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Review Article

A Review of Medicinal Plants Traditionally used to Treat Male Sexual Dysfunctions – the Overlooked Potential of *Acmella oleracea* (L.) R.K. Jansen

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ABSTRACT

Introduction: Male sexual dysfunctions are conditions of impaired sexual activity due to decreased sexual desire, impaired erection, or ejaculatory problems. These issues can hurt men's quality of life by causing suffering, frustration, and sexual intimacy avoidance. Although many agents are available to treat such conditions, they are associated with relevant side-effects that could hamper the treatment, pointing to the need for novel agents to fill the gap of patients unable to have a satisfactory result. **Methods:** This review was performed by searching terms such as "medicinal plants" "*Acmella oleracea* (L.) R.K. Jansen or *Spilanthes acmella* auct. non (L.) Murr.", together with "male sexual dysfunctions", "hypoactive sexual desire disorder", "erectile dysfunction", and "premature ejaculation" on literature indexers such as PubMed, Scopus, and ISI Web of Science. Relevant literature from the articles' references was also assessed. **Results and Discussion:** We reviewed a primer about male sexual dysfunctions (MSD); then, we describe some medicinal plants already used against MSD. Finally, some biological activities of *Acmella oleracea* are described, emphasizing its potential against MSD. Despite the importance of this medicinal plant for several activities, studies assessing its use for MSD are still lacking, even with convincing preliminary results reported. Overall, some plants have more robust scientific evidence, with randomized, placebo-controlled trials performed. Interestingly, although many plants' activities are reported, very few studies assess their action mechanism, which is critical to understanding the more indicated occasions.

Key words: Alkylamides, Premature Ejaculation, Erectile Dysfunction, Sexual Dysfunction, Phytotherapy.

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INTRODUCTION

Sexual dysfunctions are conditions of impaired sexual performance; that is, there is an impairment of the regular sexual activity, which in turn, is characterized by stages of sexual arousal and completeness of the act, bringing feelings of joy and satisfaction.[1] There are three main types of male sexual dysfunctions: sexual desire dysfunctions, erectile dysfunction, and ejaculatory dysfunctions.[2]

Hypoactive Sexual Desire Disorder (HSDD) is a persistent or recurrent disability or even absence of sexual thoughts or fantasies and sexual desire. The diagnostic considers factors such as the individual's age, hormone levels, psychiatric problems, and socio-cultural context (e.g., culture, society, religious values).[3] Erectile Dysfunction (ED) consists of a persistent or recurrent incapacity of the male to get or maintain the penile erection to perform the coitus satisfactorily.[4] Finally, Premature Ejaculation (PE) is sexual dysfunction characterized by poor ejaculatory control that bothers both man and his partner. The American Urological Association (AUA) classifies PE as lifelong (ejaculation usually occurs before the desired and within two minutes after penetration, since the patient's sexual debut), or acquired (clinically significant decrease of ejaculation latency compared to prior sexual experience during penetrative sex).[5]

Despite the available agents used to treat such conditions, their side effects can hamper some patients' compliance with the treatment.[6] This narrative review aims to describe some medicinal plants and herbal medicines traditionally used to treat sexual dysfunctions, including *Acmella oleracea* (Asteraceae) and its major compound, spilanthol. Other biological activities of this plant will be described as well. To better understand these agents' potential, we first briefly discuss the dysfunctions they are used to treat.

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METHODOLOGY

A review was performed by searching terms such as "medicinal plants" and "*Acmella oleracea* or *Spilanthes acmella* auct. non (L.) Murr.", plus "male sexual dysfunction", "hypoactive sexual desire disorder", "erectile dysfunction", and "premature ejaculation" on literature indexers such as PubMed, Scopus, and ISI Web of Science. Relevant literature from the articles' references was also assessed.

RESULTS AND DISCUSSION

Epidemiology of male sexual dysfunctions

The most common complaints of male sexual dysfunctions are hypoactive sexual desire, erectile dysfunction, and ejaculatory dysfunctions, such as premature ejaculation (PE) and delayed ejaculation (DE).[2] The prevalence of these conditions varies according to the population assessed. In Iran, for instance, a study reported that 35.6% of the men had sexual dysfunction, being that erectile dysfunction was the most common (40.4%), followed by ejaculatory dysfunction (32.2%), and sexual desire dysfunction (10.6%).[7]

In Hong Kong, a study performed with 674 men reported that 14.8% of them declared to have some form of sexual dysfunction, with a lack of sexual appetite (11.1%), ejaculatory dysfunction (4.7%), and erectile dysfunction (4.3%) being the most commons. In the study, men between 40 and 60 years old were 8 to 15 fold more prone to have erectile dysfunction than those younger than 40 years.[8]

In Canada, a recent report stated that 29.6% of men had sexual desire below what they would like in the last six months, 23.8% had erectile dysfunctions, and 24.7% had ejaculatory dysfunctions.[8] In the USA, a study performed with more than 3,000 men with ages ranging from 57 to 85 years old reported that at least 50% had a sexual dysfunction that would cause discomfort, whereas 33% had at least two sexual issues.[9]

In a study involving five countries (Brazil, Germany, Japan, Spain, and the USA), it was observed in Brazil that the prevalence of erectile dysfunction was 18.9%; the prevalence of sexual desire dysfunction was 19.9%; anorgasmia or delayed orgasm was 16.3%; premature ejaculation was 30.1%, and of multiple sexual dysfunctions was 21.4%. The data reported show that Brazil had the highest prevalence of anorgasmia and premature ejaculation.[10] In the state of Amapá, of the Brazilian Amazon, Teixeira *et al.*[11] reported 36.5% of men had premature ejaculation, 6.5% had delayed ejaculation, and 11.6% had hypoactive sexual desire disorder.

