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Perspectives on the bioactive ingredients and medicinal properties of Ashwagandha (Withania Somnifera) with special reference to reproductive effects in men and women

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Abstract
Ashwagandha *(Withania somnifera)* is one of the most renowned and revered medicinal plant in the Indian Ayurvedic system of medicine. Ashwagandha Rasayanas (tonics) are used for curing a wide variety of chronic ailments and to improve fertility in men and women, and to treat impotence in men. Results from animal studies indicate that Ashwagandha stimulates GnRH release from the hypothalamus, and consequently through the hypothalamic-pituitary-gonadal axis increases the levels of luteinizing hormone (LH) and follicular stimulating hormone (FSH). The modulation or rectification of imbalance in testicular (testosterone) and ovarian (estrogen and progesterone) hormones leads to the improvement in male and female fertility, respectively. However, Ashwagandha must not be used during pregnancy because it may cause miscarriage or premature delivery, and may harm the fetus. Ashwagandha ingredients may pass into breast milk and pose risk to the nursing infant, therefore, breast-feeding while using Ashwagandha medication is not recommended. The quest for developing new products of Ashwagandha's bio-active molecules (ginsenosides, withanolide, withanoside, withaferin) for treating neurodegenerative maladies (depression, epilepsy, Alzheimer's disease, Parkinson's disease) is continuing. Unfortunately, no large scale randomized, well-designed, double-blind, and placebo-controlled clinical trials have been done with calibrated dosages of Ashwagandha formulations to evaluate their long-term safety and efficacy. Because of the possibility of adverse clinical interactions of Ashwagandha with synthetic drugs, simultaneous oral administration of Ashwagandha and pharmaceuticals should be avoided. The focus of this review is to highlight the reversal of male/female infertility, alleviation of postmenopausal symptoms, and treatment of neurological disorders with Ashwagandha products.

Keywords: Ashwagandha's effects on male/female fertility: Ashwagandha as aphrodisiac; neuroprotective effects of ginsenosides; ashwagandha-drug interactions; ashwagandha patents.

1. Introduction

Historically, Ayurvedic remedies and ethno medicines have been used in India since times immemorial to cure human ailments. Ashwagandha *(Withania somnifera)* [L. Dunal, Family: Solanaceae] is one of the most renowned and revered medicinal plant of the Indian Ayurvedic system of medicine. Several Ayurvedic preparations containing Ashwagandha (Table 1) are marketed for the treatment of ailments ranging from anxiety and depression, low energy and stress, boost immunity, improve sexual health and fertility, rheumatic disease and arthritis, gout, and cardiovascular diseases. Ashwagandha Rasayana (tonic) protects against stress-induced gastric ulcers, promotes cognition in children with memory deficit, and benefits older persons with dementia. Ashwagandha preparations have been found useful in neurodegenerative disorders such as Parkinson's, Huntington's and Alzheimer's disease [1]. *Withania somnifera* (*Family - Solanaceae)* plant (Figure 1) is found over the huge area of South Asia, around the Mediterranean countries, and Southern region of Africa. Ashwagandha has not only been a valuable herbal remedy in the traditional Ayurvedic system of medicine, but also other parts of the world. For example, the people of Kenya called ''Maasai'' and Tanzania extracted juice from the Ashwagandha plant and utilised it for treating conjunctivitis and its berries juice was applied topically for treating ringworm disease. In Lesotho, Ashwagandha roots extract was used internally for the treatment of cold and asthma, and externally for treating bedsores in bed ridden patients [2]. In India, the Ashwagandha extracts are used as liver tonic and anti-inflammatory agents as well as for treating insomnia and upper respiratory tract disorders [2]. Experimental evidence from animals and limited number of clinical trials show that Ashwagandha is useful to rectify reproductive endocrine and fertility disorders in men and women [3, 4]. The fertility action is attributed to its specific affinity for glutamate [3] and gamma-aminobutyric acid (GABA). Ashwagandha is also known as Indian ginseng, poison gooseberry and winter cherry [10]. It contains a wide variety of bioactive phytochemicals that have shown anti-cancer, anti-neuroinflammatory, anti-stress, anti-diabetic, and cardioprotective properties. Experimental studies in rodents indicated beneficial effects of Ashwagandha in CNS-related disorders such as stress, depression, anxiety, Alzheimer's disease, Epilepsy, and Parkinson's disease due to its GABAergic and cholinergic neurotransmission modulating properties [5, 6, 9, 10]. Ashwagandha ingredients also act an antioxidant and modulate the action of superoxide dismutase (SOD), glutathione and lipid peroxidation (LPO) [7]. In adult male rats, oral administration of aqueous extract of Ashwagandha increased the expression and releases of gonadotrophic releasing hormone (GnRH) and affected the hypothalamic-pituitary-gonadal axis,

