Original Article

Herbo-mineral supplementation in men with idiopathic oligoasthenoteratospermia: A double blind randomized placebo-controlled trial

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ABSTRACT

Introduction: There is insufficient scientific data on the medical management options for idiopathic oligoasthenoteratospermia (iOATs). We conducted a double blind, randomized, placebo-controlled trial to assess the efficacy and safety of the herbo-mineral supplement, *Addyzoa*®, in infertile men with iOATs. We also evaluated its effect on semen reactive oxygen species (ROS) levels, total antioxidant capacity (TAC) and DNA fragmentation index.

Materials and Methods: Fifty infertile men with iOATS were recruited into an institutional ethics committee approved protocol from April to August 2009. Randomization was done using numbered, identical containers. Baseline semen samples were evaluated for routine parameters, ROS level, DNA fragmentation index and TAC. Drug/placebo was administered at a dose of two capsules twice a day for 3 months. All parameters were reassessed at 3 months and clinical side-effects were recorded. The study was registered with the Clinical Trials Registry of India and is available at www.ctri.in as study protocol number CTRI/2009/091/000551.

Results: Forty-four subjects completed the study, 21 in the drug arm and 23 in the placebo arm. There was no difference in baseline parameters between the two groups. Men in the drug group had significant improvement in mean total motility from 23.2 ± 17.3% to 33.4 ± 23.2% (*P*-value: 0.008) and mean progressive (Type A+B) motility from 15.7 ± 12.6% to 22.6 ± 18.0% (*P*-value: 0.024). ROS, TAC and DFI did not change significantly in either group and did not show any correlation with other semen parameters.

Conclusions: Treatment with *Addyzoa* resulted in a significant improvement in total and progressive motility in the semen of men with iOATs after 3 months of therapy. There was no change in the sperm concentration, ROS, DFI or TAC levels.

Key words: Antioxidant, drug therapy, idiopathic, infertility, oxidative stress

INTRODUCTION

Infertility is a common medical problem and the male partner is contributory in half of these cases.[1] While conditions such as a varicocele, cryptorchidism and hypogonadism are definable causes for infertility, no cause may be determined for an abnormal semen analysis in over 25% cases.[2] There are very few scientifically validated medical management options for men with such idiopathic infertility and oligoasthenoteratospermia (iOATs). This perpetuates the use of a large number of drugs of unproven benefit.[3]

Elevated reactive oxygen species (ROS) levels in the semen may be an etiologic factor for male infertility.[4] Controlled generation of ROS is essential for all aerobic life and at low levels, these highly reactive free radicals facilitate numerous sperm functions.[5-7] However, their uncontrolled production is detrimental to cell function as they damage a variety of biomolecules such as lipids, amino acids, carbohydrates, protein and DNA and adversely affect sperm function.[8]

The human ejaculate contains a number of potential sources of ROS. These include leukocytes, germ cells or abnormal sperms.[9] At the same time, a number of cellular molecules called antioxidants which protect the cell from excessive ROS-induced lipid peroxidation are also present within the ejaculate.[10] An imbalance between ROS generation and the availability of antioxidants results in oxidative stress. Infertile men have lower antioxidant levels in their

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semen and this is particularly evident in infertile men with asthenospermia. Oxidative stress is also responsible for damage to the DNA structure of the spermatozoa.[11] This is manifest by a higher level of DNA fragmentation in the semen of these men. The evaluation of oxidative stress thus has four components: Semen parameters, ROS levels, total antioxidant capacity (TAC) levels and DNA fragmentation index (DFI).

Addyzoa® (Charak Pharmaceuticals, Mumbai, India) is a herbo-mineral agent that contains *Withania somnifera* and *Emblica officinalis* as its principal constituents [Appendix 1]. Both these agents have been shown to have antioxidant properties and a potential role in managing oxidative stress-associated male infertility.[12-15] However, the lack of clinical trials in infertile men limits the use of such agents in managing iOATs. We therefore initiated a double blind, randomized placebo-controlled trial using *Addyzoa*® in men with iOATS and evaluated the effects on standard semen parameters, ROS, TAC and DFI.

