

# The importance of herbal practice in unravelling cellular and molecular pathway of erectile dysfunction

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**Abstract-** An effective sexual encounter requires a penile erection. Majority of men experience sexual difficulties as a result of lifestyle modifications such as stress, ageing, and secondary illnesses like diabetes. There are several sexual disorders that affect men nowadays, with erectile dysfunction being a major one in all ages that affects partners' sexual lives and harms their relationships. Oral phosphodiesterase-5 inhibitors are the most common treatment for erectile dysfunction, although they are ineffective in some population with certain diseases, also lead to addiction. The formulations for increasing penile erection that are now on the market are in the form of tablets, oral jelly, suspensions, creams, gels, and sprays, however due to their subpar ADME qualities, they do not work well in all populations. In addition, a variety of illnesses, including diabetes, hypertension, atherosclerosis, stress, anxiety, depression, hypogonadism, multiple sclerosis, Parkinson's, and stroke, are the main contributors to erectile dysfunction. In these contexts, our goal is before developing a new medication, it is essential to comprehend the complete mechanism underlying penile erection which is a multiple pathological pathway and complex process. The routes involved in erectile function are summarised in this review. This review also provides information on "pharmacological treatment targets for erectile dysfunction." In addition to allopathic medications, several botanicals have a significant impact on erection and sexual behaviour. This review also provides a summary of the plants that enhance sexual behaviour and how they do so.

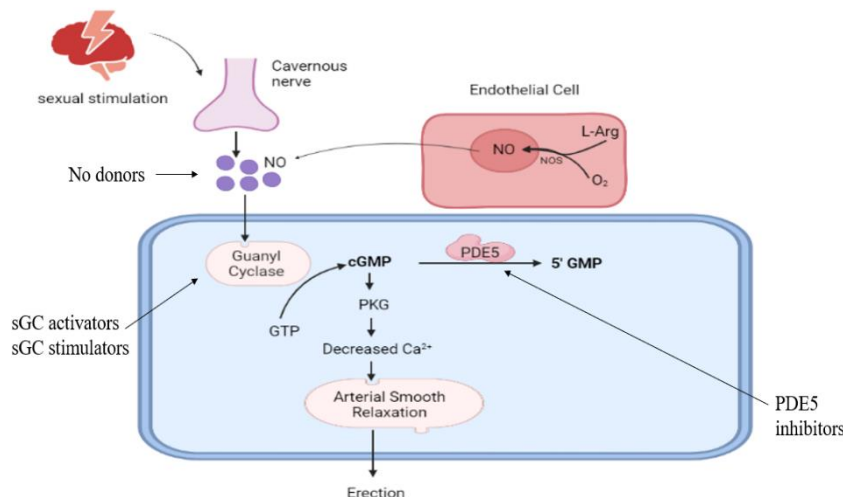
**Keywords:** Erectile dysfunction, penile erection, Nitric oxide, Rho kinase, Testosterone, Ion channels, Sirtuin, Renin angiotensin system, Central pathway, cAMP.

## INTRODUCTION:

The erection of the penis is regarded as the essential element for sexual interaction with females (1). One of the main sexual problems in men is erectile dysfunction (ED) characterised by a decline in erection (2). Historically, ED has been referred to as impotent and is regarded as the inability to obtain or maintain a firm penile erection for adequate sexual interaction (3). It is prevalent, multifactorial disorder is primarily caused by aging, psychogenic illnesses and CVS diseases. It is quite difficult to induce the penis to erection because it requires neurovascular non-adrenergic, non-cholinergic, hormonal, and psychogenic inputs (4). ED can be caused by any illness that harms and interferes with the tunica albuginea, penile arteries, nerves, blood hormone levels, smooth muscle tissue, or corporal endothelium. Diseases include heart disease, diabetes, hyperlipidemia and several other conditions are all intimately associated with erectile dysfunction. Endothelial dysfunction appears to represent a common route in such illnesses (5). More than 152 million men worldwide have ED by 2025, that number is projected to rise to 322 million (6, 7). The effects of ED on a sexual connection between male and female partners include a loss in affection and a shift in behaviour which is violent and may further undermine the relationship as well as the partners' mental wellbeing. Some men with ED experience psychosocial distress, which can progress into secondary depression. Recent prospective researches have shown that a man's psychological well-being and quality of life improve with increasing erection hardness and the number of successful intromissions. A man's relationship with his female partner improves as a result of his enhanced sexual desire, which brings about life satisfaction (8). 3-76.5% of people worldwide were found to have ED (9).

## Nitric oxide pathway

Nitric oxide (NO) is the main vasoactive Non-adrenergic and Non-cholinergic (NANC) neurotransmitter for erectile function in the corpora. Nitric oxide synthase (NOS), is an enzyme, it catalyses NO from the conversion of L-arginine to L-citrulline, in neuronal tissue, endothelium, and epithelium within pelvic and genitourinary system of humans and different species of animal. There are three forms of NOS—neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). nNOS and eNOS are largely present in the corpora cavernosa. Compared with other isoforms of NOS, Neuronal NO plays a major role in relaxation of corpora cavernosa which results in increased blood flow to penis and produces erection. Autonomic NANC dilator nerve fibres that supply the corpora cavernosa and the vascular and sinusoidal endothelium release NO which results in erection by diffuse across the smooth muscle membrane and activates soluble guanylate cyclase (sGC), which causes the production of 3', 5'-cyclic guanosine monophosphate (cGMP).