Physiopathology of erectile and ejaculatory dysfunctions

In the absence of stimuli, the penis is in a flaccid state through the adrenergic activity that exerts tonic contraction of the penis' smooth muscle.[12] That contraction is accountable for preventing arterial blood flow into the corpora cavernosa's lacunae, keeping the penis flabby. Visual, tactile, or psychogenic sexual stimuli induce nitric oxide release (NO) by parasympathetic nerve terminals and the vascular endothelium.[13] In the penis' smooth muscle cells, the NO signaling induces increases in cyclic guanosine monophosphate levels (cGMP), which, in turn, will decrease intracellular calcium concentration, relaxing the muscle.[14] Figure 1 depicts the molecular mechanisms underlying the penile smooth muscle contraction and relaxation. These processes can be reviewed on Alwaal *et al.*[15] Webb,[16] and Dean and Lue.[17]

Relaxation of penile smooth muscles allows arterial blood influx to fill the corpora cavernosa's lacunae, increasing its pressure. The pressure arousal causes compression of the venules underlying the tunica albuginea, impeding the venous return (veno-occlusion). Increased blood flow plus veno-occlusion culminate in penile tumescence and erection (Figure 2A).[18] In contrast, the detumescence occurs through adrenergic receptor activation and cGMP hydrolysis by phosphodiesterase-5 (PDE-5, Figure 1), resulting in reduced arterial blood flow and lacunae space collapse. Hence, the venules network is uncompressed, allowing venous return, regressing the erection (Figure 2A). Disturbances in any of these events can cause erectile dysfunction.

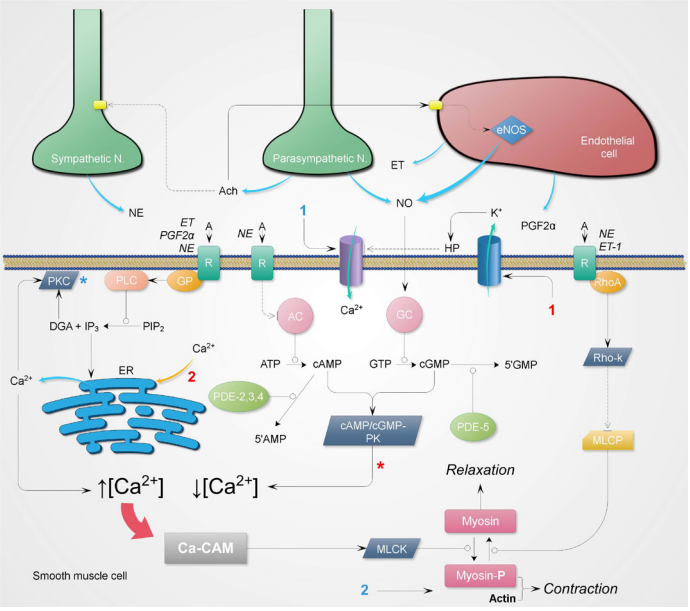

Figure 1: Schematic diagram of the main events involved in corpora cavernosa smooth muscle relaxation and contraction, causing penile erection and detumescence, respectively. Arrows with continuous lines represent conversion or stimulation; dashed arrows with straight end represent inhibition. Lines with an open circle represent catalysis. "A" represents an agonist (the possible agonists are shown near the receptor [R] in italic). NE: norepinephrine; Ach: acetylcholine; ET: endothelin; PG: prostaglandin; HP: hyperpolarization; CAM: calmodulin; PDE: phosphodiesterase: AC and GC: adenylate cyclase and guanylate cyclase, respectively; MLCP: myosin light chain phosphatase; MLCK: myosin light chain kinase; GP: G-protein; PLC: phospholipase C; PKC: protein kinase C; ER: endoplasmic reticulum; eNOS: endothelial NO synthase; Rho-K: Rho-kinase; cAMP/cGMP-PK: cAMP or cGMP-dependent protein kinases; DGA: diacylglycerol; IP3: inositol triphosphate; PIP2: phosphatidylinositol bisphosphate; Myosin-P: phosphorylated myosin. *cAMP/cGMP-PKs through phosphorylation can decrease the intracellular calcium levels in different ways, including by stimulating potassium channels' permeability that will cause hyperpolarization, inhibiting voltage-gated calcium channels (1); or induce calcium sequestration into the endoplasmic reticulum (2). *PKC is a pro-contraction enzyme that, through phosphorylation, can stimulate the permeability of calcium channels, increasing its intracellular levels (1); or by increasing calcium sensitization of contractile proteins (2). There are two contraction phases. The first is calcium-dependent (tonic phase) and occurs after the increase of these ion levels. On high levels, calcium will bind to calmodulin, and this complex will stimulate MLCK, which will phosphorylate the light chain of myosin, allowing its interaction with actin, resulting in contraction. The second is calcium-independent (phasic phase) and occurs due to the proteins' sensitization to calcium. For this phase, it is necessary to activate RhoA that will stimulate Rho-K to inhibit the activity of MLCP, maintaining myosin in its contractile state. Overall, parasympathetic stimuli will favor contraction, whereas sympathetic stimuli will induce relaxation. After contraction or relaxation of the smooth muscles, the events leading or not to erection are depicted in Figure 2A.

