wjpmr, 2020,6(2), 84-89

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

MANAGEMENT OF DRUG INDUCED SEXUAL DYSFUNCTION IN MALE RATS BY SILDINAFIL CITRATE

Sridhar S. M.[1]*, Rohit Saraswat[2], Ashok Kumar B. S.[3], Pradeep Kumar L[4]., Gopisetty Saran[2]

[1]Department of Pharmacology, Sri K.V. College of Pharmacy, Chickballapur, Karnataka, India.
[2]Department of Pharmaceutics, School of Pharmaceutical Sciences, OPJS University, Churu, Rajasthan, India.
[3]Department of Pharmacognosy, Sri K.V. College of Pharmacy, Chickballapur, Karnataka, India.
[4]Department of Pharmaceutical Chemistry, Sri K.V. College of Pharmacy, Chickballapur, Karnataka, India.

***Corresponding Author: Sridhar S. M.**

Department of Pharmacology, Sri K.V. College of Pharmacy, Chickballapur, Karnataka, India.

Article Received on 01/12/2019 **Article Revised on 22/12/2019** **Article Accepted on 12/01/2020**

ABSTRACT

Sexual dysfunction is a highly prevalent disease associated with aging as well as with several risk factors including hypertension, heart disease diabetes, depression, drug-related. The present study aimed to investigation the effect of phosphodiesterase inhibitors (Sildinafil Citrate) on sexual behavior parameters like: mount latency (ML), mount frequency (MF), intromission latency and frequency (IL & IF), Ejaculatory Latency(EL) and frequency (EF), post ejaculatory Interval (PEI). The result reveals that treatment with Sildinafil Citrate improves sexual behavior in clomipramine induced sexual dysfunction rats.

KEYWORDS: Cyprohepatdine, Clomipramine, antioxidant, sexual dysfunction. Sildinafil Citrate.

INTRODUCTION

Clomipramine (CLMP) is a tricyclic antidepressant, which has demonstrated efficacy in depression, obsessive compulsive disorder (OCD) and panic disorder. Clomipramine is the imipramine analogue of chlorpromazine. Due to its action against anxiety disorders and panic attacks, it is the only drug with 2 entries in the essential drugs list of the World Health Organization (WHO). With regards to compulsive disorders, it is now the "gold standard" of therapy against which other drugs are measured 6-10. However, chronic use of Clomipramine leads to sexual dysfunction in humans.[1,2] and neonatal males.[3]

Sildenafil and other selective phosphodiesterase type-5 inhibitors such as vardenafil and tadalafil by inhibition of type-5 cyclic GMP phosphodiesterase, enhances the duration of action of the increase in GMP elicited by nerve- and endothelium-derived NO released during erection.[4] Sildenafil has clinical efficacy in the treatment of male impotence following oral administration.[5] The most common side effects of sildenafil include headache, flushing, dyspepsia, rhinitis and visual disturbances.[6] In a retrospective study the incidence of cardiovascular events were similar in patients receiving placebo compared with men treated with sildenafil.[7] and in men with known severe coronary artery disease, sildenafil (100mg) produced only small decreases in systemic arterial and pulmonary pressure and had no effect on heart rate or cardiacoutput.[8] Moreover, sildenafil does not exacerbate myocardial ischaemia in canine models of coronary artery stenosis.[9] Therefore, these studies do not support a worsening of cardiovascular disease in connection with sildenafil treatment for ED. The clinically most important interaction for phosphodiesterase type-5 inhibitors is with nitrates. Nitrates such as nitroglycerin increases cyclic GMP content in the vascular smooth muscle in systemic arteries[10] and sildenafil by inhibition of phosphodiesterase type-5 prolongs the duration of action of cyclic GMP and results in large and prolonged decreases in systemic blood pressure in man.[11] and decreases coronary blood flow in vessels with critical stenosis in dogs.[12]

In men, sexual stimulation leads to the production of NO and the subsequent release of guanylate cyclase. Guanylate cyclase converts guanosine triphosphate to cyclic guanosine monophosphate (cGMP) and cGMP produces relaxation of the smooth muscles of the penile arteries and corpus cavernosum, resulting in increased blood flow into the penis.[13] Therefore, in the present study, we investigated the effect of Sildenafil citrate.

