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The Effect of Cisplatin and 5-Fluorouracil versus *Aloe perryi* extracts on Rat Liver and Kidney Tissues

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Abstract:

The present study was designed to compare the side effects of Cisplatin and 5-Fluorouracil with that of *Aloe perryi* leaves gel extracts. Twenty female albino rats (100 – 110 g) were used and assigned to 4 groups: group (I); control which received 1000 mg/kg distilled water for 30 days, group (II); intraperitoneally with 1.5 mg/kg of Cisplatin and 20 mg/kg 5-FU for 14 days; group (III) treated by *Aloe* aqueous extract (1000 mg/kg for 30 days), group (IV) treated by *Aloe* methanolic extract (1000 mg/kg for 30 days), at the end of the experiment they were anesthetized and liver and kidney were removed for histopathological studies. There was a decrement in bodyweight and relative liver and kidney weight recorded in Cisplatin and 5-FU group when compared with Aloe aqueous and methanolic extracts and control group. Histopathological investigation of the liver and kidney tissue of the control, *Aloe* aqueous, and methanolic extracts groups were found to be normal in structure. However, Congestion, hemorrhage, inflammatory cells infiltration, dilatation, fatty changes, vacuolation, fibrosis, and pyknosis showed histopathological changes in liver tissue of group II (intraperitoneally with Cisplatin and 5-FU for). Moreover, the histopathological analysis showed that the glomerular shrinkage, dilation, degeneration, congestion, vacuolation, and tubular shrinkage were the kidney histopathological changes in group II. It was concluded that *Aloe perryi* aqueous and methanolic leaves extracts have no side effects on liver and kidney tissues of rats as compared to Cisplatin and 5- fluorouracil.

INTRODUCTION

Cancer is the sign of death. It threatens the world especially the developing countries (Iqbal, 2021a,b; WHO, 2017), with incidence of various cancer types (Amjad *et al.,* 2020a; Iqbal and Ashraf, 2020) and high mortality rate (Amjad *et al.,* 2020b). Several factors discriminate the biology cancer (Ali *et al.,* 2015; Ashraf *et al.,* 2018; Iqbal, 2020; Iqbal *et al.,* 2021; Irfan *et al.,* 2016). Various techniques are used for the treatment of cancer (Din *et al.,* 2016; Yuan *et al*., 2008). Chemotherapy is the reliable treatment of cancer that uses chemical agents to stop cancer cells growth. More than half of cancer patients rely on chemotherapy regimens to treat and decrease the completion of cancer. Several combination regimens have been studied to improve overall response rate and survival (Yuan *et al*., 2008).

Cisplatin and 5-fluorouracil (5-FU) are some of the chemotherapy regimens commonly used for the treatment of various cancers (Yeo *et al*., 2005; Lin *et al*., 2006a; Yuan *et al*., 2008). This regimen recorded high response rates in cancer treatment (Alvarez-Cabellos, 2007; Ajani, 2008; Dank *et al*., 2008) associated with some clinical symptoms include myelosuppression, diarrhea, vomiting, and mucositis (Cheah *et al*., 2014). Moreover, it does not distinguish between cancer and normal cells (Minami *et al*., 2010) and it also exhibit severe undesirable side effects like neurotoxicity, ototoxicity (Rabik and Dolan, 2007), hepatotoxicity (Kim *et al*., 2004; Ray *et al.,* 2007; Pal *et al*., 2008) and nephrotoxicity (Isaka and Rakugi, 2009; Park *et al*., 2009).

The antimetabolic agent (5-FU) is activated by thymidine phosphorylase into fluoro-deoxy uridylate (5 fluoro 2'deoxyuridine 5'monophosphate, 5-FdUMP) which inhibits thymidylate synthase, thus blocking DNA synthesis. It is also converted to 5-fluorouridine monophosphate (5-FUMP) and can be incorporated with RNA and interfere with RNA processing and function (Shoemaker *et al*., 2004). 5-fluorouracil is metabolized mainly in the liver within about 10 minutes due to the presence of Dihydropyrimidine dehydrogenase (DPD), the initial and rate-limiting enzyme, and only a small amount excreted by the kidney (Tateishi *et al.,* 1999; Saif *et al*., 2007).

Cisplatin (*Cis*-diamine dichloroplatinum) is the prototype platinum coordination complex classified as an alkylating agent and used intravenously in the treatment of several forms of cancer. Cisplatin exerts serious side effects including liver and kidney damage (Arany and Safrstein, 2003; Liao *et al*., 2008). Moreover, Pabla and Dong (2008) mentioned that one-third of cisplatin-treated patients showed a reduction in the glomerular filtration rates, higher serum creatinine, and reduced serum magnesium and potassium levels. Although there is dearth of information about its mechanisms in nephrotoxicity and hepatotoxicity, cisplatin is hypothesized to induce apoptosis and oxidative stress (Yao *et al*., 2007).

On the other hand, plants that have pharmaceutical constituents and are used as foods were reported to have anticancer potential against various cancers with no or minimal side effects (Ezz-ELdin *et al*., 2013; Iqbal and Ashraf, 2018; Zaynab *et al.,* 2018). *Aloe* is one of these plants, it belongs to the family Aloaceae (Mothana *et al.*, 2012; Mwale and Masika, 2012; Egbuna *et al*., 2020). *Aloe* leaves gel is documented to have many active constituents such as minerals, sugars, enzymes, amino acids, and vitamins (Hamman, 2008). Previous studies reported that Aloe-emodin from *Aloe* spp. can induce apoptosis in various cancer cells such as neuroectodermal cancer cells, hepatoma, gastric cancers, bladder carcinoma, squamous cell cancer, and immunomodulatory action in various cancer cells (Reynolds and Dweck, 1999; Pecere *et al*., 2000; Kuo *et al.,* 2002; Lin *et al.*, 2006b; Chiu *et al*., 2009; Qin *et al*., 2010). Moreover, Chiu et al. (2009) mentioned that Aloe-emodin can arrest the S phase cycle in human tongue cancer squamous cells.

In Yemen, *Aloe* L. genus is represented by 20 species, including 13 endemic species (11 on the mainland and 2 on Socotra Island). *A. perryi* is one of the endemic species to Socotra Island (Al-Khulaidi, 2013), its resin aqueous extract

exerts hypoglycaemic, insulin-releasing, and hepatic antioxidant potentials in diabetic rats (Aldayel *et al*., 2020).

Based on the information mentioned above, this study was designed to investigate the effect of aqueous and methanolic extracts of *A. perryi* leaves at high doses (1000mg/kg) on liver and kidney tissues of rats as compared to cisplatin and 5- fluorouracil.

MATERIALS AND METHODS

Chemicals

Cisplatin, [cis-$PtCl_2(NH_3)_2$] solution infusion in a vial of 50 ml (1 mg/ml), and 5-Fluorouracil (5-FU) solution (fluoropyrimidine), infusion in a vial of 10 ml (500 mg/10 ml were obtained from National Oncology Center, Sana'a, Yemen.

Ethical approval

This study was carried out according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institute of Health (NAP, 1996). The protocol was approved by the Committee of Experimental Animals Care and Use, Sana'a University.

Collection of plant materials

Aloe perryi leaves were collected from Socotra Island, Yemen, and transported immediately to Sana'a under the permission of the chairman of the Environment Protection Authority–Yemen. Two specimens of collected taxa (Inflorescence and leaves) were mounted on herbarium sheaths and identified by Dr. Hassan Ibrahim, Associate Professor of Plant Taxonomy, Biology Department; Sana'a University, Yemen. Furthermore, the two mounted specimens were kept at the Herbarium of the Faculty of Science of Sana'a University by the herbarium number; BHSS 1692 and BHSS 1693.

