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SCREENING OF POTENTIAL MALE CONTRACEPTIVE DRUGS FROM NATURAL RESOURCES: AN OVERVIEW

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ABSTRACT: Rapid rising population has caused serious problems in the economic growth and all around human development especially in developing countries like India. Our future well-being depends on increased access to family planning and reproductive health services and decreased consumption by people. Family planning has been promoted through several methods of contraception. But due to series adverse effects produced by synthetic steroidal contraceptives, attention has now been given to indigenous plants for possible contraceptive effects. Thus there is a need of replace these agents by plants. The investigation of plant constituents with development of an effective, reversible and safe male contraceptive represents a potential alternative approach to birth control from the existing available methods. This review concentrates on those recent advances in science and technology that offer possible inroads for shifting the paradigm for male-based contraception. This review presents updated information gathered on scientifically proved medicinal plant (*Withania Somnifera)* and their more than 50 secondary metabolites might be can use as male contraceptive agents and other biological activity. The aim of this review is to highlight the work on various plant drugs and their bioactive extracts involved in male anti-fertility mechanism.

INTRODUCTION: The currently population explosion is one of the biggest problems facing by world. It's inevitable consequences are employment, education, housing, health care, economy and environment. Currently, world population crosses the 7 billion and increasing continuously day by day. Therefore Fertility regulating becomes issue of global health concern.

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There is a great need to support at individuals in family-planning since increasing growth rate of world's population caused negative impact on sustainable, economic growth and poverty increased especially in developing countries [1, 2].

India is also only the second country to achieve a population of 1.22 billion. India's population will exceed that of China before 2030 to become the world's most populous country, a distinction it will almost certainly never lose. That debate is by no means trivial nor resolved, yet it has declined in recent years, and, conclusively, interests in population/environment (P/E) relations have declined [3, 4].

According to World Health Organization despite many achievements in human health care in the twentieth century many of the world's population in developing countries lack regular access to affordable essential drugs [5, 6]. A part from the advantages of traditional medicine many problems must be tackled to maximize the potential of traditional medicine as a source of health care [7]. Perhaps one of the greatest arguments against traditional medicine today is the lack of scientific proof of its efficacy. In addition to a problem of efficacy traditional medicine has a problem of safety. The herbal products today represent safety in contrast to the synthetics that are regarded as unsafe to human and environment [5].

The investigation of plant constituents with antifertility properties represents a potential alternative approach to birth control from the existing available methods [8]. Therefore, a regular revision/development of high resolution analytical methods is necessary, not only for a better phytochemical description and quality control of the drugs but also for the authentication of raw materials and characterization and/or development of discrete chemo types. Furthermore, plants can act as anti-fertility agents and these plants can be classified according to their activity profile such as anti-spermatogenic plants; spermicidal and semen coagulant plants; and fertility inhibiting plants [9].

Family planning has been promoted through several methods of contraception, but due to serious adverse effects produced by synthetic steroidal contraceptives, attention has now been focused on indigenous plants for possible contraceptive effect [10, 11]. Hence, there is a need for searching suitable product from indigenous medicinal plants that could be effectively used in the place of pills [12]. Thus, as part of a long-term evaluation of potential antifertility plant, we have conducted these studies on the effects of *Withania somnifera* extract and their alkaloids on the fertility of rats.

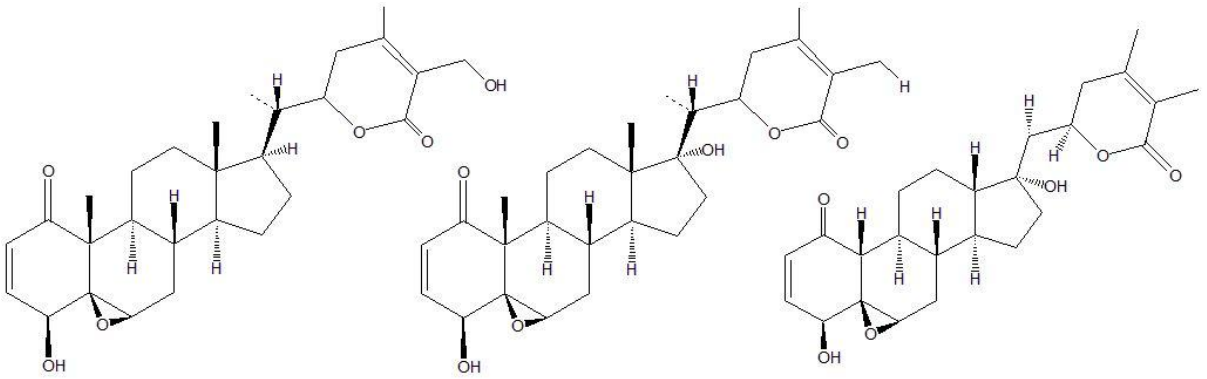
Withania somnifera Dunal (Family: Solanaceae), popularly known as Ashwagandha, Indian ginseng, or winter cherry has been used for millennia in Ayurveda, Indian system of traditional medicine [13, 14]. *Withania somnifera* appears in WHO monographs on selected medicinal plants and an American herbal Pharmacopoeia monograph [15].

Twelve alkaloids, 35 withanolides, and several sitoindosides from *Withania somnifera* have been isolated and studied [16, 17].

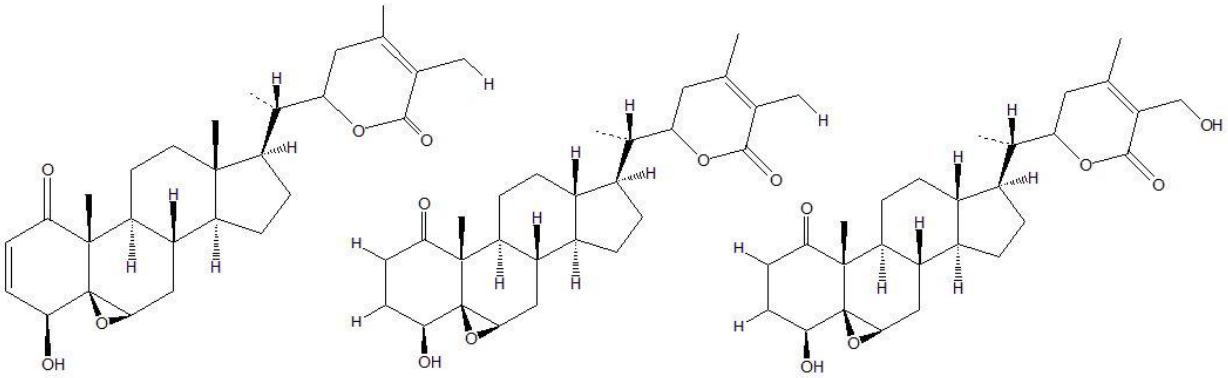
The present review deals with the documentation of some herb based male contraceptives used in India. The present study was also undertaken to determine whether plant might have any effect on male reproductive organs and spermatogenesis in rats. This study is aimed at finding out whether *Withania somnifera* alkaloids can prevent the fertility.

