

# Contribution of Phosphodiesterase-5 (PDE<sub>5</sub>) Inhibitors in the Various Diseases

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## ABSTRACT

The PDE-5 inhibitors, i.e., phosphodiesterase-5 inhibitors like sildenafil, vardenafil, and tadalafil, are the most used in premature erectile dysfunction. Many literature reviews suggest that these classes of drugs are commonly used in erectile dysfunction. Many of these reviews suggest that these inhibitors (PDE-5) are used in many other diseases apart from erectile dysfunction. So, in this review, we find the main mechanism of action of PDE-5 inhibitors in different disease conditions. These inhibitors have a major role in different diseases like erectile dysfunction, memory enhancement, cancer (cell proliferation), lower urinary tract symptoms, and pulmonary arterial hypertension. This class of drug also acts through the cGMP pathway. We found that cGMP plays an important role in different diseases like erectile dysfunction, cancer, and memory enhancement. So, in this review, we show the mechanism of PDE-5 inhibitor in different disease conditions.

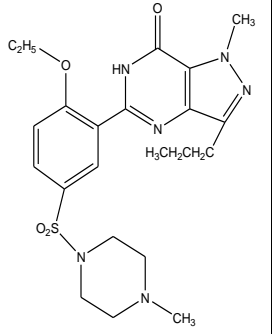
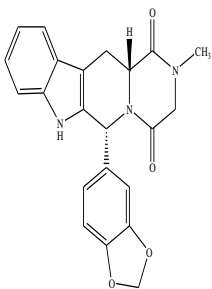
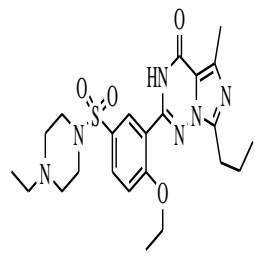
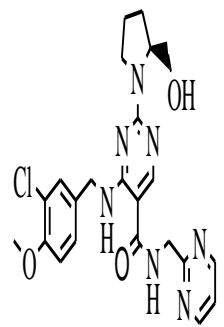
**Keywords:** PDE-5, Erectile dysfunction, Memory enhancement, cGMP, Pulmonary arterial hypertension.

## INTRODUCTION

The first phosphodiesterase-5 (PDE-5) inhibitor, sildenafil, was released in 1998. In its first six years on the market, sildenafil treated more than 20 million men. Vardenafil was authorized in 2003, giving patients a different choice<sup>[1]</sup>. A few months

later, tadalafil received approval the same year. PDE-5 inhibitors are now the standard treatment for erectile dysfunction (ED) and pulmonary arterial hypertension (PAH)<sup>[2]</sup>. In order to prevent myosin from interacting with actin, myosin is dephosphorylated by cyclic guanosine monophosphate (cGMP), which is produced intercellularly by nitric oxide<sup>[3]</sup>. This results in smooth muscle relaxation. PDE-5 inhibitors, sildenafil and tadalafil, have been approved by the Food and Drug Administration for the treatment of pulmonary hypertension. PDE-5 is also found in the smooth muscle of the walls of the arterials within the lungs<sup>[4]</sup>. In addition to increasing the number of men seeking medical care for erectile dysfunction issues, the availability of PDE-5 inhibitors has also significantly changed. But targeted treatments can stop the course of PAH and potentially restore some of the heart and lung damage. PDE-5 inhibitors were discovered for angina disease<sup>[5]</sup>. The PD5 inhibitor is present naturally in the plant *Kaempferia parviflora*. PDE-5 is one such drug. Recent research has shown that we can overcome many diseases of any kind, which comes in the use of erectile dysfunction drugs. such as memory enhancement, lower urinary tract symptoms, pulmonary arterial hypertension, and cancer<sup>[6]</sup>.

