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Central Regulation of Erectile Function by Dopaminergic D_2 Receptors: Experimental Study in Male Rats and Comparison of the Efficacy of Three Sildenafil Citrate Generics

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Abstract

Objective: This study aimed to evaluate the efficacy of three sildenafil citrate generics and to explore the role of dopaminergic D_2 receptors in the central regulation of erectile function. **Methods:** Adult male Wistar rats received different doses of three generics (Boom, Tre-Bon, Luvmax). Measured parameters included number, duration, and latency of erections, locomotion, and suspension. The most effective product was studied in association with bromocriptine (D_2 agonist) and sulpiride (D_2 antagonist). Two-way ANOVA analyses were performed. **Results:** All three generics increased the number and duration of erections, with Boom being the most effective. Low doses (5 and 25 mg) were superior to the 50 mg dose. Bromocriptine potentiated the effects of sildenafil, whereas sulpiride inhibited them. **Conclusion:** The efficacy of sildenafil generics is variable and dose-dependent. D_2 receptors play a key role in the central regulation of erection.

Keywords

Erectile Dysfunction, Sildenafil Citrate, Dopamine, D_2 Receptors, Wistar Rat

1. Introduction

Erection is a spinal reflex that can be initiated by afferent inputs from the sacral region, as well as by visual, olfactory, or imaginative stimuli. Several central neurotransmitters are involved in the control of erection, including dopamine, acetylcholine, nitric oxide (NO), and peptides such as oxytocin and corticotropin.

The melanocyte-stimulating hormone may play a facilitating role, whereas serotonin may exert either facilitating or inhibitory effects, and enkephalins are inhibitory. The balance between contractile and relaxing factors determines the degree of smooth muscle contraction within the corpora cavernosa (CC) and, consequently, the functional state of the penis. Noradrenaline contracts the CC and penile vessels through α_1-adrenergic stimulation. NO is considered the most important relaxing factor for the penile vessels and CC. The role of other mediators released from nerves or the endothelium has not been definitively established.

Erectile dysfunction (ED), defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual activity, can have multiple causes and may be classified as psychogenic, vascular, organic, neurological, or endocrine. Many patients with ED respond well to the pharmacological treatments currently available, but there are still groups of patients for whom the response remains unsatisfactory.

The drugs used may partially or completely substitute for the endogenous mechanisms controlling penile erection. Most of these agents act directly on penile tissue to facilitate smooth muscle relaxation, including oral phosphodiesterase inhibitors and intracavernous injections of prostaglandin E_1. Regardless of the underlying cause, these drugs are effective in most cases. However, drugs acting on central sites of action have so far met with limited success and are considered only as alternative therapies. This necessitates the identification of new therapeutic targets and the design of novel approaches.

Research in this field is expanding rapidly, and several new targets for future pharmacological interventions have been identified. Penile erection is the final outcome of a complex neurovascular process involving nerves, the endothelium of sinusoids and blood vessels, and smooth muscle cells in target organs. Fundamentally, erection is mediated by a spinal reflex that, depending on context, involves various central and peripheral neural pathways and/or humoral mechanisms. Within the central nervous system (CNS), tactile, olfactory, auditory, and mental stimuli are transformed and integrated.

A large number of central and peripheral neurotransmitters and transmission systems participate in this process. The different stages of neurotransmission, propagation of nerve impulses, and intracellular transduction of neuronal signals within penile smooth muscle are only partially understood. Nevertheless, it is well established that the balance between contractile and relaxing factors regulates the tone of penile vasculature and CC smooth muscle, thereby determining the functional states of the penis: detumescence and flaccidity, tumescence and erection.

Several pharmacological, physiological, and clinical aspects of erectile function and dysfunction have been previously reviewed, yet the field continues to evolve and has been the subject of several recent reviews [1].

ED has long been a concern due to the increasing evidence of its association with coronary heart disease. Indeed, several medical conditions can be causative factors of ED. According to relative risk, diabetic men are at a higher risk of de-

veloping ED (odds ratio = 3.00) compared to those with hyperlipidemia (OR = 2.29), hypertension (OR = 2.05), psychological stress (OR = 1.68), or low physical activity (OR = 1.35) [2]. Moreover, physiological aging, smoking [3], and certain classes of drugs [4] are also associated with the development of ED.

Fortunately, the treatment of ED has made remarkable progress in recent decades, particularly with the advent of the new class of type 5 phosphodiesterase (PDE5) inhibitors such as Viagra (sildenafil citrate), which alters penile hemodynamics. Nevertheless, this drug, in addition to its high cost, has several undesirable side effects such as headaches, flushing, hypertension, nasal congestion, and dyspepsia [5].

These adverse effects may arise from the dosage of sildenafil citrate recommended in prescribing information, and possibly from other parameters requiring verification. However, dosage seems to be the critical factor. Consequently, we obtained several generic formulations of this compound (sildenafil citrate) from pharmacies for evaluation.

Within this context, the present study aims to determine the minimal effective dose of sildenafil citrate and to elucidate the activating role of dopamine D_2 receptors in the central regulation of erection.

To achieve this objective, we specifically studied the sexual behavior of male rats by measuring parameters such as:

- The number of erections per rat, defined as each occasion when the penis is visible, and the animal bends to lick it [6];
- The duration of erections, defined as the time spent licking the penis before raising the head;
- The latency time is defined as the interval between the precise moment of gavage or product injection and the onset of the first biological response (erection).

After two hours of observation, the rats underwent behavioral tests using the hole-board and wire traction methods.

2. Literature Review

2.1. Anatomy of the Male Genital Apparatus

The male genital apparatus can be subdivided into four main parts:

1) The gonads
2) The genital tract
3) The accessory glands
4) The external copulatory organ [7]

The gonads consist of two testes (left and right), which are intra-abdominal during gestation and subsequently descend through the inguinal canal into the scrotum at birth.

The genital tract is composed of two sperm ducts that begin with a coiled structure capping the testis, called the epididymis. These ducts converge posterior to the bladder and fuse with the ureter (originating from the bladder) to form the

urethra, also known as the urogenital canal.

The accessory glands include two seminal vesicles, a prostate gland, and a bulbourethral (Cowper's) gland. Together, they produce the majority of the seminal plasma.

The copulatory organ is called the penis and consists of three erectile bodies: the corpus spongiosum, the corpora cavernosa, and the prepuce, whose extremity (the glans) is retractable.

