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Effect of *Withania somnifera* in the treatment of male infertility: A literature review

Maria Yasmin Paz Teixeira[1*] and Camilla Oliveira Duarte de Araujo[2]

[1]Programa de Pós-Graduação em Nutrição e Saúde, Universidade Estadual do Ceará (UECE), Av. Dr. Silas Munguba 1700, 60714-903, Fortaleza, Ceará, Brasil.
[2]Departamento de Fisiologia - Disciplina de Fisiologia da Nutrição, Universidade Federal de São Paulo (UNIFESP), Rua Botucatu, 862 - 2o andar - Ed. Ciências Biomédicas - Vila Clementino – S/N São Paulo, São Paulo, Brasil.

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The high prevalence of male infertility associated with the high costs of its conventional treatment motivated researchers to look for alternative approaches to the treatment of sexual dysfunction. The use of medicinal plants for these fins has been adopted in *Withania somnifera* which is one of the plants that has been associated with improvements in male fertility. Thus, the aim of this study was to review data available in the literature on the effect of *W. somnifera* in the treatment of male infertility. The Pubmed, Lilacs and Medline databases from 2009 to 2019 were searched and 9 articles selected, including intervention articles, systematic review and meta-analysis. Also known as Aswagandha or "Indian Ginseng", the part of *W. somnifera* most used in treating infertility is the root, mainly in the form of extract. It acts through two mechanisms: "oxidative" and "non-oxidative", both associated with improved sperm count, motility and morphology. However, further studies should be conducted investigating isolated phytochemicals to verify their true functionality.

Key words: Male infertility, male sexual disorders, *Withania somnifera*.

INTRODUCTION

Infertility means the inability to conceive after one year of unprotected sexual intercourse. Male factor infertility is the cause of 40-50% of cases and has become a significant health problem (Ayaz et al., 2018). Diagnosis occurs when seminal parameters such as sperm concentration, motility and morphology are abnormal. In these cases, it is recommended to start medical treatment (Duca et al., 2019; Vander Borght and Wyns, 2018).

Current treatments for male infertility, such as assisted reproduction techniques, have high costs and often low successful rates (10-30%) (Nejatbakhsh et al., 2016). Although hormonal (FSH-follicle replacement) and nutritional therapies (with carnitine, arginine, zinc, selenium, vitamin E, glutathione and coenzyme Q10) may be used to treat semen alterations (Duca et al., 2019), a new modality of treatment has contributed to improving the management of this issue (Nejatbakhsh et al., 2016). Alternative medicine, essentially herbal, has been projecting with the purpose of improving sperm parameters in male infertility (Sengupta et al., 2018).

The use of medicinal herbs has persisted for thousands

*Corresponding author. E-mail: yasminpazteixeira@gmail.com.

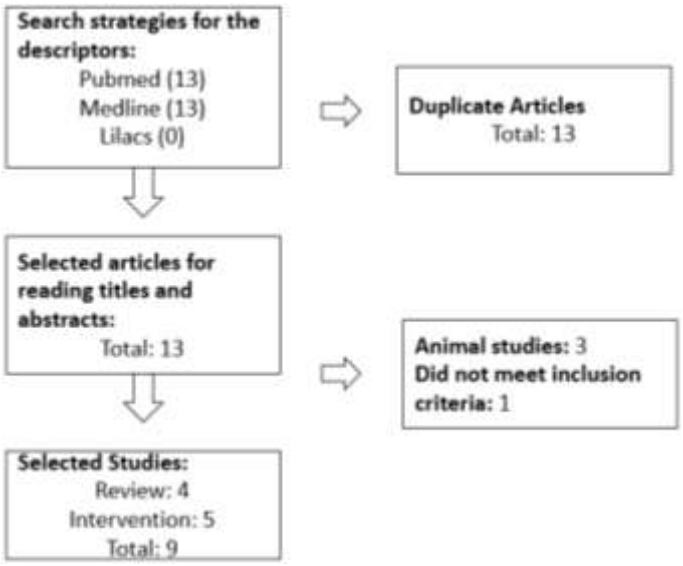

Figure 1. Flowchart of the articles search in the scientific literature.

years and continues to represent a considerable area of medical treatment in many countries, particularly in Asia, Africa and South America (Tahvilzadeh et al., 2016). According to an estimate by the World Health Organization (WHO), 80% of the world's population trust on herbal medicines for their care (Gadelha et al., 2015).