MATERIALS AND METHODS

The study was designed as a parallel group trial with 1:1 random allocation and was approved by the institutional ethics committee. Between April and August 2009, infertile men presenting to the urology clinic of our tertiary-care hospital were screened for inclusion. Infertility was defined as the inability to conceive after at least 1 year of regular, unprotected intercourse with the partner. A detailed history as per an approved performa was obtained to evaluate potential causes for infertility. A physical examination was performed to exclude cases with known factors such as varicocele, cryptorchidism, endocrine disorders, etc.

Men with no determinable cause for infertility provided two semen samples at least 1 week apart, in a sterile plastic container after sexual abstinence of 4 days. Each sample was incubated at room temperature and standard manual semen analysis was performed according to WHO guidelines.[16] The inclusion criteria for the study were:

1. Infertility (failure to conceive in 1 year)
2. Semen analysis on two occasions: Normal volume (>2 mL) with sperm counts > 5 mill/mL, and at least one of the following:
    a. Sperm counts < 20 mill/mL
    b. Motility < 50% (A+B) or 25% (A)
    c. Morphology < 50% normal forms

The following were the exclusion criteria for the study:

1. Identifiable cause for OATs
    a. Varicocele
    b. Cryptorchidism (present or treated)
    c. Orchitis (present or treated)
    d. Radiation or chemotherapy
    e. Scrotal or pelvic surgery
    f. Clinical hormonal abnormality
2. Recent febrile illness/medication (within last 3 months)

Men satisfying the above inclusion criteria were enrolled into the study after an informed consent. The second of the two semen samples was used for baseline analyses. The drug and placebo were prescribed in a dose of two capsules twice a day for 3 months.

Levels of ROS were assessed by measuring the luminol-dependent chemiluminescence with the single detector luminometer (Sirius, Berthold Detection Systems GmbH, Pforzheim, Germany) in the integrated mode for 10 min. The values were expressed as relative light unit per minute (RLU/min) per 20 million sperms. Total antioxidant capacity was assessed using the commercially available kit (Cayman Chemical Item Number 709001) as per the specifications of the kit manufacturer. The analysis was done using the analysis tool provided online at *http://www.caymanchem.com/app/template/analysis%2CAntioxidant.vm/a/z.* The SCSA (Sperm chromatin structure assay) was performed according to the procedure described by Evenson *et al*.,[17] which was used to calculate DNA fragmentation Index.

All parameters were reassessed at 3 months. Compliance was assessed through verbal record and adverse effects were noted. The primary end-point of the study was change in the semen parameters, ROS, TAC and DFI levels after 3 months of therapy.

Randomization

The drug and the placebo were prepared with identical physical appearance and were packaged in identical containers, identifiable only by their numbers. Block randomization using a computer-generated random numbers chart was used. The manufacturer shipped the bottles, after randomization, to the study site with both the investigator and patients blind to the contents of the bottles. Once 3-month data for all subjects was available, the manufacturer provided the numbers that constituted group A and B, without disclosing which group contained the active agent. Comparisons between Group A and B were done by an independent statistician. After all analyses were complete, the actual contents of Group A and B were unblinded. No post-unbliniding analyses were performed.

Statistical analysis

Statistical analyses were performed using SPSS software 2009 version. Between group differences were assessed using unpaired Student's *t*-test and Wilcoxon signed ranks tests. Correlation analyses were performed using Pearson correlation coefficient method.

Registration

The study was registered with the Clinical Trials Registry

of India and is available at www.ctri.in as study protocol number CTRI/2009/091/000551.

RESULTS

The CONSORT flow chart[18] [Figure 1] shows the patient recruitment, attrition and analysis for each group. Six patients did not complete the study. The remaining 44 subjects received the intended treatment and complied completely with the study protocol. These 44 patients were evaluated in the final analysis while data for all 50 subjects was used for baseline analysis.

The two groups were similar in demographics and all baseline data including standard semen parameters, ROS, TAC and DFI [Table 1]. Men in the *Addyzoa*® group showed a significant improvement in total sperm motility and progressive (Type A+B) motility after intervention [Table 2]. No improvement was seen in any parameter in the placebo group. Total motility improved in 50% patients, remained unchanged in 25% and deteriorated in 25% patients in the drug group. None of these changes correlated with smoking although ROS levels increased in all smokers in the drug group. There was no significant change in other semen parameters, ROS, TAC and DFI levels in either group. The levels of these parameters also did not show any correlation with standard semen parameters [Table 3]. The drug was well-tolerated and there were no adverse effects in either group.