2.2. General Anatomy of the Penis

The human penis is formed by three cylindrical bodies of erectile tissue: two parallel corpora cavernosa and a corpus spongiosum located ventrally [8], which contains the urethra. The corpus spongiosum, also composed of erectile tissue, terminates in a dilated segment known as the glans.

The arterial blood supply to the corpora cavernosa and corpus spongiosum arises from the terminal branches of the internal pudendal arteries. Venous return occurs through two main pathways: the superficial dorsal vein, which drains the corpus spongiosum, and the deep dorsal vein, which drains the corpora cavernosa.

At the venous level, there are sphincter-like structures that, upon stimulation, prevent backflow and promote engorgement.

2.3. Peripheral Regulation

2.3.1. Cholinergic Innervation

The importance of the parasympathetic system in penile erection regulation is well established. The human corpus cavernosum and penile vascular system are densely innervated by cholinergic nerves and contain a high density of acetylcholinesterase.

In rats, choline acetyltransferase and the vesicular acetylcholine transporter (VAChT) are present in most of the pelvic plexus, penile arteries, and corpora cavernosa. VAChT-positive cholinergic innervation is also abundantly found in human erectile tissue.

Since cholinergic activity corresponds to parasympathetic activity, cholinergic nerves are likely to influence penile erection indirectly, for example, through adrenergic mediation, which is a function of cholinergic nerves in erectile tissue vasodilation.

2.3.2. Purinergic Innervation

In arteries in general, ATP released from nerve terminals contributes to vascular tone regulation: it exerts a vasodilatory effect via P2Y purinergic receptors and a vasoconstrictive effect via P2X receptors.

Purinergic receptors are also present in the male external genital organ, where they regulate penile erection. In rats, $P2Y_1$ receptors have been identified in endothelial cells lining the lacunar spaces and penile blood vessels. In rabbits, $P2Y_4$ receptors have been found in smooth muscle cells, which are relaxed by ATP released from purinergic nerves.

Similarly, in the human corpus cavernosum, ATP induces smooth muscle re-

laxation in a manner comparable to NO. Therefore, ATP released by purinergic nerve terminals promotes vascular relaxation in the penis and contributes to the regulation of penile erection.

2.3.3. VIP Factors

The balance between contractile factors (e.g., noradrenaline, endothelins, angiotensins) and relaxing factors (e.g., NO, VIP-related peptides, prostanoids) regulates the degree of smooth muscle contraction in the corpus cavernosum and determines the functional state of the penis.

Neurogenic NO is considered the most important factor for the relaxation of penile vessels and the corpus cavernosum.

2.3.4. Rho-Kinase

Recent studies have suggested a role for Rho-kinase in regulating corpus cavernosum tone, and Rho-kinase antagonism has emerged as a potential new principle for the treatment of erectile dysfunction. Further research in this area may yield promising results.

2.4. Central Structures Involved in Erection

Several anatomical regions of the brain associated with sexual function have been identified. Animal studies have shown that structures controlling sexual arousal are mainly located in the limbic system (e.g., olfactory nuclei, medial preoptic area, nucleus accumbens, amygdala, hippocampus) and in the hypothalamus (paraventricular and ventromedial nuclei).

In particular, the medial amygdala, medial preoptic area (MPOA), paraventricular nucleus (PVN), periaqueductal gray, and ventral tegmental area are recognized as key structures in the central control of male sexual responses [9].

In rats, electrical stimulation of the MPOA, PVN, or hippocampal formation can induce an erection. A neural network seems to exist that includes primary afferents from the genital organs, spinal interneurons, and sympathetic, parasympathetic, and somatic components.

This network integrates peripheral information and elicits reflex erections [10]. In humans, the physiological link between these brain regions and sexual arousal remains under debate. Studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have revealed brain activation patterns correlated with various phases of the sexual response.

These activations highlight a complex neural circuit underlying sexual arousal, with only a few specific regions (the anterior cingulate cortex, insula, amygdala, secondary hypothalamus, and somatosensory cortex) being directly correlated with penile erection.

2.5. Central Regulation

1) 5-Hydroxytryptamine (Serotonin)

5-Hydroxytryptamine (5-HT or serotonin) has been implicated in the pharma-

cology of erectile function in both animals and humans. Serotonin is generally recognized as an inhibitor of male sexual behavior and involves both sympathetic and parasympathetic systems [11].

Penile erection is essentially a spinal reflex that can be initiated by stimuli from the periphery or from the central nervous system. Serotonergic neurons are found in the raphe nuclei, ventral medullary regions, and medullary reticular formation—including the rostral paragigantocellular nucleus—as well as in the lumbosacral spinal cord, associated mainly with somatic and autonomic projections [12].

Experimentally induced decreases in 5-HT levels, achieved through inhibition of serotonin synthesis using parachlorophenylalanine, destruction of 5-HT–containing axons with 5,7-dihydroxytryptamine, or electrolytic lesions of the dorsal raphe nucleus, have all been shown to enhance sexual activity [13]. Conversely, intracerebroventricular or intrathecal administration of 5-HT, as well as drugs that increase central release or synthesis of this amine, attenuate sexual activity [14]. The 5-HT pathways may be inhibitory or facilitatory depending on the amine's action on different subtypes of 5-HT receptors located in various areas of the central nervous system [15], and the effects also appear to be species-specific [16]. Intrathecal injection of 5-HT in anesthetized male rats blocks reflexive coital responses, suggesting that endogenous 5-HT may inhibit sexual reflexes [17]. Similar procedures in other experiments inhibited ejaculation and penile intromission in rats, indicating a modulatory role of 5-HT in the transmission of sensory feedback required for sexual response [18].

Multiple 5-HT receptor subtypes have been identified, and these receptors use different effector systems in different cells, possibly explaining the contradictory reports on the effects of 5-HT agonists and antagonists on sexual function. For example, activation of certain receptors can either enhance or suppress sexual behavior.

5-HT_1A, 5-HT_1B, 5-HT_2A, and 5-HT_2C receptor subtypes have been localized at different levels of the spinal cord [19]. Studies using selective agonists and antagonists for these receptors have shown variable effects on male copulatory behavior.

For instance, activation of 5-HT_1A receptors can have contrasting effects on sexual function depending on the dose and receptor localization in the brain [20]. Using immunohistochemistry, it was demonstrated that the supraspinal serotonergic control of erection at the lumbosacral level appears to be strongly associated with activation of 5-HT_2C receptors.

1-(3-Chlorophenyl)piperazine, a metabolite of trazodone, and N-trifluoromethylphenylpiperazine are considered partial agonists at 5-HT_2C receptors [21].

