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RESEARCH ARTICLE

EFFECT OF SAFED MUSLI, GRAPE SEED EXTRACT AND L-ARGININE ON SEXUAL HEALTH.

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Abstract

The use of plant or plant-based products to stimulate sexual desire and to enhance performance and enjoyment is almost as old as the human race itself. The present paper reviews the active, natural principles, and crude extracts of plants, which have been useful in sexual disorders, have potential for improving sexual behavior and performance, and are helpful in spermatogenesis and reproduction. Review of refereed journals and scientific literature available in electronic databases and traditional literature available in India was extensively performed. The work reviews correlation of the evidence with traditional claims, elucidation, and evaluation of a plausible concept governing the usage of plants as aphrodisiac in total. Data on their pharmacological activity, mechanism of action, and toxicity are reported. The present review provides an overview of the herbs and their active molecule with claims for improvement of sexual behavior. A number of herbal drugs have been validated for their effect on sexual behavior and fertility and can therefore serve as basis for the identification of new chemical leads useful in sexual and erectile dysfunction.

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Introduction:-

Male reproductive capacity was found to be deficient in nearly 50% of infertile couples according to a study carried out by the World Health Organization in 1987. Although further figures for this decade are still awaited, it is certain that stressful life style has enhanced the number of subject's suffering from one form of sexual dysfunction or the other. Main factors that decrease the probability of conception in the female partner are frequently congenital, immunological, iatrogenic, or endocrine cause. Oligozoospermia, sexual, and ejaculatory dysfunction are further responsible for inability to conceive in numerous cases. Although many synthetic drugs are available and/or used to treat these problems, some of the drawbacks for these drugs include them being expensive and also their ability to provoke serious adverse effects, effective natural treatments are therefore still in demand. Even if many of the plants or natural products claim to prove their effectiveness without scientific evidence, a number of them are active and possess biological activity, proven by scientific data. Moreover, there is a dearth of systematic review of scientific literature on experimental evidence generated for medicinal plants useful in treating erectile dysfunction and there is a need for in depth pharmacological evaluation. Advancement in the understanding of pharmacological basis of erectile and sexual functions at molecular levels is turning out to be stepping stones towards isolating the crucial physiologic factors involved in sexual arousal, thus helping to narrow down the search for aphrodisiac substances of choice. Many people do not believe in love potions or aphrodisiacs, but countless numbers of men and women have used them down through the centuries, and there is clear proof that they are still in use today. The skepticism

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towards the concept of aphrodisiac is not unjustified, although a systematic evaluation and compilation of scientific information may provide a basis for the evidence-based utilization of herbal drugs for treatment of sexual dysfunction in general

The role of SAFED MUSLI in the sperm count:

Kenjale R et al aimed to evaluate the aphrodisiac and spermatogenic potential of the aqueous extract of dried roots of *Chlorophytum borivillianum* (CB) in rats. Male Wistar albino rats were divided into four groups. Rats were orally treated with (1) CONTROL GROUP: distilled water; (2) CB 125 mg/kg/day; (3) CB 250 mg/kg/day; and (4) Viagra ((R)) group: 4 mg/kg/day sildenafil citrate and their sexual behaviour was monitored 3 h later using a receptive female. Their sexual behaviour was evaluated on days 1, 7, 14, 21 and 28 of treatment by pairing with a pro-oestrous female rat. For sperm count the treatment was continued further in all groups except the Viagra ((R)) group for 60 days. At 125 mg/kg, CB had a marked aphrodisiac action, increased libido, sexual vigor and sexual arousal. Similarly, at the higher dose (250 mg/kg) all the parameters of sexual behaviour were enhanced, but showed a saturation effect after day 14. On day 60 the sperm count increased significantly in both the CB groups, 125 mg/kg and 250 mg/kg, in a dose dependent manner. Thus, roots of *Chlorophytum borivillianum* can be useful in the treatment of certain forms of sexual inadequacies, such as premature ejaculation and oligospermia.

Hussain et al suggested the therapeutic use of natural herbs is an ancient human civilization act and the numbers of people have reliance on their pharmacological properties and preferred to use the natural herbs. People also use to consume these herbs as supplements to energize, bolster, and eventually enhance sexual ability. Polyherbal formulation (PHF) is one of these herbal amalgams that can be used to treat sexual dysfunction including erectile dysfunction, impotence, ejaculation dysfunction, and hypogonadism. The pilot study was aimed at evaluating the capacity of PHF in enhancing the spermatogenic potential of oligospermic patients. Thirty-six male patients with oligospermia were enrolled and randomized either to treatment (n = 23) with PHF (750 mg/d in three doses for 90 days) or to placebo (n = 13) in the same protocol. The preintervention semen analysis was compared with posttreatment semen analysis. Based on the postintervention semen analysis, patients were advised to undergo either in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) to assess their fertility status. After polyherbal treatment, there was a 256% increase in sperm concentration ($9.59 \pm 4.37 \times 10^6/\text{mL}$ to $25.61 \pm 8.6 \times 10^6/\text{mL}$; $P \leq 0.001$), 154% increase in semen volume ($1.7 \pm 0.14 \text{ mL}$ to $4.32 \pm 0.38 \text{ mL}$; $P \leq 0.001$), and 215% increase in sperm motility ($15.43 \pm 2.40\%$ to $48.65 \pm 5.10\%$; $P \leq 0.001$) on day 90 from baseline. Furthermore, a significant improvement and regulation were also observed in serum hormone levels with PHF treatment as compared to the placebo group. The study demonstrated the evidence on synergistic spermatogenic effect of PHF as attributed in ayurveda for the treatment of oligospermia leading to infertility.

