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Search of A Non-Toxic Therapeutic Solution to Erectile Dysfunction And/Or Impotence in Men

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ABSTRACT - The objective of this review is to highlight the common conditions of erectile dysfunction, impotence and infertility that affects majority of world's men population. To overcome the distress, unhappiness, and relationship problems, men throughout the world resorts to avail any therapy that can make their partners happy and overcome the inability to conceive. In this context, an attempt is made to focus the etiological factors, including (I) pathology of the disease (ii) addiction to alcohol and smoking habits and (iii) the adverse effects of some synthetic and natural drugs. Different available treatment modalities have been described and the toxicological manifestations of the erectogenic drugs have been discussed. Synthetic drugs are well-known for their side effects and the undesirable effect of natural drugs has not been thoroughly worked out on the assumption that they are harmless. Nevertheless, since the erectogenic drugs are a sure way to a possible conception, the adverse effects of such drugs could result in deterioration of the future generations resulting in physically crippled and mentally retarded children, in addition to syndrome menace in human population. Finally it is concluded that doctors prescribing erectogenic drugs should have a thorough knowledge of the literature on undesirable effects of such drugs. The erectogenic drugs (whether, synthetic or natural) should be regulated by strict protocols before they are available for human consumption.

KEY WORDS – Erectile dysfunction – therapy - natural and synthetic drugs - toxicity

INTRODUCTION

An erect penis has always been a symbol of virility, and fertility. The inability to obtain or maintain an erection sufficient for vaginal penetration is clinically known as erectile dysfunction and or impotence, which is a health problem of major concern among men from all geographical locations (1). Impotence is a baffling disorder that can cause considerable distress, unhappiness, and relationship problems. Even more emotionally painful for many men and their partners is their inability to conceive because the male partner is impotent. When a man suffers from impotence, premature ejaculation, or is infertile, feelings of inadequacy swell and he no longer feels 'like a man'. The mere mention of the word impotence is enough to send a shiver of fear down the spine of most men. The thought of being unable to perform is simply at direct odds with ones' image of what is manly. The problems of erectile dysfunction, impotence and infertility are common conditions that affects majority in the world (2).

The survey from Malaysia, China and India revealed many cases of erectile dysfunction. The Malay and Chinese men tended to blame their wives for their problem, unlike the Indian men, who attributed the condition to fate. Malays would prefer traditional medicine for the problem (3). In a study on pattern of erectile dysfunction in Jeddah city of Saudi Arabia, the epidemiological survey showed 73% of the patients were married with one wife, 23.5% married with two wives, and 8% were single (4). In another study, erectile dysfunction in 680 Saudi patients, El-Sakka (5) found 21.4% of less than 50 years, 20% of these patients had psychogenic problems, while 80% had organic severe erectile dysfunction. Among them 50% had severe, 40% had moderate and 10% had mild erectile dysfunction.

Pathological Conditions as the Basis of Impotence and/or Sexual Dysfunction

The known and reported causes for erectile dysfunction and impotence may be associated with diseases. These may be diabetes, hypertension, myocardial ischemia, ischemic heart disease, atherosclerosis, Peyronies's disease, testicular failure, hypogonadism, hyper-prolactinaemia, klinefelter's syndrome, cryosurgical ablation of the prostate, vascular injury, hypercholesteremia, hormonal imbalance, alcohol excess, smoking, spinal and/or intrapelvic nerve damage (6-14). The etiology of sexual dysfunction related with heart ailments (ischemic heart disease, hypertensive men, and atherosclerosis) appeared to be due to the penile arterial vascular changes causing erectile dysfunction and impotence (9). DeWire (15) also found vascular disease to be the single most common cause of erectile dysfunction and impotence. Whereas the etiological factors described for erectile dysfunction and impotence associated with diabetes were testicular failure, trauma, venous leak and hyperprolactinaemia (16). Impaired pharmacological action of nitric oxide has also been described to be the cause of diabetes-related impotence (7). Testicular cancer is also associated with impaired sexual and spermatogenic function (17).