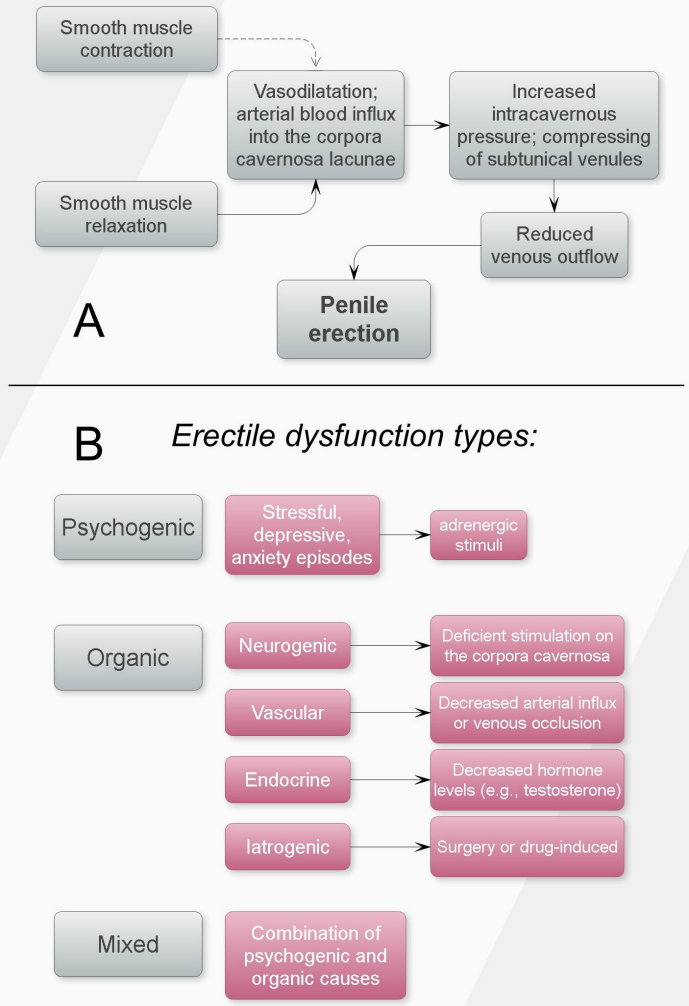

Figure 2: A) Flow diagram representing the events that will occur after smooth contraction or relaxation (depicted in Figure 1), resulting in or not on penile erection. B: Main types of erectile dysfunction.

As mentioned, the physiologic process of erection relies on erectile reflexes caused by direct penile stimulation or emotional erotic stimuli. Erectile dysfunction can be, therefore, classified into psychogenic or organic. Organic EDs can be further divided according to their physiopathology. The most common are: vascular, neurogenic, endocrines, and iatrogenic (Figure 2B). In the past, it was believed that EDs were caused mainly due to psychogenic disorders, but mounting evidence suggests now that more than 80% of cases have an organic etiology. However, even organic EDs can have a psychological component, regardless of the factor involved.[12] For this reason, we can classify an ED as mixed, which is the most common form.[13] One of the primary forms of differentiation between psychogenic and organic causes is the development; organic causes are more progressive and universal, while psychogenic causes tend to be more acute, episodic, and situational.

Psychogenic EDs are associated with stressful, depressive, or anxiety episodes, whereby sympathetic adrenergic activation causes the interruption of the necessary events for the beginning and maintenance of the erection.[19]

Neurogenic EDs are caused by a deficit of neuronal signalization in the corpora cavernosa. Some neurological disorders are often associated with ED, such as multiple sclerosis, epilepsy, Parkinson's disease, Alzheimer's disease, and spinal cord injuries.[20] Patients who underwent radical pelvic surgery are prone to a high risk of cavernous nerve injury.[13] The alterations leading to ED involve reduced NO availability to the smooth muscle, apoptosis of smooth muscle cells, and blood vessel epithelial cells.[21]

Vascular EDs are the most common organic form of ED. It is caused by two main factors: decreased arterial blood influx and disturbances of veno-occlusion. Both of them have endothelial damage as a common etiologic factor[22] caused by a primary condition – such as atherosclerosis, diabetes, dyslipidemia, or smoking – that induces vascular changes like stenosis, insufficiencies, or stiffness.[12] Stenosis and arterial insufficiencies decrease the arterial influx into the corpora cavernosa, consequently decreasing the sinusoidal engorgement; vascular stiffness, in turn, reduces the veno-occlusion since it is unable to compress subtonic venules that perform venous emptying, making the erection impossible.

Endocrine EDs are associate with androgens, especially testosterone. Androgens are essential in controlling male sexual desire and night erection.[12] Testosterone has a crucial role in regulating and expressing NO synthase and PDE-5 in the penis.[23] Hyperprolactinemia leads to ED by inhibiting gonadotropin-releasing hormones, which decreases the secretion of luteinizing hormone, accountable for testosterone secretion.[13]

Iatrogenic EDs are caused mainly by psychotropic and antihypertensive drugs.[24] Antidepressant agents, like selective serotonin reuptake inhibitors (SSRIs) and antipsychotics such as risperidone and olanzapine, are the psychotropic agents more often associated with ED.[25] Among the antihypertensive drugs, thiazides and beta-blockers are the most commonly associated with ED.[26] Surgeries are other iatrogenic causes of ED, especially radical pelvic surgery that may cause nerve or vascular trauma.[12]

Ejaculation is a sequential process culminating in semen expulsion through the urethral opening, followed by penile detumescence.[27] After erection, there is a latency period, a plateau whereby the ejaculation is retarded in which the sexual intercourse can occur.

The steps of ejaculation are emission and expulsion. During the emission, through sympathetic activity,[28] the spermatozoa and seminal fluid are secreted from the prostatic urethra.[29] In turn, the expulsion occurs through rhythmic contractions of smooth muscle from seminal structures, urethra, and striated muscle of the pelvis, expelling the content outside.

Ejaculation is highly influenced by peripheral and spinal cord nerve activity. However, it is also considerably modulated by the brain and psychological factors. Sympathetic activity controls the seminal tract's smooth muscle contraction during ejaculation, while parasympathetic activity prevents seminal fluid reflux.[30] In addition, the pudendal nerve contributes to ejaculation through pelvis striated muscle control.[31] At the spinal cord level, the main structure involved in the ejaculation is the spinal generator of ejaculation (SGE); this spinal cord area is located between the L_1 and L_2 and triggers a reflex arc that causes ejaculation. SGE also integrates inhibitory and excitatory signals from the brain and information from sexual organs, including sensitive and biochemical stimuli.[32]

PE is a condition historically tricky to analyze since the definitions and diagnostic criteria have a considerable impact on the epidemiologic data. Besides, the disease diagnostic itself could be a psychogenic factor leading to more episodes.[33] It is assumed that PE physiopathology is caused by factors that decrease the ejaculatory latency, leading to uncontrolled early ejaculation.[34] The precise mechanisms causing PE are not fully understood. Waldinger *et al.*[35] suggested that men with low levels of 5-hydroxytryptamine (5-HT) may have a lower ejaculatory threshold and may ejaculate faster with less stimulation. Some research

has been performed to assess whether there is a genetic factor involved in PE, based on the prevalence of this condition in first-degree relatives. The data suggest that a protein polymorphism accountable to transport 5-HT is a probable genetic factor involved in lifelong premature ejaculation.[36] Hormones systems also seem to have a role in PE's physiopathology, mainly oxytocin receptor alterations, decreased prolactin levels, and hypothyroidism.[37] The role of testosterone in PE physiopathology is still unclear; however, it is believed that high levels of such hormone may be associated with PE,[38] while low levels may reduce the amount of ejaculate in patients with hypogonadism, delaying the ejaculation.[39] Psychological factors such as anxiety, including sexual performance-associated anxiety, and social or personal stressors,[40] can result in increased adrenergic activity and, in succession, induce smooth muscle contractions, causing PE.[41]

