

# Nutrients and Botanicals for Erectile Dysfunction: Examining the Evidence

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## Abstract

Erectile dysfunction affects 50 percent of men ages 40-70 in the United States and is considered an important public health problem by the National Institutes of Health. Consumers are exposed to a plethora of natural products claiming to restore erection and sexual vitality. A review of the available empirical evidence reveals most naturally occurring compounds lack adequate clinical trials to support efficacy. However, arginine, yohimbine, *Panax ginseng*, maca, and *Ginkgo biloba* all have some degree of evidence they may be helpful for erectile dysfunction. Improvements in penile endothelial L-arginine-nitric oxide activity appear to be a unifying explanation for the actions of these naturally occurring agents. (*Altern Med Rev* 2004;9(1):4-16)

## Introduction

Throughout history the erect penis has been a symbol of power and virility.<sup>1</sup> In men the inability to achieve or maintain an erection sufficient for satisfactory sexual function, known as erectile dysfunction (ED),<sup>2</sup> can have a considerable impact on interpersonal relationships and quality of life. The prevalence, cost, and psychosocial impact of ED has been described as an important public health problem by a National Institutes of Health Consensus Panel.<sup>2</sup> Results of a community-based, randomized, observational survey of men conducted from 1987-1989 in cities and towns near Boston, Massachusetts, found 52 percent of men ages 40-70 had some degree of ED. Incidence of complete ED tripled – from 5 to 15 percent – between age 40 and 70, while the

incidence of moderate ED doubled from 17 to 34 percent during this same age span. In addition, 60 percent of men were estimated not to be impotent at age 40, with a decrease to 33 percent by age 70 (Figure 1).<sup>3</sup> From this data, an estimated 30 million men in the United States are affected by some degree of ED.<sup>4</sup> Researchers speculate that as baby boomers grow older and the global population ages, the prevalence of ED will more than double in the next 25 years, possibly affecting more than 330 million men worldwide.<sup>5</sup> The annual cost of ED in the United States, as estimated from the number of physician-related visits in 1985, was \$146,000,000.<sup>3</sup>

Internationally, most men with ED fail to pursue treatment due to the complex nature of sexuality, taboos, cultural restrictions, and acceptance of ED as a normal sequela of aging. Worldwide, an estimated 10 percent of patients with ED seek medical attention.<sup>6</sup> Availability of oral sildenafil (Viagra) in 1998 as the first efficacious oral treatment for ED of various causes has resulted in increased awareness and number of patients seeking treatment. Sildenafil has proven itself a valuable tool in the management of ED, but is not without limitations. While it provides symptomatic relief, it is not a cure, it is costly, and the long-term risks and benefits are unproven.<sup>7</sup> The success of sildenafil has led investigators on a feverish pursuit of other agents that can ultimately

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compete with this synthetic “love drug.”<sup>78</sup> Scientists are beginning to gather empirical data on naturally occurring compounds that have been used historically as agents to increase male sexual function.

Currently, the efficacy of most natural agents remains moderate-to-uncertain. Many natural agents used to treat ED are attractive because they provide health benefits beyond those related to ED and are inexpensive compared to prescription medications. This article explores the empirical evidence related to the efficacy of various orally available natural agents used to treat ED.

