Review Article

Scientific Medicine in Integrative Treatment of Erectile Dysfunction

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Abstract

Due to the increase in erectile dysfunction (ED) and infertility in world population, there is growing interest in the integrative treatment of these diseases. Therefore, it is raising a market with non-prescription natural supplements. Especially in menu of internet, online shops come increasingly to light new natural over the counter products. Recent sale and use of medicinal plants and their extracts in the treatment of ED are according to the declaration of the producers first of all on a number of the thousand-year-old traditions in some nations, based on the efficacy and safety of these plants, verified in the long-time healing practice. The aim of this article was to make an extensive review of the scientific and professional medical literature and to find out which medicinal plants, minerals and other active substances, sold in the natural products for ED, were evaluated in relevant clinical trials as statistically significant in their efficacy and safety. The review of the literature shows that some marketed medicinal plants and active substances lack clinical studies, the results of some clinical studies related to the same medicinal plant are controversial and some bring significantly positive effects, but their number is minimal (maximum two to five clinical studies). The future is therefore open to starting the number of new clinical trials testing the medicinal plants for the treatment of ED with possible inclusion of some of these plants in evidence-based medicine, if confirming their efficacy and safety.

Key words: Erectile dysfunction, integrative medicine, medicinal plants, minerals, magnesium, natural therapy, selenium, zinc

INTRODUCTION

Erectile dysfunction (ED) currently affects not only men in andropause, but also in the reproductive period ranging from 40 years of age; There is no exception that ED occurs in the 40 age group[1], and ED in this age group has a growing trend in the population. The increase of ED can be the whole society problem, because family planning among men in developed countries is usually at the age of 35 to 45 years and can lead to a decline in population growth. Frustration from ED is negatively reflected in family life, which threatens the harmonious family life and also concerns the working life of men leading to reduction in work and professional performance, conditioned by psychical disorders from ED. The motivation to write the review was the rise of non-prescription natural supplements in the world market designed for ED and goal was to find out:

1. Which of these medical plants, their extracts and minerals in sold supplements have been tested for efficacy and safety, particularly in relevant clinical trials;
2. If it is possible with a change in life style and the whole integrative approach to improve or heal the ED?

Recent sale and use of medicinal plants and their extracts in the treatment of ED is mainly according to the declaration of the producers on a number of the thousand-year-old traditions in some nations, based on the efficacy and safety of these plants, verified in the long-time healing practice, and based on the reality that these medicinal plants are used in this nations until today.

The possibilities of bioregeneration in ED with medicinal plants, active substances, minerals, nutrition and exercise

Throughout history, every culture has searched his environment for medicinal plants that might have health benefits. Few of

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these efforts have been more intense than the search for plant substances that enhance sexual desire and performance.

Some of the best of these traditions have survived for thousands of years to be slowly modified or improved over time. The very long-term survival and local popularity of the use of these traditional plants could be an evidence of their relative safety and effectiveness. Effectiveness of these natural active substances was verified by thousand years of healing practice. The Western medicine has largely ignored this knowledge, until recently. Now, it has started a new period in the classical medicine with a new interest in this traditional plant therapy. According to the evidence-based medicine, the goal in this period is to confirm the safety and effectiveness of these medicinal plants with clinical, prospective, controlled double-blind studies.[2]

In the review there are preferred clinical studies against experimental studies, because the thousand-year historical traditional use of medicinal plants had been verified by healing practice on humans and not on animals. Only when they were not published as the clinical study in connection to the natural supplement, they were cited as the experimental study. Here those medicinal plants and active substances are presented which are the most frequently used compounds of the sold natural products for ED. This review contains relevant clinical trials, double-blind prospective controlled trials, where the boostering effect of the medicinal plants, minerals or active substances on erection level was evaluated with objective measurements of qualitative and quantitative variables:

1. Questionnaire — International index for ED,
2. Serum variables (total testosteron, free testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), dehydroepiandrosterone (DHEA), dihydrotestosterone (DHT), estradiol, prostate-specific antigen (PSA) etc...),
3. Spermiogram (sperm count, sperm motility, sperm viability, sperm morphology, ejaculate volume),
4. Uroflowmetric parameters,
5. Measurement of the volume and hardness of erection on the certified devices.

Classification of the medicinal plants, active substances and minterals according to the mode of action on erection

1. Testosterone synthesis boosters: Zinc, *Tribulus terrestris*, saw-palmetto, bark of tree *Aspidosperma quebracho blanco*, vitamin D, *Urtica dioica*, selenium, ginger, ashwagandha, magnesium.
2. Nitric oxide (NO) production boosters, inhibitors of the PDE 5: Panax ginseng, *Butea superba*, *Gingko biloba*, *Epimedium sagittatum*, *Eucommia ulmoides* Oliv., L-arginin, L-citrulin, *Bombyx mori*.
3. Aktivators of estrogen metabolization and degradation (antagonists to xenoestrogens, estrogen balancers): Indol-3-carbinol (I3C), diindolylmethane (DIM), chrysin.

Testosterone synthesis boosters

- Activate the synthesis of DHEA.
- Unbind testosterone from SHBG (sex hormone-binding globulin), raise the free testosterone in blood.
- Act as an aphrodisiac.

Zinc

Significant depletion of the mineral zinc, associated with long-term use of diuretics, diabetes, digestive disorders, and certain kidney and liver diseases, has been shown to lead to ED.[3]

Zinc increases the level of testosterone, improves the sperm mobility and can even improve fertility.[4-6]

Tribulus terrestris

Tribulus terrestris is a flowering plant in the family Zygophyllaceae.

Country of cultivation: Native to warm temperate and tropical regions in southern Asia, throughout Africa and Australia.

Active substance: Steroid saponin, in fruits.

Effect: Diuretic, aphrodisiac, booster of fertility.

Studies with statistical significant effect

The clinical study from Government Ayurveda Medical College in India has shown 78.11% improvement in semen analysis in men with oligozoospermia ($n = 32$) treated with *T. terrestris* supplement.[7]

Another study from Iacano *et al.*[8] evaluated the effect of a new natural compound Tradamixina in order to improve male sexual function in elderly men (libido and erection) *versus* administration of Tadalafil 5 mg daily. The treatment twice a day with Tradamixina (Alga Ecklonia Bicyclis,*T. Terrestris* and other compounds) for 2 months in a double-blind controlled study improved erection and libido in elderly men without side effects of Tadalafil ($n = 35$).