**Figure 1:** Nitric oxide pathway induces erection response: NO donors, PDE5 inhibitors, sGC activators, and stimulators.

The elevated level of cyclic GMP activates a protein kinase (PKG) that activated PKG causes the phosphorylation of various proteins and ion channels which opens potassium channel resulted in an influx of K<sup>+</sup> ions and hyperpolarization of the muscle cell membrane. When these actions happen, there is a blockage of calcium channels, which results in a reduction in cytosolic calcium levels, resulting in vascular smooth muscle relaxation (4). In this approach, PDE5i continue to be the first line of treatment for ED and became more important in the management of other medical problems. (10). For the treatment of penile dysfunction, sodium nitrite (NaNO<sub>2</sub>) and a light-controllable NO donor (NOBL-1, NO-Ros) and sGC stimulators (YC-1, BAY 41-2272, BAY 41-8543, BAY 63-2521, CFM-1571 and A-350619) and sGC activators (BAY 58-2667, HMR-1766, S-3448, A-778935) are also effective in the treatment of ED (11, 12).

### Rho kinase pathway

RhoA and ROCK are found in many tissues in the body regulating numerous physiological and pathological mechanism (13). RhoA and its effector Rho-kinase causes constriction of blood vessels in the penis by inhibition of MLC Phosphatase which results in increases Myosin Light Chain phosphorylation and elevates calcium levels. There is an increase in intracellular Ca<sup>2+</sup> which binds to calmodulin and causes a conformational change and enables complex with Myosin Light Chain kinase. After subsequent phosphorylation, the myosin-actin complex causes contraction of smooth muscle which results in unfirm penis. In ED, there is an altered RhoA/ROCK activity in the penis (14). RhoA/Rho-kinase also decreases eNOS in the penis (15). ROCK inhibition targets neurological deficits in ED and induces improved erectile haemodynamics, independent of NO synthesis, and it could be an efficient treatment for ED in a patient who does not respond to PDE5 inhibitors. Inhibition of RhoA-ROCK improves erection in diabetic mellitus. RhoA-ROCK inhibitors (Y-27632) are an option for treating ED. (13).

### Role of Testosterone in erection

Androgens are important for physical and sexual activity of male and it plays a crucial role in the growth of penis, and they manage erection by various ways (16). eNOS and nNOS are essential for the erection of penis. Studies stating that treatment with testosterone restored erectile function and NOS expression in castrated animals (17). Testosterone deficiency suppress eNOS by upregulating ROS, and the decreased eNOS results in a decrease in cGMP levels in the penis (18). Testosterone activates the smooth muscle ATP-sensitive K<sup>+</sup> channels in the isolated human corpora cavernosa strips which results in the relaxation (19). Exogenous testosterone improves erectile response scores, increases the number of nocturnal erections, successful sexual encounters, and overall sexual satisfaction in men with low levels of testosterone, but has no effect on men who are eugonadal (20).

### Ion channels

In a molecular point of view, the intracellular calcium (Ca<sup>2+</sup>) concentration is the important controller of the tone of smooth muscle. Elevated levels of intracellular Ca<sup>2+</sup> causes myosin protein phosphorylation (via the myosin light chain kinase (MLCK)), results in muscle contraction. Therefore, muscle relaxation and erection are happening when the intracellular Ca<sup>2+</sup> concentration is lower (21, 22). Ion channels are expressed in almost all living cells which are also known as membrane proteins (23).

### Large-Conductance, Ca<sup>2+</sup>-Activated K<sup>+</sup> Channels (BK<sub>Ca</sub>)

The plasma membranes of eukaryotic cells are expressed with BK<sub>Ca</sub> channels, which are highly conductive channels that are selective for potassium ions. The activity of BK<sub>Ca</sub> channels were functionally expressed in vascular endothelial cells, it controls potassium ions efflux and affect intracellular Calcium levels. In response to increased cytoplasmic Ca<sup>2+</sup> concentration and membrane voltage, these channels regulate the excitability of the plasmatic membrane by activating the negative feedback

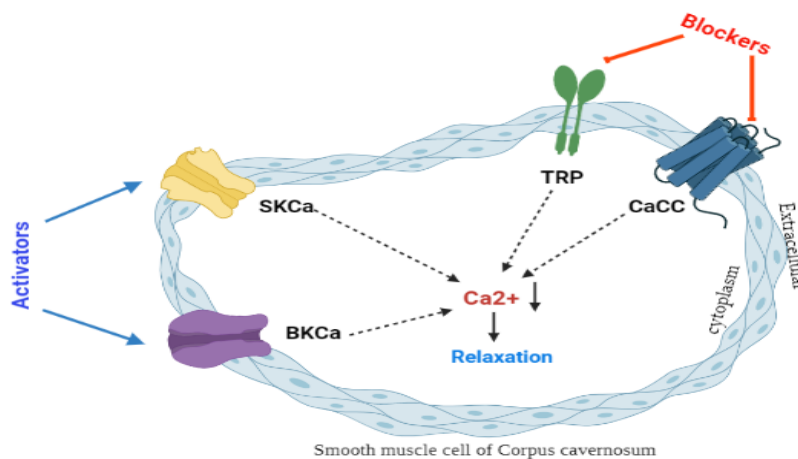
mechanism (24). The BKCa channel is a Calcium-activated potassium channel, which is activated when increases the  $\text{Ca}^{2+}$  concentration in an intracellular level or by membrane depolarization with a large conductance (25). A BKCa channel plays a key role in the controlling of vascular smooth muscle tone in physiological and in pathophysiological states, such as diabetes, hypertension, atherosclerosis, brain attack and ED (26). BKCa channel openers stabilize the cell by increasing the efflux of  $\text{K}^{+}$  ions; it leads to hyperpolarization and thus causes relaxation of smooth muscle and reduces cell excitability (27). LDD175 which is BKCa channel opener causes relaxation of erectile tissue in an endothelium-independent manner (25). Calcium activated potassium channel openers were found to relax erectile tissues and penile arteries in man (28, 29). In corpus cavernosum tissue which is present in penis, opening of BKCa channels results in the corporal smooth muscle dilation, which is important for erectile function (29).