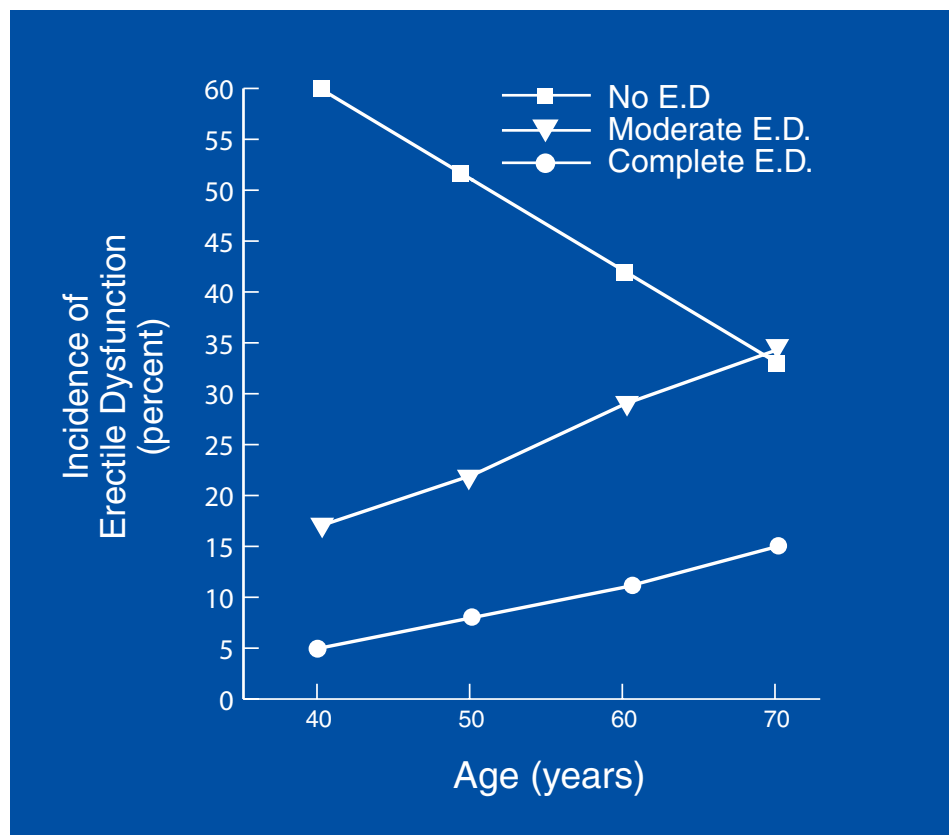
### Physiology of Normal Erection

Leonardo Da Vinci, through his dissection of cadaverous penises, was the first scientist to realize that during an erection the penis fills with blood. During his investigation, Da Vinci wrote, “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 asleep. The penis must be said to have its own mind, by any stretch of the imagination.”<sup>75</sup> Since Da Vinci’s observations 500 years ago, investigators have determined the penis does not have a mind of its own, but is largely under the control of the central nervous system.

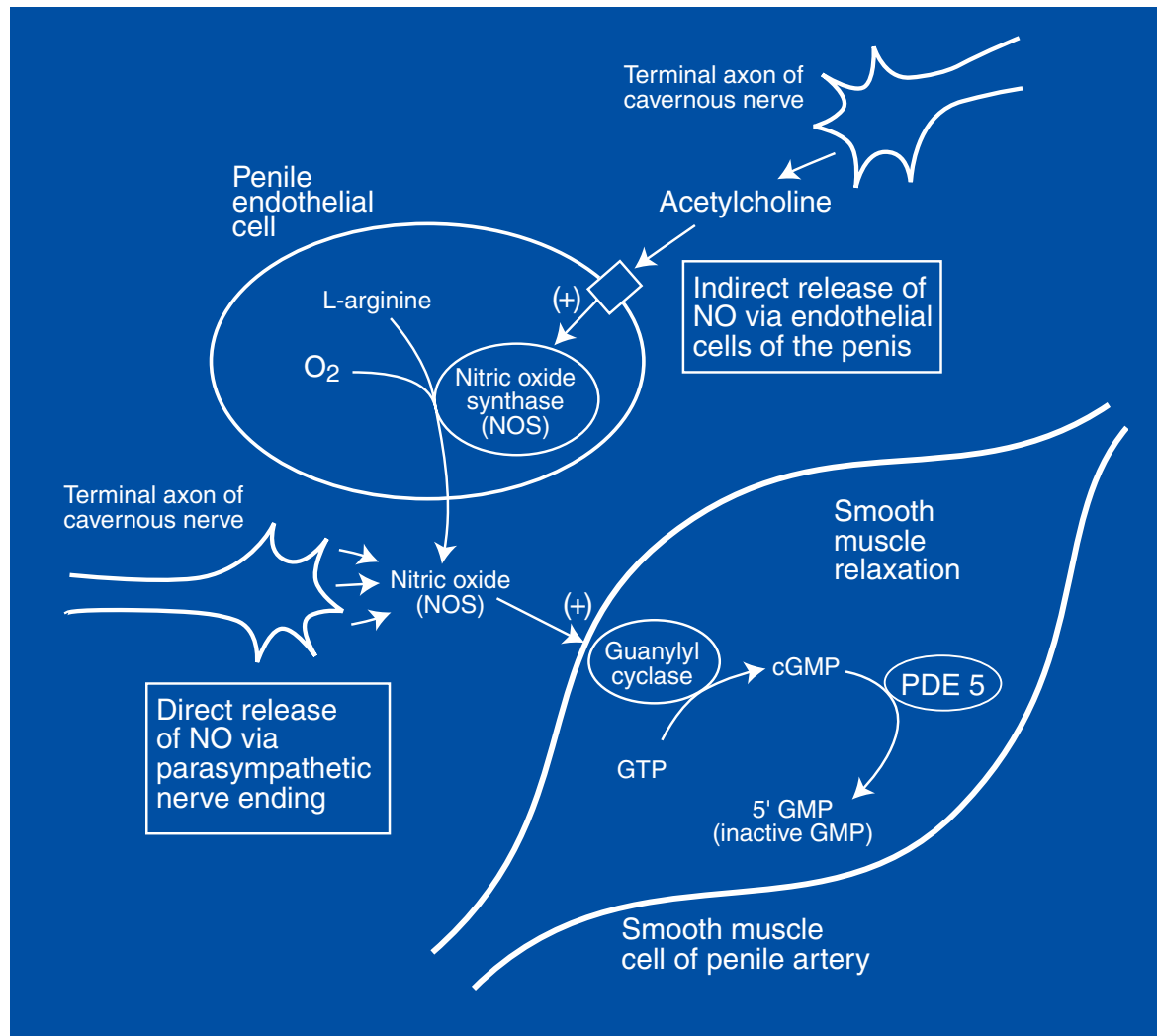
An erection requires intact psychological, neural, and vascular responses and reflects a dynamic balance of excitatory and inhibitory forces. Sexual stimulation causes excitatory signals to originate in the brain, resulting in the terminals of the axons of the parasympathetic nerves releasing