Animals

Healthy adult Wistar albino male rats (150-200 g) were used. The animals were housed individually, maintained under standard conditions (12 h light and 12 h dark cycle, 25-30ºC, 35-60% relative humidity), the animals were fed with standard rat pellet diet (Venkateshwara

enterprises, Bangalore, India) and water ad libitum. The study was approved by the Institutional Ethical Committee prior to commencement.

Induction of sexual dysfunction in male rats[14]

Sexually experienced male rats were divided into two groups, group 1 served as control and received vehicle only (normal saline) and group 2 served as Clomipramine treated group and received oral dose of 27 mg/kg Clomipramine suspension (suspension was prepared daily in Tween 80, suspended in 0.9% saline solution). Dosing was done for 30days once in a day. At the end of 30 days, after 30 min of last dosing, estrus female was introduced into respective cages and observed for mating performance and results were recorded and compared with control group. Mating performance analyses were conducted in the dark phase of the light-dark cycle under dim light condition. Assessment of IL&F, EL&EF,PEI, ML&F, were monitored for 30 min after pairing. Animals which showed minimum 25% reduction in sexual behavior were considered as sexually impaired and they were incorporated for subsequent study.

Effects of Sildinafil Citrate on sexual behavior in Clomipramine-induced sexual dysfunction male rats[15]

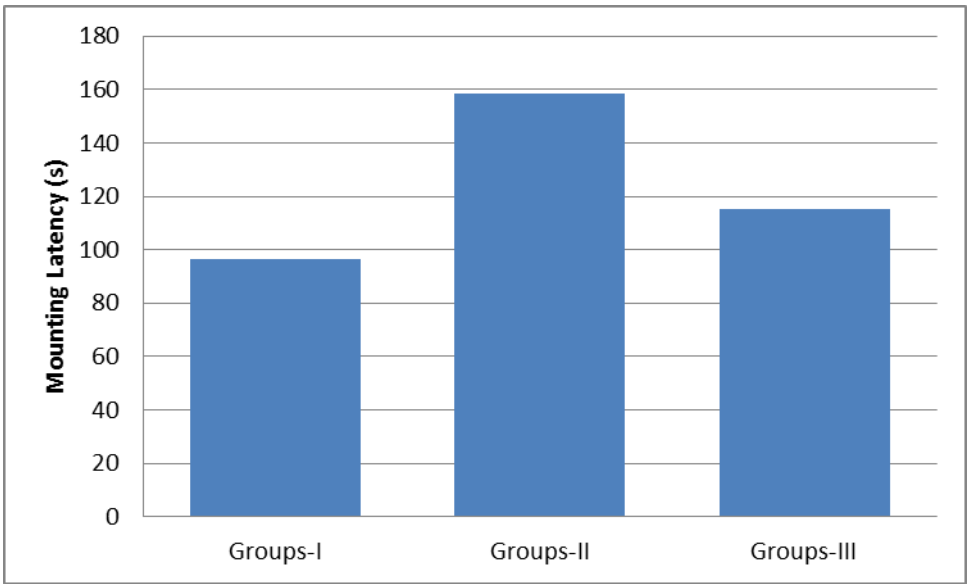
Normal sexually experienced male rats and sexually impaired male rats were employed for this investigation. Three groups of animals were formed, group I served as normal control (sexually experienced normal male rats) and received vehicle only, group II served as negative control (sexually impaired male rats, obtained from above study) and received Clomipramine suspension orally (27 mg/kg), group III (sexually impaired male rats obtained from above study), received 9mg/kg of Sildinafil Citrate orally (suspension was prepared daily in Tween 80, suspended in 0.9% saline solution) besides Clomipramine suspension (27 mg/kg). Dosing frequency was once in a day for 30 days. At the end of 30th day, after 30 min of last dosing, estrus female was introduced into respective cages and observed for mating performance and results were recorded and statistically analyzed.