#### Small-Conductance, $\text{Ca}^{2+}$ -Activated $\text{K}^{+}$ Channels ( $\text{SK}_{\text{Ca}}$ )

$\text{SK}_{\text{Ca}}$  channels were postulated to be involved in endothelium-dependent vasodilation in human and rat penile arteries (30, 31). Small and intermediate conductance  $\text{Ca}^{2+}$  activated  $\text{K}^{+}$  channels is one of the pharmacological target for the treatment of endothelial dysfunction in people having diabetics (33). Immunoblotting revealed the presence of  $\text{SK}_{\text{Ca}}$  channels in the *corpus cavernosum*. Small and Intermediate conductance calcium activated potassium channel openers such as NS4591 increases the release of endothelium-dependent vasodilators which results in the improvement of erectile function (32). NS309 is a potent activator of  $\text{SK}_{\text{Ca}}$  channels in human, whereas it is not gives action on BKCa (34).

#### $\text{Ca}^{2+}$ -Activated $\text{Cl}^{-}$ Channels ( $\text{CaCC}$ )

When voltage-dependent calcium channels are activated in smooth muscle, additional  $\text{Ca}^{2+}$  ions are allowed to enter the cell, which causes contraction. This is caused by the activation of  $\text{CaCC}$  channels, which results in the efflux of chloride. This action is necessary for the penile flaccidity by contracting corpus cavernosum. Therefore, by inactivating these channels is one of the therapeutic alternative treatments for ED (35, 36). Contraction of CCSM is due to  $\text{CaCC}$  activation, so by inhibiting  $\text{CaCC}$  results in erection (37). It was discovered that human and rat corpus smooth muscle cells exhibit calcium-activated chloride currents (38). The contraction brought on by phenylephrine is lessened by two blockers (T16Ainh-A01 and  $\text{CaCCinh-A01}$ ), which were effective at shutting down  $\text{CaCC}$  channels (39).



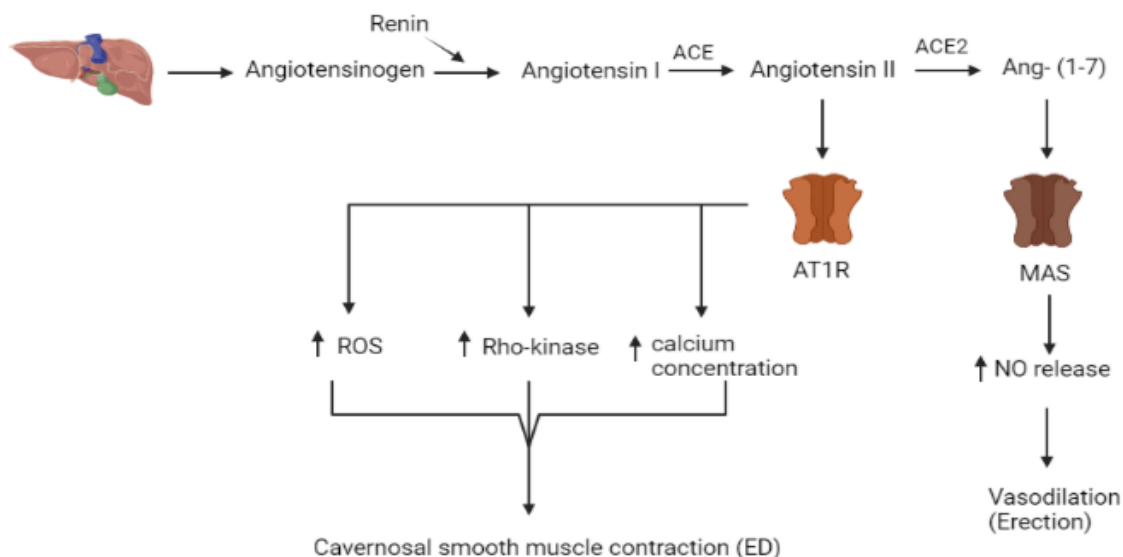
**Figure 2:** Role of various ion channels in corpus cavernosum causes erect penis so by activating  $\text{SK}_{\text{Ca}}$  and BKCa and inhibiting TRPC and  $\text{CaCC}$  results in relaxation of corpus cavernosum.