Iacano *et al.*[9] in the next study discovered that the daily treatment with a natural compound Tradamixina plus *Serenoa repens* for 2 months improved the male sexual function, improved uroflowmetric parameters, and decreased serum PSA level ($n = 100$).

Study with no significant effect

Neychev and Mitev[10] from Department of Chemistry and Biochemistry, Sofia, Bulgaria found out that *T. terrestris*

steroid saponins possess neither direct nor indirect androgen-increasing properties. In the sample, there were only 21 men and the authors concluded the article with the statement that the study has to be extended in the clarifying the probable mode of action of *T. terrestris* steroid saponins with sample size greater than 21 probands.

Also, Brown *et al.*[11] could not demonstrate the effectiveness of an androgenic nutritional supplement with *T. terrestris* designed to enhance serum testosterone concentrations and prevent the formation of dihydrotestosterone.

Saw-palmetto berries (Serenoa repens)

Saw palmettos are berries of the American dwarf tree (*Serenoa repens*, *Sabal serrulata*). The plant is found in many areas of the south-eastern United States. These fruits are rich in essential fatty acids and phytosterols. Saw palmetto is used in several forms of traditional herbal medicine, first of all in benign prostatic hyperplasia (BPH) and ED concerted with BPH. American Indians used the fruit for food and to treat a variety of urinary and reproductive system problems. The Mayans drank it as a tonic, and the Seminoles used the berries as an expectorant and antiseptic.[12]

Country of cultivation: USA

Active substance: Phytosterols in berries.

S. repens is an effective dual inhibitor of 5 alpha-reductase isoenzyme activity in the prostate. Unlike other 5 alpha-reductase inhibitors, *S. repens* induces its effects without interfering with the cellular capacity to secrete PSA.[13]

Kohut and co-authors[14] confirmed that the natural supplement (150 mg DHEA, 300 mg androstenedione, 750 mg *T. terrestris*, 625 mg chrysin, 300 mg I3C and 540 mg saw palmetto) significantly increased serum levels of androstenedione, free testosterone, estradiol and dihydrotestosterone (DHT) during week 1 to 4 ($n = 16$).

Studies with no significant effect

According to clinical study of Pyte *et al.*,[15] permixon (extract from *S. repens*) had no effect on the level of PSA. Plasma hormone levels (testosterone, DHT, estradiol, LH, and androstendion) did not change. Nine patients developed 10 side effects but they were unrelated to the treatment.

Also, Kaplan *et al.* and other authors[16,17] have not found appreciable long-term improvement in patients ($n = 64$) treated with saw palmetto. In contrast, patients treated with finasteride showed significant and durable improvement in all various parameters except voiding. No relevant study was done with extract of saw palmeto in connection with ED; despite that it is a compound of many herbal remedies for ED sold in the market.

Aspidosperma quebracho-blanco (bark tree)

Quebracho blanco is a South American tree species.

Country of cultivation: Northern regions of Argentina.

Active substance: 1% alkaloid with Yohimbin und Aspidospermin (in bark of the tree), it is a testosterone synthesis booster and an inhibitor of the the 2-methoxyidazoxam binding to human penile alfa-1 and alfa-2 adrenoceptors.

Sperling *et al.*[18] and Campos *et al.*[19] investigated that an alpha-adrenoceptor-mediated component of the pro-erectile effects of *Aspidosperma quebracho-blanco* bark extract may predominantly be caused by its yohimbine content. No relevant clinical study was done with bark extract of the *A. quebracho-blanco* in connection with ED. In the study of Santos *et al.*[20] acute and subchronic toxicity and cytotoxicity of stem bark ethanolic extract of *Aspidosperma subincanum* (EEAs) have been evaluated. In addition, phytochemical analysis was performed. Using the method of the dose by factor approach, the human safe dose was 210 mg/70 kg/day. EEAs appear to be safe and non-toxic in low doses in domestic preparations used by population having relative security.

As the number of yohimbe products on the retail market increases, concerns about their safety are raised. Reported side effects from yohimbe use include complaints such as headaches, anxiety, tension, high blood pressure, elevated heart rate, heart palpitations, and hallucinations. People with high blood pressure and kidney disease should avoid supplements containing yohimbe. Also, caution should be used when taking yohimbe in combination with certain foods containing tyramine (such as red wine, liver, and cheese) as well as with nasal decongestants containing ephedrine or phenylpropanolamine, which could lead to dangerous blood-pressure fluctuations.[21]

Stinging nettle (Urtica dioica)

Country of cultivation: Native to Europe, Asia, northern Africa, and North America.

Active substance in root: Beta-sitosterol, 3,4-divanillyltetrahydrofuran.

For thousands of years, stinging nettle has been prized by the ancient Romans and Greeks, as well as Native American tribes, to stimulate circulation, support healthy prostates and erection. Stinging nettle (root, lieaves) extracts are known as

lignans that bind with SHBG and so raise the free testosteron level in blood. Stinging nettle normalizes the ratio among free testosteron, SHBG, estrogen, and dihydrotestosteron, because it contains 3,4-divanillyltetrahydrofuran, which increases free testosterone level in blood by occupying sex hormone-binding globulin.[22]

In the experimental study, *U. dioica* significantly boosted motility, count, normal morphology of sperm cells, seminiferous tubules diameter, and the level of testosterone in treated group compared to the control male mice. According to this study, *U. dioica* hydro-alcoholic extract administration could increase the quality of spermatozoa.[23]

The clinical, prospective, controlled study from Safarinejad[24] observed the effect of therapy with *U. dioica* for BPH, patients $n = 558$, placebo group $n = 271$. By intention-to-treat analysis, at the end of 6-month trial, in the *U. dioica* group an improvement was reported in International Prostate Symptom Score (IPSS), in the maximum urinary flow rate (Qmax), the postvoid residual urine volume (PVR) decreased, but serum PSA and testosterone levels were found to be unchanged in both groups.

No clinical study was done with *U. diodica* in treatment of ED.

Vitamin D

Endothelial vascular dysfunction has been demonstrated to play an important role in pathogenesis of ED and vitamin D deficiency is deemed to promote the endothelial dysfunctions. Barassi *et al.*[25] show that a significant proportion of ED patients have a vitamin D deficiency and that this condition is more frequent in patients with the arteriogenic etiology. Low levels of vitamin D might increase the ED risk by promoting endothelial dysfunction. Insufficient levels of vitamin D may spur the production of free radicals called superoxide ions. These free radicals deplete nitric oxide (NO) in vascular cells, a molecule that causes blood vessels to relax. Men with ED should be analyzed for vitamin D levels in blood and by low level of vitamin D supplementation.

