REVIEW ARTICLE

Progression of the erectile dysfunction in the population and the possibilities of its regression with bioregeneration

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Submitted: 2013-09-08 Accepted: 2013-09-12 Published online: 2013-11-25

Key words: **erectile dysfunction; pathophysiology; xenoestrogens; natural therapy; medicinal plants**

Neuroendocrinol Lett 2013; **34**(6):482–497 **PMID:** 24378458 NEL340613R03

Abstract

Article presents the latest knowledge on the pathophysiology of erectile dysfunction (ED), the influence of xenoestrogens on ED and fertility in men and the possibilities of the blocking xenoestrogen actions with natural ingredients as well as treatment options for ED with medicinal plants. With the rising phenomenon of ED in the world there is rising a market with ED treatment products. Especially in menu of internet online shops come increasingly to light new natural over the counter products for ED treatment. Sale and use of medicinal plants and their extracts in the treatment of ED is based 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 healing practice. Aim of this article was to make an extensive review of the scientific and professional literature and to find out which medical plants, sold in the herbal products for ED, was evaluated for efficacy and safety in relevant clinical trials. The review of the literature shows, that by some marketed medicinal plants 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. The future is therefore open to starting the number of new clinical trials testing the medicinal plants in the treatment of ED with possible inclusion of some of these plants in evidence based medicine, if confirming their efficacy and safety.

INTRODUCTION

ED currently affects not only men in andropause, but also in the reproductive period ranging from 40 years of age, they are no exception men before 40 years of age (Feldman *et al.* 1994) and it has increasing tendency in the population. The increase of ED can be the whole society problem, because family planning among men in developed countries transferred to 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 of 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 and their extracts in sold supplements have been tested for efficacy and safety, particularly in relevant clinical trials ,
2. what is the causation of the increasing tendency of ED in the population.

Recent sale and use of medicinal plants and their extracts in the treatment of ED is mainly based 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 plant are used in the population until today.

1. ERECTILE DYSFUNCTION

Penile erection is a complex process involving psychogenic, hormonal, vascular, neurovascular nonadrenergic, noncholinergic input (Feldman *et al.* 1994).

On each of this levels can originate the dysfunction or the dysfunction may result from a various combinations of these causes.

Definition of ED, prevalence in the population and connection with civilizing diseases

ED is a sexual dysfunction, which refers to difficulty engaging in sexual intercourse, it is the inability to achieve or maintain an erection, absence of erection during sleep or upon awakening. Sex drive (libido) generally decrease but some men do maintain normal libido. According to the findings in the Mayo clinical study monitoring years from 1996 to 2005 (sample 1402 men) the prevalence of ED was 2% for men aged 40 to 49 years, 6% for men aged 50 to 59 years, 17% for men aged 60 to 69 years, and 39% for men aged 70 years or older (Shamloul *et al.* 2013). The MALES (Men's Attitudes to Life Events and Sexuality) study I., involved 27 839 men aged 20–75 years, who were interviewed in eight countries (United States, United Kingdom, Germany, France, Italy, Spain, Mexico, and Brazil) using a standardized questionnaire. The overall prevalence of ED in the MALES sample was 16%. ED prevalence varied markedly by country, however, from a high of 22% (Rosen *et al.* 2004). In comparison with the previous studies, the study from Switzerland, published in 2012, show the progress in developing ED noticeable. In this study one-third of young men suffer from at least one sexual dysfunction, ED or premature ejaculation (PE) (Mialon *et al.* 2012). With rise of the civilizing diseases rises also the ED in men population. In the review article from 20 studies (Kolotkin *et al.* 2012), the most studies showed a high statistical significance of correlation between obesity and lower levels of sexual functioning; especially ED. Erectile dysfunction is associated with cardiovascular risk factors as elevated systolic blood pressure, resting high heart rate, and endothelial dysfunction and predicts cardiovascular events. However, the interaction between high heart rate and elevated systolic blood pressure and the development of ED remains unclear (Kratz *et al.* 2013, Nehra *et al.* 2013). ED may be also the first clinical sign of endothelial dysfunction and a clinical marker of cardiovascular disease and metabolic syndrome. Subclinical endothelial dysfunction and insulin resistance may be the underlying pathogenesis of ED in young patients without well-known aetiology (Yao *et al.* 2013, Sai Ravi Shanker *et al.* 2013, Banks *et al.* 2013a, Cabler *et al.* 2010, Inman *et al.* 2009). Chen and co-authors (2012) have shown with the data from clinical study that metabolic syndrome (MS) is a potential and independent risk factor for ED in this study, especially in middle-age men. MS can be recognized as a warning signal for ED. Abnormal fasting blood glucose was the most significantly independent factor of MS for ED in this study.

Obesity concerns more than 200 million people in the world, with an increasing prevalence in western countries. It is closely related to multiple medical conditions, such as diabetes and hypertension. It was recently shown that testosterone deficiency syndrome and ED are in previous studies linked to male obesity. In obese male patients ED may be due to defects in corpus cavernosum relaxation, endocrine modifications and nerve signal alterations. Weight loss and increased physical activities can improve erectile function in 30% of obese patients (Lucca *et al.* 2012).

The fact is that being overweight increases the chances of erectile dysfunction. Researchers in Colorado and Pennsylvania found that an expanding waistline expands also the possibilities for erectile difficulties. The clinical study has also showen that erectile dysfunction can improve with weight loss (Tsai & Sarwer 2009).

