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Molecules of Interest

Recent findings on natural products with erectile-dysfunction activity

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Abstract

Viagra has had a profound influence on the search for natural products with erectile-dysfunction activity. To date the "natural" equivalent is not in existence but several pure compounds from nature, e.g., Yohimbine, Citrulline, two pyrano-isoflavones, berberine, forskolin and others, have either been re-examined or are new potential candidates. Intense activity exists in the area of testing semi-purified plant extracts for erectile dysfunction activity.
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Keywords: Viagra; Pyrano-isoflavones; Yohimbine; *Tribulus terrestris*; Maca; Catuama

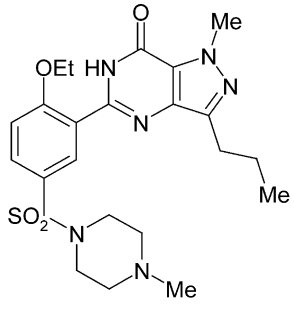
1. Introduction

The arrival of the synthetic "love drug", Viagra (**1**), has, not only, captivated the public imagination, but has led to a flurry of activity to:

(i) re-assess "old" natural products for their use as agents to combat impotence, and,
(ii) unearth a new natural product which can truly compete with Viagra **1**.

The term "erectile-dysfunction" (E-D) has become commonplace as a result of the widespread use of Viagra (**1**), and needs to be defined. Goldstein (2000) describes it as "*a consistent inability to get or keep an erection that is satisfactory for sexual performance*." On this basis the legendary love potions such as Spanish fly, glandular products from musk deer and civet cats, varieties of natural oats (*Avena sativa*), ginseng, belladonna, and erotic foods such as fish and oysters, do not qualify as E-D agents and are more appropriately named aphrodisiacs (Choudhary and Ur-Rahman, 1997).

Five hundred years ago Leonardo da Vinci is quoted as having said that "the penis does not obey the order of its master, who tries to erect or shrink it at will, whereas, instead the penis erects freely while its master is fast asleep. The penis must be said to have its own mind..." (Goldstein, 2000). Current findings in the area of penile erection show, without a doubt, that da Vinci erred in his analysis since the penis is now known to be controlled by the central nervous system. This statement is aptly illustrated by a study of the action of Viagra.



(1) Viagra (Sidenafil)

2. How Viagra works

On sexual stimulation (visual or otherwise) the terminals of the axons of the parasympathetic nerves release

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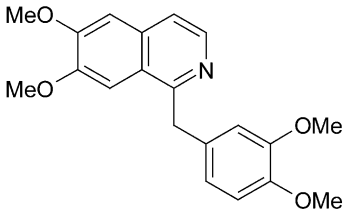
nitric oxide (NO) gas. The gas diffuses into the smooth muscle cells that line the arteries of the *corpus cavernosum* (spongy erectile tissue) and activates the enzyme guanylate cyclase (GC). The latter converts the nucleotide guanosine triphosphate (GTP) into cyclic guanosine monophosphate (c.GMP). The c.GMP in turn causes the smooth muscle cells around the penis to relax, leading to dilation and increased influx of blood into the penile tissue. This blood is essentially trapped in the penis and results in an erection (Palmer, 1999).

The erection ceases after a while because c.GMP is hydrolysed by phosphodiesterase type 5 enzyme, (PDE5) into *inactive* GMP. (The PDE5 enzyme resides in the penile tissues). Viagra's role is to inhibit the hydrolyzing action of the PDE5 with the result that active c.GMP can accumulate "undisturbed" and prolong the erection through increased blood flow (Fig. 1).

