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Sildenafil Beyond Erectile Dysfunction and Pulmonary Arterial Hypertension: Thinking About New Indications

Running head: Thinking about new indications of sildenafil

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ABSTRACT

Sildenafil, approved two decades ago, is the inhibitor of Phosphodiesterase 5 (PDE5). First of all, it was designated for angina pectoris but soon it showed a wonderful efficacy in erectile dysfunction (ED) and then pulmonary arterial hypertension (PAH).

Due to the distribution of phosphodiesterase (PDE) in almost all organs, maybe it effects other diseases. Hence, a great number of investigations began to understand the role of PDEi in different organs. Preliminary research on sildenafil in cell culture and animal models has yielded promising results. Soon a greater number of animal researches and clinical trials joined them. The results disclosed sildenafil can have beneficial effects in each organ such as heart, liver, kidney, brain, intestines and etc. Furthermore, it has significantly improved the prognosis of organ ischemia in various animal models. Clinical trials in several diseases, such as recurrent spontaneous miscarriage, fatty liver disease, bronchopulmonary dysplasia (BPD), heart failure, premature ejaculation (PE) brought promising results.

Although some clinical trials are available on the effects of sildenafil on various diseases, further studies on humans are needed to consolidate the ultimate effects of sildenafil. The aim of this review is describing the effects of sildenafil on each organ and explaining its mechanisms of action. Further, other PDE inhibitors such as tadalafil and vardenafil have been briefly discussed in parts of this review.

Keywords: Sildenafil, Inflammation, Ischemia, Heart Failure, Cancer, Abortion.

INTRODUCTION

Sildenafil ,approved in 1998, is an oral and rapidly-absorbable drug for erectile dysfunction and, recently, for Pulmonary arterial hypertension [1]. The discovery of sildenafil was the result of a project performed by Pfizer's European Research HQ. They aimed to find a selective inhibitor of Phosphodiesterase 5 (PDE5) to augment the vasodilation induced by NO (nitric oxide). Meanwhile, they hoped to use this kind of drug to relieve angina in ischemic heart disease and did not imagine it would be useful in erectile dysfunction (ED) [2]. It acts through inhibition of PDE5. PDE5 is responsible for catabolizing cGMP (cyclic GMP) and converting it into GMP. cGMP itself is part of NO signaling pathway and activates cGMP-dependent protein kinase (PKG). PKG phosphorylates other proteins and participates in muscle relaxation [3]. One of these proteins is a charybdotoxin-sensitive K^+ channel. Activation of this type of k^+ channel is critical for hyperpolarization and vasorelaxation of smooth muscle cell [4]. Indeed, sildenafil collaborates with NO to preserve the high level of intracellular cGMP. Sildenafil does not inhibit generally guanylate cyclase but only the soluble guanylate cyclase. NO activates soluble guanylate cyclase and this enzyme produces cGMP to induce the remaining signaling pathway of vasodilation. The NO/cGMP signaling pathway is not limited to vasorelaxation, and scientists have found that sildenafil is involved in regulating platelet function, and synaptic transmission [5, 6]. PDE5 is expressed virtually in all organs such as corpus covernosum, blood vessels, uterus, liver, kidney, bladder, prostate and intestines and it makes sense to develop the expansion of therapeutic indications of sildenafil in near future [7, 8].

Insert Figure 1 here

ED is an abnormal alteration of erectile response, including its organic, relational and psychological aspects. Many neurogenic, vasculogenic and endocrine mechanisms may be involved in its pathophysiology [9]. ED is a common problem with a growing prevalence. This relationship is strongly correlated with age. Meta-analyses showed that its prevalence varies from 20% before age of 30 to 90% in subjects over 70 year-old [10].

Phosphodiesterase inhibitors such as sildenafil are among the best choices for the treatment of ED [11]. Consumption of phosphodiesterase inhibitors in ED showed they are safe drugs without

cardiovascular side effects. Their most important but very rare iatrogenic effects of them are increased risk of ischemic optic neuropathy and sensorineural hearing loss. Although these two complications are important, but their incidence is very low and sildenafil is safe [12]. The serendipitous discovery of sildenafil was the milestone and breakthrough in the treatment of ED because nearly all of the patients with organic, psychogenic and mixed etiology responded to that [13, 14]. [13]. It is statistically effective in all age groups with higher response in young patients. The most common adverse effect of sildenafil is flushing and headache [15]. Interestingly, a novel investigation reported sildenafil reduces inflammatory mediators in patients with vasculogenic erectile dysfunction. Sildenafil decreased interleukin-6 (IL-6), C-reactive protein (CRP), fibrinogen and tumor necrosis factor-α (TNF-α) in the blood of these patients [16].

Pulmonary arterial hypertension (PAH) is a condition of increased pulmonary arterial resistance. It occurs mainly because of endothelial dysfunction. Endothelial dysfunction in PAH predominantly is associated with impaired production of vasodilators, overproduction of vasoconstrictors, vascular smooth muscle hypertrophy, and remodeling of blood vessel [17, 18]. These abnormal changes increase the pulmonary arterial pressure to more than 25 mmHg, which is normally below 15 mmHg [19]. The abnormally elevated pulmonary arterial pressure endangers the heart and causes right-sided heart failure. The eventual outcome ends in shortened life-expectancy. Contemporary therapeutic algorithm of PAH includes calcium channel blockers, endothelin antagonists, phosphodiesterase inhibitors and prostacyclin analogues [20]. Sildenafil suppresses inflammation and prevents remodeling of pulmonary arterial [21]. Observing such anti-inflammatory effects of sildenafil in patients with ED and PAH has encouraged scientists to go further and seek more therapeutic indications for sildenafil.

However, ED and PAH are currently two therapeutic indications for the administration of sildenafil, a notable number of studies have recently been performed to investigate the effect of sildenafil in other fields. Results from previous studies are clues for future decision making and help researchers plan the next step. This review article aims to illuminate the beneficial uses of sildenafil in several diseases and explains its possible contribution in clinical practice.

PROTECTIVE EFFECT OF SILDENAFIL ON ISCHEMIC ORGAN

During recent years, several animal models attempted to find out whether the collaboration of sildenafil with NO/cGMP pathway and the subsequent vasodilatation is helpful in ischemia/reperfusion or not. Animal models possessed the maximal resemblance to what actually happens in humans.

Khatib et al, demonstrated sildenafil and ordonafil restricted the myocardial infarct size in an ischemia/reperfusion model of the isolated rabbit heart. Also, the release of CK-MB (creatine kinase-MB) from the heart was lower in the treated groups [22]. Harmoniously, sildenafil improved the success rate of cardiopulmonary resuscitation after porcine-induced arrest in pigs. Treated animals had higher 24-h survival rate. In addition, the drug inhibited apoptosis in their myocardium and decreased the activity of angiotensin II- angiotensin II type I receptor axis [23].

Further studies claimed the enhancement of VEGF/angiopoietin-1 and ERK phosphorylation play a role in such cardioprotective effects [24, 25].

Valatsasou et al, examined the effect of sildenafil on the limb ischemia/reperfusion. Mice were fed a high-cholesterol diet. Femoral artery was ligated in one of the hind limbs for a constant period. Sildenafil (1 mg/Kg intraperitoneally for 7 days) improved arterial flow in a long-term follow-up, as proven by Doppler imaging. Besides, sildenafil alleviated the inflammatory status and reduced the tissue plasminogen activator inhibitor-1 (tPAI-1), soluble E-selectin (sE-Selectin) and soluble intracellular adhesion molecule-1(sICAM-1) [26]. Further studies disclosed sildenafil stimulates angiogenesis in ischemic limb through protein kinase G (PKG) [27]. A similar study was performed on rat's skeletal muscle, in that immunohistochemically exhibited sildenafil protected soleus muscle against caspase-3 expression and apoptosis [28].

In a rat model of lung ischemia/reperfusion, pretreatment with sildenafil significantly decreased the pro-apoptotic markers such as bax, caspase 3, p53 and inflammatory cytokines. Simultaneously, it increased bcl-2 and preserved alveolar structure of lung [29]. Sildenafil, both orally (1 mg/kg) or topically (0.5 mg/kg), significantly increased skin flap viability in rats [30]. Likewise, vardenafil and tadalafil could decrease necrotic area [31-33]. Similarly, sildenafil (1.4 mg/kg) saved the ovaries

against both ischemia and torsion with a prominent decrease in oxidative stress and histological damaging score, as well as simultaneous increase of SOD (superoxide dismutase) [34].