2) Dopamine

Dopamine is the principal catecholamine in the central nervous system and is involved in numerous physiological functions, including sexual behavior. It exerts facilitating effects on sexual motivation, copulatory performance, and genital reflexes [22].

Dopaminergic neurons include an incerto-hypothalamic system projecting to the MPOA and PVN [23]. In the MPOA, dopamine controls both genital reflexes and sexual motivation [24].

Dopaminergic neurons have also been identified in the caudal hypothalamus, forming a diencephalo-spinal dopaminergic pathway that innervates the lumbosacral spinal cord [25]. Thus, dopamine may participate in the central regulation of both autonomic and somatic reflex components of penile erection, as confirmed by the effects of apomorphine. Dopamine receptors in mammalian tissues are classified as D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4), based on their binding properties and ability to activate or inhibit adenylyl cyclase [26].

In the CNS, both receptor families are associated with erectile function. An important discovery was the expression of all dopamine receptors of the D_2-like family (D_2, D_3, and D_4) in the cell bodies of oxytocinergic neurons in the PVN and MPOA [27], providing strong neuroanatomical evidence that dopamine and dopamine receptor agonists can directly activate oxytocinergic neurons involved in erectile function.

The role of dopamine in sexual function is further supported by studies demonstrating that several dopamine receptor agonists, such as apomorphine, induce penile erection after systemic administration in mammals [28]. However, these drugs often cause side effects such as nausea and vomiting, limiting their clinical use.

In rats and rabbits, the pro-erectile effect of apomorphine is reversible. Erection induced by dopaminergic stimulation involves oxytocinergic neurotransmission [29]. Dopaminergic neurons interact with oxytocinergic cell bodies within the PVN, and penile erection induced by apomorphine is prevented by oxytocin antagonism. Conversely, oxytocin injection into the PVN induces erections that are not inhibited by dopamine receptor blockade, suggesting that dopaminergic neurons activate oxytocinergic neurons in the PVN and that oxytocin release mediates the erectile response [30].

3) Oxytocin

In the paraventricular nucleus (PVN) of the hypothalamus, pharmacological, immunocytochemical, and electrophysiological studies have identified a group of oxytocinergic neurons projecting to extrahypothalamic brain regions and the spinal cord that influence erectile function. When activated—by dopamine, excitatory amino acids, oxytocin itself, or hexarelin-like peptides—these neurons trigger penile erection [31].

Oxytocin facilitates erectile function and sexual behavior in animals such as mice, rats, rabbits, and monkeys. This may also occur in humans, since plasma oxytocin levels increase in response to sexual stimuli, particularly ejaculation [32].

Oxytocin induces penile erection not only when injected into the lateral cerebral ventricle or PVN but also when administered into other extrahypothalamic regions such as the ventral tegmental area [33], hippocampus, and posterior amygda-

loid nucleus [34], structures of the limbic system believed to play essential roles in motivation and reward processes.

Erectile responses are blocked by oxytocin antagonists and by electrolytic lesions of the PVN. Oxytocin-induced erections are also abolished by castration and restored by testosterone administration.

Oxytocin appears to exert a self-activating mechanism involving stimulation of oxytocinergic receptors located on the cell bodies of neurons within the PVN.

4) Noradrenaline

A small number of nuclei, including the locus coeruleus, send noradrenergic fibers from the forebrain to the spinal cord to control penile erection. Evidence for supraspinal noradrenergic mechanisms in the mediation of penile erection remains fragmentary.

Noradrenergic neurons from the A5 region and locus coeruleus project to the spinal cord areas involved in erection [35]. Available data suggest that increased central noradrenergic activity stimulates sexual function, whereas its reduction inhibits it.

Reported that male sexual behavior was suppressed in rats after direct injection of the α_2-adrenergic receptor agonist clonidine into the MPOA, and that this suppression was reversed by pretreatment with selective α_2-adrenergic antagonists [36].

Although several α_2-adrenergic antagonists, notably yohimbine, have been shown to enhance sexual responses in rats, their therapeutic efficacy in men with ED is relatively low, casting doubt on the significance of central noradrenergic mechanisms in erectile regulation.

5) GABA

Studies on the role of γ-aminobutyric acid (GABA) in penile erection indicate that this neurotransmitter acts as a modulator of autonomic and somatic reflex pathways involved in erection. In male rats, high GABA concentrations have been measured in the medial preoptic area [37], while GABAergic fibers and receptor sites have been localized in the parasympathetic sacral nucleus and bulbocavernosus motor nucleus [38].

Injection of muscimol (a GABA_A receptor agonist) into the PVN dose-dependently reduces penile erection induced by apomorphine and NMDA. This reduction parallels a decrease in NO_2 and NO_3 production. In contrast, baclofen (a GABA_B receptor agonist) is ineffective [39].

Injection of GABA receptor agonists into the MPOA decreases copulatory behavior in male rats [40], while injection of GABA receptor antagonists into this region enhances such behaviors [41]. Systemic or intrathecal administration of baclofen at the lumbosacral level decreases the frequency of erections in rats. Activation of GABA_A receptors in the PVN reduces penile erection induced by apomorphine, NMDA, or oxytocin in male rats.

Stimulation of GABA_A and GABA_B receptors can have distinct effects (inhibitory or excitatory) on penile erection depending on the brain region involved.

GABA_A receptors in the PVN inhibit erection under various conditions.

6) Acetylcholine

The central role of acetylcholine (ACh) in the regulation of penile erection is primarily inferred from limited neuropharmacological studies involving systemic or intracerebral administration of muscarinic agonists or antagonists, and from brain lesion experiments [42]. These studies suggest that cholinergic mechanisms, operating mainly in the hippocampus and MPOA, may play a regulatory role in erectile function.

7) Nitric Oxide (NO)

The role of NO in the central neuromediation of penile erection was revealed by experiments showing that intracerebroventricular or PVN injections of NO inhibitors prevent penile erectile responses induced in rats by dopaminergic, oxytocinergic, corticotropin, 5-HT_2C agonists, or NMDA. This inhibitory effect of NO inhibitors is reversed when administered concomitantly with L-arginine, the substrate for NO synthesis. The subsequent release of NO triggers activation of oxytocinergic neurons, leading to penile erection.

8) Sex Hormones

Androgens, particularly testosterone, exert both central and peripheral effects, influencing penile erection [43]. They are necessary—but not sufficient—for sexual desire in men, are essential for maintaining libido, and play a key role in regulating erectile capacity [44]. In men with normal gonadal function, however, no clear correlation exists between circulating testosterone levels and erectile function [45].