Synthetic Drugs as the Basis of Sexual Dysfunction and Impotence

Many of the allopathic drugs used therapeutically in the treatment of cardiovascular diseases, diabetes and cancer are reported to have adverse effects on sexuality, spermatogenic function and are known to alter the human socio-sexual cycle (17-21). With some drugs the relationship between the onset of symptoms and the taking of medication is obvious and predictable, as is the case with estrogens for prostate cancer. Leuprolide, an analogue of gonadotrophin releasing hormone is also used to treat prostate cancer by chemical castration. Testosterone secretion is inhibited and impotence follows. The more commonly encountered situation is the man who may have dwindling erectile function over a period of months or years, and who is prescribed a medication reported as a possible cause of impotence. These drugs include some of the β-blockers, H_2-receptor antagonists, e.g. cimetidine and some of the psychotropic drugs (22-25).

Search for a Therapeutic Solution to Sexual Dysfunction and/or Impotence.

The search of an effective, safe and easy to administer drug for use in erectile dysfunction, impotence and fertility has been a perennial pursuit of most societies from times immemorial to throughout the history. Treatments for these disorders have been the availability of ginseng, rhinoceros horn and other dubious herbs to enhance potency. The discovery of testosterone in the late 1930s and its use to relieve the impotence in hypogonadal men was a major step forward in this field. Many substances used for recreational purposes (or sometimes abused) were also thought to have profound effects on sexual performance (26-28). Space age synthetics have provided a means of manufacturing effective devices for implantation into and to take over the role of the corpora cavernosa. During this time the synthetics have witnessed the emergence of an entirely new approach to the management of erectile dysfunction and impotence, namely the use of drugs to control blood flow to and from the corpora cavernosa. In the past decade there has been a significant change in the management of patients with sexual dysfunction both because of their improved understanding of erectile physiology, and also because of the development of new and effective medical therapies. Attention has been focused increasingly on the prosexual effects of oral pharmacological agents with central neurotransmitter actions. The role of various dopaminergic, adrenergic, and serotonergic agents in particular, has been intensively investigated in both human and animal studies. Some of these drugs have been considered for their potential role in the treatment of sexual dysfunction, while others have contributed to our understanding of basic neuro-physiological processes in sexual arousal (29). The standard medical treatment of erectile dysfunction and impotence ranges from relatively noninvasive measures to the placement of prosthetic devices within the penis. The therapeutic options include: Medications (both synthetic and natural sources), psychotherapy, intercavernosal injection, penile prosthesis, and vacuum constrictive devices.

Medications from Synthetic Sources

Many drugs in the modern pharmacological treatment (both injection and oral) of erectile dysfunction and/or impotence involved according to problems include testosterone, yohimbine, trazodone and apomorphine, phentolamine, prostaglandin E, arginine and sildenafil which are required for libido and arousal problems (30-35). Endogenous nitric oxide is reported to exert a significant role in the physiology of the cavernous tissue, operating chiefly as the principal mediator of erectile function (36) and alterations in the biology of

nitric oxide account for various forms of erectile dysfunction (37). Furthermore, animal studies have confirmed the presence of nitric oxide synthase (the enzyme that catalyzes nitric oxide production) in penile nerve fibers from a mid-shaft segment (38). In another treatment of erectile dysfunction and impotence the combination of aphrodisiacs with other medicinal mixtures is widely used. One of the most useful drugs of this type used in patients with erectile dysfunction is Afrodor 2000 (a special mixture of sedatives, aphrodisiacs and vitamin E) (39). Of the ejaculatory disorder therapies, treatments for premature ejaculation are the best studied. Favorable results have been obtained with clomipramine, paroxetine and fluoxetine (40).