Table 1: Patient demographics and baseline parameters

Parameter (Mean ± SD)	Group A (Drug) (*n* = 25)	Group B (Placebo) (*n* = 25)	*P* value
Age in years	32 ± 5.09	29.6 ± 2.88	NS
Smoking +	6	3	NS
Diabetes +	1	0	NS
Previous treatment	13	15	NS

NS = Not significant

DISCUSSION

Management of idiopathic male infertility with OATs is a difficult clinical problem. The condition occurs frequently but the lack of scientific data in support of drug therapy reduces it to being purely empirical with no clear guidelines on which drug should be used and for what duration.[3] A part of the problem is the inability of a semen analysis to accurately predict the fertility potential. Although it is still considered the fundamental diagnostic step in the

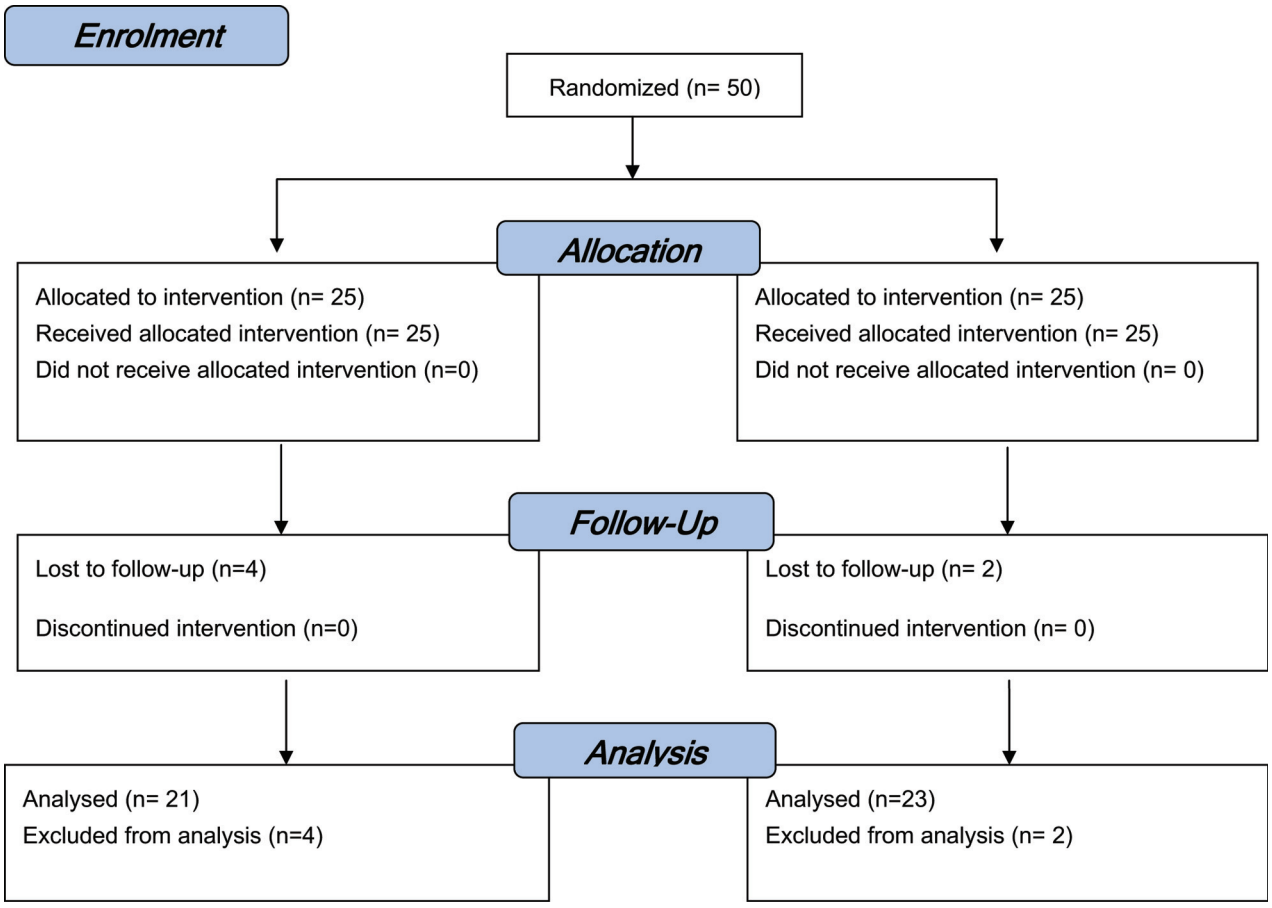

Figure 1: CONSORT 2010 flow diagram

Table 2: Seminal parameters in drug and placebo group before and after 3 months of treatment