**Table 1.: (Pharmacology of PDE-5 Inhibitors)**

DRUG NAME	SILDENAFIL	TADALAFIL	VARDENAFIL	AVANAFIL
INTRODUCTION	An effective medication for treating ED (erectile dysfunction) and PAH (pulmonary arterial hypertension) is sildenafil a PDE-5 inhibitor.	A PDE-5 inhibitor called tadalafil is used to treat PAH, benign prostatic hyperplasia and ED.	The drug is an inhibitor of PDE -5 used to treat ED.	PDE-5 inhibitor avanafil is used to treat ED. Avanafil works by blocking a certain PDE-5 enzyme that is present in several bodily tissues, most notably in the CC penis.
MECHANISM OF ACTION	The physiological mechanism underlying the erection of the penis occurs when the corpus cavernosum (CC) release nitric oxide (NO), a substance cGMP is created after NO activates the enzyme guanylate cyclase, which leads to the relaxation of the smooth muscle of the CC and the opening of the blood vessels. This isolated human CC is not immediately relaxed by sildenafil, but it does enhance the effects of nitric oxide by blocking the action of PDE-5, which breaks down cGMP levels in the CC. Sildenafil inhibits PDE-5 to raise cGMP levels in the CC, which stimulates smooth muscle relaxation and blood flow into the CC, in a similar manner. Sexual pleasure boots local NO generation when there is no sexual arousal, sildenafil has little effect at the recommended dosage.	cGMP causes smooth muscle to relax, which increases blood flow to the due to the CC improvement in functioning by PDE-5 inhibition.	The cGMP specific PDE type-5 is specifically inhibited by vardenafil. The CC, one of the penis two sponges like areas is where smooth muscle relaxes to begin the process of erection. NO is produced upon stimulation from endothelial cells and nerve terminal in the CC. The production of cGMP in the CC smooth muscle cells is raised as a result of nitric oxide activation of the enzyme guanylate cyclase. Erection result from the cGMP induced relaxation of smooth muscle and increased blood flow to the penis.	The cGMP-specific PDE type 5 that breaks down cGMP in the CC, which is found around the penis, is inhibited by avanafil. Nitric oxide is locally released in response to sexual excitement, and this nitric oxide induces the production of cGMP by the enzyme guanylate cyclase.
IUPAC /CHEMICAL NAME	5-(2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl)-1-methyl-3-propyl-1H-pyrazolo [4, 3-d] primidine-7(6H)-one.	(6R, 12aR)-6-(1, 3-benzodioxol-5-yl)-2-methyl-2, 3, 6, 7, 12, 12a-hexahydropyrazino [1, 2:1, 6] pyrido [3, 4, -6] indole-1, 4-dione.	2-(2-ethoxy-5-(4-ethylpiperazin-1-ylsulfonyl)phenyl)-5-methyl-7-propylimidazo [1, 5-f] [1, 2, 4] triazin-4(3H)-one.	(S)-4-(3-chloro-4-methoxybenzylamino)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide.
STRUCTURE				
MOLECULAR FORMULA	C <sub>22</sub> H <sub>30</sub> N <sub>6</sub> O <sub>4</sub> S.	C <sub>22</sub> H <sub>19</sub> N <sub>5</sub> O <sub>4</sub> .	C <sub>22</sub> H <sub>32</sub> N <sub>6</sub> O <sub>4</sub> S.	C <sub>23</sub> H <sub>26</sub> ClN <sub>7</sub> O <sub>3</sub> .
MOLECULAR WEIGHT	474.6 g mol <sup>-1</sup> .	389.4 g mol <sup>-1</sup> .	488.6 g mol <sup>-1</sup> .	483.9 g mol <sup>-1</sup> .
INTERACTION	-Captopril. -Alprazolam. -Benzyl alcohol.	-Zanamvir. -Tramadol.	-Amlodipine. -Alcohol. -Benzapril.	-Chlorpromazine. -Chronic alcohol. -Dapsone.
HALF -LIFE	3-5 hours	17-21 hours	4 hours	5 hours
BRAND NAME	-Viagra. -Vizarsin. -Revatio.	-Cialis. -Entadfi. -Alyq.	-Levitra. -Staxyn.	-Spedra. -Stendra.
	-Bladder pain. -Burning feeling in the chest	-Indigestion. -Pain in our arms and	-Flu like symptoms. -Stuffy.	-Flushing (redness or warmth).

SIDE EFFECT	or stomach. -Tenderness in the stomach area. -Irregular heartbeat. -Ankles.	legs. -muscle aches. -Back pain.	-Priapism. -Tinnitus. -Headache.	-stomach upset. -Vision change. -Sudden vision loss. -Shortness of breath.
USES	-Erectile Dysfunction. -Pulmonary arterial hypertension.	-Pulmonary arterial hypertension. -Erectile dysfunction. -Benign prostatic hypertention. -Lower urinary tract symptoms.	-Erectile dysfunction.	-Erectile dysfunction.

**PDE-5 FUNCTION IN VARIOUS DISEASES**

**ERECTILE DYSFUNCTION**

**What is erectile dysfunction?**

The inability to obtain and preserve an erection that is strong enough for copulation is known as ED (impotence). Being occasionally troubled with erection issues is not usually a cause for panic. But if erectile dysfunction persists, it may have a negative impact on your relaxation, make you feel insecure, and stress you out<sup>[7]</sup>. It has also become a risk factor for heart disease. Difficulties getting or keeping an erection can also be a sign of an underlying medical condition that needs to be treated<sup>[8]</sup>.

**FUNCTION**

Erectile dysfunction, which affects men, usually contributes to male sexual anxiety. He suffers from erectile dysfunction when the penis of a man does not stiffen and expand when he is sexually stimulated<sup>[7]</sup>. A male frequently suffers an erection after being sexually stimulated because his body reacts by boosting blood flow. Growing older makes erectile dysfunction more common<sup>[9]</sup>. According to Massachusetts male ageing research (MMAR), erectile dysfunction was present in 40% of men in their 40s and nearly 70% of men in their 70s. The causes of erectile dysfunction are old age, smoking, hypertension, heart disease, diabetes, and as a result of radical prostatectomy<sup>[10]</sup>.