Sudipta kumar et al suggested that **Shweta Musali (*Chlorophytum borivillianum* (CB))** is a traditionally used herb for its benefits in male sexual and general health. In the recent past, the herb has attained much commercial significance, both in domestic and international markets. However, limited clinical data is available to establish its traditional claims. The study aimed to evaluate the effect of the water soluble extract of CB root tubers on semen and testosterone in healthy adult males. The research was designed as a randomized, double-blind, placebo-controlled, trial upon the volunteers registered from the outpatient department (OPD) with age ranging from 20 to 40 years. Water extracts of CB and placebo was administered in the patients of groups A and B, for 12 weeks, in two divided doses of 500 mg. Assessment was done based upon Semen (Volume, Liquefaction Time, Sperm Count, Sperm motility) and Serum Testosterone levels parameters. Highly significant improvement was noted in the above parameters after administration of CB extract in comparison to Placebo. Hence it was concluded that the trial drug was effective in improving male sexual health.

Effect of Shweta Musali (*C. borivillianum*) on various parameters after 12 weeks of administration and comparison with the Placebo Group (No. of volunteers - 15 in each group)^[3]

Parameter	Group A						Group B					
	Mean BT	Mean AT	Diff.	SD	Paired t	P value	Mean BT	Mean AT	Diff.	SD	Paired t	P value
Semen volume (ml)	2.406	2.6067	0.2	0.1134	6.831	<0.001	2.467	2.4133	0.0133	0.1187	0.435	>0.1
Sperm count (millions/ml)	80.933	83.667	2.733	2.219	4.771	<0.001	80.4	79.933	0.4667	1.9952	0.9059	>0.1
Sperm motility (motile%)	59.6	61.467	1.867	1.4573	4.961	<0.001	59.267	59.933	0.667	2.2573	1.144	>0.1
Sperm morphology (normal %)	66.667	71.667	5	3.7796	5.123	<0.001	67.733	67.677	0.333	2.9681	0.435	>0.1
Liquefaction time (minutes)	12.467	14.133	1.667	1.496	4.315	<0.001	12.6	12.4	0.2	1.0142	0.7638	>0.1
Serum testosterone (ng/dl)	477.07	481.73	4.667	7.432	2.432	<0.5	475.13	481.13	6	14.162	1.641	>0.1

BT: Before Treatment, AT: After Treatment, SD: Standard deviation

Sharma G et al. suggested that arsenic has a suppressive influence on spermatogenesis and induces impairment in male reproductive system due to oxidative stress. The study aimed to test the arsenic induced toxicity and protection by *Chlorophytum borivilium*. The effect of sodium arsenite (4 mg/(kg body weight (bw) x day)) via double distilled water without or with *C. borivilium* (800 mg/(kg bw x day)) was evaluated in Swiss albino mice for 30 days. The radical scavenging activity of the aqueous *C. borivilium* root extract was measured using DPPH (1,1-diphenyl-2-picryl hydrazyl) radical. Qualitative assessment of various cell types in the testis, sperm count and motility, testicular activity of lipid peroxidation (LPO), reduced glutathione (GSH), acid and alkaline phosphatase, and cholesterol and serum testosterone were monitored. Arsenic treatment showed a significant increase in LPO, acid and alkaline phosphatase, cholesterol and decrease in sperm count, sperm motility, GSH and serum testosterone. Combined treatment showed significant decrease in LPO, acid and alkaline phosphatase, cholesterol and elevation in sperm count, sperm motility, GSH and serum testosterone. Testicular histopathology showed that *C. borivilium* had reduced degeneration of germ cell in the seminiferous tubules and loss of sperms induced by arsenic intoxication. The results thus led us to conclude that administration of *C. borivilium* root extract is found to be protective against arsenic induced toxicity.

Giribabu N, Kumar et al states that *C. borivilium* root extract treatment to diabetic rats maintained near normal body weight, blood glucose, HbA1c, lipid profile and insulin levels with higher HOMA- β cell functioning index, number of Islets/pancreas, number of β -cells/Islets however with lower HOMA-insulin resistance (IR) index as compared to non-treated diabetic rats. Negative correlations between serum insulin and blood glucose, HbA1c, triglyceride (TG) and total cholesterol (TC) levels were observed. *C. borivilium* root extract administration prevented the increase in lipid peroxidation and the decrease in activity levels of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) with mild histopathological changes in the pancreas of diabetic rats. *C. borivilium* root maintains near normal levels of these metabolites and prevented oxidative stress-induced damage to the pancreas in diabetes.

