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# The protective effect of sildenafil on liver sinusoidal obstructive syndrome after oxaliplatin-based chemotherapy: An experimental animal study

## Sildenafil'in oksaliplatin esaslı kemoterapi sonrası karaciğerde gelişen sinüsoidal obstruktif sendrom üzerine koruyucu etkisi: Deneysel bir hayvan çalışması

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**Abstract**

Aim: Sinusoidal obstructive syndrome (SOS) that develops due to oxaliplatin-based chemotherapy influences morbidity and mortality following surgical treatment of colorectal liver metastases. The aim of this study was to evaluate the protective effect of sildenafil on liver damage (sinusoidal obstructive syndrome (SOS)) that develops due to oxaliplatin-based chemotherapy.

Methods: An experimental animal study was conducted and a total of 42 rats were randomly separated into 4 groups as Sham, intraperitoneal chemotherapy (ipCT), ipCT+low-dose sildenafil treatment, and ipCT +high-dose sildenafil treatment. The ipCT was applied once a week for 5 weeks. Histochemical analysis was made in the livers removed from rats.

Results: Parenchymal, stromal, and vascular changes were examined, and no statistically significant difference was determined between the groups with respect to the severity of sinusoidal dilatation ($P$=0.243). The groups significantly differed with regards to centrilobular, peliotic changes and hepatocellular changes ($P$<0.001).

Conclusion: Sildenafil has a protective effect against liver damage that develops due to oxaliplatin-based chemotherapy and prevents the development of SOS during chemotherapy in colorectal cancer patients. Therefore, it could be considered as a treatment strategy.

**Keywords:** Oxaliplatin, Sinusoidal obstructive syndrome, Sildenafil, Colorectal cancer, Liver metastasis

**Öz**

Amaç: Oksaliplatin bazlı kemoterapinin karaciğer metastazlı kolon kanserli hastalarda kullanımı karaciğer hasarına (sinüsoidal obstruktif sendrom (SOS)) neden olarak; metastaz rezeksiyonu sonrasında mortalite ve morbiditeyi arttırır. Bu çalışmamızda; sildenafilin kolorektal kanserlerin karaciğer metastazları için oksaliplatin bazlı kemoterapi sonucunda gelişen karaciğer hasarı, (SOS) üzerindeki koruyucu etkisini değerlendirmeyi amaçladık.

Yöntemler: Deneysel bir hayvan çalışması yürütüldü ve toplam 42 rat rastgele Sham, intraperitoneal kemoterapi (ipCT), ipCT + düşük doz sildenafil tedavisi ve ipCT +yüksek doz sildenafil tedavi grupları olarak 4 gruba ayrıldı. İpCT, 5 haftalık bir süre boyunca haftada birkez uygulandı. Ratlardan çıkarılan karaciğerlerde histopatolojik analiz yapıldı.

Bulgular: Parankimal, stromal ve vasküler değişiklikler incelendi ve sinüzoidal dilatasyonun şiddeti açısından gruplar arasında istatistiksel olarak anlamlı bir fark bulunmadı ($P$=0,243). Dört grup arasında sentrolobüler değişiklikler açısından istatistiksel olarak anlamlı fark saptandı ($P$<0,001). Peliotik ve hepatosellüler değişikliklerin değerlendirilmesinde gruplar arasındaki fark istatistiksel olarak anlamlı bulundu ($P$<0,001).

Sonuç: Sildenafil, kolorektal kanser hastalarında kemoterapi sırasında oksaliplatin bazlı kemoterapinin bir sonucu olarak gelişen SOS gelişimini önleyerek karaciğer hasarına karşı koruyucu bir etkiye sahip olması nedeniyle, kemoterapi esnasında tedaviye eklenmelidir.