Pilz *et al.*[26] investigated in a randomized controlled trial testosteron and 25-hydroxyvitamin D [25(OH)D] level before and after supplmentation of vitamin D in 56 healthy overweight men undergoing a weight reduction program. Compared to baseline values, a significant increase in total testosterone levels (from 10.7 ± 3.9 nmol/L to 13.4 ± 4.7 nmol/L; $P < 0.001$), bioactive testosterone (from 5.21 ± 1.87 nmol/L to 6.25 ± 2.01 nmol/L; $P = 0.001$), and free testosterone levels (from 0.222 ± 0.080 nmol/L to 0.267 ± 0.087 nmol/L; $P = 0.001$) was observed in the vitamin D-supplemented group. By contrast, there was no significant change in any testosterone measure in the placebo group. The results suggest that vitamin D supplementation might increase testosterone levels.

Risk factors associated with a higher CVD (cardiovascular disease) risk also associate with a higher ED risk. Such factors include diabetes mellitus, hypertension, atherosclerosis with Inflammation in the vascular endothelium, and vitamin D deficiency, which is one of several dynamics that associates with increased CVD risk.[27]

Selenium

Selenium (Se) is an essential element involved in normal gonadal development, gametogenesis, and fertilization. Molecular studies show that the gonads actively take up and store Se, most of which is incorporated in the glutathione peroxidase enzymes. Mirone *et al.*[28] provided a systematic review of the original molecular studies, prospective observational data and randomized controlled trials on the role of Se in reproductive function conducted in the past 30 years. A critical appraisal of these findings suggests that Se supplementation produces a bell-shaped response curve, with negative effects observed for both low and high concentrations. The few available clinical trials support the use of Se supplementation (<200 μg/day) to improve male infertility, although their pre-treatment assessment of Se levels in enrolled subjects is inconsistent and their quality and size are insufficient to enable general recommendations. How best to assess Se in terms of cut-off value, sample type (serum, semen, other fluids) and the specific outcome of interest remains to be clarified. In the meantime, assessment of serum Se levels followed by low-dose replacement therapy when necessary is a reasonable approach to improve male idiopathic infertility.[29]

T ürk *et al.*[30] in the clinical study compared the level of zinc, selenium, glutathione peroxidase activity and antioxidant status in following groups of men with infertility:

1. Severe inflammation in prostate (>10(6) white blood cells in prostate secretion; $n = 29$),
2. Severe leukocytospermia, (>10(6) white blood cells in semen; $n = 31$),
3. Mild inflammation, (0.2-1mol/L white blood cells in semen or prostate secretion; $n = 24$),
4. Non-inflammatory oligozoospermia ($n = 32$) and
5. Healthy controls ($n = 27$). Male patients in all groups had reduced level of antioxidative activity, selenium and zinc in their seminal plasma.

The purpose of another study was to investigate how exhaustive exercise affects testosterone levels and plasma lactate in cyclists who were supplemented with oral zinc and selenium for 4 weeks. For this reason, 32 male road cyclists were selected equally to four groups:

1. PL group (placebo);
2. Zn group (zinc supplement — 30 mg/day);
3. Se group (selenium supplement — 200 μg/day); and
4. Zn-Se group (zinc-selenium supplement).

After treatment, free, total testosterone, and lactate levels of subjects were determined before and after exhaustive exercise. Resting total, free testosterone, and lactate levels did not differ significantly between groups, and were found to be increased by exercise ($P > 0.05$). Serum total testosterone levels in the Zn group were higher than in the Se group after exercise ($P < 0.05$). Serum-free testosterone levels in the Zn group were higher than the other groups ($P < 0.05$). There was an insignificant difference between levels of lactate in the four groups after exercise ($P > 0.05$). The results showed that 4-week simultaneous and separately zinc and selenium supplementation had no significant effect on resting testosterone and lactate levels of subjects who consume a zinc and selenium sufficient diet. It might be possible that the effect of zinc supplementation on free testosterone depends on exercise.[31]

Ginger (Zingiber officinale)

Ginger is the rhizome of the plant *Zingiber officinale*, consumed as a delicacy spice.

Country of cultivation: Southern china, Maluku, India, Jamaica, West Africa and the Caribbean.

Active substances in root: Volatile oils (borneol, camphene, citral, eucalyptol, linalool, phenllandrene, zingiberine and zingiberol penols: Gingerol, zingerone and shogaol).

There are many experimental animal studies conducted that have shown that ginger supplementation statistically significantly boosts the testosterone level in blood.[32-35]

But I have found only one clinical prospective controlled study from the University in Tikrit in Iraq.[36] They observed for 3 months the effect of ginger supplementation on semen parameters, serum level of FSH, LH a testosterone in infertile men ($n = 75$), and as a control group they used healthy men ($n = 25$). The researchers did not publish how much ginger the men received or the form in which they were given to consume. The supplementation raised the sperm count (16.2%), the sperm motility (47.3%), the sperm viability (40.7%), the normal sperm morphology (18.4%), the ejaculate volume (36.1%). Serum variables FSH (17.6) and LH (43.2%) significantly increased after treatment as compared to before treatment with ginger; serum testosterone level increased after treatment to 17.7%. The concentration of the toxic malondialdehyde (MDH) in the men's blood decreased and the concentration of the protective glutathione rose. MDH is a marker for free radical activity. This confirms the theory that ginger works above all, probably by activating endogenous antioxidants and by destroying harmful molecules in the testes. The present study recommends the use of ginger by Iraqi community as a food additive.

Ashwagandha (Withania somnifera)

Ashwagandha (Indian ginsneg) is a plant in the Solanaceae or nightshade family. It is used as an herb in Ayurvedic medicine.

Country of cultivation: India, Nepal.

Active substances in roo: Steroidal lactones.

