Egypt. J. Rad. Sci. Applic., Vol. **26**, No. 1-2, pp. 1-12 (2013)

Gastro Hepatic Protective Effects of Sildenafil in γ-Irradiated Rats

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SILDENAFIL is a potent specific inhibitor of phosphodiestrase-5 (PDE-5), which ultimately increases intracellular cyclic guanosine monophosphate (cGMP). Sildenafil commercially named Viagra; was studied for its gastro hepatic protective activity through acute exposure of rats to γ-rays.

The experimental groups of rats were: Sildenafil [1 mg/ kg, intra venous (i.v.), in 0.2 ml saline] / day for 5 days and then exposed to 6 Gy γ-rays after 1 h of the last injection (sildenafil+ γ-rays group). Controls received saline as a vehicle/ for 5 day; sildenafil group received drug alone for 5 days, and γ-rays group received saline (without drug) for 5 days and exposed to 6 Gy γ-rays after 1 h of the last injection. All groups were decapitated on the 6^{th} day.

Gamma rays increased the level of malondialdehyde (MDA) and the activity of myeloperoxidase (MPO) but, lowered the levels of nitric oxide (NO) and reduced glutathione (GSH) as well as lowering the activities of superoxide dismutase (SOD) and catalase (CAT) in both stomach and hepatic tissues.

Sildenafil administrated before γ-rays significantly reduced the level of MDA and the activity of MPO while elevating levels of NO and GSH plus activities of SOD and CAT in both stomach and hepatic tissues compared to control and sildenafil groups.

Conclusion: The data reveals that sildenafil pre-treatment has a protective effect against γ-rays-induced gastro hepatic dysfunction and supports the possible use of sildenafil as a protective agent in γ-irradiated rats.

Keywords: Silenafil, stomach, liver, γ-rays, rats.

Several studies have shown that, in addition to treating erectile dysfunction, sildenafil can prevent or decrease tissue injury. In *vivo* and in *vitro*, early treatment with sildenafil ameliorated the progression of renal damage in partial nephrectomy (Rodriguez-Iturbe *et al.*, 2005) and provided a protection against heart ischemic injury in man (Khan *et al.*, 2012). In addition, administration of

sildenafil may be useful against ischemic injury in liver, stomach and lung (Duffin *et al.,* 2008, Eriksson *et al.,* 2011 and Liu and Fang, 2012).

Ionising radiation exposure results in the generation of reactive oxygen species (ROS) that are highly damaging to cells, DNA, lipids and proteins and consequently the whole cell physiology may be changed (Matuo *et al.,* 2008). Excessive production of ROS have been described as one of the probable pathogenic factors of gastric mucosal and hepatic lesions associated with inflammatory processes (Noh *et al.,* 2011 and Riosa *et al.,* 2010). Both enzymatic and non-enzymatic antioxidant defences can't prevent the ROS increases, thus, they may exert deleterious actions on the gastro hepatic tissues (Rocha et al., 2011). Inflammatory bowel disease including ulcerative colitis and hepatic injury are gastro hepatic disorders induced by ionising-radiation characterized by intestinal inflammation and hepatic tissue damage (Demirel *et al.,* 2011 and Verma *et al.,* 2011). Since the mechanisms of gastro hepatic injury in irradiated animals have not been completely elucidated, many studies have been attempted to find an ideal protective therapy (El-Ghazaly et al., 2011 and Sinha et al., 2011). However, the effects of sildenafil on gastro hepatic dysfunction induced by γ-rays remain to be established. In this study, several parameters that could potentially affect the sildenafil efficiency were investigated in stomach and hepatic tissues of γ-irradiated rats.