suggesting thereby the potential beneficial effects of Ashwagandha on the reproductive system. Due to its gonadotrophic activities and associated neuroendocrine effects, it has been used as an aphrodisiac and for the treatment of male erectile dysfunction [8]. Evidence gathered from animal studies and limited number of clinical trials show that Ashwagandha is useful for treating reproductive hormones and fertility disorders in men and women [3, 4]. In adult Wistar rats, Ashwagandha extract increased the sperm count and sperm motility [4]. The fertility action was attributed to its specific affinity for glutamate [3] and gamma-aminobutyric acid (GABA). Ashwagandha's GABA-mimetic action in the central nervous system (CNS) suggests that it is inhibitory in nature and is directly related to gonadotrophin-releasing hormone (GnRH) activity, which regulates the secretion of FSH and LH hormones from the pituitary gland [11]. The release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) is stimulated by GnRH release. In addition, LH and FSH are involved in synthesis of hormones; androgens from testicles and progesterone and estrogen from ovaries. GnRH release is associated with GnRH neurons which is regulated by steroid hormones and growth hormones. GABA, glutamate and various Neurotransmitters provide input to GnRH and triggers its release which activates the release of LH and GnRH from pituitary gland. Therefore, GABA plays a major role in the stimulation and regulation of GnRH secretion and ultimately fertility [11, 12].

In India, Ashwagandha products are sold in the form of tablets, capsules, Churna, and liquid preparations (Rasayana) and some formulations are indicated aphrodisiacs or for enhancing sexual performance in men. Ashwagandha is the main constituent of formulations such as Ashwagandha-taila, Ashvagandha - rishata, Ashwagandha-rasayana, and Saraswata-churna etc. [13]. The different Ashwagandha preparations, their indications and recommended doses are summarized in Table 1.

Table 1: Ashwagandha products sold in India and their recommended uses*.

Formulation Name	Manufacturing company	Recommended Dose	Indications
Ashwagandha Tablets	Himalaya Wellness	1 tablet twice daily	Used as aphrodisiac, sexual health, improving energy levels.
Ashwagandha Churna	Patanjali Divya	2-5 G, once or twice daily with lukewarm water or milk	Used as rejuvenating agent, anti- depressant and relieves stress
Ashwagandha Churna	Patanjali	1-2 capsules twice daily	Relieve fatigue, stress, generalised weakness, joint pain.
Ashwagandha Churna	Dabur	¼ to ½ teaspoonful twice a day with milk	Improve stamina, boost energy level and immunity.
Ashwagandha Capsules	Organic India	Not given	Improving vitality and energy
Nutrilite Ashwagandha Tablets	Amway	One tablet, 1-2 times/day	Supporting vitality, easing stress, Calming the nervous system, boosting body's functioning and revitalizing the body
Amycordial Tonic	Aimil Pharmaceuticals	2-3 teaspoonful thrice a day	Indicated for rheumatic ailments, arthritis, gout, cardiovascular diseases, anti-hypertensive.

Disclaimer: * The authors have no commercial interest in the sale of Ashwagandha products marketed by different companies in India or somewhere else.

2. Causes of infertility in men and women

Fertility problems can occur in both women and men, and can have multiple causes. Inability to conceive within a period of one year with unprotected intercourse is known as Infertility [15]. The occurrence of infertility is a serious reproductive disorder which is known to inflict 80-90 million people worldwide [16]. Infertility may be primary or secondary reproductive condition. In primary infertility, the couple is unable to produce a child even once, and in case of secondary infertility couple is unable to conceive again [17]. The causes for male infertility includes dysfunction of hypothalamus and pituitary gland which further decrease the Growth hormones, FSH, LH as well as testosterone. Other causes are dysfunction of ejaculation, testicular tumour, environmental factors including exposure to toxins, pesticides, heavy metals, medications (caffeine, cimetidine), alcohol [15]. In addition lifestyle factors has played immense role in male infertility. Factors like Obesity reduces the testosterone levels and enhance the estradiol levels. The causes of female infertility includes Pituitary Adenoma, Hyperprolactinemia is the most popular adenoma associated with pituitary gland and is a contributing factor for amenorrhea. Drugs such as antidepressants, cimetidine and estragon are known to interfere with secretion of prolactin [5]. other causes include Polycystic Ovarian Syndrome and ovaries consist of multiple small follicular cyst, disorders of fallopian tubes, uterine disorders and endometriosis. The emergence of new therapies such as Testosterone replacement therapy (TRT) plays an immense role in the treatment of hypogonadism. However, there are major concerns and adverse effects related to it [18, 22]. TRT is becoming important areas of interest in infertility associated with obesity. A reduction in weight up to 20 kg and decline up to 8kg/m^2 was demonstrated in a study conducted for 5 years of TRT. 92 subjects of this study showed the improvement in erectile dysfunction [22]. Testosterone therapy is also found to be effected in metabolic syndrome and hypertension associated infertility [23, 24].