Ashwagandha has been described in traditional Indian Ayurvedic medicine as an aphrodisiac that can be used to treat male sexual dysfunction and infertility. Pilot study from Indian researsches[37] was conducted to evaluate the spermatogenic activity of Ashwagandha root extract in oligospermic patients. Forty-six male patients with oligospermia (sperm count <20 million/mL semen) were enrolled and randomized either to treatment with a full-spectrum root extract of Ashwagandha (675 mg/day in three doses for 90 days) or to placebo in the same protocol. Semen parameters and serum hormone levels (testosterone, LH) were estimated at the end of 90-day treatment. There was a 167% increase in sperm count (9.59 ± 4.37 × 106/mL to 25.61 ± 8.6 × 106/mL;), 53% increase in semen volume (1.74 ± 0.58 mL to 2.76 ± 0.60 mL), and 57% increase in sperm motility (18.62 ± 6.11% to 29.19 ± 6.31%), 17% increase in serum testosterone level (from 4.45 ± 1.41 ng/mL), 34% increase in LH (from 3.97 ± 1.21 mIU/mL) on day 90 from baseline. The improvement in these parameters was minimal in the placebo-treated group. The present study adds to the evidence on the therapeutic value of Ashwagandha, as attributed in Ayurveda for the treatment of oligospermia leading to infertility.

The two experimental studies[38,39] concluded that use of Ashwagandha may be detrimental to male sexual competence and has direct spermatogenic influence on the seminiferous tubules of immature rats presumably by exerting a testosterone-like effect.

Magnesium

A study from Maggio *et al.*[40] with 399 ≥65-year-old men has shown that magnesium intake statsistically significantly affects the secretion of total IGF-1 and increases testosterone bioactivity. This observation suggests that magnesium can be a modulator of the anabolic/catabolic equilibrium disrupted in the elderly people and that magnesium levels are strongly and independently associated with the anabolic hormones testosterone and IGF-1.

The study by Cinary *et al.*[41] was performed to assess how 4 weeks of magnesium supplementation and exercise affect the free and total plasma testosterone levels of sportsmen practicing tae kwon do and sedentary controls at rest and after exhaustion. The testosterone levels were determined at four different periods:

1. Resting before supplementation,
2. Exhaustion before supplementation,
3. Resting after supplementation, and
4. Exhaustion after supplementation in three study groups, which are as follows:

Group 1. sedentary controls supplemented with 10 mg magnesium per kilogram body weight. Group 2. tae kwon do athletes practicing 90-120 min/day supplemented with 10 mg magnesium per kilogram body weight. Group 3. tae kwon do athletes practicing 90-120 min/day receiving no magnesium supplements. The free plasma testosterone levels increased at exhaustion after supplementation compared to resting levels. Exercise also increased free testosterone levels relative to sedentary subjects. Similar increases were observed for total testosterone. The results show that supplementation with magnesium statisticaly significant increases free and total testosteron.

Nitric oxide production boosters, inhibitors of the PDE 5

- *Panax ginseng*,
- *Butea superb*,
- *Gingko biloba*,
- *Epimedium sagittatum*,
- *Eucommia ulmoides* Oliv,
- l-arginin and l-citrulin,
- Extract from male *Bombyx mori*.

The role of nitric oxide in ED

Nitric oxide (NO) is believed to be the main vasoactive nonadrenergic, noncholinergic neurotransmitter and chemical mediator of penile erection. The signal NO is released from central and peripheral nerve endings and from endothelial cells and activates a cascade reaction, which ultimately leads to an increased cellular concentration of cGMP (cyclic guanosine monophosphate). This second messenger molecule induces a series of events that lead to smooth-muscle relaxation through a regulation of the activity of calcium channels as well as intracellular contractile proteins that affect the relaxation of corpus cavernosum smooth muscle [Figure 1a,b].

Based on sexual stimulation there is rise in the central and peripheral neuronal depolarization evoking synthesis of the neurotransmitter — neuronal NO (nNO) in the synapsis, it starts the initiation of the tumescence. The blood inflow to the penile artheries activates the shear stress in the arterial walls and it further activates the production of the endotelial NO (eNO) in the endothelium of the artherial wall. Production of eNO promotes the tumescence up to the physiological erection.[42]

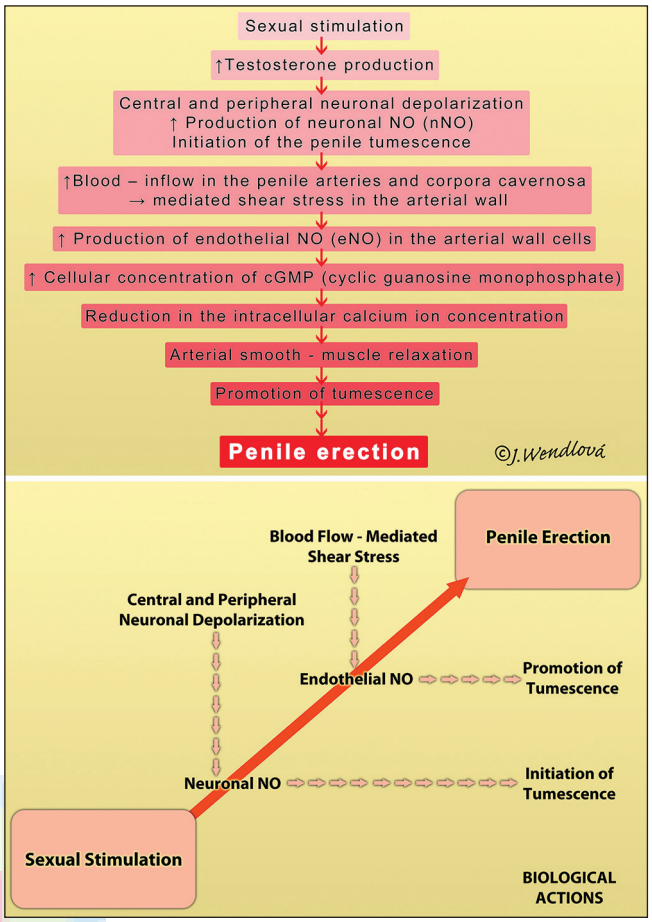

Figure 1: Regulatory mechanism of the physiologycal penile erection

Vascular actions of NO include the following:[42-44]

- Direct vasodilatation (flow dependent and receptor mediated),
- Indirect vasodilatation by inhibiting vasoconstrictor influences (e.g., inhibits angiotensin II and sympathetic vasoconstriction),
- Anti-thrombotic effect — inhibits platelet adhesion to the vascular endothelium, inhibits the platelet aggregation,
- Anti-inflammatory effect — inhibits leukocyte adhesion to vascular endothelium; scavenges superoxide anion,
- Anti-proliferative effect — inhibits smooth muscle hyperplasia.