Preparation of Gel extraction

Aloe perryi leaves were firstly washed under running tap water then rinsed with distilled water. The spines around the leaves were removed using a knife and the thick epidermis was removed to collect the solid mucilaginous gel with a sterilized spoon. Gel was cut into small pieces and blended in an electric blender for 3 min (Saritha *et al*., 2010).

Methanolic extract was prepared by a Soxhlet extraction apparatus by using methanol (95%) as a solvent, the extract was filtered using Whatman No.1 filter paper. The filtrate was concentrated under vacuum at 40°C (Bisi-Johnson *et al*., 2011) in a rotary evaporator.

Sterilized distilled water was used to prepare the aqueous extract, under shaking by using Gallenkamp, orbital incubator, at 80°C (Bhaya and Saini, 2008) for 3 hrs. The obtained extract was filtered and lyophilized using freeze dryer (LABCONCO, Freezone 4.5, USA).

The dried crude extracts were collected, weighed and packed in dark glass containers and stored at -20°C until used. *Aloe* methanolic and aqueous extracts were dissolved in distilled water at a high dose (1000 mg/kg b.w.) just before using and were orally administrated by gastric tube.

Animals

Twenty adult female albino rats (100 – 110 g) were obtained from the animal house of the Faculty of Sciences, Sana'a University, Yemen. The animals were kept in plastic cages under controlled room temperature (23-25°C) with a 12 hours light/ dark cycle. Animals had free access to laboratory pellet foods and tap water. The animals were acclimatized for one week prior to the commencement of the experiment.

Experimental design

Rats were randomly divided into 4 groups each comprising of 5 rats. Control group (I) was orally administered with 1000 mg/kg distilled water for 30 days, chemotherapy group (II), intraperitoneally administered with 1.5 mg/kg of cisplatin and 20 mg/kg 5-FU for 14 days, group (III), orally administered with 1000 mg/kg *A.*

perryi aqueous extracts for 30 days. Group (IV) orally administered with 1000 mg/kg *A. perryi* methanolic extract for 30 days. All the treatments were given once daily. At the end of the experimental period all rats were euthanized with ether, livers and kidneys were quickly excised. The experiment was conducted in accordance of the ethical guidelines and internationally accepted principles for laboratory use and care in animal research.

Cisplatin and 5-Fluorouracil injection

Rats in group II were intraretinally injected with cisplatin (1.5 mg/kg b. w.) and 5-Fluorouracil (20 mg/kg b. w.) as a single dose a day for 14 days according to the methodology mentioned by Sakurai et al. (2004).

Body weight and organs weight

Body weights of the individual in 4 groups were measured twice weekly to determine weight changes during treatment. At the end of the experiment, liver and kidney of the rats were excised and weighed. The relative liver and kidney weight were calculated by dividing the organ weight by body weight and then multiplying by 100.

Histopathological studies

For histopathological examination, livers and kidneys from each group were collected, an appropriately sized portion of the livers and kidneys were fixed in 10% formalin, dehydrated in ascending grades of ethyl alcohol, cleared in xylol and mounted in molten paraffin at 58ºC. Sections of liver and kidney with 3µm thickness were cut using a microtome. Sections were, stained with Harris Hematoxylin and Eosin and investigated for any structural changes (Bancroft *et al*., 1994; El-Sayyad *et al*., 2009).

Micromorphometric measurements of liver and kidney sections

To support the histopathological results, liver central vein and portal vein diameters were calculated to evaluate the dilation size. Kidney glomerular space and medullary tubules diameters were also recorded to estimate the amount of glomerular dilation and tubular shrinkage. All the measurements were carried out by using the ocular and stage micrometer and applied with ImageJ software program.

Statistical analysis

The results are expressed as mean ± SD. The results were analyzed by a one-way analysis of variance ANOVA using Graph Pad Prism 8.0.2. Differences with a P-value 0.05 were considered statistically significant.

RESULTS

Animal behavior

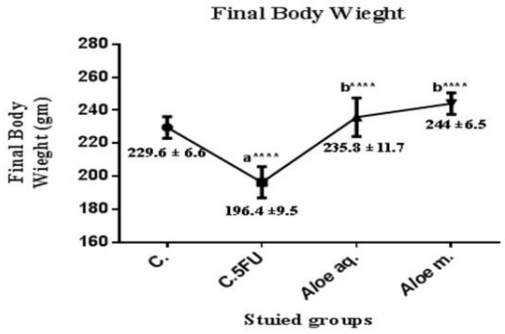
Individuals of the control group were active, responded very quickly to stimuli, and had a good appetite, whereas the animals of the chemotherapy group became less active, and gathered themselves at one corner of the cage, their appetite was greatly reduced. In addition, ulcerations around the eyes and mouth and loss of skin furring were also observed in this group. Furthermore, rats of groups III and IV (*A. perryi* extracts) showed the same observations as in the control group.

Bodyweight and organs weight

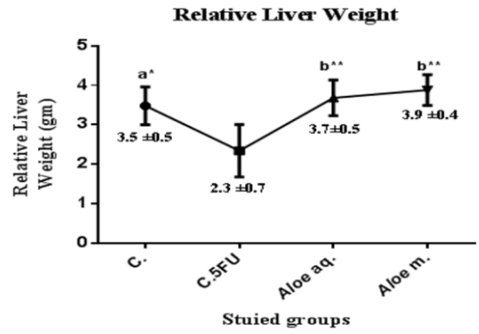
Bodyweight was measured twice a week at 1, 5, 10, 14 days post-treatment. Figure 1 illustrates that intraperitoneally treatment with cisplatin and 5-FU caused significant inhibition in the mean of weight ($p = 0.0001$) as compared to control group. Treatment with *Aloe* aqueous and methanolic extracts resulted in weight gain which was comparable and not significantly different from the control group, but significant when compared to cisplatin and 5-FU group ($p < 0.0001$). Furthermore, rats treated with methanolic extract have non-significantly higher body weight than rats in aqueous extract group.

Relative liver and kidney weight in cisplatin and 5-FU group was significantly lower when compared to the control group ($p = 0.01$). Liver and kidney relative weight in *Aloe* extract group was non-significantly higher than that of control group. Besides, organs weight in methanolic

extract group was non-significantly higher than that of aqueous group, but significantly when compared to cisplatin and 5-FU group (p = 0.001). The body weight and relative organs weight of all groups were shown in Figure (1).



(a)



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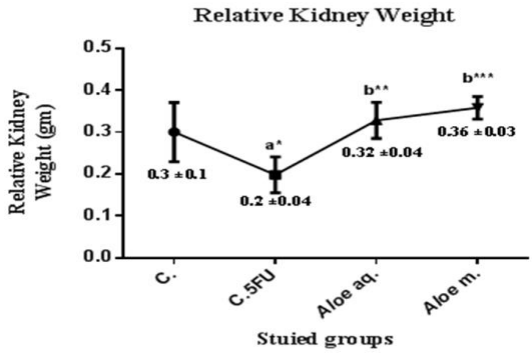


(c)

Fig. 1. Body weight (a), Relative Liver (b) and Kidney weight (c) of rats treated with D.W, (C.), C.5FU, *A. perryi* aqueous extract *and A. perryi* methanolic extract represented by mean ± SD (n = 5).