Hormonal Therapy

For all men with androgen deficiency, whether this results from primary testicular disease such as Klinefelter's syndrome or from gonadotrophin deficiency, the mainstay of treatment is testosterone. Today testosterone may be administered in a number of different routes. It may be given orally in the form of testosterone undecanoate (Andriol). Previously the only oral form of testosterone was alkylated derivative, methyltestosterone, which is no longer used because of its hepatotoxic potentials. The other forms of testosterone used are testosterone enanthate (Primoteston Depot), testosterone esters (Sustanon) by intramuscular injections. Sometimes, depending on the need, testosterone pellets are implanted. Androgens are reported to be necessary for the normal development of the penis and their deficiency results in significant structural abnormalities. Data from experimental animal studies show that androgens support erectile function through a direct effect on the erectile tissue and their concentration of nitric oxide synthase-containing nerves (41-43).Testosterone enhances libido, frequency of sexual acts and sleep-related erections (42, 44). Very occasionally, a man with impotence may be found to have hypothyroidism which, if present, should be treated by slow introduction of thyroxine. The doses may be adjusted according to the clinical response and on the basis of the concentrations of thyroid stimulating hormone (TSH) concentrations. However, adequate treatment of hypothyroidism does not guarantee the return of normal sexual function. Hyperprolactinaemia is uncommon but very important as it is one condition for which a specific treatment is available. It results in loss of libido and impotence by reduction of plasma testosterone contents and possibly by some other mechanisms. To cure hyperprolactinaemia, treatment of bromocriptine (Parlodel) is given to reduce the secretion of prolactin. Bromocriptine, a drug that blocks prolactin secretion through the pituitary, is useful in normalizing prolactin levels and results in improved sexual performance in men with elevated prolactin levels (45, 46). Experimental studies revealed injections of gonadotropin releasing hormone and human chorionic gonadotropin have been found to improve the semen quality, oligozoospermia and spermatogenic dysfunction in dogs, thereby restoring their fertility (47).

Yohimbine

The FDA has approved only one natural product derived medicine for impotence: yohimbine, an alkaloid isolated from the bark of the yohimbe tree (Pausinystalia johimbe), native to tropical West Africa. Yohimbine hydrochloride (an alpha 2-adrenoceptor antagonist) increases libido, but its primary action is to increase blood flow to erectile tissue. Contrary to a popular misconception, yohimbine has no effect on the testosterone level. When used alone, yohimbine is very beneficial in sexual arousal, sexual performance and ejaculation (48-51). If combined with strychnine and testosterone, it is even more effective.

Sildenafil Citrate (Viagra)

Sildenafil (Viagra) holds promise as a new effective treatment for penile erectile dysfunction (52, 53) and has been recently approved by Food and Drug Administration, as the first oral agent indicated for the treatment of impotence. Unlike other therapies for erectile dysfunction, Viagra does not directly induce penile erection. The drug works by mimicking the smooth muscle relaxant effects of nitric oxide (NO), the principal neurotransmitter in the penis. Local release of NO is induced by sexual stimulation and erection is dependent on this neurotransmitter and its second messenger, cGMP. Viagra, an orally active, selective inhibitor of the predominant isoenzyme (phosphodiesterase) that inactivates cGMP, produces its pro-erectile effect by increasing cGMP levels.

Oral Prostaglandin E_1

Limaprost, an oral prostaglandin (PGE_1) derivative, has been found to be an effective treatment for erectile dysfunction (54). Oral prostaglandin E1 (limaprost) has been described to be very useful in organic and psychogenic impotence, however patients with the history of Diabetes mellitus, hypertension, or pelvic surgery showed relatively poor responses to oral prostaglandin E1 (10, 55). Several new developments in this area are currently under way.

Combination of Papaverine and Prostaglandin E_1

A combination of two natural products (papaverine and prostaglandin E_1) respectively from Papaver somniferum and from sheep seminar vesicle tissue has been recognized as competent vasodilators. These products have been found to possess potential against male impotence (56). However, the combined use of these products has been found to cause priapism (extended erection), local fibrosis and pain.

Berberine

Berberine is an alkaloid, widely distributed in nature and occurs in Berberis plants such as Berberis aristata and B. vulgaris. Studies of Chiou et al., (57) have found berberine to cause a relaxant effect on the rabbit corpus cavernosum tissue, which is attributable to both endothelial-dependent and –independent properties. Furthermore, these authors found that the former component is apparently due to the release of NO from sinusoidal endothelium, the endothelium-independent mechanism involved in berberine relaxation might be linked to Cholera Toxin- and 4-Amino Pyridine-sensitive K^+ channel activation in the cavernosal vasculature.

Forskolin

Forskolin, a diterpene is present in an Indian herb *Coleus forskohlii*. Mulhall et al. (58) found Forskolin to be as an intracavernosal vasoactive agent in the management of vasculogenic impotence. These authors further found that the effect of Forskolin might be related to its influence on cyclic adenosine monophosphate (cAMP) which is well known to increase the duration of erection.

L-Citrulline

L-citrulline, combined with calcium phosphate and other extenders, is marked as STIMULIN. The preparation is claimed to improve sexual stamina and ease erectile dysfunction. The active ingredient in the formulation is L-citrulline, which occurs naturally in watermelon (59).