There is a recent case-report explaining how vaginal sildenafil modified ovarian damage during its torsion. Sildenafil decreased ovarian edema and improved its perfusion and venous return in the patient [35]. Combination of sildenafil and atorvastatin, after cerebral ischemia, improved behavioral tests in mice and recovered their function [36]. Similarly, tadalafil could accelerate neurological function recovery after cerebral ischemia in rats [37]. Immediate treatment with sildenafil after cerebral ischemia mitigated the injury and decreased infarct size [38]. Meanwhile, delays in treatment with sildenafil after focal cerebral ischemia in rats, enhanced functional and structural recovery as well as neurogenesis [39]. Interestingly, sildenafil (10 mg and 30 mg) was examined in a clinical study with 12 patients suffering from cerebral vasospasm following subarachnoid hemorrhage. Angiography was done on day 7 for CVA assessment. Angiographic response to sildenafil was observed in 60% of low-dose group and 71% of high-dose group. The diameter of vessels increased by average of 62% without side effect [40].

Sildenafil alleviated intestinal and liver damage during occlusion of superior mesenteric artery and diminished oxidative stress [40]. Taking lower dosage before portal vein ligation, decreased hepatic tissue damage and suppressed MPO (myeloperoxidase), ICAM-1 and release of liver enzymes [41].
Likewise, its lower dosages improved injury score during intestinal ischemia/reperfusion [42]. Sildenafil has the same effect on renal ischemia/reperfusion. It is able to prevent the leukocytes infiltration, oxidative stress and apoptosis in kidney [43, 44]. Its contribution in obviation of renal ischemia/reperfusion injury is mediated by peroxisome proliferator-activated receptor γ (PPAR-γ) [45]. A recent study demonstrated that sildenafil orally or its local delivery presents a renoprotective function in canine species. Except restricting production of cytokines and expression of caspase-3, it increased the expression of Nrf2 (nuclear factor erythroid 2-related factor 2) and eNOS (endothelial nitric oxide synthase) in the kidney [46]. Vardenafil could improve antioxidant activity in rat model of intestinal volvulus and reduce tissue damage [47]. Tadalafil acted through the same mechanism in liver ischemia and prevented apoptosis [48].
Sildenafil successfully minimized the destructive effect of torsion/detorsion on testicular architecture of rats, decreased oxidative stress and cleaved caspase-3 and conserved seminiferous tubules [49-53].

Vardenafil and tadalafil can protect against testicular and ovarian torsion and decrease apoptosis [54-57]. These PDE inhibitors can protect against other organs ischemia which have not been mentioned here and it seems their effect is similar to sildenafil in this regard. These findings explain the potential of sildenafil or other PDE inhibitors in interacting with and modifying many signaling pathways. The multi-disciplinary function of PDE inhibitors against ischemia saves the ischemic organ and minimizes the extent of damage.

BENEFICIAL EFFECTS OF SILDENAFIL IN CARDIOVASCULAR SYSTEM

Many researches claim that sildenafil is a cardioprotective drug. The results revealed that it hinders cardiac hypertrophy and prevents heart failure. Sildenafil (100 mg/kg/day for 5 days) improved systolic and diastolic performance of heart in a mice model of angiotensin II-induced heart failure. It decreased cardiac hypertrophy and apoptosis of cardiomyocytes [58]. Early molecular alteration of left ventricle such as ERK and calcineurin pathway in the condition of pressure overload was ameliorated by sildenafil [59]. Pretreatment with sildenafil reduced the risk of post-ischemic arrhythmia in dogs [60]. Likewise, it improved biochemical status of myocardium after an episode of ventricular fibrillation (VF) in piglets. The drug pushed their energy metabolism to aerobic metabolism and the treated group had higher ATP and ADP levels and lower lactate levels in their myocardium [61]. Guazzi et al, investigated the effect of long-term administration of sildenafil (50 mg twice daily) in patients with heart failure. It showed several advantageous effects without side effects. Sildenafil lowers pulmonary artery pressure and breathlessness, enhanced brachial artery flow-mediated dilatation and promotes ventilation during activity [62]. Sildenafil (100 mg) dilates pericardial arteries in patients with coronary artery disease and disrupts platelet activation. Its potency was significant for improving severe myocardial ischemia, however its potency was less than isosorbide dinitrate [63]. A recent clinical trial with a longer duration of treatment (50 mg, three times a day for six months) in patients with chronic stable LV failure (left ventricle failure) collected convincing results on the beneficial effects of sildenafil in heart failure. In this study, sildenafil improved LV ejection fraction and 6 minute walking test, as well as Doppler-derived variables from LV diastolic function [64]. Pretreatment with tadalafil (10 mg/kg) could significantly minimize infarct

size after coronary artery occlusion in rats [65]. Similar to sildenafil other PDE inhibitors possess cardioprotective properties. Tadalafil could prevent doxorubicin-induced heart failure through attenuation of protein kinase G-induced disulfide formation [66]. Likewise, tadalafil augments heart's contractile function and its catecholamine responsiveness [67].

A single dose of sildenafil (100 mg) improved the maximum walking time of patients with arterial claudication [68]. Eight weeks of treatment with sildenafil (100 mg/day) in patients with Raynaud's phenomenon secondary to systemic sclerosis increased finger blood flow both before and after exposure to cold [69]. A recent but small clinical trial in patients with secondary Raynaud's phenomenon showed that topical use of sildenafil cream %5 significantly hones blood flow in digital arteries [70]. In contrast, on demand sildenafil cannot reduce the frequency, disability, or duration of attacks [71, 72]. Bellando-Randone and colleagues have shown that bosentan and sildenafil together can foster the results of nailfold video capillaroscopy (NVC)**,** Raynaud condition score (RCS) in the secondary Raynaud's phenomenon. The results of combination therapy was better than each alone [73]. Tadalafil (20 mg, daily) could improve digital lesions of patients with secondary Raynaud's phenomenon whom were resistant to calcium channel blockers or other vasodilators [74]. It was shown that vardenafil can benefit patients with primary Raynaud's phenomenon and secondary Raynaud's phenomenon with limited cutaneous scleroderma. It decreased RCS and the number and duration of Raynaud's phenomenon [75]. Chronic administration of sildenafil (25mg three times a day) in men with type 2 diabetes improves endothelial function and increases flow mediated-dilatation. A significant reduction were also observed in the C-reactive protein, interleukin 6, intercellular adhesion molecule and vascular adhesion molecule levels [76]. Another study with the same target population showed that chronic use of sildenafil (100 mg/day, for three months) decreased p-selectin, low-density lipoprotein (LDL), post-prandial blood glucose and HbA1c,while increased HDL (high-density lipoprotein) [77]. Sildenafil improves vascular endothelial activity in diabetic rats. It was observed that downregulation of endothelin receptor, iNOS and NADPH oxidase is implicated in such effect [78]. In addition, sildenafil promotes angiogenesis through protein kinase G/MEK/MAPK (mitogen-activated protein kinase) pathway and stimulates the proliferation and migration of endothelial cells [79].

Insert Figure 2 here

However, many preclinical and some clinical studies suggested sildenafil as a cardioprotective agent, and clinical trials are currently opposed this concept. Some of them claim that sildenafil has no beneficial effects, and few suggest it as a deteriorating factor [80, 81].

PROTECTIVE EFFECT OF SILDENAFIL ON NEUROINFLAMMATION

As mentioned, sildenafil has shown significant anti-inflammatory properties. These findings prompted researchers to measure the effect of sildenafil in neural damage.

Sildenafil can reduce IFN-γ, and IL-1β levels, enhance glutathione S-transferase pi, and protect the myelin structure/ultrastructure in cuprizone-induced demyelination model. Inhibition of inducible NO synthase (iNOS) may be part of the protective effect of sildenafil [82]. Inducible NOS is most commonly involved in inflammatory conditions and neurodegenerative disease in which NO is produced in large amounts. After binding of NO to soluble guanylyl cyclase (sGC), cGMP signaling cascades are activated and leading to cGMP-dependent responses. The cGMP signal can be terminated by the action of several PDEs. Subsequently, sildenafil enhances the accumulation of cGMP, the main NO signaling molecule. Sildenafil cannot reduce the levels of inflammatory cytokines such as IL-1β, IFN-γ, COX-2 and TNF-α in mice without iNOS. The inhibition of iNOS activity induces enhancement of IL-1β, IL-6, and TNF-α levels and, in other hand a persistent increase of iNOS expression downregulate the TNF receptor. High concentration of cGMP coregulate this feedback mechanism. Anti-inflammatory effects of sildenafil mainly is by inhibiting iNOS, and cGMP-iNOS feedback [82, 83]. Another study was performed in rats with hepatic encephalopathy and portocaval shunt. Sildenafil improved spatial learning behavioral tests such as radial and Morris water mazes. It decreased the elevated level of IL-1β (interleukin-1β), TNF-α, P38 component of MAPK, NMDA (N-methyl-D-aspartate) receptors and GABAa (gamma aminobutyric acid receptor type a) in the hippocampus of these animals [84]. Sildenafil restricted neuroinflammation in an experimental autoimmune model of encephalitis in mice. Oligodendrocyte glycoprotein peptide (MOG35–55)-induced encephalitis is a surrogate for multiple sclerosis (MS) in humans. Sildenafil prevented the axonal destruction and enhanced remyelination. It happened because sildenafil

decreased microglial activity and ICAM-1expression and. Instead, it increases T regulatory activity and astrocytes to isolate the inflamed foci [85].