Research in Australia that tracked the health of 95,000 men for three years indicates that even only minor erectile difficulties indicate that the man has so-called "silent" heart disease. So not just sex life but also the life may be in significant danger. This study of men over age 45 is the largest study to date examining the link between erectile dysfunction and heart disease. It was found that men with erectile dysfunction had a greater risk of requiring hospital admission for heart disease even if they had no history of heart problems. They were also at greater risk of premature death from any cause (Banks *et al.* 2013b).

Multiple health-compromising factors are associated with ED. These should act as red flags for health professionals to encourage them to take any opportunity to talk about sexuality with their young and middle aged male patients and to do serious differential diagnoses of ED. Erectile function of penis reflect very accurately the common health of the man, especially the still athero-

sclerotic process of the arteries and therefore the question about erectile possibility would have been a part also of anamnestic internal investigation.

2. ETHIOLOGY AND CLASSIFICATION OF ED

ED is classified according to ethiology as organic or nonorganic.

2.1. Organic ED

(Andersson *et al.* 2011, Foocharoen *et al.* 2012, Giuliano, Droupy 2013, Ende 1990)

2.1.1. *Hormonal dysbalance:* decreased testosterone synthesis (cavernosal fibrosis): aging, male andropause, nutrition deficiency, hypothyreodism, primary od secondary hypogonadism, chronical stress, hepathopathy, too – strict dieting without animal fats (deficit of cholesterol),

2.1.2. *Penile organ dysfunction,*

2.1.2.1. Arterial inflow dysfunction (atherosclerotic plaques): atherosclerosis, diabetes mellitus, hypertension, obesity with metabolic syndrome, hyperlipoproteinemia,

2.1.2.2 Veno-occlusive dysfunction: micro blood clots in penis veins, posttraumatic or congenital venous disorders, thromboembolic disease,

2.1.2.3. Venous leakage: describes the condition, where the blood escapes from the penis and thus a good erection cannot be achieved, blood leaks from penis out as fast as it infills, because the corpora cavernosa are insufficient, they are fibrotic and cannot completely fill up and compress the penile veins, leakage should not be confused with venous insufficiency, in fact it is a cavernousal fibrosis and/or penile arterial atherosclerosis,

2.1.2.4. Dysfunction of penile tissue (muscles, connective tissue): myopathy, muscle athrophy, dermathomyositis etc..,

2.1.3. *Neurological diseases* – nerve signal alterations (stroke, diabetic autonomic neuropathy, multiple sclerosis, Parkinson disease, multiple system atrophy, epilepsy, spinal cord and pelvic injury in lumbosacral area, peripheral nerve disorders, and herniated discs in lumbar area).

2.1.4. *Certain prescription medications*,

2.1.5. *Metabolic and endocrinological environmental disruptors,*

2.1.6. *Chronic periodontitis (*Oğuz *et al.* 2013)

2.1.7. *Benign prostatic hyperplasia, chronic kidney diseases.* Epidemiological studies have confirmed that benign prostatic hyperplasia (BPH) and ED are correlated, independent of age or comorbidities. Although researchers have not yet established a direct causal relationship between the two problems, several pathophysiological factors may serve to explain it, which include the alteration in nitric oxide bioavailability, increased autonomic activity, α1-adrenergic receptor hyperactivity, imbalance of RhoA/Rho-kinase, and metabolic syndrome X. Men seeking care for BPH should always be screened for sexual function and complaints of ED. Enzyme phosphodiesterase type 5 (PDE5) inhibitors show promise as a future treatment for lower urinary tract symptoms secondary to BPH (Fan 2013). Also the chronic kidney diseases such as chronic irritable bowel syndrome, chronic renal insufficiency with haemodialysis, renal transplant syndrome, radical nephrectomy are associated with ED (Chao *et al.* 2013, Mekki *et al.* 2013, Rathi & Ramachandran 2012)

2.2. Nonorganic ED, psychogenic ED

(Monseny 2010, Persu *et al.* 2009, Ponseti *et al.* 2009)

2.2.1. Depression,

2.2.2. Performance anxiety (when the man is pressed by a intolerable partner to perform well sexually, he is distressed and develop the performance anxiety),

2.2.3. Anxiety, panic attacks,

2.2.4. Chronic stress at work or in the family,

In the special literature it is used also another classification of ED:

1. psychogenic,
2. hormonal,
3. arteriogenic,
4. venogenic,
5. combined arteriogenic – venogenic,
6. neural – nerve signal alterations.

Psychogenic ED shows a high incidence and prevalence among men, with a significant impact on the quality of life. Few neuroimaging studies have investigated the cerebral basis of erectile dysfunctions observing the role played by prefrontal, cingulate, and parietal cortices during erotic stimulation. In spite of the well-known involvement of subcortical regions such as hypothalamus and caudate nucleus in male sexual response, and the key role of nucleus accumbens in pleasure and reward, poor attention was paid to their role in male sexual dysfunction. In the recent study (Kopp *et al.* 2013) it was determined the presence of grey matter (GM) atrophy patterns in subcortical structures such as amygdala, hippocampus, nucleus accumbens, caudate nucleus, putamen, pallidum, thalamus, and hypothalamus in patients with psychogenic ED. Seventeen outpatients with psychogenic ED and 25 healthy controls

were recruited for structural MRI session. Significant GM atrophy of nucleus accumbens was observed in patients with respect to controls. Shape analysis showed that this atrophy was located in the left medial-anterior and posterior portion of accumbens. Left nucleus accumbens volumes and GM atrophy of left hypothalamus in patients correlated with low erectile functioning as measured by IIEF-5 (International Index of Erectile Function). The results suggest that atrophy of nucleus accumbens plays an important role in psychogenic erectile dysfunction. This change can influence the motivation-related component of sexual behaviour and this findings help to elucidate a neural basis of psychogenic erectile dysfunction (Cera *et al.* 2012). So the question is: Is a psychogenic ED also previous organic?

