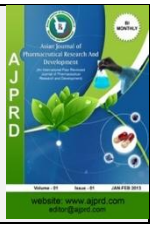
Available online on 15.08.2021 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research



Open Access

Review Article

Review: The Discovery and Development of Sildenafil Citrate

Eza Azhara Septifani, Rina Desni Yetti, Ridho Asra*

School of Pharmaceutical Science (STIFARM), Padang, Indonesia

A B S T R A C T

Background: Sildenafil citrate is a new drug that is still being marketed as patented products, namely Viagra and Revatio. The process of developing drugs using Sildenafil citrate was originally intended as a drug for heart disease. However, in the process of development, it turns out to function more as a drug for erection problems because it can increase erections in men. In the process of development, the use of sildenafil citrate still raises pros and cons so that it requires more intense research in the development of sildenafil citrate.

Purpose: this review article aims to discuss thediscovery and development of sildenafil citrate.

Data Source: The author created this review article using the literature study method relevant to thepurpose of the review. Sources of information The literature was taken from various online journal search sites such as digital libraries, Google, Google Scholar, Pub Med, Science Direct, and E-resources with the key terms "discovery" and "development" combined with the term "sildenafil citrate".

Conclusion: The results of the review analysis obtained information that sildenafil citrate works as a PD5 inhibitor and has gone through clinical trials before being marketed commercially. Sildenafil at the right dose is reported not to interfere with fertility levels, is not teratogenic, non-genotoxic, and has no potential carcinogenic so that it can be consumed. In its development, research on sildenafil citrate is not limited to the treatment of erectile dysfunction but can also be used as a treatment for wounds, heart, lung, and chronic kidney diseases.

Keywords: The Discovery, Development, Sildenafil Citrate.

A R T I C L E I N F O: Received 28 March 2021; Review Complete; 25 July 2021 Accepted; 03 August 2021 Available online 15 August 2021

Cite this article as:

Septifani EA, Yetti RD, Asra R, Review: The Discovery and Development of Sildenafil Citrate, Asian Journal of Pharmaceutical Research and Development. 2021; 9(4):108-117. **DOI:** http://dx.doi.org/10.22270/ajprd.v9i41018

***Address for Correspondence:**

Ridho Asra, School of Pharmaceutical Science (STIFARM), Padang, Indonesia

INTRODUCTION

Sildenafil citrate is one of the new types of drugs that are still being marketed as patented products, namely Viagra and Revatio. Sildenafil is one of the compounds used in the treatment of erectile dysfunction or better known as the anti-impotence phosphodiesterase inhibitor class. In addition to being used in the treatment of erectile dysfunction, sildenafil is also used in pulmonary arterial hypertension (PAH) [1, 2]. The mechanism of action of this drug is through inhibition of the conversion of guanylate triphosphate to cyclic guanosine monophosphate (cGMP). cGMP is a vasodilator neurotransmitter in tissues. The catabolism of cGMP is mediated by the enzyme phosphodiesterase. Three high-selectivity type 5 phosphodiesterase isoenzymes were found in genital tissue, which decreased cGMP catabolism. Inhibition of phosphodiesterase in nongenital tissues produces an adverse effect [3]. Based on the history of this powerful drug, actually, Pfizer scientists from England found sildenafil as a drug for high blood pressure and heart disease, but because it has side effects, one of which is increasing penile erection and its effectiveness as a medicine for high blood pressure and heart disease is not optimal, so Pfizer scientists make sildenafil as an erectile dysfunction drug[4].Recent developments Sildenafil citrate (Viagra) is more widely used as a drug for erection problems so it is widely used by herbal medicine manufacturers. However, there is still some

controversy about the use of Sildenafil citrate (Viagra) as a drug for erection problems because of the side effects caused by Sildenafil citrate (Viagra) [5].

It is necessary to know how the steps involved in identifying and developing the Sildenafil citrate drug which includes the testing of the drug's action, followed by a determination that explains the process of the compound based on its chemical structure (in silico), then continued with preclinical testing (in vitro and in vivo) and clinical research to see the reaction of drugs to the human body. If the testing stage has been passed, then the registration stage is the final stage to obtain a distribution permit from the authorized party in order to strengthen the drug safety statement [6].

Based on this, the author is interested in conducting a review study on the history of the discovery and development of Sildenafil Citrate. The method used in this review is a literature study. It is hoped that in the future this review can be used as a reference and information by other researchers for the further development of Sildenafil citrate (Viagra) by conducting an analysis of the content and risk factors as well as its prospects in the pharmaceutical world.

METHODS AND DATA

The method that the author used in this review was to conduct a literature study both within the country and abroad. The literature search was carried out in a structured manner to obtain the most current and relevant discussion for the purpose of the review. The literature was taken from various online journal search sites such as digital libraries, Google, Google Scholar, Pub Med, Science Direct, and E-resources with the key terms.

RESULTS AND DISCUSSION

History of Sildenafil Discovery

Sildenafil citrate is a class of hard drugs that can only be obtained and can only be used based on a doctor's prescription and is commonly used in the treatment of erectile dysfunction in men[7]. Initially, scientists at the British drug company Pfizer, Peter Dunn and Albert Wood, intended to make drugs to lower high blood pressure and angina or chest pain associated with coronary heart disease. At that time, in 1989, they created sildenafil citrate, Viagra's pharmaceutical name [8].

The beginning of the discovery of sildenafil citrate was in 1986, Simon Campbell and David Roberts conducted research with the target of finding drugs that have anti-angina effects. The theoretical basis obtained is that nitrates are effective agents for the short-term treatment of angina but their use is limited because they cause tachyphylaxis. On this basis, a drug that can function as a PDE5 inhibitor was developed [2, 3]. In 1987, Pfizer discovered several compounds that have anti-angina effects, namely Zaprinast which is an antiallergic drug and Pyrazolopyrimidinones as a PDE5 inhibitor[9]. In 1989 UK-92,480 (sildenafil citrate) was selected as a candidate for clinical development for cardiovascular disease (angina) [8].

In 1990, Peter Ellis and Nick Terret: noted that drugs capable of acting as PDE5 inhibitors may be useful in treating erectile dysfunction, through pre-clinical trials and the development of dosage forms (tablets) [10]. A year later, a phase I study of sildenafil for the treatment of angina-single dose studies was initiated including healthy volunteers[11]. In 1992, the first and only Phase II clinical trial of sildenafil as an antianginal agent found moderate hemodynamic effects. The Phase I (II) study of angina studies-multiple dose studies in healthy volunteers showed that erection was a side effect of drug use[3]. Late 1993, the first pilot study of sildenafil for the treatment of erectile dysfunction in Bristol, England. Men use the drug 3 times a day for a week. Early in 1994, a second pilot study of sildenafil for the treatment of erectile dysfunction showed that a single dose was able to induce erections. Research on sildenafil has focused on the treatment of erectile dysfunction[12].