3. Chemistry of the Ashwagandha Plant

Withania Somnifera falls in the class of Adaptogen in Ayurvedic system of medicine. It gives resistance to the adverse effects of variety of physical, chemical or biological agents. Presently its mechanism of action is still unknown. They are mainly glycosides or alkaloids of the plant. Till now nearly 35 chemical constituents have been known to be extracted and identified. The active chemical constituents are alkaloids (Isopelletierine, Anaferine) steroidal lactones (withaferin), saponins that contain additional acyl group and Withanolide that contains a glucose molecule at carbon no. C_{27} (Sitoindoside IX and X) [25]. It is also noted that *Withania somnifera* is rich in iron as well. Withanolide are the Steroidal lactones present in W. Somnifera have structure like ergostane framework. The C_{28} molecule gets oxidized at C_{22} and C_{26} to form a six-membered lactose ring structure. The most important constituents in the plant roots are Alkaloids and

Flavonoids. Flavonoids of the plant have antioxidant nature [25]. Free radical scavenger enzymes were reported to be reactivated in-vivo due to these two alkaloids – withaferin A and sitoindosides VII-X [26]. Considerable amount of lactate and lactate dehydrogenase (LDH) are also present in the roots of the *Withania Somnifera* [25]. Ashwagandha has shown many therapeutic effects in humans owing to presence of a wide variety of chemical constituents. However, in this review article, we will primarily be addressing the reproductive effects of Ashwagandha in men and women, especially its effects on reversal of infertility. Among variety of chemical constituents present in it. They can be grouped as per there proportion in which they are present. There is a complex nature of certain active components since they exhibit various pharmacological activities.Besides all other chemical ingredients, Withanolide $\{C_{28}H_{38}O_6\}$ is present in the maximum concentration [27]. Nearly 35 compounds belonging to the class of Withanolide have been isolated from the roots of Ashwagandha. Among these chemicals, Withanoside V, withaferin A, Withanolide A, and withanolide B are the important active constituents [27]. Purported medicinal applications of Withanolide are: withaferin A as anti-tumor, apoptotic and anti-inflammatory; Withanolide A as neurological, immunological and anti-stress; Withanolide B and Withanoside V for neuro-regeneration (Table 2).

Table 2: Medicinal applications of Ashwagandha ingredients

Chemical Constituent	Uses
Withaferin A	Anti-tumor, apoptotic and anti-inflammatory
Withanolide A	Neurological, immunological and anti-stress
Withanolide B, Withanoside V	Neuro-regeneration

4. *In vitro* permeability evaluation of different Withanolides

Table 3 shows the in vitro permeability results of major Withanolides derived from the Ashwagandha roots. Devkar *et al*. (2015) [27] analyzed the permeability characteristics and extent of absorption of major withanolides using the Sino-Veda Madin-Darby canine kidney (MDCK) cell culture system. Some withanolides were found to be highly permeable, whereas others showed low permeability. The reason for poor permeability of withanoside IV & V was attributed to the presence of glucose moiety linked at carbon no. C_3 that makes them higher molecular weight compounds and hydrophilic-polar molecules [28].

The bioavailability of orally administered drugs depends up on their biochemical properties (molecular weight, lipid solubility and nonpolar nature), and transportation through the intestinal epithelium. Bioavailability is defined as the "portion of the dose of the drug that is absorbed from its site of administration and reaches system circulation in unchanged form" depends upon the permeability and transportation characteristics, The bioavailability of a drug administered by the intravenous route is 100%, which is not possible to achieve for drugs administered by various other routes such as oral, intramuscular, subcutaneous, intraperitoneal, percutaneous, through rectum or vagina etc. Based on the permeability characteristics (Table 3), it seems that the bioavailability of different Withanolides will most likely correspond with their cell culture system values. Further studies with animal and human intestinal cells are needed to predict the extent of absorption and bioavailability of different withanolides.

Table 3: Permeability characteristics of major Withanolides in the cell culture system.

Chemical Compound	Permeability
Withanolide A	High
1,2-Deoxywithastramonolide	High
Withanone	High
Withanolide B	High
Withanoside IV	Low
Withanoside V	Low
Withaferin A	Impermeable

4.1 *In vivo* studies done with Ashwagandha

To evaluate the toxic potential of Ashwagandha, its methanolic extract was administered orally to Wistar rats at a dose >2,000 mg/kg. Daily consecutive dosing for 14 days did not show any adverse effects on organ atrophy, hypertrophy and degenerative lesions. The results of this study showed that Ashwagandha extract (standardized for Withaferin A) did not cause any toxic effects in male and female rats up to a dose level of 2,000 mg/kg [29]. Although this rat study revealed high margin of safety for this herbal drug, more preclinical and clinical studies are needed to ensure the long-term safety of Ashwagandha ingredients.

