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Review Article

IMPENDING CONTRACEPTIVES THAT MIGHT BE A POSITIVE METHODOLOGY TOWARDS THE MALE CONTRACEPTION

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ABSTRACT

The total population has been developing dramatically; be that as it may, right now, the decisions for male contraception are restricted. This study investigates continuous explores of male contraceptives. This study article is primarily based on the thought of contraception that must be needed toward the increasing population and giving the ideal strategy to control the fertility of humans and animals. This review featured the recent oral male contraceptives that may be revolutionary products in our world as means of contraception. The audit article considers that these contraceptives are customarily utilized for their spermicidal activities and their fundamental hormones of the awkwardness for fertility and the mechanism of activity of the impact of the antifertility of contraceptives. The present study offers up-to-date data gathered on the contraceptives used for anti-fertility activity in males. The goal of this study is to spotlight the work on the anti-fertility effect of contraceptives. Therefore these products can provide options and lowering fertility would be higher than different contraceptives. This article can also assist investigators in developing the newer contraceptive preparation for anti-fertility activity in males. The innovations in this field are important to focus on current, more intense medication having a less detrimental effect on the body function and that can be administrable on its entity, less expensive, and quite reversible.

Keywords: Oral male contraceptive, Male contraception, Spermatogenesis, Antifertility, Male fertility, Natural contraceptives

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INTRODUCTION

Today, overpopulation is a major problem in developing countries and the population of the world is currently about 7.6 billion, and if the present trends continue, it is expected to rise to 11.2 billion in 2100, 8.6 billion in 2030, 9.8 billion in 2050 [1]. In 2001-2011, increasing in the population of our country is greater than the 180 million [2]. Both the government and non-governmental associations are attempting to manage the human populace, although the results are unsatisfactory. One of the possible causes for unsatisfactory results could be the limited availability of contraceptive alternatives in our country [3]. However, Women are the extreme users of contraceptives in the world. Female contraceptives are successful in preventing unplanned pregnancy; nevertheless, some women are unable to utilize these contraceptives due to side effects [4, 5]. As a result, the development of the male contraceptive will aid couples in family planning [6].

The struggle against male contraception by physically preventing the meeting of egg and sperm (condoms, experimental vas occlusion procedures, and vasectomy) or through inhibiting spermatogenesis (hormonal and non-hormonal approaches) [6]. Around 30% of people presently rely upon condoms and vasectomy as male strategies of fertility restriction, even though these strategies have their negative consequences. The major disadvantages of condoms and vasectomy are the inability to reversible and their high failure rate [7]. Men should be able to utilize a contraceptive that is safe, effective, reversible, and fast-acting. Furthermore, it should not interfere with other androgen-dependent processes. And also, the technique of application must be simple and inexpensive. Many herbal or natural extracts have been utilized in the old Ayurvedic medical system to treat various ailments, and this extract has also been employed in maintaining and boosting fertility [8]. Some molecules derived from natural herbs in stages other than clinical development indicate natural products as potential novel medicine sources [9].

MATERIALS AND METHODS

This study was oriented with a wide variant fact of contraception around the world. To date, no further assessment investigated the dose, the components of factors, and method of action of the contraceptives antifertility impact.

Search strategy

Data were collected by searching the keywords: male infertility, oral male contraceptive, male contraception, antifertility, in international databases such as Web of Science (ISI), Pubmed, research gate, Google scholar, Science direct, etc.

Why the need for male contraceptives

The ideal male contraception ought to be sexually independent and act quickly. Several investigations in a variety of nations have been conducted to determine the acceptability of male contraception. Nowadays, it increases the female contraceptive option of 40-45% of worldwide pregnancies not yet planned. Several examinations have been completed to develop hormonal and non-hormonal male contraceptives. An assortment of new molecules is as yet being worked on the oral male contraceptive that has few side effects. The objective is to develop male contraceptive techniques that will permit both men and women [10].

Process of formation of sperm is carried out by the process of spermatogenesis in which two hormones first is luteinizing hormone (LH) which works on Leydig cell for testosterone production and other is Follicle-stimulating hormone (FSH) which works on Sertoli cells for giving nutrition to spermatozoa and protect the cell and both hormones are important in the formation of spermatozoa or sperm. There are various stages involved in the formation of sperm [11, 12].