Essentially, the effect of medicinal plants on male reproductive function is associated with their antioxidant activity, since they present in their compositions phytochemical compounds able to inhibit spermatic membrane lipid peroxidation. Among these compounds are polyphenols, flavonoids and tannins, which act in various processes of the male reproductive system, such as spermatogenesis and steroidogenesis (Ahmadi et al., 2016; Lohiya et al., 2016; Mansouri et al., 2016). *Withania somnifera*, locally known as Aswagandha or "Indian Ginseng" is an Indian-origin herb that has been widely used in Brazil for its adaptogenic potential (Lohiya et al., 2016). Although commonly used in its countries of source as part of the treatment of erectile dysfunction, oligozoospermia, endocrinological reproductive problems and other male reproductive problems (Gupta et al., 2013; Kumar et al., 2015), in Brazil, it is still rarely used as complementary treatment for male infertility. Knowing that medicinal plants are recognized as a safe, effective and economical alternative and considering that *W. somnifera* has been used in the treatment of reproductive disorders, the aim of this study was to review the available data in literature on its effectiveness in improving male infertility.

METHODS

A literature review was performed using three databases: Pubmed, Lilacs and Medline, in order to identify scientific articles published from 2009 to 2019. Search was performed based on the descriptors "Male Infertility" or "Infertile Men" to describe the population, *"W. somnifera*" "Aswagandha" or "Indian Ginseng" to describe the intervention, and "Sperm Parameters" "Sexual Dysfunctions or "Men's Sexual Health" for the outcome.

Human intervention studies were included, as well as systematic reviews and meta-analyzes. Male reproductive disorders with the following diagnoses were included: Oligozoospermia (reduced sperm count in semen), asthenozoospermia (decreased sperm motility), azoospermia (absence of sperm), oligoastenozoospermia (low sperm concentration and motility) or teratozoospermia (altered sperm morphology). Animal studies were not included.

The publications were pre-selected by titles, which had to include the full terms and/or references to male infertility and *W. somnifera;* thereafter the abstracts were read. Articles that met the inclusion criteria entered the study, otherwise, they were excluded. After searching, Endnote X8 was used to remove duplicate articles.

The flowchart (Figure 1) describes the study selection process. Finally, 9 articles were selected for discussion.

RESULTS

General features

Found in hot, dry regions of the semi-arid climate, *W. somnifera* originates from South Africa, the Middle East, India, and China (Dar et al., 2015). In India, *W. somnifera* is a medicinal plant and both the whole plant and its parts are used in medicinal treatments. From ancient times, *W. somnifera* root has been used as adaptogen, diuretic, sedative, antioxidant and aphrodisiac (Narinderpal et al., 2013). Other parts of the plant, such as leaves and fruits, have been used as an analgesic, memory stimulant, anti-neoplastic, antimicrobial and anti-inflammatory agent (Sengupta et al., 2018).