* P< 0.05; **: P< 0.01; ***: P< 0.001 & ****: P < 0.0001

Macroscopically

The liver in Group I (control) and Group III and IV *(A. perryi* extracts*)* appeared well lobulated without any lesion (Figure 2 A, E and F). Liver in cisplatin and 5-FU group shows color changes like yellow scattered potions (Figure 2B), blue-black parts on the upper surface (Figure 2C), white strips in the inner surface (Figure 2D). Kidney in control and *Aloe* extracts groups had well-formed, brown cortex and white medulla (Figure 3A), while kidney of cisplatin and 5-FU group showed some abnormalities like orang scattered parts in the cortex and pinkish medulla (Figure 3B), pale cortex and pink medulla (Figure 3C), brown soft cortex (Figure 3D). No gross pathological lesions were observed in Aloe liver (Figure 3E and F) and kidney (Figure 3E and F) treatment. It also showed no deformities in the color or texture when compared to control.

Liver section in the control group showed radiating cords of polygonal hepatocytes with rounded nuclei and eosinophilic cytoplasm. Hepatocytes cords are separated by hepatic sinusoids which are signed by Kupffer cells (Figure 4A). In contrast, cisplatin and 5-FU induced liver section showed some histopathological changes such as congested portal vein, enlarged bile duct (Figure 4B), congested, dilated blood vessel, inflammatory cells infiltration and pyknotic nuclei indicating apoptosis (Figure 4C), congested central vein and hemorrhage (Figure 4D), fibrosis (Figure 4E), vacuolation in the hepatocytes (Figure 4F), fatty changes in the hepatocytes (Figure 3G). However, groups treated with *Aloe* extracts (aqueous and methanolic) exhibited normal histological structures similar to that of the control (Figures 4H and 4I).

Histological examination of the kidney revealed that the control group kidney appeared with normal cortex (glomeruli, proximal and distal tubules) (Figure 5A). However, Cisplatin and 5-FU caused induced tubular vacuolation (Figure 5B), glomerular degeneration, congestion, (Figure 5C), dilatation in Bowman's space, congestion (Figure 5D), tubular necrosis (Figure 5E) and tubular shrinkage (Figure 5F). Instead, groups treated with *Aloe* extracts (aqueous and

methanolic) exhibited normal histological structures similar to that of the control (Figure 5G and 5H).

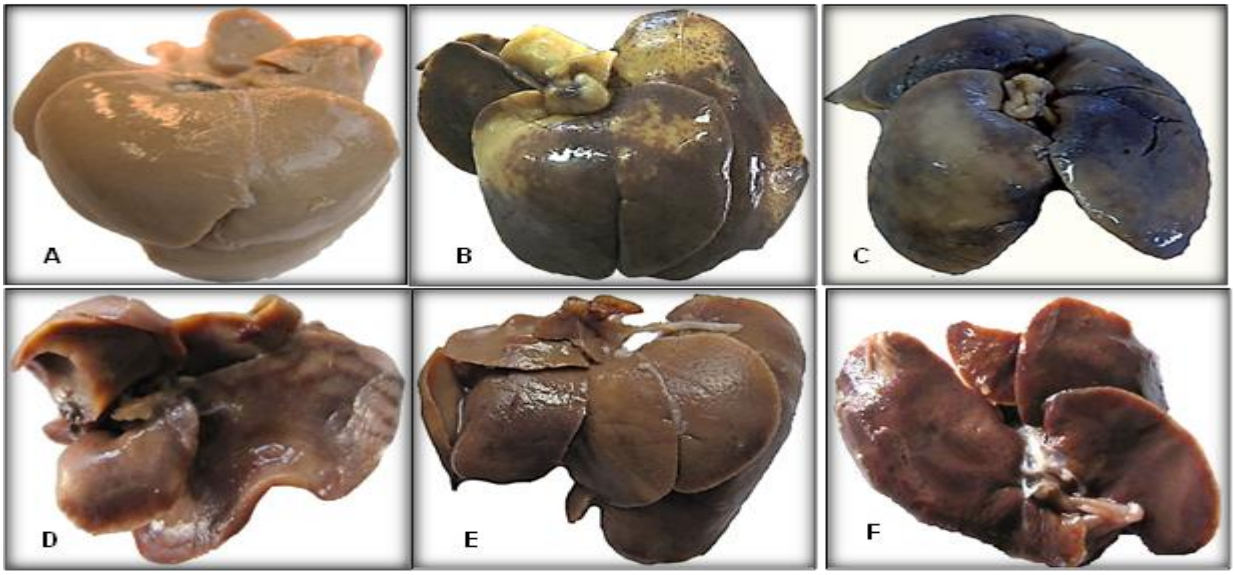


Fig. 2. Macroscopic changes in rat liver: - **A.** Group I (D.W-treated liver) shows normal structure; **B – D.** Group II (liver treated with cisplatin + 5 Fluorouracil shows yellow scattered parts (B), blue-black parts (C) and white strips (D)); **E.** Group III (Liver treated with *Aloe* aqueous extract (1000 mg/kg) shows normal structure; **F.** Group IV (*Aloe* methanolic extract (1000 mg/kg) shows normal structure).

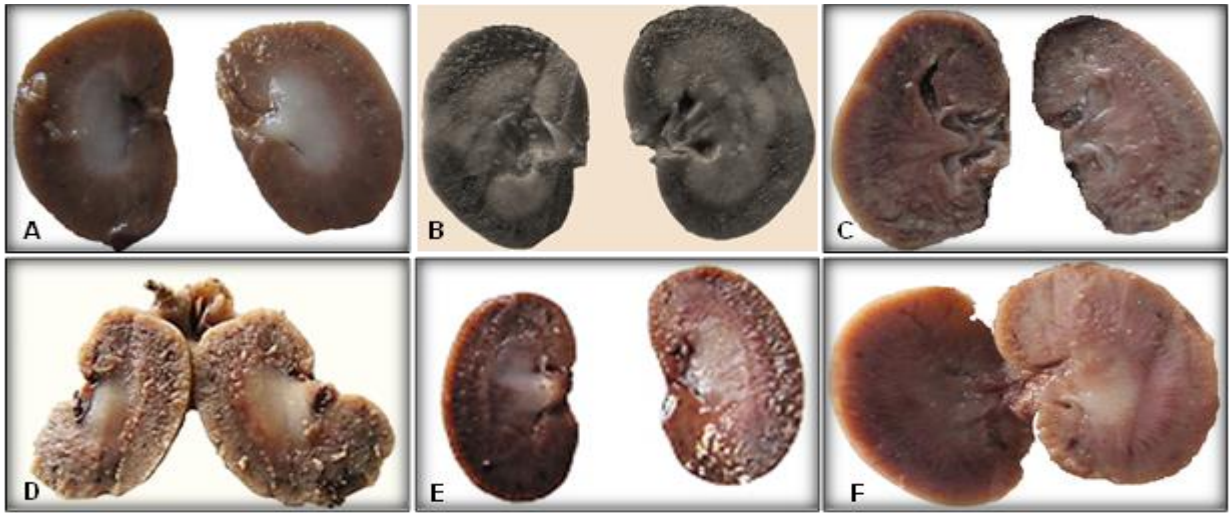


Fig.3. Macroscopic changes in rat kidney: **A. Group I** (D.W-treated kidney) shows normal cortex and medulla structure; **B-D Group II** (Kidney treated with cisplatin + 5 Fluorouracil) shows cortex orang scattered parts and pinkish medulla(B), pale cortex and pink medulla(C), brown soft cortex(D); **E. Group III** (Kidney treated with *Aloe* aqueous extract (1000 mg/kg)) shows normal cortex and medulla structure and **F. Group IV** (Kidney treated with *Aloe* methanolic extract (1000 mg/kg)) shows normal cortex and medulla structure.