Parameter (mean ± SD)	Group A (Drug)			Group B (Placebo)		
	Baseline[a]	3 months	*P* value	Baseline[b]	3 months	*P* value
Standard semen analysis						
Sperm concentration (million/ml)	32.6 ± 26.9	30.9 ± 25.6	0.31	31.9 ± 32.0	21.2 ± 16.8	0.15
Total sperm motility (%)	23.2 ± 17.3	33.4 ± 23.2	0.008**	27.9 ± 20.1	34.1 ± 21.1	0.07
Active sperm motility (a+b %)	15.7 ± ± 12.6	22.6 ± 18.0	0.02**	18.4 ± 12.8	21.0 ± 14.7	0.20
Normal morphology (%)	34.1 ± 10.7	33.0 ± 14.3	0.80	34.3 ± 5.2	33.8 ± 16.0	0.85
TAC (mM)	4.8 ± 2.7	4.5 ± 3.5	0.20	3.9 ± 2.3	4.5 ± 3.5	0.35
DFI (%)	40.8 ± 9.9	41.7 ± 9.0	0.98	39.9 ± 10.8	41.8 ± 9.5	0.22
ROS (RLU/min per 20 × 10^6 sperms)	3410841 ± 312456	3539733 ± 253432	0.66	2293950 ± 491657	2157751 ± 381605	0.52

**Significant improvement; [a,b] Baseline semen parameters between the two groups were not statistically different

Table 3: Correlation between semen parameters, ROS, TAC and DFI levels

Pearson's coefficient (*P*-value)	Concentration	Motility	Motility (a + b)	Morphology	ROS	TAC
Motility	−0.16 (0.46)					
Active motility	0.06 (0.76)	0.81 (0.001)				
Morphology	−0.02 (0.91)	0.32 (0.15)	0.24 (0.30)			
ROS	−0.10 (0.68)	0.02 (0.90)	−0.04 (0.87)	0.24 (0.13)		
TAC	0.29 (0.18)	−0.12 (0.57)	0.03 (0.88)	0.11 (0.64)	0.03 (0.89)	
DFI	−0.18 (0.42)	−0.23 (0.31)	−0.26 (0.25)	−0.20 (0.39)	−0.23 (0.33)	−0.25 (0.26)

evaluation of male infertility, it is well known that men with normal values may continue to be infertile while men with 'subnormal' values are able to procreate.[19] This has led to a search for additional parameters that may be predictive of the fertility of a man. ROS and oxidative stress have been shown to have significant impact on sperm functions and this has resulted in a potential area for therapeutic intervention.[20-22] Abnormal levels of ROS and antioxidants are associated with measurable sperm DNA damage.[23] Despite this increased interest, there is little scientific data in support of antioxidant therapy with most literature presenting conflicting information.[22]

Phytotherapeutic agents have been a part of the treatment armamentarium for conditions such as infertility in a number of ancient medicinal systems.[24] Most of these agents suffer from a lack of rigorous scientific evaluation, resulting in a limitation of their acceptability and use.

W. somnifera belongs to a class of drugs known as adaptogens in the Indian medical systems. It contains a large number of biologically active ingredients, the most important of which are alkaloids, steroids and iron. This agent has been attributed with anti-inflammatory properties and an anti-stress effect.[25] In addition, it has been shown to have antioxidant properties. In a study on rats, levels of the antioxidants superoxide dismutase, catalase and glutathione peroxidase were increased in the frontal cortex after oral administration of *W. somnifera* for 21 days.[26] *W. somnifera* also inhibited lipid peroxidation when administered simultaneously with lipopolysaccharides and peptidoglycans.[27]

In a recent publication on the potential role of *W. somnifera* in male infertility due to stress, Mahdi *et al*.,[28] included 60 men with normozoospermic infertility into three groups of 20 each, one with no stress and non-smokers, one group of smokers and one with stress as defined by the Stress Anxiety Index and cortisol levels. Another 60 normal, healthy, fertile men were included as controls. They reported an improvement in stress, antioxidants and semen quality in all treated men. In another study on infertile men, Ahmad *et al.* recruited 75 fertile healthy men and 75 infertile men, 25 of whom were normozoospermic, 25 had oligozoospermia and 25 had asthenospermia. All subjects received *W. somnifera* for 3 months. Therapy with *W. somnifera* resulted in improved antioxidant activity, lower lipid peroxidation, improved levels of vitamins A, C and E and improved semen parameters.

