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Possible Mode of Action of *Mondia whitei*: An Aphrodisiac used in the Management of Erectile Dysfunction

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Abstract: Erectile Dysfunction (ED) is a common condition in older men between the ages of 40 to 70 years caused by physiological and psychological factors. Among many methods used in ED treatment is orthodox pharmaceutical like Viagra, but many medicinal plants are used traditionally for the treatment of ED and infertility, one of which is *Mondia whitei*. The aim of this review is to analyze pathways of penile erection and scientific findings that support the traditional use of *M. whitei* to propose its possible mode of action as a potential aphrodisiac. Studies have shown that it significantly and progressively enhanced human spermatozoa *in vitro*, reduce mutant latency of sexually inexperienced male rats toward receptive female rats and increased frequency of penile erection *in vivo*. Crude extract of *M. whitie* at 200 mg kg^{-1} increases NOS activity with corresponding increased NO, cGMP levels *in vivo* supporting results from pre-incubation of carvernosal tissue *in vivo* with crude extract and its chloroform fractions with marked increased NOS activity; NO and cGMP levels at 0.01 mg g^{-1} tissue which oppose an *in vitro* studies with hexane extract (400 μg mL^{-1}) that caused blockade of voltage-operated calcium channels. *Mondia whitei* may synergistically activating NOS for cGMP generation with cross activation of PKA to generate cAMP; block the receptor-operated and voltage-operated calcium channels to prevent entry of calcium during depolarization that completely abolished contractile effect of calcium to enhance penile erection. More importantly cGKI can be an interesting target for *M. whitei* for the treatment of ED in the development of new drug.

Key words: *Mondia whitei*, penile erection, nitric oxide, adenylyl cyclase, cGMP

INTRODUCTION

Erectile Dysfunction (ED), also known as impotence, is the repeated inability to achieve or maintain an erection firm enough for satisfactory sexual intercourse. This is a common

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condition in older men between the ages of 40 and 70 years. This can be caused by physical factors such as heart disease, diabetes, high blood pressure and hormonal problems and psychological factors such as stress, anxiety, depression and relationship problems (Wespes *et al*., 2004; British Society for Sexual Medicine, 2007; National Health Service Clinical Knowledge Summaries, 2008).

The Massachusetts Male Aging Study showed that the prevalence of erectile dysfunction of any degree is 39% in men 40 years old and 67% in those aged 70 years, extrapolating to over twenty million men in the United States alone with ED (Feldman *et al*., 1994). Atherosclerosis is the cause of approximately 40% of erectile dysfunction in men older than 50 years. Among the most commonly recognized conditions associated are high blood pressure, lipid problems (cholesterol, triglycerides), diabetes and cigarette smoking. In patients with diabetes mellitus, irrespective of type, the prevalence of erectile dysfunction is approximately 50% (range 20 to 75%) with the prevalence dependent on patient age, duration of diabetes and severity of the diabetes (Kaiser and Korenman, 1988). Other chronic disease states associated with a high prevalence of erectile dysfunction include chronic renal failure, hepatic failure, multiple sclerosis, Alzheimer's disease, sleep apnea and chronic obstructive pulmonary disease. Endocrine disorders such as low testosterone and thyroid problems may be associated also with ED. Pelvic trauma, pelvic surgery (major prostate, bladder and bowel operations) and pelvic radiation therapy are associated with erectile dysfunction. Direct trauma to the perineum (bicycle injury) can cause vascular problems in the penis and lead to erectile dysfunction that may be treatable by penile artery bypass surgery (Lilius *et al*., 1976; Goldstein *et al*., 1982; Melman *et al*., 1985; Kaufman *et al*., 1994; Mumarriz *et al*., 1995; Zonszein, 1995).

Many orthodox pharmaceuticals like sildenafil (Viagra) and vardenafil (Levitra) have been effective for the promotion of penile erection, but these drugs are quite expensive and beyond the reach of the ordinary worker. However, medicinal plants have been used for centuries as viable alternatives, with anecdotal evidence of their effectiveness for management of ED.

Effective therapy has been available for some time and currently includes many orthodox pharmaceuticals like sildenafil (Viagra), Vardenafil (Levitra) and Tadalafil (Cialis); urethral suppositories, vacuum devices, penile injection and a variety of surgical treatment including penile implants. However, among these methods medicinal plants have been used for centuries as viable alternative with anecdotal evidence of their treatments as substance that increase libido, potency, enhance sensory experience during coitus. Some of these include *Ambra grisea*, *Panax ginseng*, *Xanthoparmelia scabrosa* and *Mondia whitei* (Ernst-Russel *et al*., 1999; Nantia *et al*., 2009).