Chemical Constituents: The analysis of total metabolome of plant is important to extend our understanding of complex biochemical processes within a plant. Significant technological advances in analytical systems like NMR, GC–MS and HPLC have opened up new avenues for plant metabolomics research aimed at rapidly identifying a large number of metabolites quantitatively and qualitatively. This has become an important area of investigations in pharmacology and functional genomics of medicinal plants. The metabolic constituents, particularly secondary metabolites differ with the variety of W. somnifera, tissue type and sometimes with growth conditions. An impressive number of steroidal lactones have been isolated and identified from w. somnifera plants originating from different sources and geographical regions. The name given to this group of compounds is withanoloides and they are derived from an ergostane-type skeleton in which C-22 and C-26 form a characteristic 6-member lactone.

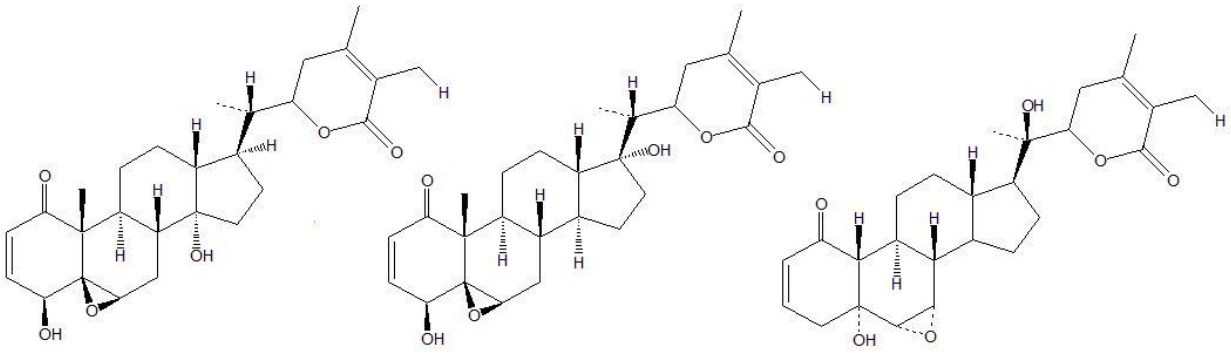
Several bioactive alkaloids and sterol lactone based phytochemicals, e.g. ashwagandhine, cuscohygrine, isopelletierine, anaferine, cuscohygrin, anhygrine, tropine, psudotropine, isopeletrin, sitoindosides (saponins), the diversely functionalized withanolides, withanones, withanamides, withasomidienones and glycowithanolides have been isolated from different parts of this plant [18, 19, 20, 21, 22, 23, 24]. At present, more than 12 alkaloids, 40 withanolides, and several sitoindosides have been isolated and reported from aerial parts, roots and berries of *Withania Somnifera*. The major chemical constituents of these plants, withanolides, are mainly localized in areal part, and their concentration usually ranges from 0.08% dry weight (DW) [18, 25, 26]. Molecular structures of several secondary metabolites and there derivative compounds are given below.



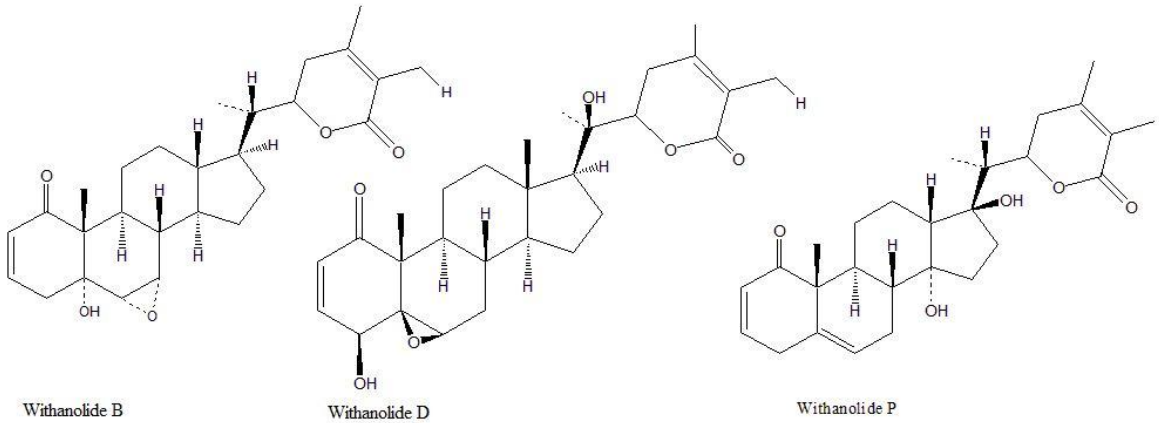
Withaferin A | 17-Hydroxy withaferin A | 17-Hydroxy, 27-deoxy withaferin-A



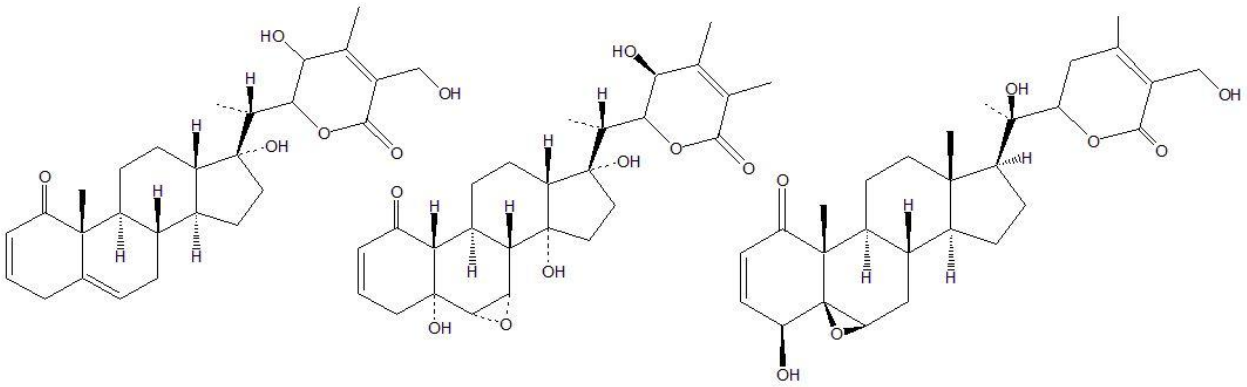
27-Deoxy withaferin A | 2,3- Dihydro withaferin A | 2,3- Dihydrodeoxy withaferin A