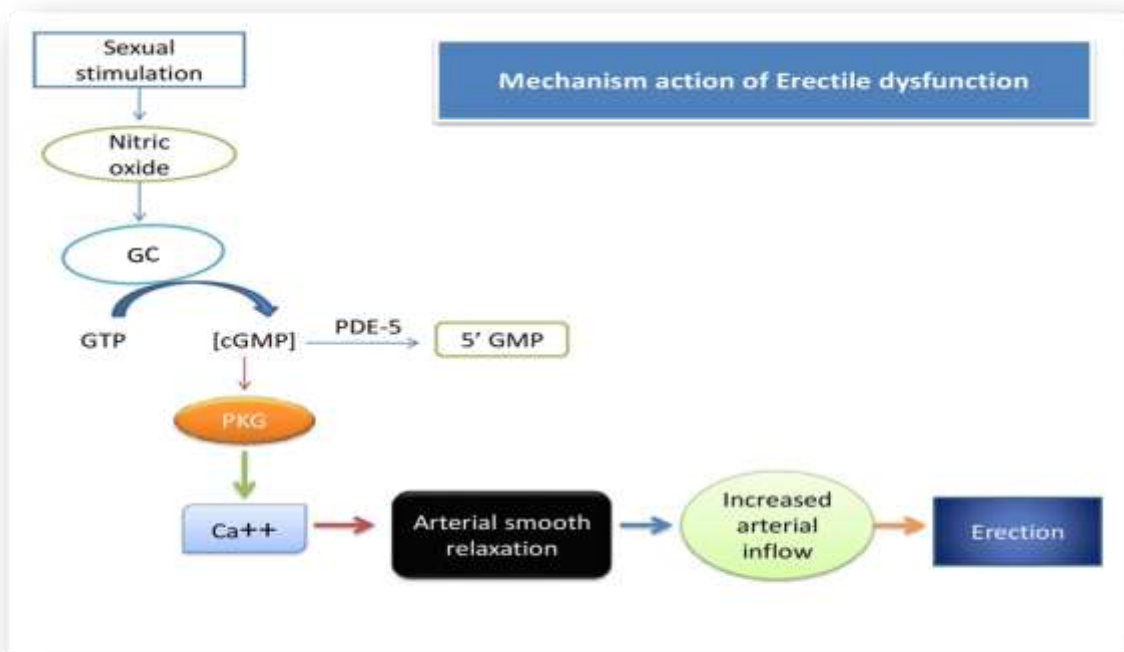


Figure 1. Mechanism action of Erectile dysfunction

## (2) MEMORY ENHANCING

### What is memory enhancing?

Memory means your capacity for remembering is your memory. To enhance anything means to elevate its worth, quality, or attractiveness. Different encoding tasks that improve memory in a manner quite similar to self-referential encoding are being developed by research as part of a new strategy<sup>[11]</sup>. The process of enhancing memory is called memory improvement. Researchers have done to assist individual in enhancing their memory, who is suffering from memory deficiencies, age-related memory loss, and people's desire to enhance their own memory<sup>[12]</sup>. Additionally, research has been conducted to identify the variables that affect memory and cognition. There are several methods for enhancing memory, including cognitive training, psychopharmacology, nutrition, stress reduction, and exercise<sup>[13]</sup>. Different approaches may be found for each method to affect memory. Additionally, neuroimaging has offered neurobiological support for all-encompassing strategies for memory improvement<sup>[14]</sup>.

## FUNCTION

Sildenafil is known to inhibit the PDE type 5 specific to cGMP very selectively. According to research, sildenafil may enhance memory by extending the induced ARC and pCREB intervals. According to certain studies, PDE type 5 inhibitors may increase the amount of cGMP generated by the central nervous system<sup>[15]</sup>. Vasodilation is a recognized side effect of PDE5 inhibitors, which is probably caused by cGMP. Therefore, the improved blood flow and accompanying higher glucose metabolites may be related to the memory-improving effects of PDE-5 inhibitors<sup>[16]</sup>. Recent research has shown that sildenafil can be used for erectile dysfunction as well as for memory enhancement. Human studies have focused on the effects of PDE-5 inhibitors on cerebral blood flow in the central nervous system<sup>[17]</sup>. In individuals with pulmonary hypertension who had lower cerebral blood fluid and attenuated vascular responsiveness, sildenafil improved cerebrovascular reactivity and boosted neurovascular coupling<sup>[18]</sup>. Alzheimer's disease risk was decreased among those who used sildenafil. Sildenafil reduced Alzheimer's biomarkers and improved proliferative potential in human neurons<sup>[19]</sup>.