Statistical analysis

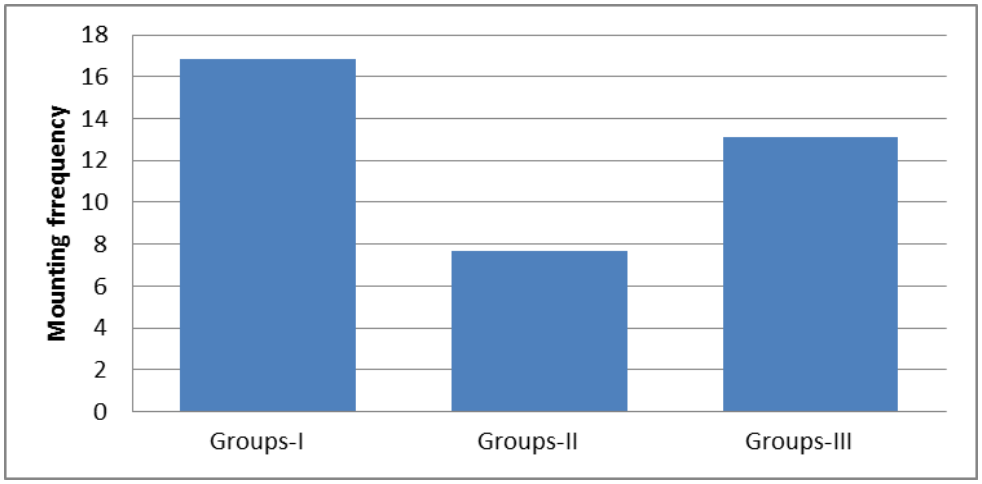
Data were presented as the mean ± SEM. The data were subjected to analysis of variance (ANOVA) followed by Tukey's test. $p < 0.05$ was taken as significant.

RESULTS

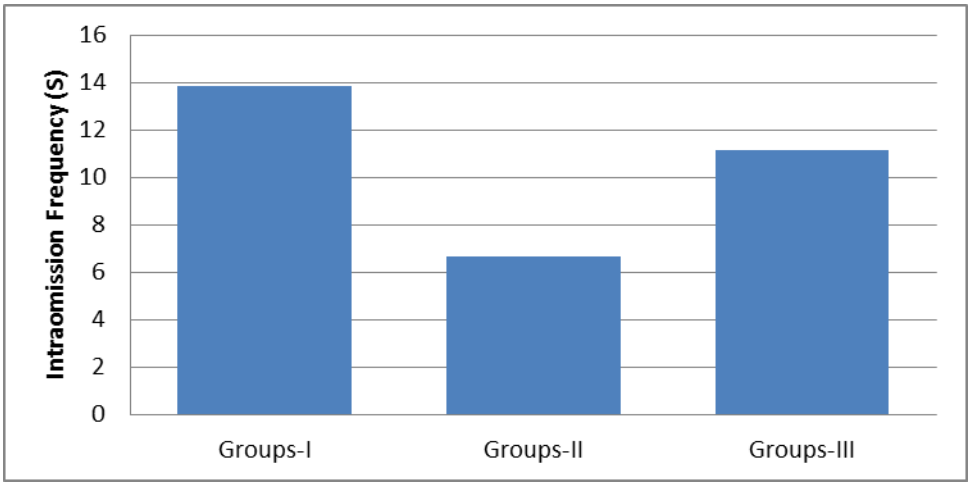
The results of sexual behavior analysis showed that in group I, normal rats exhibited usual sexual behavior, evident by ML (96.41± 2.4),MF (16.83 ± 1.2), IF (13.83± 1.7), EF (3.5 ± 1.2), IL (123.83 ± 1.77), EL (128.8 ± 1.03), and PEI (173.5 ± 1.43). In Clomipramine treated group (group II), males demonstrated diminished sexual behavior as reflected by decreased ML (158.2 ± 1.2), CF (7.33± 1.23) MF (7.67 ± 0.42), IF (6.28 ± 1.49), EF (1.08± 1.1) and increased IL (184.16 ± 1.11), EL (180.6 ± 1.04), and PEI (233.16 ± 2.4) in comparison to normal control. On the other hand, animals of Sildinafil Citrate treated group (group III), restored sexual performance significantly compared to Clomipramine treated group (group II). The males of group III showed significant increase in the frequencies ML (115.23 ± 1.4), MF (13.12 ±1.24), IF (11.12 ±1.06), EF (3.26 ±1.17) and decrease in latencies IL (151.12 ±1.88), EL (161.12 ±1.1), PEP (213.2 ±1.24) in relation with normal control.