- Spermatogonia divides into spermatogonia A and its another intermediate spermatogonia and spermatogonia B.
- Spermatogonia A(1) is called stem cells which continually divides into further spermatogonia and the spermatogenesis process occurs.
- Spermatogonia B is then divided into the 1° spermatocytes that undergo meiotic division.
- 1°spermatocytes then meiotic divide into 2° spermatocytes and then to appear round and haploid cells called as spermatids.

Mechanism of action for male contraception

- Development of antispermatogenic agents to inhibit sperm production.

- Prevention of sperm maturation.
- Prevention of sperm deposition.
- Prevention of sperm transfer in the vas deference.

Role of hormonal contraception

Hormonal contraception plays an important role in contraceptive techniques. The below fig. (fig. 1) shows how hormonal contraception can occur [11, 12].

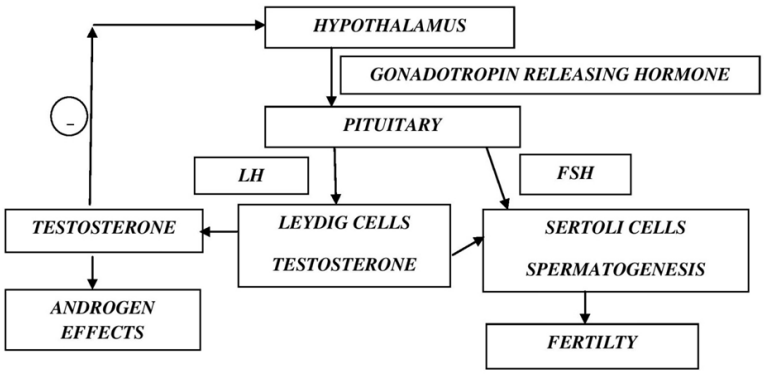

Fig. 1: Flow chart of the hormonal contraception

The journey or life travel of sperm

Spermatogenesis starts in the brain. The hypothalamus issues GnRH which activates the pituitary gland to activate FSH and LH. These hormones then work on Sertoli cells and Leydig cells in the testicle. Many processes are supported by Leydig cells, which create testosterone in the bloodstream. The role of spermatogenesis is supported by Sertoli cells. Sperm goes through the seminiferous tubules and to the epididymis as storage, development to functional sperm, and then transfer from the epididymis through the vas deference to the urethra and ultimately out of the body after the Sertoli cell process called spermiation [13].

Available methods for males as a contraceptive

Condoms

Condom as a barrier method has been used for many years by men all around the world. These are originally made from the animal intestines. Condoms are generally produced using the latex elastic material because these are most effective in the prevention of sexually transmitted diseases like HIV, gonorrhea, etc. But as a disadvantage, condoms have a high failure rate on the improper use and breakage of it which is 4 percent in time [14]. But many men do not like the use of condoms as it reduced sexual pleasure [15]. To reduce the side effect of latex allergies, Polyurethane condoms can be a great option. Although, these condoms are less effective in the prevention of pregnancy as compared to latex condoms because of their loose fit [16].

Vasectomy

Vasectomy is the surgery wherein the vas deference is cut and then ligated, to avoidance of the stream of sperm from the testicle. In the world, about 60 million people have undergone the vasectomy procedure. In the United States, around half a million people have vasectomized annually [17]. As a highly effective method in the conception of males, having disappointment rate of around one percent and lesser serious complications [18]. Vasectomy is only used for men who don't want any fertile activity in the future. Still, around 4-6 percent of people wish for reversal fertility as a reason for the death of a child and remarriage [19]. As a result of these considerations, vasectomy cannot be recommended as a reversible contraceptive method. But it can be a very satisfactory method that does not interested in a future pregnancy [20].

Withdrawal

It is also known as the coitus interruptus method. This method is a primary method to avoid pregnancy by 4-6 percent of people in the United States [21]. However, the Withdrawal method is not accepted as a contraceptive method by the medical community. A study has attempted to focus on this method that it may be long or short time effective as how it is practiced.

Several efficacy studies that were done in the history of male contraception

- A study conducted by World Health Organization (WHO) examined the intramuscular injection (i. m) of Testosterone enanthate 200 mg per w. In this around, 70 percent of men got azoospermia, and 1 pregnancy was found during the trial [22]. In another study in which severe oligospermia was found in men i. e less than 3 million/ml of sperm count in it [23]. Several side effects were found that are mood swing, weight gain, libido change, altered liver function, etc [23].