The action of Viagra has been described in some detail in order that the usual test for measuring E-D in new compounds is understood. There is no unanimity amongst researchers on the parameters which should be used to gauge sexual prowess. Perusal of research results so far also indicates that there is no complete animal model for assessing activity of new compounds. This is related to the fact that human cerebral aspects of sex are far more important than the basic instinctive functions observed in animals. In the usual procedure strips of smooth muscle of rabbit *corpus cavernosum* are mounted in an organ bath. After allowing the strips to equilibrate in physiologic salt solution, the relaxation of the muscle (pre-contracted with phenylephrine) is measured after the addition of successive doses of the test substances. A positive result under the above conditions confirms the presence of a smooth muscle relaxant. It reveals little about the mechanism of the action and it cannot serve as a blueprint for creating the specific response in humans (Kim et al., 1998).



(2) Papaverine

3. Some natural products with erectile-dysfunction activity

3.1. Dehydroepiandrosterone

Dehydroepiandrosterone [(**3**), DHEA] is the major secretory steroidal hormone of the adrenal gland and its isolation dates back to 1934. In a comprehensive study

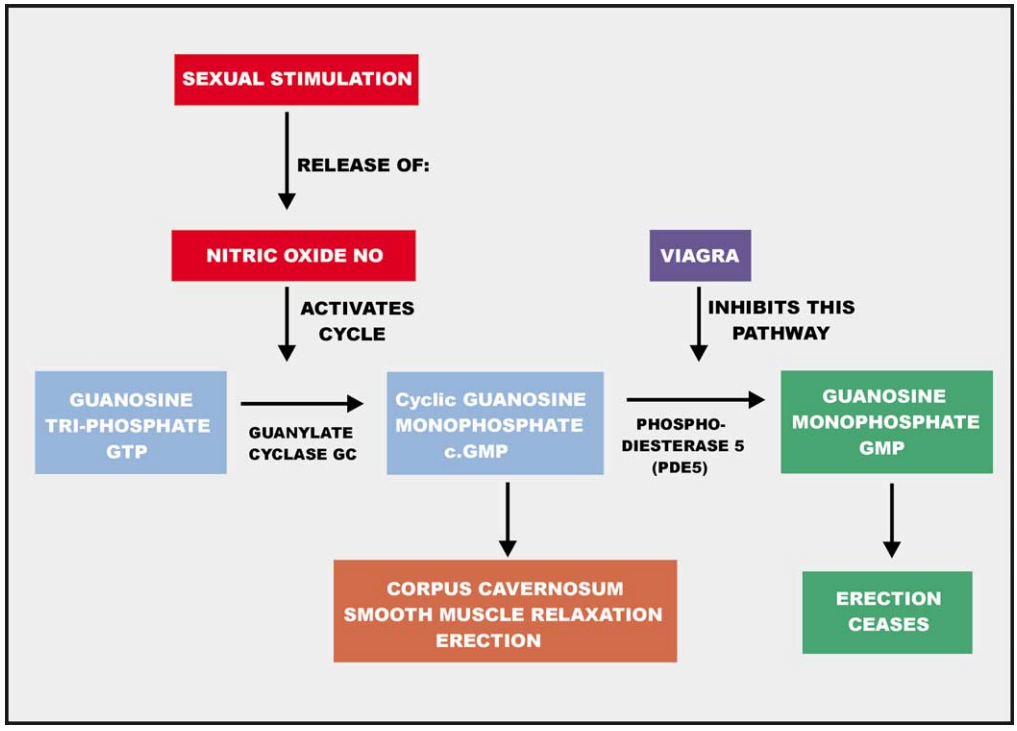
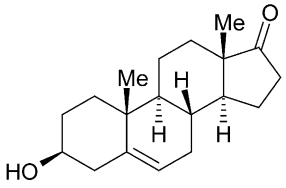


Fig. 1. Action of Viagra in the E-D cycle (Chew et al., 2000).

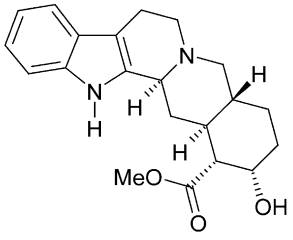
(Feldmann et al., 1994) of 17 hormones it was shown that only DHEA showed a strong inverse correlation to E-D. A more recent investigation (Reiter et al., 1999), was carried out on 40 men of mean average age 56 in order to study the effects of DHEA on patients with E-D. The results suggest that daily oral supplementation of the hormone produces a rise in serum levels of DHEA, concomitant with increase in sexual performance and satisfaction.