Additional animal studies have shown the preventive effects of sildenafil on demyelination by modulating the AMPK–IKβα–NFκB (nuclear factor kappa) signaling pathway [86]. The exciting findings of an MS model in mice have shown that sildenafil stimulates the maturation of oligodendrocytes through the NO/PKG pathway and produces the ciliary neurotrophic factor (CNTF) as a promyelinating factor [87]. A Clinical study demonstrated that administration of sildenafil in ED with concomitant MS improves quality of life [88].

Consistently, sildenafil diminishes LPS-induced inflammation by suppressing ROS (reactive oxygen species)-associated with MAPK/NF-κB pathways in the microglia [89]. Likewise, sildenafil, L-NAME (L-N^G-Nitro arginine methyl ester, a NOS inhibitor) and aminoguanidine (selective iNOS inhibitor) reversed the biochemical and behavioral changes in LPS-induced depression of mice [90].

Sildenafil yield an improvement of cognitive function during acute stress mediated by reduced oxidative stress [91]. It alleviated memory loss in mice model of Alzheimer's disease, and inhibited β-amyloid accumulation and attenuated inflammation. Its preventive effects on cognitive disorder were performed through cGMP/PKG/pCREB (cAMP response element-binding protein) [92]. Also, it improved noise-induced memory loss in mice by reducing oxidative stress and inflammation [93]. Similar to sildenafil, tadalafil preserved long-term memory and improved synaptic plasticity in rat model of hepatic encephalopathy. Tadalafil enhanced plasticity through PKA/PKG/CREB/BDNF/NeuN/synaptophysin and upregulated glutamate receptors [94]. Tadalafil decreased oxidative stress in the hippocampus of mice and caused memory enhancement [95, 96]. Tadalafil improved mild cognitive impairment of patients whom consumed it because of erectile dysfunction [97]. Although, more research is needed to show how sildenafil and tadalafil affect human neurodegenerative disease, initial findings of the drug's effect on murine model disclosed that PDE inhibitors can attenuate inflammation through various mechanisms. In addition, several specific molecular mechanisms have been shown to be involved in its effects on MS, encephalopathy, and cognitive impairment.

Insert Figure 3 here

SILDENAFIL AND LUNG DISEASES

Although sildenafil has been approved for pulmonary arterial hypertension (PAH), researches have shown that it has beneficial effects on many other lung diseases. Moreover, animal studies exhibited the use of sildenafil in PAH is accompanied with the reduction of many inflammatory mediators and the modulation of several intracellular signaling molecules such as MAPK, AKT, NF-kβ and ERK [98].

Sildenafil (50 mg/kg/day, twice daily, subcutaneous injection) alleviated bronchopulmonary dysplasia in rat's pup exposed to hyperoxia. It increased cGMP and alveolarization, improved angiogenesis and survival, prevented fibrin deposition, erupts inflammation and right ventricular hypertrophy (RVH) [99]. Further animal study have shown that sildenafil contributes in lung recovery by activating hypoxia-induced growth factor-α (HIF-α) and overexpression of VEGF [100]. A meta-analysis of five clinical studies in preterm infants showed that sildenafil may decrease PAP and respiratory scores without clear evidence of its effect on mortality rate [101].

A small size randomized clinical trial in patients with cystic fibrosis could show that a single dose of sildenafil (50mg) could increase VO_2 peak levels and 4 weeks of treatment even increased exercise capacity, FEV_1 and exercise toleration [102]. Similarly, sildenafil decreased the activity neutrophil elastase in patients with cystic fibrosis [103]. The drug augmented exercise capacity in children with cystic fibrosis, but simultaneously significantly reduced FEV_1 [104].

Sildenafil preserved the histopathological structure of the airways in acrolein-induced airway inflammation of rats. It attenuated the production of pro-inflammatory cytokines such as TNF-α, as well as barricaded leukocytes migration and mucus hypersecretion. Moreover, sildenafil prevented epithelial hyperplasia and metaplasia [105]. Inversely, Al Qadi et al, claimed that sildenafil and L-arginine, the substrate for NO production, will worsen the airway hyper-responsiveness in the animal model of asthma [106]. Tadalafil (1 mg/kg for 8 weeks) could significantly prevent airway hypersensitivity and modulate inflammation by decrease of inflammatory cells, TNF-α, TGF-β and oxidative stress [107]. Sildenafil citrate (10 mg/kg/day subcutaneously for 14 days) reduced lung fibrosis in a rat model of pulmonary fibrosis by reducing the expression of inflammatory cytokines [108]. Furthermore, sildenafil lowered inflammation in a rat model of severe scald burn, which

indicates acute lung injury [109]. In meconium-induced acute lung injury in neonatal rats, sildenafil had a strong effect on lung tissue preservation and attenuate the burst of inflammation. Meaningfully, its effect on reducing inflammation is comparable to dexamethasone [110]. During acute lung injury, the drug prevents apoptosis, the leakage of neutrophils into inflamed foci, and relieves pulmonary edema [111]. The results suggest that sildenafil may be a new option for treatment of lung diseases, particularly those associated with an underlying inflammatory response.

Insert Figure 4 here

PDE-5-INHIBITORS FOR CIRRHOTIC PORTAL HYPERTENSION

Cirrhotic patients suffer from increased portal vein pressure which can lead to formation of esophageal varices and threaten their lives. Decreased NO production in their liver and increased activity of PDE5 are implicated in increased resistance of hepatic sinusoids and pathophysiology of portal hypertension. Hence, PDE5 inhibitors such as sildenafil has been proposed as a potential treatment option for portal hypertension [112]. In a small trial, sildenafil 50 mg was orally administered for cirrhotic patients with portal hypertension. However, sildenafil could not significantly decrease portal pressure but it significantly decreased pulmonary arterial pressure and sinusoidal resistance. Meanwhile, NO and cGMP were significantly increased in hepatic vein [113]. Another small study claimed that vardenafil (10 mg) can decrease portal pressure of cirrhotic patients. Simultaneously, vardenafil increased their portal flow [114]. Daily administration of udenafil 75-100 mg for compensated preascitic liver cirrhosis significantly decreased portal pressure in a phase II clinical trial without any significant cardiovascular adverse effects [115]. There are also case reports about the beneficial effects of PDEIs on portal pressure [116, 117]. There are controversial results from several studies in this regard and large size trials are needed to uncover the ultimate effect of PDEIs on portal vein hemodynamics [118-120].

BENEFICIAL EFFECTS OF SILDENAFIL IN GENITOURINARY SYSTEM

Sildenafil has been used in ED for two decades. In recent years, more evidence has been found for sildenafil in urology. Herein, two of its useful uses may be in BPH (benign prostatic hyperplasia) and

LUTS (lower urinary tract symptoms). In fact, it limits the progression of BPH and reduces its symptoms through various mechanisms. This reduces inflammation in the enlarged prostate, prevents smooth muscle and stromal proliferation, diminishes sphincter tonicity and relaxes muscle fibers in bladder and prostate [121]. In the absence of asymptomatic inflammatory prostatitis, Eryildirim et al, demonstrated chronic use of sildenafil improves LUTS in patient with ED and concomitant LUTS [122]. As well, tadalafil is a good therapeutic option for LUTS secondary to BPH [123, 124]. The beneficial effects of sildenafil on genitourinary system is expanding over time, and some articles have suggested it as one of the most effective drugs for premature ejaculation (PE) [125]. One clinical trials shows that the combination of dapoxetine and sildenafil is the most effective medication for PE [126].

SILDENAFIL IN GASTROINTESTINAL (GI) TRACT AND WOUND HEALING

An acetic acid-induced colitis model in rats showed sildenafil (5 mg/kg/day) preserved colon microarchitecture and decreased lipid peroxidation, myeloperoxidase (MPO) activity, TNF-α and IL-1β, while increased glutathione (GSH) levels [127]. The colitis model with TNBS (Trinitrobenzene sulfonic Acid) had similar results. This time, in an additional group, L-NAME reversed the protective effects of sildenafil [128, 129]. Likewise, glibenclamide reversed some of the protective effects of sildenafil, indicating that K^+ channels were involved in the protective effect of sildenafil in colitis [130]. Apart from the protective role of sildenafil in colon, it was able to minimize the damage extent in the indomethacin-induced gastropathy in rats through the NO/cGMP [131]. However, it cannot increase the production of prostaglandin in the stomach mucosa, but it reduced MPO activity and leukocytes immigration [132, 133]. It also prevented indomethacin-induced small intestine ulcer in rats with the same mechanism [131]. In addition to confronting NSAIDs, sildenafil could relive stomach injury in ethanol-induced gastric injury. Its protective activity has been lost after the addition of L-NAME, ODQ (guanylate cyclase inhibitor) and glibenclamide. It indicates that NO/cGMP/K_{ATP} pathway involved in sildenafil protective effect [134]. Interestingly, daily administration of sildenafil modulate inflammation and bone loss in the experimental periodontitis model of rats [135].