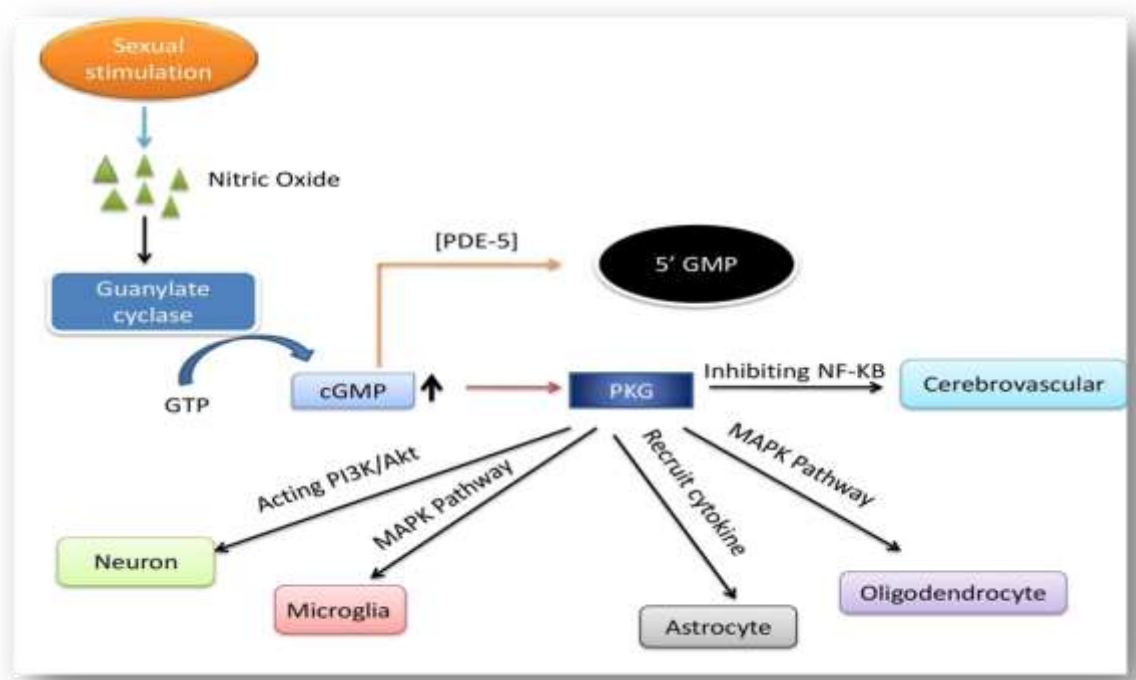


Figure 2. Mechanism action of memory enhancing

### (3) CANCER

#### What is cancer?

A condition known as cancer is one in which a small percentage of the body cells spring out of the monitoring and prevalence to other bodily areas. The billions of cells that make up the human body are almost everywhere cancerous cells can start growing<sup>[20]</sup>. Cell proliferation and multiplication is a process where human cells divide to produce new cells. When the body regenerates its cells, the old or injured ones die and are replaced by new ones<sup>[21]</sup>. Cancerous tumours can travel to distant regions of the body to produce novel tumors, invade neighboring tissues, or both (a process called metastasis)<sup>[22]</sup>. "Malignant tumor" can also refer to cancerous growth. Leukemia and other blood malignancies, like others, frequently do not develop into malignant tumours<sup>[23]</sup>.

#### FUNCTION

Numerous organisations have examined the potential anti-cancer properties of sildenafil and vardenafil, which have been shown to

inhibit the development of tumour cells and trigger in vitro apoptosis of B-cells, chronic lymphocytic leukaemia cells in a caspase-dependent manner<sup>[24]</sup>. It has also been demonstrated that sildenafil and other PDE-5 inhibitors trigger apoptosis in a number of cancers, including colon cancer and chronic lymphatic leukemia<sup>[25]</sup>. Cisplatin is a cytotoxic medication that is widely used to treat malignant tumors. It produces cisplatin DNA adducts, and it exerts its cytotoxic activity, arresting the cell cycle and inducing apoptosis<sup>[26]</sup>. Both in vitro and in vivo studies have shown that the chemo adjuvant effects of sildenafil increase cancer cell death. particularly in clinical trials, sildenafil reduces tumour growth as compared to chemotherapy alone<sup>[27]</sup>. Sildenafil may also lengthen the half-life of certain small molecule inhibitors, including docetaxel, which is used in the treatment of lung cancer. The combination of sildenafil and cisplatin resulted in a considerable decrease in tumour volume<sup>[28]</sup>.