Pyrano-isoflavones

The pyrano-isoflavones from roots of Eriosema kraussianum are found to cause relaxation of corpus cavernosum smooth muscles (60).

Isolated Experimental Studies

Experimental studies in early eighties revealed (-) Deprenyl treatment in rats induced a true, long-lasting aphrodisiac effect on sexually sluggish male rats. Whereas pargyline facilitated the sexual performance of rats transiently (61). Claus et al., (62) found methaqualone to stimulate erectile functions and copulation status in monkeys. N-n-propyl-norapomorphine, a potent dopamine receptor stimulant is reported to produce a dose-related sexual stimulant effect characterized by recurrent episodes of penile erection in experimental animals (63).

Intraurethral Applications

The intra-urethral applications of minoxidil and the alprostadil, 'Muse' have demonstrated significantly greater activity for erectile function than other topical therapies (40, 64, 65).

Intercavernosal Self-Injection

The introduction of intracavernosal administration of vasoactive drugs has revolutionized diagnosis and treatment of sexual impotence (66). Injection of drugs that dilate the penile arteries is a popular method of treatment of erectile dysfunction due to vascular insufficiency. The most common drugs used include papaverine, prostaglandin E1, and phentolamine (67-72).

Intracavernous self-injections for erectile disorders are performed using a variety of drugs and drug mixtures. Only alprostadil and the combination of papaverine with phentolamine are widely used. Alprostadil is very well tolerated; however, penile pain is a serious problem in a significant proportion of patients. Experiments conducted on lidocaine (73) revealed 1% lidocaine with intracorporeal prostaglandin E1 is very effective in the treatment of erectile dysfunction with alleviation of pain and enhancement of erectile effect. In addition, intracavernous injection of vasoactive drugs are observed to be an effective alternative in the treatment of men with persistent psychogenic impotence when sex therapy was unsuccessful in a study on 153 patients (74). Moxisylyte, a competitive noradrenaline antagonist, has been recently reported to be effective in the treatment of impotence. Intracavernous injection of moxisylyte at 10-30 mg can induce an erection adequate for intercourse in most of the patients (75).

Penile Prostheses

The "gold standard" for the treatment of erectile dysfunction is the surgical insertion of a penile prosthesis (76, 77). Implantation of such a device is the "treatment of choice in most cases of complete erectile loss" (77). Three forms are available: semirigid, malleable, and inflatable. The effectiveness, complications, and acceptability vary according to type. The main problems of all three are mechanical failure, infection, erosion of the connective tissue, and irreversible damage to erectile tissue. Obviously, insertion of a penile prosthesis should be viewed not as the first step in the treatment

of erectile dysfunction, but rather the very last step, after all other attempts have proved futile.

Furthermore, to combat the impotence and erectile failure, the penile implants have become very common as a physical treatment. A study on 20 men with Peyronie's disease (78) reported that these patients underwent placement of a malleable penile prosthesis. The implantation of the prosthesis in these cases straightened the penile shaft in all cases but a variable degree of deviation of the glans penis persisted in seven cases and led to dissatisfaction in 2 out of 16 patients. However, it was concluded that malleable penile implants are safe and effective in the treatment of Peyronie's disease associated with impotence.

Vacuum Constrictive Devices

Vacuum constrictive devices literally pump blood into the erectile tissue. Most of these devices consist of a vacuum chamber, a pump, connector tubing, and penile constrictor bands. The vacuum chamber is large enough to fit over the erect penis. The connector tube runs to the pump from a small opening at the closed end of the container. An elastic constrictor band is placed around the base of the chamber. Water-soluble lubricant is applied to the open end of the cylinder and to the entire penis. The chamber is placed over the flaccid penis, and an airtight seal is obtained (79).

The pump (some are battery-operated) creates a vacuum in the chamber. The negative pressure draws blood into the penis, to produce an erection like state. The constrictor band is then guided from the vacuum chamber onto the base of the penis. The erection is maintained because the blood is trapped in the penis. Although manufacturers and many physicians state that vacuum devices have revolutionized the management of erectile dysfunction, patient acceptance does not reflect this enthusiasm. Vacuum constrictive devices are generally effective and are extremely safe, but for some reason a significant number of patients quit using them. The reason may be that the devices are somewhat uncomfortable, cumbersome, and difficult to use; it takes patience and persistence to master the process. Most vacuum devices require both hands and the assistance of the sexual partner. Patients may quit using these devices because they may impair ejaculation and cause discomfort. Patients and partners complain about the lack of spontaneity that results from the use of vacuum devices. Despite these short comings, vacuum constrictive devices have been used successfully by many men with erectile dysfunction (77).