(3) Dihydroepiandrosterone (DHEPA)

3.2. Yohimbine

Yohimbine (**4**) is an indole alkaloid with α_2-adrenergic blocking activity. It comes from the bark of the West African tree *Corynanthe yohimbe* and its first isolation was in the early 1930s.

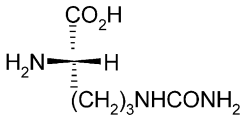


(4) Yohimbine

The bark of the tree is traditionally used to enhance sexual prowess and virility. A drug marketed as Afrodex, and claimed to have aphrodisiac powers remained on the African market until 1973. The drug consisted of a combination of yohimbine hydrochloride, methyl testosterone and *Nux vomica* (Sonda et al., 1990). Renewed interest in yohimbine for E-D has prompted several new investigative (including chemical) trials. Indications are that in some cases yohimbine can improve sexual performance (Ernst and Pittler, 1998). There are, however, indications of undesirable side-effects such as hypertension, anxiety, manic symptoms and undesirable interactions with commonly-used medications (Guirguis, 1998).

3.3. L-Citrulline

When L-citrulline [(N^5-aminocarbonyl)-L-ornithine] (**5**) is part of a formulation with calcium phosphate and other extenders, it is marketed under the trade name STIMULIN. The preparation is claimed to improve sexual stamina and ease E-D. The active ingredient in the formulation is L-citrulline which occurs naturally in watermelons.

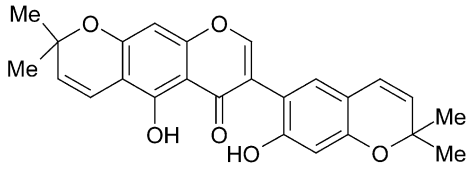


(5) L-Citrulline

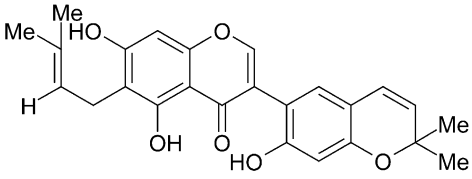
L-citrulline was first isolated in the 1930s, but its use as dietary supplement is of relatively recent origin. The activity of L-citrulline is attributed to its ability to release NO which, in turn, results in increased blood flow to the body, including the penis. Hard scientific facts on the mode of action of L-citrulline are difficult to find at present.

3.4. Pyrano-isoflavones

In a very recent publication Drewes et al. (2002) describe two new pyrano-isoflavones (**6**,**7**), from the roots of *Eriosema kraussianum*. These compounds test positively in the E-D test. Compared with Viagra, (**6**) and (**7**) attain values of 85 and 65% respectively, when assessing relaxation of *corpus cavernosum* smooth muscle.



(6) Kraussianone 1

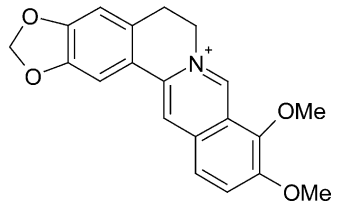


(7) Krausianone 2

The two compounds occur in a plant genus which has a centuries-long tradition of use by the indigenous people of Kwa-Zulu Natal for the treatment of male impotence. It is of interest to note that Indian people in a part of Venezuela, use the root decoction of *Eriosema rufum* against sterility in women.