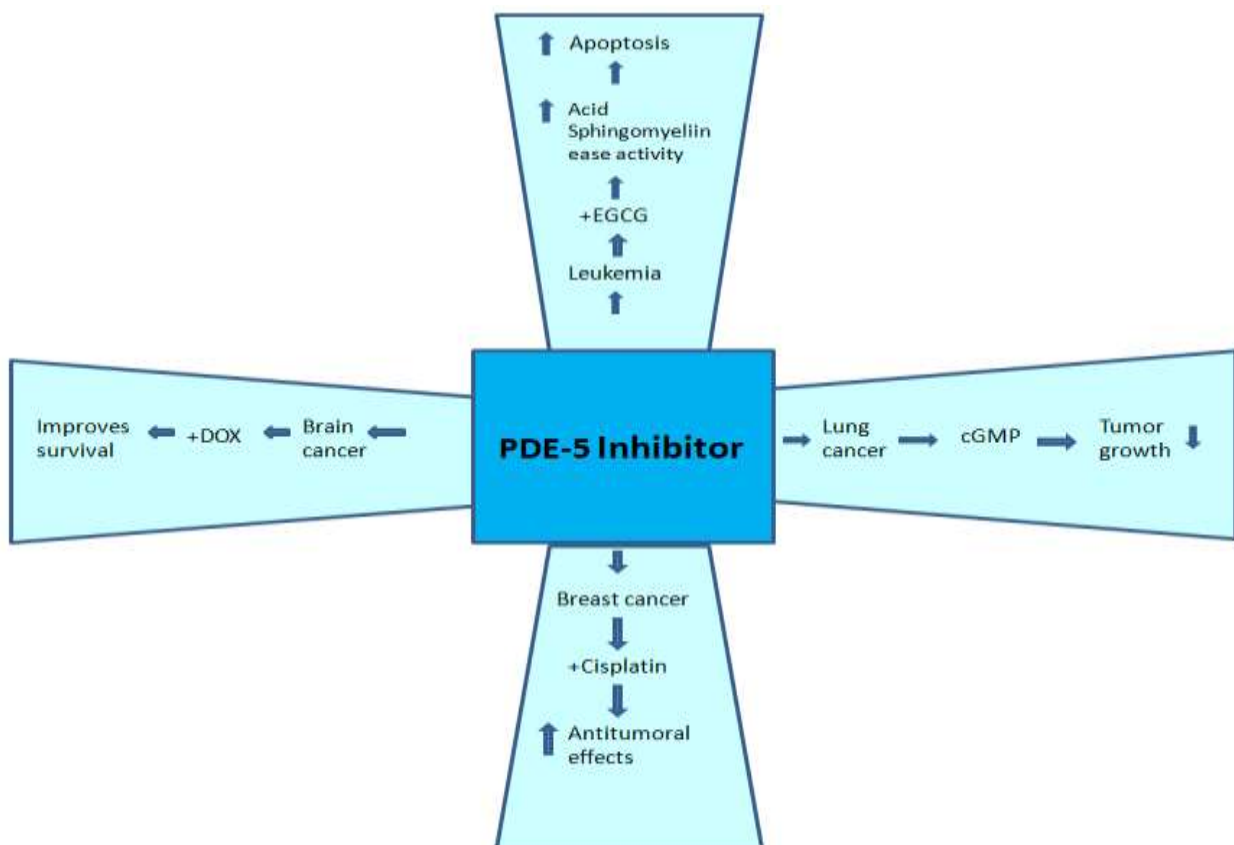


Figure 3. Mechanism of action

#### (4) LOWER URINARY TRACT SYMPTOMS (LUTS)

##### What is a LUTS?

LUTS symptoms include irritating symptoms such as recapitulation, exigency, intemperance, and nocturia, as well as voiding or resistant symptoms such as hesitancy, poor and irregular stream, stress, prolonged maturation, the sensation of a sketchy bladder emptying, dribbling, and so on<sup>[29]</sup>. Quantitative symptom indices are the most effective way to assess the intensity of LUTS. The American Urological Association (AUA) symptom index is the most extensively used tool for assessing the intensity of symptoms<sup>[30]</sup>. Population-based studies' findings have demonstrated that aged patients are more likely to experience moderate-to-severe LUTS and Qmax decreases. The growth of LUTS in the ageing male population has frequently been linked to the growing prostate or BPH since both prostatic enlargement and LUTS development are age-dependent<sup>[29]</sup>. In actuality, "prostatism" was the name used to describe the cluster of obstructive and irritable symptoms seen in elderly males. About 40% of older men get lower urinary tract problems, although women are also affected<sup>[31]</sup>.