#### Transient Receptor Potential Channels (TRPC)

TRPC plays larger role in cellular  $\text{Ca}^{2+}$  signalling. TRP channel initiates cellular  $\text{Ca}^{2+}$  signalling directly (40). TRPC1, TRPC3, TRPC4 and TRPC6 expression was confirmed by RT-PCR, immunohistochemistry (IHC) and western blot in human and rat corpus smooth muscle (CSM) tissues. The mRNA expression of TRPC4 and TRPC6 was elevated in diabetic rat than that of normal ones. Rats with diabetes had higher TRPC4 channel expression in CSM cells. In those diseased rats, the restoration of erectile function was accomplished by down-regulating TRPC4 with a dominant negative (DN) form. Changes in the TRPC4 ion channel are one of the pathophysiological factors contributing to the development of ED, and it may be a target for treatment, it also gives idea for giving new drug development by targeting these ion channels (41). Stimulation of TRPC6 channels results in increased intracellular  $\text{Ca}^{2+}$  ion concentrations. Gene transfer of  $\text{TRPC6}^{\text{DN}}$  causes reduction in calcium level in human CSM and restored erectile function. TRPC plays a major role in controlling intracellular  $\text{Ca}^{2+}$  level concentration (42).

#### Renin Angiotensin System (RAS)

Angiotensin II (Ang II) is the key substance in the Renin-Angiotensin system, which controls physiologic processes in the human body. If Ang II levels are increased abnormally which results in constriction of blood vessels, endothelial dysfunction, vascular remodelling, and insulin resistance, which leads to various diseases such as diabetes, cardiac hypertrophy, atherosclerosis, hypertension (43). Components of the RAS are present in many organs and tissues, such as heart, brain, kidney, blood vessels, and penis and they functioning in a paracrine manner (44). The Ang II were present in both cavernous and systemic blood, Angiotensin II levels were thirty percent higher in the cavernous blood (45). Ang II acts on angiotensin receptor type I (AT1R) which causes elevate the intracellular calcium level, inhibition of myosin light chain phosphatase, elevates oxidative stress, and suppress NO in cavernosal smooth muscles that causes contraction which results in flaccid penis (46). Angiotensin II was injected into the corpora cavernosa stop spontaneous erections, but losartan injections into the same region have the opposite effect (47). Renin-angiotensin system components were up regulated in diabetic rats which resulted in increasing Ang II levels. Studies shows that, the administered Losartan blocks the effect of Ang II causing downregulation of AT1R and decreases the Ang II produced locally results in partially restored erectile function (48). In corpus cavernosum, Ang II is present, by inhibiting Ang II helps to improve erectile function (49). AT1R causes constriction of blood vessels through calcium-dependent and independent manners. AT1R is a GPCR which is activated by Ang II, these activation leads to activation of phospholipase, which it releases inositol trisphosphate and diacylglycerol, these causes increase in intracellular calcium level. Inhibition of myosin light chain phosphatase is brought about by Ang II activating the RhoA/Rho-kinase-mediated calcium independent pathway via AT1R (50, 51). Another salient function of AT1R is to activate nicotinamideadenine dinucleotide phosphate (NADPH) oxidase, increasing the production of ROS which in turn reduces NO level and also activate RhoA/Rho-kinase activity (52, 53, 54). Contrary to Ang II, it has been demonstrated that Ang-(1-7) promotes erection in the erectile tissues by activating the MAS receptor and inducing vasodilation by raising NO levels (56, 57). In hypertensive individuals, ACE inhibitors have neutral impact on erectile function. Studies support this claim and indicate that ACE inhibitors are less effective than ARBs in terms of erectile function, possibly as a result of insufficient angiotensin II production blockade. (55). Through Mas, AVE 0991 enhances penile erection in a NO-dependent way. (57).



**Figure 3:** Renin angiotensin system plays a role in both erect and flaccid penis. AT1R activation causes ED but MAS receptor activation causes erection. So by using AT1 receptor blockers or MAS receptor activators results in erection.

### Sirtuin (SIRT6)

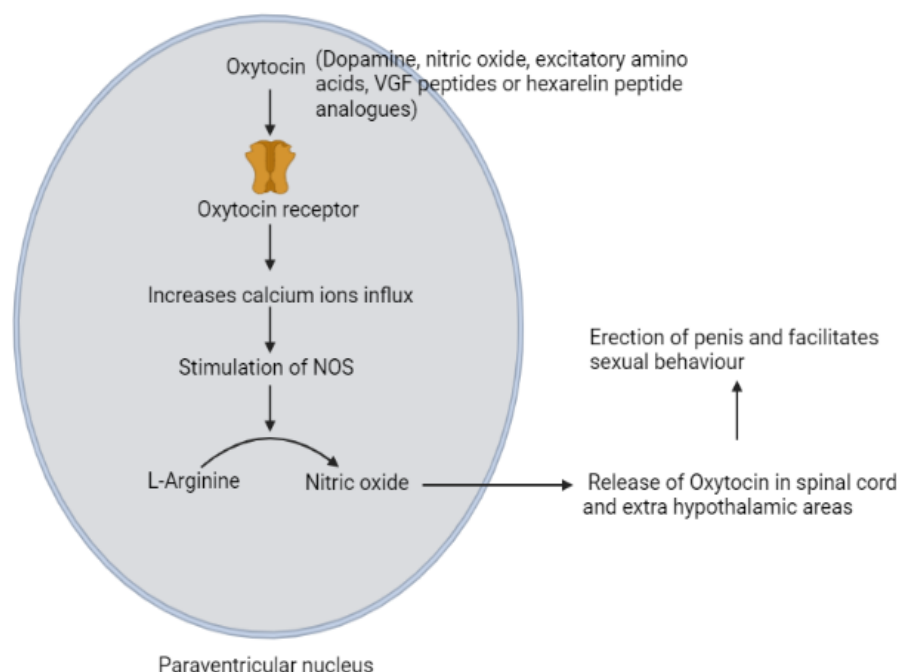
SIRT6 are NAD<sup>+</sup>-dependent deacetylases involved in the control of gene expression, metabolism, ageing, and cancer (58). Seven types of SIRT6 (SIRT6 1-7) have been identified with different structures, cellular localizations, and tissue expressions in mammals. Based on the sequence similarities eukaryotic SIRT6 have been divided into four groups: class I (SIRT1, SIRT2, and SIRT3), class II (SIRT4), class III (SIRT5), and class IV (SIRT6 and SIRT7) (59). SIRT1 is the important and one of the majorly studied one in the SIRT6 family (60). In an age-dependent manner, SIRT1 level was decreased, which is observed mainly in the arteries, it proves that the aging is involved in the CVS (61). Level of these enzymes declines with age (62). SIRT1 was expressed in cavernosal tissue, in corpora of diabetic rats, SIRT1 level was downregulated. The resveratrol (SIRT1 activator) administration upregulated the SIRT1 expression and it restored the erectile function (63). Endothelial SIRT1 plays a distinctive role in vasoprotection by controlling different proteins, including eNOS. For the maintenance of endothelial function, SIRT1 and eNOS regulate each other in a synergistic manner through positive feedback mechanisms in endothelial cells (64). SIRT1 elevates endothelium-dependent vascular relaxation by activating eNOS. A novel approach for treating difficult cases of erection problem involves simultaneously activating eNOS with Resveratrol and inhibiting PDE5 with a PDE5 inhibitor (65).