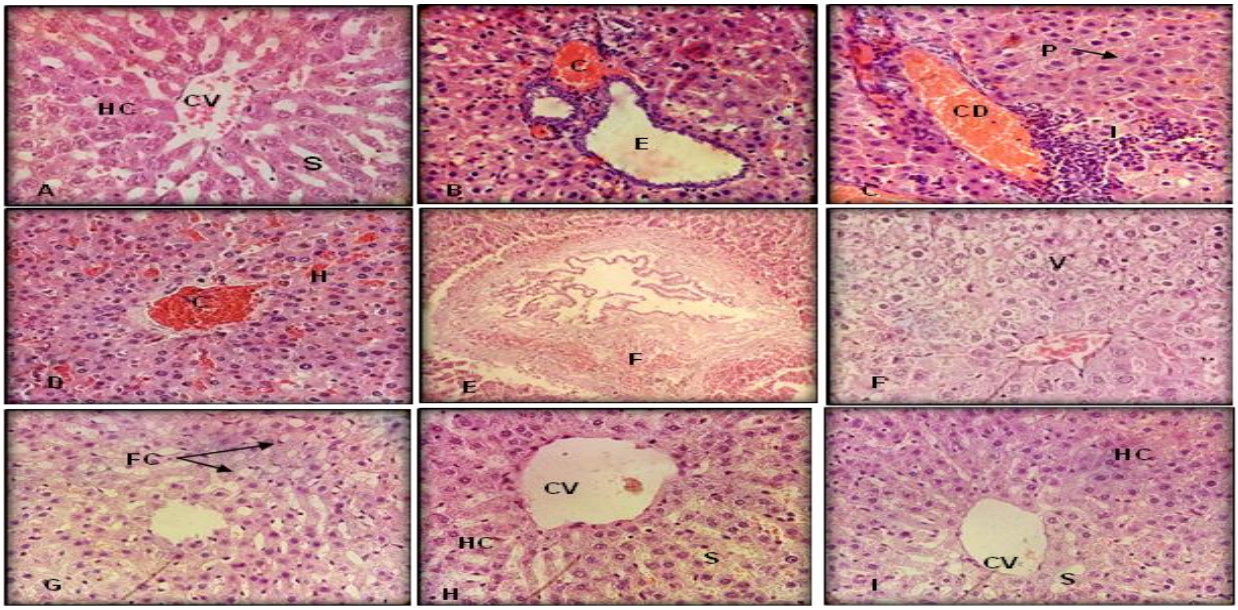


Fig. 4. Photomicrograph of rat liver sections: **A. Group** I: Liver section shows normal central vein (CV), hepatocytes (H) and sinusoids (S); **B- G Group II**: **B.** Liver section shows congested portal vein (C) and enlarge bile duct (E); **C**. Liver section shows congested, dilated blood vessel (C),pyknotic nuclei (P) and infiltration(I); **D**. Liver section shows congested central vein (C) and hemorrhage (H); **E.** Liver section shows fibrosis (F); **F.** Liver section shows vacuolation in the hepatocytes (V); **G.** Liver section shows fatty changes of the hepatocytes(FC); **H. Group III**: Liver section shows normal structure. **I**. **Group IV:** Liver section shows normal structure. (E& H X 400).

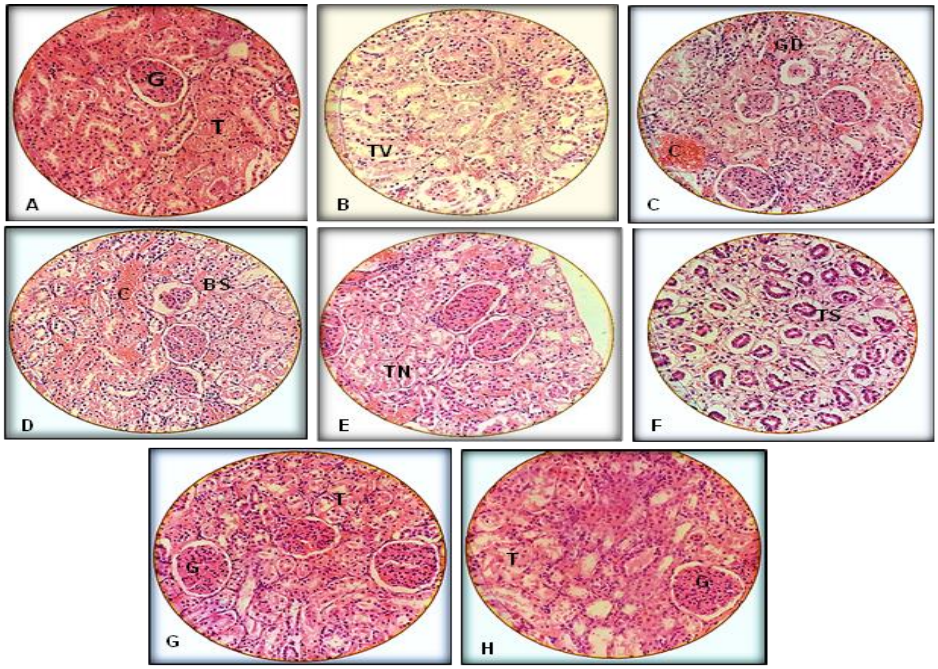
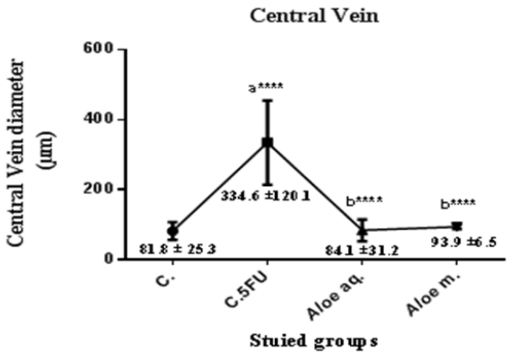


Fig.5. Photomicrograph of rat kidney sections: **A. Group I**: kidney section shows normal cortex, normal glomerulus (G) and normal tubules (T).**B-F**. **Group II**: **B.** kidney section shows tubular vacuolation (TV); **C.** kidney section shows congestion(C) and glomerular degeneration (GD); **D.** kidney section shows congestion(C) and dilatation in Bowman's space (BS). **E.** kidney section shows a Tubular necrosis (TN). **F.** kidney section shows a Tubular shrinkage (TS). **G. Group III:** Kidney section shows normal structure. **H. Group IV:** Kidney section shows normal structure (E &H X 400).

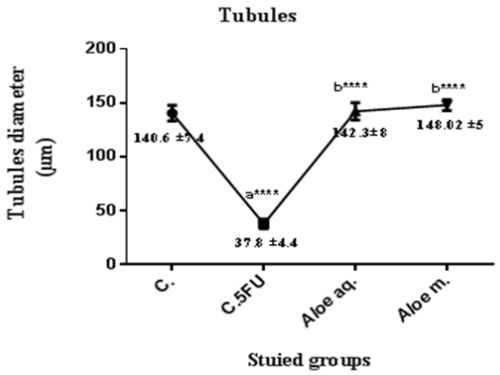
Micromorphometric measurements of the liver and kidney sections

Liver central vein and portal vein in cisplatin and 5-FU group showed significant increment in the diameter as compared to control group (p< 0.0001). *Aloe* aqueous and methanolic extracts failed to induce significant increments in the central vein and portal vein diameters.