4.2 Clinically important interactions Ashwagandha with synthetic drugs

Self-medication with herbal medicines and Ayurvedic remedies is becoming quite common these days. Occasionally, serious drug-herbal interaction between orally administered allopathic drugs have occurred in humans. Different constituents of Ashwagandha may change the activity of poly-glycoprotein transporters (PGps) and metabolizing CYP-450 isozymes in the gastrointestinal tract and alter the absorption, distribution and metabolism of synthetic drugs. Therefore, prior to prescribing allopathic drugs to their patients, doctors should ask questions if they are taking any herbal remedy or Ashwagandha for treating a disease.

Ashwagandha, commonly referred as India ginseng, consists of saponins called ginsenosides [30, 31, 32].It has been reported that ginsenosides are metabolised by intestinal bacteria. Metabolites of ginsenosides such as compound K, have shown anticancer properties [32, 33, 34]. The bacterial flora follows subsequent deglycosylation reactions [35]. Rb1 and Rd of group PPD are converted to compound K after metabolism [36]. However, Rg3 to Rh2 and Rh 5 to Rh3. Rg1 and Re group of PPT are converted to Rh1 and F1 respectively [37, 38].

In a study conducted to analyse the effect of naturally occurring ginsenosides and intestinal degraded product of ginsenosides on hepatic CYP450, it was found that there was no inhibition against human CYP3A4, CYP2A6 or CYP1A2 by naturally occurring ginsenosides. However, Intestinal metabolite inhibited CYP450 mediated reactions. CYP2C9 was inhibited weakly by protopanaxatriol (PPT), protopanaxadiol (PPD) and compound K; CYP3A4 was strongly inhibited by protopanaxadiol (PPD), and protopanaxatriol (PPT). The study suggests that orally given natural ginsenosides may interfere with CYP450 reactions by intestinal metabolites [45].

It is essential to study drug interaction with herbal medicines particularly when the drug has low safety index. Herbal drug such

as Ashwagandha may interact with Warfarin which shows a very low therapeutic index. In such cases it becomes crucial to keep the drug effect in a range that reaches the target level to show pharmacological effect. A highly impacted study showed enormous decrease in activity of Warfarin, when it was consumed with Ashwagandha. However, before Ashwagandha the anticoagulant therapy was stabilised [46, 47]. *In vitro* studies and experimental animal studies reports inhibition of platelet aggregation by ginsenosides. Thromboplastin time has also reported to be elevated [48]. Therefore, it is important to discontinue the use of herbal drug such as Ashwagandha, two weeks before the surgical procedures [49].

5. Ashwagandha's effects on female sexual function and fertility

The reproductive cycles in women start at puberty and continue till menopause, the age of which varies in different races and ranges from nearly 55-70 years of age. Female sexual arousal disorder (FSAD), hypoactive sexual desire (HSD), lack of organism, and hormonal imbalance not only cause loss of libido, but also female sexual dysfunction (FSD) and fertility problems. In some women, loss of libido or FSAD occurs due to painful intercourse, vaginismus, or chronic genital tract infections. Because of reduced sexual arousal and libido, painful intercourse due to large penis size or vaginal sensitivity, lower lubrication or vaginal dryness, several women are unable to achieve orgasmic pleasure and also suffer from infertility [39]. In some cases, unhealthy marital relationship, ill health, diabetes, and neurodegenerative disorder as well as psychogenic factors can adversely affect the women's sexual health and fertility.

In addition to these factors, stress, depression, and psychiatric problems are responsible for causing FSAD and lowering of sex drive. Other health problems like obesity, diabetes mellitus lower sex drive and cause FSAD. In today's modern lifestyle, chronic stress, anxiety and depression are quite common. Women under chronic stress are often less motivated and enthusiastic towards sexual activities. Stress-induced elevation of cortisol in blood stream is linked with gonadal and sexual dysfunction [39]. Ashwagandha products are useful for treating stress-related conditions and help to bring normalcy in the sympathetic nervous system, restore adrenal function and deceases cortisol levels in blood and consequently improve sexual health [39].

Sex hormones (estrogen, progesterone, testosterone) reduction or imbalance also accounts for FSD in women. Lack of sexual desire in women can occur due to the decline of estrogen and testosterone in postmenopausal and old age women. Testosterone decline reduces sexual desire in women and causes erectile dysfunction in men. Ashwagandha root extract increases the blood levels of testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH) as well as prolactin in women [39]. High levels of FSH in women are generally associated with sub-fertility or infertility. High FSH in serum leads to loss of ovarian function and premature ovarian failure before 40-45 years of age. Optimum level of FSH is needed for the stimulation and ripening of ovum in the follicles. In child-bearing -age women, LH stimulates ovulation and promotes the Graafian follicle to turn into corpus luteum. However, LH beyond the normal reproductive range or higher than ideal concentration often cases polycystic ovary syndrome (PCOS) and infertility [40].