Psychotherapy

Psychological therapies for impotence are useful in some cases. Psychological factors are rarely the cause of erectile dysfunction. Nonetheless, impotence can lead to psychological disturbances. Even in cases of clear-cut organic erectile dysfunction, repeated inability to attain or sustain an erection leads men to frustration, anxiety and anticipation of failure. Learning stress reduction techniques (relaxation exercises, biofeedback, and deep-breathing exercises, for example) may help reduce anxiety. In addition, psychological treatment may be especially beneficial for patients who are depressed. (80). While there are no reports on the involvement of natural products in psychotherapy, in one experimental study, McInnis et al. (81) found aromatherapy by ginger root oil, to enhance the mating capacity of medfly (*Ceratitis capitata*).

Medications from natural sources

In addition to nutritional measures and exercise, plant-based, or herbal medicines are often used in the natural treatment of erectile dysfunction. Improving sexual desire and function is possible using plant-based medicines that (1) improve the activity of the male glandular system (2) improve the blood supply to erectile tissue, and (3) enhance the transmission or stimulation of the nerve signal. A number of natural agents occur to boost sexual function and could be appropriately described also as aphrodisiacs. These are Spanish fly, glandular products from musk deer and civet cats, varieties of natural oats (Avena sativa), ginseng and belladonna (59, 60).

Yohimbe

The yohimbe tree (Pausinystalia johimbe) is the source of yohimbine, the only FDA-approved drug from natural sources for the treatment of erectile dysfunction. Because of the yohimbine content of yohimbe bark, the FDA classifies yohimbe as an unsafe herb (82). Studies on reproductive, cytological and biochemical toxicity revealed yohimbe to induce spermatozoa abnormalities and chromosomal aberrations, in addition to reduction of fertility in Swiss albino mice. The data on biochemical parameters showed increase of malondialdehyde and depletion of Non-protein Sulfhydryl Groups (NP-SH), proteins, RNA and DNA in testicular cells (83).

Muira puama Extract

One of the best plants to use for erectile dysfunction or lack of libido is muira puama (Ptychopetalum olacoides), which is also known as potency wood. This shrub is native to Brazil and has long been used as a

powerful aphrodisiac and nerve stimulant in South American folk medicine (82). A recent clinical study has validated its safety and effectiveness in improving libido and sexual function in some patients (84). At the Institute of Sexology in Paris, France, Dr. Jacques waynberg (one of the world's foremost authorities on sexual function) supervised a clinical study involving an extract of muira puama. The study involved 262 patients who complained of lack of sexual desire and the inability to attain or maintain an erection. Extract of muira puama was effective in helping many of these men. Within two weeks, at a daily dose of 1 to 1.5 grams of the extract, 62% of patients with loss of libido claimed that the treatment had dynamic effect; 51% of patients with "erection failures" felt that muira puama was of benefit. However the exact mode of action of its constituents in the sexual function is not known.

***Lepidium meyenii* (maca)**

Lepidium meyenii has been known and used in the Andean mountains for 2000 years. It has nutritional value, which is employed by the Andean Indians to enhance fertility and sexual behavior in both sexes (85, 86).

***Ginkgo biloba* Extract**

Extract of *Ginkgo biloba*, is one of the most popular plant medicines in France and Germany. In Germany, over 5 million prescriptions are written each year for ginkgo extract. In the United States, ginkgo extract is available in health food stores. Numerous clinical studies have demonstrated that ginkgo extract is extremely beneficial in treating vascular insufficiency. In clinical trials, patients with chronic cerebral arterial insufficiency and patients with peripheral arterial insufficiency have responded favorably to ginkgo extract (87). In addition to its use in cerebral insufficiency and impotence in males, senility (88), the Ginkgo biloba extract has been shown to be extremely beneficial in the treatment of erectile dysfunction due to lack of blood flow (89). However, Ginkgo biloba treatment was found to have adverse effects, including chromosomal aberrations, rate of pregnancy and pre-implantation loss in rodents. Studies on biochemical parameters revealed role of free radical species in the induced changes in testis chromosomes and the reproductive function (90).