Conventional treatments of erectile dysfunction and premature ejaculation

The most common treatments for ED are psychotherapy, pharmacotherapy, testosterone therapy, and penile devices.[18] Oral drugs and intracavernous injections can improve erectile function in men with ED.[6] Also, there are benefits in treating diseases or risk factors involved in ED, like weight loss, exercising, stress relief, and quit smoking.[6,42,43] When the etiology is unclear, the therapy is made in steps, beginning with the change of habits, followed by PDE-5 inhibitors treatment, and vacuum erectile devices, if necessary. Second-line therapies include intracavernous injection of vasoactive compounds and intraurethral suppository of Prostaglandin E1 (Alprostadil), which is gaining increasing attention as a second-line option for ED management.[6,44] Surgical approaches are reserved for those not responding to more conservative treatments.[44]

There are psychotherapy techniques that aim to readjust the patient's relation to his sensorial experiences, such as sensory concentration, sensory awareness, correction of wrong sexuality concepts, and treatment of interpersonal issues. These approaches are helpful for patients whose ED has psychogenic or social causes.[18]

The first-line pharmacological treatments for ED are the PDE-5 inhibitors. These agents hamper PDE-5 to decrease cGMP levels, causing decreased intracellular calcium levels, relaxing the penis smooth muscle, allowing the influx and permanence of blood in lacunae spaces, ultimately improving the erection.[18] Patients using these medicines still require sexual stimuli, both physical and mental, to trigger the erection.[45] The five most popular commercial PDE-5 inhibitors are sildenafil, tadalafil, vardenafil, udenafil, and mirodenafil.[13] Patients under such medication can experience visual changes due to the compound's interaction with the retina's phosphodiesterase-6, especially sildenafil.[18] Other possible side effects are headaches, stomach aches, facial flush, and nasal congestion.[46] It is worth emphasizing that the combination of PDE-5 inhibitors with psychological intervention has better results than these treatments performed isolated.[47]

Injectable treatments are performed through intracavernous or transurethral injection of vasoactive compounds, mainly prostaglandin E_1 (alprostadil), increasing AMPc levels and decreasing intracellular calcium levels; hence, causing relaxation of the penis smooth muscle and erection.[18] These agents are capable of causing erection regardless of the sexual desire.[13] Contraindications for this treatment include a history of priapism, falciform disease, multiple myeloma, and thrombocytopenia. Besides, in the case of transurethral application of a suppository (e. g. MUSE), contraindications include urethral narrowing and urethritis.[18]

Despite the uncertainties of testosterone's role in ED treatment, reposition therapy is often recommended to men with low levels of this hormone, as in hypogonadism.[48] In such patients, it is often observed a significant improvement of the erection.[49] Testosterone has also been combined with PDE-5 inhibitors in men over 65 years old with low testosterone levels.[50]

Vacuum constriction devices hold the blood in the penis through negative pressure while an elastic band is put in the penis base, making it difficult for the blood to exit. Other types of devices are surgically implanted penile prostheses that can be malleable or inflatable.[51] There is a high level of approval for these methods among patients.[52]

Surgeries are indicated for patients with counterindications or who experienced collateral effects or are refractory to pharmacotherapy. They are also indicated for patients with ED associated with penile fibrosis, priapism, severe infection, and structural or vascular anomalies caused by genital or pelvic trauma. Surgical procedures include inserting a penile prothese or vascular reconstruction.[12]

Another common male sexual dysfunction is PE. The treatment for this condition can be pharmacological or non-pharmacological. Among the non-pharmacological methods are psychological counseling and behavioral techniques; however, these latter have diverging results regarding IELT scores. Both can be adopted combined with pharmacological approaches, which include topical agents and oral drugs. The main oral drugs used against PE are selective serotonin reuptake inhibitors (SSRIs), tramadol, PDE-5 inhibitors, alpha-adrenergic blockers, and clomipramine.[6] Oral drugs can cause systemic collateral effects, such as serotoninergic syndrome and suicide in young patients. On the other hand, topic agents act locally, with minimal systemic effects, but can cause allergic response.[53]

Until the mid-'90s, the standard PE treatment was psychotherapy without drugs, as these agents were applied in therapy only after.[54] Despite the psychological influence in the physiopathology of PE, some studies claim that they are secondary to one primary cause; hence, psychotherapy could help improve the patient's psychological state, but it would not treat the cause in lifelong PE.[55] Nevertheless, psychological approaches and pharmacotherapy are often used combined,[56] and this integrated approach has better results than isolated ones.[57,58] Psychological interventions are necessary under circumstances where there are relationship issues with a critical psychological factor.[53]

Some techniques, such as the "stop-start",[59] "squeeze technique",[60] and pre-coitus masturbation,[61] aim to improve PE patients' ejaculation latency. Some of them have equivalent efficacies, but overall, they do not have enough scientific basis.

The SSRIs are used in the pharmacological treatment of PE. It is known that these antidepressant agents have a range of collateral effects that might be used therapeutically for other issues, including PE since they can increase ejaculation latency. Although this action's mechanism is not fully understood, about 50% of the patients under SSRI treatment report increased ejaculation latency. For this reason, these agents became the first "off-label" choice in the treatment of PE, and eventually, SSRIs were adopted in some guidelines as the first-line treatment of lifelong PE.[62] This class's main drugs are sertraline, fluoxetine, paroxetine, and citalopram.[55] Among these agents, paroxetine seems to have a higher capacity to increase the intravaginal ejaculation latency time (IELT), from 1.5 min to 7.7 min after treatment, according to some studies.[63] On the other hand, dapoxetine and tramadol are the drugs whose efficacy has been more intensely studied.[64 65]