The article is focused on the role of nitric oxide, testosterone, stress and xenoestrogens in the pathophysiology of ED, because it is known from phytopharmacy, that on these levels act the most used medicinal plants and natural supplements.

3. PHYSIOLOGY AND PATHOPHYSIOLOGY

3.1. 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 1).

Based on sexual stimulation there rise the central and peripheral neuronal depolarisation 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 father activates the production of the endotelial NO (eNO) in the endothelium of the artherial wall. Production of eNO promots the tumescence up to the physiological erection (Loscalzo *et al.* 2013).

Biosynthesis of NO involves a two step oxidation of L-arginine to L-citrulline. The proposed mechanisms involve an initial hydroxylation of L-arginine, leading to the formation of N-hydroxy-L-arginine, which can also act as a substrate for NOS (nitric oxide synthase). This is followed by oxidation of the intermediate, using a single electron from NADPH (nicotinamide adenine dinucleotide phosphate) to form L-citrulline and NO (Luiking *et al.* 2012, Mayer *et al.* 1998).

Impaired NO bioactivity is a major pathogenic mechanism of erectile dysfunction. As was demonstrated the concordant action of nNO and eNO is needed to physiological errection, therefore treatment of ED often requires combinations of psychogenic and drug therapies.

Enzyme PDE 5 (phosphodiesterase type 5) has a degradative action on the cGMP.. and hinders the smooth muscle realaxation. A PDE 5 inhibitors are the most effective pharmaceutical drugs (avanafil, lodenafil, mirodenafil, sildenafil citrate etc...) used to block the degradative action of PDE 5 on cGMP in the smooth muscle cells lining the blood vessels supplying the corpus cavernosum of the penis. These drugs are

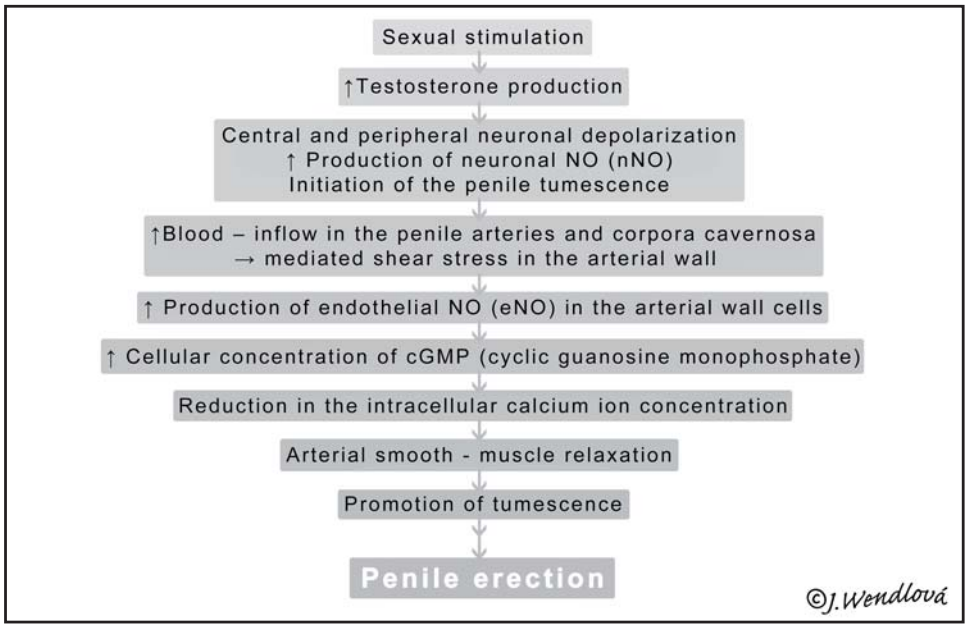

Fig. 1. Regulatory mechanism of the physiologicla penile erection

used in the treatment of erectile dysfunction, but the important message is, that they are ineffective without sexual stimulation.

Vascular actions of NO include the following (Loscalzo *et al.* 2013, Luiking *et al.* 2012, Shamloul *et al.* 2013):

- 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.

3.2. The role of testosterone in ED

(Lejeune *et al.* 2013, Patel *et al.* 2012)

Androgens are essential for the development, growth and maturation of th erectile tissues, for preventing cardiovascular diseases, osteoporosis, and depression in men. Testosterone low production lead to corpora cavernosum atrophy with concomitant structural alterations of the dorsal penile nerve, vascular endothelial alterations, reduction of the smooth muscle component in the arterial wall and increase in the deposition of extracellular matrix and cavernosal fibrosis. Androgens regulate the protein synthesis in the smooth muscle and in the connective tissue of the corpora cavernosa. Degrease in the androgens production leads to a decrease in the protein synthesis and it could give rise to the switch from synthesis of elastic fibres to collagen fibres, which is the basis of cavernosal fibrosis. The penile tissue loses his elasticity and stiffness.