Damiana

The leaves of the damiana (*Turnera diffusa*) have been used in the United States since 1874 as an aphrodisiac and "to improve the sexual ability of the enfeebled and aged." (90). Despite any clinical support, damiana use is very popular. Damiana is thought to slightly irritate the urethra, thereby increasing the sensitivity of the penis (91). Damiana is seldom used alone; most often it is recommended along with other commercial herbal preparations. If an individual desires the benefit of damiana on its own, drinking a daily cup of damiana tea should be sufficient to produce urethral irritation (91).

***Eurycoma longifolia* (Jack)**

Experimental studies on rats revealed *Eurycoma longifolia* (Jack) to increase sexual potency and aphrodisiac potentials in male rats as revealed by mountings, intromissions and ejaculations (92).

Cordyceps sinensis

Zhongcao (an edible mushroom) combined with *Cordyceps sinensis* (a fungus) and an insect larva, has been known Chinese traditional medicine to treat general debility and to enhance sexual capacity. The sex stimulating property of *Cordyceps sinensis* has been reported to be due to a protein component that contributes hypotensive and vasorelaxant properties of the herb (93).

Tribulus terrestris

Tribulus terrestris (devil's thorn) is found in Southern Africa and is used medicinally as a tonic for diarrhea and diseases of throat and eyes. The additional use of the extracts from T. terrestris has been described due to the presence of protodioscin in this plant , which improves sexual desire and enhances erection (94, 95). A commercial preparation of T. terrestris is sold under the trade name of Libilov.

***Eurycoma Longifolia* extracts**

Eurycoma longifolia (Simaroubaceae) is found in forests of Malaysia and is used as an antimalarial, cytotoxic, anti-ulcer and anti-pyretic natural drug. It is recently figured in press for its reputed use to increase male virility. Subsequent researches found that rats treated with Eurycoma longifolia displayed enhanced sexual arousal (92, 96).

Catuama

Catuama is a combination of four plants – Paullina cupana, Trichilia catigua, Zingiber officinalis and Ptychopetalum olacoides. The combination of these plants (Catuama), in more recent times is promoted as an aphrodisiac. On rabbit corpus cavernosum, catuama brings about relaxations (97).

Aspidosperma ulei

Plants that belong to the genus Aspidosperma (Apocynaceae) are known to be very rich in indole alkaloids and have an ethnomedical history of use as traditional remedies for erectile dysfunction. In a recent study, Compos et al., (98) found Aspidosperma

ulei root bark to posses pro-erectile effects that result from an alkaloidal rich fraction.

Red Onion Peel Extract (FRS 1000)

FRS 1000 is a beverage containing flavonoids extracted from onion peel is reported to show improvement of male sexual function. FRS 1000 has a strong phosphodiesterase 5A inhibitory activity, which is considered to be important for treatment of erectile dysfunction (99).

Love Stone and Chan su

In China and West India, potent such as love stone and Chan we are in wide spread use against impotence and erectile failure. These aphrodisiacs are prepared from toad venom (100). However, these are known to be very toxic and have resulted in fatal poisonings.

Beetle Eating

The Chinese and Malays have been reported to use live beetles (Pale bus dermestoides) to enhance their sexual function (101). However, later on it was found that ingestion of live beetles represented a potential public health hazard in that these beetles were able to serve as a host for the human-infecting tapeworm Hymenolepis diminuta (101).

Pork harboring cysticerci

In small isolated populations of Mexico, people prefer the taste of pork harboring cysticerci because certain triatomids are thought to have aphrodisiac properties and are therefore eaten (102).

Libido (Libid, Libbido, Erosom and Ardorare)

A commercial product, Libido (Libid, Libbido, Erosom and Ardorare, names used in different markets), which is based on components derived from fertilized, partly incubated chickens' eggs, has been used to treat diminished sexual desire in men (103).

Nutrition Supplements

There are certain drugs, which are effectively used for erectile dysfunction and impotence. However, they are available in the markets under the banner of nutrition supplements. These supplements are royal jelly; seven seas multivitamins; minerals and siberian ginseng extract; gamma oil evening prim' rose oil; royal bene sun naturals (yohimbe+royal jelly+vitamin E); standardized siberian ginseng; golden royal jelly; nature's finger print "Milk thistle seed extract"; bee pollen; passion booster formula enhance sexual vitality for men and women; habb-e-nishat; neurotone, natura-vigor; redkooga ginseng; honey bee; bee sting. In addition to erotic foods such as fish and oysters (59, 60, 104, 105).

