Clinical Evaluation of Effect of *Sufoofe Muallif* in the Management of Quilatte *Haiwane Manwiya* (Oligospermia)

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Abstract

Infertility is a common condition with important psychological, economical, demographical and medical implications. WHO estimates that "60-80 million couples worldwide are currently suffering from infertility." *Quilatte Haiwane Manwiya* (oligospermia) is one of the most common causes of male infertility. In conventional system, various drugs are being used to increase sperm count, but these drugs are expensive and their long term use produces several adverse effects too. Therefore, keeping in the mind about the need of the hour an open, uncontrolled clinical trial was carried out on 30 infertile patients of *Quilatte Haiwane Manwiya*. Each patient was given trial formulation *Sufoofe Muallif* - 5 grams once daily for 60 days. The assessment of efficacy of treatment was carried out on the basis of objective parameters (Semen analysis for sperm count, motility, morphology and hormone profile for serum testosterone, LH, FSH). The results were analyzed statistically by using Wilcoxon matched-paired signed ranks test, one tail paired-T test and Kruskal- Wallis test. After the trial, significant improvement was found in various objective parameters; sperm count (10.53 ± 1.30 to 18.06 ± 2.57, $P<0.001$), sperm motility (21.70 ± 3.80 to 46.56 ± 5.06, $P<0.001$) and sperm morphology (76.2 ± 6.40 to 91.9 ± 4.22, $P<0.01$). The changes in hormone profile (serum Testosterone, LH, FSH) were not significant ($P>0.05$). Safety parameters were remained within normal limits after the trial. This study suggests that *Sufoof Muallif* has exhibited a good response in the improvement of semen markers; sperm count, sperm motility and sperm morphology. Furthermore, no adverse effect was observed and safety parameters remained within normal limits. Thus it might be concluded that the Test drug is safe and effective for the treatment of *Quilatte Haiwane Manwiya* (oligospermia).

Keywords: *Quilatte Haiwane Manwiya*, Oligospermia, Unani medicine, *Sufoofe Muallif*, *Quillate mani*

Introduction

Infertility is defined as the failure of a couple to achieve conception after one year of regular unprotected intercourse (Bradon *et al*., 2002; Jonathan, 2002). Infertility is a distressing problem for about 10-15% of world's population, with the incidence increasing over the years (Leon Speroff *et al.*, 1999). However, it affects both men and women; male factor contributes for about 30-40% cases of infertility (Sengupta *et al*., 1998). A recent study has indicated that there is a decrease in sperm density over a period of past fifty years (Dhaliwal *et al*., 2001). Despite of remarkable advancement in pharmacotherapy, infertility

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continues to raise significant economic and personal burden to the society. Male infertility, with its clinical and psychosocial implications, poses a significant challenge to the physicians and to the society as a whole.

Quilatte Haiwane Manwiya (oligospermia) is one of the most common causes of male infertility. It is a condition in which the sperm count is decreased to less than 20 million/ml of semen (Walsh, 2002). The important causes include varicocoele, cryptorchidism, klinefelter's syndrome, damaged testes due to trauma or infections (tuberculosis, syphilis, mumps), neoplasm of testes, kidney and liver diseases, smoking, alcoholism, wearing tight under garments, working at high temperature places like welding, dyeing, blast furnace, cement and steel factories etc (Smith, 1997).

In conventional system, various drugs like testosterone, clomiphene citrate, tamoxifene and HCG are being used to increase sperm count, but these drugs are expensive and their long term use produces several adverse effects like gynaecomastia, hepatic carcinoma, deep vein thrombosis, lowering of HDL and rise in LDL etc (Tripathi, 2006). However, in Unani system of medicine there are ample of single as well as compound drugs which are used for male sexual weakness (*Zoafe bah*) and infertility since the time immemorial.