Tan P et al have performed a systematic review and meta-analysis to evaluate the effect of phosphodiesterase-5 (PDE5) inhibitors on sperm parameters. Mean value and its standard deviation (mean \pm standard deviation) were used to perform quantitative analysis. Statistic heterogeneity scores were assessed with the standard Cochran Q test and I^2 statistic. Eleven studies embraced a total of 1317 participants and 19 subgroups or trials were included. Acute administration of PDE5 inhibitors had no effect on semen volume (mean value [MD]=0.26; 95% confidence interval [CI]: 0.00-0.48) and sperm concentration (MD=2.04; 95%CI: -2.95 to 7.04). However, the percentage of motile spermatozoa (MD=7.05; 95%CI: 2.59-11.51), the percentage of total progressive motility (MD=6.23; 95%CI: 2.43-10.04), and rapid progressive motility (MD=3.11; 95%CI: 0.23-5.99) were increased after oral PDE5 inhibitors treatment. Interestingly, these significant changes were observed only in infertile men but not in normal patients (MD=6.89, $P < .001$ vs MD=0.67, $P = .71$; MD=6.64, $P = .001$ vs MD=2.11, $P > .05$; and MD=3.89, $P = .04$ vs MD=0.92, $P = .59$, respectively). The percentage of morphologically normal spermatozoa also increased in infertile men (MD=12.15; 95%CI: 5.16-19.15). Limited evidence showed the linearity, abnormal forms of spermatozoa, as well as reproductive hormones (total testosterone, free testosterone, luteinizing hormone, and follicle-stimulating hormone) did not benefit from PDE5 inhibitors treatment. Oral PDE5 inhibitors treatment could modestly increase the sperm motility and morphology in infertile men.

Different factors leading to Erectile Dysfunction(ED):

Steven A et al states that the prevalence of erectile dysfunction (ED) and associated risk factors has been described in many clinical settings, but there is little information regarding men seen by primary care physicians. Independent factors associated with ED was identified in a primary care setting. Survey was done, a cross-sectional sample of 3921 Canadian men, aged 40 to 88 years, seen by primary care physicians. Participants completed a full medical history, physical examination, and measurement of fasting blood glucose and lipid levels. The International Index of Erectile Function to define ED was used as a score of less than 26 on the erectile function domain. The overall prevalence of ED was 49.4%. The presence of cardiovascular disease (odds ratio [OR], 1.45; 95% confidence interval [CI], 1.16-1.81; $P < .01$) or diabetes (OR, 3.13; 95% CI, 2.35-4.16; $P < .001$) increased the probability of ED after adjustment for other confounders. Among those individuals without cardiovascular disease or diabetes, the calculated 10-year Framingham coronary risk (OR, 1.03 per 1% increase; 95% CI, 1.02-1.05; $P < .001$) and fasting blood glucose levels (OR, 1.14 per 18-mg/dL [1-mmol/L] increase; 95% CI, 1.04-1.24; $P < .01$) were independently associated with ED. Erectile dysfunction was also independently associated with undiagnosed hyperglycemia (OR, 1.46; 95% CI, 1.02-2.10; $P = .04$), impaired fasting glucose (OR, 1.26; 95% CI, 1.08-1.46; $P = .004$), and the metabolic syndrome (OR, 1.45; 95% CI, 1.24-1.69; $P < .001$). Cardiovascular disease, diabetes, future coronary risk,

and increasing fasting glucose levels are independently associated with ED. It remains to be determined if ED precedes the development of these conditions.

Richars B et al mentioned that Erectile dysfunction (ED) affects approximately 34% to 45% of men with diabetes and has been demonstrated to negatively impact quality of life among those affected across all age strata, with a greater impact on those with permanent—rather than intermittent—ED. Recent reports describe up to one-third of newly diagnosed men with diabetes have ED at presentation, with upward of 50% of men 6 years after diagnosis. In addition, studies indicate that 40% of men with diabetes greater than 60 years of age have complete ED. Recent studies have reported that alteration of the cyclic guanosine monophosphate (cGMP)/nitric oxide (NO) pathway among men with diabetes with impaired vascular relaxation is related to endothelial dysfunction. Among men with diabetes, risk factors include increasing age, duration of diabetes, poor glycemic control, cigarette smoking, hypertension, dyslipidemia, androgen-deficiency states and cardiovascular disease (CVD). ED as a marker of potential cardiovascular (CV) events has been reported by numerous investigators. In fact, ED has been shown to be significantly associated with all-cause mortality and CV events. Diabetic retinopathy has been shown to correlate with the presence of ED. Organic causes of ED include microvascular and CV disease, and neuropathy. In addition, psychological or situational factors may cause or contribute to ED. In spite of the overwhelming amount of data linking ED and diabetes, it is often neglected by clinicians treating men with diabetes. Compared with the general population, multiple studies have reported that men with diabetes have higher rates of hypogonadism. One report described a correlation between glycemic control and testosterone levels. Importantly, phosphodiesterase type 5 (PDE5) inhibitors appear to be less effective in men with diabetes with hypogonadism. In this population, treatment of nonresponses to PDE5 inhibitors with testosterone replacement is successful in roughly 50% of individuals. In addition, ED is a side effect of many drugs commonly prescribed to men with diabetes, such as certain antihypertensive and antidepressants. Obstructive sleep apnea (OSA) is commonly associated with ED and, like diabetes, is an independent risk factor for the presence of ED.