On the other hand, glomerular space diameter in kidney treated with cisplatin and 5-FU was significantly increased as compared to control group (p= 0.0006). Medullary tubules in kidney treated with cisplatin and 5-FU showed a significant decrement in diameter as compared to the control group (p< 0.0001). Nevertheless, groups treated with *Aloe* extracts (aqueous and methanolic extracts) didn't show any significant changes in the glomerular space and tubular diameter as compared with the control group. Figure (6) showed the Micromorphometric measurements of the Central vein and Portal vein (liver sections), Tubules, and Glomerulus (kidney sections) in all groups.



(a)



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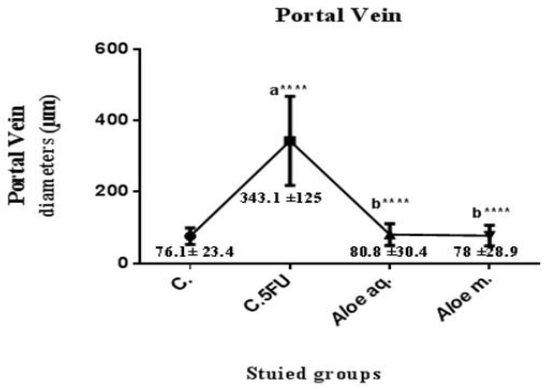

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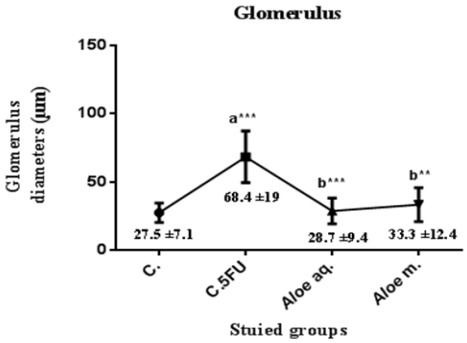

(d)

Fig. 6. Central Vein diameter (a), Tubules diameter (b), Portal Vein diameter (c) and Glomerulus (d) diameter in rats treated with D.W (C.), C.SFU, *A. perryi* aqueous extract and *A. perryi* methanolic extract represented by mean ± SD (*n* = 5)

*** P< 0.05; **: P< 0.01; ***: P< 0.001; ****: P < 0.0001.**

DISCUSSION

The present study revealed that intraperitoneally injection with cisplatin and 5-FU resulted in many symptoms such as less activation, ulcerations around eyes and mouth, loss of skin furring and reduction of appetite. This result is in accordance with that of Al-Hamdany and Al-Hubaity (2014) and Abdelmeguid et al. (2010). The intraperitoneal method allows a high amount of cisplatin and 5-FU to inter the peritoneal cavity without increasing the systemic toxicity (Liu *et al*., 2012). *Aloe* extracts did not cause any behavioral changes in rats, indicates that the plant is not harmful at the level tested. This supports the reason why the plant is used widely as a therapeutic remedy (Viljoen, 2008).

In this study, rats treated with 1.5 mg/kg of cisplatin and 20 mg/kg 5-FU for 14 days showed a significant decrease in body weight as compared to control. This result is in agreement with that of Abdelmeguid et al. (2010) and King and Perry (2001). The loss of the body weight could be due to loss of skeletal muscles and adipose tissue (Devlin, 1997) or correlated with the decreased food intake as a result of the mucositis and ulceration of the mouth that cause difficulty in eating and drinking (Taguchia and Razzaque, 2005; Stringer *et al.*, 2007; Cheah *et al.*, 2014).

This study also recorded a significant reduction in the relative liver and kidney weights in cisplatin and 5-FU group compared with the control group. This result agrees with earlier studies (Arhoghro *et al*., 2012; Abdel Moneim *et al*., 2014), who recorded the decrement of relative liver and kidney weight induced by cisplatin and disagree with the findings of Gelen et al. (2018), who reported an increment in the relative weight of liver and kidney treated with cisplatin and 5-FU. Measurement of liver and kidney relative weight is a more accurate approach to determine the changes in liver and kidney size compared to the measurement of liver and kidney weight alone as the liver and kidney weight depends on the size of the rat. The reduction of the organs weight in chemotherapy-treated rats caused hepatic and renal lesions.

Rats treated with *A. perryi* extracts showed non-significant increase in body weight and organs relative weight as compared to the control group. This result agrees with the result of Venu (2007) who recorded an increment in the body weight of individuals treated with *Aloe* extract and referred the gain of body weight to the nutritive compounds in *Aloe*. In Contrast, this result disagrees with the findings of Mwale and Masika (2012) who recorded a decrement in the relative weight of liver and kidney treated with *Aloe* extract and referred the decrement to the plant deleterious effects on the organs.

Macroscopic observations of the liver and kidney in all groups revealed color changes in liver and kidney induced by cisplatin and 5-FU. This agrees with that of Bano and Najam (2019) who found some of these changes in the 5-FU treated liver.

The present investigation showed many histopathological abnormalities in the liver of cisplatin and 5-FU compared to control group. These include haemorrhage, inflammatory cells infiltration, central vein and portal vein congestion, fatty changes, vacuolation, fibrosis and pyknotic nuclei indicating apoptosis. This result agrees with that of the previous studies (El-Sayyad *et al.,* 2009; Ahmed and Ghobara, 2013; Al-Hamdany and Al-Hubaity, 2014; Afolabi *et al*., 2016) who reported nearly the same changes. 5-FU was found to produce liver toxicity associated with some abnormalities (Zorzi *et al*., 2007). The pathophysiological mechanisms underlying this toxicity is yet to be elucidated but increased oxidative stress, apoptosis and inflammation have all been associated with 5-FU toxicity (Summya *et al*., 2014; Kumar *et al*., 2003) explained the dilatation and congestion of the central vein, portal vein and sinusoids as a result of inflammatory reaction by histamine and prostaglandin secreted from mast cells and some other inflammatory cells and cause vasodilatation and local increase of blood flow associated with engorgement of capillary bed which become more permeable to the fluid rich in proteins thereby increasing blood viscosity and red blood cells aggregate forming congestion and clotting. Cetin et al. (2011)

explained the fatty changes that noticed in the liver induced by 5-FU as a form of cytoplasmic lipid droplets seen as clear ring-like cells which peripheral nuclei resulted from alteration in the fat metabolism leading to lipid accumulation in the hepatocytes particularly affecting the hepatocytes in the centrilobular and midzonal region which are less resistant to injury since they receive less enriched blood with nutrients and oxygen than those in the periportal area. The Liver is known to accumulate significant amounts of cisplatin, second only to the kidney (Stewart *et al*., 1982), thus hepatotoxicity can be associated with cisplatin treatment (Liao *et al*., 2008). Clinical evidence of cisplatin-induced liver injury has been demonstrated by elevated activities of serum enzymes and bilirubin levels, and the development of jaundice (Moriya *et al*., 2000). Kishimoto et al. (2000) explained the apoptosis noticed in the cisplatin-induced liver as the mechanism of cisplatin action in killing cells by forming DNA adducts, causing G2 arrest in the cell cycle, triggering apoptosis.