In 1997, the enzyme PDE5 was detected in the corpus cavernosal tissue of the penis and suggested that the mechanism of action of sildenafil in the treatment of erectile dysfunction is to inhibit PDE5 [13]. In 1998, 21 clinical trials of sildenafil, now known as Viagra, were conducted, including nearly 4500 men with erectile dysfunction[14]. A year later, Viagra was registered with the FDA[15]. In 2000, the US FDA approved Viagra as an oral medication for the treatment of erectile dysfunction[15,11]. In 2001 the first IV placebo-controlled study was conducted to evaluate the effect of different doses (sildenafil) in treating patients[16]. The year 2003 was the first published case report that was successful in the treatment of patients with pulmonary hypertension using sildenafil[17]. In 2004 there was another case report regarding the success of sildenafil in treating pulmonary hypertension with oral sildenafil, a phase III trial was conducted regarding the effect of sildenafil in pulmonary hypertension [18]. In 2006, sildenafil was approved by the FDA and EMEA as a therapeutic agent for pulmonary hypertension[19].

Clinical and Pre-Clinical Trials

Pre-clinical Trials

Clinical and pre-clinical trials were conducted to analyze the dosage and side effects of sildenafil citrate before being marketed. In 2004, D Abbott, P. Comby and C. Charuel have conducted clinical trials of sildenafil citrate by applying the LD 50 threshold [20]. In these pre-clinical trials, several doses of preparations were used which were tested on rats orally and dermally. In the pre-clinical test, subchronic and chronic toxicity tests were also conducted with the results that there were specific effects on beagle pain syndrome in dogs, marked intestinal dilatation in mice and adaptive reversible hepatocellular hypertrophy and secondary hypertrophy in mice. However, this effect was not relevant in humans, so a second preclinical study was conducted [21].

The results of the preclinical test II, namely that there was a morphometric thickness of the retinal layer from human visual disturbances, showed that there was no difference in the use of therapy with controls in experimental rats and dogs after 24 hours of treatment [22]. The results of the

second preclinical test indicate that sildenafil does not interfere with fertility, is not teratogenic, is not genotoxic and has no potential carcinogenic [16]. The results of the preclinical II test mentioned the side effects of the drug so that based on these results, pharmacological research can be carried out to determine the bioavailability, dosage and pharmacokinetic effects of a single oral dose on food.

The study used 4 single oral doses of sildenafil, namely 25,50,100 and 200 mg on 32 objects which resulted in 41% bioavailability, food can slow absorption with an average T for 1 hour is 29%. The recommended dose proportion based on this study is 25-200 mg [23]. The pre-clinical test was then continued at the clinical trial stage in table 2 as follows.

Toxicity Test

A toxicity test was performed on mice. Mice received sildenafil for 18 or 24 months daily the dose was increased to 30 mg/kg. Death was seen on observation in the third month, marked by abdominal swelling associated with GI dilation. This results in total weight loss before death[24].

Rats received sildenafil for 24 months daily, the dose was increased to 60 mg/kg. No difference in mortality was observed during testing. Bodyweight decreased at high doses compared with controls. An increased incidence of thyroid follicular cell hyperplasia is seen. Sildenafil is not carcinogenic to mice and rats. There is no clastogenic activity either in vivo or in vitro and does not show genotoxicity [25].

Male and female rats received sildenafil daily, the dose was increased to 60 mg/kg. In previous repeat-dose studies in rats and dogs, there was no association between sildenafil administration and changes in testicular or ovarian weight and histopathology. In the fertility study, there was no relationship between sildenafil administration and mating habits, pregnancy success, and other reproductive parameters. Thus, it does not affect fertility in general [25].

Teratogen Test

Data on the safety and tolerability of sildenafil citrate have been analyzed from a series of studies in the treatment of erectile dysfunction. A total of 4274 patients (2722 sildena®l, 1552 placebo; age range 19 ± 87 years) received double-blind treatment for a period of up to six months, and 2,199 received long-term open sildenafil up to 1 year. The most frequently reported side effects (all causes) were headache (16% sildena®l, 4% placebo), flushing (10% sildena®l, 1% placebo), and dyspepsia (7% sildena®l, 2% placebo).) and most are transient and mild or moderate. These side effects reflect the pharmacology of phosphodiesterase type 5 inhibitors. No cases of priapism have been reported. Discontinuation rates due to adverse events (all causes) were comparable for patients treated with sildena®l (2.5%) and placebo (2.3%). In an open-label extension study, 90% of patients completed long-term treatment, with only 2% withdrawing due to side effects. Sildenafil is a well-tolerated oral treatment for erectile dysfunction[14,19.] Sildenafil citrate significantly decreased the percentage of T-cells producing TNF- and showed a tendency to decrease IFN-γ, when stimulated with PMA [25, 26].

Endometrial thickness in 1452 female patients receiving sildenafil citrate was significantly higher than in the control group (placebo or no treatment). Sildenafil citrate is effective in increasing endometrial thickness, clinical pregnancy rate, and biochemical pregnancy rate in women with thin endometrium. This treatment is a potential therapeutic intervention for thin endometrium[27]. The optimal liposome formulation was coated with a bioadhesive polymer (chitosan and HPMC). An increase in liposomal size and zeta potential was observed for all coated liposomal formulations. HPMC-coated liposomes showed greater bioadhesion and higher entrapment efficiency than chitosan-coated formulas. In vitro release studies demonstrated prolonged release of sildenafil from coated liposomes compared to uncoated liposomes and sildenafil solutions. Ex vivo permeation studies revealed enhanced permeation relative to layered against uncoated liposomes [28, 29].

Transient sildenafil-induced glutamate changes in the brainstem may reflect increased excitability of brainstem neurons. CGRP does not cause brainstem or thalamic glutamate changes, suggesting that CGRP exerts a more headache-inducing effect on peripheral trigeminal pain pathways[30].Sildenafil may induce coronary steal or cause vasodilation leading to hypotension in patients with pre-existing cardiovascular disease, particularly in those with preexisting cardiovascular disease. patients undergoing nitrate therapy[31]. Sildenafil citrate is a widely used erectile dysfunction drug that is usually associated with transient visual symptoms in normal doses. At high doses, sildenafil citrate can cause persistent retinal toxicity in certain individuals[32]. Sildenafil citrate is reported to have low oral absorption, multiple side effects, and delayed onset of action[33]. The two most common side effects are headache and flushing which are brief and easily treatable[18].