Materials and Methods

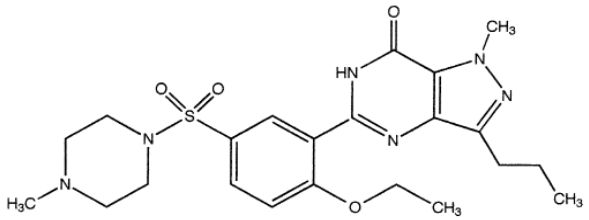
Animals and Sildenafil administration

Male Sprague Dawley rats (Holding Company for Biological Products and Vaccines, Cairo, Egypt), weighing 100-122 g, were acclimated to place for 1 week in the animal experimental research laboratory NCRRT, Cairo, Egypt. Rats were placed in plastic cages, subjected to a daily 12 h light: dark cycle at 22± 3°C room temperature and 60± 5% relative humidity. They were fed maintenance diets according to Reeves (1997). Sildenafil; Viagra, Pfizer, USA, tablets were dissolved in saline. Sildenafil; 1 mg/kg in 0.2 ml saline were administrated according to Soydan *et al.* (2009).

The study protocol

Rats were divided into 4 groups (each of 8 rats): control group; 0.2 ml saline as a vehicle/ day for 5 days were administered to rats through the tail veins, sildenafil group; 1 mg/ kg, i.v., in 0.2 ml saline)/ day for 5 days, γ-rays group;

received daily 0.2 ml saline for 5 days and exposed to 6 Gy γ-rays (0.43 Gy/ min, NCRRT, Cairo, Egypt) after 1 h of the last injection and sildenafil+ γ-rays group; rats received daily sildenafil doses for 5 days and exposed to 6 Gy γ-rays after 1 h of the last injection. All groups were decapitated on the 6th day. Stomach and liver samples were collected and stored at −70 °C for subsequent analysis.



(1-[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine. $C_{22}H_{30}N_6O_4S$).

Fig. 1. Chemical structural of sildenafil.

Analysis of stomach and hepatic tissues

In stomach and liver samples, MDA content was processed and measured as described by Rocha *et al.* (2011). NO content was measured by determination of nitrite, the stable end product of NO radicals as described by Green et al. (2000). GSH content was measured according to the method described by Sedlak and Lindsay (1968). CAT, MPO and SOD activities were processed and measured as described by Aebi (1984), Bradley *et al.* (1982) and Sun *et al.* (1988), respectively. Proteins were measured as described by Bradford (1976).

Statistical analysis

Data is expressed as the means± S.D. Statistical evaluations were done by Duncan's multiple range test and analysis of variance (ANOVA), using the Statistical Package for Social Studies. Level of significance was set at $P< 0.05$.

Results

Administration of sildenafil alone without γ-irradiation resulted in non-significant changes in all stomach and hepatic tissues parameters studied (Fig. 2-7). The quantification of MDA, NO and GSH in the γ-irradiated animals showed significant increase in MDA contents in both stomach and hepatic tissues and significant decrease of NO and GSH in both stomach and hepatic tissues as compared to the control groups (Fig. 2-4).

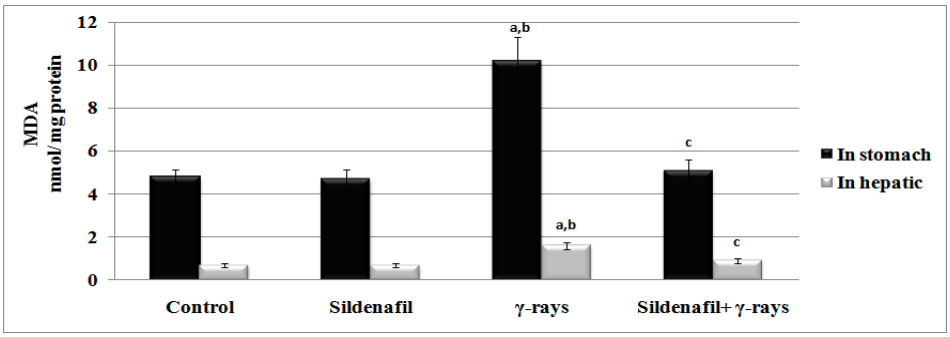


Fig. 2. Effect of sildenafil and/ or γ-rays on stomach and hepatic MDA in rat groups.

a, significantly different from the control group.
b, significantly different from the sildenafil group.
c, significantly different from the γ-rays group.