Tamler R et al states that testosterone levels and erectile function are known to decline as men age, leading to hypogonadism and erectile dysfunction (ED). Men with type 2 diabetes mellitus (T2DM) have a particularly high prevalence of hypogonadism and ED. This population also has an increased risk for cardiovascular diseases, as well as exposure to other metabolic and cardiovascular risk factors, such as obesity. Several professional societies have recommended screening men with T2DM for testosterone deficiency. Hypogonadism is generally suspected when morning levels for total testosterone are < 300 ng/dL and clinical signs and symptoms typically associated with androgen deficiency are present. While hypogonadism and ED have emerged as predictors of cardiovascular disease and may respond to the lifestyle changes commonly recommended for patients with diabetes and the metabolic syndrome, the literature on whether treatment with testosterone supplementation affects outcomes beyond well-being and sexual function is still emerging. Primary care providers should be aware of this dysmetabolic cluster affecting their male patients and its importance, and, given the common occurrence of hypogonadism, ED, and T2DM, diagnosis of 1 of these conditions should elicit inquiry into the other 2 conditions.

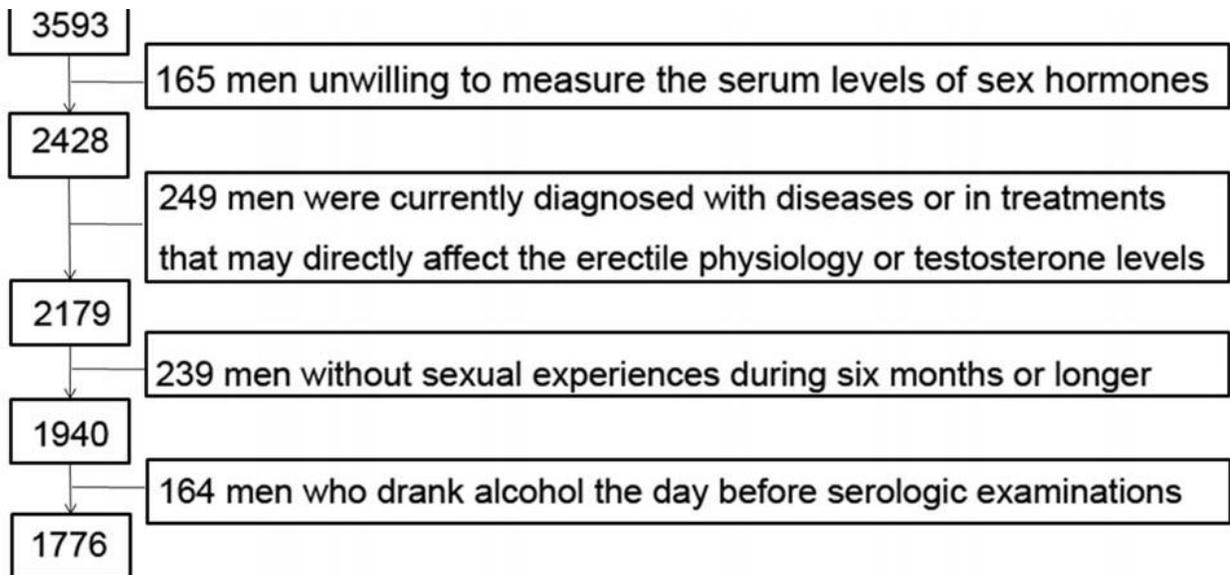
Al Hayek et al stated a high prevalence of low serum testosterone (LST) in men with type 2 diabetes have been reported worldwide. The study was to determine the prevalence and associated factors of LST in men with type 2 diabetes. Overall, 36.5% of patients with diabetes had TT level < 3 ng/ml and 29% had symptoms of androgen deficiency. Of those with serum testosterone level < 3 ng/ml, 80.2% had symptoms of androgen deficiency, 16.9% had primary hypogonadism (HG), and 83.1% had secondary HG. Univariate analysis showed a significant relationship between ages, income, education, body mass index (BMI), smoking, duration of diabetes, diabetic nephropathy, diabetic neuropathy, and HbA1c. Multivariate logistic regression analysis indicated age, income, BMI, and diabetic neuropathy as the independent risk factors of LST. The prevalence of LST among men with type 2 diabetes is high. Age, income, BMI, and diabetic neuropathy were found to be the independent risk factors for LST.