Panax ginseng

Ginseng is any one of 11 species of slow-growing perennial plants with fleshy roots, belonging to the genus *Panax* of the family Araliaceae.

Countries of cultivation: Ginseng is found only in the Northern Hemisphere, in North America and in eastern Asia (mostly Korea, north-eastern China, Manchuria, Bhutan, and eastern Siberia), typically in cooler climates. *Panax vietnamensis*, discovered in Vietnam, is the southernmost ginseng known.

Active substance: Ginsenosides.

Panax ginseng is a well-known herb in traditional Chinese medicine (TCM). Recently, there have been a number of studies on this herb. For *P. ginseng*, it has been shown to have an anti-inflammatory activity, improves pulmonary function, ED, cognition in patients with Alzheimer's disease and promotes sexual arousal in menopausal women as well as prevents cancer.[45,46] Erectile function of patients ($n = 143$) in the tissue-cultured mountain ginseng extract (TMGE)-treated group significantly improved. The authors suggest that TMGE could be utilized for improving erectile function in male patients.[47] In the Korean experimental study it was shown that the Korean ginseng berry extract GB0710 was more potent in ED than the red ginseng root extract.[48]

Hong *et al*.[49] investigated the efficacy of Korean red ginseng for ED using the International Index of Erectile Function, measurement of the volume and hardness of erection (RigiScan, UroHealth Systems, Laguna Niguel, California), hormonal levels and penile duplex ultrasonography with audiovisual sexual stimulation. A total of 45 patients and 45 controls with clinically diagnosed ED were enrolled in a double-blind, placebo controlled, and crossover study. The ginseng dose was 900 mg three times daily. The data showed significant improvement of all followed variables; the Korean red ginseng can be used as effective alternative for treating male ED.

Jang *et al*.[50] have done a systematic search conducted on 20 electronic databases without language restrictions. Hand-searches included conference proceedings and scientific medical databases. All randomized clinical studies (RCT) of red ginseng as a treatment for ED were considered for inclusion. The searches identified 28 potentially relevant studies, of which 7 met the inclusion criteria. Methodological quality was assessed using the Jadad score. Collectively these RCTs provide suggestive evidence for the effectiveness of red ginseng in the treatment of ED. However, the total number of RCTs included in the analysis, the total sample size and the methodological quality of the primary studies were too low to draw definitive conclusions. Thus, more rigorous studies are necessary.

Butea superba (BS)

Butea superba (BS) is a herb native to Thailand, thought to be an aphrodisiac by locals. It is abundantly distributed in the Thai deciduous forest and has been popular among Thai males for its supposed effects on rejuvenation and sexual vigour.

Country of cultivation: Thailand.

Active substance: Sterols (β-sitosterol, campesterol and stigmasterol), flavonoids and flavonoid glycosides in tuberous roots.

In the controversial study by Cortés-González *et al*.,[51] a natural health product containing BS was found to be more effective than sildenafil in the first part of the clinical study ($n = 32$), but in the second part of the study, using another batch of BS, the positive result could not be repeated and no effect was recorded. The conclusion is that the first preparation of BS was most likely blended with a phosphodiesterase-5 inhibitor, later confirmed by the supplier of BS (a natural health products company) after their own analysis.

In contrast, a 3-month randomized double-blind clinical trial from Thai investigators[52] was carried out in among Thai volunteers with ED. There was a significant upgrading in four of the five descriptive evaluations of the International Index of Erectile Dysfunction-5 (IIEF-5) questionnaire. Estimation of the sexual record indicated that 82.4% of the patients exhibited noticeable improvement. Hematology and blood chemistry analysis revealed no apparent change. The plant preparation appears to improve the erectile function in ED patients without apparent toxicity.

In the scientific literature there is a case clinical repost of Thai male, aged 35 years, without any underlying disease. The chief complaint of this patient was a feeling of increased sexual drive. He gave the history of no use of narcotic and regular intake of vitamin, but he had just taken locally made capsule of herb BS for a few weeks because he was suffering from hair loss. Physical examination revealed no significant abnormality, laboratory investigations and showed increased dihydrotestosterone. This patient was advised to stop ingestion of this herb, and follow-up after 1 week revealed that the patient had no feeling of increased sexual drive and dihydrotestosterone had decreased to normal level. This case report bring out new information that BS can also act as a testosterone production booster.[53]

Gingko biloba

Ginkgo biloba is a unique species of tree with no close living relatives. The ginkgo is a living fossil, recognizably similar to fossils dating back 270 million years. Native to China, the tree is widely cultivated and it has various uses in TCM and is also consumed as a food.

Countries of cultivation: China, Japan, Thailand, USA, Europe.

Active substance: Flavonoid glycosides (myricetin and quercetin) and terpenoids (ginkgolides, bilobalides); these active substances are shown to exhibit reversible, nonselective monoamine oxidase inhibition, as well as inhibition of reuptake at the serotonin, dopamine, and norepinephrine transporters, with all but the norepinephrine reuptake inhibition fading in chronic exposure.

A triple-blind (investigator, patient, statistician), randomized, placebo-controlled trial of G. *biloba* 240 mg daily was carried out. Following a 1-week (generally 12 weeks) control, Ginkgo was given to 24 patients with sexual impairment due to antidepressant drugs. There were some spectacular individual responses in both groups, but no statistically significant differences.[54]

The aim of other study was to examine the effect of G. *biloba* on antidepressant-induced sexual dysfunction ($n = 19$). This study did not replicate a prior positive finding supporting the use of G. *biloba* for antidepressant, especially SSRI (serotonin reuptake inhibitors), induced sexual dysfunction.[55]

In an open trial G. *biloba* was found to be 84% effective in treating antidepressant-induced sexual dysfunction predominately caused by selective SSRIs, ($n = 63$). Women ($n = 33$) were more responsive to the sexually enhancing effects of G. *biloba* than men ($N = 30$), with relative success rates of 91% *versus* 76%. *Ginkgo biloba* generally had a positive effect on all four phases of the sexual response cycle: Desire, excitement (erection and lubrication), orgasm, and resolution (afterglow).[56]

Epimedium sagittatum (ES)

Epimedium sagittatum is a genus of flowering plants in the family Berberidaceae. There are about 50 species, the majority of which are endemic to China and in TCM, extracts of many from these species are used as aphrodisiacs.

Country of cultivation: China, Japan.