Mondia whitei is from the Periplocaceae family and its root has been used by many traditional medicine practitioners in Ghana for the management of ED and infertility. There seem to be little empirical scientific data to support this ethno medical use. This review is therefore, to analyse the pathways of penile erection and the scientific findings on *Mondia whitei* to propose the possible mode of actions.

PATHWAYS THAT REGULATE PENILE SMOOTH MUSCLE RELAXATION

Penile erection is the end result of smooth muscle relaxation in the penis mediated by a spinal reflex and involves central nervous processing and integration of tactile, olfactory, auditory and mental stimuli (Fig. 1). The reflex involve both autonomic and somatic afferents and modulated by supraspinal influences peripherally, the balance between contractant and relaxant factors control the tone of penile vasculature and of the smooth muscle of the

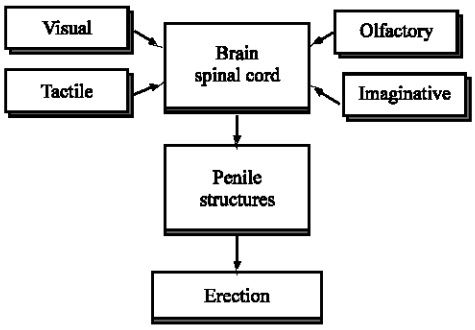

Fig. 1: Showing the central nervous processing and integration of tactile, olfactory, auditory and mental stimuli that results in penile erection due to smooth muscle relaxation in the penis mediated by a spinal reflex

Corpora Carvernosa (CC) and determine the functional state of the penis; detumescence and flaccidity, tumescence and erection (Andersson, 2001).

Cyclic Guanosine Monophosphate (cGMP) Pathway

During arousal Nitric Oxide Synthase (NOS) is activated for the release of Nitric Oxide (NO) from the nonandrnegic nancholinegic (NANC) endings in the walls of the arteries and sinusoids of the penile CC (Andersson and Wanger, 1995; Burnett, 1997) endothelial cells lining the blood vessels and sinusoid if the CC to the neurovascular nerve bundles which stimulate soluble Guanylase Cyclase (GC). Atrial Natriuretic Factor (ANF) acts via the membrane-bound GC. The activated GC from both sources then catalyze the conversion of guanosine triphosphate (GTP) to cGMP which activates cGMP-dependent protein kinase (cGKI) and to a lesser extent protein kinase A (cAK; De Saenz and Moncada, 1996; Klotz *et al*., 2000). Activated cGKI and cAK phosphorylate phospholamban, a protein that normally inhibits the Ca^{2+} pump within the membrane of the sarcoplasmic reticulum. The Ca^{2+} pump is then activated and, consequently, the level of free cytoplasmic Ca^{2+} is reduced, resulting in smooth muscle relaxation. Similarly, the protein kinases activate the cell-membrane Ca^{2+} pump, leading to a decreased sarcoplasmic Ca^{2+} concentration (Somlyo and Somlyo, 1994; Karaki *et al*., 1997; Hedlund *et al*., 2000) which induces a loss of contractile tone of the penile smooth muscle and an increase of blood flow in the cavernous body resulting in erection (Fig. 2).

Cyclic Adenosine Monophosphate (cAMP) Pathway

Corporal smooth muscle relaxation is mediated via the intracellular cyclic nucleotide/protein kinase messenger systems through β-adrenegic receptors (β-ARs), agonists activate membrane-bound adenylyl cyclase, which generates cAMP. The cAMP then activates protein kinase A (or cAK) and to a lesser extent, protein kinase G. The cavernous body is richly supplied with nerves containing Vasoactive Intestinal Polypeptide (VIP) VIP receptors coupled to G-Proteins to adenylyl cyclase leads to an increase in cAMP, which in turn activates cAMP-dependent protein kinase, without affecting the cGMP levels (Hedlund *et al*., 1995; Miller *et al*., 1995), Prostagladin E_1 (PGE_1) also increase the intracellular concentrations of cAMP in the corpus cavernosum smooth muscle cells through EP receptor stimulation (Palmer *et al*., 1994; Lin *et al*., 1995; Cahn *et al*., 1996; Traish *et al*., 1997). The generation of cAMP activates cAK phosphorylate phospholamban, a protein