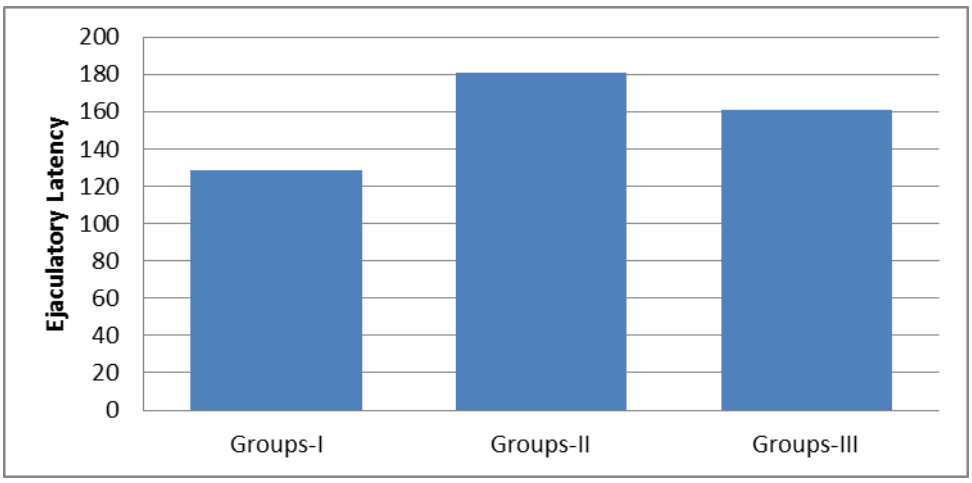
Graph 1: Effect of Sildinafil Citrate on Mounting Latency in Clomipramine induced sexual dysfunction male rats. Group-I: vehicle treated; Group-II: Clomipramine treated; Group-III: Sildinafil Citrate treated. Values are the mean ± SEM, n = 6; a $p < 0.05$ and d $p < 0.01$, a: compared to normal control; d: compared to negative control. Data were analyzed by ANOVA followed by Tukey's test.



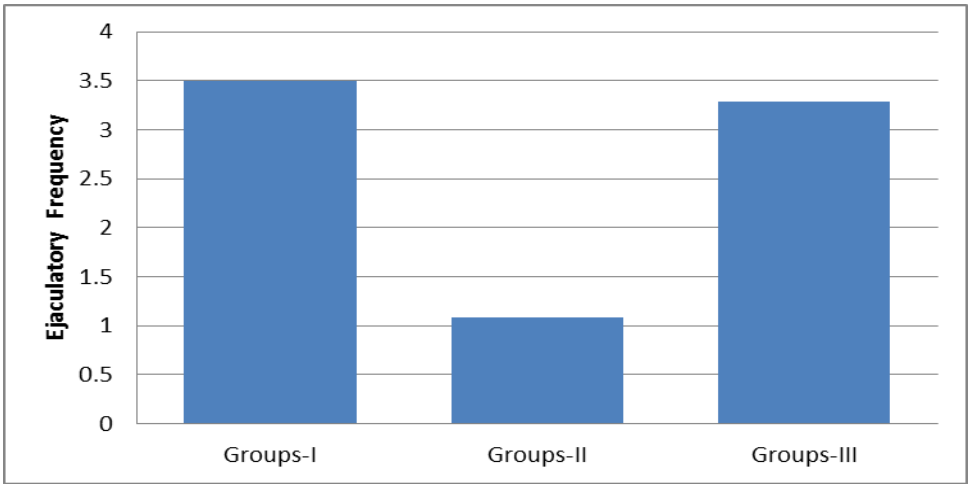
Graph 2: Effect of Sildinafil Citrate on mounting frequency in Clomipramine induced sexual dysfunction male rats. Group I: vehicle treated; Group-II: Clomipramine treated; Group-III: Sildinafil Citrate treated. Values are the mean ± SEM, n = 6; a, p < 0.05 and d p < 0.01, a,: compared to normal control; d : compared to negative control. Data were analyzed by ANOVA followed by Tukey's test.