##### FUNCTION

LUTS, such as urgency, frequency, and dribbling, are frequently seen in men with BPH. Adrenergic drugs, despite having side effects like orthostatic hypotension, vertigo, and sexual dysfunction, have been the cornerstone of pharmacological cure for LUTS<sup>[32]</sup>. Large scale epidemiologic research points to a clear connection between LUTS and ED, and PDE-5 inhibitors are useful in the cure of erectile dysfunction<sup>[33]</sup>. In numerous randomised controlled trials in men with and without concurrent erectile dysfunction, the PDE-5 inhibitors (sildenafil, tadalafil, and vardenafil) have proved effective in the cure of LUTS<sup>[34]</sup>. An open-label study of males with erectile dysfunction was the first trial to look at the use of phosphodiesterase-5 inhibitors in the cure of lower urinary tract symptoms. Sildenafil was administered before engaging in sexual activity as needed<sup>[35]</sup>. The severity of lower urinary tract symptoms was also reduced. All individuals with severe lower urinary tract symptoms first reported moderate symptoms, while 60% of men with moderate LUTS in the beginning reported some symptoms<sup>[36]</sup>.

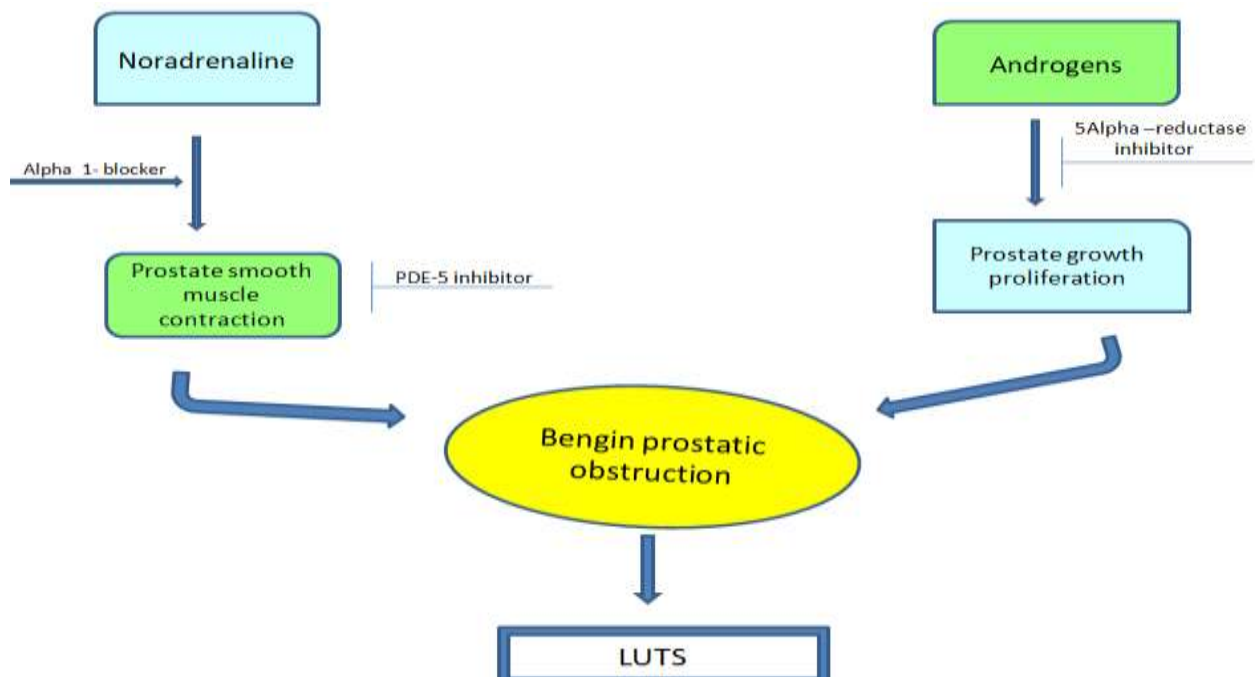


Figure 4. Mechanism of action

## 5) PULMONARY ARTERIAL HYPERTENSION

### What is PAH?

High blood pressure in the arteries flowing from the heart to the lungs is known as PAH. PAH causes the small arteries in your lungs to constrict or block. Blood pressure in your lungs rises because it is harder for blood to pass through them<sup>[37]</sup>. Your heart must work harder to pump blood through those arteries, and with time, the heart muscle weakens. It could eventually result in cardiac failure<sup>[38]</sup>.

### FUNCTION

Sildenafil may also have antiproliferative effects on pulmonary vascular smooth muscle cells since it specifically inhibits PDE type 5, which increases intercellular cGMP buildup and boosts nitric oxide-mediated vasodilation<sup>[39]</sup>. Sildenafil may be helpful in the cure of PAH. In our double-blind, placebo-controlled clinical trial, we looked at how well three doses of sildenafil worked and how well they were tolerated by people with PAH<sup>[35]</sup>.