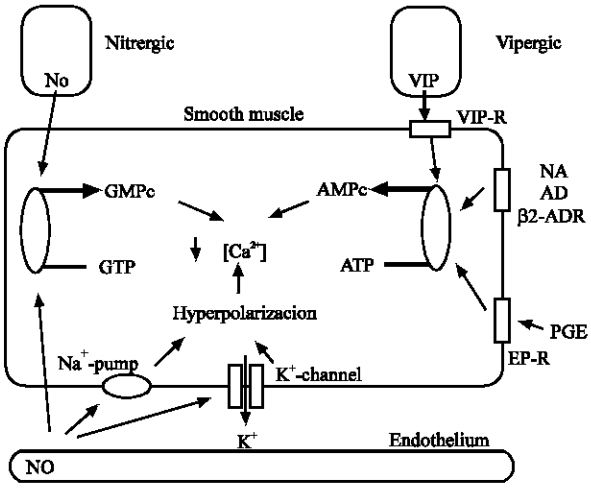

Fig. 2: The three pathways that regulate penile smooth muscle relaxation: cGMP, cAMP and hyperpolarization. (NA = noradrenaline, AD = adrenaline, β-ADR = β 2-adrenergic receptor, EP-P = prostaglandin E receptor, VIP-R = vasoactive intestinal peptide receptor, Na^+-pump=Na^+-K^+-ATPase, NO nitric oxide) (From Saenz de Tejada and Moncada)

that normally inhibits the Ca^{2+} pump within the membrane of the sarcoplasmic reticulum. The Ca^{2+} pump is then activated and, consequently, the level of free cytoplasmic Ca^{2+} is reduced, resulting in smooth muscle relaxation. Similarly, the protein kinases activate the cell-membrane Ca^{2+} pump, leading to a decreased sarcoplasmic Ca^{2+} concentration (Somlyo and Somlyo, 1994; Karaki *et al*., 1997; Hedlund *et al*., 2000) which induces a loss of contractile tone of the penile smooth muscle and increase of blood flow in the cavernous body resulting in erection (Fig. 2).

Hyperpolarisation

One of the mechanisms by which cyclic nucleotides induce the relaxation of smooth muscle is through the opening of potassium (K^+) channels; the distribution of K^+ across the corporal smooth muscle cell membrane ensures that the opening of potassium channels will lead to efflux of K^+ from the smooth muscle cell, down their electrochemical gradient. The movement of positive charge out of the cell results in hyperpolarization and an inhibitory effect on transmembrane Ca^{2+} flux through L-type voltage-dependent calcium channels and ultimately, smooth muscle relaxation. The activity of this channel is increased following cellular activation of either the cAMP pathway by 8-Bromoadenosine-cAMP or PGE_1 s (Lee *et al*., 1999) or the cGMP pathway by 8- Bromoadenosine-cGMP (Fig. 2) (Wang *et al*., 2000).

PENILE SMOOTH MUSCLE CONTRACTION

The major intracellular receptors for cGMP, cGMP protein kinas (PKG) and phosphodiestrase type 5(PDE5) are abundant in vascular smooth muscle cells, including those of the penis, PDE5 catalyze the hydrolysis of the second messenger cGMP, which is involved in signal pathways of cavernous smooth muscle back to GTP, thereby decreasing

blood flow in the penis. After cessation of erotic stimuli, nitric oxide release from the parasympathetic nerves of the penis declines and the cGMP level in the smooth muscle cells falls because of a decrease in synthesis coupled with the ongoing degradation of cGMP by PDE5. These muscle cells return to the more contracted state and the penis becomes more flaccid because of the reduced amount of blood in the corpora. Alteration in either psychological, hormonal, neurological, vascular, or cavernosal factors can cause some degree of erectile dysfunction (Ballard *et al*., 1996, 1998; Bivalacqua *et al*., 1999; Küthe *et al*., 2000, 2001).

Activation of the sympathetic nervous system, which occurs, for example, with performance anxiety, results in inhibition of erection. With increased sympathetic tone, norepinephrine is released at alpha1-adrenoceptors located on the cavernous smooth muscle cell. Norepinephrine activates membrane-bound phospholipase C, which induces cleavage of phosphoinositol diphosphate to inositol triphosphate and diacylglycerol. Both inositol triphosphate and diacylglycerol cause an increase in intracellular Ca^{2+}, which in turn activates myosine light chain (MLC) kinase and leads to an increase in phosphorylated MLC (Somlyo and Somlyo, 1994; Karaki *et al*., 1997). This enables the smooth muscle cell to contract and thus prevent erection. In addition, endothelial vasoactive compounds, such as endothelia 1, angiotensin II and thromboxane A2, which have smooth muscle contractile properties, can also interfere with smooth muscle relaxation and prevent erection.

MONDIA WHITEI AS AN APHRODISIAC

Mondia whitei is from the Periplocaceae family has been used by many traditional medicine practitioners in Ghana for the management of ED, It is also know to increase libido and also for the management of low sperm count.