The drug improved the healing process of colon anastomosis and reduced the formation of intra-abdominal adhesion bands. Indeed, it increased angiogenesis and collagen maturity and reduced

inflammation [33, 136]. Derici et al, showed that sildenafil (10 mg/kg once daily for 10 days) increased angiogenesis in the wound healing process in the abdominal wall of rats [137]. Supporting these findings, sildenafil had a suppressive role in the inflammatory phase of bone fracture healing while and in its repair phase [138]. Hachulla et al indicated sildenafil (20 mg three times daily for 12 weeks) can improve the healing process of ischemic digital ulcers in patients with systemic sclerosis [139]. It was shown that tadalafil can facilitate diabetic wound healing through acceleration of angiogenesis and epithelialization [140]. Assembling Polycaprolactone suture with tadalafil improved wound healing in rats [141]. Daily administration of tadalafil (1 mg/kg) prevented burn-induced necrosis in rats [142]. There is also clinical reports of beneficial effects of tadalafil for wound healing which prevented limb amputation [143]. According to the findings, PDE inhibitors prevent ulceration and promotes wound healing by enhancing angiogenesis and attenuating inflammation.

Insert Figure 5 here

THE PROMISING EFFECTS OF SILDENAFIL IN LIVER AND KIDNEY

However, sildenafil was tested in other organs and the liver was neglected for a while. The researchers found out Sirt1 (a deacetylating agent in regulation of metabolism [144], AMPK, and eNOS regulate hepatic energy metabolism and inflammation. Therefore, they used a combination of drugs dealing with these molecules to harness fatty liver disease and hepatic steatosis. They chose metformin, leucine and sildenafil. These drugs together reversed the detrimental effect of high-fat diet on the liver of mice and reduced inflammatory cytokines and fibrosis mediators. Although, they were prosperous together, one or two of them failed to achieve the same result [145]. A randomized clinical trial showed that taking this composition (metformin 500 mg + sildenafil 1 mg + leucine 1100 mg) twice daily for 16 weeks, reduces hepatic fat by 15.7% [146], as evidenced by MRI. In addition to the protective effect of sildenafil against NASH (non-alcoholic steatohepatitis), it reduces liver damage in the animal model of ASH (alcoholic steatohepatitis) [147]. Administration of sildenafil in carbon tetrachloride-induced liver damage, reduced AST, ALT, ALP and increased total protein, ultimately modulated hepatocyte injury [148]. Combination of diosmin (100 mg/kg/day) and tadalafil (10 mg/kg

twice daily) could protect against cholestasic liver cirrhosis of rats by attenuation of p38/MAPK/NF-kβ axis and downregulation of iNOS [149].

Sildenafil (3 mg/kg/day for 8 weeks) augmented the protective role of telmisartan (10 mg/kg/ day for 8 weeks) against diabetic nephropathy in a streptozotocin-induced diabetic model and saved renal microarchitecture [150]. Sildenafil citrate (50 mg/day for one month) reduced HbA1c and microalbuminuria in male patients with type 2 diabetes [151]. Sildenafil (0.4 mg/kg/day) reduced creatinine in cisplatin-induced nephrotoxicity, diminished apoptosis and decreased renal injury in histopathology [152]. Tapia et al, examined the effect of sildenafil in a rat model of 5/6 nephrectomy which induces renal fibrosis [153]. They concluded that sildenafil (5 mg/kg/day) ameliorated arteriolar remodeling, reduced single-nephron hyperfiltration and hypertension, reduced proteinuria and prevented histopathological changes in residual kidney. In contrary, other anti-hypertensive drugs such as reserpine, hydralazine, and hydrochlorothiazide cannot modulate glomerular hemodynamics, proteinuria and histopathological changes [154]

SILDENAFIL AND CANCER

Interestingly, Islam et al, indicated administration of sildenafil (5.7 mg/kg/day) decreased polyps number to 50% in dextran-sulfate sodium (DSS)-induced colitis in mice. Polyps were more differentiated in the treated group. Furthermore, treated group had lower expression of inflammatory markers [155].

Sildenafil in combination with non-toxic dose of paclitaxel reduced inflammation in melanoma via diminishing IL-4, IL-6, IL-8, TNF-α, INF-γ (interferon-γ), VEGF and many other inflammatory mediators. It also increased the activity of anti-tumoral T-cells and the expression of TCR (T-cell receptor) in mice with melanoma. The main reason for this phenomenon is the suppressive effect of sildenafil on NO production and expression of iNOS and ARG-1 (arginase-1, participating in the immunosuppressive property of tumors). These two mechanisms, confronting inflammation and immunosuppression, are the major contributory effects of sildenafil in the treatment of melanoma

[156]. Surprisingly, long-term use of sildenafil in mice with melanoma significantly prolonged their survival and confined tumor progression and metastasis [157].

In a retrospective study, men treated with phosphodiesterase 5 inhibitors such as sildenafil, tadalafil and vardenafil had a lower chance of prostate cancer [158]. A multicenter study in North America claimed that there was a negative correlation between PDE inhibitors and prostate cancer but was not statistically significant [159]. Also, PDE inhibitors can reduce hypoxia-induced resistance of prostate cancer to doxorubicin and diminish the surviving cells by 51% [160]. In addition to in vivo studies, there are numerous in vitro studies that claim the anti-cancer properties of sildenafil. Most concluded that the anti-tumoral effects of sildenafil is due to the promotion of apoptosis in tumoral cells, enhance concomitant chemotherapy and stimulation of immune cells [157, 161]. Some of them can detect the pathways of sildenafil in the treatment of cancer. For example, Das et al observed sildenafil increase the doxorubicin-induced apoptosis of prostate cancer cells by potentiation of CD95 signalling pathway [162]. It was observed that tadalafil can potentiate tumor-specific immunity ex vivo which happens through increase in T cell number and decrease in myeloid-derived suppressor cells [163]. Similarly, tadalafil (20 mg/day) decreased T regulatory cells and myeloid-derived suppressor cells but increased CD8+ T cells in patients with head and neck squamous cell carcinoma [164].

Chen et al demonstrated that sildenafil restricts tumor proliferation and viability by reducing HSP90 expression (heat shock protein 90) and degrading PKD2 (protein kinase D2) [165]. These molecule are involved in tumor growth, invasion and angiogenesis [166, 167]. The breast cancer of mouse model highlighted the importance of sildenafil. The animal model showed that the addition of sildenafil to doxorubicin reduced tumor size by 4.7 times [165]. Recently it has been shown that phosphodiesterase 5 inhibitor could relater cancer cell resistance to chemotherapy (130). Most interestingly, in an in-vitro study sildenafil and one of its analogues contributed the differentiation of human neuroblastoma cell line IMR-32. Their effect was accompanied by the activation of AMPK/ACC (acetyl-CoenzymeA carboxylase) and PI3K/Akt signaling pathways [168].

In addition to the advantageous effect of sildenafil on tumor chemotherapy, it can alleviate the side effects of chemotherapy and radiotherapy. Sildenafil strongly reversed the increased level of ROS in irradiated bovine aortic endothelial cells [169]. Likewise, sildenafil citrate topical hydrogel 5% was

examined in irradiated skin of the rats. Radiation was selected at a 45 Gy dose to induce skin wound. Sildenafil hydrogel caused higher wound contraction, reduction of skin injury, and increased tensile strength, protein recovery, and nitric oxide production [170]. Sildenafil not only modulated skin injury and promoted its reconstruction, but also shortens the repairing time [171]. Prophylaxis and treatment with sildenafil modified radiation-induced proctitis in the rats, lowered the histopathological score and reduced the production of inflammatory cytokines [172].

According to recent findings, sildenafil restricts the growth of cancer and simultaneously protects the normal tissues. Adding sildenafil to current cancer treatment protocols appears to have beneficial effects with the least hazard.

Insert Figure 6 here

OTHER ADVANTAGEOUS UTILITIES

Previous studies have shown that the higher endometrial leukocyte infiltration, especially NK (natural killer) cell infiltration is associated with a higher rate of miscarriage [173, 174]. Intravaginal sildenafil (25 mg, four times a day for 36 days) in women with recurrent miscarriage, successfully reduced the activity of NK cells and amplified endometrial thickness [175]. The first case-report of four Egyptian patients with recurrent miscarriage showed that sildenafil interestingly prevented abortion. Concomitantly, it also reduced oxidative stress, TNF-α, CD3+CD56+ NKT cells and increases the level of anti-oxidants during gestation [176]. In a randomized trial, sildenafil was even better than estradiol valerate to improve endometrial vascularity and the prosperity of IUI (intra-uterine insemination, 20% vs 14%) [177]. In another clinical trial, Mohamed and colleagues showed that sildenafil citrate (20mg, orally, four time daily for 3 weeks) increased endometrial thickness [178]. Another trial revealed that sildenafil (50 mg/kg/day, orally) improved endometrial thickness, implantation rate, and chemical pregnancy rate in women with poor endometrial response and frozen embryo. Excitingly, it increased the ratio of progesterone and progesterone/estrogen [179]. Sildenafil also enhanced anti-oxidants levels and decreased MDA in patients [180]. A recent clinical trial of 66 infertile women with a history of repetitive IVF failure was performed to evaluate the effect of sildenafil on these patients. Suppository sildenafil (100 mg/day) doubled the success rate of chemical

pregnancy [181]. Sildenafil (20 mg , three time a day) and NO skin patch both were both effective in preventing abortion in the first trimester of pregnancy in women with a history of recurrent spontaneous first trimester abortion [182]. In addition to high doses of sildenafil, low dose (20 mg per day) increase the probability of pregnancy and prevent abortion in other clinical trial [183]. Sildenafil confronts inflammation, reduces NK cells, and improves endometrial and hormonal status to increase the chance of pregnancy in whom had a history of recurrent spontaneous abortion.