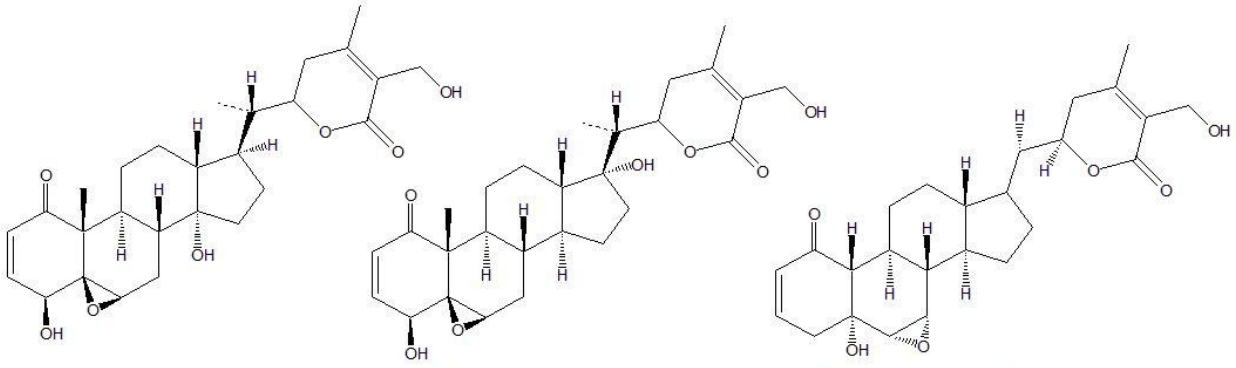
14α- Hydroxy 27-Deoxy withaferin A | 17α- Hydroxy 27-Deoxy withaferin A | Withanolide A



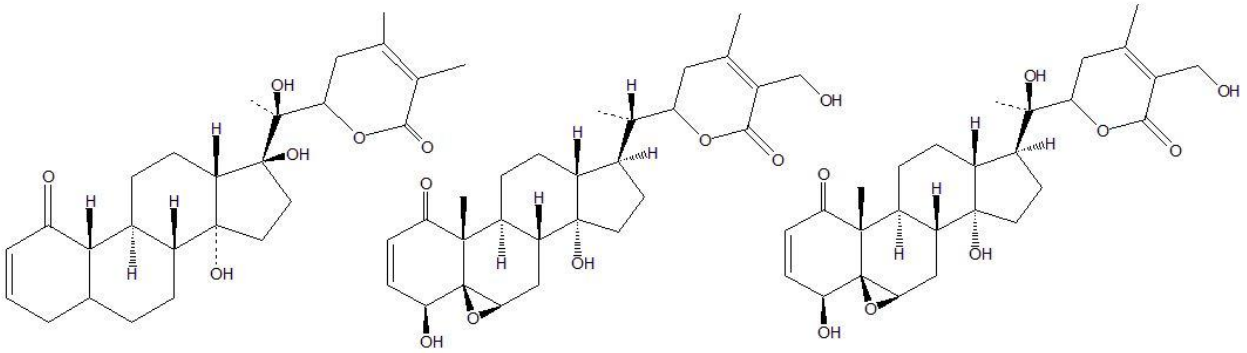
Withanolide B | Withanolide D | Withanolide P



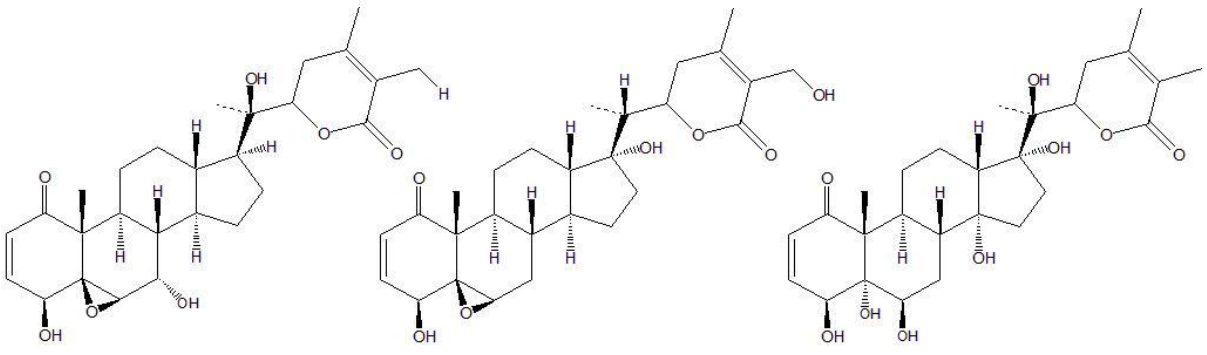
Withanolide Q | Withanolide R | 27-Hydroxy withanolide D



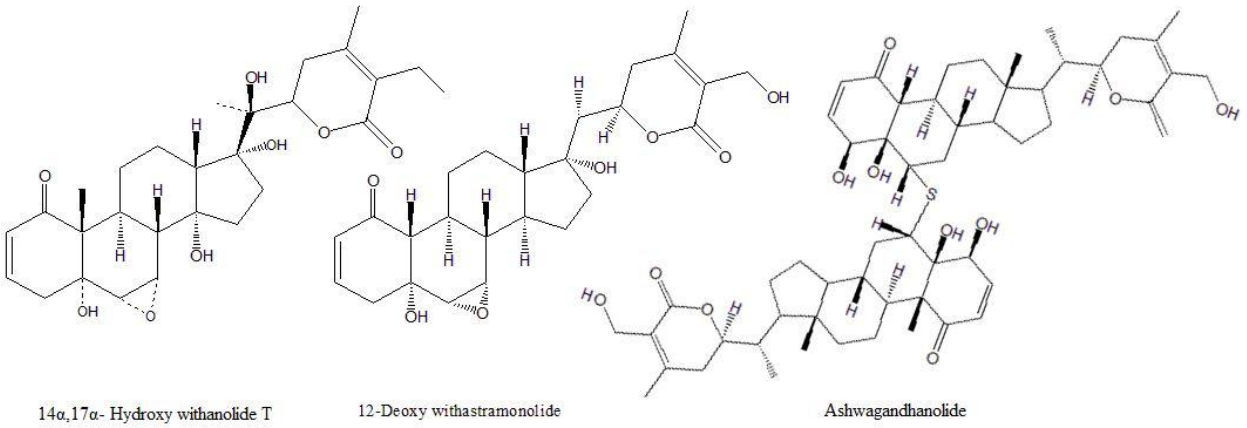
14α- Hydroxy 27-Hydroxy withanolide D | 17α- Hydroxy 27-Hydroxy withanolide D | 27-Hydroxy withanolide B