nitric oxide (NO) gas directly and indirectly via endothelial cells in the penis (Figure 2). Simultaneously, the outflow from the sympathetic nerves is inactivated. NO gas diffuses into smooth muscle cells lining the arteries of the corpus cavernosum (spongy erectile tissue) acting as a chemical messenger, which activates guanylate cyclase (GC) within the muscle. Subsequently, GC converts the nucleotide guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP), which raises the intracellular concentration of cGMP. Guanosine monophosphate in turn causes smooth muscles of the penile arteries to relax, causing more blood to flow into the organ. The spongy erectile tissue of the penis becomes engorged with blood, causing compression of the veins that normally drain blood from the penis. Pressure created by the additional blood squeezes the veins until they are nearly closed, trapping blood within

*Figure 1. Incidence of Erectile Dysfunction in Relation to Age*



**Figure 2.** Release of Nitric Oxide into Penile Smooth Muscle directly from Terminal Axon of Cavernous Nerves and via Penile Endothelial Cells



the corpus cavernosum and producing an erection. The erection eventually subsides because cGMP is hydrolyzed by phosphodiesterase type 5 enzymes (PDE5) to inactive GMP.

The sympathetic nervous system is responsible for maintaining the penis in the flaccid state. An increase in activity of the sympathetic nervous system, caused by such things as stress or exposure to cold, stimulates the muscles of the penile arteries to contract allowing blood to escape from the penis. Conversely, a reduction of sympathetic nervous system activity enhances

erection. During REM sleep when the sympathetic nervous system is turned off, pro-erectile pathways predominate resulting in a nocturnal erection. Nocturnal erections are thought to serve as a sort of penis maintenance by providing a flush of oxygenated blood to re-energize the organ.<sup>5</sup>

A quality erection is crucial to reproduction and perpetuation of the human species. It is so critical for procreation that the capacity to create an erection has been wired into the nerve circuits at the base of the spine. The ability to generate an erection can be preserved in men with spinal cord injuries where communication between

the brain erection generating centers and the spinal cord is lost.<sup>5</sup> Physical stimulation of the penis sends sensory signals via the pudendal nerve to the erection-generating center located in the sacral segments of the spinal cord. The incoming signals activate interneurons, which then stimulate the parasympathetic neurons to release NO gas into smooth muscle cells that line arteries of the corpus cavernosum. The NO gas diffuses into the smooth muscle and triggers an erection. If this reflex arc remains intact an erection is possible.<sup>5</sup> While Da Vinci incorrectly predicted the penis has a mind of its own, it does have the ability to function independently from the brain.

### Testing Substances for Erectile Activity

Any compound that promises sexual potency has the potential to be extremely profitable. Drug and health food stores are loaded with agents purported to alleviate male sexual problems. Much of the perceived benefit of available products is based on popular or cultural belief and personal testimonials. Several natural compounds that have been used for centuries as agents to improve male sexual function are now the subjects of scientific investigation. Unfortunately, there is no accepted uniform method for identifying substances that enhance male erectile function.

The isolated rodent corpus cavernosum is a common model used to assess erectile activity of compounds. Strips of smooth muscle isolated from rabbit or rat corpus cavernosum are mounted in an organ bath. The strips of muscle are allowed to equilibrate in physiologic salt solution. The muscle is pre-contracted with phenylephrine and the relaxation of the muscle is measured after the addition of successive amounts of the test substance. Relaxation of the cavernosum is considered a positive result for the test substance.

Other animal models to assess ED activity include observations of rodent behavior when given various doses of test substance. Studies cite increases in sexual responsiveness (as defined by a decreased latency to onset of erection), increase in frequency of copulatory attempts (indicative of sexual arousal), and decreased latency to

ejaculation (measure of performance). Other copulatory behaviors include male rat orientation toward receptive female rats (anogenital sniffing, licking, and mounting), the environment (climbing, raring, exploration), and themselves (nongenital and genital grooming).