6. Ashwagandha effects on menopausal symptoms

Ashwagandha in addition to Ashokarista (Asokarishtam) and Praval Pishti in Ayurveda (Indian system of medicine) was administered in a combination therapy. It was reported that menopausal effects were delayed by significant percentage. A study was conducted on 52 patients who were aged between 40-55 years, all of them being prone to amenorrhea for more than 12 months at least. Out of which 51 successfully completed the study. This reported to provide relief from post menopause symptoms like hot flushes, heart discomfort, sleep problems, depressive mood. With this Vasomotor, psychological, physical and sexual scales have even showed improvement from before. In this research over the top is was find out that this therapy had no side effects nor adverse effects and ashwagandha could be added to the normal diet on normal basis [53].

7. Ashwagandha's effects on male sexual function and fertility

Infertility is one of the most common disorders in human reproduction. Male infertility can result from incapacity to copulate or incapacity to fertilise an ovum. Erectile dysfunction (ED) in men is associated with psychological distress, depression and low self-esteem, and can result in divorce and economic loss. The most important reproductive processes in adult males are libido, erection and spermatogenesis. The spermatogenesis commences at puberty with mitotic multiplication of spermatogonium in the seminiferous tubules. The spermatogonium increase in number and undergo reduction division. They are termed as primary spermatocytes which still contains 46 chromosomes. After completion of first step in the meiosis, two cells are formed with chromosome number reduced to 23 and are termed as secondary spermatocytes. Further on completion of step II meiosis each cell again divides into two but with the same chromosomal number. The spermatids develop in Sertoli cells and are subsequently transformed to motile spermatozoa or sperms. The motile sperm are stored in the epididymis for further maturation [41]. In humans, the spermatogenesis cycle takes about 75-80 days. Aerobic metabolism of human sperm leads to a formation of various reactive oxygen species (ROS), to some extend which are crucial for sperm capacitating, acrosome reaction and oocyte fusion. To neutralise the toxic effects of ROS, seminal plasma, and spermatozoa are equipped with certain sets of antioxidant mechanisms [9, 26]. Reactive oxygen species are the molecules which lack in electron containing oxygen element in them. Peroxides, super oxides, singlet oxygen are some common examples of the same. Varieties of species like superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase are identified in seminal plasma which are body's mechanism to lower the oxidative stress [3]. Along with these, high concentration of thiol groups, ascorbic acid and uric acid are also present in the semen. Traces of ascorbic acid, uric acid and glutathione are present in sperms with large concentration of thiol groups. The abandoned production of ROS leads to surplus hike in ROS concentration followed by seminal oxidative stress. This oxidative stress causes injury to the membrane of the sperm and deterioration to other significant properties like sperm motility and morphology. After studying various oxidative biomarkers (e.g. lipid peroxides {LPO}) before and after the administration

of *Withania Somnifera* it was reported that successive lowering of LPO, control proportion of ROS and recovered seminal plasma activity. Alanine is alpha amino acid which has a protective role in oxidative stress. In addition to this it lowers lipid peroxidation and boosts the sperm concentration and motility. Roots of *Withania somnifera* have shown significant properties to increase Alanine concentration in semen.

Sexual hormones or the androgens very much coordinate with criteria of semen quality. Testosterone plays a vital role in sexual drive and libido stimulation. The process of spermatogenesis is also gets restrict with unusual lowering of testosterone (3).High rise in the FSH levels reflects the damage caused to seminiferous tubules. Testosterone (T), Luteinizing hormone (LH), Follicle stimulating hormone (FSH), Prolactin (PRL) were used as markers to study the semen quality. In oligozoospermic (low concentration of sperms in semen) males' concentration of FSH and PRL were found to be higher than in normozoospermic (normal sperm count) males. While the concentration of LH and T levels were beneath the normal. To counter this abnormal level of hormones direct hormonal supplements had brought in practice. The results were nonetheless appreciable in addition to several side effects. Therefore, *Withania Somnifera* is used more commonly to recover the sex hormones in male infertility treatment being safe method than any artificial methods adopted before [3].

8. Clinical effects Ashwagandha

8.1 Effects on men

It was observed in a sample size of nearly forty human infertile males ranging from 22 and 40 years of age. Having semen factor responsible for infertility. The sperm count of these men were not less than 5 million/mL nor greater than 20 million/mL with a total motility of nearly 10-30% only. All the men had a usual sexual intercourse with gynecological normal females possibly having no female infertility for nearly a year or more. Males with primary erectile functions were not selected for this study.