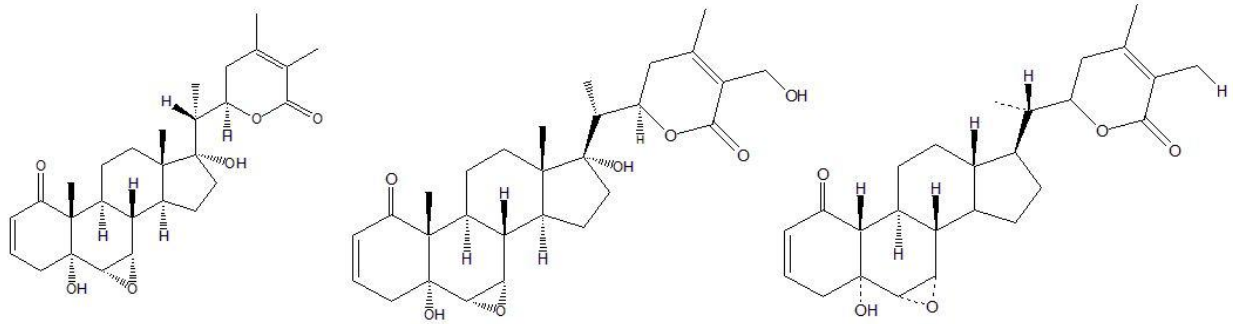
5*β*, 6*β*-epoxy withanolide E | 14α- Hydroxy withanolide G | 14α- Hydroxy withanolide H



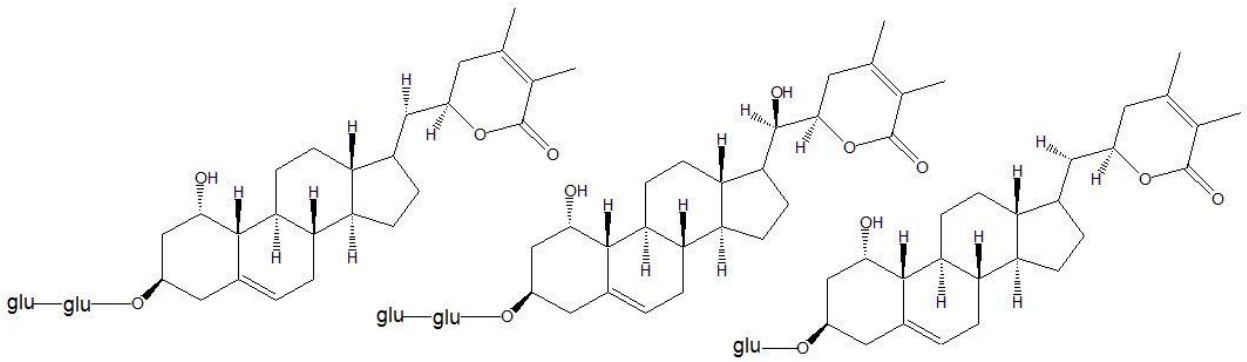
7α- Hydroxy withanolide J | 17α- Hydroxy withanolide J | 5*α*,6*β*- Hydroxy withanolide S



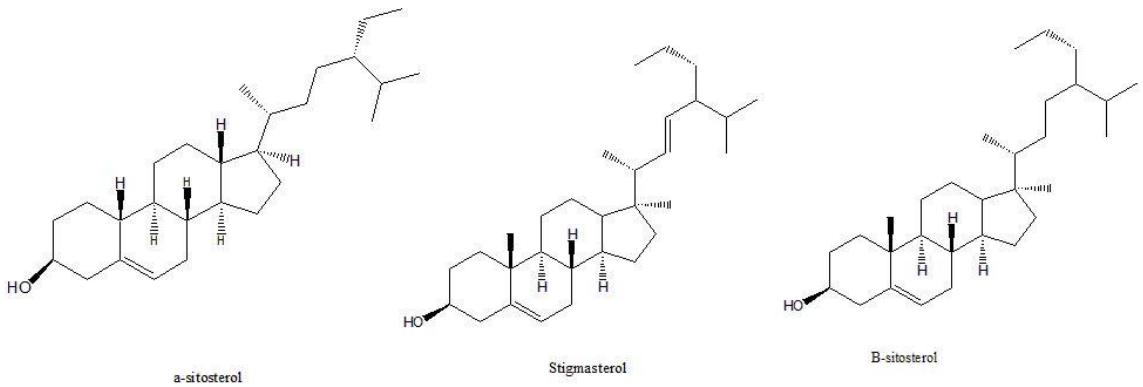
14α,17α- Hydroxy withanolide T | 12-Deoxy withastramonolide | Ashwagandhanolide



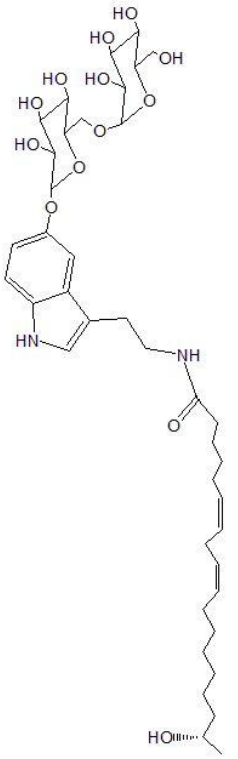
Withanone | 27-Hydroxy withanone | 17α- Hydroxy withanone



