

Erectile dysfunction

Recommending non-prescription ED remedies: Is OTC OTT?



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Over the counter (OTC) preparations are widely available for nearly every condition you care to think of and erectile dysfunction (ED) is no exception. So what do we tell our patients when asked if they are beneficial? The simple answer is that most (but not all) OTC preparations, whilst

having some rationale that may suggest they have a role in the treatment of a specific disorder, have not been subject to rigorous trials that can enable healthcare professionals to confidently recommend them. Moreover, we are also not in a position to comment scientifically upon their safety. Thus recommending drugs OTC is probably OTT ('over-the-top'). This quarter's section highlights two articles at each end of the OTC spectrum.

Supporting OTC preparations

It is now well known that there is a complex link between insulin resistance, vascular dysfunction and inflammation, and oxidative stress. Uncertainty remains as to which is the initiating factor although many believe it is the development of oxidative stress that is the primary insult.¹ It is not surprising therefore that ED, which is associated with vascular abnormalities, is so common in diabetes. Thus any compound that

has anti-oxidant properties may be beneficial in treating both ED and diabetes. Ryu et al (see below) have examined the anti-oxidant and free radical-scavenging effects of ginseng (using Korean red ginseng [KRG]) upon erectile function in diabetic rats. Of those diabetic rats fed KRG, there appeared to be a preservation of erectile function and cavernous malondialdehyde/ glutathione levels (markers of lipid peroxidation and free radical-scavenging activity) compared with the diabetic rats fed a normal diet. Thus the authors appropriately concluded that oxidative stress in cavernous tissue may contribute to ED, and that KRG and other anti-oxidative compounds are worthy of further investigation in its treatment.

Tarnishing OTC preparations

Conversely Fleshner et al (see right) examined seven herbal products that were marketed for the treatment of ED, available through the internet or local health food stores. Although these products had been marketed as natural products devoid of adverse effects, two of these preparations were found to contain pharmacological doses of either sildenafil or tadalafil, which could have precipitated serious unwanted adverse events in susceptible patients.

It would appear therefore that whilst some OTC products may have inherent benefit, there is significant risk in recommending them at present given the comparatively relaxed attitude to their regulation.

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PDE-5 inhibitors found in herbal ED products

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 In North America, regulatory authorities consider herbal products to be food; as such, these products are not subject to the same rigorous approval processes as pharmaceutical products.

2 In this study, seven brands of herbal tablets or capsules marketed for erectile dysfunction (ED) were purchased.

3 Blinded analysis for contamination with sildenafil, tadalafil or vardenafil was carried out using high-performance liquid chromatography and mass spectrometry.

4 Of the seven products tested, one was found to have pharmacological doses of sildenafil (mean, 30.2 mg per capsule), while another had pharmacological doses of tadalafil (mean, 19.77 mg per tablet).

5 No contamination with vardenafil was found.

6 The fact that the pharmaceutical products do not occur naturally led the authors to the conclusion that there must have been deliberate contamination.

7 Given that the pharmaceutical products detected have been shown to have potentially fatal interactions with nitrates, it is clearly of concern that herbal products for ED are being marketed as free of adverse effects.

8 The authors stress the need for improved regulation of natural health products.

Fleshner N, Harvey M, Adomat H et al (2005) Evidence for contamination of herbal erectile dysfunction products with phosphodiesterase type 5 inhibitors. *Journal of Urology* **174**(2): 636-41

¹Laight DW, Desai KM, Anggard EE, Carrier MJ (2000) Endothelial dysfunction accompanies a pro-oxidant, pro-diabetic challenge in the insulin resistant, obese Zucker rat in vivo. *European Journal of Pharmacology* **402**(1-2): 95-9

UROLOGY

Ginseng shows promise in ED

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 This study examined the effect of Korean red ginseng in 84 male rats.

2 Diabetes was induced using an intraperitoneal injection of streptozotocin 90 mg/kg on day 2 after birth and was classified as either 'short term' (mean period of diabetes, 22 weeks) or 'long term' (mean period, 38 weeks).

3 For both short-term and long-term diabetes, ten rats were fed 30 mg/kg of Korean red ginseng three times weekly for 4 weeks, while 22 were

fed a normal diet; in addition, there were ten age-matched controls for each group.

4 Maximal intracavernous pressure after nerve stimulation was significantly lower ($P < 0.01$) in diabetic rats fed a normal diet, in either group, than in age-matched controls.