**Anahtar kelimeler:** Oxaliplatin, Sinüsoidal obstrüktif sendrom, Sildenafil, Kolorektal kanser, Karaciğer metastaz

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## Introduction

Colorectal cancer remains one of the most frequent cancers throughout the world and it is related with high mortality rates. An important prognostic factor is the presence of metastases. The liver is the most common site of metastasis. It develops in approximately 50% of colorectal cancer patients and 25% have liver metastases at diagnosis [1]. The best treatment method in patients with metastasis in the liver only is liver resection, which aims to remove all metastatic lesions [2]. Unfortunately, surgery is not appropriate for many patients due to a combination of factors such as size, localization, and the number of liver metastases. Neoadjuvant chemotherapy is currently applied to these patients who are initially considered inoperable to shrink the metastases, so the patient becomes eligible for surgery [3]. Chemotherapy regimens which are widely used for this purpose consist of a combination of thymidylate synthase inhibitors (5-FU/folinic acid or capecitabine), oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). In the recent years, bevacizumab or cetuximab antibody treatments have been added to these regimens [4]. However, all these options are associated with chemotherapy-related liver damage (CTRLD), regarding which 3 forms have been defined: Steatosis, steatohepatitis, and sinusoidal obstructive syndrome (SOS) [5,6]. In the development of regimen-specific liver damage, the use of oxaliplatin was found to associate with SOS and nodular regenerative hyperplasia, and the use of irinotecan, with steatohepatitis [7-9].

The aim of this study was to evaluate the protective effect of sildenafil citrate against chemotherapy-related liver damage and determine the inflammatory response in tissue healing and micro-circulatory hemodynamics.

## Materials and methods

### Study design

A total of 42 male Wistar Albino rats, each weighing 200-250 gr were used in the study. The animals were obtained from the Experimental Animal Breeding and Research Laboratory of Ankara University. Guidelines for the Care and Use of Laboratory Animals' published by the National Institute for Health (NIH publication no.85-23, 1996 revised) were followed. The procedures used and the care of animals were approved by the Ankara University Animal Experiments Local Ethics Committee (Approval no: 201-2-11, dated 11/22/2014).

### In vivo chemotherapy model

Four groups were created: Sham group, Folfox group, Folfox+ low dose sildenafil group, and Folfox+ high dose sildenafil group. To create direct toxicity on the liver, oxaliplatin 6mg/kg, followed by 5FU (50mg/kg) and folinic acid (90mg /kg) were administered intraperitoneally to all rats in the study groups once a week for 5 weeks (FOLFOX regime). To determine the effects of sildenafil on oxaliplatin-related liver damage, rats in the low and high-dose groups were administered 1mg/kg/day and 20mg/kg/day sildenafil, respectively, with oral gavage. The doses applied were determined according to previous studies [6,7]. The Sham group was used as a comparison group only and comprised 6 rats. Each of the study groups comprised 12 rats. During the study period, 1 rat in the oxaliplatin group, 4 in the oxaliplatin+low-dose sildenafil group and 3 in the oxaliplatin+high-dose sildenafil group died. All rats were kept in standard laboratory conditions and fed standard laboratory rat food for the duration of the experiment. At 5 days after the final dose of oxaliplatin, all the rats were administered ketamine HCL (80mg/kg) and xylazine hydrochloride (12mg/kg) for anesthesia and muscle relaxant. A laparotomy was made to each animal with a 2.5cm-long midline incision. After laparotomy, hepatectomy was performed, after which the animals were sacrificed. The livers removed from the rats were placed in formalin for pathological examination.

### Histological examination

The tissue samples were fixed in formalin and embedded in paraffin blocks. Sections, 5µm in thickness, were cut and stained with hematoxylin and eosin (H&E). Category classification of sinusoidal dilatation, nodular regeneration, centrilobular or portal vein lesions, centrilobular vein and perisinusoidal fibrosis and steatosis was made as follows: For sinusoidal dilatation, 0= None, 1= Mild (involvement limited to one-third of the centrilobular area), 2= Moderate (two-thirds of the centrilobular area), 3= Severe (full involvement of the lobular area or centrilobular involvement extending with congestion to adjacent lobules), for nodular regeneration, 0= None, 1= Mild (focal nodular hyperplasia, not evident with H&E staining but evident with reticular staining) 2= Moderate (focal nodular hyperplasia, evident with both H&E and reticular staining), 3= Severe ( widespread nodular hyperplasia on both reticular and H&E staining), for centrilobular or portal vein lesions, and centrilobular perisinusoidal and vein fibrosis, 0= None, 1= Mild (<50% of veins and sinusoids in 20 areas at x 200 magnification), 2= Moderate (>50% of veins and sinusoids in 20 areas at x 200 magnification), for steatosis, 0= None, 1= Mild (10%-30% of hepatocytes), 2= Moderate (in 30%-60% of hepatocytes), 3= Severe (>60% of hepatocytes). Peliosis, perisinusoidal hemorrhage and hepatocellular changes were evaluated as absent or present.

### Statistical analysis

Data were analyzed using SPSS-16 software (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). Differences between the groups with respect to the severity of the lesions formed after different regimens were assessed with the Pearson Chi-square test. A value of $P<0.05$ was considered statistically significant.