Sildenafil intravitreally, diminished damage in the mice model of optic nerve crush. It preserved the RGCs number and inhibited apoptosis. In addition, it attenuated oxidative stress [184, 185]. A clinical study with 4 patients showed the possible contribution of sildenafil to protect the photoreceptors in age-related and vitelliform macular degenerations [186].

The visual side effects (functional blindness, blue and blurred vision and enhanced light sensitivity) caused by sildenafil are indeed retinal in origin and attributed to be competitive inhibitors of PDE6 due to the similarity of amino acid sequence and the secondary structural in catalytic site. PDE6 enzyme is the key effector enzyme for the visual transduction cascade in the retina of mammalian eyes and its location in photoreceptor cells [187, 188].

In addition, again because of the most similarity of catalytic site of PDE11 with PDE5, tadalafil (dual inhibitor of PDE5 and PDE11) causes back and muscle pain (myalgia) since PDE11 enzymes are highly abundant in skeletal muscle cells [187].

Table1. The beneficial effects of sildenafil with data of the authors' study with respective doses.

CONCLUSION

Considering the distribution of PDE5 in different organs, it necessitates to find out its function. Targeting such a molecule may play a role in managing several diseases. Sildenafil can inhibit PDE5 and collaborate the NO pathway. Administration of sildenafil was promising in ED and PAH. Numerous animal models and fewer clinical trials are trying to reveal the advantageous utility of sildenafil in other diseases and expand its therapeutic indications. However, they were prosperous in the first step, future clinical trials are needed to validate the similar effects on humans and weigh its pros and cons.

CONFLICT OF INTEREST

Authors indicate that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

In this study every member respectively performed these responsibilities:

Moein Ala (performed the literature search and wrote the assay), Razieh Mohammad Jafari (drafted and critically revised the assay), and Ahmad Reza Dehpour (Supervision and Conceptualization).

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FIGURE CAPTIONS

Figure 1. This schematic picture illustrates the collaboration of sildenafil with the NO/cGMP pathway and exhibits the mechanism for facilitating smooth muscle relaxation after administration of sildenafil.

Figure 2. This figure shows the involvement of several mechanisms in the beneficial effects of sildenafil on the cardiovascular system.

Figure 3. This picture attempts to classify the most prominent effects of sildenafil on CNS diseases and to explain its elaborate mechanisms.

Figure 4. This image depicts the possible mechanisms of the protective effects of sildenafil in diseases afflicting the lung and airways.

Figure 5. This image shows the contributory effect of sildenafil on the gastrointestinal tract and explains its mechanisms of action.

Figure 6. This scheme shows the possible contributory mechanisms of sildenafil to inhibit tumors progression.

Author	Year	Topic Area	Respective Doses
Khatib SY.	2019	Sildenafil and ordonafil restricted the myocardial infarct size in an ischemia/reperfusion model of the isolated rabbit heart	1 mg/L of sildenafil or ordenafil perfused isolated rabbit heart for 5 min
Wang G, et al.	2015	Sildenafil improved the success rate of cardiopulmonary resuscitation after porcine-induced arrest in pigs.	0.5 mg/kg
Koneru S, et al.	2008	Sildenafil have cardioprotective effects	0.7 mg/kg
Das A, et al.	2009	Sildenafil have cardioprotective effects	1 µM, 10 min acute intracoronary infusion in early phase, 0.71 mg/kg ip in delay phase
Valatsou A, et al.	2017	Sildenafil improved arterial flow on the limb I/R	1 mg/Kg for 7 days ip
Senthilkumar A, et al.	2007	sildenafil stimulates angiogenesis in ischemic limb	10 mg/kg, Daily for 7 days
Armstrong DMFdO, et al.	2013	sildenafil protected soleus muscle	1 mg/kg, Gavage
Shih P-K, et al.	2013	lung I/R	10 mg/kg, Lavage
Ayyildiz A, et al.	2005	Sildenafil increased skin flap viability in rats	1 mg/kg orally or topically 0.5 mg/kg
Kaya B, et al.	2015	Vardenafil and tadalafil decrease necrotic area	10 mg/kg/day Gavage for3 days
Kayiran O, et al.	2013	Tadalafil could decrease necrotic area	5 mg/kg, Daily for 7 day
Ayten R, et al.	2008	Vardenafil and tadalafil decrease necrotic area	8 mg/kg, i.p
Celik M, et al.	2014	Sildenafil saved the ovaries against both ischemia and torsion	1.4 mg/kg, oral gavage
Ganla KN, et al.	2019	Sildenafil decreased ovarian edema and improved its perfusion and venous return in the patient	25 mg 8 hourly, vaginal
Wang QM, et al.	2013	Combination of sildenafil and atorvastatin, after cerebral	0.3 mg/kg, gavage, Daily for 6 days

		ischemia, improved behavioral tests in mice	
Zhang L, et al.	2006	Tadalafil accelerated neurological function recovery after cerebral ischemia in rats	2 mg/kg or 10 mg/kg orally every 48 h for 6 days starting 24 h after stroke onset
Zhang RL, et al.	2006	Sildenafil decreased infarct size after cerebral ischemia	3 mg/kg, Daily for 7 days
Inan M, et al.	2013	Sildenafil alleviated intestinal and liver damage during occlusion of superior mesenteric artery	50 mg/kg, gavage
Savvanis S, et al.	2014	Lower dosage of Sildenafil decreased hepatic tissue damage	0.3 mg/kg intraperitoneal
Moore HM, et al.	2020	Sildenafil protected Intestinal I/R	dose ranges of 0.01 to 10 mg/kg, ip
Zahran MH, et al.	2015	Sildenafil protected Renal I/R	1 mg/kg, gastric gavage
Oruc O, et al.	2010	Sildenafil protected Renal I/R	1 mg/kg, single dose
Mohey V, et al.	2016	Sildenafil protected Renal I/R	0.5, 1 mg/kg, i.p
Zahran MH, et al.	2019	Renoprotective function in canine species	1 mg/kg, orally or local delivery
Doğan G,et al.	2019	Vardenafil improved antioxidant activity in rat model of intestinal volvulus	1 mg/kg, i.p
Bektas S, et al.	2016	Tadalafil acted in liver ischemia	2.5 mg/kg, 10 mg/kg
Zavras N, et al.	2014	Sildenafil minimized the destructive effect of torsion/detorsion on testicular architecture of rats	0.7 mg/kg, i.p
Kostakis ID, et al.	2017	Sildenafil protected testicular I/R of rats	0.7 mg/kg, i.p
Beheshtian A, et al.	2008	Sildenafil minimized the destructive effect of testicular torsion/detorsion	0.7 mg/kg, i.p
Abdel-Rahman MM, et al.	2016	Sildenafil minimized the destructive effect of torsion/detorsion on testicular of rats	0.7 mg/kg, i.p

Erol B, et al.	2009	Vardenafil protected testicular torsion	1 mg/kg, i.p
Wu Z, et al.	2015	Tadalafil protected testicular torsion	0.5 mg/kg, 2 mg/kg, Daily gavage
Arikan DC, et al.	2010	Tadalafil protected ovarian torsion	5 mg/kg, single dose, i.p
Yurtcu E, et al.	2015	Vardenafil protected ovarian torsion	1 mg/kg, 2 mg/kg, i.p
Westermann D, et al.	2012	Sildenafil improved systolic and diastolic performance of heart in a mice model of heart failure	100 mg/kg/day for 5 days
Imai Y, et al.	2018	Sildenafil ameliorated early molecular alteration of left ventricle.	200 mg/kg for two days
Nagy O, et al.	2004	Pretreatment with sildenafil reduced the risk of post-ischemic arrhythmia in dogs	2 mg/kg, orally
Zhang Q, et al.	2014	Sildenafil improved biochemical status of myocardium after an episode of ventricular fibrillation in piglets	0.5 mg/kg, i.p
Guazzi M, et al.	2007	Sildenafil lowered pulmonary artery pressure and breathlessness, enhanced brachial artery flow-mediated dilatation.	50 mg, twice daily
Halcox JPJ, et al.	2002	Sildenafil dilated pericardial arteries in patients with coronary artery disease, disrupted platelet activation and Improved severe myocardial ischemia.	100 mg
Elhakeem WA, Khairy H.	2019	Sildenafil improved LV ejection fraction in heart failure in patients with chronic stable LV failure (left ventricle failure).	50 mg, TDS for six months
Sesti C, et al.	2007	Pretreatment with tadalafil minimized infarct size after coronary artery occlusion in rats.	10 mg/kg
Prysyazhna O, et al.	2016	Tadalafil prevented doxorubicin-induced heart failure.	1 mg/kg
Lawless M, et al.	2019	Tadalafil augmented heart's contractile function.	20 mg Daily