After castration or other causes of androgen deficiency, libido generally decreases, and erectile and ejaculatory functions may also decline. Administration of testosterone restores sexual interest and activity in adult men with hypogonadism or post-castration [46].

2.6. Transmitters and Mediators

Noradrenaline plays two major roles in the activation pathways of penile smooth muscle. According to [47], it generates inositol trisphosphate (IP_3), which activates a cytosolic Ca^{2+} oscillator, and also triggers the Rho/Rho-kinase signaling pathway to increase the Ca^{2+} sensitivity of the contractile machinery. Furthermore, Ca^{2+} activates chloride-sensitive channels, leading to membrane depolarization. This Ca^{2+}-dependent oscillatory activity synchronizes the contraction of neighboring smooth muscle cells in the corpus cavernosum, enabling coordinated penile contraction.

3. Materials and Methods

3.1. Materials

3.1.1. Biological Material

Adult, sexually inexperienced male Wistar rats weighing between 250 g and 350 g and aged 120 to 180 days were used in our experiments. The animals were raised

under standard laboratory conditions at ambient temperature (29˚C ± 2˚C) and relative humidity (85% ± 3%). They were fed a standard commercial pellet diet (FACI). Before experimentation, the animals were acclimated for one week in the testing room.

3.1.2. Equipment

The hole-board test apparatus consisted of a board with 16 holes arranged in a 4 × 4 configuration (**Figure 4**). A photoelectric cell located within each hole triggered an automatic counter each time the animal dipped its head into a hole. The counter, connected to the board, provided a direct measure of exploratory activity. In addition, two lateral photoelectric beams traversing the board's surface recorded the animal's locomotor movements whenever the beams were interrupted.

The wire traction test apparatus consisted of a board with two vertical bars, 30 cm apart, connected by a horizontal metal wire 30 cm above the base.

3.1.3. Chemical Products

Three generic formulations of sildenafil citrate were purchased from pharmacies:

- **BOOM:** 100 mg sildenafil citrate per tablet, manufactured by Secumed Pharma.
- **TRE-BON:** 100 mg sildenafil citrate per tablet, manufactured by Taurian Pharma.
- **LUVMAX:** 100 mg sildenafil citrate per sachet of flavored gel, manufactured by Gujarat Liqui Pharmacaps Pvt. Ltd.

In addition, the following compounds were used:

- **D_2 dopamine receptor agonist:** Bromocriptine.

A 25 mg sample of bromocriptine salt (molecular weight = 654.595 g/mol) was dissolved in 10 mL of DMSO to obtain a stock solution. The required volume of this stock solution corresponding to a treatment of 0.1 mg/kg body weight was administered daily to each rat by intraperitoneal injection after weighing.

- **D_2 dopamine receptor antagonist:** Sulpiride.

Sulpiride (molecular weight = 344.44 g/mol) was prepared by dissolving 1.656 g in 24 mL of DMSO to obtain a 69 mg/mL stock solution. A volume of this solution equivalent to a dose of 40 mg/kg body weight was injected intraperitoneally into each rat daily after weighing.

3.2. Methods

We examined three generic brands of sildenafil citrate (Tre-Bon, Boom, and Luvmax) obtained from pharmacies by comparing three doses of each (5 mg, 25 mg, and 50 mg) to assess their effectiveness.

The doses selected in the present study (5, 25, and 50 mg/kg, administered to male rats) were established based on commonly accepted methodological recommendations for interspecies extrapolation. We applied the body surface area normalization method [48], considered the most robust approach for converting animal doses into human equivalents [49]. According to this approach, the Human Equivalent Dose (HED) is calculated as follows:

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \times (\text{Km\_animal/Km\_human})$$

using the reference values of Km = 6 for the rat and Km = 37 for the human adult.

On this basis, the doses of 5, 25, and 50 mg/kg correspond respectively to HEDs of approximately 0.81, 4.05, and 8.11 mg/kg. For a standard adult weighing 70 kg, these equivalents represent approximately 57 mg, 284 mg, and 568 mg. These choices are consistent with established preclinical practices and safety recommendations for determining a potential clinical starting point [50]. This approach makes it possible to account for interspecies differences in metabolism, body surface area, and clearance, while remaining in line with the doses used in previous rat studies.

Each unit dose of each generic was administered orally (by gavage) to a group of four rats for three consecutive days. Control animals received distilled water.

The control group, having received distilled water, serves as a reference for evaluating the effects of active treatments in standard statistical analyses of pharmacological studies on animal models. Typically, its data (such as baseline erectile responses) are integrated through tests such as ANOVA or Student's t-test to compare the means of treated groups with the control, confirming the significance of the observed differences (e.g., the superior efficacy of the generic "Boom" at low dose).

The control values define the basal level (often close to zero for induced responses), allowing the calculation of percentage increases or ratios (e.g., intracavernous pressure/arterial pressure). Without explicit data in the Results section, they were used for p-value thresholds ($p < 0.05$), as in studies on sildenafil in Wistar rats, where controls validate the absence of a vehicle effect.

The following table presents the mean ± SEM values of the control alongside those of the treated groups (e.g., Boom, bromocriptine + sildenafil, sulpiride + sildenafil) for a clear visual comparison. This enhances transparency, especially since the results omit baseline values, but follow CONSORT standards for preclinical studies.

The most effective product was subsequently selected to study the central regulation of erectile function through dopaminergic D_2 receptors. Control rats received DMSO.

For this purpose, sildenafil was administered orally, either alone or in combination with an agonist (bromocriptine, intraperitoneally) or an antagonist (sulpiride, intraperitoneally) of D_2 dopamine receptors.

The biological parameters measured after product administration included:

- **Number of Erections per Rat:** each time the penis was visible and the animal bent to lick it;
- **Duration of Erections:** the time the rat spent licking its penis before raising its head;
- **Latency Period:** the time elapsed between gavage or injection and the onset of the first erectile response;
- After two hours of observation, rats underwent behavioral tests using the hole-

board and wire traction apparatus.

Prior to the experiments, rats were pretreated with distilled water before administration of sildenafil alone, and with DMSO before combined treatment with bromocriptine or sulpiride and sildenafil.

3.2.1. Number of Erections

Total number of complete erections observed over a standardized 30-minute period post-injection, an erection being defined as a visible and sustained penile rigidity lasting at least 10 seconds.

3.2.2. Duration of Erections

Cumulative duration (in seconds) of erections per animal, measured from the onset of rigidity until complete relaxation.