Yang C. et al mentioned that Erectile dysfunction (ED) is a global disease affecting a large number of people. Some studies have found a relationship between low-grade inflammation and ED. We hypothesized that the immune system might play a key role in the outcome of ED. Five immune agents (C3, C4, IgA, IgM, and IgG) were collected based on the Fangchenggang Area Male Health and Examination Survey (FAMHES), using methods of a traditional cross-sectional analysis. Results repeated the significant association between ED and metabolic syndrome, obesity, and so forth. However, there seemed to be no positive relation between the tested indexes and ED risk in the baseline analysis (C3: $P = 0.737$; C4: $P = 0.274$; IgA: $P = 0.943$; IgG: $P = 0.069$; IgM: $P = 0.985$). Then, after adjusting for age and multivariate covariates, a potentially significant association between ED and IgG

was discovered ($P = 0.025$ and $P = 0.034$, respectively). Meanwhile, in order to describe the development of ED on a gene level, SNP-set kernel-machine association test (SKAT) was applied with the known humoral immune genes involved. The outcomes suggested that PTAFR (binary P value: 0.0096; continuous P value: 0.00869), IL27 (0.0029; 0.1954), CD37 (0.0248; 0.5196), CD40 (0.7146; 0.0413), IL7R (0.1223; 0.0222), PSMB9 (0.1237; 0.0212), and CXCR3 (0.0849; 0.0478) might be key genes in ED, especially IL27, when we restricted the family-wise error rate (FWER) to 0.5. Study shows that IgG and seven genes (PTAFR, CD37, CD40, IL7R, PSMB9, CXCR3, and especially IL27) might be key factors in the pathogenesis of ED, which could pave the way for future gene and immune therapies.

Ming L. et al mentioned that, Testosterone is essential for the regulation of erectile physiology, but the relationship between low testosterone and erectile dysfunction (ED) has not been firmly established. A consecutive series of 1776 men aged 20–77 participated in the routine physical examination from September 2009 to December 2009 in Guangxi, China. ED was assessed using the five-item International Index of Erectile Function (IIEF- 5) questionnaire. Total testosterone (TT), sex hormone binding globulin (SHBG) and other biochemical profiles were measured. Free testosterone (FT) and bio-available testosterone (BT) were calculated based on Vermeulen's formula. Data were collected with regard to smoking, alcoholic drinking, physical activity and metabolic syndrome. The prevalence of ED (IIEF-5,22) was 47.6%. Men with ED were significantly older, and more prone to smoke cigarettes (\$20 cigarettes/day) or drink alcohol (\$3 drinks/week), and more likely to have elevated blood pressure ($P = 0.036$) or hyperglycemia ($P,0.001$) compared with those without ED. The significant increase in SHBG with age was parallel to its increase with increasing severity of ED ($P,0.001$). The obscure increase in TT across the ED status was detected without significance ($P = 0.418$), but TT was positively associated with ED after adjustment for age [odds ratio (OR) = 1.02, 95% CI (confidence interval): 1.00–1.04]. FT and BT were inversely associated with ED (OR = 0.14, 95%CI: 0.06–0.33; OR = 0.92 (95%CI: 0.89–0.96, respectively) in the univariate analysis, and this inverse association appeared to be independent of smoking status, alcoholic drinking, physical activity, hypertriglyceridemia and hyperglycemia.

FT and BT are inversely related to worsening ED, whereas the positive association between TT and ED is most likely due to the increase in SHBG.



Flow chart of recruitment. ^[19]

The role of NO from Larginine in sexual health:

Kowaluk EA mentioned sodium nitroprusside (SNP) is thought to exert its vasodilating activity, at least in part, by vascular activation to nitric oxide (NO), but the activation mechanism has not been delineated. The study has examined the potential for vascular metabolism of SNP to NO in bovine coronary arterial smooth muscle subcellular fractions using a sensitive and specific redox-chemiluminescence assay for NO. SNP was readily metabolized to NO in subcellular fractions, and the dominant site of metabolism appeared to be located in the membrane fractions. NO-generating activity was significantly enhanced by, but did not absolutely require, the addition of a NADPH-

regenerating system, NADPH per se, NADH or cysteine. A correlation analysis of NO-generating activity (in the presence of a NADPH-regenerating system) with marker enzyme activities indicated that the SNP-directed NO-generating activity was primarily membrane-associated. Radiation inactivation target-size analysis revealed that the microsomal SNP-directed NO-generating activity was relatively insensitive to inactivation by radiation exposure, suggesting that the functioning catalytic unit might be quite small. A molecular weight of 5 to 11 kDa was estimated. NO-generating activity could be solubilized from the crude microsomes with 3-[(3-cholamidopropyl)-dimethylammonio]-1-propane sulfonate, and the solubilized extract was subjected to gel filtration chromatography. NO-generating activity was eluted in two peaks: one peak corresponding to an approximate molecular weight of 4 kDa, thus confirming the existence of a small molecular weight NO-generating activity, and a second activity peak corresponding to a molecular weight of 112 to 169 kDa, the functional significance of which is unclear at present.