In the brain, low testosterone levels are associated with a reduction in erectile signalling. There is a low production of the nonadrenergic, noncholinergic neurotransmitter nNO (neuronal NO) in the brain and also in the penile neuronal synapsis. Low production of nNO activates the low production of neurotransmitter eNO in the arterial wall, referring to penile erection. The metabolic connection in co-action of testosterone production on one side and neuronal and endothelial NO production on the other side is considerable. The sexual stimulation boosts the testosterone production.

Recent experimental evidence showed that testosterone also regulates the expression of the enzyme PDE 5. As age advances, the gonadal steroid hormones, in particular, testosterone production decreases, nerve conduction slows, decreases the production of nNO and eNO and the efficiency of the vascular circulation of the penis is reduced.

Also, as age advances the collagen/elastic fibres ratio in the corpora cavernosa increases, on the behalf of collagen fibres. Aging and the testosterone production decrease leads to a progressive fibrotic process of the corpora cavernosa, to the involution of the penis (Iacono *et al.* 2012a).

3.3. The effect of xenoestrogens

3.3.1. *Xenoestrogens* – metabolic and endocrinological environmental disruptors.

One of the causation of the ED in young men can be the environmental contamination with endocrine disrupting chemicals (EDCs), namely xenoestrogens. Xeno literally means "strange" or "foreign", so these estrogens are foreign for the human body. This is an appropriate description since they refer to compounds that mimic the effects of natural estrogens despite not being identical in structure. These estrogen mimics have the ability to bind to the same receptors that estrogen binds to and block the effects of natural estrogen and induce the estrogen dominance. In this way they disrupt the body's natural hormone balance (Kerdivel *et al.* 2013).

Xenoestrogens (XE) may alter reproductively-relevant or nonreproductive, sexual behaviours. In addition, XE may have significant effects on neurodevelopmental processes, influencing the morphology of sexually-dimorphic cerebral circuits. Exposure to XE is more dangerous if it occurs during specific 'critical periods' of life, such as intrauterine, perinatal, juvenile or puberty periods, when organisms are more sensitive to hormonal disruption (Marino *et al.* 2012).

Studies conducted over the past 50 years have clearly shown a continual decline in semen quality accompanied by an increase in male reproductive disorders during this period in industrial countries. As healthy gametes are a prerequisite for healthy children, such disorders are a significant problem not only for the current society, but also for future generations. These male reproductive disorders have been attributed to xenobiotics, and particularly to xenoestrogens, which have steadily increased in diversity and concentration in the environment and food. Epidemiological, clinical, and experimental studies have suggested that excessive exposure to estrogens and xenoestrogens during fetal and neonatal development may induce testicular developmental disorders, leading to alterations in the adult male fertility. Recently, it was clearly demonstrated in the clinical and experimental studies that fetal and neonatal testes are very sensitive to estrogens, as the inactivation of estrogen receptor α increases steroidogenesis and the inactivation of estrogen receptor β enhances development of the germ cell lineage in the male (Delbes *et al.* 2006).

Xenoestrogens can play a major role in the regulation of male reproductive function. In humans, a decrease in sperm count and an increase in the incidences of testicular cancer, cryptorchidism and hypospadia have been observed in many countries over the last 50 years (Delbès *et al.* 2005).

Gyllenhammar and co-authors (2012) have published a very important study. The first aim of this study was to investigate possible sources of xenoestrogens nonylphenol (NP) and bisphenol A (BPA) exposure from food, by analyzing the levels of NP and BPA from a Swedish supermarket food, based on the Swedish per capita food consumption. A second aim was to investigate blood serum levels of NP and BPA, as well as NP-ethoxylates, among young women in Sweden (n=100). Moreover, associations between food consumption and blood NP and BPA levels were studied. In food, NP was to some extent found at levels above limit of quantification (LOQ 20 ng/g fresh weight) in fruits, cereal products, vegetables, and potatoes. BPA levels above LOQ (2 ng/g fresh weight) were found in fish, meats, potatoes, and dairy products. The estimated mean intakes per capita were (medium bound) 27 μg NP/day and 3.9 μg BPA/day, showing that food is a source of BPA and NP in the general Swedish population. In blood serum, free NP above limit of detection (LOD 0.5 ng/g) was detected in 46% of the study participants while detectable levels of total NP (LOD 0.8 ng/g) were observed in 43%. A significantly higher total consumption of fruits and vegetables was reported in questionnaires by participants with NP levels at or above LOD than among women with levels below LOD. This result is supporting the market basket results of relatively high NP and BPA levels in these types of food.