Unlike drugs that require daily treatment, such as fluoxetine, dapoxetine was developed for on-demand use since it has fast absorption and a short half-life. For these reasons, it is approved in some countries to treat PE.[55] However, dapoxetine may not be the best choice for all patients since some men prefer continuous use, stating that on-demand use

might impair sexual intercourse spontaneity. A study report that up to 90% of the patients abandoned the dapoxetine treatment in one year.[66]

Although the doses required in PE treatment are lower than those used in treating depression, SSRIs are associated with some adverse effects and may be counter-indicated for some patients. The most common collateral effect are nausea, fatigue, headache, mental confusion, and diarrhea.[55]

Tramadol is an opioid analgesic agent. A significant study reported that this drug increased 2.4 times the average IELT in men with PE, and further systematic reviews corroborated this IELT improvement,[6] which seems to be more effective than paroxetine, lidocaine gel, and sildenafil.[65,67] Interestingly, almost no adverse effect or tolerance problem was reported.[68] However, the association of this drug with SSRIs can significantly increase serotoninergic syndrome risk.[69]

As for PDE-5 inhibitors, sildenafil increased the patients' confidence, ejaculatory control perception, sexual satisfaction and decreased the refractory time for a second erection after ejaculation in men with PE. However, the IELT improvement reported is considered low.[70]To avoid oral drugs that act systemically, topical anesthetic agents are simple therapeutic options of local applications that reduce the penis sensibility. That is why condoms have also been used in PE treatment.[55] Some of these agents are lidocaine and prilocaine. Different preparations can be achieved by combining these anesthetics as a cream or aerosol. Decreased PE was observed in patients using these compounds,[71] besides improved satisfaction.[72] Notably, the patients reported few collateral effects, such as allergic response and loss of erection caused by excessive penile sensibility loss.[73]

SS-cream (severance secret cream) is a topical agent from Korea derived from nine different natural products. It is believed that it acts through vasoactive and local anesthetic activity, decreasing penile sensibility and the ejaculatory reflex arc.[74] The main disadvantage of this cream is the unpleasant color and odor on the penis. Other possible adverse effects include local irritation, burning sensation, and delayed ejaculation.[75] Finally, another topical agent is resiniferatoxin, a chemical agent extracted from cactus similar to capsaicin that can cause decreased sensibility and excitability changes in afferent fiber terminations.[76]

Medicinal plants used against male sexual dysfunctions

Despite a considerable number of conventional treatments for male sexual dysfunctions, there are some issues about their contraindications, the patients' adaptation to them, cost, and the fact that some men may have several conditions concomitantly.[77] In this context, medicinal plants and herbal medicines besides *A. oleracea* have gained patients' and health professionals' attention. However, just as in the current conventional treatments, plant-derived treatments should also be evidence-based.[78]

Researchers worldwide report plants' biological activities to develop new approaches for treating urinary symptoms, spermatozoa constitution, sexual desire, and other issues.[79,80] Medicinal plants are used to treat all kinds of sexual issues – increasing sexual desire, sexual performance, improving erectile dysfunction, and ejaculation latency. Some of them have a more robust scientific base than others.

Aphrodisiac agents stimulate the sexual instinct by increasing libido, increasing sexual potency, or increasing sexual pleasure.[81] Oral treatments with products derived from *Tribulus terrestris* L. were reported to improve the erection, sexual behavior, and intracavernous pressure. Also, some studies claim that *T. terrestris* treatment was associated with improved androgen levels, such as testosterone, which may be one underlying mechanism accountable for the aphrodisiac effect. The erection improvement is believed that is caused by increased NO release, triggering the erection cascade.[82,83]

Lepidium meyenii Walp. is an herb popularly known as "Maca" whose roots are used in the Andean region for its aphrodisiac activity and fertility improvement. One double-blind clinical study reported a small but significant improvement by the treatment compared to placebo regarding erectile function. Besides, the satisfaction profile significantly improved among treated patients, whereas this was not observed in the placebo group.[84] This is corroborated by a pre-clinical study performed with rodents where *L. meyenii* increased the number of intromissions, the number of sperm-positive females, and decreased the latency to erection in male rats with ED.[85]

Ginseng is a group of plants from the family Araliaceae. Studies with these plants, mainly the red ginseng (*Panax ginseng* C.A. Meyer), show a potent aphrodisiac effect. Experimental data indicate that it can relax the smooth muscle and improve erectile function in rodents.[86,87] which is probably attributed to NO signaling.[86] Two systematic reviews analyzed randomized clinical trials performed with red ginseng. In the first review, Jang *et al*.[88] evaluated the results of seven randomized clinical trials, totalizing 363 male patients, with ages between 24 and 70 years, with ED between one and 30 years. The treatment duration ranged between four and 12 weeks, and the doses varied from 600 mg to 3 g per day. From these seven studies, six were placebo-controlled, and all of the six reported improvements of the erectile function, superior to the placebo. Four of these trials used standard questionnaires – such as the International Index of Erectile Function (IIEF) and the Watts Sexual Function Questionnaire – to evaluate the sexual function, and all of them reported positive effects by the treatment compared to placebo.

The second systematic review was performed by Borrelli *et al*.[89] with several herbal preparations. The review included 24 randomized controlled studies, of which five evaluated the red ginseng's efficacy as a mono-preparation (n = 399). Three of them were already included in the first study mentioned, and two were published after it. The treatment duration varied between two and three months. According to its IIEF score (IIEF-5, IIEF-15, or IIEF-EF), four studies evaluated ED and reported significant improvement compared to the control. The metanalysis indicates improvement in four of the five domains of the IIEF-15 questionnaire. As for the levels of serum testosterone levels, there were no significant differences compared to the placebo.

***Mondia whitei* (Hook**.f.) Skeels is a bindweed from Africa whose roots are used as aphrodisiac spices. Extracts of this plant exert their effect by relaxing vas deferens and corpora cavernosa vessels. Watcho *et al*.[90] two electrodes where inserted into the bulbospongiosus muscles and the ejaculatory motor pattern was recorded on a polygraph after urethral and penile stimulations, intravenous injection of saline (0.1 ml/100 g showed that this plant's bioactive compounds could also slow down the ejaculation, and, despite it slow up the medullary circuit, its control seems to operate at the supraspinatus level and is not mediated by dopamine.