In Unani system of medicine, most of Unani scholars particularly Ibn Sina (980-1037 AD), Zakaria Razi (865-925 AD), Ismail Jurjani (1110 AD) and Rabban Tabri (810-895 AD) have elaborately discussed sexual diseases in their respective treatises. They have mentioned the causes, symptoms, complications, treatment and management of various sexual diseases under the caption of *Zoafe bah*. In fact, *Zoafe bah* is a broad term which encompasses different disease entities like *Istirkhae Qazeeb* (Erectile dysfunction) *Surate Inzaal* (Premature ejaculation) and *Qillate Mani* (oligospermia) etc. The concept of *Qillate Mani* (*Qillat*- less, *Mani-semen*) can be correlated with the concept of oligospermia (Oligo-less, spermia-spermatozoa). The literal meaning of oligospermia is *Qillate haiwane manwiya*. The important causes of *Qillate mani* are *kasrate istifragh*, excessive use of *mudirrat*, *sue mizaj* of *alaate mani*, excessive use of drugs like *afyoon* (opium) and *bhang* and excessive riding etc (Ahmad, 1954; Kabiruddin, YNM; Majusi, 2010; Razi, 2007).

The exact aetiopathogenesis of *Qillate haiwane manwiya* is not described in classical Unani literature but on the basis of its cause it can be concluded that *Sue mizaj* of *alaate mani* alter the production of *mani* due to excessive *Baroodat*, *Yaboosat*, *Hararat* or *Ratubat* in *alaate mani*. For the spermatogenesis, there is a need of balance in temperament of particular organs. In case of *Sue mizaj* of the *alate mani* the process of spermatogenesis slow down production of *Mani* and thus causing oligospermia. (Kabiruddin, YNM)

Keeping all these facts in mind, a protocol of an observational clinical trial has been planned to conduct a preliminary clinical study on *Quilatte Haiwane Manwiya* (oligospermia). A commonly used Unani pharmacopoeial compound drug, *Sufoofe Muallif,* was selected for the study. Its ingredients of are *Talmakhana, Salab misri, Singhara, Gonde kekar, Mazu sabz, Mastagi Rumi, Nishasta gandum* and *Shakar safed (*Lateef, 1986). These drugs possess properties like *Muwallide Mani, Mughallize Mani, Muqawwie bah, Mumsik* and *Musammine badan* which form a rational basis for proposed hypothesis that the ingredients of selected compound formulation owing to their above cited properties may be beneficial in patients of oligospermia.

Methodology

The present observational, open uncontrolled clinical study was conducted at National Institute of Unani Medicine hospital, Bangalore, India. Before initiation of the project, a comprehensive protocol was framed and put forth for ethical clearance from the Institutional Ethical Committee. This study was conducted from February, 2012 to March, 2013. The protocol of the trial was framed for the study and accordingly findings are recorded on CRF. The inclusion criteria consisted of being aged from 21 to 50 years infertile males, having sperm count less than 30 million/ml (Mushtaq, 2007) and willing to follow up and for semen examination. Those individuals who were suffering with chronic renal diseases, chronic cardiac ailments, chronic liver diseases, thyroid dysfunctions, any organic disease of testes and related organs of spermatogenesis, etc or receiving any medication were not included in the study. Patients fulfilling the inclusion criteria were given the information sheet having details regarding the nature of the study, the drug to be used, method of treatment etc. Patients were given enough time to go through the contents of informed consent sheet. They were given the opportunity to ask any question and if they agreed to participate in the study, they were asked to sign the informed consent form. Eligible patients were selected from OPD of NIUM Hospital, Bangalore. Complete history and examination including general physical and systemic examinations were carried out with special attention to endocrine and genital examination, and recorded on a prescribed proforma which was designed in accordance with the objectives of the study. Several investigations were carried out with the aim to exclude the patients with pathological conditions such as Semen Analysis, Hormone Analysis (Serum Testosterone, FSH, LH), Hb%, TLC, DLC, ESR, Blood Sugar-F/PP, KFT (Blood urea, serum creatinine) , LFT (SGOT, SGPT, Alkaline Phosphatase), Urine (Routine and Microscopic). The sample size of the study was limited to 30 patients and the treatment period was determined as 60 days. *Sufoof Muallif* was given to patients in a dose of 5 gram/day for 60 days. Follow up of the patient was done after every 15 days period upto

60 days. At each visit patient was inquired about any side effect of the drug and safety parameters were evaluated before and after treatment. Assessment of the efficacy of test formulation was carried out on the basis of objective parameters. Semen analysis (Semen volume, sperm count, sperm motility and morphology) and hormone analysis (Serum Testosterone, LH, FSH) of each patient was performed before and after treatment. The objective parameters were analysed by using Wilcoxon matched-paired signed ranks test, one tail paired-T test and Kruskal Wallis test.