Toxicity of Erectogenic Medication and Deterioration of Future Generations

Exposure of female parent to drugs and chemicals during pregnancy is well documented to affect the progeny, but little attention has been given to the possibility of paternally mediated adverse drug effects on pregnancy outcome. The erectile dysfunction and/or impotence caused by (chemical compounds, drugs and/or different diseases, including diabetes, cardiovascular diseases, Peyronies's disease, testicular failure, hypogonadism, hyperprolactinaemia, Klinefelter's syndrome, cryosurgical ablation of the prostate, vascular injury, hypercholesteremia, hormonal imbalance, alcohol excess, smoking, spinal and/or intrapelvic nerve damage) is genetically not harmful, so long as the victims do not have an urge for an erection and sexual intercourse with woman of reproductive age. However, when the victims have a desire for sex by using erectogenic drugs, the influence of such drugs on sex functions should be known. These are spermatogenic dysfunction due to spermatozoa abnormalities, chromosomal aberrations including translocations and reproductive toxicity, otherwise, the enjoyment can cause deterioration in the future generations resulting in physically handicapped and mentally retarded children, in addition to typical syndromes. Thus, there is an increasing need to identify the erectogenic drugs, which may be responsible for chromosomal aberrations. Because, if the human zygotes with such aberrations are implanted in the uterus and survive up to second to third month pregnancy, they are most likely to result in abortions. However, a substantial fraction of human zygotes with chromosomal instability and defective DNA repair mechanisms approach to a full term of pregnancy and are known to cause congenital malformations and increase the frequency of syndromes. Thus there is a substantial increase in the frequency of mentally retarded and physically handicapped individuals in the human population, in addition to certain syndromes such as Down's Klinefelter's, Turner's, Patau's Edward's, cancer syndromes (106-113) and several other disease syndromes. It is possible that the sterility, partial-sterility and erection problems may increase in future generations due to the induced genetic damage caused by chromosomal aberrations and rearrangements such as translocations (114, 115). Today, whenever, we see an individual with some physical deformity, first thing that comes to our mind is that this could be the result of mutations and reproductive toxicity due to

xenobiotically induced toxins. Nevertheless, experience in managing these toxicological manifestations of erectogenic drugs is still limited and a well-defined method for its treatment is lacking.

In addition to potential effects on the quantity and quality of spermatozoa produced, the induction of chromosomal aberrations and the reproductive toxicity and the related toxicity in the progeny, the exposure of male parents to toxic drugs and chemical compounds may have a direct effect on the conceptus via their presence in semen (116). Earlier studies have shown a wide range of compounds to enter semen (117). Many drugs that are found in semen can be readily absorbed by the vagina (118) and can affect both the female partner and the progeny. Vinblastine in semen has been associated with vulvo-vaginitis in women (119). Pretreatment of male rats with high doses of estradiol results in uterine hypertrophy and hyperplasia in the female partner (120). Thalidomide has been shown to enter the semen (121) and there is evidence suggesting an effect on progeny (122). Thus drugs in seminal fluid may be absorbed by the mother and affect the conceptus at any time during pregnancy from fertilization on.

It has long been known that a large array of chemical compounds and medications including anticancer drugs can induce chromosomal aberrations and associated congenital malformations (123). These substances are also known to affect the male reproductive tract by inhibiting spermatogenesis (124-126). Short-term paternal exposure to methadone or morphine is reported to result in an increased prenatal mortality and decreased birth weight in offsprings (127, 128). Experimental studies revealed exposure of male mice to erythrosine to induce sperm abnormality, cause spermatogenic dysfunction and induce germ cell mutagenicity. It is also shown to affect spermatogenesis, testicular function and reproductive performance (129). Khil'kevich et al. (130) found nicotine to induce gametotoxic effect related with the disturbance of differentiation dynamics of spermatocytes causing an increase in the level of pathological maturation divisions in the male offsprings. Increased chromosomal aberrations and sperm shape abnormalities in rodents have been observed by organo-phosphorus pesticide Edifenphos (Hinosan) (131) and herbicide paraquat (132). Inhalation of methyl chloride (an industrial gas) in rats is found to induce dominant lethal mutations in sperm located within vasdeferens and epididymis at the time of exposure (133). Chronic low dose treatment of male rodents with cyclophosphamide has been reported to result in malformations and increased pre-and post-implantation loss and behavior abnormalities in the progeny (134, 135).