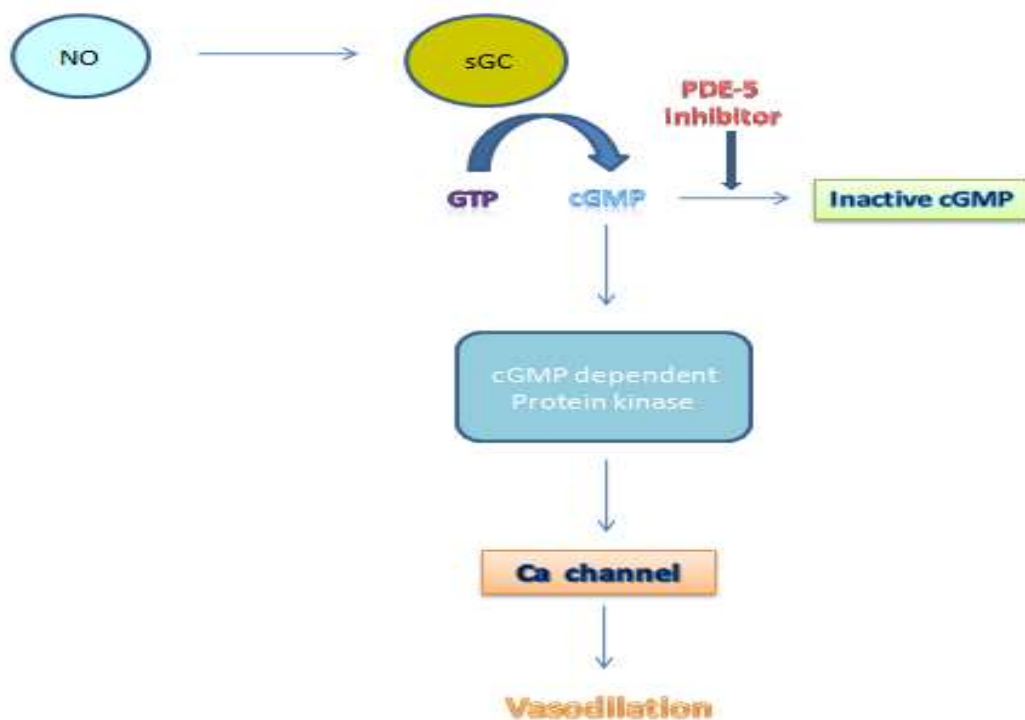


Figure 5. Mechanism of action

### CONCLUSION

PDE-5 inhibitors, also known as phosphodiesterase-5 inhibitors, are the most commonly used treatments for erectile dysfunction. Sildenafil and tadalafil are now the most commonly used for sexual pleasure. But recent literature suggest that their drugs have beneficial action in many diseases apart from erectile dysfunction with the help of cGMP pathways. This pathway plays an important role in many diseases, like erectile dysfunction, cancer and other diseases. Now we can call that PDE-5 inhibitors have a major role in many diseases. The memory-enhancing properties

of PDE-5 inhibitors are the unique features of this class of drugs. So, we can say that PDE-5 plays a major role in memory, cancer, and ageing.

### REFERENCES

1. Huang SA, Lie JD. Phosphodiesterase-5 (PDE5) Inhibitors In the Management of Erectile Dysfunction. *Pharm Ther* 2013;38:407.
2. Falk JA, Philip KJ, Schwarz ER. The emergence of oral tadalafil as a once-daily treatment for pulmonary arterial hypertension. *Vasc Health Risk Manag* 2010;6:273.