Treatment with sildenafil has been reported to be well tolerated in men with type 1 diabetes[34]. However, it is necessary to continue to develop to minimize the occurrence of side effects caused by sildenafil citrate. A combination drug containing 0.5 mg of testosterone and 50 mg of sildenafil for arousal disorders. The prototype (formulation 1) consisted of a testosterone solution for sublingual administration and a sildenafil tablet administered 2.5 hours later. Dual route/multiple-release fixed-dose combination tablets (formulation 2) use the sublingual and oral routes for systemic uptake. The tablet has a sildenafil inner core with a polymeric time delay coating and an outer polymer layer containing testosterone. It is designed to increase dosing practicality and reduce the potential for temporal non-adherence through avoiding relatively complex temporal dosing schemes. The dual-route/multiple-release fixed-dose combination tablet met the design criteria and was considered suitable for further clinical testing [35]. Sildenafil citrate ODT administered without or with water was bioequivalent or met the bioequivalence criteria compared to conventional sildenafil citrate tablets administered with water under fasting

conditions in healthy Chinese men, thus offering a convenient alternative method of oral administration [36]. Sildenafil citrate hydrogel containing microemulsion showed in vitro results that were suitable for use as a transdermal drug delivery system [33].

In addition to its use as a treatment for erectile dysfunction, Sildenafil Citrate (SC) is a US FDA-approved drug, it has been used to treat wounds due to the stimulating activity of nitric oxide (NO) in tissues. The percentage of wound contraction, re-epithelialization, tensile strength, and biochemical parameters such as hydroxyproline, collagen, total protein and NO content at the dermal level proved the wound healing efficacy of the prepared SCH. Moreover, histopathology confirmed that SCH promotes re-epithelialization, collagen synthesis, deposition, and skin regeneration. The results showed that SCH had no skin toxicity and accelerated wound healing. Thus, the prepared SCH showed promising skin wound healing properties against traumatic wounds [37,38].

In the case of cardiac disease, Sildenafil has direct positive chronotropic and inotropic effects along with coronary vasodilator action, confirming that caution should be exercised in the use of sildenafil for patients with ischemic heart disease, obstructive hypertrophic cardiomyopathy and/or ventricular. arrhythmia. The information on sildenafil reported in this study may help establish guidelines for assessing the cardiac safety of the newer type-5 phosphodiesterase inhibitors [39]. Early intervention with sildenafil prevents RV hypertrophy and RVF development, T-tubule remodeling and Ca2+ handling dysfunction [40].

In lung treatment, SLD nano-transformers were prepared using a modified lipid hydration technique[41]. The STARTS-1 and -2 trials and the 2012 US Food and Drug Administration (FDA) product labeling for the use of sildenafil in pediatric patients with pulmonary hypertension improved communication and mission alignment with regard to pediatric drug trials [41]. Administration of sildenafil shows beneficial effects and is likely to be used in chronic kidney disease. Taking sildenafil with a supplement with adenine (Sildene) should not cause obvious symptoms, so the dosage is based on adenine-induced weight loss. In another part of the trial results, it was found that Adenine-induced nephrotoxicity has altered the gross morphology of the kidney and induces renal fibrosis and tissue destruction, necrobiotic tubular cells with interstitial hemorrhage[42]. The combination of sildenafil and gemfibrozil can be used in the treatment of cisplatin-induced nephrotoxicity [43].

Clinical Trials

Phase I

In phase 1 clinical trial, a single dose of sildenafil citrate was administered to a single male volunteer for 10 consecutive days. The result is that patients have an antianginal effect, erection has not been reported in previous single-dose studies, even with doses as high as 200 mg. There have been reports of erections in some patients but they have not been noticed. After that, male volunteers were given a dose of 3x1 sildenafil citrate for 10 consecutive days. The results reported that volunteers experienced penile erections more often or lasted longer than usual. There are other side effects such as headache and indigestion [13].

PHASE II & PHASE III

In phase 2 and 3 clinical trials, the results showed that sildenafil therapy had no clinically significant effect on PDEs 1-4 and 7-11. Effects on PDE5, may have a clinically significant effect through inhibition of PDE6. Subsequent in vitro and in vivo investigations confirmed that the visual side effects were due to PDE6 inhibition. Sildenafil which has an effect on PDE6 was carried out by toxicological tests. In a long-term preclinical study, continuous inhibition of PDE6 by sildenafil did not cause damage to the structure and function of the eye. Short-term and long-term clinical studies also confirm transient visual side effects and lack of long-term consequences. All other side effects can be attributed to PDE5 inhibition. Thus, headache, flushing, and nasal congestion are all thought to be associated with a vasodilator effect [20].

PHASE IV

In phase 4 clinical trials, all studies showed positive results. Viagra was found to be well-tolerated and effective in a very large proportion of patients. Viagra has unmatched efficacy and safety and is likely to remain the standard treatment for ED [24].

Development of Sildenafil Citrate

Sildenafil citrate, an oral phosphodiesterase type 5 inhibitor (PDE5), was the first oral drug approved for the treatment of erectile dysfunction (ED) by the US Food and Drug Administration (FDA) and the European Medicines Evaluation Agency [44, 49]. The following is a picture of the tertiary structure of PDE 5.

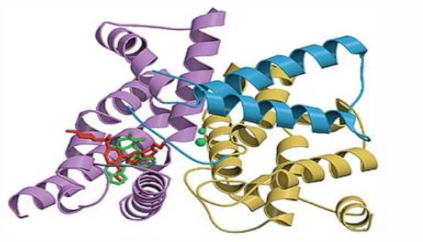


Figure: 1 The tertiary structure of PDE 5

The chemical compound in sildenafil citrate works by increasing levels of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum indirectly by inhibiting the enzyme type 5 diesterase (PDE 5) by increasing nitric oxide (NO). This causes smooth muscle relaxation and dilation of blood vessels leading to increased blood flow into the corpus cavernosum. This effect is exploited for patients with erectile dysfunction[45]. The chemical structure of sildenafil is very similar to the cyclic guanosine monophosphate molecule that competes with it, in the type-5 phosphodiesterase enzyme. Sildenafil binds to the enzyme phosphodiesterase-5, preventing the breakdown of cyclic guanosine monophosphate through competitive inhibition. The onset of action of sildenafil could be as short as 20 minutes and the duration of the action can be as long as three part-time (18 hours). The safety of sildenafil has been established in many studies before and after an agreement with doses as high as eight times the maximum recommended dose and meets the requirements of the physicochemical and microbiological stability [18 ,46]. Here is a picture of the complex PDE5 and GMP.