Omarjee L, et al.	2019	Sildenafil improved the maximum walking time of patients with arterial claudication	100 mg, single dose
Andrigueti FV, et al.	2017	Sildenafil increased finger blood flow in patients with Raynaud's phenomenon secondary to systemic sclerosis.	100 mg/day for 8 weeks
Wortsman X, et al. 2018	2018	Sildenafil honed blood flow in digital arteries in patients with secondary Raynaud's phenomenon.	topical use of sildenafil cream %5
Bellando-Randone S, et al.	2016	Bosentan and sildenafil fostered the results of nailfold video capillaroscopy (NVC), Raynaud condition score (RCS) in the secondary Raynaud's phenomenon.	Long-term treatment with sildenafil, 3 to 6 months
Shenoy PD, et al.	2010	Tadalafil improved digital lesions of patients with secondary Raynaud's phenomenon whom were resistant to calcium channel blockers or other vasodilators	20 mg, Daily
Caglayan E, et al.	2012	Vardenafil helped patients with primary Raynaud's phenomenon and secondary Raynaud's phenomenon with limited cutaneous scleroderma.	10 mg, twice daily
Aversa A, et al.	2008	Sildenafil in men with type 2 diabetes improved endothelial function and increased flow mediated-dilatation.	25 mg, TDS
Mandosi E, et al.	2015	Sildenafil decreased p-selectin, LDL, post-prandial blood glucose and HbA1c and increased HDL	100 mg/day, 3 months
Luo L, et al.	2011	Sildenafil improved vascular endothelial activity in diabetic rats.	12 mg/kg, Daily, p.o.
Pyriochou A, et al.	2007	Sildenafil promoted angiogenesis and proliferation of endothelial cells.	10 μM

Raposo C, et al.	2013	Sildenafil protected neural damage.	25 mg/kg
Hernandez-Rabaza V, et al.	2015	Sildenafil improved spatial learning behavioral tests	50 mg/L, in drinking water for 6 weeks
Pifarre P, et al.	2011	Sildenafil prevented the axonal destruction and enhanced remyelination.	10 mg/kg, s.c. for 8 days
Nunes AKS, et al.	2015	Sildenafil prevented demyelination.	25 mg/kg, orally
Díaz-Lucena D,et al.	2018	Sildenafil stimulated the maturation of oligodendrocytes and produced CNTF as a promyelinating factor in MS model in mice.	10 mg/kg, Daily
Fowler CJ, et al.	2005	Sildenafil improved erectile dysfunction in men with concomitant MS.	25–100 mg
Zhao S, et al.	2011	Sildenafil decreased LPS-induced inflammation in the microglia.	3, 10, 30, 100 μM
Tomaz VS, et al.	2014	Sildenafil reversed the biochemical and behavioral changes in LPS-induced depression of mice.	5 mg/kg
Ozbeyli D, et al.	2015	Sildenafil improved the cognitive function during acute stress.	25mg/kg, Daily
Zhang J, et al.	2013	Sildenafil alleviated memory loss in mice model of Alzheimer's disease.	10 mg/kg, i.p for 10 days
Sikandaner HE, et al.	2017	Sildenafil improved noise-induced memory loss in mice.	15mg/kg, orally for 14 days
França MER, et al.	2019	Tadalafil preserved long-term memory.	15 mg/kg, gavage for 15 days
Al-Amin MM, et al.	2014	Tadalafil caused memory enhancement.	5 mg/kg, orally for 4 weeks
Bhatia P, et al.	2010	Tadalafil caused memory enhancement.	5, 10 mg/kg p.o.
Urios A, et al.	2019	Tadalafil improved mild cognitive impairment of patients.	5 mg/day, for 6 month

Kiss T, et al.	2014	Sildenafil has been approved for pulmonary arterial hypertension (PAH), and many other lung diseases.	2 mg/kg Daily, orally for 28 days
De Visser YP, et al.	2009	Sildenafil alleviated bronchopulmonary dysplasia in rat's pup exposed to hyperoxia.	50 mg/kg/day, twice daily, subcutaneous injection
Park H-S, et al.	2013	Sildenafil contributed to lung recovery.	100 µg/g, Daily, i.p
van Der Graaf M, et al.	2019	Sildenafil may decrease PAP and respiratory scores in preterm infants.	Initial dose range 0.3-1.5 mg/kg/day, with a maximum dose of 6–8 mg/kg/day
Rodriguez-Miguelez P, et al.	2019	Sildenafil increased exercise capacity, FEV1 and exercise toleration trial	50 mg, for 4 weeks
Taylor-Cousar JL, et al.	2015	sildenafil decreased the activity neutrophil elastase in patients with cystic fibrosis	20 or 40 mg p.o., TDS for 6 weeks
Reisi M, et al.	2020	Sildenafil augmented exercise capacity in children with cystic fibrosis, but simultaneously reduced FEV1	1 mg/kg p.o, T.D.S for 3 months
Wang T, et al.	2009	Sildenafil preserved the structure of airways in acrolein-induced airway inflammation of rats	25 mg/kg, gavage 0.5 h before acrolein exposure
Al Qadi-Nassar B, et al.	2007	sildenafil will worsen the airway hyper-responsiveness in the animal model of asthma	20 mg/kg, i.p for 7 days
Abdelaziz RR, et al.	2016	Tadalafil prevented airway hypersensitivity and modulate inflammation	1 mg/kg, for 8 weeks
Yildirim A, et al.	2010	Sildenafil citrate reduced lung fibrosis in a rat model of pulmonary fibrosis	10 mg/kg/day subcutaneously, 14 days
Gokakin AK, et al.	2013	Sildenafil lowered inflammation in a rat model of severe scald	10, 20mg/kg

		burn acute lung injury	
Song J, et al.	2016	Sildenafil preserved lung tissue In meconium-induced acute lung injury in neonatal rats	25 mg/kg lavage, 30 minutes after meconium
Kosutova P, et al.	2018	Sildenafil relieves pulmonary edema during acute lung injury	1 mg/kg, intravenous
Lee KC, et al.	2008	Sildenafil could not significantly decrease portal pressure but it significantly decreased pulmonary arterial pressure and sinusoidal resistance.	50 mg, orally
Deibert P, et al.	2006	Vardenafil decreased portal pressure of cirrhotic patients	10 mg
Kreisel W, et al.	2015	Udenafil decreased portal pressure in a phase II clinical trial without any significant cardiovascular adverse effects	75-100 mg, Daily
Deibert P, et al.	2007	Beneficial effects of PDEIs on portal pressure	10 mg Tadalafil
Deibert P, et al.	2018	Beneficial effects of PDEIs on portal pressure	20 mg, twice a day
Eryildirim B, et al.	2010	Sildenafil improves LUTS in patient with ED and concomitant LUTS	50 mg, twice weekly for 4 weeks
Roehrborn CG, et al.	2008	Tadalafil is a good therapeutic option for LUTS secondary to BPH	2.5, 5, 10, 20 mg Daily for 12-week
Abu El-Hamd M, et al.	2018	Sildenafil with dapoxetine is the most effective medication for PE	50 mg
Iseri SO, et al.	2009	Sildenafil preserved colon microarchitecture in an acetic acid-induced colitis model in rats	5 mg/kg, Daily
Karakoyun B, et al.	2011	Sildenafil reversed the TNBS colitis model	25 mg/kg, Daily
Margonis GA, et al.	2015		25 mg/kg, oral gavage, Daily
Fakhfouri G, et al.	2012	Sildenafil treated colitis by K+ channels	1 mg/kg
Kato N, et al.	2009	Sildenafil prevented indomethacin-induced small intestine ulcer in	3-20 mg/kg, p.o