## Results

The type of histopathological lesions according to the groups were summarized in Tables 1 and 2. The analysis of distribution of pathological lesions in the groups were presented in Table 3.

Table 1: Distribution of lesions according to groups

| Pathology lesions | Sham group (n=6) | | | | Folfox group (n=11) | | | | Folfox+low-dose sildenafil group (n=8) | | | | Folfox+high-dose sildenafil group (n=9) | | | | *P*-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | M | Mod | S | N | M | Mod | S | N | M | Mod | S | N | M | Mod | S | |
| Sinusoidal dilatation | 3 | 3 | 0 | 0 | 0 | 5 | 4 | 2 | 2 | 2 | 3 | 1 | 1 | 5 | 3 | 0 | X2=11.6. *P*=0.243 |
| Nodular regeneration | 6 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | |
| Centrilobular changes | 6 | 0 | 0 | 0 | 0 | 6 | 5 | 0 | 5 | 3 | 0 | 0 | 0 | 9 | 0 | 0 | X2=49.9 *P*<0.001 |
| Steatosis | 6 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | |

N: None, M: Mild, Mod: Moderate, S: Severe

Table 2: Analysis of the distribution of the pathology lesions in groups

| Groups | Sinusoidal dilatation | Centrilobular changes | Hepatocellular changes | Peliosis (Perisinusoidal hemorrhage) | Nodular regeneration | Steatosis |
|---|---|---|---|---|---|---|
| Sham(n=6) | 3(50%) | - | - | 1(16.6%) | - | - |
| Folfox(n=11) | 11(100%) | 11(100%) | 10(90.9%) | 5(45.4%) | - | - |
| Folfox+low-dose sildenafil (n=8) | 6(75%) | 3(37.5%) | 1(12.5%) | - | - | - |
| Folfox+ high-dose sildenafil(n=9) | 8(88.8%) | 9(100%) | - | - | - | - |
| P-value | 0.243 | <0.001 | <0.001 | <0.001 | - | - |

Table 3: Hepatocellular and peliotic changes according to the groups

| Pathology lesions | Sham group (n=6) | | Folfox group (n=11) | | Folfox+low-dose sildenafil group (n=8) | | Folfox+high-dose sildenafil group(n=9) | | *P*-value |
|---|---|---|---|---|---|---|---|---|---|
| Hepatocellular changes | + | - | + | - | + | - | + | - | x2=63.7 |
| | 0 | 6 | 10 | 1 | 1 | 7 | 0 | 9 | *P*<0.001 |
| Peliosis (Perisinusoidal hemorrhage) | 1 | 5 | 5 | 6 | 0 | 8 | 0 | 9 | x2=46.7 *P*<0.001 |

+ : present - : absent

Sinusoidal dilatation (Figure 1) was determined in all groups at different degrees of severity (Table 1). Centrilobular changes were lowest (37.5%) in the Folfox+ low dose sildenafil group. Nodular regeneration and steatosis were not observed in any of the groups (Table 1). Hepatocellular changes (Figure 2), and perisinusoidal hemorrhage were observed highest in the Folfox group ($P$<0.001).

Peliosis (Figure 3) was observed in both sildenafil groups. Although sinusoidal dilatation and centrilobular changes were observed in all 3 groups, it was seen less in the sildenafil groups and primarily at a lower rate in the FOLFOX+low-dose sildenafil group ($P$<0.001).