They were treated with one capsule that contains high concentration full spectrum root extract of Ashwagandha containing not less than 225mg of the extract. It was given orally for 3 times a day and this was continued for a period of 12 weeks. After 12 weeks of intake off Ashwagandha root extract the result reported was great in terms of helping in the infertility in males. The sperm concentration was reported a hike by 100% or even more in certain cases. Nearly a surge of 53 % in semen volume released per ejaculation and a boost by 57% in sperm motility were such hard to ignore benefits of Ashwagandha. Serum concentration of testosterone and LH were raise by 17% and 34% respectively [42]. It became clear that Ashwagandha was really an effective cure for infertile males, oligospermic males (the one with low sperm count). While this experimentation no adverse effects were reported which made its use more prominent.

8.2 Effects of Ashwagandha in women

Experiments were conducted on females with a High Concentration Ashwagandha Root Extract (HCARE) which was administered to a group of females nearly the age of 21-50, participating in a constant heterosexual relationship for over a year, either earlier or presently committed in sexual function for several years. These group of women were selected for this study on a common base categorization that all of them were suffering from FSD with having one or the other disorder: -

1. Hypoactive sexual desire disorder (HSDD)
2. Female sexual arousal disorder (FSAD)
3. Female orgasmic disorder (FOD)
4. Combined genital and subjective arousal disorder

Because of HCARE treatment, there was increase in sex drive in the females, all kinds of arousal disorders were no longer evident and females were more frequently able to reach orgasm. It was observed that with HCARE treatment and a counselling program women could have an early orgasm, pleasure, satisfaction, better natural lubrication and successive arousals rather than just counselling programs [39].

This made the use of Ashwagandha (Withania Somnifera) more popular for female sexual disorder.

9. Neuroprotective Effects Ginsenosides present in *Withania somnifera*

Ashwagandha (Indian Ginseng) is also known for its Neuroactive potential. Recent pharmacological surveys have revealed that it has a monitoring effect on the central nervous system. Ginseng can reinforce the cerebral cortex excitatory and inhibitory processes and decrease the debility of the brain process. The ginseng also shows a protective and fortifying nature due to the presence of the constituents named ginsenosides in them [50].

In a study anticonvulsant effects of individual ginsenosides Rb1, Rb3, Rd was compared and in addition combined effect of ginsenoside was also compared. The results show that combined effect of (Rb1 +Rb3) either with Rd or without Rd ginsenoside has immense anticonvulsant effects when induced in Pilocarpine and PTZ models [51].

The antidepressant effect of ginsenoside Rg1 was explored in a mice model of depression and a mouse model of chronic mild stress (CMS) depression. The results suggests that that Rg1 reversed hippocampal neurogenesis and and reduced dendritic spine density. Further, it was found that antidepressant activity of ginsenoside Rg1 was due to BDNF and regulation of hippocampal neurogenesis [52].

Ginsenosides are the chief active ingredients extracted from roots, fruits, stems, and leaves of ginseng. They have a unique biological activity and medicinal value. Each ginsenoside plays a significant pharmacological role. The pharmacological trials have displayed that ginsenosides possess various biological activities such as anticancer, anti-inflammation, antioxidation, antiaging, antifatigue and other physiological function.

According to the recent studies, it was stated that ginsenosides show a positive impact on the nervous system, the cardio vascular system, and the immune system but on the other hand it was also found to be slightly toxic. Although there are many studies on ginsenosides for nervous system dysfunctions such as sensation, movement, consciousness, and autonomic nervous disorders, the definite mechanism is still in the elementary phase.

The neuroprotective effects of ginsenosides are mainly emphasised on anti-aging, nerve growth factor, cytokines, and signalling pathways [50]. Ginsenosides are suggested for treating various neurological disorders such as:

1. Depression
2. Epilepsy

3. Alzheimer's disease
4. Parkinson's disease

In this review, we have recapitulated the numerous uses and the proposed mechanism of actions of Ashwagandha as well as have pointed out the gaps in our knowledge for further research and purported therapeutic applications in humans.

10. Miscellaneous medicinal benefits of Ashwagandha

Ashawagandha has not only proven useful in the reversal of infertility in men and women, but has also shown other beneficial effects depicted in Figure 5. Namely, management of stress and obesity, anti-diabetic, anti-oxidant, anti-inflammatory, analgesic, muscle repair, cardiovascular protection, and neuroprotection.

Ashwagandha is known to increase blood testosterone levels in men. Such action can modulate pathways that promote sexual desire and libido, reverse erectile dysfunction, and improve sperm parameters. The antioxidant properties of Ashwagandha may protect the human sperm from lipid peroxidation and DNA damage.While in females, the reproductive mechanism of action is not that simple. Ashwagandha may help to regulate menstrual cycle, enhance sexual desire and induce greater probability of orgasmic pleasure in women. Whether or not Ashwaganda would increase testosterone level in women and create reproductive hormonal imbalance is not known. Female infertility is a multifactorial and complex phenomenon. More clinical studies are needed to assess Ashwagandha's mechanism of action in infertile females. Furthermore, efforts should be made to elucidate the chemical structure of active compounds responsible for the reversal of infertility in men and women.