In sildenafil+ γ-rays groups of rats, MDA, NO and GSH contents were reversed and became insignificant in comparison with corresponding control groups in both stomach and hepatic tissue, Fig. 2-4.

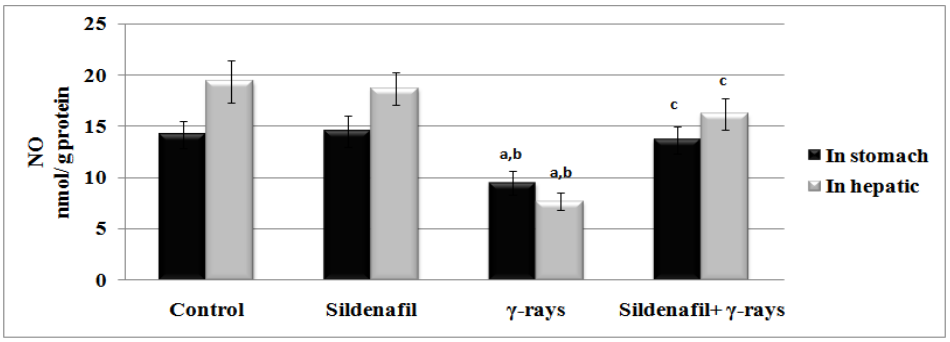


Fig. 3. Effect of sildenafil and/ or γ-rays on stomach and hepatic NO in rat groups.

Legends as in Fig. 1.

The estimation of the activities of MPO, SOD and CAT in the γ-irradiated animals showed significant increase of MPO activities in both stomach and hepatic tissues and decrease of SOD and CAT activities in the two tissues as compared to the control groups, Fig. 5-7. In sildenafil+ γ-rays groups, MPO and SOD activities were changed significantly compared to the γ-rays groups in stomach tissue and was insignificant from the control groups in hepatic tissue only, while the CAT activity was significantly increased in stomach and hepatic tissues. The increased CAT activity was insignificant in stomach tissue only as compared to the control group, Fig. 5-7.

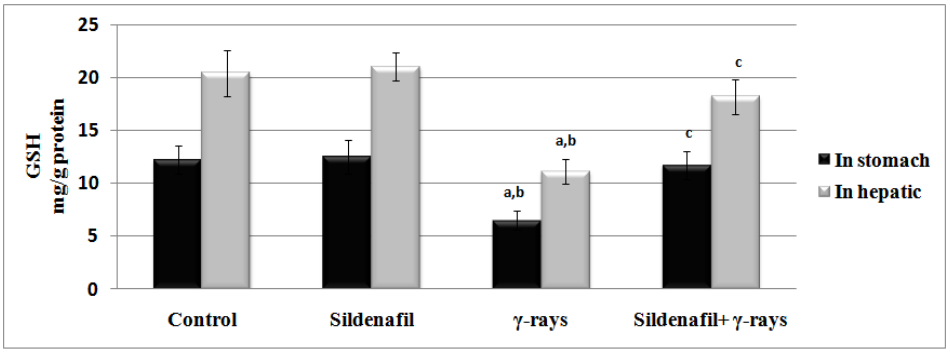


Fig. 4. Effect of sildenafil and/ or γ-rays on stomach and hepatic GSH in rat groups.

Legends as in Fig. 1.

CAT activities were significantly increased in stomach and hepatic tissues. The increased became insignificant in stomach tissue only in comparison with corresponding control group, Fig. 4-6.