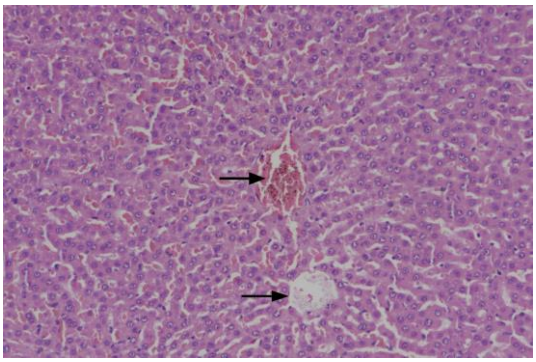

Figure 1: Widespread dilatation in the sinusoids

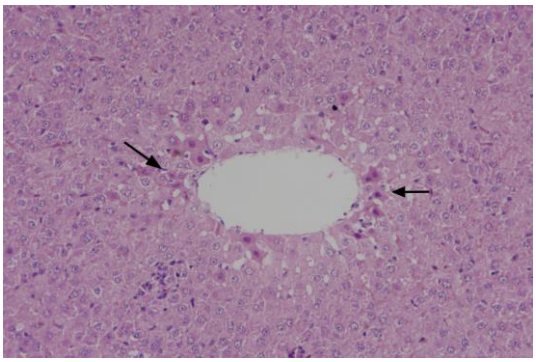

Figure 2: Degenerated Hepatocytes

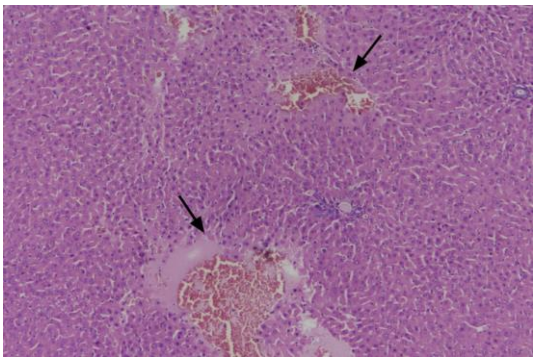

Figure 3: Foci of perisinusoidal hemorrhage

## Discussion

Until the development of modern chemotherapy regimens, the only known reason for SOS was the use of pyrrolizidine alkaloids. SOS has been noted in patients who received myeloablative chemotherapy before bone marrow transplantation and recently in colorectal cancer patients with liver metastasis, following the application of platinum-based chemotherapy [8]. In addition, some studies have reported that there is a relationship with SOS in the tumor-free area of the liver in approximately 45% of patients with who received oxaliplatin-based chemotherapy before resection of colorectal liver metastasis [9]. In patients receiving oxaliplatin-based chemotherapy, an association was found between the development of SOS and increased need for perioperative transfusion (especially in major hepatectomies), high perioperative morbidity, a longer postoperative stay in hospital and increase in complications, such as post-hepatectomy liver failure characterized by cholestasis, ascites and prolonged prothrombin time [10, 11]. Using a model of liver damage which developed after oxaliplatin -based chemotherapy, Tamandl et al. demonstrated a relationship between SOS and a short survival period after liver resection performed due to early recurrence of the disease and colorectal liver metastasis [9]. Vreuls et al. determined a correlation between SOS and significantly low tumor response in oxaliplatin treatment [12]. Therefore, when surgeons are planning liver resections after systemic chemotherapy, they must ensure that there is sufficient preoperative liver functional reserve to avoid postoperative complications.

Various risk factors have been related to the development of SOS: Patients with an abnormal preoperative g-glutamyl transferase level, advanced age, female gender, tumor size>5cm, the 15-minute retention rate of indocyanine green, increased number of chemotherapy cycles and a short period between the end of chemotherapy and liver resection [9]. Previous studies have reported that some non-invasive blood tests can be used such as preoperative platelet count (<167,000), aspartate aminotransferase platelet ratio index (APRI) or FIB-4 scoring system (calculated with a formula based on AST, platelet count and age) to predict high-grade lesions of SOS [10]. Although results have been promising, further evaluation is required for the routine use of these tests, because SOS lesions are heterogenous, the reliability of liver biopsy is reduced, and false negative results may occur.

Sinusoidal endothelial cells (SECs) play a significant role in maintenance of normal sinusoid structure. SECs express metalloproteinases (MMP), enzymes responsible for extracellular remodeling. SECs maintain hepatic stellate cells (HSCs) in a quiescent state through VEGF stimulated NO production, and promote reversion of activated collagen–producing HSCs to a quiescent state [13]. SECs are a major cellular target for several toxins. One explanation for this is their location, which results in their direct exposure to drugs absorbed by the intestinal tract and transported to the liver by portal circulation [14]. Over activation or injury of SEC exerts proinflammatory, proadhesive, and procoagulant properties.

SOS develops because of a spectrum of lesions including sinusoidal dilatation following toxic liver damage

primarily targeting sinusoidal endothelial cells (SEC), perisinusoidal fibrosis, nodular regenerative hyperplasia (NRH) and peliosis [3, 12]. Previous experimental studies have shown that more toxic damage is formed earlier in the SECs than in the hepatocytes. In the pathogenesis of SOS development, there is a reduction in SEC glutathione level and NO levels, an increase in the expression of matrix metalloproteinases (MMP), and vascular endothelial growth factor (VEGF) as well as activation of clotting factor [15]. DeLeve et al. showed that NO level reduced in the hepatic veins of rats during SOS induction [16]. In another study of SOS induction by DeLeve et al, the severity was seen to increase with the application of N(G)-nitro-L-arginine methyl ester (L-NAME), which is a non-selective inhibitor of NO synthase and ameliorate with an infusion of V-YRRO/NO, which is a liver selective NO donor pre-medication [17].