5 In contrast, erectile function was not impaired in diabetic rats fed Korean red ginseng in either group.

6 Additionally, assessment of malondialdehyde (an index of oxidative stress) and glutathione (an indicator of free radical scavenging) suggested that antioxidant activity of Korean red ginseng may be responsible for the observed preservation of potency.

Ryu JK, Lee T, Kim DJ et al (2005) Free radical-scavenging activity of Korean red ginseng for erectile dysfunction in non-insulin-dependent diabetes mellitus rats. *Urology* **65**(3): 611-5

‘Glutathione levels were significantly lower in men with diabetes and ED than in men without diabetes but with ED.’



Consensus study stresses need to assess and manage CV risk factors in ED

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The relationship between erectile dysfunction (ED) and

cardiovascular (CV) disease has been highlighted by recent studies.

2 A consensus study from the *Second Princeton Consensus Conference* examined a CV risk stratification algorithm developed by the First Princeton Consensus Panel.

3 The importance of assessing and managing CV risk factors for all men with ED was stressed.

4 It is noted that there is growing evidence to support lifestyle intervention in men with ED.

Kostis JB, Jackson G, Rosen R et al (2005) Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *American Journal of Cardiology* **96**(2): 313–21



Gene transfer therapy for ED is found to be safe in a phase I trial

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Gene transfer therapy is a potential alternative to PDE-5 inhibitors for the treatment of erectile dysfunction.

2 This ongoing phase I trial (the first of its kind in humans) aims to investigate the safety of intracavernous injection of *hMaxi-K*, a plasmid vector expressing the *hSlo* gene.

3 Of the 15 men who have so far undergone screening (an independently analysed laboratory examination and physical assessment), six have had treatment approved; three received a 500 µg dose and three received a 1000 µg dose.

4 No treatment-related adverse events have been reported.

5 Germline transmission is another concern, but *hMaxi-K* has not been detected in semen down to the level of 1 copy per µg of total DNA.

6 It is planned to test a 5000 µg dose in three more men.

Melman A, Bar-Chama N, McCullough A, Davies K, Christ G (2005) The first human trial for gene transfer therapy for the treatment of erectile dysfunction: preliminary results. *European Urology* **48**(2): 314–8



Tadalafil 20 mg three times weekly proves efficacious

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 This study (n=4262) was designed to establish the preference of men with erectile dysfunction for tadalafil 20 mg on demand or three times weekly (the authors state that the latter offers a more normal sex life).

2 The treatment protocol consisted of randomisation to one regimen for 5–6 weeks, then a 1-week washout period, and finally cross-over to the other regimen for 5–6 weeks.

3 Both regimens were found to be efficacious and well tolerated.

4 The question ‘Which treatment regimen did you prefer?’ was answered by 3861 men; 57.8% preferred the on-demand regimen of tadalafil, while 42.2% preferred the three-times-weekly regimen.

Mirone V, Costa P, Damber JE et al (2005) An evaluation of an alternative dosing regimen with tadalafil, 3 times/week, for men with erectile dysfunction: SURE study in 14 European countries. *European Urology* **47**(6): 846–54



Glutathione levels depleted in men with ED and type 2 diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 A decrease in the levels of the antioxidant glutathione has been linked to a deterioration of endothelial cell functions; for instance, the associated reduction in nitric oxide synthesis impairs vasodilation in the corpora cavernosa.

2 The hypothesis tested in this study was that glutathione levels are reduced in men with type 2 diabetes and erectile dysfunction (ED).

3 The participants comprised 64 men with diabetes and ED, 20 men with diabetes but without ED, 47 men without diabetes but with ED and 26 men without diabetes or ED.

4 Glutathione levels were significantly lower in men with diabetes and ED (mean, 1670.74±437.68 µmol/l) than in men without diabetes but with ED (mean, 1930.63±581.01 µmol/l; *P*<0.01).

5 Likewise, glutathione levels were significantly lower in men with diabetes and ED (mean, 1670.74±437.68 µmol/l) than in men with diabetes but without ED (mean, 2084.20±118.14 µmol/l; *P*<0.001).

6 In addition, glutathione levels were found to be negatively correlated with fasting blood glucose levels (*r*=−0.34; *P*<0.01) and duration of diabetes (*r*=−0.25; *P*<0.05).

7 The authors use the results to suggest that glutathione administration is a possible treatment consideration for ED.

Tagliabue M, Pinach S, Di Bisceglie C et al (2005) Glutathione levels in patients with erectile dysfunction, with or without diabetes mellitus. *International Journal of Andrology* **28**(3): 156–62

‘57.8% of men asked preferred the on-demand regimen of tadalafil, while 42.2% preferred the three-times-weekly regimen.’