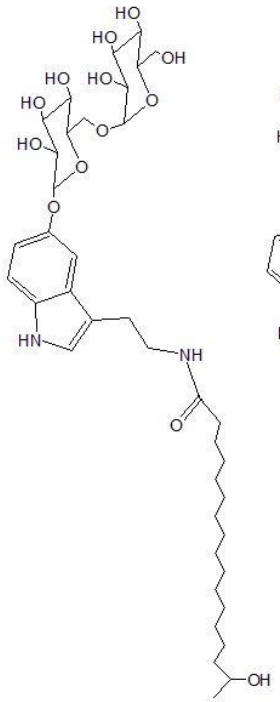
Withanoside-IV | Withanoside-VI | Physagulin



a-sitosterol | Stigmasterol | B-sitosterol

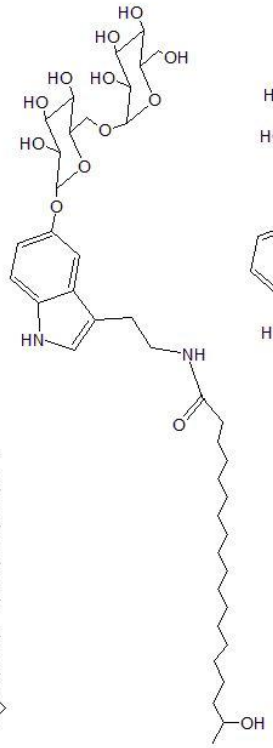


Withanamide A

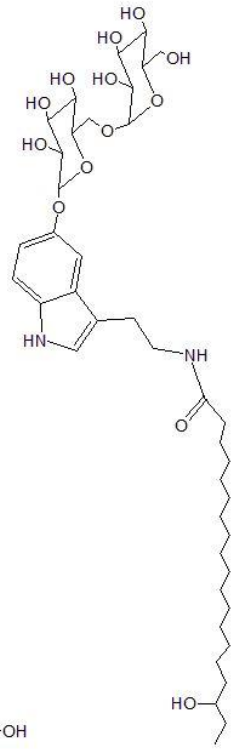


Withanamide B

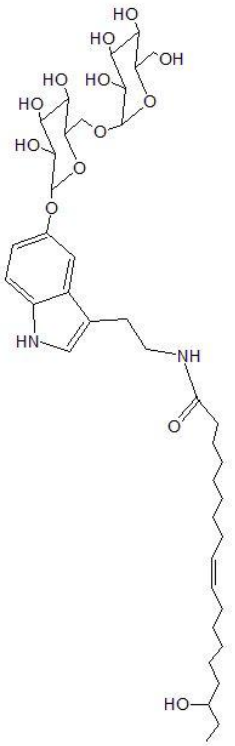
Withanamide C



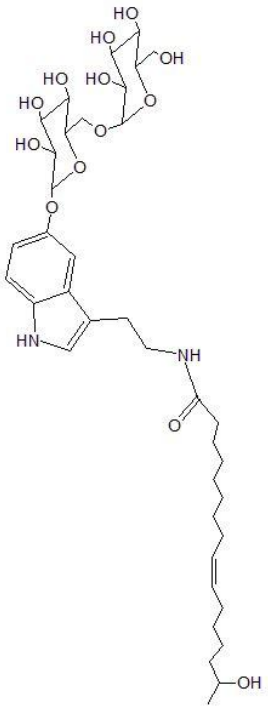
Withanamide D



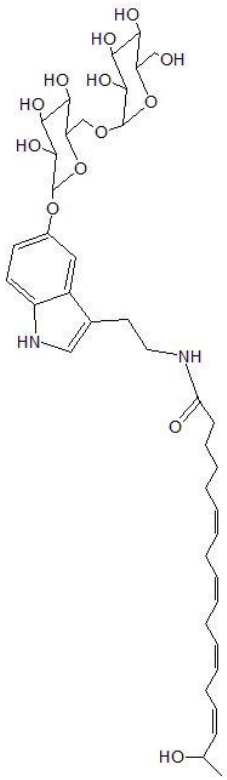
Withanamide E



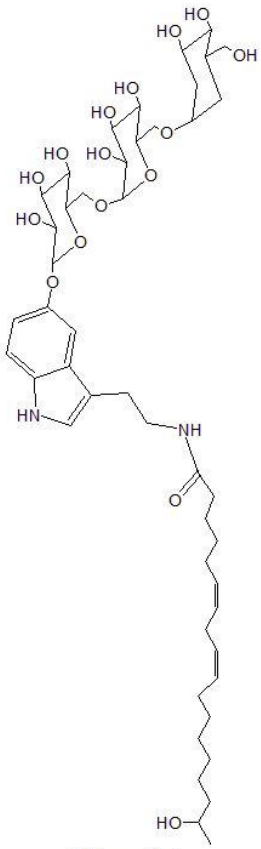
Withanamide F



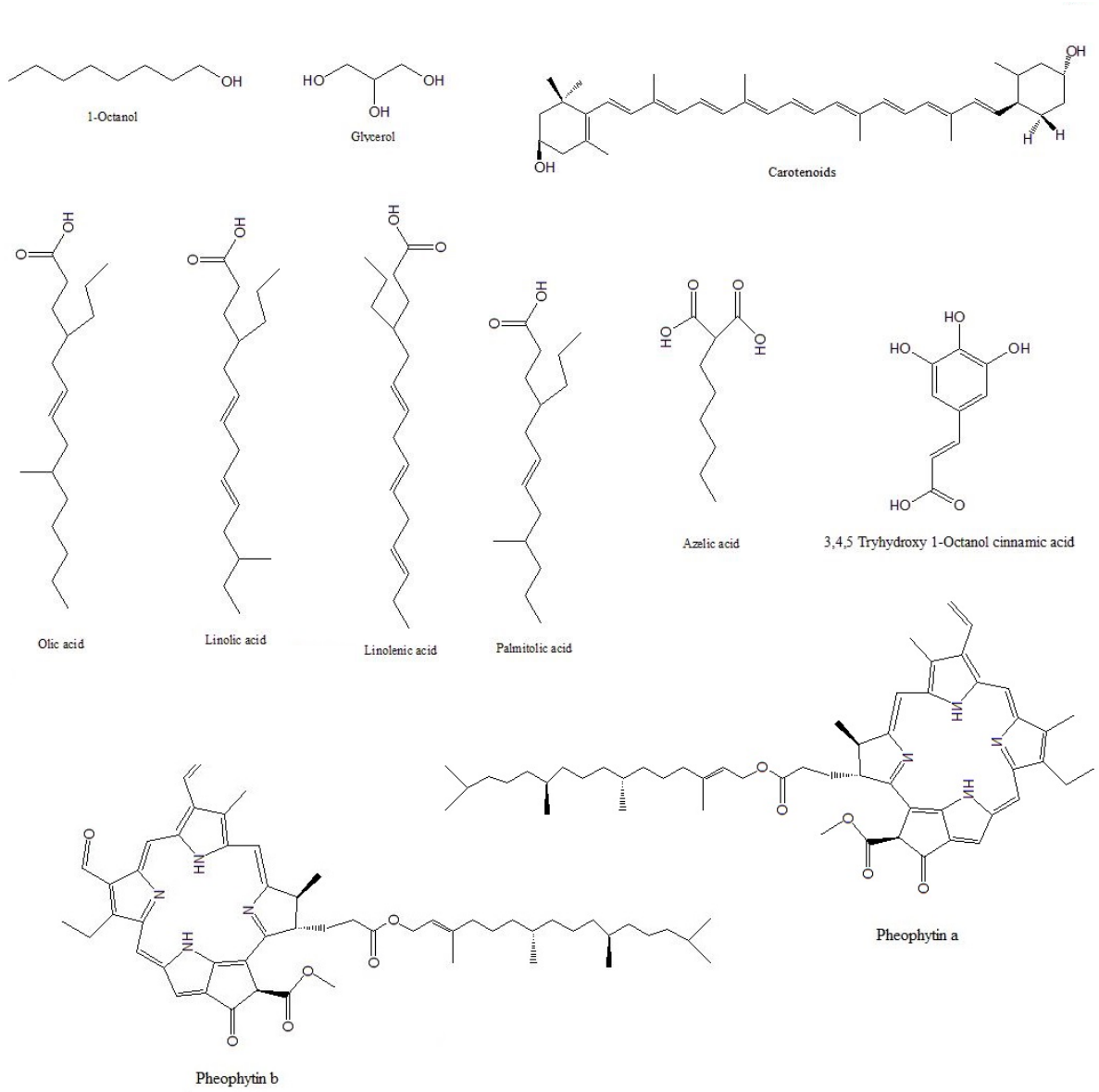
Withanamide G



Withanamide H



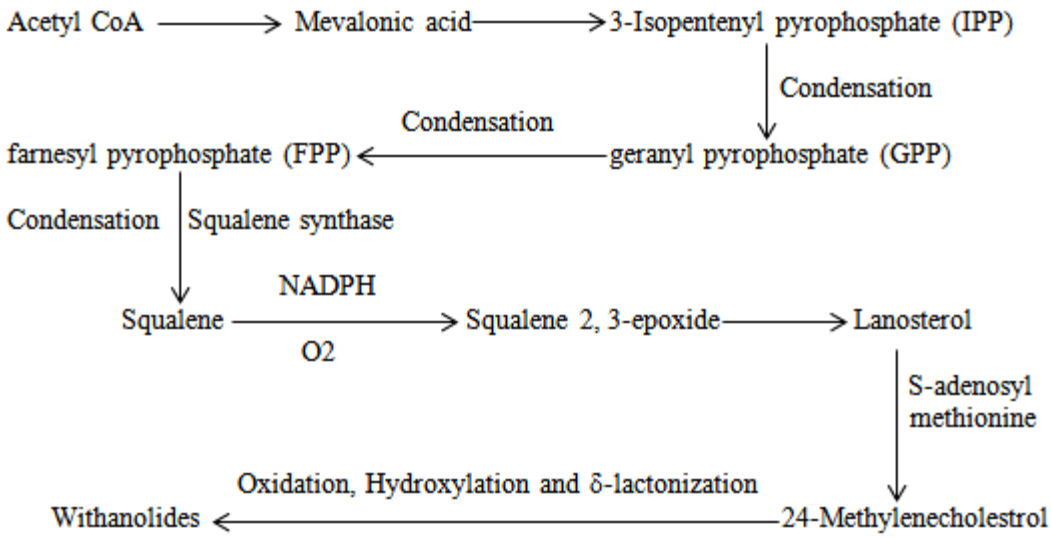
Withanamide I



Biosynthesis of Withanolides: The first step is the activation of acetate by its conversion to acetyl Co-enzyme A, abbreviated as acetyl CoA. Mevalonic acid is biosynthesized by two units of acetyl CoA. The (R)-mevalonic acid loos one atom of carbon and converted into isopentenyl pyrophosphate (IPP). Farnesyl pyrophosphate (FPP) is synthesized by condensation of three molecules of isopentenyl pyrophosphate (IPP) with a reaction intermediate molecule of geranyl pyrophosphate (GPP).

Further condensation of Farnesyl pyrophosphate (FPP) takes place in the presence of squalene synthase enzyme and NADPH to produce squalene. squalene is catalyzed by NADPH-linked oxide to make squalene 2, 3-epoxide and lanosterol is formed latter by ring closure. 24-Methylenecholestrol may be a biosynthetic precursor of steroidal lactones which might be produced by S-adenosyl methionine catalyzed biochemical reactions with lanosterol as substrate. It has been proposed that the hydroxylation in C22 and δ-lactonization between C22 and C26 of 24-methylenecholestrol yields withanolides [27, 28, 29]. Schematic diagram shown below gives an overview of important steps in the withanolide biosynthetic pathway.

Advantage of development of Herbal Male Contraception: Continued efforts over the past three decades to develop additional methods of male contraception have made some significant contributions in the field. However, there is still no method available in the field of male contraception that satisfies the essential criteria of safety, efficacy, economy and complete reversibility [30, 31, 32, 33].



The development of a viable male contraceptive agent of universal appeal has been a difficult task. For a method to succeed, it must be safe and must ensure that:

(i) Production of good quality spermatozoa is totally blocked (azoospermia) or affected to a highly significant extent (oligozoospermia accompanied by impairment in quality, in particular fertilizing ability) hence causing infertility in >90% of the volunteers tested;
(ii) Androgen-dependent accessory sex gland function and libido should not be impaired; and finally
(iii) The process should be reversible after cessation of drug treatment.

Biological activity:

Effect on Male Reproductive Hormones: Fertility regulating hormones like Testosterone, Luteinizing hormone, Follicular stimulating hormone plays an important, pivotal role in maturation, spermatogenesis and the maintenance of accessory sex organs [34]. The structural and functional integrity of reproductive tissues depends on these circulating hormones [35].

Therefore, any small change in this content may cause infertility. It is noted that antifertility agents work by disrupting or desynchronizing pre-ovulatory and pre-implantation events. Antifertility activity is often due to estrogenic activity, but can also be due to anti-estrogenic activity [36, 37].

The effect on testosterone level of rat's accordance Abdel-Magied has been shown a significant reduction of testosterone level of Somnifera-treated rats. The aqueous extract of *Withania Somnifera* is able to decrease the serum level of FSH and to increase the LH level in male rats [38]. Impaired action of the LH on the gonadal organ is a suggested mechanism for decreasing the reproductive hormone levels mainly progesterone from luteal cells [39]. Regarding this fact, present results in the increasing of the LH level cannot be justified.

Effect on Cholesterol: Cholesterol is a steroid metabolite found in the cell membranes and transported in the blood plasma of animals. It is an essential structural component of mammalian cell membranes, an important component for the manufacture of bile acids, steroid hormones, and fat soluble vitamins [40, 41].The effect of W.somnifera on cholesterol is a reduction in cholesterol level of blood in diabetic W.somnifera treated group relative to diabetic control group has been observed [25]. *Maytenus emargineta* plant extracts also showed same effect on male albino rats [43].