The association of erectogenic drugs and toxicity has not been well documented in literature with the exception of a few. In China and West India, aphrodisiacs such as love stone and Chan su are known to contain bufotenine, bufadienolides, resibufogenin, buffalin and cinobufagin. These components are also present in toad venom or secretions and are cardiotonic steroids that cause symptoms similar to digoxin. Toxicity from toad venom poisoning is similar to digoxtoxicity and carries a high mortality rate. Seven cases of healthy men are reported who developed vomiting, bradycardia and fatal dysrhythmias after ingesting love stone and/or Chan su (100, 136). Acute poisoning resulting in death is reported by the ingestion of cantharidin for aphrodisiac purposes (137, 138). Deaths have been reported to be associated with ingestion of substances marketed as topical aphrodisiacs containing naturally occurring cardio active steroids (139). Inhalation of "poppers" for their aphrodisiac effect is also found to be a reason of poisoning due to tissue hypoxia, which results due to the failure of methemoglobulin to bind oxygen (140). Yohimbine can induce anxiety, panic attacks, and hallucinations. Other side effects include elevation of blood pressure and heart rate, dizziness, headache, and skin flushing. Yohimbine should not be used by those with kidney disease or psychological problems or by women. Agranulocytosis is reported to be associated with yohimbine use. Viagra is absolutely contraindicated in patients who are taking any chronic nitrate drug therapy or who utilize short acting nitrate-containing medications, due to the risk of developing potentially life-threatening hypotension. In addition, the combination of Viagra and inhaled nitrates, such as amyl nitrates or "poppers" (an illicit recreational drug) could prove to be fatal and should be avoided. The increase in the endogenous production of nitric oxide has been implicated in the development of certain diseases, genotoxicity and cancer (141).

The patients who use physical intracavernous injections like papaverine in combination with phentolamine or surgical implantations of certain vasoactive drugs often suffer from priapism, fibrosis, hematomas and corporeal pain and the formation of nodules or plaques in the corpora cavernosa (142, 143). In some cases a superficial gangrene develops in the penis after insertion of a malleable penile

prosthesis (144).There is abundant work on the pharmacological potentials of the erectogenic drugs used in erectile dysfunction and/or impotence, however, there is a paucity of literature regarding the influence of these drugs on spermatogenic dysfunction, pathological, endocrinological, biochemical changes, general and reproductive toxicity including the impact on spermatozoa, dominant lethal mutations and testicular chromosomes including translocations, which are known to be carried and deteriorate the future generations by syndrome menace.

CONCLUSION

The problems of erectile dysfunction, impotence and infertility are baffling disorders that can cause considerable distress, unhappiness and relationship problems. The etiologies are pathological conditions, hormonal deficiencies and adverse effects of synthetic and/or natural drugs. Although a large number of therapeutic measures exists and are being discovered, the pursuit of the most effective therapy with least side effects is still a dream in the scientific circles. The toxicity of synthetic drugs is well known, whether they are consumed orally or by injection (intraurethral and/or intercavernosal). The penile prostheses, vacuum constrictive devices are difficult to use and have their own drawbacks. The natural drugs may be toxic but not much work on toxicity is done, based on the belief that they are safe. However, the reported work on toxicity of plant products shows some adverse effects and interactions. Since, the erectogens are a sure way to a possible conception, the adverse effects of such drugs could result in deterioration of the future generations resulting in physically crippled and mentally retarded children, in addition to syndrome menace in human population. The toxic erectogens should be avoided by men in reproductive age or should not be available for free sex. The doctors prescribing erectogenic drugs should have a thorough knowledge of the literature on toxicity of such drugs. The erectogenic drugs (whether, synthetic or natural) should be regulated by strict protocols before they are available for human consumption. Finally, at present stage, psychotherapy, non-toxic erectogens and antioxidant-oriented nutrients appear to be the only suitable therapeutic measures for erectile dysfunction and impotence.

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