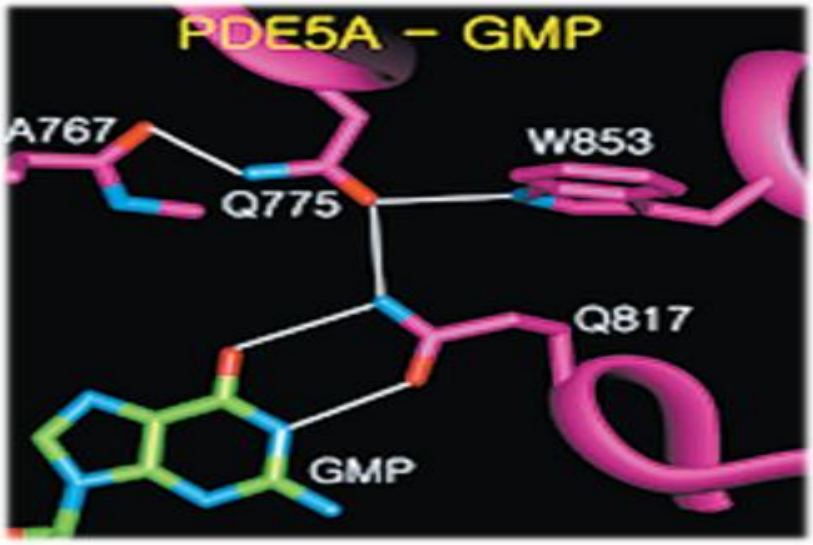


Figure 2: PDE5-GMP Complex

Chemically, sildenafil citrate is a synthetic compound. Sildenafil citrate also has groups that may be identified by spot testing. Several functional groups found in sildenafil citrate compounds are secondary and tertiary amines, carbonyl, imine, methyl, heterocyclic nitrogen, and benzene. These functional groups can be reactedwith several reagents so that different colors are produced from the reagent blanks. The structure of sildenafil citrate can be seen in Figure 3.

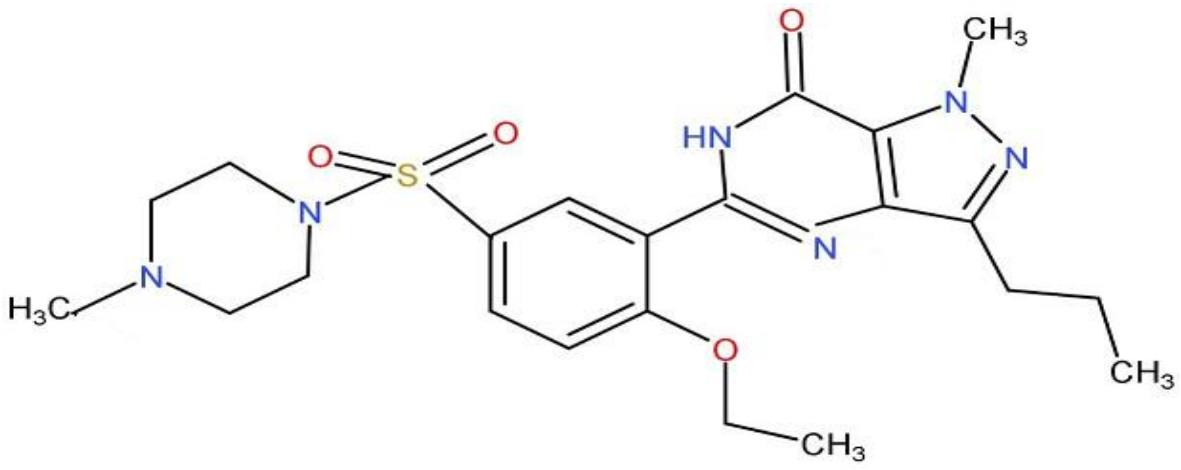


Figure 3: The structure of sildenafil citrate

The synthesis of sildenafil citrate can be seen in Figure 4.