Found throughout Africa and the Americas, *Guibourtia tessmanni* (Harms) J. Leonard is another plant used for its aphrodisiac activity. Watcho *et al*.[90] reported pro-ejaculatory effects associated with this plant attributed to the spongiosum bulb's rhythmic contraction, a mechanism that seems to be mediated by the dopaminergic system.

Mounting evidence points to the role of dopamine as a key neurotransmitter for ejaculation control.[91] It is thought that dopamine activation of D_2-type receptors in supraspinatus sites increases SGE excitability, while high levels of 5-HT decrease it.[92,93] This inhibitory effect can explain the impact of chronic antidepressant uses on sexual function. Alternatives to such medication include some plant-derived products that can change serotonin reuptake with fewer side effects.[94]

Hypericum perforatum L. experimental data points hyperforin as the major bioactive compound of the plant. Products from this plant can inhibit serotonin reuptake, increasing its concentration, and this

effect is proportional to hyperforin concentration.[94] As previously mentioned, some antidepressant agents are used to treat PE since they can increase ejaculation latency by increasing serotonin levels. However, *H. perforatum* could be a more secure approach with fewer side effects, according to Thomas *et al.*[95] who showed the ejaculation retardant effect of this plant in rats.

Icariin main active molecule of *Herba epimedii*, a plant used for centuries in Chinese traditional medicine as an energetic and pro-erectile agent. The compound was reported to be accountable for the plant's aphrodisiac activity, triggered by increased intracavernous pressure and increased NO synthase expression in the corpora cavernosa.[96,97]

Yohimbine (a.k.a. Ioimbina) is isolated from *Pausinystalia johimbe* (K.Schum.) Pierre ex Beille barks, a three from Africa. This agent works as an antagonist of α_2-type adrenergic receptors and is reported to work in some psychogenic ED patients.[98–100]

Muira puama (a.k.a. Marapuama) is the popular name of *Ptychopetalum olacoides* Bentham (Olacaceae) – a plant from the North of Brazil – historically used by traditional communities for its aphrodisiac, tonic, and stimulating effects. The first studies performed with this plant date back to the beginning of the XX century with Weigel,[101] who reported the possible aphrodisiac effects in this plant. Waynberg[102] reported that from a group of men with decreased libido, 60% of them had improvement after receiving treatment with this plant, and 50% of men with impaired erection reported benefits too. In another study performed with women, an improvement in sexual desire, sexual fantasies, and the capacity to reach orgasm were observed.[103] However, the latter study was performed with the extract of Marapuama combined with *Ginkgo biloba*, a product named Herbal vX.

Formulations are a common practice within this field, but they could hamper the accurate description of the compounds used. Since then, several researches have been performed to evaluate the composition and effects of *P. olacoides*, which point to a compound named "muirapuamine" as the active principle accountable for the stimulating effect. However, just like "guaranine" of guarana and "mateine" of mate herb are chemically identical to caffeine but have different names due to their different origins, it is possible that "muirapuamine" could be caffeine too.[104] The mechanisms underlying the aphrodisiac and pro-erectile effects underlying such compound still have to be elucidated. However, it could be due to a relaxation of the cavernosal smooth muscle[105] and reversing functional tissue changes in the penis due to aging and fibrotic processes.[106,107] It is important to remember that most of such studies were carried out using formulations instead of *P. olacoides* extract or isolated "muirapuamine".

E-MA-H and E-MA-HP are two herbal formulations composed of plants known for their aphrodisiac activity; the latter is composed of adding two additional ingredients in the former (7 and 9, respectively). These formulations were reported to statistically improving scores such as the IIEF (international index of erectile function) and IPE (index for premature ejaculation) compared to placebo. Patients who received E-MA-H had a 48.5% improvement to achieve the erection during sexual activity, and patients who received E-MA-HP had a 48% improvement in their capacity to keep the erection after penetration.[77]

An overview of *Acmella oleracea* (L.) R.K.Jansen (*Spilanthes acmella* auct. non (L.) Murr.)

Acmella oleracea (L.) R. K. Jansen is popularly known as "Jambú" (Figure 3A), typically found in the Amazon rainforest, especially in the State of Pará (Brazil). The plant can have different names according to the geographic area. In Brazil, it can also be known as "botão de ouro" (gold button), "abecedaria", "agrião-do-Pará", "agrião-do-Norte", and "agrião-do-Brasil". It can be known as "toothache plant", "eyeball plant", and "paracress".[108,109]

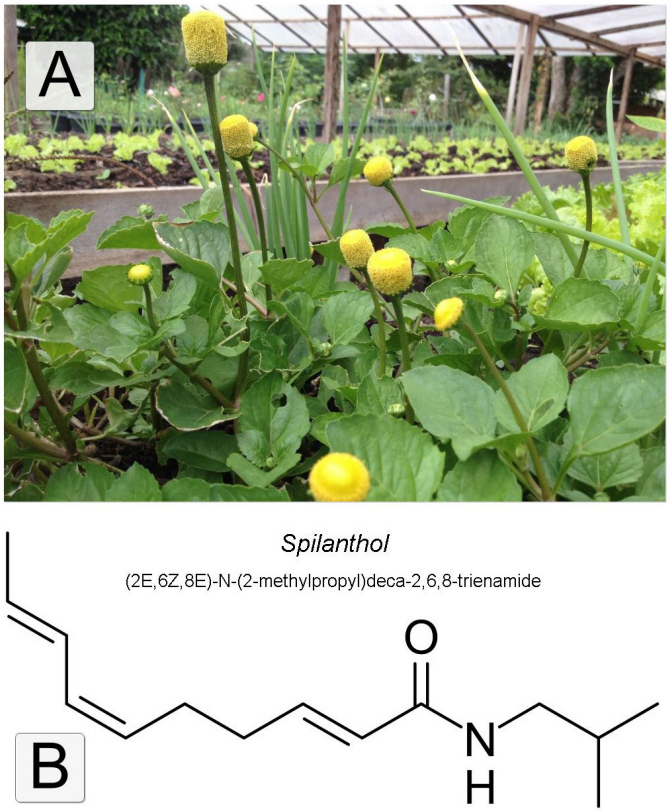

Figure 3: A) A sample of *Acmella oleracea* showing its characteristics inflorescence (photography taken by the authors). B): The structure of spilanthol, the main N-alkylamide of this plant.