- Another study conducted in Australia combined Testosterone pellets with Depot Medroxy Progesterone Acetate (DMPA). In this study, around 94 percent of men got azoospermia and no further pregnancy was found per year. No further androgenic effects were found during the trial [24].

- In China trial was conducted as long-acting Testosterone undecanoate (TU) 1000 mg, which is a loading dose and then after 500 mg given dose monthly. This trial shows around 95 percent got azoospermia. Several side effects were included like libido change, weight gain, the problem of acne, etc [25, 26].

- In the Asian continent, mostly men got severe oligozoospermia state with the use of androgen alone and addition of progestin compound are required to achieve more results. The WHO and other partners conducted phase 2 clinical trials in four continents with 10 international sites [27]. Testosterone undecanoate (TU) 1000 mg with added progestin Norethisterone Enanthate 200 mg for 26 w as per every 8 w and further extended to 56 w for efficacy period. Around 96 percent of men got azoospermia and four pregnancies were found. Several side effects were noted like weight gain, acne, pain at injected site, changed libido, etc.

- Another study was conducted as daily administration of transdermal gel of testosterone with oral progestin medroxyprogesterone acetate 20 mg per d resulted in a contraceptive effect. After a few months of treatment, around 80 to 90 percent of men diminished the sperm concentration to less than one million/ml with one pregnancy occurring [28].

Various contraceptives that can be major approaches for men

Triptonide

The researchers Wei Yan *et al.* found an inventive strategy in which they discovered a new herbal compound that is an impactful, secure

and reversible male contraceptive agent in pre-scientific animal models. With immense work in the past decade in developing the male non-hormonal male contraceptive has been restricted. The herb compound called *Triptonide* is extracted from the plant named *Tripterygium wilfordii Hook* by chemical synthesis. *Triptonide* is sometimes used to treat a variety of issues, including inflammatory diseases. i. e rheumatoid arthritis [29]. A single dose of *Triptonide* causes the sperm minimal quantity and no movement in it with greater penetration and men will be infertile in 3-6 w. But upon cessation of treatment, fertility returned to its normal stages in 4-6 w. *Triptonide* targets the Plakoglobin and disturbs their relation with SPEM1 during the spermatogenesis process. No toxic effect was found. A group of analyses suggested that *Triptonide* targets on the very last step of sperm meeting that will produce immotile sperm for fertilization. On the development of immotile sperm, it will not giving any effect on the testis cells. As result, studies on primates will give an idea to suggest effective treatment for human males also and clinical test soon to be developing non-hormonal male reversible contraceptive [29].

N,N-Dimethylacetamide

FDA approved excipient which is found as a male contraceptive agent named as N,N-Dimethylacetamide which is previously used as a pharmaceutical agent for inserted in humans as a type of solvent that can enhance the insoluble drug application. Mainly any excipient does not produce any biological activity but these excipients possess the contraceptive activity which inhibits the process of spermatogenesis and causes infertility in men in recent studies. And can reverse its effect on cessation of treatment. Administration of DMA molecule in rats for eight weeks causes infertility and no pups were born with treated animals. Also does not affect the performance of a hormonal function. Fertility regains upon halted the treatment and after that pups were born. DMA also affects a post-meiotic phase of the spermatogenesis process to gain the reversibility of conception [30]. In studies of bromodomain inhibitor toward affinity of BET protein, JQ1 achieved contraceptive properties in mice. The contraceptive effect was attained to inhibit the testis-specific BRDT protein. At a high dose, JQ1 possesses a side effect that is not tolerated than at that point rather than JQ1, DMA which has a low-affinity bromodomain inhibitor and is tolerated by people and afterward utilized as FDA approved excipients. It mainly targets spermiogenesis via inhibiting BRD4, not BRDT which is a target of JQ1 [31]**.** DMA has an excellent penetration tendency into the skin and is injected as a drug solubilizer in humans. eg. In chemotherapy, busulfan treatment facilitated in children shows DMA is not toxic and cleared from the body easily and safe for humans. In future studies, DMA can be a great contraceptive if used as a topical gel. DMA depot patch is a great idea as a slow rate drug delivery system.