E. officinalis is the other major constituent of *Addyzoa*®. This plant product, known as Indian gooseberry or *Amla*, is also believed to have significant antioxidant properties with animal experiments showing its ability to reverse oxidative stress through antioxidant properties.[29-31] It has, however, not been evaluated in male infertility.

We found a significant improvement in the motility among our subjects receiving Addyzoa®. Motility impairment is one

of the well-documented ill-effects of oxidative stress.[32,33] El-Taeib *et al.* evaluated ROS levels in the seminal plasma of 20 men with iOATS and 10 fertile controls using a carbonyl protein detection method and correlated these with light microscopy and ultrastructural analysis of sperms using electron microscopy.[32] iOATs patients had significantly higher ROS levels and axonemal anomalies when compared with controls. Carbonyl protein levels also correlated with axonemal anomalies and decreased forward progressive sperm motility. Earlier studies have also found motility to be the most responsive parameter to antioxidant therapy. Lenzi *et al.* have published two well-conducted randomized studies using carnitine and levo-carnitine as antioxidants for iOATS.[34,35] Similar to our results, they noticed a significant improvement in motility alone. Ghanem *et al.*,[36] in 2010, reported a randomized controlled study using clomiphene as an antiestrogen and vitamin E as an antioxidant in a group of men with idiopathic infertility. They reported a significantly improved pregnancy rate, sperm counts and progressive motility in the treated group. However, the authors did not evaluate changes in estrogen levels or oxidative stress, the proposed mechanism of action of these drugs. Men with severe oligospermia were included in both groups and almost half the pregnancies reported occurred within the first 3 months, even before the effect of drug is likely to be evident.

Our study is limited by our inability to demonstrate a cause and effect relationship between oxidative stress and infertility. While most of the literature on the effects of *W. somnifera* in infertility is related to its antioxidant property, we found no change in the oxidative stress parameters in any of our patients. This could be because of two reasons. First, the parameters assessed by us may not be sufficient to detect the effects of *W. somnifera*. It is known that there are a large number of ROS and antioxidants and it is still unclear which ones are responsible for oxidative stress related infertility. El-Taeib *et al.* have suggested that the carbonyl protein detection method may be a more sensitive way of detecting ROS though this is still to be universally accepted.[32] Second, the mode of action may not be antioxidant properties at all. *W. somnifera* has a large number of active ingredients and it remains to be proven which ones change in infertile men. Since *Addyzoa*® itself has a large number of constituents, it is impossible to know which the active agent in these cases is.

While the only other study on *Addyzoa*® reported pregnancy rates of 22%,[37] another limitation of our study is the lack of pregnancy data. We have previously referred to our inability to follow patients for long periods and this hampers collecting pregnancy data.[38] Our study is also limited by its clinical applicability. While statistically significant benefits have occurred in motility, these may not translate into clinical benefit. This is true for most published literature on medical therapy for idiopathic OATs. The two studies of Lenzi quoted above are remarkably similar in their findings or lack thereof.[34,35] Our study is also limited by the small number of patients and short duration of therapy.

In the absence of any significant data on medical management of iOATs, a common clinical problem, we believe our study at least lays a foundation on which empirical therapy can be based. The lack of any adverse effects strengthens this belief and may spur additional evaluations of traditional medical therapies.

CONCLUSIONS

Treatment with *Addyzoa*® resulted in a significant improvement in total and progressive motility in the semen of men with idiopathic OATs after 3 months of therapy. However, there was no change in the sperm concentration, ROS, DFI or TAC levels and its exact mechanism of action remains unknown.