This herbaceous plant's height varies from 30 to 60 cm and has an almost creeping habit. Its leaves are compound, membranous, petiolate, and opposite, while the stem is cylindrical and fleshy, with decumbent branches. The roots are taproots systems without knots but with plentiful lateral ramifications. This plant's inflorescences are composite with small yellow-colored flowers arranged in a 1 cm capitulum.[110] *A. oleracea* develops better in hot wet regions – the predominant Amazon climate – multiplying through its seeds or rooted stems.[111]

Jambú is widely used in northern Brazilian cuisine, where it is used in traditional foods.[112] The plant is used in culinary mainly due to its salty taste and to attenuate some mixtures' bitter taste.[113] Also, there is a gastronomical interest in the plant's sensorial changes, described as a tingling sensation, increased salivation after chewing the leaves, and increased appetite.[114]

Besides being used in culinary, *A. oleracea* is used for centuries for treating toothache – which is the root of one of its popular names, "toothache plant" – and other oral cavity pains due to its analgesic proprieties.[115] Other activities evaluated in extracts of *A. oleraceae* or its compounds are larvicidal effect against disease-transmitting mosquitoes,[116,117] antifungal,[118,119] antibacterial,[120,121] analgesic, anti-inflammatory and antipyretic,[121-124] diuretic,[125] vasorelaxant,[126] and weight loss inducing.[127] Due to the utilization of *A. oleraceae* in traditional medicine and the growing interest of pharmaceutics and cosmetic industries, its cultivation in Brazil's Midwest and Southeast regions has increased.[128] The major compound from *A. oleracea* is Spilanthol [IUPAC name (2E, 6Z, 8E)-N-isobutyl-2,6,8-decatrienamide[129] (Figure

3B), which is present in different parts of the plant. The molecule is an olefinic N-alkylamide with an isobutyl sidechain that weighs 221.339 g/mol and represents the plant's major phytochemical compound. When pure, it is described as a burning viscous oil whose color is pale or light yellow.[128] Like other alkylamides, it is an amphiphilic compound with a polar amide and a less polar aliphatic chain; therefore, it can be extracted using solvents with varied polarity.

Alkylamides are secondary metabolites found in several plant families, including the Asteraceae.[130] They are classified according to their carbon chain: olefinic alkylamides, like spilanthol, have double bonds, while acetylene alkylamides have at least one triple bond. The first species where was detected an olefinic alkylamide was *Heliopsis longipes* (Asteraceae). Initially, it was thought that the species was an *Erigeon affinis;* hence the compound was called "affinin". However, studies in the '30s proved that affinin and spilanthol, extracted from "Spilanthes" species, were the same compound, explaining this secondary name of spilanthol.[131] Other species containing spilanthol are *Acmella ciliate*, *A. oppositifolia*, *A. radicans*, *A. brachyglossa, A. ciliate, A. paniculata, A. uliginosa,* and *Welelia parviceps.*[132] The compound is accountable for the sensorial and other biological effects of jambú.[128]

Da Rocha *et al*.[112]popularly known as jambú is marketed in fairs as a female aphrodisiac and has several pharmacological activities already confirmed, among them the sexual stimulant action. The objective of this study was to evaluate the effects of the oral administration of the hydroethanolic extract of *A. oleracea* flowers (EHAo reported that spilanthol was the major compound in the hydroethanolic extract from the flowers of *Acmella oleracea* (84%). The authors mentioned that the results are in line with previous reports, where spilanthol concentration ranged between 84% and 90%. Although spilanthol is present in several plant parts, the higher content seems to be in the inflorescences.[109,119] Spilanthol can cross the oral mucosae, skin, blood-brain barrier, and intestine, besides increasing the dermis permeability to some compounds.[133-135]

Carvalho *et al*.[136] evaluated the acute toxicity of *A. oleracea*'s flower hydroethanolic extract in zebrafish. They assessed treatments through immersion and orally. The authors reported behavioral, hepatic, kidney, intestine changes, and even death depending on the dose, with an LC_{50} of 148.42 mg/kg. De Souza *et al*.[137] treated adult zebrafish (male and female) through immersion with doses up to 200 μg/L and reported few tissue changes in the gonads, not impairing the reproduction. On the contrary, the number of laid eggs increased with the highest concentration. However, the authors reported that the highest concentrations could induce embryos teratogenicity, which were also exposed to the solution. These results can be due to ontological or species-specific factors since *A. oleracea* is considered safe by the European Food Safety Authority and is widely used as a flavoring agent.[138] In addition, the study performed by Sharma *et al*.[139]Spilanthes acmella (L. did not find any signs of acute toxicity in rats treated with doses up to 150 mg/kg.

Evidences of *Acmella oleracea* against male sexual dysfunctions

Interestingly, *Acmella oleracea* (= *Spilanthes acmella*) is used in folk medicine for sexual dysfunctions in different parts of the world, including Brazil[140] and India.[139] This drew the attention of different researchers aiming to evaluate the efficacy of the plant.

In Brazil, Regadas[140] carried out a randomized, double-blind, placebo-controlled cross-study to evaluate the effect of a topical *A. oleracea* cream on sexual performance. Only couples with a stable relationship for at least six months were included in the study; all men were between 18 and 60 years old without ED complaints. The author reported that the treatment could: a) increase the male sexual desire compared to the basal level ($p = 0.0002$), which was significantly higher compared to the placebo group ($p = 0.0008$); b) increase the male sexual satisfaction compared to the basal level ($p = 0.0003$) and the placebo ($p = 0.0006$). An improvement was observed in 50% of patients treated with jambú cream, while in placebo was 0%. 86.5% of the patients stated that the cream increased sexual arousal. There were no significant differences in the ejaculation latency, indirectly estimated through a questionnaire instead of the IELT, which can influence the results. Overall, the results suggest that the topical application of the cream on the male genitalia increased the sexual desire and satisfaction, and the treatment was safe, but no differences were observed in the ejaculation latency. Although the author did not evaluate the precise molecular mechanism, he suggested that the effect could be due to the cream's tingling activity in the glans. The mechanism whereby *A. oleracea* compounds exert their tingling sensation is currently unknown. However, other plant-derived alkylamides with similar tingling activity – such as hydroxy-α-sanshool – exert this effect by exciting neurons by inhibiting pH-sensitive background two-pore potassium channels (KCNK channels).[141]