Spermicidal activity: The spermicidal method constitutes a key tool for the prevention of undesired pregnancies. Spermicidal activity is dose and time depended study in which measure the minimum concentration spermicidal agent required to kill hundred percent of one million of sperm within 20 seconds. The complete immobilization of sperm conforms by viability test [44]. The spermicidal effect could be exploited for the development of a product that avoids the undesirable effect of traditional spermicides, making it possible to evaluate the

biodiversity in a different biological context such as human reproduction [45, 46]. From literature review it has been indicated that *W. somnifera* and *O. sanctum* have spermicidal effect in vitro of rat sperms (Fransworth NR). During the last few years a more scientific and systematic study has conformed recorded usefulness of number of these plant drugs. In the present review work has been surmised in the term of table, therefore there is no need to give details here. Antispermatogenic activity, Antifertility, Spermicidal activity of plants have been showed in **table 1**.

TABLE 1: LIST OF MALE ANTIFERTILITY ACTIVITY OF MEDICINAL PLANTS FROM 2001 TO 2012

S. No.	Name of plant	Use of Plant Part	Extract	Type of Activity	Experimental model	References
1	*Tabernaemontana divaricate*	Leaf	Ethanol Extract	Antifertility	Rat	47
2	*Solanums urattense*	Seed	Aqueous	Cauda sperm	Rat	48
3	*Leptadenia hastata (Pers.)*	Leaf and Steam	Ethanol Extract	Anti-spermatogenic	Rat	49
4	*Aegle marmelos*	Leaves	Acid-base extraction	Antifertility	Rats	50
5	*Madhuca Indica*	Leaves	Alcoholic	Antifertility	Rats	51
6	*Dioscorea esculenta (L.)*	Tuber	Ethanol	Antifertility	Rats	*52*
7	*Borassus flabellifer Linn*.	Roots	Ethanol	Antifertility	Rats	53
8	*Azadirachta indica*	Leaf	Aqueous	Antifertility	Rats	54
9	*Carica papaya* L	Seed	Chloroform	Antifertility	Rats	55
10	*Annona squamosa (Linn.)*	Root	Methanol	Reversible Contraceptive Efficacy	Rats	56
11	*Azadirachta Indica (Neem*	Leaf	Aqueous	Spermicidal Activity	Rats	57
12	*Terminalia bellirica*	Barks	Benzene and Ethanol	Effect on reproductive ducts	Rats	58
13	*Capparisa phyla*	whole plants	Ethanol	Reproductive toxicity	Rats	59
14	*Lagenaria breviflora*	Fruit	Ethanol	Spermatozoa morphology and characteristics	Rat	60
15	*Withania somnifera*	Root	Aqueous	Sex hormones	Rat	61
16	*Terminalia bellirica*	Barks	Ethanol	Contraceptive Effect	Rat	62
17	*Pergularia daemia*	Leaves	Ethanol	Antifertility	Rat	63
18	*Meliaaza drach* L	Seeds oils	Oils	Antifertility	Rat	64
19	*Massularia acuminate*	Stem	Aqueous	Androgenic Potentials	Rat	65
20	*Amaranthus spinosus Linn*	stem	Aqueous	Spermatogenic effects	Rat	66
21	*Amaranthus spinosus Linn*	Morphi-ne	Aqueous	Inhibition of reproductive ducts	Rat	67
22	*Hypericum perforatum*	Dust	Aqueous	Antifertility	Rat	68
23	*Fadogia agrestis*	Stem	Aqueous	male reproductive	Rat	69
24	*Chromolaenaodoratum*	Leaves	Aqueous	Anti-androgenic	Rat	70
25	*Ruta graveolens* and *Cannabis saliva*	Stem	Alcoholic	Spermatogenic effects	Rat	71
26	*Dendrophthoe Falcata*	Stem	Methanol extract	Contraceptive efficacy	Rat	72
27	*Ruta graveolems L*	Root	Ethanol	Antiandrogmic activity	Rat	73
28	*Strychnospotatorum*	Seed	Methanol	Contraceptive Efficacy	Rat	74
29	*Carica papaya*	Seed	Ethanol	Toxicological	Rat	75
30	*Crotalaria juncea Linn*	Seed	Ethanol	Spermatogenesis	Rat	76
31	*Achyranthes aspera*	Stem	Ethanol	Spermicidal	Human	77
32	*Lepidiummeyenii*	Hypocot	Aqueous extract	Interfere Testicular function	Rat	78

33	*Ruta graveolens* L	Seed	Aqueous extract	Anti-androgenic	Rat	79
34	*Carica papaya*	Seed	Alkaloids	Interfere Reproductive functions	Rat	80
35	*Lepidium meyenii*	Seed	Alkaloids	Antispermatogenic	Rat	81
36	*Rumex steudelii*	Seed	Methanol	Antifertility	Rat	82
37	*Crotalaria juncea* Linn	Seed	Methanol	Antispermatogenic Effects	Mice	83
38	*Crotalaria juncea* Linn	Seed	Methanol	Antisteroidogenic	Mice	84
39	*Azdirechta indica*	Seed	Ethanol	Spermicidal	Rat	85
40	*Ricinus communis*	Stem	Ethanol	Antifertility	Rat	86
41	*Quassia amara*	Stem	Ethanol	Reproductive toxicity	Rat	87
42	*Crotalaria juncea* Linn	Seed	Ethanol& Aqueous	Antifertility	Rat	88
43	*Lepidiummeyenii*	Root	Ethanol	Aphrodisiac and enhance fertility	Human	89
44	*Quassia amara*	leaf	Ethanol	Reproductive toxicity	Rat	90
45	*Stephania hernandifolia*	Leaf	Aqueous extract	Affect androgenesis	Rat	91
46	*Martynia annua*	Root	Ethanol extract	Antifertility	Rat	92
47	*Achyranthes aspera Linn*	Stem	Ethanol	Effects on reproductive functions	Rat	93
48	*Sarcostem maacidum*	Stem	Ethanol	Antispermatogenesis	Rat	94
49	*sarcostemma acidum*	Stem	Petroleum Ether	Antisteroidogenesis	Rat	95
50	*Calebrooking Oppositifalia*	Leaf	Ethanol	Antifertility	Rat	96
51	*Cynomorium coccinem and W. somnifera*	Stem	Aqueous	Testicular development	Rat	97

Clinically therapy:

Anticancer study: The extensive clinical studies conducted by us have shown that WS has capability to produce beneficial effects in variety of cancer patients. It may have potential to eliminate various kinds of toxins causing proliferation of cancerous cells and acts as strong detoxifying agent. The studies demonstrate that WS and its chemical ingredients are effective in prevention and treatment of different kinds of cancer like colon cancer, lung cancer, blood cancer, skin cancer, breast cancer, renal cancer, fibro sarcoma, prostate cancer and pancreatic cancer [98, 99].