Current animal models do not provide an accurate method of assessing ED activity of new compounds. Animal models do not allow for human cerebral aspects of sex to be evaluated and rely only on the basic mechanical or instinctive sexual functions observed in animals. In addition, human trials for ED can be difficult to interpret because most include some degree of subjective self-evaluation. Despite complications in assessing ED activity of various compounds, randomized, controlled trials are generally considered the most accurate technique for determining causality.

### Natural Agents Used to Treat ED *Arginine*

L-arginine is the biologic precursor of NO, which is involved in a variety of endothelium-dependent physiologic effects.<sup>9</sup> Impaired endothelial L-arginine-NO activity has been demonstrated in atherosclerotic coronary arteries in humans and animal models.<sup>10-13</sup> Impaired penile endothelial L-arginine-NO activity also appears to play a role in the pathogenesis of ED.<sup>14</sup> Similar mechanisms have been established for alterations in L-arginine-NO pathways for both ED and atherosclerosis, supporting the concept there is a reduction in NO bioavailability contributing to vascular changes in both conditions.<sup>15</sup>

The prevalence of ED among men with ischemic heart disease is approximately 75 percent.<sup>16</sup> In addition, ED is associated with other conditions, including hypertension, dyslipidemia, diabetes, and smoking.<sup>17-19</sup> It has been hypothesized that vasculogenic erectile function is a manifestation of atherosclerosis and that the endothelial L-arginine-NO pathway provides a unifying explanation for such an association.<sup>15</sup> The risk of moderate or complete ED in patients with cardiovascular risk factors was 11 percent higher than in an age-matched, disease-free control

cohort.<sup>3</sup> Studies have also shown correlations between the presence of ED and clinical or subclinical ischemic heart disease. Anderson et al demonstrated that patients with severe vasculogenic ED (assessed by duplex sonography) had a 16-percent risk of suffering severe, although asymptomatic, ischemic heart disease.<sup>20</sup> Greenstein et al found correlations between ED and the number of coronary vessels occluded on angiography.<sup>21</sup>

Human clinical trials of L-arginine for ED have yielded mixed results. In one small, uncontrolled trial of men with ED who were administered 2.8 g arginine per day for two weeks, positive results were demonstrated. Forty percent of men in the treatment group reported improvement, compared to none in the placebo group.<sup>22</sup> In a larger, double-blind trial, 50 men with confirmed ED were administered 5 g L-arginine per day or matching placebo for six weeks. Thirty-one percent of patients taking L-arginine reported a significant subjective improvement in sexual function, while objective variables assessed remained unchanged. All patients reporting subjective improvements had had initially low urinary NO excretion, which had doubled by the end of the study.<sup>23</sup> It can be speculated that L-arginine may be more effective in ED patients with alterations in endothelial L-arginine-NO activity and a reduction in NO availability.

Researchers interested in further investigation of the effect of endogenous NO for ED found significant improvement in men given a combination of oral pycnogenol (oligomeric proanthocyanidins; OPCs) from pine bark and L-arginine. Pycnogenols have been shown to stimulate the enzyme nitric oxide synthase (NOS) for enhanced production of NO.<sup>24</sup> The combination of pycnogenol and L-arginine is thought to have a synergistic effect on the production of NO by stimulating activity of NOS with pycnogenol and providing the substrate for this enzyme with arginine. The three-month trial consisted of 40 men, ages 25-45. During the first month patients received only 1.7 g L-arginine daily; the second month 40 mg pycnogenol twice daily was added to the protocol; during the third month the dosage

of pycnogenol was increased to 40 mg three times daily. After the first month five percent of patients experienced a normal erection. The following month, with the addition of 80 mg pycnogenol, 80 percent of men reported normal erection, and after the third month of treatment this increased to 92.5 percent. These men also experienced a decrease in time until erection developed in response to stimulation, as well as extended duration of erection.<sup>25</sup>

The majority of studies using L-arginine to treat ED show positive treatment results. One that did not was a randomized, placebo-controlled, crossover comparison of 1.5 g L-arginine daily versus placebo.<sup>26</sup> Patients were treated with 500 mg L-arginine three times daily or matching placebo for 17 days. After a seven-day washout period the L-arginine and placebo groups were switched. The dose of L-arginine in this study, however, was smaller than previous positive studies.