It has been difficult to identify patients at risk of developing parenchymal damage following preoperative chemotherapy. It has been shown in rats that the administration of MMP -2/-9 inhibitors or a glutathione infusion has prevented the development of SOS by reducing SEC damage [18]. In hematopoietic stem cell transplantation, when treatment is given with glutamine, which is a probable glutathione synthesis stimulant, hepatic functions of patients were protected [19, 20]. On the other hand, it has been researched as to whether anticoagulants such as heparin and defibrotide, prostaglandin E1, plasminogen activator, ursodeoxycolic acid and pentoxifylline are sufficient to prevent the development of SOS related to hematopoietic stem cell transplant [21].

Oxaliplatin is a third-generation platinum compound consisting of a platinum atom conjugated to diamino cyclohexane and oxalate groups [22]. Some platinum compounds, such as OX, lead to generation of reactive oxygen species (ROS) and glutathione depletion in SEC, resulting increased oxidative stress in SECs [23,24]. Thrombocytopenia and alteration in platelet function have recently been observed with severe OX-related SOS [25].

Sildenafil was developed in 1985 for the treatment of hypertension and is a phosphodiesterase-5 inhibitor (PDE5i) drug. The PDE5i effect is usually to provide relaxation of the blood vessels by increasing the NO level while inducing guanyl monophosphate (cGMP) degradation [26]. Previous animal and clinical studies have shown that by inhibiting vasodilation, thrombocyte aggression and adhesion, sildenafil had positive effects on anastomosis, bone and skin healing and systemic inflammation, such as an increase in microcirculatory hemodynamics and an amelioration of the inflammatory process [27].

Liver damage was created using an oxaliplatin-based chemotherapy regimen in the current study. Centrilobular, peliotic and hepatocellular changes significantly differed between the groups. No steatotic or nodular regenerative changes were observed in any of the groups, which was most likely because the sinusoidal changes seen in liver damage were not severe, and chemotherapy dosage and duration may have affected the process. When the treatment groups were compared with the control group, peliosis was observed in both sildenafil groups. Although sinusoidal dilatation and centrilobular changes were observed in all 3 groups, it was seen less in the sildenafil groups and primarily at a lower rate in the FOLFOX+low-dose sildenafil group. Hepatocellular changes were not observed at all in the FOLFOX+ high-dose sildenafil group and seen at a lower rate in the sildenafil groups, compared to the control group.

The results obtained in this study are encouraging on the topic of prevention against liver damage that develops as a result of oxaliplatin-based chemotherapy. Further supportive clinical studies of drugs to be used against the active mechanisms in SOS pathophysiology may yield more successful results. Confirming the results with biochemical analyses may strengthen the results. We studied only one (sildenafil) drug to prevent SOS, which could be a potential bias.

**Conclusion**

The ideal strategy for patients with colorectal cancer liver metastasis receiving preoperative FOLFOX-based chemotherapy is the administration of drugs to prevent SOS development throughout chemotherapy. This approach could be of value to those with a large tumor burdens requiring prolonged preoperative chemotherapy.