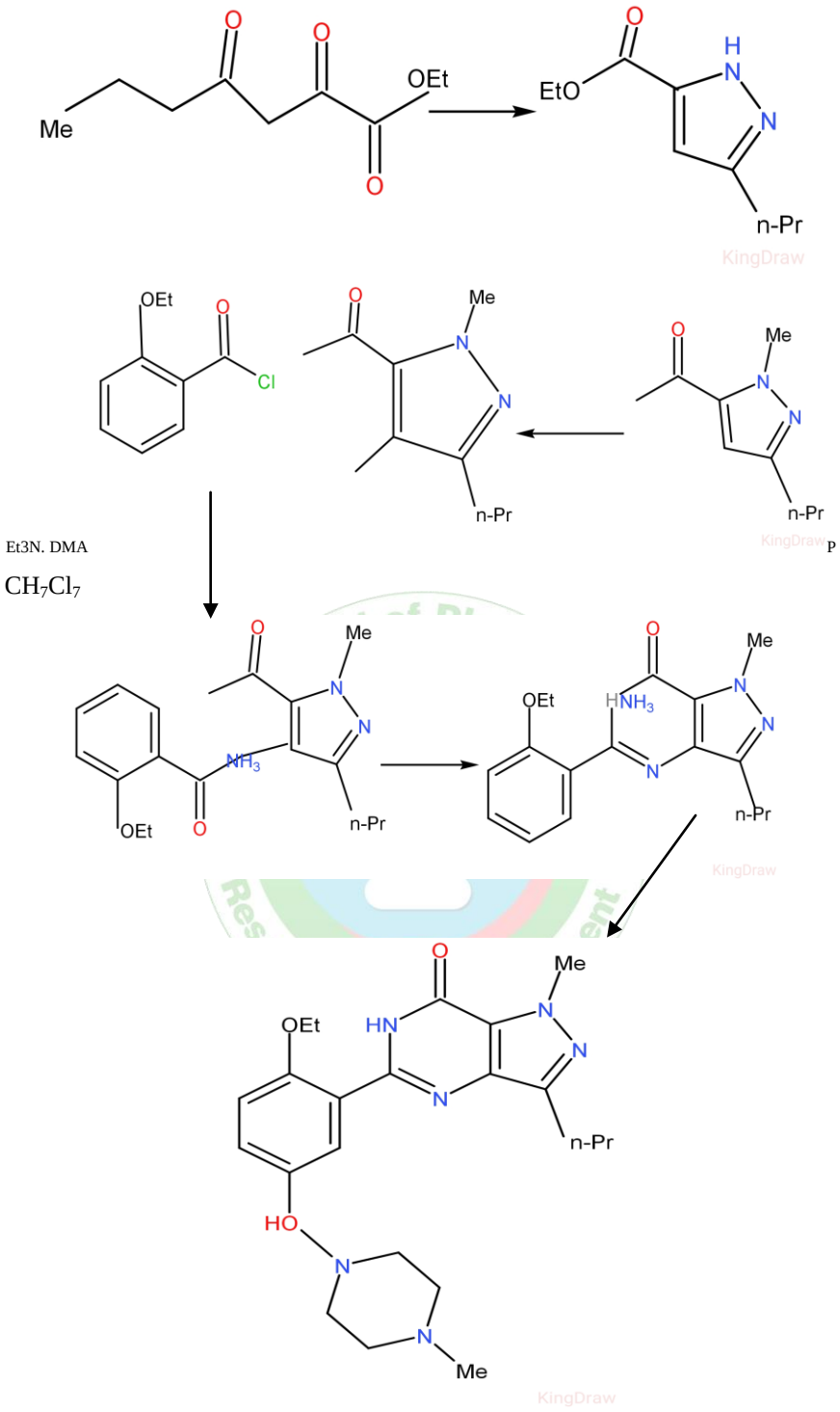


Figure 4: Synthesis of sildenafil citrate

There are 2 types of sildenafil obtained from crystallization: sildenafil (1) and sildenafil citrate monohydrate (2). The techniques used are (i) crystallization from saturated solution, (ii) addition of antisolvent, (iii) reflux and (iv) evaporation method. Crystallization is complete if the process is carried out at acidic pH and cold temperatures in a day. The crystal structure of the free base of sildenafil and the salt form differ from the different growth conditions which lead to differences in stability [47].Several adverse effects of oral use of sildenafil in the treatment of erectile dysfunction have been reported. So it is necessary to develop a topical dosage form that works locally. The results obtained were that in the test group, 5 patients (12.5%) had a full erection with the onset of erection 7.4 ±3.6 minutes, 5 patients (12.5%) had a moderate erection, 30 patients (75%) did not have an erection. In the control group, there were 28 patients (70%) having a full erection, the onset of erection 37.8 ± 14.9 minutes, 6 (15%), and 6

(15%) moderate erection. It is necessary to develop a transdermal delivery of sildenafil using synthetic/natural materials [48]. In a study to examine the effect of topical sildenafil on wounds using mice, it was reported the use of cutaneous NO in wound repair. The results showed that in the test group the wound area improved 15% from its initial size on day 7, 26% on day 14 and 46% on day 21. In the control group, wound healing was slowed down. Sildenafil cream causes a lot of migration of fibroblasts and macrophages, increases vascularity, collagen regeneration, epithelialization. Thus sildenafil is useful in wound healing[49].

Marketing of Sildenafil Citrate

Sildenafil citrate is commonly found in herbal medicine for men as a drug used to treat sexual dysfunction. This drug is included in the category of hard drugs, so the use of this drug must be with a doctor's prescription. Sildenafil citrate or better known is marketed under the brand name Viagra. This drug is widely used to treat diseases associated with emerging vascular dysfunction. Viagra was approved in many major markets in 1998, and was first launched in the United States in April 1998 (with an initial dose of 50 mg and the option of increasing the dose to 100 mg or reducing it to 25 mg, depending on effectiveness and tolerance). The launch of Viagra revolutionized the therapy of ED[16,50]. Sildenafil citrate can be found in the form of tablets, gels or creams[51]. The accessibility of prescription drugs manufactured outside the United States, particularly sildenafil citrate (an innovator product, Viagra®), has been made much easier because it has been commercially marketed including using the internet [52].

Example of a developed Sildenafil Citrate Preparation

Development of a drug-optimized self-nano emulsifying lyophilized tablet to address the aforementioned problem. The solubility of sildenafil in various surfactants, oils and cosurfactants has been tested. An optimized formulation of the self-nanoemulsion loaded with small droplet sizes was developed by applying a special cubic model of the mixture design. The formula containing 10% oil mixture, 60% surfactant, and 30% cosurfactant had a droplet size of 65 nm with an optimum ratio of 0.4% fumed silica, 0.1% hydroxypropyl methylcellulose, and 0.4% sodium starch glycolate. showed satisfactory results in disintegration and dissolution studies. In vivo pharmacokinetic studies demonstrated a higher bioavailability (1.44 times) and a fast absorption profile for the study tablets compared to commercially available tablets [53].

The pharmacological basis of the NO/cGMP pathway and the rationale and clinical use of PDE5 inhibitors in addition to ED are discussed in different diseases. This pathway can be seen in Figure 5.