Trial Formulation (Sufoofe Muallif)

Talmakhana (*Asteracatha longifolia*)	100 gms
Salab misri (*Orchis latifolia*)	80 gms
Singhara (*Trapa bispinosa*)	150 gms
Gonde kekar (*Acacia arabica*)	150 gms
Mazu sabz (*Quercus infectoria*)	75 gms
Mastagi rumi (*Pistacia lentiscus*)	75 gms
Nishasta gundum (Starch)	100 gms
Shakar safed (Sugar)	730 gms

Method of preparation and mode of administration of test drug

Proper identification of the ingredients of the Unani formulation was done by chief pharmacist, National Institute of Unani Medicine, Bangalore, to ensure their originality and authenticity. The single drugs then were cleaned by weeding out unwanted material and impurities and pounded to fine powder.

Results and Observations

Overall 30 patients completed the trial according to the study protocol. *Sufoof Muallif* was generally well tolerated and no remarkable adverse events were reported in the test group. The mean score for sperm count pretreatment (0 day) was 10.53±1.30 while the same post-treatment (60^{th} day) was 18.06 ± 2.57 ($p<0.01$). The mean and SEM scores for sperm motility on 0 day were 21.70±3.80 and for 60^{th} day were 46.56±5.06 ($p<0.01$). The mean and SEM scores for sperm morphology on 0 day were 76.2 ± 6.40 and for 60^{th} day were 91.9 ± 4.22 ($p<0.01$). The mean and SEM scores for serum testosterone on 0 day were 4.66 ± 0.32 and for 60^{th} day were 4.67 ± 0.32 ($p>0.05$). The mean and SEM scores for serum LH on 0 day were 5.8 ± 0.44 and for 60^{th} day were 6.3 ± 0.47 ($p>0.05$). The mean and SEM scores for serum FSH on 0 day were 6.7 ± 0.89 and for 60^{th} day were 7.08 ± 0.89 ($p>0.05$).The baseline and after treatment values of objective parameters are depicted in Table 1.

Table 1

	Mean ± SEM											
	Sperm Count (million/ml)		Sperm Motility		Sperm Morphology		Serum Testosterone		Serum LH		Serum FSH	
	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT
Test Group	10.53 ± 1.30	18.06 ± 2.57	21.70 ± 3.80	46.56 ± 5.06	76.2 ± 6.40	91.9 ± 4.22	4.66 ± 0.32	4.67 ± 0.32	5.8 ± 0.44	6.3 ± 0.47	6.7 ± 0.89	7.08 ± 0.89
P-Value	p<0.001		p<0.001		p<0.01		p>0.05		p>0.05		p>0.05	

Discussion

The improvement in the sperm count would be because of *Muqqawie bah, Muwallide mani, Mughallize mani* and *Musammine badan* activities of most of the ingredients of Test drug i.e. Talmakhana (*Asteracatha longifolia*), Salab misri (*Orchis latifolia*), Singhara (*Trapa bispinosa*) and Nishasta (Starch). These results are in conformity with the properties of the drugs as indicated by Unani scholars such as Ibn Rush'd, Ibn Sina, Hakeem Abdul Hakeem, Najmul Ghani and Kabeeruddin etc. (Ibn Rushd, 1987; Ghani,YNM; Kabeeruddin, 2010; Haleem, 2009; Kabeeruddin, 2007). Modern scientific clinical and experimental studies have also proved aphrodisiac and spermatogenic properties of some ingredients of Test drug like *Asteracantha longifolia, Trapa bispinosa* and *Orchis latifolia* (Chauhan *et al.*, 2009; Agarwal *et al.*, 2003; Mayank *et al*., 2008).

Chemical analysis of various test drugs show that apart from different chemical constituents they possess various nutritional elements such as carbohydrate,