In this study, kidneys treated with cisplatin and 5-FU showed histopathological changes such as tubular vacuolation, congestion, glomerular shrinkage, dilatation in Bowman's space, tubular necrosis and tubular shrinkage. These findings are analogous to that of Ezz-Din et al. (2011). It has been reported that cisplatin is catabolized primarily in the liver, as dihydrouracil, and the reduced compound is then cleaved to α-fluoro-β-alanine, ammonia, urea, and carbon dioxide. Both the toxicity and antitumor effect are potentiated if the catabolism is blocked by inhibiting dihydrouracil dehydrogenase. King and Perry (2001) and Gao et al. (2006) explained the nephrotoxicity to the increment of malondialdehyde and decrement of glutathione concentrations in the renal tissues treated with 5-FU. Glutathione (GSH) was reported to protect the cells from cytotoxic damage induced by many compounds and it is generally known as a potent factor in the control of lipid peroxidation (Mansour *et al.,* 1999). Aggressive hydration with saline (two liters of 5% dextrose in 0.5 *N* saline) has been used to reduce cisplatin-induced nephrotoxicity (Taguchia and Razzaque, 2005).

On the other hand, rats treated with *A. perryi* aqueous and methanolic extracts at a high dose (1000mg/kg) didn't show any histological changes in the liver and kidney tissues. This result agrees with that of Ali et al. (2019) who reported no gross and histological changes in the liver and kidney treated with *A. vera* extract and they stated that the LD_{50} values for *A. vera* was found to be >5000 mg/kg for oral administration.

Micromorphometric measurement in liver and kidney in this study recorded significant increment in the central and portal veins diameter in cisplatin and 5-FU, induced liver indicating the high dilation of blood vessels. Cisplatin and 5-FU also induced a significant increment of bowman space diameter and a significant increment in tubular diameter. *A. perryi* extracts didn't show any significant changes in the liver and kidney diameters compared to the control group.

On the whole, cisplatin and 5-FU caused significant liver and kidney pathological changes, while *A. perryi,* gel extracts didn't cause significant pathological changes in the selected parameters. Further investigations are needed to put up with a prepared chemo-herbotherapy regimen to treat cancer and protect from the side effects.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article

REFERENCES

Abdelmeguid, N.E., Chmaisse, H.N., Abou Zeinab, N.S., 2010. Silymarin Ameliorates Cisplatin – Induced Hepatotoxicity in Rats:Histopathological and Ultrastructural studies. Pak. J. Biol. Sci., 13(10): 463-479.

Abdel Moneim, A.E., Othman, M.S., Aref, A.M., 2014. *Azadirachta indica* attenuates cisplatin-induced nephrotoxicity and oxidative stress. Biomed. Res. Int., 11 pages.

Afolabi, O.K., Adeleke, Ugbaja, G.E.R.N., 2016. Crocin Alleviates 5-Fluorouracil-induced Hepatotoxicity through the abrogation of Oxidative Stress in Male Wistar rats. Asian Pac. J. Health Sci., 3(2):58-68.

Ahmed, H.A., Ghobara, M., 2013. Histological Study of the Effect of Cisplatin on the Liver of Adult Male Albino Rat. Int. J. Acad. Res., 1(1): 22-33.

Ajani, J.A., 2008. Optimizing docetaxel chemotherapy in patients with cancer of the gastric and gastroesophageal junction: evolution of the docetaxel, cisplatin, and 5-fluorouracil regimen. Cancer., 113: 945-955.

Aldayel, T.S., Alshammari, G.M., Omar, U.M., Grace, M.H., Ann, L., Yahya, M.A., 2020. Hypoglycaemic, insulin releasing, and hepatoprotective effect of the aqueous extract of *Aloe perryi* Baker resin (Socotran Aloe) in streptozotocin-induced diabetic rats. J. Taibah Univ. Sci., 14(1): 1671–1685.

Al-Hamdany, M.Z., Al-Hubaity, A.Y., 2014 . The histological and histochemical changes of the rat's liver induced by 5-fluorouracil. Iraqi J. Vet. Sci., 28(2): 95-103.

Ali, M.D., Naseer, M.A., Mirza, M.A., Alam, M.D.S., 2019. Hematological, biochemical, and histopathological study of the plant extract of *Terminalia chebula* Reitz., Aloe vera Linn., and *Tamarindus indica* Linn. on animal model: A comparative study. Natl. J. Physiol. Pharm. Pharmacol., 9(3): 268-275.

Ali, H.M., Bhatti, S., Iqbal, M.N., Ali, S., Ahmad, A., Irfan, M., Muhammad, A., 2015. Mutational analysis of MDM2 gene in hepatocellular carcinoma. Sci. Lett., 3(1): 33-36.

Al-Khulidi A., 2013. Flora of Yemen. the sustainable natural resource management project (SNRMP II). EPA and UNDP Republic of Yemen.

Alvarez-Cabellos, R., Garcia-Carbonero, R., Garcia-Lacalle, C., Gomez, P., Tercero, A., Sanchez, D., Paz-Ares, L., 2007. Fluorouracil-based chemotherapy in patients with gastrointestinal malignancies: influence of nutritional folate status on toxicity. J. Chemother., 19: 744-749.

Amjad, S., Saleem, M., Ashraf, A., Iqbal, M.N., 2020a. Prevalence of Cancer Types in Patients attending Mayo Hospital Lahore, Pakistan. Int. J. Mol. Microbiol., 3(2): 25-34.

Amjad, S., Saleem, M., Ashraf, A., Iqbal, M.N., 2020b. Mortality Rate of Cancer in Patients attending Mayo Hospital Lahore, Pakistan. PSM Microbiol., 5(3): 72-78.

Ashraf, A., Xiong, X., Iqbal, M.N., Lin, Y., 2018. BRCA Mutations and Survival Outcome in Young-onset Breast Cancer. Int. J. Molec. Microbiol., 1(2): 56–57.

Arany, I., Safrstein, R.L., 2003. Cisplatin nephrotoxicity. Semin Nephrol., 23: 460–464.

Arhoghro, E.M., Ikeh., C., Uwakwe, A.A., Ekpo, K.E., Anosike, E.O., 2012. Curative potential of aqueous extract of scent leaf (*Ocimum gratissmum*) on cisplatin induced hepatotoxicity in albino wistar. rats. J. Pharm. Innov., 1(4): 1-8.

Bancroft, J.D., Cook, H.C., Stirling, R.W., 1994 . Manual of histological techniques and their diagnostic application Edinburgh; New York, Churchill Livingstone; pp:457-458.

Bano, N., Najam, R., 2019. Histopathological and biochemical assessment of liver damage in albino Wistar rats treated with cytotoxic platinum compounds in

combination with 5-fluorouracil. Arch. Med. Sci., 15(4): 1092–1103.

Bhaya, S., Saini, M.R., 2008. Antioxidative effect of Aloe vera leaf extract against radiation- induced oxidative stress. Pharmacol. Onl., 2: 671-682.

Bisi-Johnson, M.A., Chikwelu, L., Obi, C.L., Hattori, T., Oshima, Y., Shenwei, L.S., Kambizi, L., Jacobus, N., Eloff, J.N., Vasaikar, S.D., 2011. Evaluation of the antibacterial and anticancer activities of some South African medicinal plants. BMC Complement Altern. Med., pp: 11-14.

Cetin, A., Arslanbas, U., Saraymen, B., Canoz, O., Ozturk, A., 2011. Effects of grape seed extract and Origanum onites essential oil on cisplatin-induced hepatotoxicity in rats. Int. J. Hematol. Oncol., 21(3): 133-139.