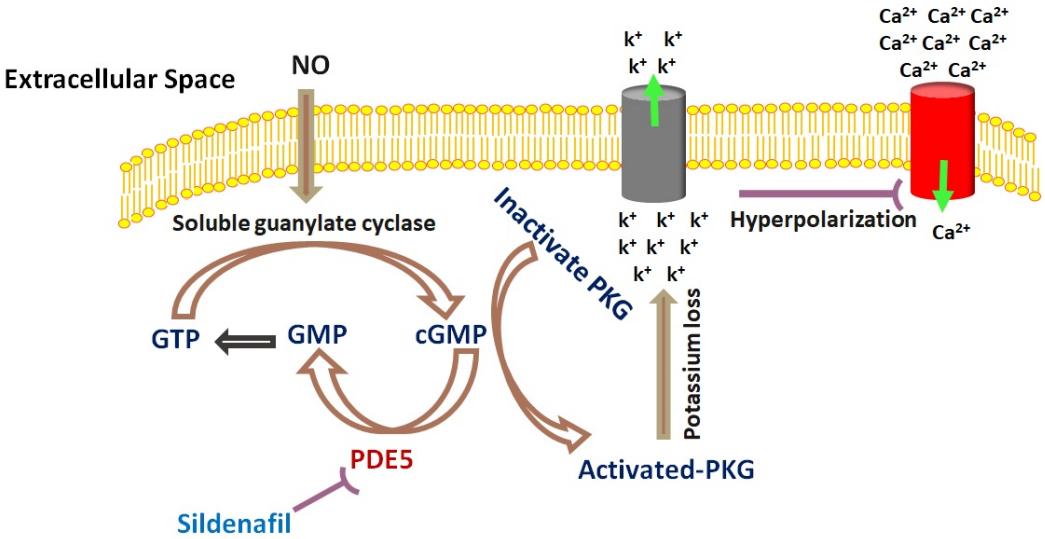
		rats	
Santos CL, et al.	2005	Sildenafil prevented indomethacin-induced gastropathy in rats	1, 4, 10 mg/kg
Medeiros JVR, et al.	2008	sildenafil could relive stomach injury in ethanol-induced gastric injury	1 mg/kg, Gavage
Soares DM, et al.	2018	Sildenafil modulated inflammation and bone loss in the experimental periodontitis model of rats	10 mg/Kg, for 30 days
Cakir T, et al.	2015	Sildenafil improved the healing process of colon anastomosis and reduced the formation of intra-abdominal adhesion bands	10 mg/kg, for 5 days
Derici H, et al.	2010	Sildenafil increased angiogenesis in the wound healing process in the abdominal wall of rats	10 mg/kg once Daily for 10 days
Kilinc CY, et al.	2015	Sildenafil had a suppressive role in the inflammatory and repair phase of bone fracture healing	1 mg/day in rats drinking water
Hachulla E, et al.	2016	Sildenafil improved the healing process of ischemic digital ulcers in patients with systemic sclerosis	20 mg TDS for 12 weeks
Jarad AS, et al.	2020	Tadalafil facilitated diabetic wound healing	5 mg /kg, Orally
Soufdoost RS, et al.	2020	Assembling Polycaprolactone suture with tadalafil improved wound healing in rats	Tadalafil releasing polycaprolactone suture, releasing about 125 to 210 µg of tadalafil during 15 days.
Singer AJ, et al.	2018	Tadalafil prevented burn-induced necrosis in rats	1 mg/kg Daily
Davenport C, et al.	2015	Beneficial effects of tadalafil for wound healing which prevented limb amputation	20 mg, TDS
Bruckbauer A, et al.	2016	Sildenafil with metformin, leucine reversed the detrimental effect	25 mg/kg

		of high-fat diet on the liver of mice and reduced fibrosis mediators.	
Chalasani N, et al.	2018	The composition of metformin + sildenafil + leucine reduces hepatic fat by 15.7%	sildenafil 1 mg twice daily for 16 weeks
Li J, et al.	2005	Sildenafil reduces liver damage in the animal model of alcoholic steatohepatitis	10 mg/kg, Daily
Molehin OR, et al.	2018	Sildenafil in carbon tetrachloride-induced liver damage modulated hepatocyte injury	5 mg, 10 mg, 20 mg/kg, p.o
Ali FEM, et al.	2018	Combination of diosmin and sildenafil protect against cholestasic liver cirrhosis of rats	10 mg/kg, twice daily
El-Mahdy NA, et al.	2016	Sildenafil augmented the protective role of telmisartan against diabetic nephropathy and saved renal microarchitecture	3 mg/kg, Daily for 8 weeks
Grover-Páez F, et al.	2007	Sildenafil citrate reduced HbA1c in male patients with type 2 diabetes	50 mg, Daily for one month
Lee KW, et al.	2009	Sildenafil reduced creatinine in cisplatin-induced nephrotoxicity	0.4 mg/kg, Daily
Tapia E, et al.	2012	Sildenafil ameliorated arteriolar remodeling, reduced single-nephron hypertension, prevented histopathological changes in residual kidney.	5 mg/kg, Daily
Islam BN, et al.	2017	Sildenafil decreased polyps number to 50% in dextran-sulfate sodium (DSS)-induced colitis in mice.	5.7 mg/kg, Daily
Meyer C, et al.	2011	Sildenafil significantly prolonged survival and confined tumor progression and metastasis in mice with melanoma	long-term use

Chavez AH, et al.	2013	Men treated with sildenafil, tadalafil and vardenafil had a lower chance of prostate cancer	retrospective study
Jamnagerwalla J, et al.	2016	There was a negative correlation between PDE5i and prostate cancer	multicenter study
Hamilton TK, et al.	2013	PDE5 inhibitors reduce hypoxia-induced resistance of prostate cancer to doxorubicin and diminish the surviving cells by 51%	100 nM
Das A, et al.	2010	Anti-tumoral effects of sildenafil is due to the promotion of apoptosis in tumoral cells	5, 10, 15 µM
Das A, et al.	2016	Sildenafil increased the doxorubicin-induced apoptosis of prostate cancer cells	5, 10, 15 µM
Califano JA, et al.	2015	Tadalafil can potentiate tumor-specific immunity ex vivo	20 mg, Daily
Weed DT, et al.	2015	Tadalafil decreased T regulatory cells and myeloid-derived suppressor cells in patients with head and neck squamous cell carcinoma	20 mg, Daily
Greish K, et al.	2018	Sildenafil reduced tumor size by 4.7 times in addition by doxorubicin in animal model	1, 30, 100 µM
Dar MI, et al.	2020	sildenafil contributed the differentiation of human neuroblastoma cell line	an in-vitro study
Wortel RC, et al.	2019	Sildenafil alleviated the side effects of chemotherapy and radiotherapy	5 µM at 5 minutes before radiation
Kulshrestha S, et al.	2019	Sildenafil citrate caused reduction of skin injury in irradiated skin of the rats.	topical hydrogel 5%

Yavuz E, et al.	2018	Prophylaxis and treatment with sildenafil modified radiation-induced proctitis in the rats	10 mg/kg/day 7 days before radiation or 15 days after radiation
Jerzak M, et al.	2008	Intravaginal sildenafil amplified endometrial thickness in women with recurrent miscarriage	25 mg, four times a day for 36 days
El-Far M, et al.	2009	Sildenafil interestingly prevented abortion	25 mg, vaginally, 4 times a day for 24 days
Mangal S, et al.	2016	Sildenafil improved endometrial vascularity and the prosperity of IUI (intra-uterine insemination)	25 mg, vaginally, 4 times a day, from day 8^{th} of the cycle.
Mohamed MA, et al.	2019	Sildenafil citrate increased endometrial thickness	20mg, orally, four time daily for 3 weeks
Firouzabadi RD, et al.	2013	Sildenafil improved endometrial thickness, implantation rate, and chemical pregnancy rate in women with poor endometrial response and frozen embryo.	50 mg/kg, Daily, orally
El-Far M, et al.	2014	Sildenafil enhanced anti-oxidants levels in unexplained recurrent miscarriage patients	25 mg intravaginally, 4 times/day for 24 days 25 mg intravaginally, 3 times/day for 13 days
Moini A, et al.	2020	Sildenafil doubled the success rate of chemical pregnancy history of repetitive IVF failure	100 mg, Daily Suppository
Gamea RMR, et al.	2018	Sildenafil and NO skin patch were effective in preventing abortion in the first trimester of pregnancy in women	20 mg, TDS
Bahaa HA.	2018	Sildenafil low dose increased the probability of pregnancy and prevent abortion	20 mg, Daily
Zahavi A, et al.	2019	Sildenafil preserved the RGCs number in the mice model of optic nerve crush.	24 µg/3µL intravitreally, 24 µg/300µL, ip

Goldenberg-Cohen N, et al.	2014	Sildenafil diminished damage in the mice model of optic nerve crush.	0.24 µg/3µl intravitreally
Coleman DJ, et al.	2018	Sildenafil protected the photoreceptors in age-related and vitelliform macular degeneration	40 mg b.i.d