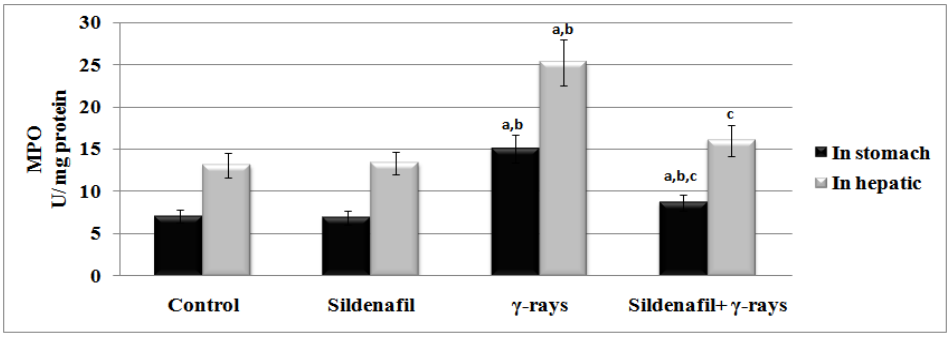


Fig. 5. Effect of sildenafil and/ or γ-rays on stomach and hepatic MPO in rat groups.

Legends as in Fig. 1.

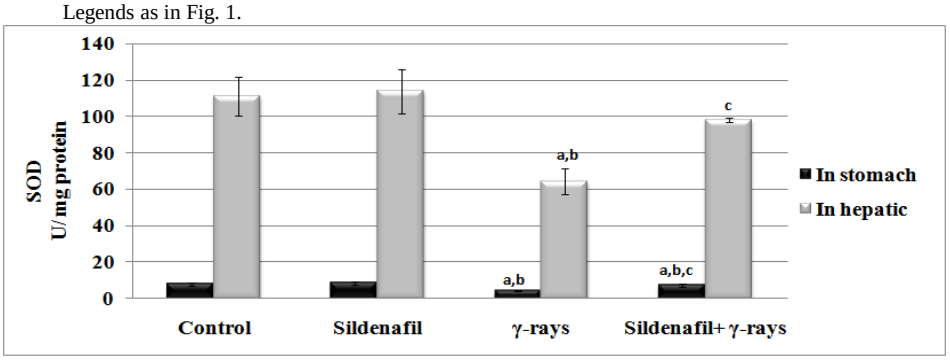


Fig. 6. Effect of sildenafil and/ or γ-rays on stomach and hepatic SOD in rat groups.

Legends as in Fig. 1.

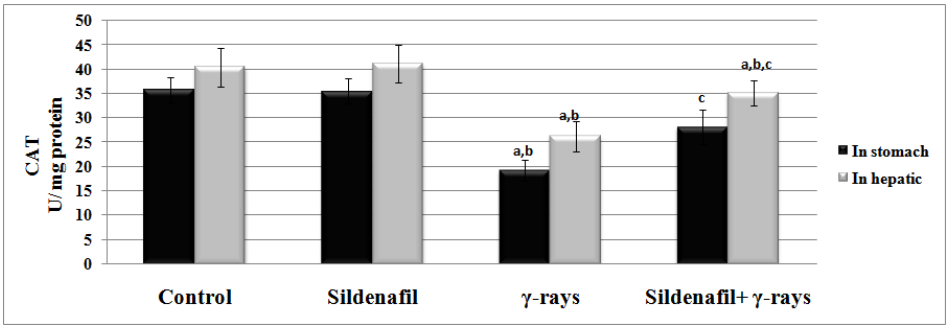


Fig. 7. Effect of sildenafil and/ or γ-rays on stomach and hepatic CAT in rat groups.

Legends as in Fig. 1.

Discussion

The cells of the gastric tract have an antioxidant defence system capable of preventing the cytotoxicity of ROS through mechanisms that involve the action of enzymes and compounds which bind to oxygen radicals and prevent their harmful actions (Riosa *et al.*, 2010). Sildenafil, acting via nitric oxide (NO)-dependent mechanism, prevented indomethacin-induced gastropathy (gastric mucosa damage) possibly through a reduction of leukocyte adhesion and maintenance of gastric blood flow (Aydinli *et al.*, 2007 and Santos *et al.*, 2005). Liver-related diseases are still among the leading causes of morbidity and mortality all over the world (Park *et al.*, 2012). Since oxidative stress is one of the main causes of radiation-induced liver injury (Verma *et al.*, 2011). The authors suggest that, the ability of sildenafil to suppress oxidative stress in hepatic tissues can be potent candidates for liver protection.