Silva FH et al evaluated the effects of compound 4C on functional and molecular alterations of erectile function in murine models that display low NO bioavailability, SCD transgenic mice, and endothelial NO synthase and neuronal NO synthase double gene-deficient (dNOS^{-/-}) mice, focusing on the dysregulated NO-cGMP-phosphodiesterase type 5 (PDE5) pathway and oxidative stress in erectile tissue. Wild-type, SCD, and dNOS^{-/-} mice were treated with compound 4C (100 μmol/kg/d, 3 weeks). Intracavernosal pressure in anesthetized mice was evaluated. Corpus cavernosum tissue was dissected free and mounted in organ baths. SCD and dNOS^{-/-} mice displayed a priapism phenotype, which was reversed by compound 4C treatment. Increased corpus cavernosum relaxant responses to acetylcholine and electrical-field stimulation were reduced by 4C in SCD mice. Likewise, increased sodium nitroprusside-induced relaxant responses were reduced by 4C in cavernosal tissue from SCD and dNOS^{-/-} mice. Compound 4C reversed PDE5 protein expression and reduced protein expressions of reactive oxygen species markers, NADPH oxidase subunit gp91^{phox}, and 3-nitrotyrosine in penises from SCD and dNOS^{-/-} mice. In conclusion, 3-week therapy with the NO donor 4C reversed the priapism in murine models that display lower NO bioavailability. NO donor compounds may constitute an additional strategy to prevent priapism in SCD.

Tom F Lue et al states that the cyclic nucleotide signaling pathway mediates the smooth-muscle relaxing effects of nitric oxide necessary for normal erectile function. Down-regulation of this pathway is central to the pathophysiology of many forms of erectile dysfunction (ED), which is often associated with other chronic diseases (e.g. hypertension, type 2 diabetes mellitus) and treatments (e.g. certain drugs, radical prostatectomy). Conversely, selective inhibition of the enzyme that catalyses the degradation of cGMP (phosphodiesterase type 5, PDE-5) promotes erectile responses to sexual stimulation.

Jiaming Wen et al mentioned Priapism as prolonged and persistent penile erection, unassociated with sexual interest or stimulation, and is one of the many serious complications associated with sickle cell disease (SCD). The study evaluated the role of the NO-cGMP signaling pathway in priapism in Berkeley murine model of SCD (SS). These results showed that SS mice exhibit amplified corpus carvenosum relaxation response mediated by NO-cGMP signaling pathway. Intervention in this signaling pathway may be a potential therapeutic target to treat SCD priapism.

Hull EM et al states that Nitric oxide (NO) may mediate penile erection by inhibiting smooth muscle of the corpora cavernosa, thereby allowing vasodilation of the corpora. In order to test the role of NO in the sexual function of intact male rats, either the precursor of NO (L-arginine, L-Arg) or an inhibitor of its synthesis (NG-nitro-L-arginine methyl ester, NAME) was administered systemically before tests of copulation, ex copula genital reflexes, or sexual motivation/motor activity. NAME impaired copulation in a dose dependent manner. It also decreased the number of ex copula erections, but it increased the number of ex copula seminal emissions and decreased the latency to the first seminal emission. L-Arg marginally increased the number of penile reflexes, but had no other effects. NAME had no effect on sexual motivation or motor activity. The results indicate that nitric oxide promotes erection in intact male rats, probably by mediating filling of the corpora cavernosa. The data also suggest that NO inhibits seminal emission, probably by decreasing sympathetic nervous system activity; this may help prevent premature ejaculation.

Nagendra SC et al stated that, Nitric Oxide-Based Mechanism of Sexual Behavior Nitric oxide (NO) is an atypical regulatory molecule having the dual role as a secondary messenger/neurotransmitter. It has been implicated in diverse physiological functions. Findings so far indicate that NO may also be a major neuronal messenger. In particular, it is an established physiological mediator of penile erection and in the brain; NO synthase is highly concentrated in structures directly or indirectly involved in sexual behavior (olfactory bulb, supraoptic and paraventricular nuclei, amygdala, septal structures, etc.). Recent studies suggest that NO is a major physiological

stimulus for relaxation of penile vasculature and trabecular smooth muscle, essential for penile erection. Relaxation of the trabecular smooth muscle of the corpus cavernosa leads to a decreased vascular resistance and increased blood flow to the penis. Alongside the increased flow, venous outflow is reduced by the compression of the subtunical venules. The combination of increased inflow and decreased outflow causes penile engorgement and erection. NO from the vascular endothelium of the sinusoids and from the nonadrenergic, no cholinergic, and cavernosal nerves appears to mediate the vasodilatation. The new drug used for the treatment of erectile dysfunction, and sildenafil acts by potentiating the effect of NO by inhibiting the specific enzyme phosphodiesterase-V that terminates the action of NO generated cGMP in the penile vasculature. Many medicinal herbs and drugs derived from these herbs have been shown to have effects on the NO signaling pathway.