3.2.3. Latency of the First Erection

Time (in minutes) elapsed between treatment administration and the appearance of the first complete erection.

Erectile responses were assessed over a 30-minute period in an isolated observation cage. An erection was recorded if the penis reached maximum rigidity (angle > 45˚ relative to the abdomen). The count corresponds to the total number of erections, the duration to the cumulative time of rigidity, and the latency to the delay until the first erection.

3.3. Statistical Analysis

Two-way analysis of variance (ANOVA) was used to evaluate each behavioral variable and test the differences [product × dose] through multiple comparisons of means, using Scheffé's F-test [51].

4. Results and Discussion

4.1. Results

Our results are organized into two parts: the first concerns an efficacy survey of generic drugs sold in pharmacies (study on 3 generics); in the second part, the most effective generic is used in the presence of a dopamine D_2 receptor agonist or antagonist to study the central regulation of erectile function.

4.1.1. Comparison of Sildenafil Generics

1) Number of Erections

A two-way ANOVA shows that the 3 sildenafil generics significantly increase the number of erections [$F(2, 99) = 44.013$, $p < 0.0001$] with an efficient dose effect [$F(2, 99) = 6.684$, $p = 0.0019$], without real interaction between product and dose [$F(4, 99) = 0.704$, $p < 0.5911$].

A post hoc analysis using Fisher's PLSD test shows that the effects of the 3 generics differ significantly from each other, with the most pronounced effects produced by Boom ($p < 0.001$ in all comparisons) (**Figure 1**).

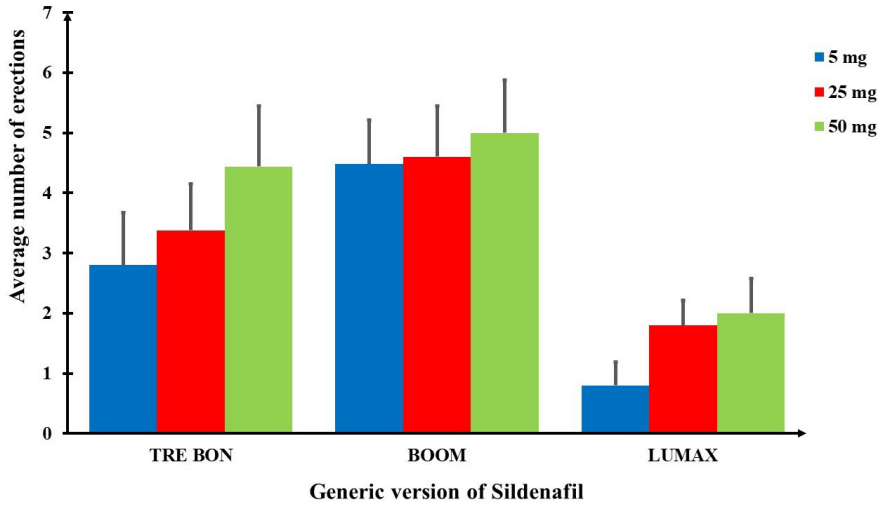

Figure 1. Graph showing the average number of erections by sildenafil generics.

2) Duration of Erections

A two-way ANOVA shows an effective treatment effect of the 3 sildenafil generics on the average duration of erections [$F(2, 99) = 59.691$, $p < 0.0001$] with an efficient dose effect [$F(2, 99) = 1.744$, $p = 0.1802$] and a significant product × dose interaction [$F(4, 99) = 11.229$, $p < 0.0001$].

Fisher's PLSD test shows that "Tre-Bon" and "Boom" produce longer erection durations than "Luvmax" ($p < 0.0001$ in both comparisons), while "Tre-Bon" and "Boom" show no significant difference ($p = 0.1044$) (Figure 2).

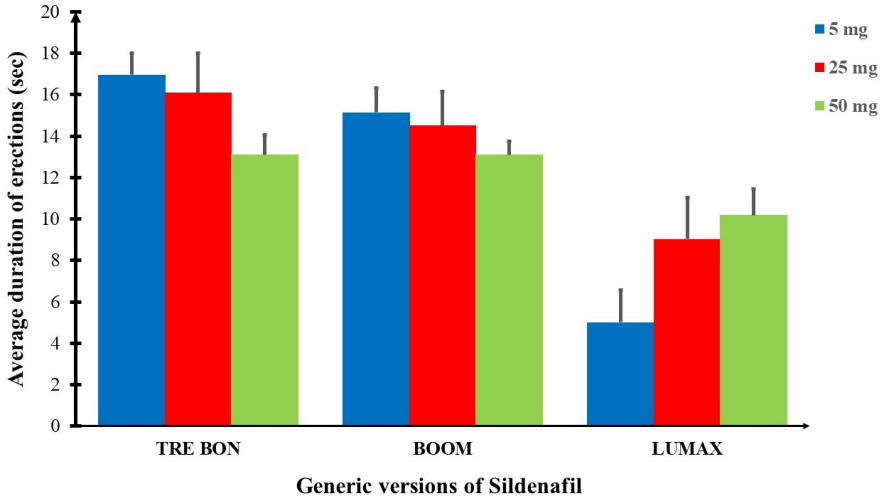

Figure 2. Graph showing the average duration of erections by sildenafil generics.

3) Latency

Latency is the time between product administration and the first erection. A two-way ANOVA shows that the average latency time does not vary significantly between generics [$F(2, 99) = 1.123$, $p < 0.3294$], but different doses of the same generic produce different effects [$F(2, 99) = 11.545$, $p < 0.0001$], with credible prod-

uct × dose interactions [F(4, 99) = 3.179, p < 0.0167] (Figure 3).

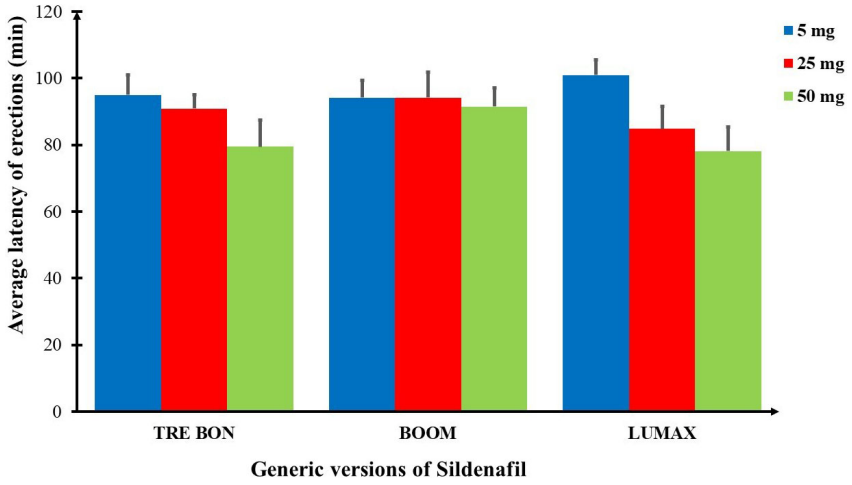

Figure 3. Graph showing the average latency of erections by sildenafil generics.