The degree of lipid peroxidation in tissues was measured by determining the amount of MDA, which relate directly to the level of injury to tissues (Kerman *et al.*, 2011) and also significantly associated with increased apoptosis in gastric tissue of animals (Li *et al.*, 2011). In the present study, administration of sildenafil before irradiation decreased the level of MDA in both stomach and hepatic tissues when compared with the irradiated groups. These decreases in MDA levels suggest a protective effect of sildenafil on rat tissue due to its antioxidant effect and the inhibition of ROS. In accordance with several studies, sildenafil has an anti-inflammatory property via the inhibition of ROS (Yildiz *et al.*, 2011).

Interplay between inflammatory reaction and the cell membrane of organs causes relative NO-deficiency as a result of reaction of NO with oxygen radicals (Bongartz *et al.,* 2005). Exposure of animals to γ-rays caused significant decreases in NO levels in stomach and liver tissue homogenates. Excess production of $O2^{-}$ in pathologic conditions such as irradiation syndrome causes the formation of peroxynitrite (Ortega Mateo and de Artinano, 2000). In the present study, administration of sildenafil significantly increased the NO levels in stomach and hepatic tissues compared with irradiated groups suggesting a possible physiological response by decreasing oxidative damage as a result of increasing NO production. PDE-5 inhibitors augment the action of NO that inhibits the expression of NADPH-oxidase (Arikan *et al.,* 2010), which in turn reduces the irradiation-injury in the tissues.

Several studies reported that the MPO activity level could be a marker of endothelial dysfunction (Ahluwalia *et al.,* 2004) and an indicator of neutrophil infiltration in ulcerogenic lesions (Rocha *et al.,* 2011). The presence of oxygen free radicals (Kutsuna *et al.,* 2010), inflammatory mediators and extra vacated leukocytes (Hassoun *et al.,* 2011) may also contribute to the physiological dysfunction observed after ischemia-reperfusion injury in gastro hepatic tissue. Furthermore, gastric muscle is very vulnerable to inflammation and during the reperfusion period, the generation of oxygen free radicals interferes with the function of cells by disrupting ionic homeostasis (Kutsuna *et al.,* 2010). In the present study, exposure to γ-rays resulted in excessive MPO production, as recognized by Sener *et al.* (2006). Administration of sildenafil significantly decreased the MPO activity in stomach and hepatic tissues comparing with irradiated groups, where, sildenafil prevents oxidant generation, cytokine production and neutrophil accumulation (Iseri *et al.,* 2009).

SOD and CAT are the most important enzymes in the antioxidant defence system, which is responsible for protecting tissues against the deleterious effects of ROS (Tawfik *et al.,* 2010). Decreased tissue SOD and CAT activities in the irradiated groups may have occurred as a result of consumption of enzymes by ROS during oxidative stress. The beneficial effect of sildenafil administration against γ-irradiation-induced damage was confirmed by the increased level of both SOD and CAT in rat stomach and hepatic tissues. Recently it was found that sildenafil increases SOD and CAT activities in testicular injury in rats (Beheshtian *et al.,* 2008).

Sildenafil has comparable effect on portal hemodynamics, improves portal liver perfusion and induces a drop of portal pressure (Bremer *et al.,* 2007). Furthermore, the absence of hepatotoxicity in irradiated rats treated with sildenafil is consistent with the tolerance of sildenafil demonstrated in alcohol-fed animal models (Boniface *et al.,* 2010). In addition, it has been shown that sildenafil pre-treatment has a protective effect against ileal dysfunction and damage induced by intestinal irradiation in the rat (Soydan *et al.,* 2009).