Active substance: Icaritin (in roots and shoots)

Icaritin works by increasing levels of NO. It has been demonstrated to relax rabbit penile tissue by NO and PDE-5 activity.[57] Other research has demonstrated that injections of Epimedium extract directly into the penis of the rat result in an increase in penile blood pressure[58] and have confirmed that *E. sagittatum* is a potent inhibitor of the PDE 5. An Italian study modified icaritin structurally and investigated a number of derivatives. Inhibitory concentrations for PDE-5 close to sildenafil could be reached. Moreover, the most potent PDE-5 inhibitor of this series was also found to be a less potent inhibitor of phosphodiesterase-6 (PDE-6) and cyclic adenosine monophosphate-phosphodiesterase (cAMP-PDE), thus showing it to have more specificity for PDE-5 than sildenafil.[59] No clinical study with ES and its effectiveness and safety by ED has been published.

Eucommia ulmoides Oliv (EUO)

Eucommia is a small tree native to China. It is near threatened in the wild, but is widely cultivated in China for its bark and is highly valued in herbology such as TCM.

Countries of cultivation: China, Europe, North America.

Active substance: Iridoid glucoside geniposidic acid (bark).

To explore the pharmacodynamic and pathological mechanism of *Eucommia ulmoides Oliv* (EUO) in improving erectile function some experimental studies were done in China. In conclusions these studies showed that EUO enhances the expression of nNO and eNO in penile tissue and improves erectile function in rats.[60,61] I have not found the clinical study with EUO treatment in ED.

L-arginin and L-citrulin

L-arginin is classified as a semiessential or conditionally essential amino acid.

L-citrulline is a non-essential α-amino acid. Its name is derived from citrullus, the Latin word for watermelon, from which it was first isolated in 1914 by Koga & Odake. Biosynthesis of NO in the endotelilial wall involves a two-step oxidation of L-arginine to L-citrulline catalized by nitric oxid synthase (NOS) [Figure 2].

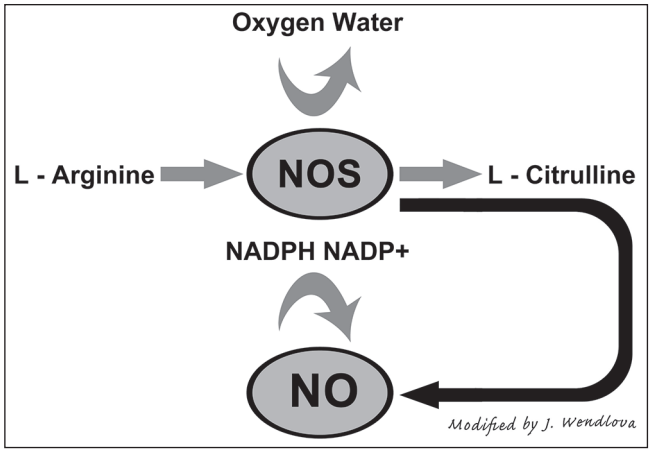

Figure 2: Biosynthesis of L-citrulline

Efficacy and safety of L-arginine aspartate 8 g combined with 200 mg of adenosine monophosphate for intermittent treatment of mild-to-moderate ED were compared with the placebo group in the clinical trial (treated group $n = 26$, control group $n = 26$). This pilot phase II study showed that the on-demand oral administration at a high dosage of L-arginine aspartate-adenosine monophosphate combination may be effective in patients with mild-to-moderate ED, is very well tolerated and could be tested as a safe first-line therapy in a larger size phase III study.[62]

Paroni *et al.*[63] have investigated the plasma concentration of asymmetrical dimethylarginine (ADMA), an inhibitor of NOS, symmetric dimethylarginine (SDMA) and L-arginine concentrations in patients with ED. They compared plasma levels of ADMA, SDMA and L-arginine in 61 men with ED of arteriogenic and non-arteriogenic origin. The L-arginine/ADMA and the L-arginine/SDMA ratios in arteriogenic ED subgroups were significantly lower than in both controls ($P < 0.05$) and non-arteriogenic ED patients ($P < 0.05$); the two ratios in non-arteriogenic ED patients did not differ from those in the controls ($P > 0.05$). In conclusion, the ADMA and SDMA concentrations are significantly higher and L-arginine/ADMA ratio lower in patients who have arteriogenic ED compared with both patients with non-arteriogenic ED and controls. The negative correlation between ADMA and severity of ED is present only in patients with arteriogenic ED. ADMA can be used as a parameter for distinction arteriogenic from non-arteriogenic ED patients.

Cormio *et al.*[64] have showed in the controlled clinical study (treated group $n = 24$, control group $n = 24$), that the supplementation with L-citrulline has been proved to be safe, effective and psychologically well accepted by patients. Its role can be as an alternative treatment for mild to moderate ED, particularly in patients with a psychological fear of the synthetic PDE-5 enzyme inhibitors.

Extract from male Bombyx mori

Bombyx mori is an economically important insect (silkworm), being a primary producer of silk. A silkworm's preferred food is mulberry leaves.

Countries of rearing: China, Japan, eastern regions of Russia, Korea.

Male silkworm moth extract was used in China as an aphrodisiac for centuries. *B. mori* is loaded with important nutrients, minerals and amino acids which can help provide both energy and drive. It can also act as a vasodilator increasing blood flow to penis. This extract is also found to act as an androgen, which can increase desire and drive in both men and women. Male silkworm extract is hard to come by, because in order to get it, the silkworm must emerge fully from its cocoon which then destroys the valuable silk fibers. I have not found any clinical study investigated extract from male *B. mori*; however, they are many natural sexual male enhancement pills on the market. Male *B. mori* has a trypsin-type protease, called initiator in the secretion from the posterior segment of the ejaculatory duct, that is thought to be involved in the acquisition of sperm motility.[65]

An experimental study by authors from Korea[66] was designed to investigate the effects of male silkworm pupa powder (SWP) on the levels of NOS expression, eNO, glutathione (GSH); testosterone, lipid peroxidation; libido; and erectile response of the corpus cavernosum of the rat penis. They induced ED in the study animals by oral administration of 20% ethanol over 8 weeks. The testosterone concentration did not increase significantly. SWP-administered male rats showed increased GSH levels in the corpus cavernosum. The level of eNO and eNOS expression in the corpus cavernosum of SWP-administered male rats increased significantly. The findings implicate a multifactorial role of SWP. The antioxidative activity of SWP may defend penile cells against active oxygen species, decrease the fatigue of the penile tissue, and enhance erectile function. In conclusion, SWP may be useful as a preventive or therapeutic material to counteract alcohol-induced ED symptoms.