4) Locomotion

A two-way ANOVA shows that sildenafil generics have a strong effect on locomotion [F(2, 99) = 29.828, p < 0.0001], without significant effects of dose [F(2, 99) = 0.160, p = 0.8521], nor product × dose interaction [F(4, 99) = 0.538, p = 0.7079].

Fisher's PLSD test shows significant differences between the generics, with "Luvmax" producing the highest locomotor activity (p < 0.001), and "Boom" inducing the lowest inhibition (p = 0.0016) (Figure 4).

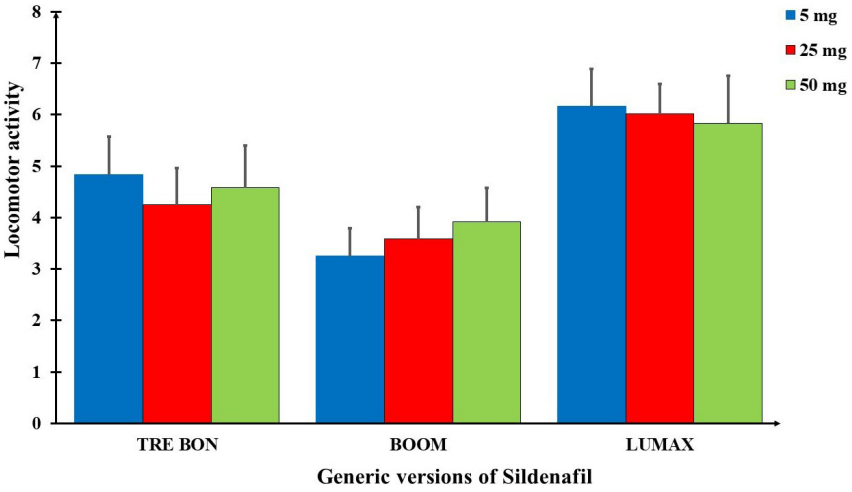

Figure 4. Graph showing the average locomotor activity by sildenafil generics.

5) Suspension Duration (Wire-Gasping Time)

Two-way ANOVA shows a strong treatment effect of sildenafil generics on suspension duration [F(2, 99) = 10.666, p < 0.0001], without significant effects of dose [F(2, 99) = 0.725, p = 48.70], nor product × dose interaction [F(4, 99) = 0.155, p = 0.9605].

Fisher's PLSD test shows that "Boom" significantly increases suspension duration compared to "Tre-Bon" ($p < 0.0080$) and "Luvmax" ($p < 0.0001$) (Figure 5).

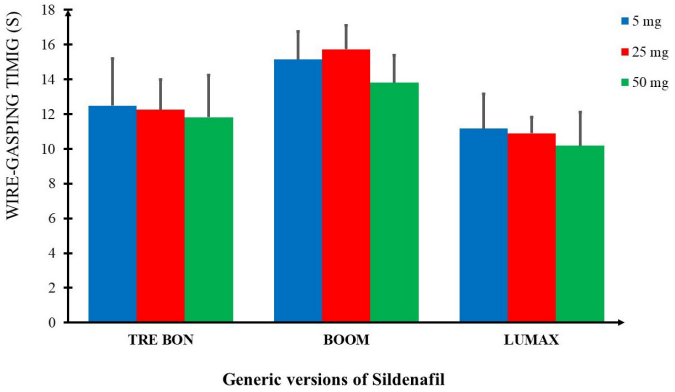

Figure 5. Graph showing the average suspension durations by sildenafil generics.

4.1.2. Central Regulation of Sildenafil by Dopamine D_2 Receptors

Central regulation of sildenafil was tested using a central D_2 receptor agonist (bromocriptine) and antagonist (sulpiride). D_2 dopamine receptors are involved in the reward and pleasure circuit (e.g., pleasure from eating and sexual pleasure). Treatments used were: 1) DMSO; 2) Sildenafil alone; 3) Sildenafil + Bromocriptine; 4) Sildenafil + Sulpiride.

1) Number of Erections

Two-way ANOVA shows that the 3 treatments significantly modify the number of erections [$F(2, 33) = 81.257$, $p < 0.0001$]. Fisher's PLSD test shows that compared to sildenafil alone, bromocriptine + sildenafil greatly increases the number of erections ($p < 0.0001$), while sulpiride + sildenafil inhibits this number ($p < 0.0001$) (Figure 6).

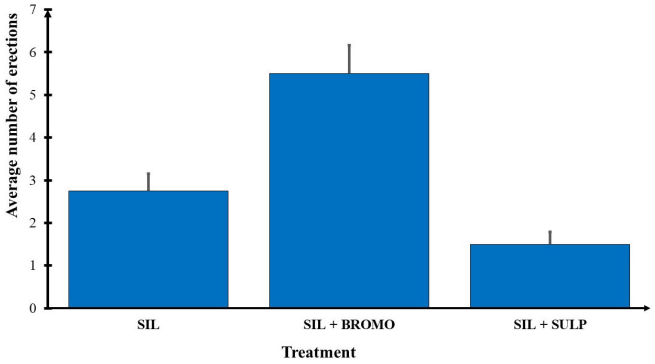

Figure 6. Graph showing effects of bromocriptine and sulpiride on sildenafil-induced erectile activity.

2) Duration of Erections

Two-way ANOVA shows an effective treatment effect on average erection duration [$F(2, 33) = 80.216$, $p < 0.0001$]. Fisher's PLSD test shows that bromocriptine + sildenafil produces longer erections than sildenafil alone ($p < 0.0001$), while sul-

piride + sildenafil reduces erection duration compared to sulpiride alone ($p = 0.0009$).

"Sulpiride + sildenafil reduces erection duration compared to sildenafil alone, confirming D_2-dependent inhibition." This aligns with the antagonist role of sulpiride on dopaminergic pro-erectile pathways (Figure 7).