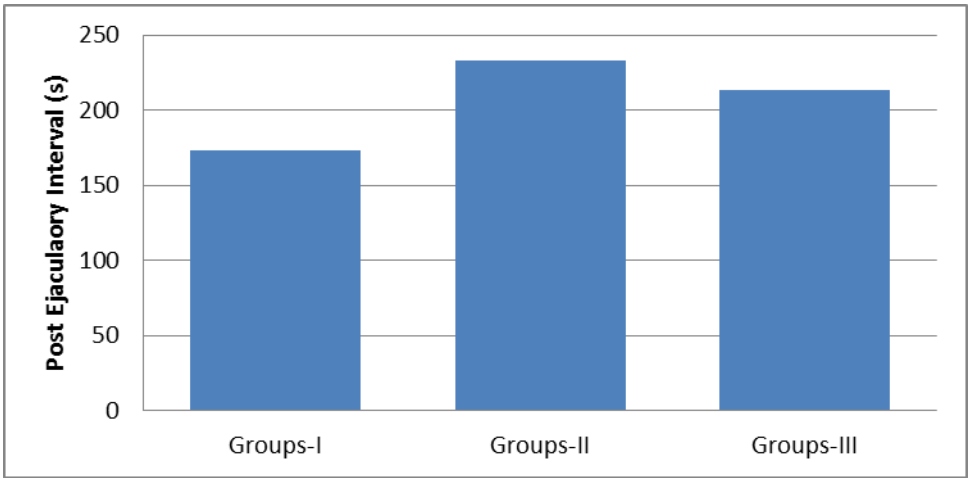
Graph 3: Effect of Sildinafil Citrate on intromission frequency in Clomipramine induced sexual dysfunction male rats. Group I: vehicle treated; Group-II: Clomipramine treated; Group-III: Sildinafil Citrate treated. Values are the mean ± SEM, n = 6; a, p < 0.05 and d p < 0.01, a,: compared to normal control; d : compared to negative control. Data were analyzed by ANOVA followed by Tukey's test.



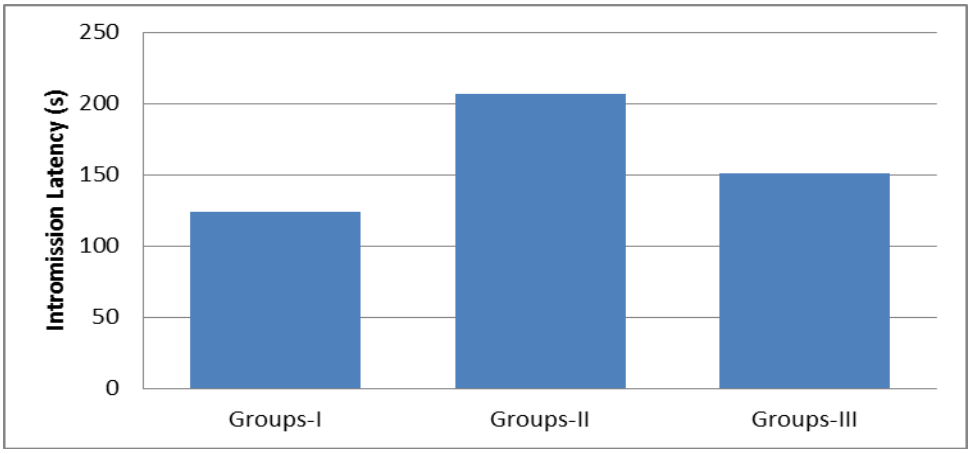
Graph 4: Effect of Sildinafil Citrate on Ejaculatory Latency in Clomipramine induced sexual dysfunction male rats. Group I: vehicle treated; Group-II: Clomipramine treated; Group-III: Sildinafil Citrate treated. Values are the mean ± SEM, n = 6; a, p < 0.05 and d p < 0.01, a,: compared to normal control; d : compared to negative control. Data were analyzed by ANOVA followed by Tukey's test.