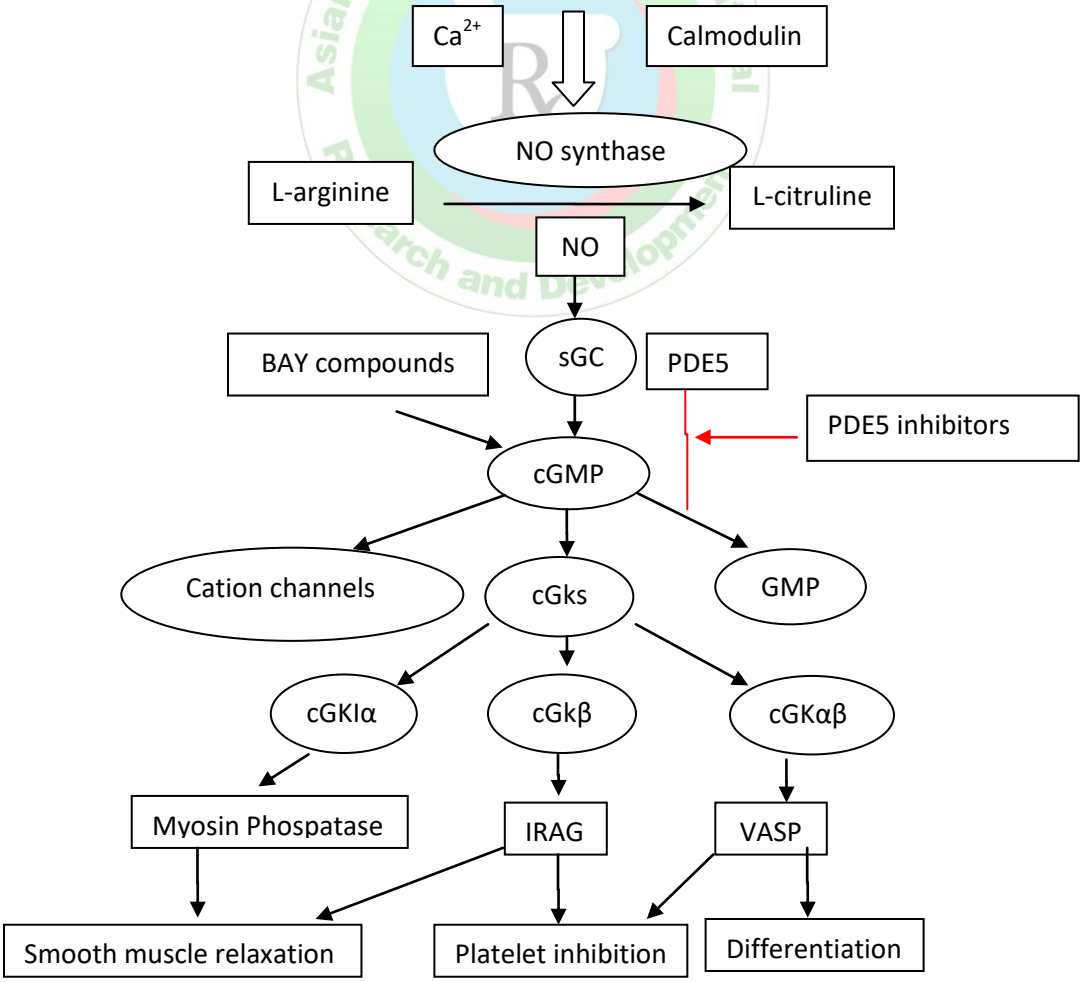


Figure 5: Cellular signaling with NO and cGMP

A simple, easy-to-apply, and green infrared spectroscopic method was developed and validated for the quantitative determination of sildenafil citrate in tablets with manufacturing formulas. The homogenized tablet powder with a known mass content (%, m/m) of sildenafil citrate was mixed with paracetamol to form a standard mixture with different percentages of sildenafil citrate in the total amount of sildenafil citrate and paracetamol (designated as R). The unknown tablet sample was finely ground and mixed with paracetamol to form a test mixture having an R value of about 50%. The standard mixed infrared spectrum, measured in total attenuated reflectance mode, in the wavenumber zone from 1800 cm 1 to 1300 cm 1 was selected and processed by partial least squares regression to form a calibration model for the quantitation of sildenafil citrate in the unknown sample. The spectral responses of the test mixture and calibration model were used to determine the exact mass content (%, m/m) of sildenafil citrate in the unknown powdered tablet sample. This method was fully validated in terms of linearity, precision and accuracy according to the requirements of current guidelines and proved to be reliable and suitable for the intended application [54].

On the other hand, sildenafil is produced as a topical drug in the form of gels and creams [55,56]. The results of Mehdi and Saedi's research with the test group treated with 1% sildenafil gel and placebo tablets and the control group in the form of 100 mg sildenafil tablets showed the conclusion that there is still a need for transdermal development with synthetic and herbal ingredients percutaneous absorption so that it can increase its effect on dysfunction[48]. This is supported by Gursoy's research which showed that the wound area improved faster than the control group. Sildenafil cream causes a lot of migration of fibroblasts and macrophages, increases vascularity, collagen regeneration, epithelialization so that it is beneficial for wound healing [57].

CONCLUSION

Sildenafil citrate was originally a male erectile dysfunction drug that was discovered by the Pfizer company which was later developed under the name Viagra. Sildenafil citrate works as a PD5 inhibitor and has gone through clinical trials before being marketed commercially. Sildenafil at the right dose is reported not to interfere with fertility levels, is not teratogenic, non-genotoxic, and has no potential carcinogenic so that it can be consumed. In its development, research on sildenafil citrate is not limited to the treatment of erectile dysfunction but can also be used as a treatment for wounds, heart, lung, and chronic kidney diseases.

REFERENCE

1. A. R. Mccullough, “Review Empat Tahun Sildenafil Citrate,” 2002; 4: 26–38.
2. I. Goldstein, T. F. Lue, H. Padma-Nathan, R. C. Rosen, W. Steers, and P. A. Wicker, “Sildenafil in the treatment of erectile dysfunction.,” *N. Engl. J. Med.*, 1998; 339(10):1397–1404, 1998.
3. I. Goldstein, A. L. Burnett, R. C. Rosen, P. W. Park, and V. J. Stecher, “The Serendipitous Story of Sildenafil: An Unexpected Oral Therapy for Erectile Dysfunction,” *Sex. Med. Rev.*, vol. 7, no. 1, pp. 115–128, 2019, doi: 10.1016/j.sxmr.2018.06.005.
4. Rohmah R, Salawati T, Larasaty ND. 2019. Perilaku Penjual Obat Kuat (Aphrodisiac)di Wilayah Kota Semarang. Prosiding Mahasiswa Seminar Nasional Unimus.2019; l.2:46 - 51.
5. Eriska Boru S. Analisis Kandungan Sildenafil Sitrat Dalam “Pil Biru” Yang Dijual di Daerah Ciputat. 2014: Jakarta. http://repository.uinjkt.ac.id/dspace/bitstream/123456789/25537/1/Eriska%20Boru%20Saragih-%20fkik.
6. Hairunnisa, H. Sulitnya Menemukan Obat Baru di Indonesia. *Majalah Farmasetika*, 2019; *4*(1):16-21.
7. Angga Tiya W.S., “Analisis Sildenafil Sitrat Pada Jamu Tradisional Kuat Lelaki Merk a Dan B Dengan Metode Kromatografi Cair Kinerja Tinggi,” *Pharmacy*, 2010; 07(02): 24–34.
8. P. J. Dunn, S. Galvin, and K. Hettenbach, “The development of an environmentally benign synthesis of sildenafil citrate (Viagra™) and its assessment by Green Chemistry metrics,” *R. Soc. Chem.*, 2004; 11(2):223–22, 2004, doi: 10.1039/b815986f.
9. H. W. Hamilton, D. F. Ortwine, D. F. Worth, and J. A. Bristol, “Synthesis and Structure-Activity Relationships of Pyrazolo[4,3-d]pyrimidin-7-ones as Adenosine Receptor Antagonists,” *J. Med. Chem.*,1987; 30(1):91–96.doi: 10.1021/jm00384a016.
10. N. K. Terrett, A. S. Bell, D. Brown, and P. Ellis, “Sildenafil (Viagra(TM)), a potent and selective inhibitor of type 5 CGMP phosphodiesterase with utility for the treatment of male erectile dysfunction,” *Bioorganic Med. Chem. Lett.*, 1996; 6(15):1819–1824.doi: 10.1016/0960-894X(96)00323-X.
11. I. H. Osterloh, “The discovery and development of Viagra® (sildenafil citrate),” *Sildenafil*, 2004; 1–13. doi: 10.1007/978-3-0348-7945-3_1.
12. M. C. Maytom *et al*., “A two-part pilot study of sildenafil (VIAGRA™) in men with erectile dysfunction caused by spinal cord injury,” *Spinal Cord*, 1999; l(37):110–116. doi: 10.1038/sj.sc.3100803.
13. J. Y. Jeremy, S. A. Ballard, A. M. Naylor, M. A. W. Miller, and G. D. Angelini, “Effects of sildenafil, a type-5 cGMP phosphodiesterase inhibitor, and papaverine on cyclic GMP and cyclic AMP levels in the rabbit corpus cavernosum in vitro,” *Br. J. Urol.*, 1997; 79(6):958–963. doi: 10.1046/j.1464-410x.1997.00206.x.
14. G. Wagner, “Clinical safety of oral sildenafil citrate (VIAGRA™) in the treatment of erectile dysfunction—by Morales et al,” *Int. J. Impot. Res.*, 1998; 10(2):74 doi: 10.1038/sj.ijir.3900335.
15. J. R. Fishman and L. Mamo, “What’s in a Disorder: A Cultural Analysis of Medical and Pharmaceutical Constructions of Male and Female Sexual Dysfunction,” *Women Ther.*, 2002; 24:179–193. doi: 10.1300/J015v24n01.
16. F. Giuliano, G. Jackson, F. Montorsi, A. Martin-Morales, and P. Raillard, “Safety of sildenafil citrate: Review of 67 double-blind placebo-controlled trials and the postmarketing safety database,” *Int. J. Clin. Pract.*, 2010; 64(2):240–255, doi: 10.1111/j.1742-1241.2009.02254.x.
17. Y.-P. Xie *et al*., “Sildenafil Prevents and Reverses T-tubule Remodeling and Ca2+ Handling Dysfunction in Right Ventricle Failure Induced by Pulmonary Artery Hypertension,” *Hypertension.*, 2013; 23(1):1–7, doi: 10.1161/HYPERTENSIONAHA.111.180968.Sildenafil.
18. A. R. McCullough, “Four-year review of sildenafil citrate.,” *Rev. Urol.*, 2002; 4(3):S26-38[Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/16986012%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1476025.
19. H. A. Ghofrani, I. H. Osterloh, and F. Grimminger, “Sildenafil: From angina to erectile dysfunction to pulmonary hypertension and beyond,” *Nat. Rev. Drug Discov.*, 2006; 5(8):689–702: doi: 10.1038/nrd2030.
20. D. Abbott *et al.*, “Preclinical safety profile of sildenafil,” *Int. J. Impot. Res.*, 2004; 16(6):498–504. doi: 10.1038/sj.ijir.3901232.
21. S. G. Moreira, R. E. Brannigan, A. Spitz, F. J. Orejuela, L. I. Lipshultz, and E. D. Kim, “Side-effect profile of sildenafil citrate (Viagra) in clinical practice,” *Urology*, 2000; 56(3):474–476. doi: 10.1016/S0090-4295(00)00649-X.
22. D. R. J. Glenn, N. McClure, S. L. Cosby, M. Stevenson, and S. E. M.