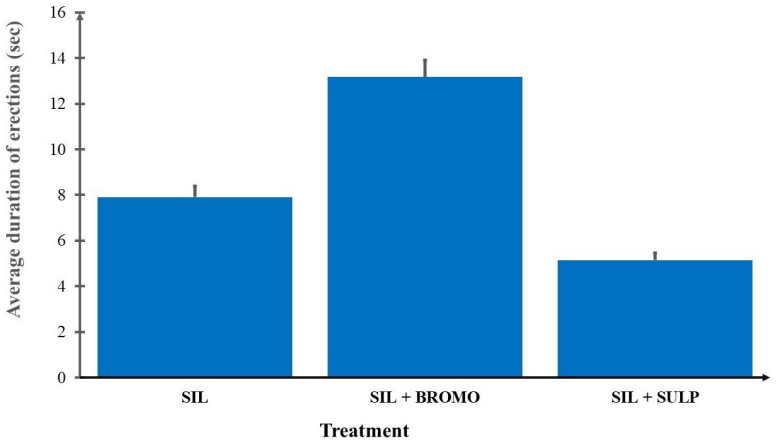

Figure 7. Graph showing effects of bromocriptine and sulpiride on duration of sildenafil-induced erections.

3) Latency

Two-way ANOVA shows a significant treatment effect on average latency time [$F(2, 33) = 14.850$, $p < 0.0001$]. Although bromocriptine tends to reduce latency, the treatments do not show significant differences between them (Figure 8).

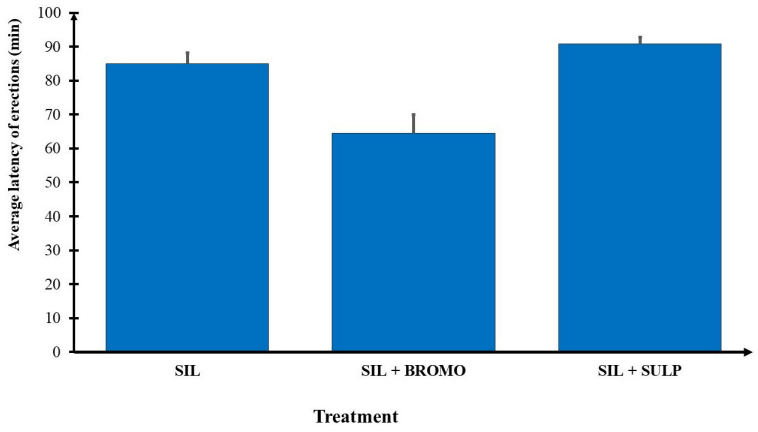

Figure 8. Graph showing effects of bromocriptine and sulpiride on latency of sildenafil-induced erections.

4) Locomotion

Two-way ANOVA shows that treatments significantly modify locomotor activity [$F(2, 33) = 33.601$, $p < 0.0001$]. Fisher's PLSD test shows that bromocriptine significantly increases locomotor activity compared to sildenafil ($p < 0.0001$), while sulpiride significantly reduces it ($p < 0.0017$) (Figure 9).

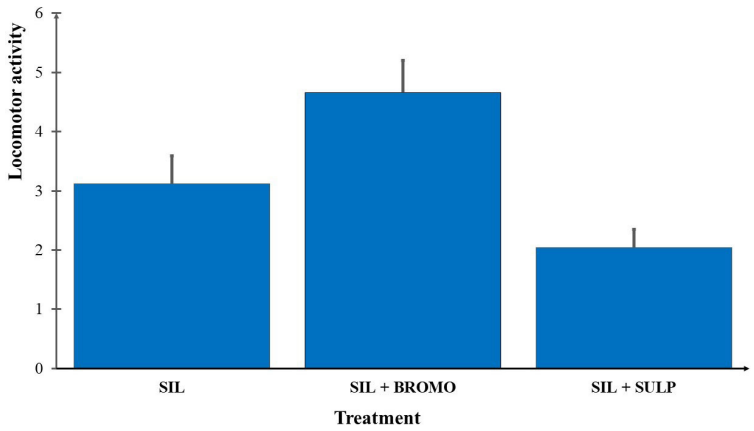

Figure 9. Graph showing effects of bromocriptine and sulpiride on sildenafil-induced locomotor activity.

5) Suspension Duration (Wire-Gasping Time)

Two-way ANOVA shows a dominant treatment effect on suspension duration [$F(2, 32) = 17.202$, $p < 0.0001$]. Fisher's PLSD test shows that both bromocriptine and sulpiride reduce suspension duration compared to sildenafil ($p < 0.0001$ for both) (Figure 10).

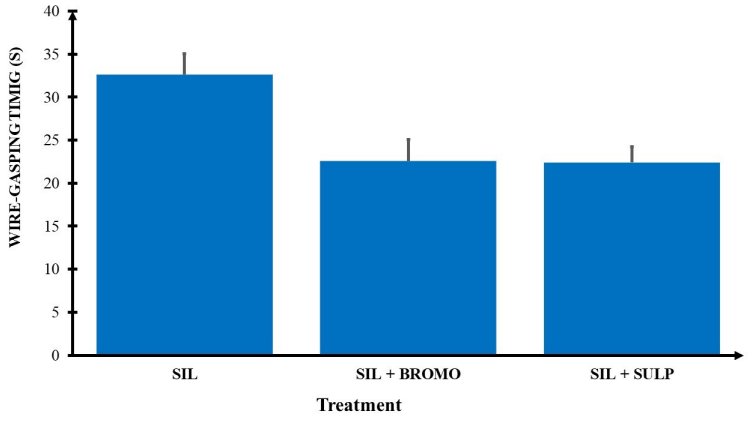

Figure 10. Graph showing the effects of bromocriptine and sulpiride on suspension duration induced by sildenafil.

4.2. Discussion

The primary objective of our study was to compare the biological efficacy of three generic formulations of sildenafil citrate marketed in pharmacies in Côte d'Ivoire. In order to evaluate the quality and functional bioequivalence of these products, we analyzed the key physiological responses of erectile function in the animal model: the average number of erections, their duration, and the erectile latency time.

Our results highlight a surprising dichotomy between the administered dose and the biological response obtained. Against all expectations, the lowest doses (5 mg and 25 mg) induced a highly significant increase in the number and duration of erections compared to the higher dose of 50 mg. This phenomenon of biological

response saturation was also suggested by [52], who demonstrated that the inhibition of type 5 phosphodiesterases (PDE5) reaches a plateau beyond a certain plasma concentration threshold. Conversely, the administration of 50 mg showed a paradoxical clinical trend: although it increases the number of erectile episodes, it significantly reduces their average duration as well as their latency.