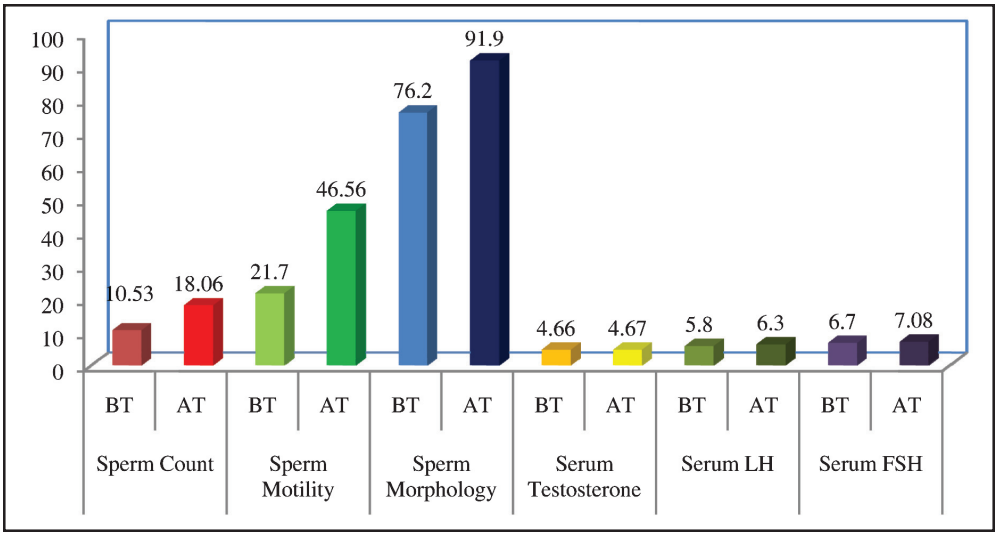

Figure 1

protein, minerals like Ca, Mg, Fe, Zn and Cu etc, and vitamins such as thiamine, riboflavin, pantothenic acid and pyridoxine etc (Patra *et al*., 2009; Singh *et al*., 2010). These chemical constituents and vitamins are essential for the process of spermatogenesis (Zakai *et al*., 2011). Therefore, the effect of Test formulation might be due to presence of these elements. The studies of Tikkiwal *et al*. and Wong *et al.,* 2002 reveal that Zinc and folic acids are responsible for improvement in sperm count and motility.

The improvement in the sperm motility might be due to *Muqqawie bah, Muwallide mani, Mughallize mani* properties of the various constituents of test formulation which have been documented in Unani literature (Ibn Rushd, 1987; Ghani,YNM; Kabeeruddin, 2007, 2010; Haleem, 2009). Different researches have documented the antioxidant (Trommer *et al.*, 2005; Kaur *et al*., 2008; Chryssavgi *et al*., 2008) and immunomodulatory (Patel, 2010) activities of *Mazu*, *Mastagi*, *Singhara* and *Samaghe Arabi* which are ingredients of *Sufoofe Muallif*. By virtue of these antioxidant and immunomodulatory properties test drug is effective in improving sperm motility. As it has been proved by the studies of Carmely *et al.* (2009) and Bansal *et al.* (2009) etc. that antioxidant and immunomodulating agents play a major role in improving the process of spermatogenesis, increasing sperm motility and viablility.

Before and after treatment values of sperm morphology were subjected to statistical analysis by using Wilcoxon matched-paired signed ranks test and it was found that the difference between the Mean ± SEM scores of sperm motility pre and post treatment was statistically significant ($p<0.01$).

Hormone analysis of each patient was performed for serum testosterone, LH and FSH. The values of LH and FSH were analyzed statistically by using one tail paired-T test and it was found that the difference between the Mean ± SEM scores of serum testosterone was not significant ($p> 0.05$).

Zakai *et al.* (2011) mentioned that for the management of oligospermia, the rational approach is to focus on enhancing those factors which promote sperm formation which is closely linked to nutritional status. Therefore, it is critical that men with low sperm counts have optimal nutritional intake. In addition to consuming a healthful balanced diet, there are several nutritional factors that deserve special place viz vitamin C and other antioxidants, fats and oils, zinc, folate, vitamin B, arginine, and carnitine spermatogenesis. As various drugs of our Test formulation specially *Talmakhana* and *Singhara* have *Musammine badan* property, and also the chemical analysis proved the presence of various important nutritional factors like carbohydrate, proteins, minerals and vitamins such as thiamine, riboflavin, pantothenic acid and pyridoxine etc (Patra *et al.,* 2009; Singh *et al*., 2010). The chemical constituents present in the ingredients

of Test formulation may further facilitate the process of spermatogenesis and thereby effective in improving sperm count and motility.