3.5. Berberine

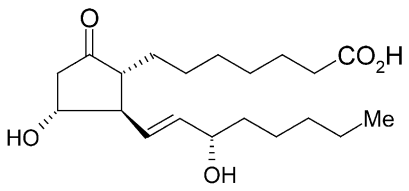
Berberine (**8**) is an alkaloid widely distributed in nature and occurs in Berberis plants such as *Berberis aristata* and *B. vulgaris*. Chiou et al. (1998) have undertaken a very detailed study on the relaxation of the *corpus cavernosum* and raised intravenous pressure by berberine (**8**) in rabbit. For these tests male New Zealand rabbits were used to obtain the *corpus cavernosum* tissue and the intravenous pressure change measured after intercavernosal injection of berberine. The overall results show that berberine possesses a relaxant effect on the rabbit *corpus cavernosum* tissue which is attributable to both endothelial-dependent and -independent properties. The authors are of the opinion that berberine has the potential to be used as a drug for intravenous injection therapy. It is pointed out that while paperverine (see below) appears to be more effective than berberine in inducing penile erection, the duration of tumescence caused by berberine is considerably longer. Also, berberine causes only a transient hypotensive action.



(8) Berberine

3.6. Papaverine and prostaglandin E_1

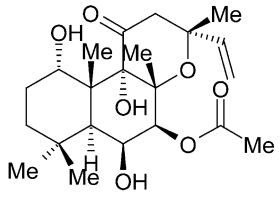
A combination of two natural products from *Papaver somniferum* and from sheep seminal vesicle tissue respectively, has received renewed attention as a potential combination against male impotence (Zaher, 1998). It should be emphasized that both papaverine (**2**) and prostaglandin E_1 (**9**) are recognized vaso-dilators. Research findings based on a clinical trial on 100 impotent male patients indicated that papaverine plus PGE_1 was more effective than PGE_1 alone. The procedure was not without its complications, however, and re-inforced the earlier findings (Junemann and Alken, 1989) that papaverine, phentolamine and PGE_1, as a combination gave rise to side effects such as priapism (extended erection), local fibrosis, and pain.



(9) Prostaglandin PGE_1

3.7. Forskolin

The source in nature of the diterpene forskolin (**10**) is the Indian herb *Coleus forskohlii*. It is of relatively recent origin (1977) and possesses vasodilatory and cardiostimulatory properties. In view of the cyclic AMP-dependent effects produced by forskolin, it has found use as an agent for the treatment of congestive cardiomyopathy, glaucoma and asthma.



(10) Forskolin

Forskolin has also been investigated (Mulhall et al., 1997) as an intracavernosal vasoactive agent in the management of vasculogenic impotence. In in vitro tests, forskolin and PGE_1 alone caused concentration-dependent relaxation. Combination of the two agents resulted in synergistic response. Clinical investigation in 31 patients showed no adverse effects. Overall 61% of these reported improvement in rigidity of the penis and/or erection duration using a combination of forskolin, papaverine, phentolamine and PGE_1.

4. Preparations consisting of whole extracts, purified extracts or a mixture of identified compounds from natural sources

As the length of the following section will show, there is an upsurge, worldwide, but particularly in ''developing countries'', in the use of ''natural'' medicines. There is the general belief that many ailments of humanity can be cured by this treatment. This ignores the fact that in the first instance, plants produce a wide variety of metabolites to *ensure their own existence* and not necessarily that of mankind.

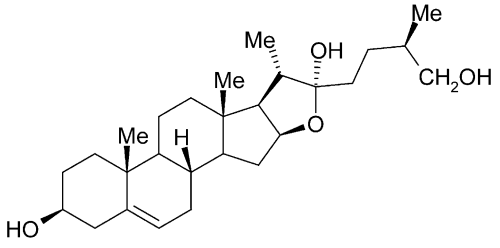
4.1. Preparations from Tribulus terrestris

T. terrestris (devil's thorn) is a prostrate annual widespread in southern Africa in flood plains and disturbed areas. It is used medicinally as a tonic for diarrhoea and diseases of the throat and eyes. Sheep graze on it but under certain conditions it brings out sensitivity to light (tribulosis) on those parts of the sheep's head that are not covered by wool. In the years 1926–1927 it was estimated that more than half a million sheep died of the disease in southern Africa.