Faibo HS et al, patients with heart failure (HF) display erectile dysfunction (ED). However, the pathophysiology of ED during HF remains poorly investigated. The study aimed to characterize the aortocaval fistula (ACF) rat model associated with HF as a novel experimental model of ED. The molecular and functional studies were done to evaluate the alterations of the nitric oxide (NO) pathway, autonomic nervous system and oxidative stress in the penis. Male rats were submitted to ACF for HF induction. Intracavernosal pressure in anesthetized rats was evaluated. Concentration-response curves to contractile (phenylephrine) and relaxant agents (sodium nitroprusside; SNP), as well as to electrical field stimulation (EFS), were obtained in the cavernosal smooth muscle (CSM) strips from sham and HF rats. Protein expression of endothelial NO synthase (eNOS) and neuronal NO synthase (nNOS) and phosphodiesterase-5 in CSM were evaluated, as well as NOX2 (gp91phox) and superoxide dismutase (SOD) mRNA expression. SOD activity and thiobarbituric acid reactive substances. HF rats display erectile dysfunction represented by decreased ICP responses compared to sham rats. The neurogenic contractile responses elicited by EFS were greater in CSM from the HF group. Likewise, phenylephrine-induced contractions were greater in CSM from HF.

Giusepp PS. et al mentioned that, L-arginine supplementation has been related to increase maximum strength and improvement of hemodynamic parameters in several diseases. The aim was to evaluate the effect of L-arginine supplementation and resistance training on muscle mass, hemodynamic function and DNA damage in healthy rats subjected to a low-arginine concentration diet. The administration of isolated L-arginine supplementation and its association with resistance training promoted less damage in leukocytes DNA. In conclusion, the L-arginine supplementation showed synergistic effect with resistance training regarding leukocyte genomic stability in a low-L-arginine diet scenario.

The role Grape Seed Extract in maintaining the sexual health:

In the study of Hala AH et al, Natural dietary antioxidants are studied for their ability to protect cells from miscellaneous damage. Grape seed extract (*Vitis vinifera* L., Vitaceae) is a potent antioxidant. The study aimed to investigate the protective effect of grape seed extract (GSE) against the possible testicular dysfunction caused by aluminium chloride (AlCl₃) in male rats. Twenty sexually mature male albino rats were divided into four equal groups, the first served as negative control, the second received AlCl₃ (20 mg/kg bw, 1/ 20 LD 50), the third administered GSE (75 mg/kg bw), and the fourth received AlCl₃ and treated with GSE. Doses were given once daily via gavage for 70 consecutive days. The results revealed that, AlCl₃ induced significant decrease in final body weight, sex organs relative weight, sperm concentration, motility and viability, serum testosterone concentration and superoxide dismutase (SOD) activity, with significant increase in sperm abnormalities and thiobarbituric acid reactive substance (TBARS) concentrations. Moreover, AlCl₃ induced apparent alteration in the histological structure of the testis. Treatment with GSE ameliorated the harmful effects of AlCl₃, this was also proved histopathologically by the noticeable improvement in the testis tissues. It may be concluded that GSE may be promising as a natural therapeutic agent in AlCl₃-induced reproductive toxicity and oxidative stress in the male rat testes.

Tian et al states that, Cisplatin (CIS) is widely applied for its antihematological malignancies properties and as antitumor drugs. However, it could cause testicular damage related with oxidative stress and testosterone synthesis disorder. Studies reported that grape seed procyanidins extract (GSPE) could improve CIS induced-testes lesion via scavenging free radicals in animals, although its mechanisms were unclear. Therefore, the purpose of the study was to explore the antagonistic mechanisms of GSPE on CIS-induced testes lesion. Rats were treated with 10 mg/kg by weight CIS by intraperitoneal injection singly on the 11th day, and different doses of GSPE were administered via intragastric gavage for 15 days consecutively. The results showed that GSPE improved the pathological changes of testicular tissue, and the decreased concentrations of testosterone in serum

induced by CIS. GSPE inhibited CIS-induced oxidative/nitrative stress, as well as increased the mRNA and protein levels of testosterone synthetase in rat testes. In conclusion, the main protection exerted by GSPE on CIS-induced testicular toxicity is related to its effects including suppressing oxidative/nitrative stress and up-regulating expression of testosterone synthetase.

Yongfang Lei et al investigated the potential of grape seed-derived polyphenols extract (GSP) to protect against testosterone-induced benign prostatic hyperplasia (BPH) in castrated rats. After a 5 week experimental period, the prostatic levels of proinflammatory cytokines and plasma androgen level were measured by enzyme linked immunosorbent assay. Prostatic oxidative stress was evaluated by detecting the activities of antioxidant enzymes. Additionally, the prostatic levels of extracellular signal-regulated kinases (ERK), p38, protein kinase B (PKB/AKT), nuclear factor (NF) κ B and intercellular cell adhesion molecule (ICAM) were determined using western blot analysis. It was found that GSP ameliorated the testosterone-induced high androgen level, over-expressions of NF κ B and ICAM, and the high phosphorylation levels of ERK, p38 and AKT, as well as normalized antioxidant enzyme activities and regulated the proinflammatory cytokines. These results suggested that GSP had prostatic protective nature via regulating the androgen-MAPK/AKT-ICAM pathway and eventually alleviating the prostatic inflammatory responses and oxidative stress.