In Unani system of medicine the principle of treatment is based on the concept of organ protection, strengthening and maintenance of the *Quwa* (faculties) at its equilibrium (*etedal*). The faculties at their equilibrium are balanced inherently to maintain the normal function of that organ or system. It has been mentioned that each organ has been gifted with special *Quwat* for its optimal functioning. *Unsiyaen* (Testes) are the *azae raesa* (vital organs) for *Quwwate tanasuliya* (Reproductive power). In case of derangement of function (*zoaf*) of any organ, the drugs enhancing its power (*muqawwi advia*) are advocated. This is the reason why in Unani system of medicine, for every organ and system there is a group of tonic drugs (*muqawwi advia*) proposed that safe guard its larger interest and bring it near to its equilibrium, if some derangement in its structure or function takes place. Therefore, most of the sexual diseases are being treated on the basis of concept of *Taqwiyate aaza*. The ingredients of Test formulation are bestowed with the properties like *Muqawwie bah*, *Muwalllide mani* and *Muqawwie aam* (general tonic) etc, by virtue of these actions these drugs potentiated the functions of testes. Thus it may be presumed that the observed significant differences in the values of sperm count and motility would be due to *Muqqawie bah, Muwallide mani* and *Mughallize mani* activities of the ingredients of *Sufoofe Muallif*. Thus we can say that scientific studies and reported effects of individual ingredients of Test drug are in confirmatory to a great extent with that of our hypothesis as well as the inferences we drew out of the present study.

In order to determine toxicity of test drug, safety parameter i.e. complete haemogram, LFT and KFT were carried out before and after the treatment in each patient. It was found that all the safety parameters were within the normal levels after the completion of trial. This suggests that Test formulation can be used safely at mentioned therapeutic dose.

This discussion is helpful to draw the conclusion that the Test formulation is safe and effective for the management of oligospermia and can be used for long period without any adverse effect. However, the long term studies with a larger sample size are required to elucidate other pharmacological actions of Test formulation.

Study Limitations and strengths:

The main limitation of this trial was the duration of the trial and by longer follow up; we might reach to more favourable changes in objective parameters. The strength of this trial is its novelty in the infertile group of males.

Conclusion

On the basis of above results and observations it may be concluded that the Test drug is safe and effective and can be used potentially in the management of oligospermia. Further long term and large scaled phase III and IV trials are advocated to explore other important chemicals and pharmacological actions of the Test formulation.

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References

Agrawal, H.S.K., Kulkarni, K.S., 2003. Efficacy and Safety of Speman in patients with Oligospermia: An Open Clinical Study. *Indian Journal of Clinical Practice* 2(14): 29-31.

Ahmed, Bashir, 1954. Mujarrebate Bashir, Raja Ram press, Lucknow, pp. 22-3.

Anonymous, 1986. Qarabadeene Majeedi, 9th edition, All India Unani Tibbi Conference, New Delhi, pp. 24-28, 43-99, 109-128, 320-399, 410-414.

Bansai, Amrit Kaur, Gurmail Singh Bilaspuri, 2009. Antioxidant effect of vitamin E on motilityviability and lipid peroxidation of cattle under oxidative stress. *Animal Science Papers and Reports* 27 (1):5-14.

Brandon, J., Bankowski, Amy E., Hearne, Nicholas C., Lambrou, Harold E., Fox, Edward E., Wallach, 2002. The Johns Hopkins Manual of Gynaecology and Obstetrics. Lippincott Williams and Wilkins Publishers, 2nd Edition, pp. 157.

Carmely, A., Meirow, D., Peretz, A., 2009. Protective effect of the immunomodulator AS101 against cyclophosphamide-induced testicular damage in mice. *J. Clin. Endocrinol. Metab*. 94: 4180–*6*.

Chauhan, N.S., Sharma, V., Dixit, V.K., 2009. Effect of *Asteracantha longifolia* seeds on sexual behaviour of male rats. *Nat. Prod. Res.* 1(9):14.

Chryssavgi, G., Vassiliki, P., Athanasios, M., Kibouris, T., Michael, K., 2008. Essential oil composition of *Myrtus communis* L. and *Pistacia lentiscus*L: Evaluation of antioxidant capacity of methanolic extracts. *Food chemistry* 107(3):1120-30.

Dhaliwal, L.K., Gupta, K.R., Majumdar, S., 2001. Treatment of Oligospermia with Speman: A Formulation of Plant Origin. *Indian Medical Gazette,* pp. 375-79.

Ibn Rushd, 1987. Kitabul Kulliyat, CCRUM, New Delhi, pp. 302.

Jonathan, Berek, S., 2002. Novak's Gynaecology. Lippincott Williams and Wilkins Publishers, pp. 400-407.