The toxicity of the *B. mori* extract is very low. It can promote the growth of under-aged male mice and increase markedly the weight of the prostate glands, seminal vesicles and preputial glands in castrated male mice. The results of the experiments have shown that *B. mori* extract has androgen-like action.[67]

Activators of estrogen metabolization and degradation

(antagonists to xenoestrogens, estrogen balancers):

- Indol-3-carbinol (I3C).
- Diindolylmethane (DIM).
- Chrysin.
- Other estrogen-inhibiting foods.

In spite of current lack of clinical studies investigating the anti-estrogen effect of I3C and DIM in men with ED and infertility caused with xenoestrogen intoxication, occasioning the estrogen dominance, the market is selling off a lot of preparations containing I3C and DIM for the ED and infertility by men with elevated serum level of estrogens. Manufacturers of these products start in the indication from clinical studies with I3C and DIM that showed effectiveness in restoring physiological estrogen metabolism in estrogen-dependent diseases, such as some types of breast cancer in women (elimination of estrogen predominance, the possibility to shift estrogen metabolism to

the production of 2-hydroxy or 2-methoxy estrogen metabolites, called the "good" estrogens).[68]

Indole-3-carbinol

I3C (C_9H_9NO) is produced by the breakdown of the glucosinolate glucobrassicin, which can be found at relatively high levels in cruciferous vegetables such as broccoli, cabbage, cauliflower, brussels sprouts, collard greens and kale and is also available in a dietary supplements. I3C is the subject of on-going experimental and clinical research into its possible anticarcinogenic, antioxidant, anti-atherogenic and antiestrogenic effect.[69,70]

In the experimental studies by Bradlow and Michnovicz,[71,72] the two leading scientists in I3C research, it was demonstrated that dietary indoles in cruciferous vegetables induce synthesis of cytochrome P450 enzymes and can prevent generation of tumors in various animal models. Because estradiol metabolism is also cytochrome P450 mediated and linked to breast cancer risk, indoles may similarly reduce estrogen-responsive tumours in humans. The results from experimental studies indicate that I3C strongly influences estradiol metabolism in humans and may provide a new chemopreventive approach to estrogen-dependent diseases. I3C could inhibit the proliferation of both estrogen-dependent and -independent breast tumour cells, and LTr-1 is an antagonist of estrogen receptor function.

In the clinical studies Michnovicz and Bradlow[73-77] investigated the effects in humans of short-term oral exposure to I3C (6-7 mg/kg/day over 7 days). They used an *in vivo* radiometric test, which provided a highly specific and reproducible measure of estradiol 2-hydroxylation before and after exposure to I3C. In a group of 12 healthy volunteers, the average extent of reaction increased by approximately 50% during this short exposure ($P < 0.01$), affecting men and women equally. Also, the urinary excretion of estrogen metabolites, 2-hydroxyestrone (2OHE1) and estriol (E3) was significantly increased by I3C, further confirming the ongoing induction of 2-hydroxylation. These results indicate that I3C predictably alters endogenous estrogen metabolism toward increased 2-hydroxylated estrogen (catechol estrogens) production, thereby providing a novel "dietary" means for reducing estrogen-dependent cancer risk and other estrogen-dependent diseases.

In the future we can expect in connection to higher exposure of xenoestrogens in the population that xenoestrogen-induced ED will also rise. I have not found the clinical study in connection with I3C treatment of hyperestrogenism by men caused by xenoestrogen exposure.

Diindolylmethane

3,3′-Diindolylmethane (DIM) is a compound derived from the digestion of I3C, found also in cruciferous vegetables such as broccoli, Brussels sprouts, cabbage, cauliflower, and kale. The reputation of *Brassica* vegetables as healthy foods rests in part on the activities of DIM.

DIM is the bioactive compound which helps defend women and men against estrogen's adverse metabolites. DIM has been used since 1987 in animal studies, proven to be non-toxic and a potent aid against estrogen adverse effects.[78]

The mechanism by which DIM induces its beneficial actions has been shown to involve a reduction in estrogen receptors activity, promotion of synthesis of healthy estrogen metabolites and support for selective cells apoptosis, which removes damaged or sick cells.[79]

Cruciferous indoles stimulate the estrogen metabolism into predominantly 2-hydroxy and 2-methoxy estrogen synthesis, known as "good estrogens"; these active metabolites act as antioxidants and have the power to eliminate damaged or cancerous cells throughout the body. Deficiency in these phytonutrients may cause an increased production of adverse groups of estrogen metabolites, 16-hydroxy and 16-methoxy estrogens, known as "bad estrogens," which cause increased oxidative stress, DNA damage and promotion of cancer cell formation.

Supplemental use of DIM in humans helps shift estrogen metabolism to favor the production of 2-hydroxy or 2-methoxy estrogen metabolites over the 16-hydroxy or 16-methoxy estrogen metabolites. Increased ratios of 2/16-hydroxy (or methoxy) estrogens is correlated with protection against cancer.[71]

The positive influence of cruciferous vegetables on human estrogen metabolism and estrogen-dominant diseases is very well-known in the scientific literature and has also been verified in other clinical studies.[80-83]

On the most supplements wit DIM there are following indications:

- Exposure to xenoestrogen chemicals (pesticides, herbicides, petroleum-based products), ED induced by xenoestrogen exposure.
- Estrogen therapy.
- Steroid use (on or off drugs).
- Aging.
- Obesity.
- Elevated PSA.
- Pre- and post-menopausal symptoms.

- Deficient diet (deficit in vegetables).
- Increased inherited risk for estrogen-related cancer.

Chrysin

The equilibrium of sexual hormones in both sexes is controlled by the enzyme aromatase, a member of the cytochrome P450 superfamily, which catalyzes the conversion of androstenedione and testosterone into estrone and estradiol, respectively. Flavonoids are diphenolic compounds present in whole grains, legumes, fruits, and vegetables that are strongly implicated as protective in coronary heart disease, stroke, and cancer. One flavonoid, chrysin, found in high concentrations in honey, propolis and some plants, including the *Passiflora cearulea*, has been shown to be an inhibitor of aromatase enzyme activity. These foods are often used as supplements, particulary by sportsmen for their energetic and antioxidant properties. The aim of clinical study from Cambelunghe *et al.*[84] was to verify if daily treatment for 21 days with propolis and honey, containing chrysin, would modify urinary concentrations of testosterone in volunteer male subjects. In fact, aromatase inhibition by chrysin could block the conversion of androgens into estrogens with a consequent increase of testosterone, eventually measurable in urine samples. The obtained data did not show alterations of the levels of testosterone in the volunteers after 7, 14, and 21 days of treatment in comparison with baseline values and compared with measurements on the control subjects at the same time. In conclusion, the use of these foods for 21 days at the doses usually taken as oral supplementation does not have effects on the equilibrium of testosterone in human males.