Adel Alkhedaide et al mentioned that Cadmium (Cd) is the most prevalent toxic metal present in livestock feed; therefore, the present study aimed to examine the ameliorative effects of grape seed extract (GSE) on cadmium chloride (CdCl₂)-induced testicular dysfunction of Wistar rats. Male adult Wistar rats (40 rats; n=10/group) were divided into four equal groups. Group one was used as a control, and was given **ad libitum** access to food and water. Groups 2–4 were treated with CdCl₂ [5 mg/kg body weight (BW)], GSE (400 mg/kg BW, orally), and GSE plus CdCl₂, respectively. Blood and testicular tissues were collected and assayed for biochemical and histopathological changes, respectively. Testicular genes were expressed using semi-quantitative RT-PCR analysis. The results of the study demonstrated that there was a decrease in serum testosterone levels following CdCl₂ toxicity, which were normalized after GSE co-administration. Furthermore, CdCl₂ significantly increased the serum levels of malondialdehyde, and decreased levels of antioxidants. At the histopathological level, the testes of the CdCl₂ group exhibited congestion, edema in the interstitial blood vessels, irregular arrangement of the epithelial lining of the seminiferous tubules, and degeneration and sloughing of the spermatogenic cells, which accumulated in the center of the seminiferous tubules. Such pathological alterations were ameliorated following treatment with GSE in the CdCl₂ plus GSE group. The immune histochemical expression of B-cell lymphoma 2-associated X protein was high in the CdCl₂ group, and low in the control and GSE groups. Co-treatment with GSE and CdCl₂ exhibited ameliorative effects on the immune reactivity of B-cell lymphoma 2-associated X protein. CdCl₂ toxicity induced a significant down regulation in the mRNA expression levels of cytochrome P450 cholesterol side-chain cleavage enzyme, cytochrome P450 17A1, 3 β -hydroxysteroid dehydrogenase (3 β -HSD), 17 β -HSD, androgen receptor, steroidogenic acute regulatory protein, and follicle-stimulating hormone receptor. GSE administration exhibited a stimulatory effect on steroidogenesis-associated enzymes, and co-treatment with GSE and CdCl₂ normalized and upregulated the mRNA expression levels of these examined genes. The study concluded that GSE has beneficial protective effects against the deleterious effects of CdCl₂ on the testis.

Hasona NA scrutinised the ameliorative properties of grape seed extract (GSE) in dexamethasone (DEX)-induced testicular and thyroid dysfunction associated with oxidative stress in male albino rats. Thirty-two healthy adult male albino rats were divided into four groups of eight animals each: normal, DEX control, DEX + GSE (200 mg/kg body weight) group and DEX + GSE (400 mg/kg body weight) group. The body weight gain and testes weight were assessed. Plasma testosterone and thyroid profile were determined. Testicular glucose-6-phosphate dehydrogenase (G-6-PDH), acid phosphatase (ACP), total protein and glutathione (GSH) levels, as well as catalase (CAT) activity also histopathological changes of the testis were evaluated. DEX treatment caused a significant decrease in body weight gain and weight of testes. Significant alterations in enzymatic and nonenzymatic antioxidants were observed. Moreover, a marked reduction in plasma testosterone levels and thyroid profile was observed. The administration of GSE significantly attenuated the deleterious effects of oxidative stress induced by DEX, as well as attenuated DEX-induced testicular and thyroid damage. Furthermore, DEX induced histological alterations in the testis. GSE ameliorated the injurious effects of DEX and improved the histological alterations in the testis.

Conclusion:-

Various herbs have been used by people of different cultures to treat conditions of male infertility or for treatment of reproductive disorders. These herbs have also been advocated for improving sexual desire as well as sexual performance and erectile dysfunction, vasodilatation, increased testosterone level, brain monoamines, effect on pituitary-gonadal axis, and so forth are suggested mechanism for its action of these herbs. In absence of clinical efficacy and safety data on these herbs, people are skeptical to use them. There is an urgent need to conduct clinical studies to support traditional claims and to work out cellular and molecular mechanism involved. In some cases, drugs action is direct and involves chemical alteration of the neurons, which governs sexual arousal or function. Having discussed the basis for the role of herbs, it is important to understand the role of modern pharmacology and an insight of herbs into the control of the sexual behavior in the human body. Moreover, the cross talk of various pathways involved must also be taken into account to come up with a molecular pathway to find a lead molecule of herbal origin of the treatment of various forms of sexual dysfunction.

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