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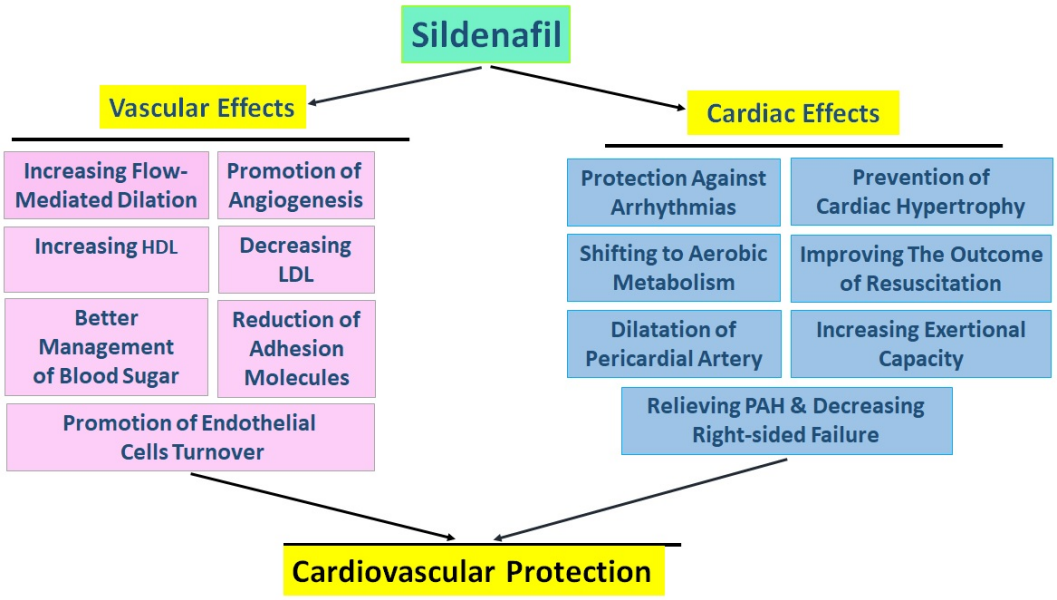

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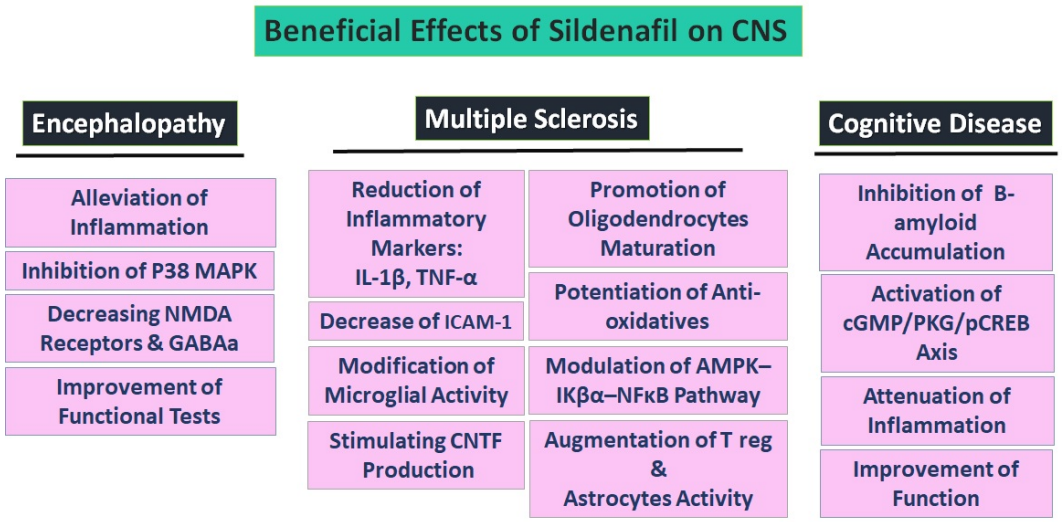

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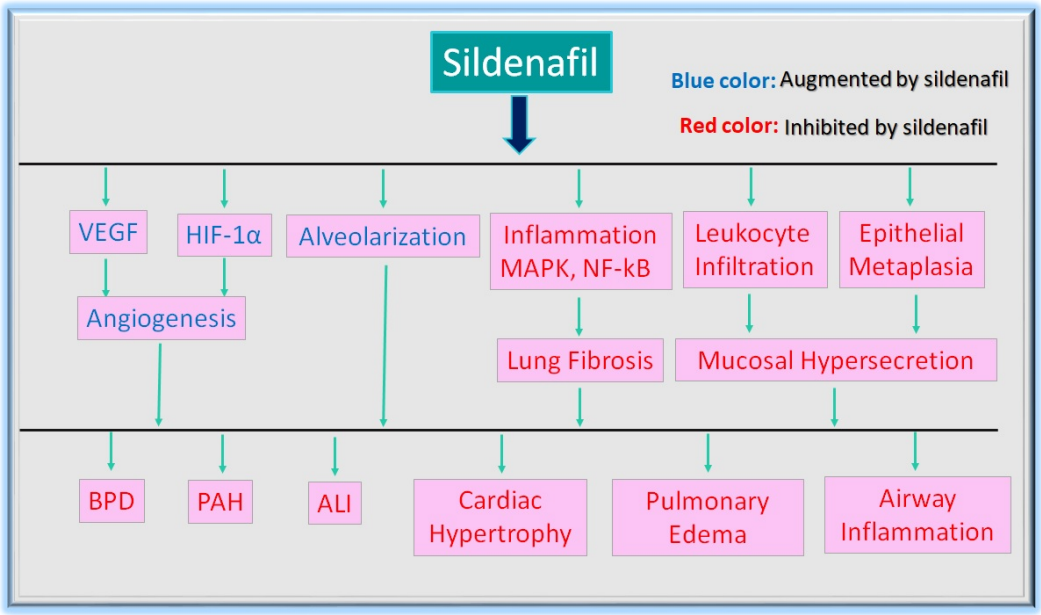

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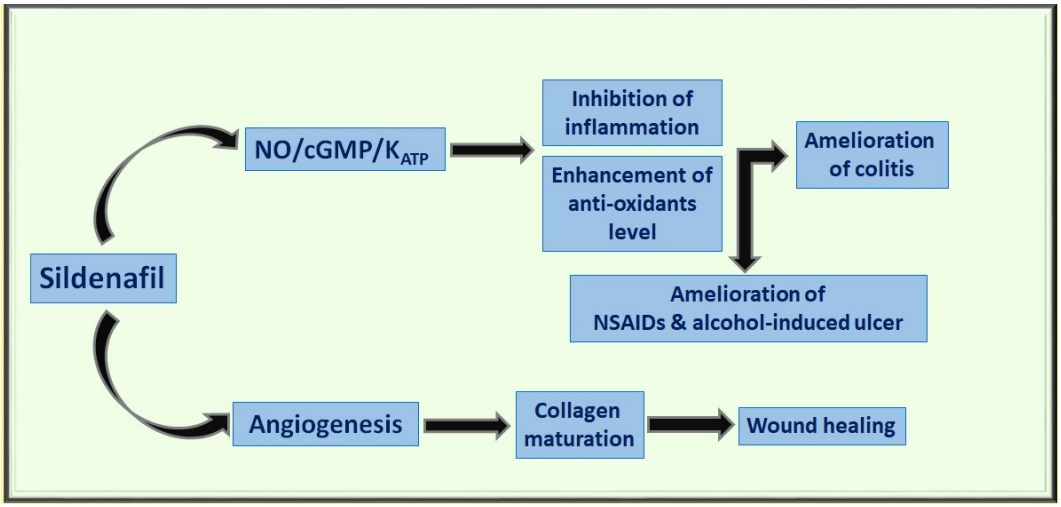

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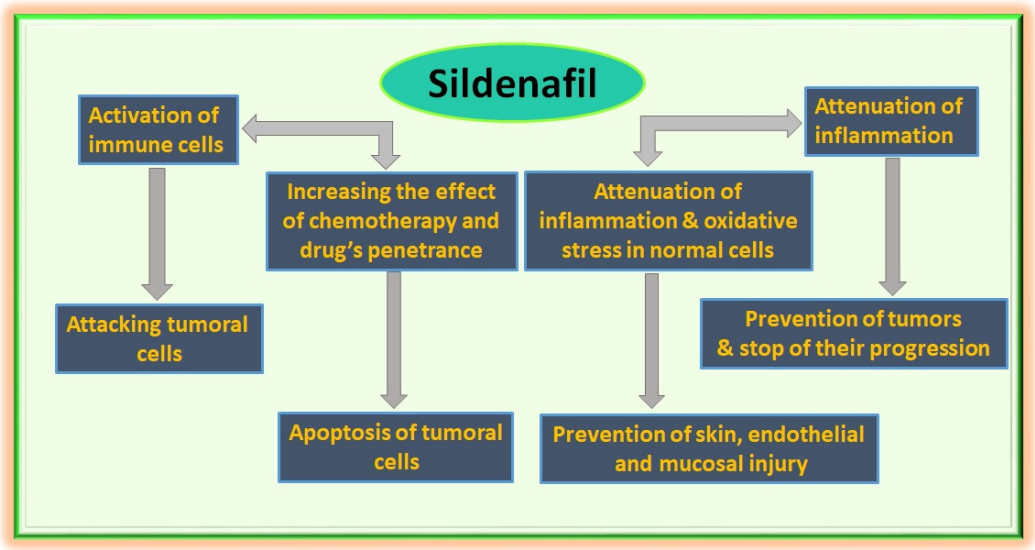

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