Some scientific researchers have shown the anecdotal evidence of *Mondia whitei* effectiveness as an aphrodisiac. Motility parameters on aqueous administration to human spermatozoa *in vitro* showed significantly enhanced total motility as well as progressive motility in a time-dependent manner. These findings support the use of *Mondia whitei* especially in men affected with asthenozoospermia (Lampiao, 2007), but its mode of action is not clear. The effect of aqueous and hexane extract of *Mondia whitei* have also been shown to sexually enhanced sexually inexperienced male rats (Watcho *et al*., 2007).These were through the reduction of the hesitation time of the sexually inexperienced males towards receptive females as indicated by the significant decrease ($p<0.001$) in the mount latency. This suggest that the aqueous and hexane extract of *Mondia whitei* may act by inducing changes in levels of neurotransmitters, modulating the action of these neurotransmitters on their target cells or by increasing androgen levels (Suresh-Kumar *et al*., 2000) which confirms the demonstration of adrenergic effect of aqueous (Watcho *et al*., 2004) and hexane (Watcho *et al*., 2005) extracts of *Mondia whitei* on chronic administration *in vivo* in rats.

In an investigation of the pro-sexual activity of *Mondia whitei,* isolated hexane compounds MH_2 (mixture of α-amyrine and β-acetate) and MH_6 (-sitosterol) were used orally to treat sexually inexperienced male albino rats at 0 mg kg^{-1} (control), 10 or 50 mg kg^{-1} and one hour after administration, mounts and intromiscence frequencies, penile erection and ejaculation latency were measured for 60 min. The results shows that MH_2 and MH_6 significantly increased the mount frequency, penile erection $p<0.001$) and ejaculation latency where as the intromiscence frequency remained unchanged when compared to control. This studies my account for the pro-erectile effect of *Mondia whitei* and supports its traditional use as an aphrodisiac (Watcho *et al*., 2006a).

All these have not shown its action chemically. From the early discussions, there are many potential targets for the development of new drug for the treatment of ED. This could be through the activation of Nitric Oxide Synthase (NOS), inhibition of PDE5 or through the intracellular protein kinases mediating cGMP and cAMP or through the sensitization of Ca^{2+} independent of NO or by hyperpolarisation. An *in vitro* studies to investigate the effects of the methylene chloride: methanol (CH_2C_{12}:MeOH, 1:1) extract of the dried roots of *Mondia whitei* Linn and its hexane and methanol fractions on potassium chloride (KCl) and adrenaline (Adr)-induced contractions of rat vas deferens showed that the hexane fraction of *Mondia whitei* extract contain biochemical molecules that block both the receptor-operated and voltage-operated calcium channels, thus preventing the entry of calcium during depolarization of vas deferens by KCl and adrenaline (Watcho *et al*., 2006b) due to the fact that all the *M. whitei* samples produced rightward shift of the concentration-response curves to KCl and Adr with a decrease of the maximal response to the contractile agents at high concentration of the plant extracts (400 μg mL^{-1}) compared with control. In calcium-free physiological salt solution, the hexane fraction of *M. whitei* produced rightward shift to the concentration-response curve to $CaCl_2$ and completely abolished the contractile effect of calcium at high concentration (400 μg mL^{-1}).

However, a preliminary studies of ethanolic extract of *Mondia whitei in vivo* increases levels of cGMP (Ofosuhene, 2005) the pathway that capora cavernosa smooth muscles is relaxed for penile erection as in the case of sildenafil (Viagra) and Vardenafil (Levitra) and Tadalafil (Cialis). Further studies on the modulation of penile erection in rabbits by *Mondia whitei* with the view to determine its mode of action where the *in vivo* effect of the ethanolic crude extract and the effect of the ethanolic crude extract, chloroform and petroleum ether fractions in vitro on cavernosal tissue suggests that *M. whitei* may influence erectile function through activation/stimulation of NOS with corresponding increases in tissue NO and cGMP levels and that certain chemical constituents present in the chloroform fraction may be responsible for biological activity. As a result of the crude extract increased NOS by 7% at 200 mg kg^{-1} with corresponding increases in NO (88%) and cGMP (480%) levels with slightly reduced of sildenafi (15.9-37.5%) The *in vivo* results also corroborate with the pre-incubation of cavernosal tissue *in vitro* as the crude extract of *M. whitei* and its chloroform fraction markedly increased NOS activity (26-132%) and levels of NO (25%) and cGMP (50-400%) at 0.01 mg g^{-1} tissue but these were reduced to near control levels when their concentrations were increased to 0.10 mg g^{-1} tissue whilst the petroleum ether fraction had no effect (Quasie *et al*., 2010).

CONCLUSION

Enough scientific evidence have support the anecdotal use of *M. whitei* as an aphrodisiac and it may be working synergistically by activating NOS that increases the level of cGMP that can cause cross activation for the generation of cAMP as well as hyperpolarisation. Since the *in vitro* studies proves that *M. Whitei* can cause blockade of voltage-operated calcium channels, it is likely to directly activate cGK1 that can be an interesting target for pharmacological intervention in the management of ED.

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