### Central pathway

An approach for target erectile dysfunction would be not only targeting the peripheral pathways but also the central pathway plays an importance role in erection. Central pathways are involved in the regulation of penile erection. Several brain areas are involved in induce erection activity, these areas such as the medial preoptic area (MPOA), the paraventricular nucleus (PVN) of hypothalamus, the amygdale, the hippocampus, the ventral tegmental area, and the bed nucleus of the stria terminalis, the nucleus



accumbens, the medulla oblongata and the spinal cord. Here the PVN of hypothalamus and the VTA are play a major role and particularly important. Various neurotransmitters are involved in the regulation of erection (NO, dopamine, oxytocin, Ach, glutamate, hexarelin peptide, MSH, adrenocorticotrophic hormone and pro-VGF) (66, 67). Oxytocin induces copulatory activity and erection of penis by stimulating its own neurons which present in the paraventricular nucleus of rats. In the cell bodies of oxytocinergic neurons, oxytocin binds to its own receptors, which raises the  $\text{Ca}^{2+}$  ion levels in these cells and stimulates NOS, an enzyme that uses  $\text{Ca}^{2+}$  calmodulin aids in the conversion of L-arginine to NO. The nitric oxide that is produced also activates oxytocinergic neurons, which causes the release of oxytocin in the spinal cord and extra-hypothalamic regions of the brain. This results in penis erection and promotes sexual behaviour through a different pathway than the GC-cGMP mechanism. In addition to being stimulated by oxytocin alone, oxytocinergic neurons in the PVN are also activated by other neurotransmitters like dopamine, nitric oxide, excitatory amino acids, VGF peptides or hexarelin peptide analogues, drugs that elevate NO level (NO donors), or the inhibition of cannabinoid 1 receptors in the PVN. GABA, opioid peptides/opiate drugs inhibit the oxytocinergic neurons, results in decrease in drug/neuropeptide-stimulated sexual activity (68). Dopamine is the important neurotransmitter in the central nervous system (CNS), which stimulates motivation of sex, copulatory action (69). In the PVN of brain, dopamine activates the oxytocinergic neurons by increasing intracellular  $\text{Ca}^{2+}$  level causes the nNOS activation (66). Dopamine activates oxytocinergic neurons by binding on its dopamine receptors of the D2 family (D2, D3, D4) which are present in the oxytocinergic cell bodies in the rat PVN, and are mainly D2 and D4 subtypes which results in penile erection (68, 70, 71, 72). Glutamic acid acting mainly on NMDA receptors and also activates oxytocinergic neurons which results in the erection of penis (68, 73, 74). It is still unknown exactly how GH secretagogue, peptides derived from VGF, and peptides connected to hexarelin stimulate oxytocinergic neurons when injected into the PVN. However, it is likely that these peptides act on unidentified receptors in the oxytocinergic cell bodies in the PVN region, which when activated also stimulates the oxytocinergic neurons and results in erect penis (68, 75, and 76).



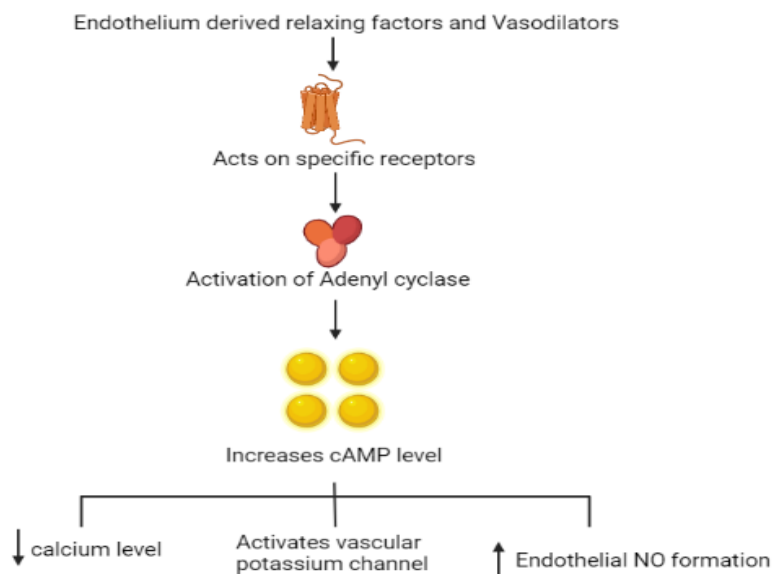
**Figure 4:** In central pathway, by activating oxytocin receptor or the substance which activates oxytocin improves erectile function.