W. somnifera contains a wide variety of phytochemicals

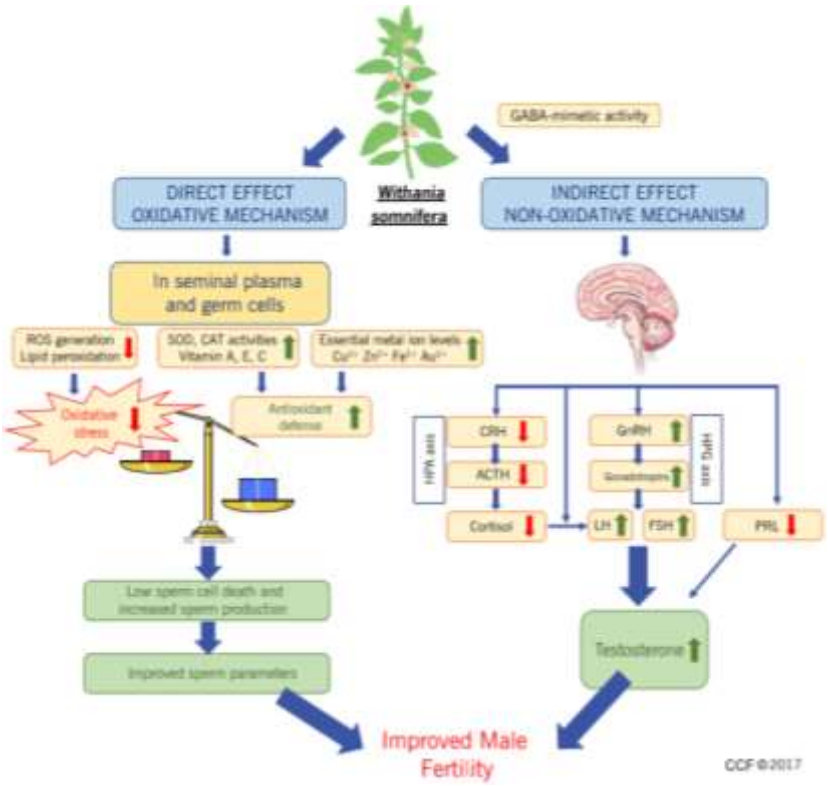

Figure 2. The proposed mechanism of action of *Withania somnifera*. Green arrows indicate an increase, while red arrows indicate a decrease. ACTH: Adrenocorticotropic hormone; CAT: catalase; CRH: corticotropin-releasing hormone: GABA: gamma-aminobutyric acid; GnRH: Gonadotropin releasing hormone; PAH: hypothalamus-pituitary-adrenal; HPG: hypothalamus-pituitary-gonadal; ROS: reactive oxygen species; SOD: superoxide dismutase; PRL: prolactin; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone.
Source: Adapted from Segpunta et al. (2018).

giving rise to a range of biological implications. In preclinical studies, it has demonstrated antimicrobial, anti-inflammatory, anti-tumor, anti-stress, neuroprotective, cardioprotective and antidiabetic properties (Dar et al., 2015).

In addition, this plant is known for its potential to promote health and longevity by preventing the aging process, enhancing defense against disease, revitalizing the body in debilitated conditions, enhancing an individual's ability to resist environmental effects and creating a sense of mental well-being (Durg et al., 2015).

Due to its pronounced anti-stress qualities, this species of plant is named "somnifera", which means "sleep inducer". The pharmacological effects and folk uses of *W. somnifera* are like those of Korean ginseng tea. For this reason, it is also known as Indian ginseng (Dar et al., 2015).

W. somnifera extract is one of the widely used herbal medicines for the treatment of infertility and sexual dysfunction. It contains more than 80 types of phytochemicals, among which are alkaloids and flavonoids. Its root is the most used part for certain purposes, as it has antioxidant, anti-apoptosis and anti-inflammatory properties and exerts positive effects on the male reproductive system, improving semen quality by regulating sex hormone levels and inhibiting lipid peroxidation (Azgomi et al., 2015).

Mechanisms of action

The exact mechanisms underlying the reproductive effects of *W. somnifera* are not yet well elucidated however, several studies have shown that its phytochemical components may exert major effects on the male reproductive system through antioxidant and detoxicant properties, regulation of sex hormones, GABA-mimetic action (Tahvilzadeh et al., 2016; Kumar et al., 2015; Ambiye et al., 2013). The mechanisms by which *W. somnifera* is capable of exerting effects on the male reproductive system and fertility can be divided into oxidative and non-oxidative mechanisms as shown in Figure 2 (Sengupta et al., 2018; Mahdi et al., 2011).

DISCUSSION

Oxidative mechanism

First, it is important to note that reactive oxygen species cannot be only harmful as several biological reactions at the chemical level are by then catalyzed. From fertility point of view, an optimal concentration of reactive oxygen species (ROS) is required for sperm maturation, capacitation, hyperactivation, acrosome reaction, zona pellucida binding and sperm-oocyte interaction (Agarwal et al., 2014).

However, excessive production of reactive oxygen species (ROS) may be among the main causes for the onset of male reproductive dysfunction, as the sperm membrane presents high amounts of polyunsaturated fatty acids, making them susceptible to lipid peroxidation (LPO) (Bisht and Dada, 2017). A high concentration of ROS or low antioxidant intake can lead to the process known as oxidative stress, resulting in the disruption of sperm cell DNA and/or RNA molecules (Esmaeili et al., 2015). Thus, antioxidants in seminal plasma protect germ cells against such damage and prevent the formation of ROS (Aitken, 2016).

The antioxidant action of *W. somnifera* has been determined by the amount of LPO produced. It has been observed that compounds extracted from *W. somnifera* are able to donate electrons and stop the destructive chain reaction of free radicals, thus decreasing the general charge of ROS (Gadelha et al., 2015). *Withania* flavonoids have been reported to have potent antioxidant activity that can counteract the formation of ROS in infertile men. Two alkaloids, sitoindosides VII-X and withaferin A, have been shown to activate the major free radical scavenging enzymes in vivo (Ahmad et al., 2010).