3.3.2. Occurrence of the xenoestrogens in environment

A. Synthetic xenoestrogens:

1. Pesticides and herbicides: DDT (Dichlorodiphenyl trichloroethane), DDE (Dichlorodiphenyldichloroethylene), Dieldrin, Endosulfan, Heptachlor, Lindane/ Hexachlorocyclohexane, Methoxychlor, 4-nonylphenol and derivatives (Wozniak & Murias 2008),
2. Industrial surfactants: emulsifiers for emulsion polymerization, laboratory detergents (Z Behr *et al.* 2011),
3. Electrical oils, lubricants, adhesives, paints: polychlorinated biphenyls (PCBs) (Birkett & Lester 2003),
4. Plasticizers, monomers for polycarbonate plastic and epoxy resin: Bisphenol A, phthalates: Benzylbutylphtalate, Diphenylphtalate, Perfluorooctanoic acid *(PFOA)* is used to make Teflon and Gore-Tex (Ben-Jonathan & Steinmetz 1998, Cooper *et al.* 2011).
5. Metalloestrogens (a class of inorganic xenoestrogens, heavy metals): mercury, Co, Cu, Ni, Cr, Pb, Cd (Wozniak & Murias 2008),
6. Preservatives in personal care products (cosmetics: moisturizers, deodorants, hair sprays, shampoo, body washes, perfumes, creams etc.): Parabens (methylparaben, ethylparaben, propylparaben and butylparaben (Darbre & Charles 2010),
7. Fungi: Zearalenone, is a mycoestrogen produced by Fusarium sepcies of fungi, mycoestrogens are commonly found in stored grain. They can come from fungi growing on the grain as it grows or after harvest during storage. Mycoestrogens can be found in silage (Warth *et al.* 2013, Koraïchi *et al.* 2013).

B. Natural xenoestrogens (phytoestrogens)

Natural xenoestrogens are plant-derived xenoestrogens, phytoestrogens. Because the primary route of exposure to these compounds is by consumption of phytoestrogenic plants, they are sometimes called "dietary estrogens." Phytoestrogens include flavonoids, isoflavonoids, chalcons, coumestans, stilbenes, lignans, ginsenosides and other saponins, as well as the recently discovered tetrahydrofurandiols (Lóránd *et al.* 2010).

3.3.3. Xenoestrogens – *The mode of action*

Both human estradiol (E_2) and xenoestrogens (diethylstilbestrol, coumestrol, bisphenol A, DDE, nonylphenol, endosulfan, and dieldrin) act via a membrane version of the estrogen receptor-α on pituitary cells, and can provoke Ca^{++} influx via L-type channels, leading to prolactin (PRL) secretion. These hormone mimetics can also cause the oscillating activation of extracellular regulated kinases (ERKs). However, individual xenoestrogens differ in their potency and temporal phasing of these activations compared to each other and to E_2. It is perhaps in these ways that they disrupt some endocrine functions when acting in combination with physiological estrogens (Słomczyńska 2008, Długosz *et al.* 2008, Watson *et al.* 2007).

Xenoestrogens have wide structural diversity, but all have in common lipophillic phenolic rings and other hydrophobic components, a characteristic they share with human steroid hormones and related nuclear receptor-activating compounds. From these experimental studies we know, that the xenoestrogens cause increased production of the prolaktin. We also know from the clinical endocrinology that hyperporlactinemia suppress the testosterone production and raise the dihydrotestosteron production. So it can be the one pathway of xenoestrogen action by man. By women the xenoestrogen induced hyperprolactinemia stimulates the uterine, vaginal and breast (mammary) growth and differentiation Xenoesterogens are measurable in the human breast and they are known factors in breast cancer development. Bispenol A is the most investigated xenoestrogen in experimental and clinical studies. Bisphenol A shares the similarities in structure, metabolism and action with diethylstilbestrol. A known human teratogen and carcinogen. Xenoestrogens, alter serum lipid concentrations or metabolism enzymes that are necessary for converting cholesterol to steroid hormones. This can ultimately alter the production of oestradiol, testosterone and/or other steroids (Bo *et al.* 2012).

3.3.4. Xenoestrogens and *ED*

Xenoestrogens disrupt the physiological ratio between testosterone and estrogen in man with lowering the testosterone level and increase the estrogen level. Normally, the testosterone level in men is 10 times higher than estrogen level (10:1).

Research in California shows that the more xenoestrogen BPA (bisphenol-A) has one man in urine, the more he has risk for erectile dysfunction. BPA is a chemical used in the manufacture of some plastics BPA is available in beverages from aluminium soft drink and beer cans, canned food and dental sealants, as well as some plastic soft drink and water containers. Avoiding food and drink from cans and plastic containers will lower exposure to this toxin (and possibly lower the risk of ED and prostate cancer) (Li *et al.* 2010).

Clinical symptoms of disrupted ratio between testosterone and estrogen:

Clinical symptoms of l*ow level of testosterone:*

1. Reduced sex drive,
2. ED,
3. Ejaculatory problems — having no orgasm or, just as bad, having premature ejaculations,
4. Disturbed sleep and depression,
5. Heart disease and atherosclerosis,
6. Osteoporosis,
7. Prostate enlargement/cancer,
8. Loss of muscle,
9. Fatigue,
10. Irritability,
11. Thinning skin,
12. Poor concentration and memory lapses

Clinical symptoms of *the high level of estrogen:*

1. Swelling of the prostate,
2. Muscle atrophy, weight gain (abdominal fat),
3. Moodiness,
4. Stimulation of breast growth (gynecomastia),
5. ED,
6. Deprivation of man mentality.

Follow-up experimental and clinical studies are needed for obtention relevant knowledge in this field.

3.4. Chronic stress and ED

Chronic stress, emotional loneliness and overloading at work are the main phenomenon in the developed knowledge-based society. Chronic stress disrupts the homeostasis in neurotrnasmiters and in the korticosteroids synthesis. In connection with the ED it is unfavourable the increased production of cortisol. Cortisol lowers the production of DHEA (dehydroepiandrosterone) and the consequence is the low production of testosterone.