The work of Adimoelja (2000) in Indonesia and Adaikan et al. (2000) in Singapore has drawn attention

to a potential additional use of the extracts from *T. terrestris*. These researchers have presented evidence that protodioscin, a compound present in the *T. terrestris* extracts, can improve sexual desire and enhance erection.

It is suggested (Adimoelja, 2000) that the protodioscin produces the reported effects by its conversion to dehydroepiandrosterone (DHEA). Chemically protodioscin is a complex molecule ($C_{51}H_{84}O_{22}$) and has at its core the furost-5-ene-3,22,26-triol nucleus (**11**). There are sugar moieties attached at C-3 and the C-26 hydroxyl group (Shao et al., 1997). A commercial preparation of the *T. terrestris* preparation is sold under the trade name of Libilov.

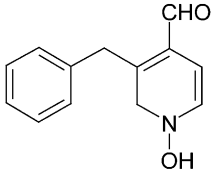


(11) Furost-5-ene-3,22,26-triol

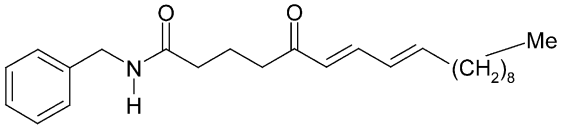
4.2. Lipidic extract from Lepidium meyenii (maca)

The plant *L. meyenii* belongs to the *Solanaceae* and has been known and used in the Andean mountains for 2000 years. While it has nutritional value it is also employed by the Andean Indians for enhancing fertility and sexual behaviour in both sexes (Muhammad et al., 2002; Cicero et al., 2000).

Some of the chemical substituents of maca are (**12**) and (**13**) (Muhammad et al., 2002). Recent press releases indicate that the extract of "maca" has been patented in the United States (Pure World Botanicals, 2001). The patent has been denounced by representatives of the Peruvian farmers. The basis of their objections is the fact that indigenous knowledge and widespread use of "maca" has existed for centuries.



(12) Macaridine

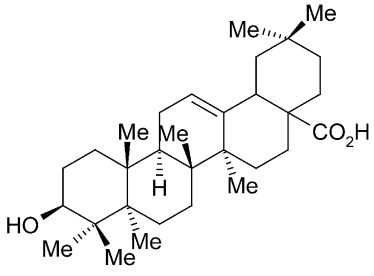


(13) N-benzyl-5-oxo-6E,8E-octadecadienamide

4.3. Ginseng from Panex ginseng or P. quinquefolius

The herbal tonic known commonly as ginseng enjoys extremely widespread use. Some chemical evidence supports the stimulatory action of the extract from *P. ginseng* or *P. quinquefolius*, but the US Food and Drug administration (FDA) have found no evidence of enhanced sexual experience resulting from its ingestion (Choudhary and Ur-Rahman, 1997). Earlier studies on Korean red ginseng (Choi et al., 1995) are in line with the conclusions of the FDA and the authors state that "no complete remission of E-D was noted, but partial responses were reported."

Root extracts of ginseng contain a variety of compounds such as steroids, peptides, triterpenoidal D-glucosides, specifically panaxsapogenin (**14**) (Choudhary and Ur-Rahman, 1997).



(14) Panaxsapogenin

4.4. Eurycoma Longifolia extracts

E. Longifolia (Simaroubaceae), commonly called Tongkat Ali, is native to the jungle of Malaysia (Ang and Sim, 1998). Antimalarial, cytotoxic, anti-ulcer and anti-pyretic properties have been claimed for it over the years. Recently, it has figured prominently in the popular press on account of its reputed use to increase male virility. For this reason several research groups have examined it for this property, notably using sexually experienced male rats (Ang and Sim, 1998). It was found that rats treated with a specific dose of the extract, twice daily, displayed behaviour of rats with enhanced sexual arousal (Ang and Sim, 1998; Ang et al., 2001).