Graph 5: Effect of Sildinafil Citrate on Ejaculatory frequency in Clomipramine induced sexual dysfunction male rats. Group I: vehicle treated; Group-II: Clomipramine treated; Group-III Sildinafil Citrate reated. Values are the mean ± SEM, n = 6; a, p < 0.05 and d p < 0.01, a,: compared to normal control; compared to negative control. Data were analyzed by ANOVA followed by Tukey's test.



Graph 6: Effect of Sildinafil Citrate on Post Ejaculatory Interval in Clomipramine induced sexual dysfunction male rats. Group I: vehicle treated; Group-II: Clomipramine treated; Group-III: Sildinafil Citrate treated. Values are the mean ± SEM, n = 6; a, p < 0.05 and d p < 0.01, compared to normal control; compared to negative control. Data were analyzed by ANOVA followed by Tukey's test.



Graph 7: Effect of Sildinafil Citrate on Intromission Latency in Clomipramine induced sexual dysfunction male rats. Group I: vehicle treated; Group-II: Clomipramine treated; Group-III: Sildinafil Citrate treated. Values are the mean ± SEM, n = 6; p < 0.05 and d p < 0.01, compared to normal control: compared to negative control. Data were analyzed by ANOVA followed by Tukey's test.

DISCUSSION

Sexual activity is a multifaceted activity, involving complex interactions between the nervous system, the endocrine system, the vascular system and a variety of structures that are instrumental in sexual excitement, intercourse and satisfaction. Normal male sexual response cycle can be functionally divided into five interrelated sequence that occur in a defined sequence: libido, erection, ejaculation, orgasm, and detumescence. Problem anywhere in the entire sequence may lead to sexual dysfunction. Sexual dysfunction is a common side effect of psychoactive medications as well as a number of other frequently prescribed medications. Considerable attention has been recently focused on antidepressants, perhaps because of their widespread use and because they are often taken for long periods of time (e.g., months or years). Clomipramine is the imipramine analogue of chlorpromazine. Compared to other tricyclic antidepressants (TCA), it has a greater effect upon dopamine blockade and serotonin uptake inhibition. This has implications for prolactin release and orgasmic dysfunction mediated through $5HT_2$ receptors.[16,17] Moreover, peripheral antimuscarinic and alpha-adrenergic blockade effects have also been implicated in the mechanism of Clomipramine-induced orgasmic dysfunctions. Sexual dysfunctions such as decreased libido, delayed orgasm, difficulties in maintaining an erection, and inhibition of ejaculation are common side effects of Clomipramine.

CF, PEP, ML, MF, IF,IL, EF and EL are useful indices of vigor, libido and potency[10] An increase in ML (Graph 1) MF (Graph 2) reflects sexual motivation and increase in the number of IF (Graph3), IL (Graph-7) EF (Graph 5)and PEI (Graph 6) shows the efficiency of erection, penile orientation and the ease by which ejaculatory reflexes are activated. Therefore, the increase in sexual parameters, enhanced sexual behavior of male rats. Results of sexual performance analysis showed that remarkably increases the PEI, MF, ML, IF,IL and EF, of sildenafil citrate. Whereas in Clomipramine-induced experimental rats PEI, MF, ML, IF,IL and EF decreases remarkably. Mount latency, Mount frequency, intromission frequency & latency and ejaculatory frequency & latency post ejaculatory pause are indicators of sexual motivation are inversely proportional to sexual motivation.[18] According to biological theory, serotonin reuptake inhibitors increase the accumulation of serotonin in the synapse, which lead to delayed or inhibited ejaculation and ejaculatory inhibiting effects of serotonin in the brain are enhanced.[19] Therefore, the decrease in the PEI, MF, ML, IF,IL and EF observed in Sildinafil Citrate treated animals might imply stimulation of sexual motivation and arousability as compared to Clomipramine treated group. It may also be an indication of enhanced sexual appetitive behavior in the male rats. All these facts further support the sexual function improving effect of the Sildinafil Citrate.