11. Discussion

Self-medication with phytotherapies and complementary remedies, including vitamins and micronutrients, is becoming popular these days. People believe that dietary supplements and traditional herbal medicines are free from any harmful effects and cause lower incidence of side effects than allopathic drugs. However, adverse reactions (ADRs) and case studies have shown that the multiple ingredients, often of unknown concentrations, in herbal products or dietary supplements may be associated with toxic effects such as immune suppression, allergies/asthma, endocrine disorders, loss of appetite, and may also produce some other undesirable effects. Some ADRs of herbal remedies, traditional medicines and dietary supplements may not be detected after a short-term exposure. Three, 6 or 12 months may be needed to see ADRs. Clinically important, and occasionally life-threatening, adverse interactions have occurred in humans when allopathic drugs, especially cardiovascular medications, are taken along with herbal remedies and fruit juices. Since self-prescribing popularity of herbal remedies, fruit juices and dietary supplements is growing, physicians should inquire before prescribing, whether their patients are consuming any interacting juice or herbal product and either instruct their patients to stop consuming such products or adjust drug dosage to compensate for drug-herbal/juice effects. Collaborative efforts are required from patients, physicians, pharmacists, nurse, and industry (drug manufacturers, suppliers of herbal remedies, juices and nutraceuticals) to minimize or possibly prevent any potential risks associated with the concomitant use of botanical products and interacting drugs. Post-marketing surveillance is also needed to determine potential drug-herb-juice interactions.

According to World Health Organization (WHO) estimates, nearly 80% of the world's population uses phytotherapies or complementary alternative medicines (CAM) for curing various ailments [WHO, 2008). More than 50% modern drugs have originated from plants and pursuit for the discovery of new medicines from plants is the subject of intensive global ongoing research. In 2015, the Nobel Prize in Physiology and Medicine was awarded to William Campbell, Satoshi Omura, and Youyou Tu for the discovery of two major natural products: (43) avermectin and its derivative ivermectin isolated from the soil microorganism *Streptomyces avermitilis*, and (44)artemisinin, isolated from the plant *Artemisia annua* L. (Asteraceae). Both these drugs have proven highly useful for treating malaria with artemisinin and lymphatic filariasis and onchocerciasis with avermectin. The Nobel Prize award in the field of phytotherapy has not only put phytomedicines into the limelight, but also has recognized the importance of thousands-year-old medicinal system practiced in China, India and other countries of the world. The emerging evidence suggests that plant-based ethno medicines, CAM, functional foods, and nutritional therapies are our best hope in achieving sustainable health for all humans globally. Considering the high cost of synthetic drugs, the people of developing countries are desperately looking for cost-effective and affordable plant-derived remedies for treating communicable (e.g., bacterial, viral, fungal, parasitic etc.) and non-communicable diseases like infertility, male erectile dysfunction, cardiovascular disorders, diabetes mellitus, obesity, cancer, chronic pain, psychiatric and neurodegenerative diseases etc.

Sexual pleasure and procreation are physiological needs of mammalian species, and is an integral part of psycho-social side of human behaviour. Great sexual experiences with their partners and to conceive a child are related to normal health and wellbeing. Since sexual health plays a vital role in human life, treatment of any sexual disorder is often sought by men and women all over the world. As was alluded to earlier, the causes of sexual dysfunction, infertility, loss of libido, or any other sexual condition may be due to anatomical defects in sexual organs, reproductive hormone abnormalities, psychogenic factors, old age as well as the permutation or combination of these various entities.

A randomized pilot study was conducted in 46 oligospermia male patients (treatment group = 21, and placebo group =25). Ashwagandha root extract (675 mg/day) was given in tree doses for 90 days. In comparison with the baseline values, there was a 167% increase in sperm count, 53 % increase in semen volume, and 57% increase in sperm motility on 90th day of treatment. In addition, compared with the baseline values, testosterone increased by 17% and LH by 34% after treatment with Ashwagandha root extract. In comparison, only minimal improvements in the semen parameters and hormone levels were observed in the placebo group [42].

The antioxidant vitamins A, E, and C appeared to better sexual health in men [3]. Testicular oxidative stress during spermatogenesis appears to cause sperm abnormalities and infertility in men. The antioxidant properties of Ashwagandha may protect the sperm from lipid peroxidation and DNA damage, improve semen quality and reverse male infertility.

In women, stress is considered as a major cause for not achieving successful orgasms. Ashwagandha seems to relieve stress by lowering serum cortisol level (stress biomarker). It seems to work by improving mental, physical and sexual health in impotent couples.