The notion that ED and ischemic heart disease may not occur coincidentally in the same patients is clinically relevant. Although the data on efficacy of L-arginine is mixed, it appears to benefit a limited number of patients. It would appear to be of greatest benefit in patients with alterations in endothelial L-arginine-NO activity and a reduction in NO availability. Patients with concomitant ED and ischemic heart disease might doubly benefit from treatment with L-arginine and increased NO availability. Supplementation with L-arginine on a regular basis may increase sexual function as well as improve other aspects of vascular disease. Patients who respond positively to L-arginine have the added benefit of spontaneous response to their partner's stimulation without the necessity of taking a prescribed pill in advance.

### ***Yohimbine***

Yohimbine is an alkaloid derived from the African tree, *Pausinystalia yohimbe*. Yohimbine has been used as a pharmacological agent in the treatment of ED for over 70 years. The drug is pharmacologically characterized as an alpha-2-adrenergic receptor antagonist. Its activity is mediated by blocking presynaptic alpha-2-

adrenergic receptors in the brain. Through a reduction of brain and spinal cord norepinephrine levels the sympathetic inhibitory tone that suppresses sexual arousal is blocked. A blockade of presynaptic alpha-2 adrenergic receptors by yohimbine subsequently enhances NO release from the penile nerves.<sup>27</sup>

Studies in animals have shown yohimbine has a positive effect on male sexual performance.<sup>28,29</sup> Human studies have also shown an advantage of yohimbine over placebo.<sup>30-33</sup> Although yohimbine appears to have therapeutic benefit, it has not yet been subjected to scientifically rigid human clinical trials. There have been fewer than a dozen controlled human trials of yohimbine for ED and most of them lack sufficient power for credible statistical analysis. In addition, clinical trials of yohimbine have been criticized for having methodological problems and inconsistent data.<sup>34</sup>

A systematic review published in 1998 of rigorous controlled trials of yohimbine for erectile dysfunction concluded yohimbine is a reasonable therapeutic option that should be considered as an initial pharmacological intervention.<sup>35</sup> In this review, studies were only considered for analysis if they were randomized, placebo-controlled, double-blind clinical trials with adequate statistical evaluation. Without exception, the seven trials evaluated suggest yohimbine is relatively safe and more effective than placebo. It was further concluded its cost and oral administration make it an attractive therapeutic option.

One of the more exceptional trials was a multicenter, double-blind, crossover study of 61 men with ED. Participants received 5.4 mg yohimbine hydrochloride three times daily for eight weeks or placebo. Subsequently, they were crossed over for another eight weeks. After the first eight weeks of treatment 36.7 percent of the treatment group and 12.9 percent of the placebo group reported restoration of erection. In the placebo group this figure rose to 41.9 percent after crossover to drug.<sup>36</sup>

A second notable study was a partial crossover study on 82 patients with ED. Participants received tablets of 5.4 mg yohimbine

hydrochloride or placebo. Initially the dose was one tablet four times daily, which was increased by one tablet daily to a maximum of two tablets four times daily. After one month placebo-treated patients were crossed over to yohimbine and yohimbine patients continued in the same manner. If adverse effects occurred, dosage was reduced by one tablet per day until side effects diminished. After one month of treatment 14 percent of the treatment group experienced full-stimulated erections, 20 percent had a partial response, and 65 percent reported no improvement. Three patients reported a positive placebo effect.<sup>37</sup> It took two to three weeks to establish a therapeutic effect and patients responded regardless of the etiology of ED.

Despite controversy regarding yohimbine's efficacy, it has a long history of use and encouraging preliminary research findings. Basic pharmacological and animal research information regarding yohimbine has been available for 15 years, yet it has not generated appreciable scientific and/or financial interest. One expert opinion suggests yohimbine has not captured the attention of the research community because it is an old drug that has no patent protection or commercial viability.<sup>38</sup>

Yohimbine's action on alpha-2-adrenergic receptors is not limited to erectile function and can therefore cause headache, sweating, agitation, hypertension, and sleeplessness. Long-term toxicological and carcinogenicity studies of yohimbine are not available.<sup>39</sup> Yohimbine is reportedly contraindicated in patients taking tricyclic antidepressants, phenothiazines, antihypertensive agents, or central nervous system stimulants.<sup>40</sup>

The documented, yet modest beneficial effect of yohimbine should not exclude it from the erectogenic armamentarium. Yohimbine's action on alpha-2-adrenergic receptors and subsequent enhancement of NO release by the penile arteries suggest the possibility it may work synergistically with other agents that increase NO bioavailability. Leuret et al demonstrated that on-demand administration of 3.25 g L-arginine and 6 mg yohimbine, administered 1-2 hours before intended sexual intercourse, significantly improved

erectile function in patients with mild-to-moderate ED.<sup>41</sup> Such results provide hope that continued interest in yohimbine can eventually lead to its proper evaluation as an agent for ED alone and in combination with other agents.<sup>38</sup>

### *Panax ginseng*

For 2,000 years *Panax ginseng* has had a rich medicinal history. Practitioners of Chinese medicine use it as a tonic and restorative to promote health and longevity. It has been prescribed to improve stamina, concentration, stress resistance, and work efficiency in the healthy as well as to improve well-being in patients with degenerative conditions associated with old age and chronic disease.<sup>42</sup> The tonic and adaptogenic activity of *Panax ginseng* is thought to enhance physical performance, which includes sexual stamina.

