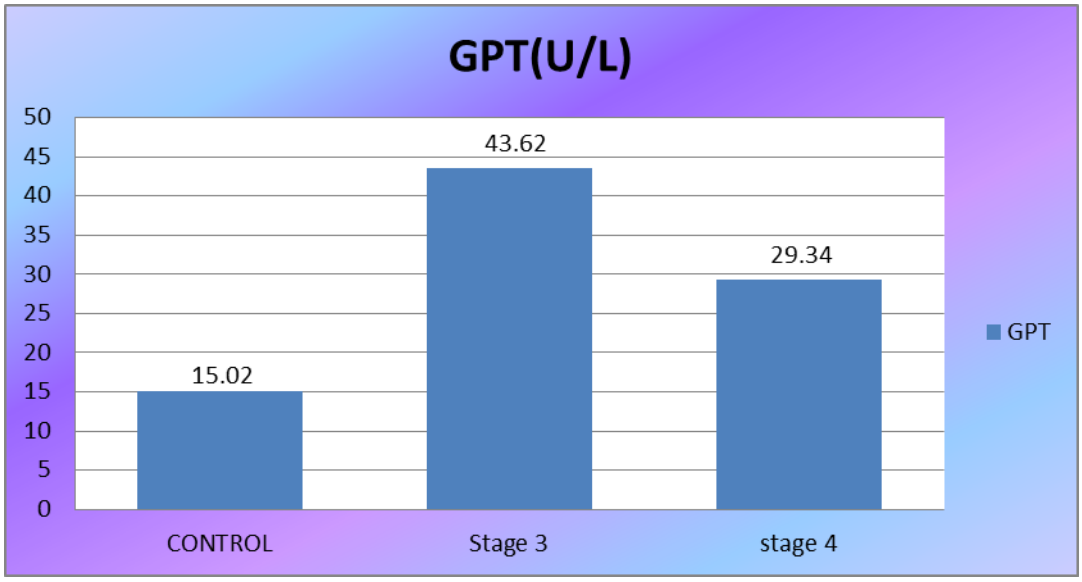

Figure (7): GPT activity in sera of the three studied groups after addition the artemisinin .

As shown in tables (2) and (3) as well in figures (4,5,6) and (7) there are significant increases in sera of GOT and GPT activities for ovarian cancer patients groups in stages 3 and 4 compared with the control group. However, there is a very significant decrease in GOT and GPT activities in sera of the control at (3ppm) concentration and ovarian cancer stage 3 and 4 groups after the addition of the artemisinin compound. GOT and GPT liver enzymes are good indicators of liver injury and are so/very important. GOT is found in cell enzymes from cellular and mitochondrial cells and also found in the liver and skeletal muscles of the heart, pancreas, kidneys, lungs, mind, leukocytes, and red cells. They are not sensitive or explicit to the liver, the elevation of GOT activity may be considered optional also for non-hepatic reasons (Prati et al., 2002). GPT was found at high concentrations in the liver, that the amount

of GPT inside the cytoplasm of liver cells is a few times greater than extracellular fluid, and that the increase is caused by the normal limit in plasma is evidence of liver damage that occurs as a result of liver cell death or liver cell layer damage (McGill, 2016). GOT and GPT activities are increased in ovarian cancer. Regarding the present research, the addition of artemisinin compound causes the significant decrease of the enzymes activities. It is emphasized that artemisinin compound can treat naturally and effectively many infections that are viral. Moreover, it is effective against the lines of human cancer cells. The evidence for this is proved by the increased rate of survival and the liver improvement as well as the development of the morphology of the tissue. Furthermore, there is a decreased GPT and GOT in the sera due to the work of the artemisinin compound. Therefore, this study has a agreement with previous studies in this respect (Alkhedaide & Ismail et al., 2018) (Rezaei et al., 2013). The current study substantially indicates that artemisinin is able to provide the protection to the liver and keeps the level of the liver maintained in a normal way. . Remarkably lactone peroxide structure constitute the basic feature in artemisinin activity, is because the process of dividing the bridge of the endoperoxide by iron, will lead to the production of reactive oxygen species (ROS). However, other studies showed different results when the artemisinin derivatives cause an increase in the hepatic enzymes levels (Onovo & Madusoromuo et al., 2016) (Silva-Pinto et al., 2017).

Conclusion :

1 **.** significant increase in the RBC, WBC and PLT level in sera of Iraqi patients with ovarian cancer has been reported compared with the control.

2 . significant increase in the GOT and GPT and activities in sera of Iraqi patients with ovarian cancer has been reported compared with the control .

3. A significant decrease in the activities of GOT and GPT after addition of artemisinin in sera of ovarian cancer patients has been reported compared to control .

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