Immunocontraception

At present, the mechanism of the noticed infertility is not known. Specialists in a few labs are working together for developing a male contraceptive immunization (vaccine) against an antigen present exclusively on spermatozoa (sperm cell). On the off chance that effective, the antibody would give a protected, cost-powerful, and reversible contraception for men. Notwithstanding, introducing such type of vaccine however testing, gives multiple obstacles. The greatest obstacle in fostering an immunocontraception antibody is to distinguish a novel antigen (immunogen) with a significant capacity in the preparation cycle which is exposed to the blood-testis barrier as the host cell's responses to the immunogen that differ among the species. The most difficult test for researchers will be to identify an immunogen that is most sensitive among the majority of males [32]. The gathering has distinguished the "*Eppin*" molecule which is a human antigen. This protein is available just in the male contraceptive tissues (epididymis and gonads). It is only a few inhibitors of the epididymal serine protease and is described by each Kunitz-type agreement and Whey Acidic Protein (WAP)-type agreement [32]. The sperm have receptors for the Eppin molecule that adheres during development in the epididymis. These *Eppin*-bound spermatozoa are covered with the protein of the semen liquid known as Semenogelin (Sg). It passes through the vas deferens region and the ejaculatory channel [32, 33]. The restricting of Semenogelin to an *Eppin* is believed to be a significant defensive occasion that happens in discharged sperm, giving antimicrobial action to the tight sperm's agglutination into a coagulum. In the course of the liquefaction of the coagulum, Semenogelin hydrolyses which liberates the sperm from it and gives the capacity to be fertile and motile. The hydrolysis of Semenogelin in the coagulum is joined by the activity of prostate-explicit enemy of gen (PSA) which is a serine protease [33]. It had been recommended that the counter *Eppin* immune response adheres to an *Eppin* on the surface of a sperm cell that disturbs the arrangement of the *Eppin*-Semenogelin and the production of spermatozoa in the discharge lose forward motility.

Dr. O'Rand and colleagues had gained ground about a protected and reversible immune contraceptive for males. The bunch revealed that 7/9 monkeys (male) inoculated with an *Eppin* grew excessive titer antibodies to the immunogen furthermore, got unfertile. 5/7 humans have excessive titer antibodies and get fertile when vaccination used to be halted. Despite the fact that *Eppin* is a significant immunogen and its standard trial viability (78%) and fractional reversibility (71%) kept a significant concern. A few different potential immunocontraceptive immunogens, exist on plasma layers of sperm and go about as receptors throughout sperm and egg communication during the essential stages of science. To begin with, the assuming receptors are a lot more years from being attempted as immune contraceptives.

Testis kinase

Concerns have been raised about the contraceptive target which is called testis-specific serine/threonine kinases (TSSKs) and, as an outcome, around the advancement of small particle kinase inhibitors, which might hinder fertile activity. Such kinases and the analogs testis-specific serine kinase substrate (TSKS), serine/threonine kinase (SSTK), and TSSK1–4 are the members of a family that are present in the testicles that provide tissue-specific focuses for developing contraceptive formulation [34]. In situ hybridization in rodents has confirmed that TSSK2, SSTK, and TSKS are post-meiotic in action. As a result of this approach, they are potential targets for reversible contraception intermediate along with saving spermatogonia and spermatocytes. This direction showed high throughput screening of TSKS phosphorylation inhibitors yields a variety of targets for contraceptives. Nonetheless, these kinase groups are no longer rigorously testis-specific or might, as a result, be unsuitable for male contraception. Tyrosine kinases, particularly the Src family and subfamilies, are another group of kinases involved in spermatogenesis [35].

11-Beta-Methyl-19-Nortestosterone 17-Beta-Dodecylcarbonate (11βmntdc)

11βmntdc is derived from the 19-nortestosterone compound. 11βmntdc is nontoxic when compared to testosterone and other modified androgens when given orally [36]. In rats, 11βmntdc suppressing the androgen composition and serum gonads and bone mineral density [36]. In a recent study a dose of 100-800 mg, suppressed the testosterone production and was well tolerated. 11βmntdc are having more balanced androgen receptor and progesterone receptor activity. A 28 d trial is still underway with a dose of 200-400 mg 11βmntdc. In the next decade, this promising compound can be suggested as a male pill.