Cheah, K., Howarth, G., Bastian, S., 2014. Grape seed extract dose-responsively decreases disease severity in a rat model of mucositis; concomitantly enhancing chemotherapeutic effectiveness in colon cancer cells. PLoS One., 9(1): e85184.

Chiu, T.H., Lai, W.W., Hsia ,T.C., Yang, J.S., Lai, T.Y., Wu, P.P., Chung, J.G., 2009 . Aloe-emodin induces cell death through S-phase arrest and caspase-dependent pathways in human tongue squamous cancer SCC-4 cells. Anticancer Res., 29: 4503–4512.

Dank, M., Zaluski, J., Barone, C., Valvere, V., Yalcin, S., Peschel, C., Wenczl, M., Goker, E., Cisar, L., Wang, K., Bugat, R., 2008. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann. Oncol., 19: 1450-1457.

Devlin, T.M., 1997. Text book of biochemistry: with clinical correlation,4th ed. New York: John Wiley and Sons Inc., 553.

Din, M., Hafeez, M., Iqbal, M.N., Ashraf, A., Alam, S., Masood, S., 2016. Parameters of Radiotherapy Techniques in Early Breast Cancer. PSM Microbiol., 01(2): 66-71.

Egbuna, C., Gupta, E., Ezzat, S.M., Jeevanandam, J., Mishra, N., Akram, M., Sudharani, N., Adetunji, C.O., Singh, P., Ifemeje, J.C., Deepak, M., Bhavana, A., Walag, A.M.P., Ansari, R., Adetunji, J.B., Laila, U., Olisah, M.C., Onyekere, P.F., 2020. Aloe species as valuable sources of functional bioactives, https://www.researchgate.net/publication/342347189. 337- 387.

El-Sayyad, H.I.,, Ismail, M.F., Shalaby, F.M., Abou-El-Magd, R.F., Gaur, R.L., Fernando, A., Raj, M.H.G., Ouhtit, A., 2009. Histopathological effects of cisplatin, doxorubicin and 5-flurouracil (5-FU) on the liver of male albino rats. Int. J. Biol. Sci., 5(5): 466-473.

Ezz-Din, D., Gabry, M.S., Farrag, A.R.H., Abdel Moneim, A.E., 2011. Physiological and histological impact of Azadirachta indica (neem) leaves extract in a rat model of cisplatin-induced hepato and nephrotoxicity. J. Med. Plants Res., 5(23): 5499-5506.

Ezz-ELdin, D.I., Soliman Gabry, M.S.I., Farrag, A.R.H., Abdel Moniem, A.E., 2013. The Protective role of neem leaves extract on cisplatin-induced polysaccharides and protein depletion in rat liver and kidney. Pak. J. Zool., 45(6): 1687-1698.

Gao, L., Ma, R., Zhou, J., Cheng, S., 2006. Changes of serum erythropoietin during Cisplatin- or 5-Fluorouracil-induced anemia in rats. Toxicol. Mech. Methods., 16(9): 501-506.

Gelen, V., Şengül, E., Yıldırım, S., Atila, G., 2018. The protective effects of naringin against 5-fluorouracil- induced hepatotoxicity and nephrotoxicity in rats. Iran J. Basic Med. Sci., 21(4): 404-410.

Hamman, J.H., 2008. Composition and applications of *Aloe vera* leaf gel. Molec., 3: 1599-616.

Iqbal, M.N., 2020. Hereditary Cancer Syndrome: Does Inherited Genetic Mutations Contribute to the Development of Cancer? Int. J. Mol. Microbiol., 3(2).

Iqbal, M.N., 2021. Breast Cancer Awareness: Current Trends and Future Approaches to Breast Cancer Management. PSM Biol. Res., 6(4): 133-135.

Iqbal, M.N., 2021. Blood Cancer Awareness: Current and Future Approaches to Lymphoma Management. PSM Microbiol., 6(3).

Iqbal, M.N, Ashraf, A., 2018. Recombinant Protein Production in Plants: Biofactories for Therapeutics. Int. J. Mol. Microbiol., 1(1): 38-39.

Iqbal, M.N., Ashraf, A., 2020. The Most Common Cancers in Pakistan: Stage at Diagnosis is a Key Indicator of Cancer Survival. Int. J. Mol. Microbiol., 3(2).

Iqbal, M.N., Ashraf, A., Ali, M.A., 2021. Epstein Barr Virus Infection as a Potential Risk Factor for Cancer. PSM Microbiol., 6(2): 60-62.

Irfan, M., Sughra, K., Iqbal, M.N., Mehmood, S., Shaheen, A., Anwar, Z., 2016. Arresting Cancer Progression by VEGF Inhibitions: An Update. PSM Microbiol., 01(2): 72-78.

Isaka, Y., Rakugi, H., 2009. Severe adverse effects of 5-fluorouracil in S-1 were lessened by haemodialysis due to elimination of the drug. NDT Plus Adv. Acc., 18(2): 152-154.

Kim, S.H., Hong, K.O., Chung, W., Hwang, J.K., Park, K., 2004 .Abrogation of cisplatin-induced hepatotoxicity in mice by xanthorrhizol is related to its effect on the regulation of gene transcription. Toxicol. Appl. Pharmacol., 196: 346-355.

King, P.D., Perry, M.C., 2001. Hepatotoxicity of chemotherapy. Oncologist., 6(2):162-76.

Kishimoto, S., Miyazawa, K., Terakawa, Y., Ashikari, H., Ohtani, A., Fukushima, S., Takeuchi, Y., 2000. Cytotoxicity of cis-[((1R,2R)-1,2-cyclohexanediamine-N,N') bis(myristato)]-platinum (II) suspended in Lipiodol in a newly established cisplatin-resistant rat hepatoma cell line. Jpn. J. Cancer Res., 91: 1326-1332.

Kumar, V., Cotran, R., Robbins, L., 2003. Basic Pathology. 7th ed. USA: Churchill Livingsone. 102 p.

Kuo, P.L., Lin, T.C., Lin, C.C., 2002. The antiproliferative activity of aloe-emodin is through p53-dependent and p21-dependent apoptotic pathway in human hepatoma cell lines. Life Sci., 71: 1879–1892.

Liao, Y., Lu, X., Lu, C., Li, G., Jin, Y.,Tang, H. 2008. Selection of agents for prevention of cisplatin-induced hepatotoxicity. Pharmacol. Res., 57: 125–131.

Lin, C.C., Hsu, C.H., Huang, C.Y., Cheng, A.L., Chen, J., Vogelzang, N.J., Pu, Y.S., 2006a. Weekly cisplatin plus infusional high-dose 5-fluorouracil and leucovorin (P-HDFL) for metastatic urothelial carcinoma: an effective regimen with low toxicity. Cancer, 106: 1269-1275.

Lin, J.G., Chen, G.W., Li, T.M., Chouh, S.T., Tan, T.W., Chung, J.G., 2006b. Aloe-emodin induces apoptosis in T24 human bladder cancer cells through the p53 dependent apoptotic pathway. J. Urol., 175(1): 343-347.

Liu, S., Fang, H., Quhu, X., Deng, X., Long, M., Xie, C., 2012. Adjuvant combined systemic chemotherapy and intraperitoneal chemotherapy for locally advanced gastric cancer. Oncol. Lett., 4(6): 1309-1314.