A recent paper (Jiwajinda et al., 2001) reports on the isolation of several quassinoids from *Eurycoma longifolia*. One of these was active as a plant growth inhibitor. It is noteworthy that these authors point out that in this instance plant growth inhibitory activity may be useful as a preliminary screening method for finding quassinoids with medicinal properties.

4.5. Herbal medicine catuama

The combination of herbs, collectively known as "Catuama" in Brazil, consists of four plants–*Paullina*

cupana, *Trichilia catigua*, *Zingiber officinalis* and *Ptychopetalum olacoides*. The individual components have also been used, separately, for centuries, for a variety of purposes (analgesic, antibacterial, cardiotonic, purgative and vaso-dilatory). However, it is the combination of the four that, in more recent times, has been promoted as an aphrodisiac.

Results from Antunes et al. (2001) on rabbit *corpus cavernosum* indicate that "catuama" brings about short-lived, dose dependent relaxations. Of the four plant extracts assayed separately *P. cupana* was the most effective in causing relaxation of smooth muscle.

The wood and bark of two closely related species of *Ptychopetalum*, *P. olacoides* and *P. uncinatum* make up the herbal medicine known in Brazil as "muira puma". It has a variety of traditional uses including the treatment of sexual impotency. Human trials carried out by a French group (Waynberg, 1990) showed the medicine to be effective in improving libido and treating erectile-dysfunction.

4.6. The herb medicine from Cordyceps sinensis

Zhongcao, an edible mushroom with an unusual association between a fungus, (*Cordyceps sinensis*), and an insect larva, is a well-known traditional medicine in China for the treatment of general debility, certain cancers and also for sexual enhancement. The latter property is not altogether surprising since recent studies by Chinese researchers (Chiou et al., 2000) indicate clearly that a protein component in *C. sinensis* contributes to the observed hypotensive and vasorelaxant properties of the herb. The vasorelaxant effect is linked to the production of NO, as is also the case with Viagra. These are preliminary results and the authors stress that further work on the mechanism of action needs to be done.

5. Conclusion

Despite the world-wide interest in Viagra and the influence it has had on the search for a natural product which can deal effectively with the problem of erectile-dysfunction, no such breakthrough has become a reality. There are promising "candidates" on the horizon but for all these additional tests relating to mechanism of action, unwanted side-effects and toxicity need to be concluded.

Acknowledgements

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References

Adaikan, P.G., Gauthaman, K., Prasad, R.N., 2000. Pro-erectile pharmacological effects of *Tribulis terrestris* extracts on rabbit *corpus cavernosum*. Ann. Acad. Med. Singapore 29, 22–26.

Adimoelja, A., 2000. Phytochemicals and the breakthrough of traditional herbs in the management of sexual dysfunction. Intl. J. Androl. 23, 82–84.

Ang, H.H., Sim, M.K., 1998. *Eurycoma longifolia* and orientation activities in sexually experienced male rats. Biol. Pharm. Bull. 21, 153–155.

Ang, H.H., Ikeda, S., Gan, E.K., 2001. Evaluation of the potency activity of the aphrodisiac in *Eurycoma longifolia*. Phytother. Res., 435–436.

Antunes, E., Gordo, W.M., de Oliviera, J.F., Texeira, T.E., Hyslop, S., de Nucci, G., 2001. The relaxation of isolated rabbit *corpus cavernosum* by the herbal medicine catuama and its constituents. Phytother. Res. 416–421.

Chew, K.K., Stuckey, B.G.A., Thompson, P.L., 2000. Erectile dysfunction, sildenafil and cardiovascular risk. Med. J. Aust. 172, 279–283.

Chiou, W.F., Chen, J., Chen, C.F., 1998. Relaxation of *corpus cavernosum* and raised intracavernous pressure by berberine in rabbit. Br. J. Pharmacol. 125, 1677–1684.

Chiou, W.F., Chang, P.C., Cho, C.J., Chen, C.F., 2000. Protein constituent contributes to the hypotensive and vaso-relaxant activities of *Cordyceps sinensis*. Life Sci. 66, 1369–1376.