These observations profoundly question the current commercial paradigm. In pharmacies, current dosages for humans frequently reach or exceed 100 mg per tablet. However, in light of our experimental data, the efficacy of sildenafil does not seem to follow a linear or exponential kinetic correlation with the increase in dose. On the contrary, an extrapolation of our results suggests that highly-dosed formulations (100 mg and more) could prove to be deleterious, or even toxic to the human body, without providing any superior therapeutic benefit. Virility and erectile performance are not exponential mathematical functions proportional to the mass of the active ingredient ingested.

This discrepancy between actual biological efficacy and the massive dosages sold on the market raises major questions regarding the motivations of pharmaceutical companies. The 100 mg pills, often sold at exorbitant prices, seem to respond to purely mercantile imperatives rather than clinical necessities.

To use a popular but revealing metaphor, there is a high risk that we are being "sold flour in pharmacies", masked behind marketing promises of disproportionate power. This observation is even more alarming concerning alternative galenic forms, notably presentations in the form of creams or gels, enhanced with multiple flavors and marketed under the prism of "the scent of love". Our clinical evaluations indicate that these topical or flavored formulations act as genuine decoys: "fragile butterflies" devoid of therapeutic substance, rarely reaching 40% of the efficacy of conventional oral forms.

Faced with this aggressive international marketing that is costly for local populations, it becomes imperative to reorient our research priorities. The traditional Ivorian and African pharmacopeia abounds with local aphrodisiacs (plants, barks, roots) whose empirical use is centuries-old. Our results suggest that it is time to scientifically validate this endogenous heritage through rigorous biochemical and clinical research, in order to offer accessible, safe therapeutic substitutes that are free from the financial speculation of multinationals.

In the second phase of our work, we explored the systemic effects of these generics beyond the purely peripheral and vascular sphere by looking for potential neuro-behavioral activities. Motor skills tests, notably the suspension duration test and the evaluation of locomotor activity. Suspension durations were recorded during the periods when the animal clung solely with its forelimbs until it fell from the wire due to fatigue. This suspension duration is mainly influenced by the increasing development of supraspinal structures on gamma motoneurons with age [53]. The activation of gamma motoneurons by supramedullary structures is mainly transmitted by impulses from the reticulospinal and vestibulospinal tracts. The continuous contraction of these muscles during suspension requires the in-

tervention of gamma fibers, which adjust the traction force and muscle tone by acting on intrafusal fibers [54].

Our study shows a reduction in the suspension duration of treated rats. Authors such as [55] and [56] obtained the same results, but with the difference that these authors used ethanol, which is different from the substance we used.

As for locomotor activity, it was measured based on the displacement of pups from one compartment to another on the hole-board apparatus for 5 minutes. The study of the development of locomotor activity reflects the maturation of the spinal circuit, as stride length and gait coordination are under the control of spinal automatism [57]. Our results show a very pronounced hyperactivity in treated male pups. This hyperactivity in treated pups could be explained by a high activation of the spinal circuit influenced by "BOOM" during the treatment. This substance could be at the origin of the spinal circuit activation, leading to exaggerated mobility in treated rats. Similar results were obtained by [58], who used sodium glutamate, which is different from "BOOM", and observed elevated locomotor activity.

One formulation particularly stood out: the generic named "BOOM". Subjects treated with "BOOM" manifested exacerbated locomotor hyperactivity, concomitant with a robust and critical reduction in suspension duration. Such a behavioral profile unmistakably demonstrates that this generic crosses the blood-brain barrier and exerts a powerful neuropharmacological impact on the Central Nervous System (CNS). It is this specific central action profile that motivated our choice to select "BOOM" to explore its interactions with dopaminergic pathways, and more particularly D_2 receptors.

D_2-type dopaminergic receptors are major neurobiological pivots of the reward and pleasure-seeking system within the mesolimbic circuit. They are physiologically involved in the motivation to consume highly palatable foods (such as chocolate or sugary substances), but also share a close pathophysiological correlation with alcohol and drug addiction behaviors. Beyond these hedonic functions, the involvement of D_2 receptors in the very architecture of erectile function has been extensively documented in the scientific literature. The foundational work of [59] on the physiology of erection, followed by the pharmacological insights, as well as the research on the central role of the paraventricular nucleus of the hypothalamus, have clearly established that erection is not merely a peripheral vascular phenomenon, but is under strict central neurochemical control where dopamine plays a primary role.

To characterize this interaction, we combined the oral administration of sildenafil in rats with systemic injections of either Bromocriptine (a direct agonist of D_2 receptors) or Sulpiride (a specific antagonist of D_2 receptors).

The results are unequivocal. Bromocriptine powerfully potentiated the effects of sildenafil citrate. We observed a vigorous and synergistic increase in the total number of erections as well as their duration, correlated with a drastic drop in latency time. This demonstrates that activation of D_2 receptors amplifies the pro-

erectile signal. Our results are supported by other authors who also obtained prolonged erection responses. This work ultimately helped establish a new understanding that modifications of penile hemodynamics include the relaxation of the cavernous smooth musculature and arteries, resulting in an increase in arterial blood flow and a vigorous increase in erection during treatment.

Conversely, the blockade of D_2 receptors by sulpiride led to a significant decrease in the number and duration of erections, while increasing erectile latency. These data confirm the indispensable and direct modulatory effect of D_2 dopaminergic receptors on induced erection pathways. This facilitating role of dopamine on sexual motivation, copulatory competence, and genital reflexes perfectly aligns with the conclusions. Moreover, as early as had demonstrated that the systemic administration of dopaminergic agonists, such as apomorphine, triggered reflex erections in mammals. However, the clinical use of these molecules remains historically limited by their disabling systemic side effects, such as nausea and emetic vomiting.

5. Conclusion

In conclusion, this study highlights two cardinal facts: on one hand, the need to regulate the dosages and marketing of generic sildenafil in Côte d'Ivoire, whose race toward higher doses appears to be scientifically unfounded and potentially toxic. On the other hand, it masterfully confirms the peripheral and central entanglement of erectile function, validating the crucial modulatory role of the D_2 dopaminergic system. The participation of dopamine in sexual physiology has been demonstrated, paving the way for future therapeutic considerations that must integrate both patient safety and the development of our local medical resources.

6. Perspectives

These pharmaceutical products are often expensive and not very effective. Research should focus on traditional plant-based medicine to avoid high financial costs in treating erectile dysfunction, which increases with aging.

Additionally, could the motor effects of these products have consequences on cardiac function in humans? This calls for caution in their use by individuals with heart conditions.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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