Kabeeruddin, M., 2007. Ilmul Advia Nafisi. Ejaz Publishing House, pp.176-7, 334-5.

Kabeeruddin, M., 2010. Makhzanul Mufradat. 2nd Edition, Idara kitabul shifa, New Delhi, pp. 151, 168, 269-70, 375-6, 387-8.

Kaur, Gurpreet, Athar Mohammad, Alam M. Sarwar, 2008. *Quercus infectoria* galls possess antioxidant activity and abrogates oxidative stress-induced functional alterations in murine macrophages. *Chem Biol. Interact.* 171(3): 272-82.

Khan, Azam., YNM, Al-Aksir, (Translated by Kabiruddin, M.), Vol 2. Ejaz Publishing House, pp. 1255-70.

Leon Speroff, Robert H. Glass, Nathan G. Kase, 1999. Clinical Gynaecologic Endocrinology and Infertility, 6th ed. Lippincott Williams & Wilkins, pp. 425.

Majusi, Ibn Abbas, 2010. Kamilus sana. (Urdu Translation by G.H. Kantoori). Idara Kitabus Shifa, New Delhi, pp. 479, 531.

Mazhar Mushtaq, Jafri Saghir Ahmed, Sheikh Abdus Salam, 2007. Human Chorionic Gonadotropin (hCG): A treatment of oligospermia. *Pakistan Journal of Medical Science* 23(6): 840-846.

Mohammed Abdul Haleem, 2009. Mufradate Azizi, CCRUM, New Delhi, pp. 70, 83.

Najmul, Ghani, YNM. Khazainul advia, Idara kitabul shifa, New Delhi, pp. 505-6, 542-3, 853-4, 1208-10, 1248-9.

Patel, S., Banji, D., Banji, O.J.F., *Patel,* M.M., Shah, K.K., 2010.Scrutinizing the role of aqueous extract of *Trapa bispinosa* as an immunomodulator in experimental animals. *Int. J. Res. Pharm. Sci.* 1(1): 13-19.

Patra Arjun, Jha Shivesh, Murthy P. Narasimha, 2009. Phytochemical and pharmacological potential of *Hygrophila spinosa* T. anders. *Phcog Rev* 3: 330-41.

Razi, Z., 2007. Kitabul Hawi, Vol 10th, CCRUM, New Delhi, pp. 243, 281-9, 295-7.

Sengupta Sree Bijoy, 1998. Gynaecology for Postgraduates and Practitioner, 1st ed. Churchill Livingstone, pp.59-60.

Singh *Gagan Deep*, Sukh charn Singh, Navdeep Jindal, Amrinder S., 2010. Physico-Chemical characteristics and sensory quality of Singhara, An Indian water chestnut under commercial and industrial storage conditions. *Afr. J. of Food Sci*. 4(11): 693- 702.

Smith Roger, P., 1997. Gynaecology in Primary Care. Williams and Wilkens Publication, pp. 356.

Thakur, Mayank, Dixit, Vinod Kumar, 2008. Ameliorative Effect of Fructo-Oligosaccharide Rich Extract of *Orchis latifolia* Linn. on Sexual Dysfunction in Hyperglycaemic Male Rats. *Sex Disabl.* 26(1): 37-46.

Tikkiwal, M., Ajmera, R.L., Mathur, N.K., 1987. Effect of zinc administration on seminal zinc and fertility of oligospermic males. *Indian J. Physiol. Pharmacol.* 31(1): 30-4.

Tripathi, K.D., 2006. Essentials of Medical Pharmacology. 6th edition. Jaypee publishers, New Delhi, pp. 291, 304-305.

Trommer, H., Neubert, R.H., 2005. The examination of polysaccharides as potential antioxidative compounds for topical administration using a lipid model system. *Inter. J. Pharm.* 298: 153-163.

Walsh, Patrick, C., 2002. Campbell's Urology, Vol 2, 8th edition. Saunders publication, pp. 1488.

Wong, W.Y., 2002. Effects of folic acid and zinc sulfate on male factor subfertility: a double-blind, randomized, placebo-controlled trial. *Fertil Steril* 77 (3): 491-498.

Zakai, Faisal, Shahbuddin, Akram, M., Ghani, Usman, 2011. Introduction to male infertility. *Journal of Medicinal Plants Research* 5(25): 5936-45.