In addition to PVN, oxytocin in the ventral tegmental area (VTA) of rats also aids in penis erection and boosts copulatory activity. In VTA, oxytocin acts on its own oxytocin receptors present in the mesolimbic/mesocortical dopaminergic neuron cell bodies which is originate from the VTA and project to the NAs and PFC. Nitric oxide production is increased as a result of this activation, which raises  $\text{Ca}^{2+}$  levels in the cell bodies of dopamine neurons and activates the NOS present in these neurons. In turn, the generated NO then activates dopamine neurons through a GC-cGMP mechanism, releasing dopamine into the NAs and PFC as well as activating as-yet-unknown pathways that return to the hypothalamic PVN, which also houses the cell bodies of oxytocin neurons that project to the spinal cord and regulate sexual behaviour and erection of penis. Glutamic acid also activates dopamine neurons in the VTA (68).

#### cAMP pathway

The cAMP-dependent protein kinase (cAK) is considered an important cAMP-binding enzyme, it involved in the control of vascular smooth muscle tone (77). Endothelium-derived relaxing factors and endothelium-independent vasodilators, including adenosine, b-adrenergic agonists, prostanoids, VIP, and CGRP causes a vascular smooth muscle relaxation via binding to a specific receptor which causes an activation of adenyl cyclase and increases in level of cAMP (78). An increase in cAMP causes decrease in calcium level and activates the potassium channel which results in relaxation of corpus cavernosum (79). Vasodilators bind to cAK results in activation of many vascular potassium channels, including adenosine triphosphate-sensitive and large conductance,  $\text{Ca}^{2+}$ -activated channels, voltage-dependent channels (80). There is an increase in endothelial NO formation is due to the activation of

cAMP-dependent signal transduction (81, 82).



**Figure 5:** cAMP pathway plays a role in erection so by activating this pathway results in erection.

#### Plants used to treat erectile dysfunction

**Table 1:**

Plant name	Observation	Reference
<i>Panax ginseng</i> (Korean ginseng)	Red ginseng influences the Nitric Oxide (NO) pathway, which causes the corpus cavernosum to expand. It also has the same effects as the hormone testosterone.	Jang DJ <i>et al.</i> , 2008. (83)
Lemon ( <i>Citrus limon</i> ) and lime ( <i>Citrus aurantiifolia</i> )	By increasing nitric oxide production, blocking the enzymes phosphodiesterase 5, arginase, ACE, MAO (monoamine oxidase), and activating antioxidant enzymes by lime and lemon juice promotes sexual behaviour in L-NAME induced erectile dysfunction in rats.	Ademosun AO <i>et al.</i> , 2022. (84)
Grape fruit	Paroxetine treated rat's results in a decrease in PDE5 and NO level. On treatment with GFP (Grape fruit peel extract) in a dose of 50mg/kg and 100 mg/kg for 28 days results in an increase in the concentration of NO and PDE5 levels and also improves antioxidant activities. This shows that erectile and protective effect of extract.	Ademosun AO <i>et al.</i> , 2022. (85)
<i>Arctium lappa</i>	<i>Arctium lappa</i> aqueous root extract was given in a dose of 300, 600, and 1,200 mg/kg to rats which results in increases in mating behaviour by elevating the testosterone level and this extract acting via central and peripheral mechanisms to produce sexual effect.	JianFeng C <i>et al.</i> , 2012. (86)
<i>Anacyclus pyrethrum</i>	Alkylamide-rich ethanol extract was given at a dose of 50, 100, and 150 mg/kg through oral to male rats, it produced dose-related effects on hormones and sperm parameters and increased testosterone level.	Sharma <i>et al.</i> , 2013. (87)
<i>Cinnamomum cassia</i>	<i>In-Vitro</i> study revealed that the <i>C. cassia</i> inhibited arginase activity (IC50 value: 61.72 ±2.20µg/ml). The extract also caused a relaxation effect up to 43% in phenylephrine induced contraction in isolated rat CCSM. In <i>in-vivo</i> , the methanolic extract <i>C. cassia</i> inhibit the Rho-kinase 2 (ROCK-II) enzyme and increased the sexual function of young male rats.	Goswami SK <i>et al.</i> , 2014. (88)
<i>Alpinia calcarata</i>	Different doses of Hot water extract (HWE) of <i>Alpinia calcarata</i> rhizome (150, 250 and 500 mg/kg) were orally administrated to male rats and their sexual behaviour was monitored (for 15 min) 3 h later using receptive	Ratnasooriya WD <i>et al.</i> , 2006. (89)