Metal ions, such as Cu^{2+}, Zn^{2+} and Fe^{2+} are cofactors for the antioxidant enzymes superoxide dismutase (SOD) and catalase and their deficiency has been observed in the sperm of infertile men (Shukla et al., 2011). Treatment with *W. somnifera* significantly improved SOD activity, catalase activity and glutathione level, eventually reducing protein peroxidation and carbonyl levels in infertile men (Durg et al., 2015).

W. somnifera root has also been shown to increase alanine concentration in semen. Alanine has a protective role against oxidative stress and can reduce LPO and thus increase sperm concentration and motility (Tahvilzadeh et al., 2016; Gupta et al., 2013).

Thus, the ability of *W. somnifera* root extract to decrease ROS can be inferred from two factors: its potent antioxidant activity and its ability to improve the concentration of metal ions that act as enzymatic cofactors (Shukla et al., 2011).

Non-oxidative mechanism

In addition to oxidative stress, other causes, such as hormonal imbalance caused by physiological or psychological factors, are also related to male infertility. Stress-related hormones, particularly glucocorticoids, have a deleterious effect on the hypothalamus-pituitary-gonadal axis (HPG) and subsequently on spermatogenesis (Chandra et al., 2012). The hypothalamus gonadotropin-releasing hormone (GnRH) stimulates the anterior pituitary to release the Stimulating Hormone Follicle (FSH) and the Luteinizing Homonium (LH); both subsequently act on the gonads, regulating spermatogenesis and testosterone production. Therefore, when the HPG axis is disrupted by hormones such as gonadotropin inhibitor hormone, prolactin (PRL) and cortisol, spermatogenesis is negatively affected (Nargund, 2015).

Furthermore, stress increases production and release of epinephrine, norepinephrine and cortisol. These hormones can have a detrimental effect on male reproductive function with two main mechanisms altering local blood flow and causing vasoconstriction in target tissues; reducing LH functional activity and testosterone level, which leads to decreased libido and oligospermatogenesis (Mahdi et al., 2011).

Due to its adaptogenic effects, *W. somnifera* can promote homeostasis, reducing stress response and normalizing cortisol levels. These characteristics were confirmed in a study that analyzed its effects on infertile men with normozoospermia who were under psychological or environmental stress (smoking) or had infertility of unknown cause (Sengupta et al., 2018).

Ambiye et al. (2013) noted that treatment with Ashwagandha root extract resulted in higher levels of testosterone and LH among infertile men, which had suboptimal values prior to therapy. Thus, they postulated that the probable reason for increased sperm concentration and motility was the higher testosterone levels provided by treatment with the extract.

In addition to these mechanisms of action, the roots of *W. somnifera* contain substantial amounts of lactate and lactate dehydrogenase (LDH). The stimulation of Krebs cycle and the consequent increase in ATP and cAMP levels observed after 3 months of treatment could help explain the achieved improvement in sperm concentration and motility (Tahvilzadeh et al., 2016).

Based on the intervention studies already performed the Table 1 was elaborated upon which summarizes the administered treatments and the effects of *W. somnifera* on sperm quality. The main conclusions of the systematic review studies are summarized in Table 2.

Conclusion

In recent years, the modern medical sciences have prospered greatly in treating infertility. However, despite major advances in synthetic products, herbal products are still a preferred choice in terms of safety and accessibility.

Table 1. Characteristics and results of human studies investigating the effects of *W. somnifera* (Ws) on the reproductive system.