3. Francis SH, Busch JL, Corbin JD. cGMP-Dependent Protein Kinases and cGMP Phosphodiesterases in Nitric Oxide and cGMP Action. *Pharmacol Rev* 2010;62:525.
4. Schwarz ER, Kapur V, Rodriguez J, Rastogi S, Rosanio S. The effects of chronic phosphodiesterase-5 inhibitor use on different organ systems. *Int J Impot Res* 2007 192 2006;19:139–48.
5. Ausó E, Gómez-vicente V, Esquiva G. Visual Side Effects Linked to Sildenafil Consumption: An Update. *Biomed* 2021, Vol 9, Page 291 2021;9:291.
6. Temkitthawon P, Hinds TR, Beavo JA, et al. *Kaempferia parviflora*, a plant used in traditional medicine to enhance sexual performance contains large amounts of low affinity PDE5 inhibitors. *J Ethnopharmacol* 2011;137:1437.
7. Sooriyamoorthy T, Leslie SW. Erectile Dysfunction. May 2022.
8. Erectile Dysfunction & Heart Disease. Available from: <https://my.clevelandclinic.org/health/disease/s/15029-heart-disease--erectile-dysfunction>.
9. Dean RC, Lue TF. Physiology of Penile Erection and Pathophysiology of Erectile Dysfunction. *Urol Clin North Am* 2005;32:379.
10. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994;151:54–61.
11. O'Hara K, Morris R, Shadbolt N, Hitch GJ, Hall W, Beagrie N. Memories for life: a review of the science and technology. *J R Soc Interface* 2006;3:351.
12. Dekkers W, Rikkert MO. Memory enhancing drugs and Alzheimer's Disease: Enhancing the self or preventing the loss of it? *Med Health Care Philos* 2007;10:141.
13. Mandolesi L, Polverino A, Montuori S, et al. Effects of Physical Exercise on Cognitive Functioning and Wellbeing: Biological and Psychological Benefits. *Front Psychol* 2018;9:509.
14. Brem A, Katharine, Ran K, Pascual-leone A. Learning and memory. *Handb Clin Neurol* 2013;116:693.
15. Jeremy JY, Ballard SA, Naylor AM, Miller MAW, Angelini GD. 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;79:958–63.
16. Ribaud G, Ongaro A, Zagotto G, Memo M, Gianoncelli A. Therapeutic Potential of Phosphodiesterase Inhibitors against Neurodegeneration: The Perspective of the Medicinal Chemist. *ACS Chem Neurosci* 2020;11:1726–39.
17. Pauls MMH, Moynihan B, Barrick TR, et al. The effect of phosphodiesterase-5 inhibitors on cerebral blood flow in humans: A systematic review. *J Cereb Blood Flow Metab* 2018;38:189.
18. Sheng M, Lu H, Liu P, et al. Sildenafil Improves Vascular and Metabolic Function in Patients with Alzheimer's Disease. *J Alzheimers Dis* 2017;60:1351.
19. Sanders O. Sildenafil for the Treatment of Alzheimer's Disease: A Systematic Review. *J Alzheimer's Dis Reports* 2020;4:91.
20. Anand P, Kunnumakara AB, Sundaram C, et al. Cancer is a Preventable Disease that Requires Major Lifestyle Changes. *Pharm Res* 2008;25:2097.
21. Blanpain C, Horsley V, Fuchs E. Epithelial Stem Cells: Turning over New Leaves. *Cell* 2007;128:445.
22. Cooper GM. The Development and Causes of Cancer. 2000.
23. Nguyen-Lefebvre AT, Horuzsko A. Kupffer Cell Metabolism and Function. *J Enzymol Metab* 2015;1.
24. Haider M, Elsherbeny A, Pittalà V, Fallica AN, Alghamdi MA, Greish K. The Potential Role of Sildenafil in Cancer Management through EPR Augmentation. *J Pers Med* 2021;11.
25. Mei XL, Yang Y, Zhang YJ, et al. Sildenafil inhibits the growth of human colorectal cancer in vitro and in vivo. *Am J Cancer Res* 2015;5:3311.
26. Dasari S, Bernard Tchounwou P. Cisplatin in cancer therapy: molecular mechanisms of action. *Eur J Pharmacol* 2014;740:364.
27. Keats T, Rosengren RJ, Ashton JC. The Rationale for Repurposing Sildenafil for Lung Cancer Treatment. *Anticancer Agents Med Chem* 2018;18:367–74.
28. Zhong L, Li Y, Xiong L, et al. Small molecules in targeted cancer therapy: advances, challenges, and future perspectives. *Signal Transduct Target Ther* 2021 61 2021;6:1–48.



29. Lepor H. Pathophysiology of Lower Urinary Tract Symptoms in the Aging Male Population. *Rev Urol* 2005;7:S3.
30. Barry MJ, Fowler FJ, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148:1549–57.
31. Brawer MK, Loeb S, Partin AW, et al. Best of the 2009 AUA Annual Meeting: Highlights from the 2009 Annual Meeting of the American Urological Association, April 25–30, 2009, Chicago, IL. *Rev Urol* 2009;11:82.
32. Laborde EE, McVary KT. Medical Management of Lower Urinary Tract Symptoms. *Rev Urol* 2009;11:S19.
33. Kaplan SA, Gonzalez RR. Phosphodiesterase Type 5 Inhibitors for the Treatment of Male Lower Urinary Tract Symptoms. *Rev Urol* 2007;9:73.
34. McMahon CN, Smith CJ, Shabsigh R. Practice pointer: Treating erectile dysfunction when PDE5 inhibitors fail. *BMJ Br Med J* 2006;332:589.
35. Hatzimouratidis K. Sildenafil in the treatment of erectile dysfunction: an overview of the clinical evidence. *Clin Interv Aging* 2006;1:403.
36. Maserejian NN, Chen S, Chiu GR, et al. Incidence of Lower Urinary Tract Symptoms in a Population-Based Study of Men and Women. *Urology* 2013;82:560.
37. Klinger JR, Elliott CG, Levine DJ, et al. Therapy for Pulmonary Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report. *Chest* 2019;155:565–86.
38. Forman DE, Sanderson BK, Josephson RA, Raikhelkar J, Bittner V, American College of Cardiology's Prevention of Cardiovascular Disease Section. Heart Failure as a Newly Approved Diagnosis for Cardiac Rehabilitation: Challenges and Opportunities. *J Am Coll Cardiol* 2015; 65:2652–9.
39. Tantini B, Manes A, Fiumana E, et al. Antiproliferative effect of sildenafil on human pulmonary artery smooth muscle cells. *Basic Res Cardiol* 2005;100:131–8.

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