	females. The high dose of HWE increases the serum testosterone level and the number of spontaneous penile erections which possess a good aphrodisiac activity.	
Horney goat weed ( <i>Epimedium</i> )	Horny goat weed contains a flavonoid Icariin. It demonstrated that there is an improvement in erectile activity after injection of intravenous icariin for a period of 4 weeks after cavernous nerve injury in rats at a dose of 1, 5, and 10 mg/kg. Icariin-treated rats increase nNOS and eNOS level and have a mild PDE5 inhibitory effect resulting in an increase in erectile function	Shindel AW <i>et al.</i> , 2010. (90)
<i>Anethum graveolens</i> (AG)	Cold immobilization at 4 °C for 30 min to decrease their mounting behaviour in rats. AG extract at a dose of 50, 150, and 450 mg/kg BW, via oral route for 14 days. AG extract elevated protein phosphorylation level in testicular lysate, suggests that AG activates tyrosine phosphorylation of testicular proteins which involved in the production of sperm and androgen. At low concentration of AG extract increases the mounting frequency with short term treatment effectively. But high dose of AG extract and increasing treatment day's produces opposite effect (could not stimulate mounting frequency).	Iamsaard S <i>et al.</i> , 2013. (91)
<i>Lepidium meyenii</i>	A 10% ethanol suspension of a purified lipidic extract from <i>Lepidium meyenii</i> (macaene: M-01 and macamide: M-02) was given two times in a day through oral route to the animals at a daily dosage of 40 mg/g body weight for 22 days. At 22 <sup>nd</sup> day there is an increase in libido and sexual potency in mice by increasing testosterone.	Zheng BL <i>et al.</i> , 2000 (92)
<i>Cyperus esculentus</i>	Raw tiger nut powder was given at a dose of 1 and 2 g/kg/d for a period of 30 days to rats. <i>C. esculentus</i> increases sexual motivation and performance of male rats through increases testosterone level.	Allouh MZ <i>et al.</i> , 2015. (93)
<i>Lecaniodiscus cupanioides</i>	The aqueous root extract of <i>Lecaniodiscus cupanioides</i> (25, 50, and 100 mg/kg) were given to sexually impaired male rats, for 5 days (single dose) via oral route, and their sexual behaviour parameters were recorded on 1 <sup>st</sup> , 3 <sup>rd</sup> and 5 <sup>th</sup> days of treatment. There is an increase in sexual drive through increased testosterone level.	Ajiboye TO <i>et al.</i> , 2014. (94)
<i>Caesalpinia benthamiana</i>	Increases sexual behaviour of male rats, due to the vasorelaxing properties of <i>C. benthamiana</i> (50 mg/kg body weight), which may be caused by an increase in NO production in the vascular bed and suppress its destruction by scavenging properties.	Zamblé A <i>et al.</i> , 2008. (95)
<i>Corchorus depressus</i>	Chloroform fraction of <i>Corchorus depressus</i> at doses of 100 mg/kg b.wt, 200 mg/kg b.wt or 400 mg/kg b.wt. Was given orally for 45 days. <i>Corchorus depressus</i> possesses aphrodisiac property through increase in testosterone level.	Kataria S <i>et al.</i> , 2013. (96)
Caffeine	Caffeine (10mg/kg, 20 mg/kg) was given for 8 weeks which results in elevated the erectile function of hyperglycemic rats by activating cGMP.	Yang R <i>et al.</i> , 2008. (97)
<i>Fadogia agrestis</i>	The aqueous extract of <i>Fadogia agrestis</i> stem (18mg/kg, 50mg/kg, and 100mg/kg) was administered orally once a day and the behaviour study was conducted at 1 <sup>st</sup> , 3 <sup>rd</sup> and 5 <sup>th</sup> days of treatment. There is an increase in sexual behavior after treatment with extract through increased testosterone concentrations in blood.	Yakubu MT <i>et al.</i> , 2005. (98)
<i>Moringa oleifera</i>	Various doses of 50% hydro-ethanolic extract of <i>Moringa oleifera</i> (10, 50, and 250 mg/kg (BW)) were given male Wistar rats via oral route. Before giving the extract, rats were immobilized for 12 hr for 7 days to develop stress. After 7 days behaviour study was conducted. There is an increased sexual performance by inhibiting MAO-B and PDE5 activities and increasing in testosterone level.	Prabsattroo T <i>et al.</i> , 2015. (99)
<i>Pedaliium murex</i>	The ethanolic extract (50, 100,150 mg/kg/day) was given for 28 days through oral route to male Wistar albino rats. Behaviour activity was conducted and serum testosterone level was checked at 0,15 <sup>th</sup> and 28 <sup>th</sup> day of treatment and further evaluated after day 7 and 15 past discontinuation of the treatment. It produces a good effect on sexual behaviour and erectile function and increases testosterone level.	Sharma V <i>et al.</i> , 2012. (100)
<i>Turnera diffusa</i>	Aqueous extract of <i>Turnera diffusa</i> (10–40 mg/kg) with or without a nonspecific inhibitor of NO synthase (L-NAME, 12.5 mg/kg) were evaluated in sluggish male rats. There is an increase in sexual motivation and sexual performance involves the participation of NO pathway, at a central level.	Estrada-Reyes R <i>et al.</i> , 2013. (101)