## References


1. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. Lancet. 1994;343:1405–10.
2. Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol. 2009;27:3677–83.
3. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg. 2004;240:644–57.
4. Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, et.al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet. 2011;377:2103–14.
5. de Meijer VE, Kalish BT, Puder M, Ijzermans JNM. Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection. Br J Surg. 2010;201097:1331–9.
6. Robinson SM, Mann J, Manas DM, Mann DA, White SA. An experimental study to identify the potential role of pharmacogenomics in determining the occurrence of oxaliplatin-induced liver injury. HPB. 2013;15:581-7.
7. Gökakın AK, Atabey M, Deveci K, Sancakdar E, Tuzcu M, Duger C, et al. The effects of sildenafil in liver and kidney injury in a rat model of severe scald burn: a biochemical and histopathological study. Ulus Travma Acil Cerrahi Derg. 2014;20:319-27.
8. Robinson SM, Mann DA, Manas DM, Oakley F, Mann J, White SA. The potential contribution of tumour-related factors to the development of FOLFOX-induced sinusoidal obstruction syndrome. Br J Cancer. 2013;109:2396-403.
9. Tamandl D, Klinger M, Eipeldauer S, Herberger B, Kaczirek K, Gruenberger B, et al. Sinusoidal obstruction syndrome impairs long-term outcome of colorectal liver metastases treated with resection after neoadjuvant chemotherapy. Ann Surg Oncol. 2011;18:421–30.
10. Soubrane O, Brouquet A, Zalinski S, Terris B, Brézault C, Mallet V, et al. Predicting high grade lesions of sinusoidal obstruction syndrome related to oxaliplatin-based chemotherapy for colorectal liver metastases: correlation with post-hepatectomy outcome. Ann Surg. 2010;251:454–60.
11. Hubert C, Sempoux C, Humblet Y, van den Eynde M, Zech F, Leclercq I, et al. Sinusoidal obstruction syndrome (SOS) related to chemotherapy for colorectal liver metastases: factors predictive of severe SOS lesions and protective effect of bevacizumab. HPB. 2013;15:858-64.
12. Vreuls CP, Van Den Broek MA, Winstanley A, Koek GH, Wisse E, Dejong CH, et al. Hepatic sinusoidal obstruction syndrome (SOS) reduces the effect of oxaliplatin in colorectal liver metastases. Histopathology. 2012;61:314–8.
13. Deleve LD, Wang X, Guo Y. Sinusoidal endothelial cells prevent rat stellate cell activation and promote reversion to quiescence. Hepatology. 2008;48:920–30.
14. McCuskey RS. Sinusoidal endothelial cells as an early target for hepatic toxicants. Clin Hemorheol Microcirc. 2006;34(1–2):5–10.
15. Fan CQ, Crawford JM. Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). J Clin Exp Hepatol. 2014;4:332-46.
16. DeLeve LD, Wang X. Decrease in nitric oxide production contributes to hepatic venoocclusive disease. Hepatology. 1999;30:218.
17. DeLeve LD, Wang X, Kanel GC, Ito Y, Bethea NW, McCuskey MK, et al. Decreased hepatic nitric oxide production contributes to the development of rat sinusoidal obstruction syndrome. Hepatology. 2003;38:900–08.
18. Deleve LD, Wang X, Tsai J, Kanel G, Strasberg S, Tokes ZA. Sinusoidal obstruction syndrome (veno-occlusive disease) in the rat is prevented by matrix metalloproteinase inhibition. Gastroenterology. 2003;125:882–90.
19. Goringe AP, Brown S, O'Callaghan U, Rees J, Jebb S, Elia M, et al. Glutamine and vitamin E in the treatment of hepatic veno-occlusive disease following high-dose chemotherapy. Bone Marrow Transplant. 1998;21:829–32.
20. Klinger M, Eipeldauer S, Hacker S, Herberger B, Tamandl D, Dorfmeister M, et al. Bevacizumab protects against sinusoidal obstruction syndrome and does not increase response rate in neoadjuvant XELOX/FOLFOX therapy of colorectal cancer liver metastases. Eur J Surg Oncol. 2009;35:515–20.

21.DeLeve LD, Valla D, Garcia-Tsao G. Vascular disorders of the liver. Hepatology. 2009;49:1729–64.
22.Kweekel DM, Gelderblom H, Guchelaar HJ. Pharmacology ofoxaliplatin and the use of pharmacogenomics to individualize therapy. Cancer Treat Rev. 2005;31:90–105.
23.DeLeve LD, Wang X, Kanel GC, Ito Y, Bethea NW, McCuskey MK, et al. Decreased hepatic nitric oxide production contributes to the development of rat sinusoidal obstruction syndrome. Hepatology. 2003;38:900–8.
24.Laurent A, Nicco C, Chéreau C, Goulvestre C, Alexandre J, Alves A, et al. Controlling tumour growth by modulating endogenous production of reactive oxygen species. Cancer Res. 2005;65:948–56.
25.Soubrane O, Brouquet A, Zalinski S, Terris B, Brézault C, Mallet V, et al. Predicting high grade lesions of sinusoidalobstruction syndrome related to oxaliplatin-based chemotherapy for colorectal liver metastases correlation with post-hepatectomy outcome. Ann Surg. 2010;251:454–60.
26.Derici H, Kamer E, Unalp HR, Diniz G, Bozdag AD, Tansug T, et al. Effect of sildenafil on wound healing: an experimental study. Langenbecks Arch Surg. 2010;395:713-8.
27.Cakir T, Ozer I, Bostanci EB, Keklik TT, Ercin U, Bilgihan A, et al. Increased collagen maturity with sildenafil citrate: experimental high risk colonic anastomosis model. Int J Surg. 2015;13:152-6.

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