Laboratory studies of *Panax ginseng* have shown it may improve vascular endothelial abnormalities by increasing the production of NO. Several studies suggest *Panax ginseng* possesses antioxidant and organ-protective action associated with enhanced NO synthesis in the endothelium of the lung, heart, kidney, and corpus cavernosum.<sup>43-45</sup> The principal active constituents of *Panax ginseng* are thought to be the saponin glycosides, ginsenosides. Ginsenosides have been shown to cause a dose-dependent relaxation of the corpus cavernosal smooth muscle in rabbits by increasing release of nitric oxide.<sup>46-49</sup>

Clinical studies have also supported the use of *Panax ginseng* to assist the phallosodynamically challenged. Choi et al demonstrated *Panax ginseng* was superior to placebo for the treatment of ED. Ninety patients were divided into three groups and given *Panax ginseng*, placebo, or trazodone orally. Frequency of intercourse, premature ejaculation, and morning erections after treatment were unchanged in all three groups. However, in the *Panax ginseng*-treated group a significant improvement in erectile parameters such as penile rigidity, girth, duration of erection, improved libido, and patient satisfaction were reported. No changes in serum testosterone were observed. The overall therapeutic efficacy

on erectile dysfunction was 60 percent for the *Panax ginseng* group and 30 percent for the trazodone and placebo groups.<sup>50</sup>

A more recent, double-blind, placebo-controlled, crossover study produced data showing *Panax ginseng* is an effective alternative for treating ED. Forty-five men diagnosed with ED were randomized and received either 900 mg *Panax ginseng* or placebo (starch capsule with ginseng flavor) three times daily for eight weeks. The first eight weeks of treatment were followed by a two-week washout period, after which the patients received crossover treatment of placebo or *Panax ginseng* for another eight weeks. Treatment efficacy was determined based on changes observed in indexes of erectile function, including the International Index of Erectile Function (IIEF), RigiScan, serum testosterone levels, and penile duplex ultrasonography with audiovisual sexual stimulation.<sup>51</sup>

Mean scores on the IIEF for *Panax ginseng* were significantly higher than for placebo after eight weeks of each treatment. Although the number of patients examined was small, the significant increases in IIEF data have been suggested to represent clinically relevant success. Penile tip rigidity, based on RigiScan parameters, was significantly better after eight weeks of *Panax ginseng* compared to placebo. No significant changes in hemodynamics on duplex ultrasonography with audiovisual stimulation were recorded. No changes in serum testosterone were observed in this or the previously mentioned human trial of ginseng for ED. The authors speculate that therapeutic efficacy of *Panax ginseng* for ED is not mediated through improvements in hemodynamics alone or a hormonal effect, but through multiple mechanisms that have not yet been completely elucidated.<sup>51</sup>

From the available data it appears *Panax ginseng* may possess the ability to improve erectile function. Preliminary conclusions suggest its primary mechanism is mediated through increased NO levels, resulting in improved penile hemodynamics. This mechanism suggests therapeutic success of *Panax ginseng* for the treatment of ED may be dependent on the presence

of impaired endothelial L-arginine-NO activity. Although *Panax ginseng* activity is modest in comparison to the current treatments of choice for ED, the possibility of increased erectile capacity, if used in concert with other mediators of NO production, should be further investigated.

### *Maca*

*Lepidium meyenii* (maca) is a root vegetable cultivated in the central Peruvian Andes that belongs to the brassica (mustard) family. Dried maca root is rich in amino acids, iodine, iron, and magnesium. Traditionally maca root has been used in the Andean region for its supposed aphrodisiac and/or fertility-enhancing properties.<sup>52</sup> Modest empirical support exists for its ability to improve male sexual function.

Rodents studies suggest maca may improve sexual behavior.<sup>53-55</sup> Scientific studies on humans are limited to one randomized, double-blind trial published in a Peruvian journal. The trial showed maca improved subjective evaluation of sexual desire in 57 men treated with 1.5 or 3.0 g maca for 12 weeks compared to placebo. No other information on this trial was attainable.<sup>56</sup>

The same Peruvian researchers followed up with an investigation of the affect of maca on serum testosterone levels. It was demonstrated that the same doses of maca (presumably doses effective for improving male sexual function) administered in healthy men did not affect serum testosterone levels. Doses of 1.5 or 3.0 g maca for 12 weeks in healthy males also produced no more side effects than placebo.<sup>57</sup>

Maca is a nutritious herbal health supplement with positive effects on overall health and nutritional status. Its continued use by Peruvians for several thousands of years as a nutritious root vegetable establishes ample evidence of safety. Specific data relating to its therapeutic value as a specific prosexual or erectile-enhancing agent is minimal.