Men with low levels of DHEA generally don't live as long, get sick more often, are more susceptible to inflammatory diseases (inflammation has recently been linked to heart disease and damaged arteries, so they are at higher risk for these conditions, too), and are depressed more often. On the other hand, men with higher levels of DHEA : perform better in physical and cognitive tests, have more energy, spend less time being sick, are slimmer and trimmer, enjoy more sex, retain their memories better, look more youthful and healthy (Kalaitzidou *et al.* 2013, Byun *et al.* 2013).

4. THE POSSIBILITIES OF BIOREGENERATION IN ED WITH MEDICINAL PLANTS, NATURAL SUPPLEMENTS, ORGANIC NUTRITION AND EXERCISE

Throughout history, every culture has searched his environment for medicinal plants that might have health benefits. Few of 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 (Ho & Tan 2011).

In the review there are preferred the clinical studies against experimental studies, because the thousand-years historical traditional use of medicinal plants was verified by healing practice on humans and not on animals. Only when there were not published the clinical study in connection to the natural supplement, it was cited the experimental study. Here are presented those medical plants, which are the most frequently 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 on erection was evaluated with objective measurements: International index for erectile dysfunction, blood chemistry parameters, and certified devices measured the volume and hardness of erection.

4.1. Classification of the medical plants and natural supplement according to the mode of action on erection

4.1.1. *Testosterone synthesis boosters*: Zn, Tribulus terrestris, Saw – palmetto, bark of tree Aspidosperma quebracho blanco.

4.1.2. *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.
4.1.3. *Activators of estrogen metabolization and degradation* (antagonists to xenoestrogens): indol-3-carbinol (I3C), diindolylmethane (DIM).

4.1.1. Testosterone *synthesis boosters*

4.1.1.1. 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 erectile dysfunction (Khedun *et al.*1995).
Zinc increase the level of testosterone, improve the sperm mobility and can even improve fertility (Jalali *et al.* 2010, Björndahl & Kvist 2011, Salgueiro *et al.* 2004).

4.1.1.2. 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 showed the 78.11% improvement in semen analysis in men with oligozoospermia (n=32) treated with Tribulus terrestris supplement (Sellandi *et al.* 2012).
Another study evaluated the effect of a new natural compound tradamixina in order to improve male sexual function in elderly men (libido and ED) versus administration of tadalafil 5 mg daily. The treatment twice a day with Tradamixina (Alga Ecklonia Bicyclis,Tribulus Terrestris and other compunds) for 2 months in double blind controlled study improved ED and libido in elderly men without side effects of Tadalafil (n=35) (Iacono *et al.* 2012b).
Iacano and co-authors (2012c) 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 (Neychev Mitev 2005) from Department of Chemistry and Biochemistry, Sofia, Bulgaria find out that Tribulus terrestris steroid saponins possess neither direct nor indirect androgen-increasing properties. In the sample there was 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 Tribulus terrestris steroid saponins with sample size greater than 20 probands.
Also Brown *et al.* (Brown *et al.* 2001) could not demonstrate the effectiveness of an androgenic nutritional supplement with tribulus terrestris designed to enhance serum testosterone concentrations and prevent the formation of dihydrotestosterone.

4.1.1.3. Saw – palmetto berries (Serenoa repens)
Saw palmetto are berries of the American dwarf tree (Serenoa repens, Sabal serrulata). The plant is found in many areas of the south-eastern United States. This 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 (Fagelman, Lowe 2001).
Country of cultivation: USA
Active substance: phytosterols in berries.
Serenoa repens is an effective dual inhibitor of 5alpha-reductase isoenzyme activity in the prostate. Unlike other 5alpha-reductase inhibitors, Serenoa repens induces its effects without interfering with the cellular capacity to secrete PSA (Habib *et al.* 2005).
Kohut und co-authors (Kohut *et al.* 2003) confirmed that the natural supplement (150 mg DHEA, 300 mg androstenedione, 750 mg Tribulus terrestris, 625 mg chrysin, 300 mg indole-3-carbinol and 540 mg saw palmetto) significantly increased serum levels of androstenedione, free testosterone, estradiol and dihydrotestosterone (DHT) during week 1 to week 4 (n=16).
Studies with no significant effect: According to clinical study of Pytel' I. *et al.* Permixon (extract from Serenoa repens) had no effect on the level of prostate-specific antigen. Plasma hormones (testosterone, DHT, estradiol, LH, androstendion) did not change. Nine patients developed 10 side effects but they were unrelated to the treatment (Pytel' *et al.* 2003).
Also Kaplan SA *et al.* and other authors (Kaplan *et al.* 2004, Mac Donald *et al.* 2012) have not found appreciable long-term improvement.by patients (n=64) treated with saw palmetto. In contrast, patients treated with finasteride had 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 on the market.

4.1.1.4. 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 testosterone synthesis booster and inhibitor of the the 2-methoxyidazoxam binding to human penile alfa 1, alfa 2-adrenoceptors.
Sperling *et al.* (2002) and Campos *et al.* (2006) 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 Aspidosperma quebracho blanco in connection with ED. In the study of Santos *et al.* (2009) acute and subchronic toxicity and cytotoxicity of stem bark ethanolic extract of *Aspidosperma subincanum* (EE*As*) 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. The EE*As* appears to be safe and non-toxic in low doses in domestic preparations used by population have relatively 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 (Riley 1994).