In the study by Brown *et al.*,[85] the effects of androgen precursors were studied, combined with herbal extracts designed to enhance testosterone formation and reduce conversion of androgens to estrogens in young men. Subjects were made to perform 3 days of resistance training per week for 8 weeks. Each day during weeks 1, 2, 4, 5, 7, and 8, subjects consumed either placebo (PL; $n = 10$) or a supplement (ANDRO-6; $n = 10$), which contained daily doses of 300 mg androstenedione, 150 mg DHEA, 750 mg *T. terrestris*, 625 mg Chrysin, 300 mg I3C, and 540 mg saw palmetto. Serum androstenedione concentrations were found to be higher in ANDRO-6 after 2, 5, and 8 weeks ($P < 0.05$), while serum concentrations of free and total testosterone were found to be unchanged in both groups. Serum estradiol level was elevated at weeks 2, 5, and 8 in ANDRO-6 ($P < 0.05$), and serum estrone level was elevated at weeks 5 and 8 ($P < 0.05$). Muscle strength increased ($P < 0.05$) similarly from weeks 0 to 4, and again from weeks 4 to 8 in both treatment groups. The acute effects of one third of the daily dose of ANDRO-6 and PL were studied in 10 men (23 ± 4 years). Serum androstenedione concentrations were elevated ($P < 0.05$) in ANDRO-6 from 150 to 360 min after ingestion, while serum free or total testosterone concentrations were unchanged. These data provide evidence that the addition of these herbal extracts to androstenedione does not result in increased serum testosterone concentrations, reduce the estrogenic effect of androstenedione, and does not augment the adaptations to resistance training. Chrysin could be an inhibitor of aromatase enzyme activity, which catalyzes the conversion of androstenedione and testosterone into estrone and estradiol, and is a preferred compound being natural over the counter products for ED. But in the clinical studies[84,85] there were no statistical significance for supplementation with chrysin as a natural activator of estrogen metabolism inhibition in men.

Other known estrogen-inhibiting foods

In addition to cruciferous vegetables, some of the other best sources are onions, green beans, berries, citrus, pineapples, pears, grapes, figs, melons, sesame seeds, and pumpkin seeds.[86]

DISCUSSION

The increase in ED, oligozoospermia and infertility in the productive age world population is mainly determined by the following factors:

1. Increase in obesity and metabolic syndrome.
2. Poor diet, deficient in important nutritional substances necessary for bioregeneration of the gonad cells and for production of sex hormones.
3. Increase in contamination of the environment food and water with metabolic and endocrinological environmental disruptors, such as xenoestrogens.
4. Chronic stress as a negative phenomenon in the rapid evolution of the knowledge-based society, marked by economic crisis, existential uncertainty, disintegrating family ties, emotional loneliness.

Affected males often find a solution to their problems in exploring natural products for ED shopping online on internet, the reasons are probably most often the following:

1. Easy availability of over-the-counter drugs, attractive advertising,
2. Acceptable price,
3. Proclaim safety without side-effects,
4. Avoid the doctor visits, saving payments for medical examination.

An overview of controlled clinical studies showed that even today there is use of natural products for ED mainly based on thousand-year-old traditions and on the efficacy and safety of these products, verified in the long-time healing practice,

especially in traditional Chinese and Indian medicine. The review of the literature confirms that some marketed medicinal plants are lacking clinical studies, the results of some clinical studies related to the same medicinal plant are controversial, and some bring significant positive effects, but their number is low (maximum four to five studies). It is interesting to note that clinical studies of scientists from countries of origin of the medicinal plants for ED, where is also thousand-year-old traditions of their use, refer to the statistical significance results in the efficacy and safety. In contrast, the results of clinical trials in the USA, Canada and other countries are often controversial or without statistical significance. The question arises whether the medicinal plants used in clinical trials of colleagues from countries, where these medicinal plants grow or are cultivated have higher content of active substances (fast processing of fresh plants, traditional recipes for their processing and their mutual combination, short shelf life, no air transport as a risk for negative effects of radiation, no effect of moisture and mechanical shocks during shipping). The future is therefore open to a number of relevant clinical investigations of medicinal plants in the treatment of ED with possible inclusion of some medicinal plants in evidence-based medicine, if confirming their efficacy and safety.

CONCLUSION

It is a pity that a civilized society has for a long time created such environment, which unfortunately can lead to a slow castration in the male population. On ED in men of productive age should be seen as a major clinical symptom, which requires precise differential diagnosis and comprehensive therapy, focusing on causations of ED. ED in productive age and especially in young men indicates serious disease:

1. Atherosclerosis, hidden coronary heart disease,
2. Tthromboembolic disease,
3. Xenoestrogen intoxication,
4. Depression, burn-out syndrome,
5. Endocrine disease,
6. Cumulative side effects of drugs,
7. Chronic infection (focus) in the body,
8. Neurological disease,
9. Chronic kidney disease,
10. Benign prostatic hyperplasia, prostate cancer.

Recommendation of a medicament or natural drug to patient with ED without differential diagnosis is therefore very simplistic and wrong therapeutic approach. Differential diagnosis in this case is imperative. In ED, induced by civilizing factors, it is possible to begin with also bioregeneration of the organism:

1. Nutrition therapy, weight loss,
2. Physical therapy, exercise,
3. Psychotherapy, education how to manage the stress and create a concept of the life, system of work (order therapy), psycho-somatic social consulting,
4. Detoxification,
5. Avoid exposure to xenoestrogen, the use of natural compounds with anti-xenoestrognic effect (I3C, DIM),
6. Use of natural plants, verified in clinical trials, which boost testosterone and NO synthesis.

Some clinical studies (also these cited in the review) have shown that the bioregeneration (nutrition therapy, exercise, body mind coordination) is in the erectile dysfunction possible with considerable success.[87,88]

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