### *Ginkgo biloba*

Recent research suggests *Ginkgo biloba* can be used to ameliorate antidepressant-induced sexual dysfunction. The notion that Ginkgo may benefit ED started with the observation that male geriatric patients on Ginkgo for memory enhancement reported improved erections.<sup>58</sup> Sexual dysfunction in these patients was determined to be secondary to antidepressant medications.

The mechanism of antidepressant-induced ED appears to be related to the therapeutic activity of selective serotonin reuptake inhibitors (SSRIs). One of the main roles of the central nervous system (CNS) in human sexual response is to suppress erections through the sympathetic nervous system and a cluster of neurons known as the paragigantocellular nucleus (PGN). The PGN neurons send signals down their axons to the erection-generating center in the spine. There the PGN neurons release serotonin, which acts as a chemical messenger within the erection-generating center that suppresses erections by inhibiting the effects of pro-erectile neurotransmitters.<sup>5</sup> As a result, NO synthase is inhibited and NO release into penile smooth muscle is reduced. Millions of Americans take SSRI drugs that work in part by increasing CNS levels of serotonin. It has been proposed that, by increasing the level of serotonin in the CNS, pro-erectile physiologic mechanisms are inhibited.<sup>59</sup>

An open trial of Ginkgo to alleviate antidepressant-induced sexual dysfunction found Ginkgo to be 76-percent effective in alleviating symptoms related to all phases of the sexual response cycle in men, including erectile function.<sup>58</sup> Thirty men were prescribed 40- or 60-mg capsules of Ginkgo to be taken twice daily, titrated up to 120 mg twice daily, as tolerated. The average dose was 207 mg daily. All patients remained on antidepressant medication. After a four-week trial period patients were evaluated for changes in sexual function based on clinical interview and self-reporting assessment by the patient. This initial investigation of Ginkgo for SSRI-induced sexual dysfunction suggested a positive response.



Subsequent trials have been less convincing. In 1999 Wheatly et al published an open trial to investigate the effect of Ginkgo on antidepressant-induced sexual dysfunction. Twenty-four patients (12 men and 12 women) reported significant improvement in sexual response after both three and six weeks of use. This trial provides little data to assess efficacy of Ginkgo for ED. There was substantial variability among responses, with both ends of the spectrum represented – two patients reported complete restoration of sexual function and two others reported no response at all.<sup>60</sup>

In 2000 Ashton et al presented minimal data to support the use of Ginkgo for sexual dysfunction related to antidepressant use. Improvement from Ginkgo was found in only three of 13 women tested and no improvement was reported in nine men.<sup>61</sup>

Subsequently, in 2002 the first placebo-controlled, double-blind trial of Ginkgo for antidepressant-induced sexual dysfunction reported no statistically significant difference in sexual function between Ginkgo and placebo. Thirty-seven patients were randomized to receive placebo or 120 mg Ginkgo daily for the first two weeks and 160 mg for the second two weeks; 240 mg was dispensed for four weeks thereafter. A questionnaire was used immediately before the medication and at weeks 2, 4, and 8 following the medication.<sup>62</sup> Ginkgo showed no statistical difference from placebo after medication.

Elevated serotonin in the CNS is thought to inhibit the effects of pro-erectile neurotransmitters in the erection-generating center of the spine. This in turn decreases the activity of NO synthase and reduces NO availability to penile smooth muscle cells. Ginkgo is presumed to mitigate the effects of SSRIs on sexual function by increasing NO availability. Marcocci et al has shown Ginkgo can strengthen the activity of NO synthase, presumably bypassing serotonin's ability to block NO production.<sup>63</sup> Chen et al has shown Ginkgo's success in the treatment of ischemia-induced cerebral dysfunction<sup>64</sup> may be mediated via NO release from both the endothelium and perivascular nitrergic nerves of the cerebral arteries.<sup>65</sup>

In addition, several studies conducted on isolated rabbit aorta have shown Ginkgo induced a dose-dependent relaxation of vascular smooth muscle.<sup>66-68</sup> Jae-Seung and Jin Haeng showed Ginkgo extract exhibited a relaxing effect on isolated human and rodent corpus cavernosum tissue.<sup>69</sup> Collectively, this evidence suggests Ginkgo has vascular smooth muscle relaxing activity in the heart, brain, and penis, and it appears NO activity provides a unifying association for Ginkgo's effects. Increasing NO bioavailability may not only improve sexual function and vascular health, but may positively impact other age-related chronic diseases.