Lewis, "Sildenafil citrate (Viagra) impairs fertilization and early embryo development in mice," *Fertil. Steril.*, 2009; 91(3):893–899.doi: 10.1016/j.fertnstert.2007.12.014.

23. A. Laties and I. Sharlip, "Ocular safety in patients using sildenafil citrate therapy for erectile dysfunction," *J. Sex. Med.*,2006; 3(1):12–27.doi: 10.1111/j.1743-6109.2005.00194.x.

24. K. E. Andersson, "PDE5 inhibitors – pharmacology and clinical applications 20 years after sildenafil discovery," *Br. J. Pharmacol.*, 2018; 175(13), :2554–2565. doi: 10.1111/bph.14205.

25. M. Zych, A. Roszczyk, M. Kniotek, B. Kaleta, and R. Zagozdzon, "Sildenafil Citrate Influences Production of TNF-α in Healthy Men Lymphocytes," *J. Immunol. Res.*, 2019, doi: 10.1155/2019/8478750.

26. L. Omarjee, A. Camarzana, S. Henni, and P. Abraham, "Nonrevascularizable buttock claudication improved with Sildenafil A case report," *Med. (United States)*, 2017; 96(8):8–11 doi: 10.1097/MD.0000000000006186.

27. X. Li *et al.*, "Effect of sildenafil citrate on treatment of infertility in women with a thin endometrium: a systematic review and meta-analysis," *J. Int. Med. Res.*, 2020; 48(11) doi: 10.1177/0300060520969584.

28. H. Refai, D. Hassan, and R. Abdelmonem, "Development and characterization of polymer-coated liposomes for vaginal delivery of sildenafil citrate," *Drug Deliv.*, 2017; 24(1): 278–288.doi: 10.1080/10717544.2016.1247925.

29. E. E. Gillis, J. N. Mooney, M. R. Garrett, J. P. Granger, and M. Sasser, "Sildenafil treatment ameliorates the maternal syndrome of preeclampsia and rescues fetal growth in the Dahl Salt Sensitive rat Ellen," *Hypertension.*, 2017; 67(3):647–653doi: 10.1161/HYPERTENSIONAHA.115.06071.Sildenafil.

30. S. Younis *et al.*, "Effects of sildenafil and calcitonin gene-related peptide on brainstem glutamate levels: a pharmacological proton magnetic resonance spectroscopy study at 3.0 T," *J. Headache Pain*, 2018; 19(1) doi: 10.1186/s10194-018-0870-2.

31. H. A. Cakmak, B. Ikitimur, B. Karadag, and Z. Ongen, "An unusual adverse effect of sildenafil citrate: Acute myocardial infarction in a nitrate-free patient," *BMJ Case Rep.*, 2012; 3–6. doi: 10.1136/bcr-2012-006504.

32. Y. Fatoumata *et al.*, "Sildenafil Citrate Induced Retinal Toxicity - ERG, OCT, and Adaptive Optics findings," *Retin Cases Br. Rep.*, 2018; 12(1): 1796–803, doi: 10.1097/ICB.0000000000000708.Sildenafil.

33. A. Atipairin, C. Chunhachaichana, T. Nakpheng, N. Changsan, T. Srichana, and S. Sawatdee, "Development of a sildenafil citrate microemulsion-loaded hydrogel as a potential system for drug delivery to the penis and its cellular metabolic mechanism," *Pharmaceutics*,2020; 12(11):1–23. doi: 10.3390/pharmaceutics12111055.

34. B. G. A. Stuckey *et al.*, "Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: Results of a randomized controlled trial," *Diabetes Care*, 2003; 26(2):279–284. doi: 10.2337/diacare.26.2.279.

35. J. Bloemers *et al.*, "Single dose sublingual testosterone and oral sildenafil vs. a dual route/dual release fixed dose combination tablet: A pharmacokinetic comparison," *Br. J. Clin. Pharmacol.*, 2016; 81(6):1091–1102. doi: 10.1111/bcp.12887.