Clove oil	Erectile function of diabetic rats was monitored before and after CEO (clove essential oil) 1 $\mu$ M and E (Eugenol) 1 $\mu$ M intra cavernosal injection. Erectile function was evaluated with the help of cavernous nerve stimulation by measuring the ICP /MAP. The results of this study are improved erectile function in diabetic rats. <i>In-vitro</i> studies revealed that the treatment with CEO and E causes a relaxation in rat Corpus cavernosum (contraction induced by KCl) in a NO/cGMP-independent manner. The current results suggest that Corpus cavernosum relaxation via potassium channels.	Yilmaz-Oral D <i>et al.</i> , 2020. (102)
Wheat germ oil (WGO)	3 ml/kg, 6 ml/kg WGO was given for a period of 5 weeks through oral route to ED induced rats. Erectile function was measured by electrical stimulation of the cavernous nerve by measuring the ICP (intracavernosal pressure)/MAP (mean arterial pressure). Erectile response was recovered after treatment.	Guyen H <i>et al.</i> , 2022. (103)
<i>Cydonia oblonga</i> Miller (Quince)	Hydro alcoholic extract of the fruits of <i>C.oblonga</i> Miller given once daily for 28 days at doses of 500 and 800 mg/kg. It was discovered that the extract greatly increased MF, mating behaviour, and attraction to females. This might be a result of extract anti-oxidative properties. It provided oxidative stress protection for the dopaminergic, serotonergic, and adrenergic neurons.	Aslam M <i>et al.</i> , 2014. (104)
<i>Eriosema kraussianum</i> N.E.Br	Five pyrano-isoflavones (kraussianones 1–5) were isolated from the root stock of <i>E. kraussianum</i> which are tested for the relaxation of rabbit penile muscle (contraction caused by calcium chloride). The most active compounds shows the activity of 75% of that found in Viagra in the ED.	Drewes SE <i>et al.</i> , 2002. (105)
<i>Ferula elaeochytris</i>	<i>Ferula elaeochytris</i> (FE) root extract (40mg/kg, <i>p.o.</i> ) was administered for 8 weeks to diabetic induced rats. Extract treated group shows elevated ICP/MAP values, restored the diminished NO relaxations. Study stating that it was due to the high antioxidant property. <i>In-vitro</i> study states that, FE [2.5, 5, 10, and 20 $\mu$ l] results in relaxation of the crura strips (contraction caused by PhE (alpha-1-adrenergic-receptor agonist; 5 $\mu$ M).	Eser N <i>et al.</i> , 2020. (106)
<i>Jatropha macrantha</i> (Müll Arg.)	Leaf ethyl acetate fraction (LEAF) at 25, 50 and 100 mg/kg, stem ethyl acetate fraction (SEAF) at 25, 50, and 100 mg/kg, respectively. LEAF showed a better effect in sexual behaviour. Results showed that, LEAF of at 50 mg/kg possess a good effect on sexual behaviour in erectile dysfunction induced (ketamine) rats than SEAF but it's not greater than sildenafil citrate (5mg/kg), this may be due to the antioxidant properties of the plant.	Tinco-Jayo JA <i>et al.</i> , 2021. (107)
<i>Myristica fragrans</i> Houtt. (Nutmeg).	100, 250, and 500 mg/kg of a 50% ethanolic nutmeg extract were administered orally over the course of seven days. Findings indicate that this extract has aphrodisiac properties, enhancing libido as a result of the plant's ability to stimulate nerves.	Tajuddin <i>et al.</i> , 2005. (108)
<i>Masularia acuminata</i>	Aqueous extract of <i>M. acuminata</i> stem (MAS) was given at doses of (50 or 100 mg/kg) orally for 2 weeks to diabetic rats. 100 mg/kg of dose possess the best erectile effects because of increases testosterone, luteinizing hormones and nitric oxide levels.	Adefegha SA <i>et al.</i> , 2022. (109)
<i>Monsonia angustifolia</i>	Aqueous extract of <i>Monsonia angustifolia</i> aerial parts was given over the course of seven days at doses of 3, 30, and 300 mg/kg. Male rats perform better during copulation after treatment because of the increased levels of testosterone.	Fouche G <i>et al.</i> , 2015. (110)
<i>Asparagus adscendus</i>	For 30 days, oral administration of 100, 200, and 300mg/kg of <i>Asparagus adscendus</i> root extract was used. As a result, rats treated with AARR extract exhibit more copulatory behaviour and have thicker testicles and accessory sex organs (epididymis, prostate, and seminal vesicles), possibly related to higher testosterone level.	Bansode FW <i>et al.</i> , 2015. (111)

### Future Perspectives:

The worldwide prevalence of ED in population must need new treatments for the growing number of patients with comorbid conditions that have become refractory to typical oral therapy. Here, we mentioned that, various pathways involved in erection. In several disease conditions or in cases of ED there is an alteration in a mechanism of erection. By understanding the mechanism of erection in a molecular level, by using this knowledge we can develop a drug or substance or substances which already exist that can able to alter the mechanism to treat erectile dysfunction. In addition to that, we also mentioned the plants which improves sexual behaviour and for treating erectile dysfunction. Hence this review helps for discover a novel drugs with clear molecular approach with less side effects for treating erectile dysfunction.

### CONCLUSION:



This review gives the pharmacological mechanism of erection and provides the information about how to approach the erectile dysfunction. NO donors, PDE5 inhibitors, Vasodilators are proven treatment for ED out of which PDE5 inhibitors are majorly used. This review gives idea about the sGC activators, sGC stimulators, SIRT1 activators, testosterone booster, Rho kinase inhibitors, Angiotension receptor 1 blockers, MAS activators, BKCa channel activators, SKCa channel activators, TRP channel blockers, CaCC blockers, compounds which activates adenylyl cyclase role in erectile function. In central pathway oxytocin and dopamine are important one to induce erection and excitatory amino acid also play a major role in erection and this review gives a list of many plants plays a major role in erection and sexual behaviour.

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