Objective	Model used in fertility status	Treatment	Effect on sperm quality	Study suggestion	Reference
1. Effect of *Ws* root powder on semen quality in infertile men with "under stress" normozoospermia	Infertile men categorized into three groups (N = 20 in each): i) heavy smokers; ii) under psychological stress iii) with infertility of unknown etiology. Control: Fertile Men (N = 60)	*Ws.* root 5 g / day for 3 months plus skimmed milk.	In infertile men, there was an increase in sperm concentration compared to pretreatment values ($p < 0.01$). In men under psychological stress, increased sperm concentration ($P<0.01$) and motility ($P < 0.05$). In male smokers, increased sperm concentration and motility ($P<0.05$, respectively).	Fractionate this herb to better understand the mechanism of action of each constituent.	Mahdi et al. (2009)
2. Effect of Ws root extract on semen quality in infertile men	Infertile men with Normozoospermia, oligozoospermia and asthenozoospermia (n = 25 for each group)	5 g / day orally for 3 months with a cup of milk	Semen volume increased in men with normozoospermia and oligozoospermia compared to pretreatment values ($P<0.01$). Sperm concentration, motility and sperm count increased significantly in men in the three groups ($P < 0.01$).	Further study is needed to explore the individual properties of active constituents.	Ahmad et al. (2010)
3. The effect of Ws administration on apoptosis and ROS and metal ion concentrations in infertile individuals	Infertile men with Normozoospermia, oligozoospermia or asthenozoospermia (n = 25 for each classification) Control: Fertile men (N = 75)	5 g / day of single dose Ws root powder with milk for a period of 3 months for both groups	Significant reduction of apoptosis in normospermic and oligospermic men and ROS concentrations in oligozoospermic and astenozoospermic men (all $p<0.05$). Treatment also significantly improved overall metal ion concentrations ($p<0.01$).	More studies with larger sample size and placebo control group	Shukla et al. (2011)
4.Effect of Ws root extract on spermatogenic activity	46 male patients with oligospermia were included and randomized to treatment with extract (n = 21) or placebo (n = 25) on the same protocol.	675 mg / day in three doses for 90 days	There was a 167% increase in sperm count ($p<0.0001$), a 53% increase in semen volume ($p<0.0001$) and a 57% increase in sperm count ($p<0.0001$) among those who received sperm treatment. In addition, a significant and regular improvement was observed in serum hormone levels with WS treatment compared with placebo.	Suggests further exploration.	Ambiye et al. (2013)
5. Comparison of the effects of Ws with pentoxifylline on sperm parameters in idiopathic male infertility	Infertile men (N = 100) were randomly allocated to groups to receive Ws or pentoxifylline.	50 participants received Ws root in 6 capsules produced in two different colors (containing 5 g of Ws root) and 50 participants received pentoxifylline in 6 capsules in two different colors (containing 800 mg of this drug and a placebo) three times a day for 90 days.	*W. somnifera* increased mean sperm count (12.5%) and progressive motility (21.42%) and improved sperm morphology as an alternative to pentoxifylline	Large-scale studies with longer follow-up could be beneficial in elucidating further details of the efficacy and effectiveness of Ws in idiopathic male infertility.	Azgomi et al. (2018)

As discussed, *W. somnifera* contains several active constituents. Although the exact mechanism of action still needs further exploration, its main effects should be the reduction of oxidative stress, the regulation of hormone levels and the improvement of detoxification processes in the body.

Due to the growing interest in the use of herbal medicines, especially those with antioxidant and reproductive support properties, it is necessary to expand the number of studies in the area, encompassing a larger population and more population and more structured methodology. This could lead to more accurate conclusions and to an establishment or change of conduct in

Table 2. Characteristics and results of review and meta-analyzes investigating the effects of *W. somnifera* (Ws) on the reproductive system.

Objective	Discussion	Study suggestion	Reference
1. Evidence based on the application of medicinal plants in the treatment of sperm abnormalities in Persian Traditional Medicine	Most herbs introduced in this study have been clinically investigated for their effects on semen parameters, including sperm count and motility, sperm viability, dead or abnormal sperm, and recovery of sperm morphology. For *Ws*, more reliable evidence was found.	Overall, studies on the effectiveness of herbal remedies proposed for male infertility are promising; However, further studies are recommended for more conclusive results in the efficacy and safety of medicinal plants.	Tahvilzade et al. (2016)
2. Role of *Ws* (Ashwagandha) in the management of male infertility	Molecular mechanisms of action have been provided to better understand how *Ws* exerts its effects.	This review is unable to declare *Ws* as a "safe" or "toxic" drug. However, from the results analyzed, it can be assumed that *Ws* is beneficial for male fertility in several respects.	Segpunta et al. (2018)
3. Effect of *Ws* on the Reproductive System: A Systematic Review of Available Evidence	Ws exerts antioxidant properties, improves semen parameters and regulates sex hormones. These effects can affect many men seeking infertility treatment as they have a lower cost benefit and do not appear to have an adverse side effect. When associated with lifestyle modification and standard medical treatment, the chances of pregnancy are increased.	Further studies with a larger population and a more structured method are proposed so that a more accurate analysis can be made.	Azgomi et al. (2018)
4. Pharmacological overview of *Ws*, Indian Ginseng	Ws is a natural product with promising pharmacological and pharmaceutical properties. it or its constituents exert multiple protective properties, such as anti-inflammatory, antioxidant, inhibiting NFK-b transcription, MAPK signaling pathways, antiapoptotic, angiogenic and stress-reducing effects.	Further clinical validation needs to be performed for your general medical use.	Dar et al. (2015)

clinical practice.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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