The results of one study showed that Ashwagandha alleviates postmenopausal symptoms: namely mild to moderate depression, mood swings, insomnia, hot flushes, and leukorrhea [55] further studies are needed to determine the safety and effectiveness Ashwagandha for treating postmenopausal symptoms in women. No studies have been done to evaluate the effects of Ashwagandha for the sexual arousal disorder in women. The decreased level of testosterone or androgen deficiency is implicated for female sexual dysfunction.

Results of a randomized controlled trial showed that Ashwagandha has a potential for skeletal muscle fibre repair and muscle building ability. Rapid muscle growth was observed with Ashwagandha dietary supplement using creatine kinase as a biomarker. Ashwagandha treatment lowered urea and lactic acid level in blood. It has antioxidant, anti-inflammatory, and analgesic activities. A combination of mechanisms could be responsible for the muscle repair and muscle building actions. In view of these observations, Ashwagandha dietary supplement may be useful for inducing rapid muscle repair and strength in athletes [54].

12. Current and future developments

Despite of the centuries-old therapeutic history behind Ashwagandha, gaps still exist in our knowledge about this important herbal remedy. For instance, the pharmacological and toxicological activities of different steroidal lactones and other bioactive moieties present in Ashwagandha remain to be worked out. The therapeutic potential of a wide variety of bioactive compounds present in the Ashwagandha roots remain unknown. Efforts should be made to identify and elucidate the chemical structures of the active compounds responsible for the reversal of infertility. The long-term safety and efficacy of tablets, capsules Churna, and liquid preparations (Rasayana) should be investigated by well-designed, randomized, placebo-controlled, double-blind clinical studies. For the benefit of doctors, pharmacist and patients, all Ashwagandha products should be prepared using good manufacturing practices and should be property labelled, including contraindications. The elderly population is more prone to adverse drug effects and polypharmacy as well as herbal-drug interactions. Elderly population should be enrolled in clinical trials to determine the dose-range of herbal remedies. Post-marketing surveillance is lacking for the phytomedicines worldwide. All these parameters need to be assessed before marketing the Ashwagandha formulations and other herbal medicines.

It is reported that Ashwagandha has cardiac arresting properties, but this serious adverse effect is not fully explored in humans and animal models.

The recommended doses and indications of Ashwagandha products sold in India by different manufacturing companies are summarized in Table 1. We don't know whether or not, the manufacturing companies hold any patents for their marketed products sold in India or abroad. The information cited in Table 1 is in the public domain. Therefore, we are not in any violation of patent or copyrights. In the footnote of Table 1, we have inserted a disclaimer the authors have no commercial interest in the sale of Ashwagandha products marketed by different companies in India or abroad.

13. Conclusions

In the Ayurveda medicinal armamentarium, Ashwagandha has remained popular for promoting health and well-being, and has proven beneficial in curing a wide array of ailments. The quest for developing new products with the bioactive molecules of Ashwagandha is continuing. Unfortunately, only a limited number of randomized, well-designed, double-blind, and placebo-controlled clinical trials have been done to evaluate the safety and efficacy of Ashwagandha formulations with calibrated dosages recommended for medical use. Results of a few clinical reports show that Ashwagandha and its phytochemicals improve reproduction in both men and women, enhance sexual activity and erectile function in men, as well as alleviate postmenopausal symptoms in women. Thus, Ashwagandha may be a safe and cost-effective non-hormonal therapy for treating reproductive disorders in humans. Nevertheless, Ashwagandha products should be avoided by pregnant women because they can cause miscarriage or premature delivery. Additionally, intrauterine exposure of Ashwagandha products on the developing fetus and their post-natal consequences in children remain unknown. Because of the possibility of excretion of Ashwagandha ingredients in breast milk, lactating women should avoid Ashwagandha medication. The withanolides and ginsenosides seem to have neuroprotective potential, but their mechanism of action remains to be ascertained. Many investigators have reported clinically important adverse interactions between herbal remedies and fruit juices with orally administered synthetic drugs. Studies are also needed to understand any adverse clinical interactions between Ashwagandha products with synthetic drugs.

14. List of Abbreviations

CVD = Cardiovascular disease
CNS = Central nervous system
ED = Erectile dysfunction
FSH = Follicle stimulating hormone
FSAD = Female sexual arousal disorder
FOD = Female orgasmic disorder
HSDD = Hypoactive sexual desire disorder
GABA= Gamma-aminobutyric acid
GnRH = Gonadotrophic releasing hormone
LH = Luteinizing hormone
LPO = Lipid peroxidation
SOD = Superoxide dismutase

15. Conflict of Interest

Dr. Harpal Buttar is the Editorial Review Board Member of J-AIM.

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NONE.

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