36. Y. Lv *et al.*, "Bioequivalence and Bioavailability of an Orodispersible Tablet of Sildenafil Citrate in Healthy Chinese Male Subjects," *Clin. Pharmacol. Drug Dev.*, 2020; 9(5):573–581. doi: 10.1002/cpdd.806.

37. S. Kulshrestha, R. Chawla, M. T. Alam, J. S. Adhikari, and M. Basu, "Efficacy and dermal toxicity analysis of Sildenafil citrate based topical hydrogel formulation against traumatic wounds," *Biomed. Pharmacother.*, 2019; 112:108571. doi: 10.1016/j.biopha.2019.01.032.

38. L. Di Luigi *et al.*, "Sildenafil reduces expression and release of IL-6 and IL-8 induced by reactive oxygen species in systemic sclerosis fibroblasts," *Int. J. Mol. Sci.*, 2020; 21(9):1–9, 2020, doi: 10.3390/ijms21093161.

39. N. J. Lubna *et al.*, "Cardiac safety profile of sildenafil: Chronotropic, inotropic and coronary vasodilator effects in the canine isolated, blood-perfused heart preparations," *J. Toxicol. Sci.*, 2016; 41(6):739–744, 2016, doi: 10.2131/jts.41.739.

40. S. M. Badr-Eldin and O. A. Ahmed, "Optimized nano-transfersomal films for enhanced sildenafil citrate transdermal delivery: ex vivo and in vivo evaluation," *Drug Des. Dev. Ther.*, 2016; 1323–1333.

41. C. A. Sable and Et.al., ACC/AAP/AHA Health Policy Statement on Opportunities and Challenges in Pediatric Drug Development: Learning From Sildenfil," *J Am Coll Cardiol*, 2017; 70(4):495–503. doi: 10.1016/j.jacc.2017.04.007.2017.

42. S. A. H. Almurumudhe, R. M. Hatem, and H. A. Hussein, "Physiological And Histological Studies Of The Effect Of Sildenafil On Adenine- Induced Nephrotoxicity In The Sprague–Dawley Rat," *Plant Arch.*, 2021; 21(1):1074–1078, 2021.

43. S. Behiry, A. Rabie, M. Kora, W. Ismail, D. Sabry, and A. Zahran, "Effect of combination sildenafil and gemfibrozil on cisplatin-induced nephrotoxicity; role of heme oxygenase-1," *Ren. Fail.*, 2018; 40(1):371–378. doi: 10.1080/0886022X.2018.1455596.

44. N. Triadisti and H. Heldawati, "Analisa Kualitatif Sildenafil Sitrat pada Beberapa Produk Jamu Sehat Pria dengan Metode Kromatografi Lapis Tipis di Wilayah Banjarmasin," *J. Curr. Pharm. Scinces*,2018; 1(2):42–47.

45. P. Y. Saraswati, H. Kartamihardja, and A. Firmansyah, "ANALISIS SPOT TEST BAHAN KIMIA OBAT SILDENAFIL SITRAT PADA SEDIAAN JAMU," *JSTFI Indones. J. Pharm. Sci. Technol.*,2012; 1(2).

46. A. Sae Yoon, S. Sawatdee, C. Woradechakul, K. Sae Chee, and A. Atipairin, "Physicochemical and microbiological stability of the extemporaneous sildenafil citrate oral suspension," *Sci. Pharm.*, 215; 83(4): 659–670. doi: 10.3797/scipharm.1505-08.

47. S. Sawatdee, C. Pakawatchai, K. Nitichai, T. Srichana, and H. Phetmung, "Why sildenafil and sildenafil citrate monohydrate crystals are not stable?," *Saudi Pharm. J.*, 2015; 23(5):504–514, 2015, doi: 10.1016/j.jsps.2015.01.019.

48. Mehdi Yonessi dan Madjid Saeedi. A Double-blind Placebo-controlled Evaluation of the Effect of Topical Sildenafilon Erectile Dysfunction. The Journal of Applied Research 2005; 5(2).

49. Akram jamshidzadeh dan negar Azarpira. 2011. The Effects of Topical Sildenafil on Wound Healing in Rat. Iranianjournal of Pharmaceutical Sciences Winter 2011; 7(1) 43-48.

50. F. Damiano *et al.*, "Analysis of illicit dietary supplements sold in the Italian market: Identification of a sildenafil thioderivative as adulterant using UPLC-TOF/MS and GC/MS," *Sci. Justice*, 2014; 54(3): 228–237. doi: 10.1016/j.scijus.2014.02.009.

51. K. L. Meadows *et al.*, "Treatment of palmar-plantar erythrodysesthesia (PPE) with topical sildenafil: a pilot study," *Support. Care Cancer*, 2015; 23, 5:1311–1319. doi: 10.1007/s00520-014-2465-z.

52. M. A. Veronin, M. T. Nutan, and U. K. R. Dodla, "Quantification of active pharmaceutical ingredient and impurities in sildenafil citrate obtained from the Internet," *Ther. Adv. Drug Saf.*, 214; 5(5):180–189. doi: 10.1177/2042098614543091.

53. K. M. Hosny, N. A. Alhakamy, M. A. Almodhwahi, M. Kurakula, A. M. Almehmady, and S. S. Elgebaly, "Self-nanoemulsifying system loaded with sildenafil citrate and incorporated within oral lyophilized flash tablets: Preparation, optimization, and in vivo evaluation," *Pharmaceutics*, 2020; 12(11): 1–22. doi: 10.3390/pharmaceutics12111124.

54. V. T. Bui, C. S. Doan, T. T. V. Tong, and D. C. Le, "Development and Validation of a Simple, Green Infrared Spectroscopic Method for Quantitation of Sildenafil Citrate in Siloflam Tablets of Unknown Manufacturing Formula," *J. Anal. Methods Chem.*, 2021; 1–10, doi: 10.1155/2021/6616728.

55. H. Patel, M. S. Panchal, and S. Shah, "Formulation and Evaluation of Transdermal Gel of Sildenafil Citrate," *Int. J. Pharm. Res. Allied Sci.*,2012; 1(3):103–118, 2012, [Online]. Available: www.ijpras.com.

56. J. Anaissie and W. J. G. Hellstrom, "Clinical use of alprostadil topical

cream in patients with erectile dysfunction: A review," *Res. Reports Urol.*, 2116; 8:123–131. doi: 10.2147/RRU.S68560.

57. K. Gursoy *et al.*, "Effect of sildenafil on wound healing: An experimental study," *Langenbeck's Arch. Surg.*, 2010; 395(6):713–718.doi: 10.1007/s00423-009-0471-2.