Another study was performed by Sharma *et al*.[139]Spilanthes acmella (L. who evaluated the effect of an ethanol extract of *S. acmella*'s flowers on the sexual behavior of 40 male Wistar rats. The rats were divided into five groups, where one received a saline solution, three received different doses of the extract (50, 100, and 150 mg/kg), and one received sildenafil. The treatment lasted 28 days, with evaluations on the 15° and 28° days of treatment, then on the 7° and 15° days after treatment. The authors collected blood samples on the 28° treatment day to assess FSH, LH, and testosterone levels. The doses of 100 and 150 mg/kg had a significant effect on LH and FSH serum levels. All three doses could significantly increase the serum testosterone levels compared to the control group. The authors reported that the treatment was a potent stimulator of sexual behavior in male rats, as evidenced by the increased frequency of mounting, penetration, and ejaculation in a dose-dependent manner; reduced latency of mounting, penetration, and post-ejaculatory interval in a dose-dependent manner. Curiously this was observed even 15 days after the treatment, suggesting a long-term effect. *In vitro*, the authors reported that 10 mg/kg of the extract could increase NO release in DS-1 cells to 21.7 μM compared to the solvent control (8.8 μM). Sildenafil, on the other hand, exerted no change on the hormonal levels, increased the sexual behavior parameters, and NO release *in vitro* (35.4 μM), but was inefficient after the end of the treatment.

Their phytochemical evaluation showed that spilanthol was present on the extract but was not the primary compound, like in studies performed in Brazil. Instead, the major compound was (2E,4E,8Z,10Z)-N-isobutyl-dodeca-2,4,8,10-tetraenamide. A possible reason for the lower content of spilanthol than the other report can be the plant's geographical area. This may indicate that the aphrodisiac activity of *A. oleracea* is not only due to the presence of spilanthol, but instead, a more general property of its N-alkylamides. In fact, there are other plants whose N-alkylamides are reported to have a beneficial effect on male reproductive parameters. For instance, Sharma *et al*.[142] reported that an N-alkylamides-rich extract from *Anacyclus pyrethrum* had a significant and dose-dependent effect on fertility parameters assessed on male rats. The authors reported increased testosterone, FSH, and LH; increased spermatogenesis; increased size of Leydig cells; increased spermatozoa motility, viability, and quantity; and increased semen fructose concentration. As the authors state, the increased LH and FSH levels suggest a stimulatory effect of the pituitary gland, evidencing activity on the hypothalamic-pituitary-gonadal axis. The authors reported 13 N-alkylamides in the extract whose structures are very similar to those from *A. oleracea*, suggesting that this mechanism is possibly involved in the plant's aphrodisiac activity.

Corroborating these results of a possible fertility improvement, the study performed by De Souza *et al.*[137] reported that fish treated with *A. oleracea* extract through immersion (100 and 200 µg/L) laid more eggs and had more spawning than control fish.

Although we emphasize the results on men, *A. oleracea* is used traditionally by both sexes. The study of Regadas[140] reported that the cream was effective for women as well. Furthermore, there are experimental reports of the aphrodisiac in female rats.[112] Interestingly, *A. oleracea* seems to work either topically or orally, although the mechanism appears different. Topically, the effect of *A. oleracea* seems to work in part due to its tingling sensation caused on the glans, as mentioned (probably due to inhibition of potassium channels, as suggested previously). However, considering that its N-alkylamides – such as spilanthol – can cross the skin[143] and increase endothelium-induced NO and prostacyclin release,[126,144] it is plausible to assume that increased NO concentrations in the erectile tissue may have a role too. A mechanism of the oral effect could be the increased testosterone levels that could improve libido even some period after the end of the treatment; there are reports that spilanthol and other N-alkylamides can cross the blood-brain-barrier,[145] but the exact molecular pathways causing this increase are still unknown.

Although there is one clinical study[140] assessing the efficacy of *A. oleracea* topically, it would be relevant to evaluate the oral treatment as well since there is evidence from pre-clinical studies of its effectiveness. Also, the molecular mechanism is not yet fully understood, and it would be an interesting subject of research. Finally, comparing the efficacy of the alkylamides would shed light on the most promising compounds for developing potential new drugs.

CONCLUSION

In a world with increasing life expectancy, in parallel with habits and lifestyles harmful to male sexual function, the number of men affected by sexual dysfunction grows annually. Despite a great variety of therapeutic options for these diseases, many of them are associated with relevant side effects that can hamper treatment success.

Some medicinal plants and herbal medicines have a huge potential for novel approaches to treat male sexual dysfunction in this context. However, several studies report the efficacy of the plant product without giving information about their chemical composition, which is crucial. Some plant products are already sold on the market, and the tendency is for more products available.

A promising plant to be used against male sexual dysfunctions is *Acmella oleracea* due to the action of its N-alkylamides – mainly spilanthol – described in this review. However, more research is needed about the compounds' precise action mechanisms to understand better how they work and to corroborate the current reports.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Contribution of the authors

Authors have read and approved the submitted manuscript, and all authors contributed similarly under the supervision of TAT, CPF and JCTC. The figures were created by ACMP, who also translated the manuscript to English.

ABBREVIATIONS

HSDD: Hypoactive sexual desire disorder; **ED**: Erectile dysfunction; **PE:** Premature ejaculation; **AUA:** American urological association; **NO:** Nitric oxide; **cGMP:** Guanosine monophosphate levels; **PDE:** Phosphodiesterase; **SSRIs:** Selective serotonin reuptake inhibitors; **SGE:** Spinal generator of ejaculation; **5-HT:** 5-hydroxytryptamine; **IELT:** Intravaginal ejaculation latency time; **IIEF**: International index of erectile function; **IUPAC**: International Union of Pure and Applied Chemistry; **KCNK channels**: pH-sensitive background two-pore potassium channels; **FSH**: Follicle-stimulating hormone; **LH:** Luteinizing hormone.

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