At the International Institute of Herbal Medicine (IIHM), Lucknow also we are conducting clinical studies to prove the efficacy of *W.somnifera* in prevention and treatment of different forms of cancer including prostate, dermatofibrosarcoma, breast cancer, fibroids of uterus, squamous cell carcinoma of penis etc. especially in last stages, and this wonder medicinal herb is found to be beneficial in many patients [100].

Anti-inflammatory Effect: Withania and withanolides being a potent inhibitor of pro-inflammatory transcription factors NF-kB and AP-1 holds promise as a novel agent for the treatment of inflammatory cascade of cardiovascular diseases [101].

Positive Inotropic Activity: Withania has been reported to reduce blood pressure due to autonomic ganglion blocking action and myocardial depressant effects as well as positive inotropic and chronotropic effects. The alkaloids had a prolonged hypotensive, bradycardiac and respiratory-stimulant action [102, 103].

Antibiotic activity: Antibiotic activity of Withaferin A is due to the presence of the unsaturated lactone-ring. The lactone showed strong therapeutic activity in experimentally induced abscesses in rabbits, the being somewhat stronger than that of Penicillin. It substantiates the reputation of the leaves as a cure for ulcers and carbuncles in the indigenous system of medicine [104]. The antibiotic activity of the roots as well as leaves has recently been shown experimentally. Withaferin A in concentration of 10µg/ml inhibited the growth of various Gram-positive bacteria, acid-fast and aerobic bacilli, and pathogenic fungi [105, 106].

Molecular targets of withaferin A: As the various pharmacological effects including immuno suppression, anti-inflammatory, anti-angiogenesis, chemoprevention, anti-tumor, and radio-12sensitizing activity of withaferin A were demonstrated, numerous studies were carried out to explore the underlying mechanisms and molecular targets of withaferin A for its biological activities. The mechanism of radio-sensitizing activity of withaferin A was proposed to be the inhibition of DNA repair by withaferin A. To test this theory, Uma Devi et al. carried out a molecular biological study which indicates that withaferin A contributes to the radio-sensitizing effect mainly through the inhibition of the homologous repair of DNA [107].

DISCUSSION: The development of a safe acceptable reversible contraceptive method for man is important steps to increase option for couples who wish to control their family size [108]. The goal of male contraceptive is focused on the inhibition of spermatogenesis process through suppression of the hormones especially androgens [109]. The principal of hormonal suppression of spermatogenesis is based on influencing the endocrine feedback mechanism between hypothalamus, pituitary and testes. Hormonal regulation of testicular function and effect of androgens, key hormone are Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH), synthesized and secreted under hypothalamic control of gonadotropin-releasing hormone (GnRH) [110].

The androgens play pivotal role of in spermatogenesis male fertility [111, 112, 113]. The testosterone main testicular androgen produced by Leydig cells under the influence of LH, LH secretion in turns regulated by hypothalamic GnRH. LH together with testicular autocrine and paracrine factors responsible for the regulation and production male sex hormone and spermatogenesis in testis [114, 115]. FSH and testosterone hormones are required for maintaining normal spermatogenesis in rats. It is shown that testosterone alone could restore qualitatively but not the number of sperms. Optimum level of FSH is required to restore the quantity production sperm [116, 117].

It has been known for a long time that sperm concentration is related to male fertility. Low concentrations are associated with low fertility [118]. A positive correlation has been established between testosterone level and motility, density and fertilizing capacity of the spermatozoa. It has been reported that androgen binding protein and testosterone produced by the Leydig cells reaches to the epididymis through the testicular fluid and maintains the Epididymis testosterone level [119, 120, 121]. Since testosterone level affect the functional integrity of testis and epididymis, motility density and viability of spermatozoa suggests that *Withania somnifera* (W S) extract treatment might altered the functional integrity of testis and epididymis responsible to cause degenerative changes in these organs, responsible for reduction of fertility in W S treated rats.

Cholesterol is not only an important component of cell membrane and of plasma lipoproteins but also the precursor of many other biologically important steroids such as bile acids and various steroids hormones. It is the principle steroid of higher animals [122, 123]. An increase in testicular cholesterol was due to tissue damage increased or decreased the cholesterol has been considered physiological significant. Since cholesterol level involve in inhibition or stimulation of sperm production [124]. The increased levels of cholesterol in the testes may be considered significant, since it is known to be precursor in androgen biosynthesis in testes and its level is intimately related to fertility and sperm output [125]. Change in level of cholesterol after the W S extract treatment caused degenerative changes in treated rats, might be due to inhibition of steroidgenesis.

The spermicidal activity tends to suggest that this active principle showed spermicidal effect at the effective concentration to immobilize and kill 100% rat spermatozoa within 20 sec may be due to blockage of some biochemical pathway like energy utilization [43]. These observations tend to suggest that this compound, in future at effective concentration, may be used in the formulation of herbal contraceptives. It is interesting to note that use of herbal contraceptives generally did not lead to permanent sterility in rodents as a model, since discontinuation of the treatment allowed a prompt return to normal fertility.

The plasma membrane plays a vital role in the process of sperm migration and fertilization. A number of spermicidal agents are known to execute their effects by structural and functional modulation of the plasma membrane [127].

Since *Withania Somnifera* (W S) extract was shown to be dose dependent activity and pointed out that at an effective concentration of W S extract shows good rat spermatozoa immobilize capacity. Most of plant spermicidal extracts /compounds act on the sperm surface, disrupting the plasma membrane. The result of the review reveals that W S treatment at different dose level manifests two principal impacts on the male reproductive system i.e. antispermatogenic and antiandrogenic effects. The W S caused androgen deprivation effects in target organs or tissues decreased the secretion of testosterone in the testis and also counteracted the action of androgens probably caused inhibition of spermatogenesis.

Withania somnifera possess good immuno modulatory anti-inflammatory, antitumor, anticancer properties and many pharmacologically and medicinally important chemicals, such as Withaferins, sitoindosides and various alkaloids, they protect the cells from oxidative damage and diseases. Although, the results from this review are quite promising for the use of this plant as a multi-purpose medicinal agent.

CONCLUSIONS: The phyto-chemistry and pharmacology of Withania has been widely investigated, but the studies on toxicology of the extracts of the plant parts in different solvents are very few. It is required to identify the novel clinical properties of the plant, the identification and isolation of the particular compound responsible for the specific activity is more important. We believe that further advancements in the analytical and separation chemistry will provide valuable insights on the toxicology and isolation of novel compounds along with the chemotypic variation of this plant.

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