CONCLUSION

In conclusion, the present study has demonstrated that Sildinafil Citrate has potential to restore the normal sexual behavior in experimental animal.

ACKNOWLEDGMENT

The authors are thankful to Sri K.V.Naveen Kiran, Chairman, Sri K.V. College of Pharmacy, Chickballapur, Karnataka for providing facilities to carry out this work successfully.

REFERENCES

1. Balon R, Yeragani VK, Polil R. Sexual dysfunction during antidepressant treatment. J Clin Psychiatry, 1993; 54: 209-12.
2. Beaumont, G.Sexual side-effects of clomipramine (Anafranil). J Int Med Research, 1977; 5(1): 469.
3. Feng P, Guan,Z, Yang, X, Fang, J.Impairment of ERK signal transduction in the brain in a rat model of depression induced by neonatal exposure of clomipramine. Brain Res., 2003; 991(1-2): 195-205.
4. Andersson KE. Pharmacology of penile erection. Cardiovascular interactions of drugs for ED U Simonsen 187 International Journal of Impotence Research. Pharmacol Rev, 2001; 53: 417 – 450.
5. Langtry HD, Markham A. Sildenafil: a review of its use in erectile dysfunction. Drugs, 1999; 57: 967 – 989.
6. Goldstein I et al. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. New Engl J Med, 1998; 338: 1397 – 1404.
7. Conti CR, Pepine CJ, Sweeney M. Efficacy and safety of sildenafil citrate in the treatment of erectile dysfunction in patients with ischemic heart disease. Am J Cardiol, 1999; 83: 29 – 34C.
8. Herrmann HC, Chang G, Klugherz BD, Mahoney PD. Hemodynamic effects of sildenafil in men with severe coronary artery disease. New Engl J Med, 2000; 342: 1622 – 1626.
9. Przyklenk K, Kloner RA. Sildenafil citrate (Viagra) does not exacerbate myocardial ischemia in canine models of coronary artery stenosis. J Am Coll Cardiol, 2001; 37: 286-292.
10. Wallis RM, Corbin JD, Francis SH, Ellis P. Tissue distribution of phosphodiesterase families and the effects of sildenafil on tissue cyclic nucleotides, platelet function, and the contractile responses of trabeculae carneae and aortic rings in vitro. Am J Cardiol, 1999; 83: 3C– 12C.
11. Webb DJ et al. Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. J Am Coll Cardiol, 2000; 36: 25– 31.
12. Ishikura F et al. Effects of sildenafil citrate (Viagra) combined with nitrate on the heart. Circulation, 2000; 102: 2516 – 2521.
13. Burnett, A.L.Nitric oxide in the penis: Physiology and pathology. Journal of Urology, 1997; 157: 320–324.

14. MT Yakubu, MA Akanji, AT Oladiji. Male sexual dysfunction and methods used in assessing medicinal plants with aphrodisiac potentials Pharmacognosy Reviews, 2007.1.49.
15. Chan, J.S, Kim, D.J, Ahn, C.H, Oosting, R.S, Olivier B. Clavulanic acid stimulates sexual behaviour in male rats. Eur J Pharmacol, 2009.
16. Blackwell, B. Antidepressant drugs In: Dukes MN Meyer's side effects of drugs. Elsevier. Amsterdam, 1984; 24-61.
17. Sorscher SM, Dilsaver SC. Antidepressant-induced sexual dysfunction in men: due to cholinergic blockade? J Clin Psychopharmacology, 1986.6.53-5.
18. MT Yakubu, MA Akanji, AT Oladiji. Aphrodisiac potentials of the aqueous extract of Fadogia agrestis (Schweinf. Ex Hiern) stem in male albino rats Asian Journal of Andrology, 2005.
19. Waldinger MD, Hengeveld MW, Zwinderman AH, Olivier B. Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. J Clin Psychopharmacol, 1998 Aug; 18(4): 274-81.