4.1.2. NO production boosters, *inhibitors of the PDE 5*

4.1.2.1. 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, phytoestrogens.

Panax ginseng is a well-known herb in traditional Chinese medicine (TCM). Recently, they are a number of studies on this herb. For P. ginseng, it has been shown to have an anti-inflammatory activity, improves pulmonary function and erectile dysfunction, improves cognition in patients with Alzheimer's disease and promotes sexual arousal in menopausal women as well as prevents cancer (Chan 2012, Ernst *et al.* 2011). 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 (Kim *et al.* 2009). In the Korean experimental study was shown, that the Korean ginseng berry extract GB0710, was more potent in ED than the red ginseng root extract (Cho *et al.* 2013).

Hong *et al.* (2002) investigated the efficacy of Korean red ginseng for erectile dysfunction using the International Index of Erectile Function, RigiScan (UroHealth Systems, Laguna Niguel, California), hormonal levels and penile duplex ultrasonography with audiovisual sexual stimulation. A total of 45 patients (45 controls) with clinically diagnosed erectile dysfunction were enrolled in a double-blind, placebo controlled, and crossover study. The ginseng dose was 900 mg 3 times daily. The data showed significant improvement of all followed variables, the Korean red ginseng can be as effective alternative for treating male erectile dysfunction.

Jang *et al.* (2008) has done a systematic searches 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 of erectile dysfunction were considered for inclusion. Methodological quality was assessed using the Jadad score. Collectively these RCTs provide suggestive evidence for the effectiveness of red ginseng in the treatment of erectile dysfunction. 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.

4.1.2.2. Butea superba (BS)

Butea superba is an herb native to Thailand, thought by locals to be an aphrodisiac. 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 from a Cortés-González *et al.* (2010) a natural health product containing BS was more effective than sildenafil in the first part of the clinical study (n=32), but in the second, 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 the opposite a 3-month randomized double-blind clinical trial from Thai investigators (Cherdshewasart *et al.* 2003) was carried out in Thai volunteers with ED. There was a significant upgrading in 4 of the 5 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. Haematology 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 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 new information, that BS can act also as a testosterone production booster (Chaiyasit, Wiwnaitkit 2012).

4.1.2.3. Gingko biloba

Ginkgo biloba is a unique species of tree with no close living relatives. The ginkgo is a living fossil, recognisably similar to fossils dating back 270 million years. Native to China, the tree is widely cultivated and it has various uses in TCM and also 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 Ginkgo biloba 240 mg daily was carried out. Following a 1-week (generally 12 weeks) control, it 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 (Wheatley 2004).

The aim of other study was to examine the effect of Ginkgo biloba on antidepressant-induced sexual dysfunction (n=19). This study did not replicate a prior positive finding supporting the use of Ginkgo biloba for antidepressant, especially SSRI (serotonin reuptake inhibitors), induced sexual dysfunction (Kang *et al.* 2002).

In an open trial ginkgo 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 ginkgo biloba than men (N=30), with relative success rates of 91% versus 76%. Ginkgo biloba generally had a positive effect on all 4 phases of the sexual response cycle: desire, excitement (erection and lubrication), orgasm, and resolution (afterglow) (Cohen & Bartlik 1998).

4.1.2.4. Epimedium sagittatum (ES)

Epimedium sagitatum 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 nitric oxide and PDE-5 activity (Chiu *et al.* 2006). Other research has demonstrated that injections of Epimedium extract directly into the penis of the rat results in an increase in penile blood pressure (Chen, Chiu 2006) and have confirmed that Epimedium 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 (Dell'Agli *et al.*2008). No clinical study with ES and its effectiveness and safety by ED has been published.

4.1.2.5. 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 Traditional Chinese medicine.

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 in improving erectile function there were done some China experimental studies. In conclusions these studies showed, that EUO enhance the expression of nNO and eNO in penile tissue and improve erectile function in rats (Kwan *et al.* 2004, Zhang *et al.* 2006). I have not found the clinical study with EUO treatment in ED.

4.1.2.6. L-arginin an 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 endotelilial wall involves a two step oxidation of L-arginine to L-citrulline catalized by NOS (Figure 2).

Efficacy and safety of L-arginine aspartate 8 g combined with 200 mg of adenosine monophosphate (AA) for intermittent treatment of mild-to-moderate erectile dysfunction (ED) were compared with placebo group in the clinical trial (n=26). This pilot phase II study

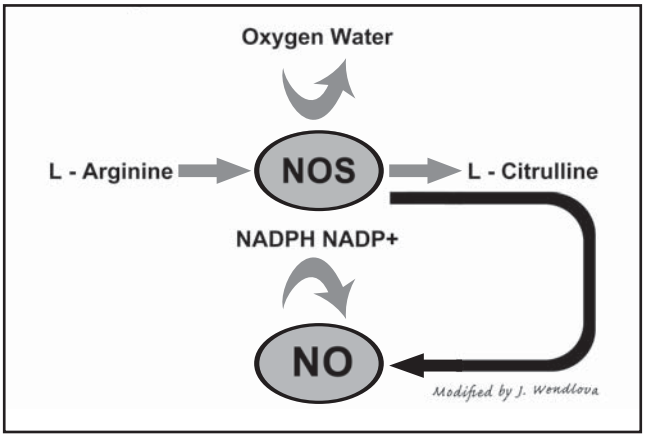

Fig. 2. Biosynthesis of L-Citrulline.

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 (Neuzillet *et al.* 2013).