Although there is minimal evidence for the use of Ginkgo alone for the treatment of ED, it may improve overall vascular perfusion by increasing NO availability. Ginkgo may not be the "magic bullet" for ED patients, but it may have a place in "whole patient" management of ED.

### *DHEA and Tribulus terrestris*

The most current epidemiological study on the prevalence of ED in the United States demonstrated an inverse relationship between serum levels of dehydroepiandrosterone (DHEA) and the incidence of erectile dysfunction.<sup>3</sup> A logical relationship exists between the increase in the prevalence of ED with increasing age,<sup>3</sup> decrease of serum DHEA levels with increasing age,<sup>70</sup> and the inverse relationship between serum DHEA levels and the incidence of ED found in the Massachusetts Male Aging Study.<sup>3</sup> The question remains if oral DHEA treatment will benefit patients with ED.

A double-blind, placebo-controlled study of 40 men with ED and low DHEA levels found DHEA at a dose of 50 mg daily for six months improved sexual performance. Efficacy of DHEA was defined as the ability to achieve or maintain an erection sufficient for satisfactory sexual performance according to the National Institutes of Health Consensus Development Panel on Impotence. The patient database was considered too small to do relevant statistical analysis.<sup>71</sup>

Despite minimal evidence supporting the clinical use of DHEA for ED, Bulgarian researchers have proposed that protodioscin extracted from the plant *Tribulus terrestris* improves erectile function via increasing DHEA levels. An abstract published in the *International Journal of Andrology* states, "Protodioscin is a phytochemical agent derived from *Tribulus terrestris* plant, which has been clinically proven to improve sexual desire and enhance erection via the conversion of protodioscine to DHEA ...."<sup>72</sup>

Several studies of questionable worth are used to support the pro-erectile effects of Tribulus. According to this research, oral Tribulus increases serum DHEA,<sup>73</sup> increases sexual function in men,<sup>74</sup> exhibits a pro-erectile effect in isolated rabbit corpus cavernosum,<sup>75</sup> and improves sexual behavior and intracavernous pressure in rats.<sup>76</sup>

Well-controlled clinical trials regarding the effects of DHEA or potential precursors to DHEA such as protodioscin are nonexistent. Due to the absence of quality research on DHEA and *Tribulus terrestris* there is minimal information regarding the long-term safety or efficacy of these agents when used to treat ED. Pro-sexual activity of these agents via increased steroid hormone production is plausible, but a clear causative relationship is yet to be determined.

## Conclusion

Adequate clinical evidence to support natural agents for the management of ED is minimal and the compounds discussed here appear to have only a modest effect. Sildenafil offers the first orally effective symptomatic treatment of ED. Oral sildenafil therapy, while effective in circumventing the cause of ED, provides only short-term symptomatic relief of the condition. Whole patient management of ED might also include psychological or relationship counseling, treatment of associated underlying chronic conditions, and the use of natural agents shown to improve derangements in penile endothelial L-arginine-NO activity. Oral supplementation with L-arginine, yohimbine, *Panax ginseng*, *Ginkgo biloba*, and maca root all appear to benefit penile endothelial L-arginine-NO activity. These substances are far

from providing a "magic bullet" or cure for ED. Practitioners and consumers should not be fooled by unsubstantiated claims made by the manufacturers of natural agents to treat ED. However, these natural agents should not be omitted from the erectogenic armamentarium. L-arginine, yohimbine, *Panax ginseng*, *Ginkgo biloba*, and maca root may provide moderate benefit while affecting underlying endothelial dysfunction that contributes to ED. If effective, these agents have the added benefit of allowing patients to respond spontaneously to their partners.

Raising the penis from a dependent position to an erect position is a complex neurovascular event modulated by psychological factors and hormonal status. For men, a rigid penis is the centerpiece of successful reproduction. Aside from its importance in reproduction, an erect penis provides pleasure, bolsters self-esteem, allows one to foster intimacy, and can act as a means to reduce stress. Erectile dysfunction is an important public health problem affecting over half of all men ages 40-70. Currently, the majority of research pertaining to ED is focused on the mechanics of penile erection. Limiting the treatment of ED to the mechanics of erection can be compared to fixing an active smoke detector by removing the battery. The cause of the condition is left ignored. We are still far from understanding how to permanently reverse some of the fundamental physiological derangements underlying ED. Truly successful treatment strategies for ED must include the interplay between the mind and the nervous, vascular, and endocrine systems that results in erection. As scientists gain increasing insight into the brain's role in controlling sexuality and the complex mechanics of erections, there is a movement toward a more holistic view of male sexual well being.

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