Mansour, M.A., El-Kashef, H.A., Al-Shabanah, O.A., 1999. Effect of captopril on doxorubicininduced nephrotoxicity in normal rats. Pharmacol. Res., 39(3): 233-237.

Minami, M., Matsumoto, S., Horiuchi, H., 2010 . Cardiovascular side-effects of modern cancer therapy. Circ. J., 74(9): 1779-1786.

Moriya, A., Hyodo, I., Nishina, T., Imaoka, H., Imagawa, A., Doi, T., Endo, H., Tanimizu, M., Tajiri, H., 2000. Extensive liver metastasis of gastric cancer effectively treated by hepatic arterial infusion of 5-fluorouracil/cisplatin. Gastric Cancer., 3: 110-115.

Mothana, R.A., Al-Musayeib, N.M., Matheeussen, A., Cos, P., Maes, L.,

2012. Assessment of the in vitro antiprotozoal and cytotoxic potential of 20 selected medicinal plants from the island of Socotra. Molec., 17: 14349-14360.

Mwale, M., Masika, P.J., 2012. Toxicological studies on the leaf extract of Aloe ferox Mill. (Aloaceae). J. Sci. Res. Essay., 7(15): 1605-1613.

National Academies Press., 1996. Guide for the Care and Use of Laboratory Animals Washington, D.C., Available from:http://www.nap.edu/ catalog/ 6492.html

Pal, S., Sengupta Sadhu, A., Patra, S., Mukherjea, K.K., 2008. Histological vis - a - vis biochemical assessment on the toxic level and antineoplastic efficacy of a synthetic drug Pt - ATP on experimental animal models. J. Exp. Clin. Cancer Res., 27: 68.

Pabla, N., Dong, Z., 2008. Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. Kidney Int., 73: 994–1007.

Park, H.R., Ju, E.J., Jo, S.K., Kim, S.H., Yee, S.T., 2009. Enhanced antitumor efficacy of cisplatin in combination with hemo HIM in tumour- bearing mice. BMC Cancer, 9: 85- 85.

Pecere, T., Gazzola, M.V., Mucignat, C., Parolin, C., Vecchia, F.D., Cavaggioni, A., Palu, G., 2000. Aloe-emodin is a new type of anticancer agent with selective activity against neuroectodermal tumors. Cancer Res., 60:2800–2804.

Qin, H.B., Zhu, M., Du, T.K., She, Q.Y., Yang, J.A., Zhu, X.L., Zhang, J.W., 2010. Effects of aloe-emodin on proliferation and migration of human gastric cancer cell line BGC-823. Acta Anatom. Sinica., 41: 909–911.

Rabik, C.A., Dolan, M.E., 2007. Molecular mechanisms of resistance and toxicity associated with platinating agents. Cancer Treat. Rev., 33: 9-23.

Ray, S., Roy, K., Sengupta, C., 2007 . In vitro evaluation of protective effects of ascorbic acid and water extract of *Spirulina plantesis* (blue green algae) on 5-fluorouracil-induced lipid peroxidation. Acta Pol. Pharm., 64: 335-344.

Reynolds, T., Dweck, A.C., 1999 . Aloe vera leaf gel: a review update. J. Ethnopharmacol., 68: 3-37.

Saif, M.W., Black, G., Roy, S., Bell, D., Russo, S., 2007. Phase II study of Capecitabine with concomitant radiotherapy for patients with locally advanced pancreatic cancer: up-regulation of thymidine phosphorylase. Cancer J., 13(4): 247-256.

Sakurai, Y., Uraguchi, T., Imazu, H., Hasegawa, S., Matsubara, T., Ochiai, M., Funabiki, T., 2004. Changes in thymidlate synthase and its inhibition rate and changes in dihydropyrimidine dehydrogenase after the administration of 5- flurouracil with cisplatin to nude mice with gastric cancer xenograft SC-1-NU. Int. Jap. Gastric Cancer Asso., 7: 110-116.

Saritha, V., Anilakumar, K.R., Farhath, K.F., 2010. Antioxidant and antibacterial activity of Aloe vera gel extracts. Int. J. Pharm. Biol. Arch., 1: 376-384.

Shoemaker, L., Arora, U., Lima, C., 2004. 5-Fluorouracil-induced coronary vasospasm. Cancer Contr., 1(1): 46-49.

Stewart, D.J., Benjamin, R.S., Luna, M., 1982. Human tissue distribution of platinum after cis-diamminedichloroplatinum. Cancer Chemother. Pharmacol., 10: 51-54.

Stringer, A.M., Gibson, R.J., Bowen, J.M., Logan, R.M., Yeoh, A.S., Keefe, D.M., 2007. Chemotherapy-induced mucositis: the role of gastrointestinal microflora and mucins in the luminal environment. J. Support Oncol., 5: 259-67.

Summya, R., Nemat, A., Sana, N., Syed, K.H., Sarwat, S., 2014. Mitigation of 5-Fluorouracil induced renal toxicity by chrysin via targeting oxidative stress and apoptosis in wistar rats. Food Chem. Toxicol., 66: 185–193.

Taguchia, T., Razzaquea, M.S., 2005. Cisplatin-Associated Nephrotoxicity and Pathological Events. Contrib. Nephrol., 148: 106–120.

Tateishi, T., Watanabe, M., Nakura, H., 1999 . Dihydropyrimidine dehydrogenase activity and fluorouracil pharmacokinetics with liver damage induced by bile duct ligation in rats. Drug Metab. Dispos., 27: 651–654.

Ven, U.B., 2007. Blog Archive. RAMESH. Aloe ferox. Available at: http://777xtrade.blogspot

Viljoen, A., 2008 . Indigenous South African Medicinal Plants Part 7: Aloe ferox (Cape aloes). S.A. Pharm. J., 1: 47.

WHO, 2017. Monitoring health for the SDGs, Sustainable Development Goals. Geneva.

Yao, X., Panichpisal, K., Kurtzman, N., Nugent, K., 2007. “Cisplatin nephrotoxicity: a review,” Am. J. Med. Sci. Am. J. Med. Sci., 334(2): 115–124.

Yeo, W., Mok, T.S., Zee, B., Leung, T.W., Lai, P.B., Lau, W.Y., Koh, J., Mo, F.K., Yu, S.C., Chan, A.T., Hui, P., Ma, B., Lam, K.C., Ho, W.M., Wong, H.T., Tang, A., Johnson, P.J., 2005. A randomized phase III study of doxorubicin versus cisplatin/ interferon alpha-2b/doxorubicin/ fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. J. Natl. Cancer Inst., 97: 1532-1538.

Yuan, J.N., Chao, Y., Lee, W.P., Li ,C.P., Lee, R.C., Chang, F.Y., Yen, S.H., Lee, S.D., Whang-Peng, J., 2008. Chemotherapy with etoposide, doxorubicin, cisplatin, 5-fluorouracil, and leucovorin for patients with advanced hepatocellular carcinoma. Med. Oncol., 25: 201-206.

Zaynab, M., Fatima, M., Abbas, S., Sharif, Y., Jamil, K., Ashraf, A., Aslam, M.M., Shabbir, A., Batool, W., 2018. Proteomics Approach Reveals Importance of Herbal Plants in Curing Diseases. Int. J. Mol. Microbiol., 1(1): 23-28.

Zorzi, D., Laurent, A., Pawlik, T.M., Lauwers, G.Y., Vauthey, J-N., Abdalla, E.K., 2007. Chemotherapy- associated hepatotoxicity and surgery for colorectal liver metastases. Br. J. Surg., 94(3): 274-86.