Paroni *et al.* (Paroni *et al.* 2012) have investigated the plasma concentration of asymmetrical dimethylarginine (ADMA), an inhibitor of nitric oxide synthase, symmetric dimethylarginine (SDMA) and L-arginine concentrations in patients with erectile dysfunction. 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 erectile dysfunction subgroups were significantly lower than both in controls ($p<0.05$) and in non-arteriogenic erectile dysfunction patients ($p<0.05$); the two ratios in non-arteriogenic erectile dysfunction 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 erectile dysfunction compared with both patients with non-arteriogenic erectile dysfunction and controls. The negative correlation between ADMA and severity of erectile dysfunction is present only in patients with arteriogenic erectile dysfunction. ADMA can be used as a parameter for distinction arteriogenic from non-arteriogenic erectile dysfunction patients.

Cormio *et al.* (Cormio *et al.* 2011) have showed in the clinical study (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 psychologically fear of the synthetic PDE-5 enzyme inhibitors.

4.1.2.7. 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. Bombyx Mori is loaded with important nutrients, minerals and amino acids which can help provide both energy and drive. It also can 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 with extract from male Bombyx mori, however they are many natural sexual male enhancement pills on the market. Male Bombyx 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 (Nagaoka *et al.* 2912).

Experimental study authors from Korea (Hong-Geun *et al.* 2012) was designed to investigate the effects of male silkworm pupa powder (SWP) on the levels of nitric oxide synthase (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 Bombyx 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 Bombyx mori has androgen-like action.

4.1.3. *Aktivators of estrogen metabolization and degradation* (antagonists to xenoestrogens): indol-3-carbinol (I3C), diindolylmethane (DIM).

In despite of current lack of clinical studies investigating the anti-estrogen effect of I3C and DIM in men with ED and infertility caused with xenoestrogens and estrogen dominance, the market is selling off a lot of preparations containing I3C and DIM for the ED and infertility 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 estro-

gen-dependent diseases, such as some types of breast cancer (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) (Nakamura *et al.* 2009).

4.1.3.1. Indole-3-carbinol

I3C (C_{9H9NO}) 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. Indole-3-carbinol is the subject of ongoing experimental and clinical research into its possible anticarcinogenic, antioxidant, anti-atherogenic and antiestrogenic effect (Weng *et al.* 2007, Bell *et al.* 2000).

In the experimental studies from Bradlow and Michnovicz (1991) 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 that LTr-1 is an antagonist of estrogen receptor function (Michnovicz & Bradlow 1990, Chang *et al.* 1999, Bradlow & Michnovicz 1986).

Michnowitcz and Bradlow (1997) investigated the effects in humans of short-term oral exposure to Indole-3-carbinol (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 and may thereby provide a novel "dietary" means for reducing estrogen-dependent cancer risk and other estrogen-dependent diseases.

In the future we can expect in connection with 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 and low testosterone level caused by xenoestrogens exposure.

4.1.3.2. Diindolylmethane

3,3'-Diindolylmethane or DIM is a compound derived from the digestion of indole-3-carbinol, 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 diindolylmethane.

Diindolymethane (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, proved to be non-toxic and a potent aid against estrogen adverse effects (Vivar *et al.* 2010).

The mechanism by which DIM induces its beneficial actions has been shown to involved a reduction in estrogen receptors activity, promotion of healthy estrogen metabolites and support for selective cells apoptosis (cell suicide), which removes damaged or sick cells (Kim & Milner 2005).

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," 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 (Bradlow & Michnovicz 1996).

The positive influence of cruciferous vegetables on human estrogen metabolism and estrogen-dominant diseases is in scientific literature very good known and was verified in many clinical studies (Abdull *et al.* 2013, Ho *et al.*2013, Liu & Lv 2013, Marconett *et al.* 2012).

On the most supplements with 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.

Other known estrogen-inhibiting foods. Some of the best and tastiest sources are squash, onions, green beans, berries, citrus, pineapples, pears, grapes, figs, melons, sesame seeds, and pumpkin seeds (Li *et al.* 2011).

DISCUSSION

The increase in ED, oligozoospermia and infertility in the productive age world population, according to clinical studies cited in the article, is mainly determined by the following factors:

1. increase in obesity and metabolic syndrome,
2. poor diet deficient of important nutritional substances necessary to bioregeneration of the gonad cells and to production of sex hormones,
3. increase in contamination of the environment and food with xenoestrogens,
4. chronic stress, negative phenomenon in the rapidly evolving knowledge society, marked by economic crisis, existential uncertainty, disintegrating family ties, emotional loneliness.

Affected males find often a solution to your problems in finding natural products for ED in the online internet store, the reasons are probably most often following:

1. easy availability of over-the-counter drugs,
2. acceptable price,
3. advertised safety without side-effects,
4. avoid the doctor visits, saving payments for medical examination.

Overview of controlled clinical studies showed that even today is the 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 by 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. It is interesting to note, that clinical studies of scientists from countries of origin herbs for ED, where is also thousand-year-old traditions of their use, refer to the statistical significance results in the efficacy and safety of medicinal plants and their extracts. 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 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. thromboembolic 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 cited clinical studies in the review have shown that the bioregeneration (nutrition therapy, exercise, body mind coordination) is in the erectile dysfunction possible with considerable success.

Declaration – conflict of interests.
The author declares, that she has no competing interests (financial or non financial).

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