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Appendix 1: Composition of *Addyzoa*® *capsule*

Name of ingredient	Latin/English name	Quantity (mg)
Powders		
Purnachandrodaya rasa		45
Suvarnavang		30
Muktashukti bhasma		30
Suvarnamakshik bhasma		30
Shilajit shuddha		30
Abhrak bhasma		15
Makardhwaj rasa		15
Rasa sindur		5
Extract of		
Gokshur	*Tribulus terrestris*	200
Ashtavarga		200
Shwet musli	*Chlorophytum arundinaceum*	150
Kapikachchhu shuddha	*Purified Mucuna pruriens*	150
Guduchi	*Tinospora cordifolia*	150
Ashwagandha	*Withania somnifera*	150
Amalaki	*Emblica officinalis*	75
Balamool	*Sida cordifolia*	75
Vridhadharuk	*Argyreia speciosa*	75
Shatavari	*Asparagus racemosus*	75
Varahikand	*Tacca aspera*	30
Chopchini	*Smilax china*	30
Vidarikand	*Ipomoea digitata*	30
Munjatak	*Eulophia campestris*	15

REFERENCES

1. Sharlip ID, Jarow JP, Belker AM, Lipshultz LI, Sigman M, Thomas AJ, *et al*. Best practice policies for male infertility. Fertil Steril 2002;77:873-82.
2. Siddiq FM, Sigman M. A new look at the medical management of infertility. Urol Clin North Am 2002:29;949-63.
3. Kumar R, Gautam G, Gupta NP. Drug therapy for idiopathic male infertility: Rationale versus evidence. J Urol 2006;176:1307-12.
4. Desai N, Sharma R, Makker K, Sabanegh E, Agarwal A. Physiologic and pathologic levels of reactive oxygen species in neat semen of infertile men. Fertil Steril 2009;92:1626-31.
5. Kodama H, Kuribayashi Y, Gagnon C. Effect of sperm lipid peroxidation on fertilization. J Androl 1996:17;151-7.
6. Rivlin J, Mendel J, Rubinstein S, Etkovitz N, Breitbart H. Role of hydrogen peroxide in sperm capacitation and acrosome reaction. Biol Reprod 2002:70;518-22.
7. de Lamirande E, O'Flaherty C. Sperm activation: Role of reactive oxygen species and kinases. Biochim Biophys Acta 2008:1784;106-15.
8. Agarwal A, Makker K, Sharma R. Clinical relevance of oxidative stress in male factor infertility: An update. Am J Reprod Immunol 2008;59:2-11.
9. Alvarez JG, Touchstone JC, Blasco L, Storey BT. Spontaneus lipid peroxidation and production of hydrogen peroxide and superoxide in human spermatozoa. Superoxide dismutase as major enzyme protectant against oxygen toxicity. J Androl 1987;8:338-48.
10. Sharma RK, Agarwal A. Role of reactive oxygen species in male infertility. Urology 1996;48:835-50.
11. Aitken RJ. The Amoroso Lecture. The human spermatozoon-a cell in crisis? J Reprod Fertil 1999;115:1-7.
12. Ahmad MK, Mahdi AA, Shukla KK, Islam N, Rajender S, Madhukar D, *et al*. *Withania somnifera* improves semen quality by regulating reproductive hormone levels and oxidative stress in seminal plasma of infertile males. Fertil Steril 2010;94:989-96.
13. Jeyanthi T, Subramanian P. Protective effect of *Withania somnifera* root powder on lipid peroxidation and antioxidant status in gentamicin-induced nephrotoxic rats. J Basic Clin Physiol Pharmacol 2010;21:61-78.
14. Hazra B, Sarkar R, Biswas S, Mandal N. Comparative study of the antioxidant and reactive oxygen species scavenging properties in the extracts of the fruits of *Terminalia chebula, Terminalia belerica and Emblica officinalis*. BMC Complement Altern Med 2010;10:20.
15. Bhattacharya A, Chatterjee A, Ghosal S, Bhattacharya SK. Antioxidant activity of active tannoid principles of *Emblica officinalis (amla)*. Indian J Exp Biol 1999;37:676-80.
16. WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction, 4th Edition: World Health Organization, Cambridge University Press, Cambridge, UK 1999. DOI: 10.2277/0521645999
17. Evenson DP, Larson KL, Jost LK. Sperm chromatin structure assay: Its clinical use for detecting sperm DNA fragmentation in male infertility and comparisons with other techniques. J Androl 2002;23:25-43
18. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. BMJ 2010;340: c332
19. Sigman M, Jarow JP. Male infertility. In: Campbell's Urology. 8th ed. Walsh PC, Retik AB, Vaughan ED, Jr, Wein AJ, editors. Philadelphia: W. B. Saunders Co.; Vol. 2. 2002. p. 1475.
20. Mahfouz R, Sharma R, Thiyagarajan A, Kale V, Gupta S, Sabanegh E, *et al*. Semen characteristics and sperm DNA fragmentation in infertile men with low and high levels of seminal reactive oxygen species. Fertil Steril 2010;94:2141-6.
21. Tunc O, Thompson J, Tremellen K. Improvement in sperm DNA quality using an oral antioxidant therapy. Reprod Biomed Online 2009;18:761-8.
22. Kefer JC, Agarwal A, Sabanegh E. Role of antioxidants in the treatment of male infertility. Int J Urol 2009;16:449-57.
23. Shamsi MB, Venkatesh S, Tanwar M, Talwar P, Sharma RK, Dhawan A, *et al*. DNA integrity and semen quality in men with low seminal antioxidant levels. Mutat Res 2009;665:29-36.
24. Scartezzini P, Speroni E. Review on some plants of Indian traditional medicine with antioxidant activity. J Ethnopharmacol 2000;71:23-43.
25. Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of *Withania somnifera (ashwagandha)*: A review. Altern Med Rev 2000;5:334-46.
26. Bhattacharya SK, Satyan KS, Ghosal S. Antioxidant activity of glycowithanolides from *Withania somnifera*. Indian J Exp Biol 1997;35:236-9.
27. Dhuley JN. Effect of ashwagandha on lipid peroxidation in stress-induced animals. J Ethnopharmacol 1998;60:173-8.
28. Mahdi AA, Shukla KK, Ahmad MK, Rajender S, Shankhwar SN, Singh V, *et al*. *Withania somnifera* improves semen quality in stress-related male fertility. Evid based complement alternat med 2009 [In Press].
29. Chen TS, Liou SY, Chang YL. Supplementation of *Emblica officinalis (Amla)* extract reduces oxidative stress in uremic patients. Am J Chin Med 2009;37:19-25.
30. Swapna G, Reddy AG, Reddy AR. Cadmium-induced oxidative stress and evaluation of *Embilica officinalis* and Stressroak in Broilers. Toxicol Int 2010;17:49-51.
31. Chakraborty D, Verma R. Ameliorative effect of *Emblica officinalis* aqueous extract on ochratoxin-induced lipid peroxidation in the kidney and liver of mice. Int J Occup Med Environ Health 2010;23:63-73.
32. El-Taieb MA, Herwig R, Nada EA, Greilberger J, Marberger M. Oxidative stress and epididymal sperm transport, motility and morphological defects. Eur J Obstet Gynecol Reprod Biol 2009;144: S199-203.
33. Omu AE, Al-Azemi MK, Kehinde EO, Anim JT, Oriowo MA, Mathew TC. Indications of the mechanisms involved in improved sperm parameters by zinc therapy. Med Princ Pract 2008;17:108-16.
34. Lenzi A, Sgrò P, Salacone P, Paoli D, Gilio B, Lombardo F, *et al*. A placebo-controlled double-blind randomized trial of the use of combined l-carnitine and l-acetyl-carnitine treatment in men with asthenozoospermia. Fertil Steril 2004;81:1578-84.
35. Lenzi A, Lombardo F, Sgrò P, Salacone P, Caponecchia L, Dondero F, *et al*. Use of carnitine therapy in selected cases of male factor infertility: A double-blind crossover trial. Fertil Steril 2003;79:292-300.
36. Ghanem H, Shaeer O, El-Segini A. Combination clomiphene citrate and antioxidant therapy for idiopathic male infertility: A randomized controlled trial. Fertil Steril 2010;93:2232-5.
37. Singh I, Kumar A, Bhandari PR. Comparison of the efficacy of addyzoa and clomiphene in male factor subfertility. Int J Gynecol Obstet India, 2001;4:33-40.
38. Kumar R, Mukherjee S, Gupta NP. Intussusception vasoepididymostomy with longitudinal suture placement for idiopathic obstructive azoospermia. J Urol 2010;183:1489-92.

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