Conclusion and further research

In conclusion, sildenafil was able to reduce gastro hepatic injury induced in irradiated rats. These findings show that sildenafil is able to decrease oxidative stress event associated with the injury induced by γ-rays-exposure.

Further studies that support these results should be performed in models more comparable to clinical cases of other tissues γ-rays-injury with regard to the dose and timing of drug administration.

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(Received: 03/03/2013;

accepted: 16/04/2013)

التأثيرات الوقائية للسيلدينافيل علي المعدة و الكبد في الجرذان المعرضة لأشعة جاما

سامح سليمان توفيق و صفوت فريد سلامة

قسمي البحوث الصحية الإشعاعية و بيولوجيا الإشعاع ، المركز القومي لبحوث وتكنولوجيا الإشعاع ، ص. ب. ٢٩ مدينة نصر ، مصر.

السيلدينافيل مثبط فعال للفوسفو ديستيراز-٥ (PDE-5) يؤدي إلي وفرة جوانوسين احادي الفوسفات (cGMP) داخل الخلايا. و هو معروف تجاريا باسم "فيجرا" ، و قد تم دراسة تأثيراته الوقائية علي كلا من: المعدة و الكبد في الجرذان المعرضة لجرعة حادة مقدارها ٦ جراي من أشعة جاما.

السيلدينافيل (١ مللي جم/ كجم من وزن الجرذان يتم تخفيفه في ٠ر٢ مللي محلول ملح فسيولوجي و يتم حقنه بالوريد يوميا و لمدة ٥ أيام) و ذلك قبل تعرض أجسام الجرذان كلها لجرعة ٦ جراي من أشعة جاما. و يتم تجهيز باقي مجموعات الدراسة كالأتي:- المجموعة الضابطة تحقن بمحلول الملح يوميا و لمدة ٥ أيام ، مجموعة السيلدينافيل تحقن بعقار السيلدينافيل يوميا و لمدة ٥ أيام و المجموعة المعرضة لأشعة جاما تحقن بمحلول الملح يوميا لمدة ٥ أيام ثم تعرض لجرعة ٦ جراي من أشعة جاما بعد آخر حقنة بساعة. يتم ذبح الجرذان في اليوم السادس و يتم تشريحهم و جمع عينات من المعدة و الكبد و حفظهما تمهيدا لإجراء التحاليل الكيموحيوية.

أظهرت النتائج أن تعرض الجرذان لأشعة جاما أدي إلي ظهور زيادة إحصائية في مستوي المالون داي الديهيد (MDA) و نشاط إنزيم الميلوبيروكسيديز (MPO) و من جهة أخري أدي التعرض لهذه الأشعة إلي خفض مستوي كلا من: النيتريك أوكسيد (NO) و الجلوتاسيون المختزل (GSH) و خفض نشاط كلا من: السوبر اكسيد ديسميوتيز (SOD) و الكتاليز (CAT) بالمعدة و الكبد. و لكن عندما تم حقن السيلدينافيل قبل تعرض الجرذان لأشعة جاما فأن ذلك أدي إلي انخفاض إحصائي بمستوي المالون داي الديهيد و نشاط إنزيم الميلوبيروكسيديز مع وجود زيادة احصائية في مستوي النيتريك أوكسيد و الجلوتاسيون المختزل بالإضافة إلي زيادة نشاط إنزيمي السوبر اكسيد ديسميوتيز و الكتاليز بكل من: المعدة و الكبد مقارنة بمستوياتهم بالمجموعة التي تعرضت لأشعة جاما فقط.

الخلاصة: تشير النتائج إلي إمكانية استخدام السيلدينافيل كعلاج و قائي من أضرار أشعة جاما علي معدة و كبد الجرذان مما يعكس إمكانية استخدام هذا العقار كعلاج واقي من الاختلال الوظيفي بالمعدة و الكبد.