Choudhary, I., Ur-Rahman, A., 1997. Elixirs of love. Chem. Br. October, 25–27.

Choi, H.K., Seong, D.H., Rha, K.H., 1995. Chemical efficiency of Korean red ginseng for erectile-dysfunction. International J. Impotence Res. 7, 181–186.

Cicero, A.F.G., Bandieri, E., Arletti, R., 2001. *Lepidium meyenii* improves sexual behaviour in male rats independently from its action on spontaneous locomotor activity. J. Ethnopharmacol. 75, 225–229.

Drewes, S.E., Horn, M.M., Munro, O.Q., Dhlamini, J.T.B., Meyer, J.J.M., Rakuambo, N.C., 2002. Pyrano-isoflavones with erectile dysfunction activity from *Eriosema kraussianum*. Phytochemistry 59, 739–747.

Ernst, E., Pittler, M.H., 1998. A systematic review and meta-analysis of randomized clinical trials. J. Urol. 159, 433–436.

Feldman, H.A., Goldstein, I., Hatzichristou, D.G., 1994. Impotence and its medical and psychological correlates. J. Urol. 151, 54–61.

Goldstein, I., 2000. Male sexual circuitry. Scientific American August, 56–61.

Guirguis, W.R., 1998. Oral treatment of erectile-dysfunction: from herbal remedies to designer drugs. J. Sex Marital Ther. 24, 69–73.

Jiwajinda, S., Santisopasri, V., Murakami, A., Hirai, N., Ohigashi, H., 2001. Quassinoids from *Eurycoma longifolia* as plant growth inhibitors. Phytochemistry 58, 959–962.

Junemann, K.P., Alken, P., 1989. Pharmacotherapy of erectile-dysfunction. Int. J. Impotence Res. 1, 71–93.

Kim, H.J., Woo, D.S., Lee, G., Kim, J.J., 1998. The relaxation effects of ginseng saponin in rabbit corporal muscle: is it a nitric oxide donor? Bri. J. Urol. 82, 744–748.

Muhammad, I., Zhao, J., Dunbar, D.C., Khan, I.A., 2002. Constituents of *Lepidium meyenii*, "maca". Phytochemistry 59, 105–110.

Mulhall, J.P., Daller, M., Traish, A.M., Gupta, S., Park, K., Salimpour, P., Payton, T.R., Krane, R.J., Goldstein, I., 1997. Intracarvenosal forskolin: role in management of vasculogenic impotence resistant to standard 3-agent pharmacotherapy. J Urol. 158, 1752–1759.

Palmer, E., 1999. Making the love drug. Chem. Br. January, 24–26.

Pure World Botanicals, 2001. Extract of *Lepedium meyenii* Roots for Pharmaceutical Application. US Patent No. 6,267,995, 31 July.

Reiter, W.J., Pycha, A., Schatzl, G., Pokorny, A., Gruber, D.M., Haber, J.C., Marberger, M., 1999. Dehydroepiandrosterone in the treatment of erectile-dysfunction: a prospective, double-blind, randomized, placebo-controlled study. Urology 53, 590–595.

Shao, Y., Poobrasert, O., Kernelly, E.J., Chin, C.K., Ho, C.T., Huang, M.T., Garrison, S.A., Cordell, G.A., 1997. Steroidal saponins from *Aspargus officinalis* and their cytotoxic activity. Planta Med. 63, 258–262.

Sonda, P.L., Mazo, R., Chancellor, M.B., 1990. The role of yohimbine for treatment of erectile-impotence. J. Sex Marital Ther. 16, 15–21.

Waynberg, J., 1990. Contributions to the Clinical Validation of the Traditional Use of *Ptychopetalum* species. Presented at the 1st International Congress on Ethnopharmacology. Strasbourg, France, June 5–9.

Zaher, T.F., 1998. Papaverine plus PGE_1 versus PGE_1 alone for intracorporeal injection therapy. Intl. Urol. Nephrol. 30, 193–196.