Nestorone (16-Methylene-17alpha-acetoxy-19-Norpregn-4-ene-3,20-Dione)

It is additionally known as segesterone acetate, a progestin that does not have androgenic, estrogen, and glucocorticoid property activity [37]. It is the purest progestin that is suggested as a less toxic male contraceptive when combined with testosterone. A preparation study conducted as Nestorone transdermal (6-8 mg/d) application with testosterone gels (10 mg/d) for 21 d that suppresses the LH and FSH levels in men [37]. Side effects may be seen as acne, increased hematocrit, weight gain, mood change, increased appetite, etc. At present, a clinical trial is under-processed in humans from four continents in 400 couples, men who used the gel daily reached

sperm concentrations of fewer than 1 million/ml and entered the 52-w effectiveness phase. Results from this study may be expected in 2021.

7-Alpha-Methyl-19-Nortestosterone (MENT)

It is derived from the 19-nortestosterone. It is tenfold more potent than testosterone alone androgen. MENT is not a 5 alpha reduced product, although it is aromatic to one that binds to the estrogen receptor [38]. In a study, etonogestrel and progestin compare with either combination with MENT implant or with T pellets for every 12 w. It suppresses the sperm concentration. Every effort in developing an implant with an appropriate drug delivery system is under process.

A strategy that is inspired by cocktail preparation

In India, Scientists developed a technology *RISUG* i. e s sperm blocking process that gives a result of azoospermia and flushed out with the help of sodium bicarbonate or DMSO can reverse fertility. Wang and colleagues injected methoxypoly(ethylene glycol)-modified AuNPs into the testis of male rats. Increasing the temperature of the testis with near-infrared light can give a short-term or permanent contraceptive effect. On the above discussion, a method inspired by colorful layered cocktail design gives an idea for contraception. In this study, a group of four materials or reagents in injected into the vas deference onward the path of sperm swimming marked as:

(1) increase temperature agent/physical barrier *PEG-AuNPs;*

(2) inhibitor sperm chemical/hydrogel solvent *EDTA*;

(3) increase temperature agent/physical barrier *PEG-AuNPs*;

(4) long term affect physical barrier: calcium alginate hydrogel (SA)

All of these components are initially injected in liquid form. After injection, the alginate hydrogel in the base cross-links into a solid, and PEG-AuNPs solidify at 37° C, preventing the end of EDTA. As vas deference is providing enough space for injection within a specific length. When it is important to regain fertility these positions are irradiated by an infrared lamp. (stage 1) On acquiring radiation (stage 2), *PEG-AuNPs* liquefy into the fluid form and in the middle *EDTA* mix gradually with *PEG* solution than the hydrogel gets mix by *EDTA* (stage 3) and the clear off naturally (stage 4). It must be noticed that as *PEG-AuNPs* melt even on removing an infrared device, *PEG-AuNPs* would not solidify and reblock the vas deference again [39]. Further examination such as determining the behavior of an animal, vas deference anatomy, and with HE staining and color reaction in urine identify the melamine concentration are carried out. This preparation *(SA/PEG-AuNPs/EDTA)* gives the contraceptive effect of reducing sperm vitality and motility. But these ingredients act on sperm differently.

Gendarussa

A plant usually in Indonesia is used as a traditional remedy known as *Justicia gendarussa.* Men in Papua, New Guinea, use this plant as a contraceptive. And also used in the treatment of pain and inflammation. An active constituent is gendarusin A and B which may be flavonoid present in it. The root and this plant's leaves are boiled in water and then swallowed to explore the contraceptive purpose for 2-3 mo. The mechanism of action is still unknown but several studies conducted to check its efficacy. This drug is still undergoing clinical trials [40].

Adjudin

Adjudin is a derivative of *lonidamine*. *Lonidamine* is partially introduced as a chemotherapeutic agent that inhibits Sertoli-spermatids junction [41]. *Adjudin* is *1-(2,4-dichlorobenzyl)-1H-indazole-3-carbohydra-zide*. This drug when taken two times a day reversibly suppresses the spermatogenesis process in rats [42, 43]. Liver inflammation and atrophy of skeletal muscle like side effects were observed in the 29-d study trial [44]. Researchers investigate with FSH-β mutant with adjudin to focus on Sertoli cells to reduce its dose for getting the contraception effect [45].

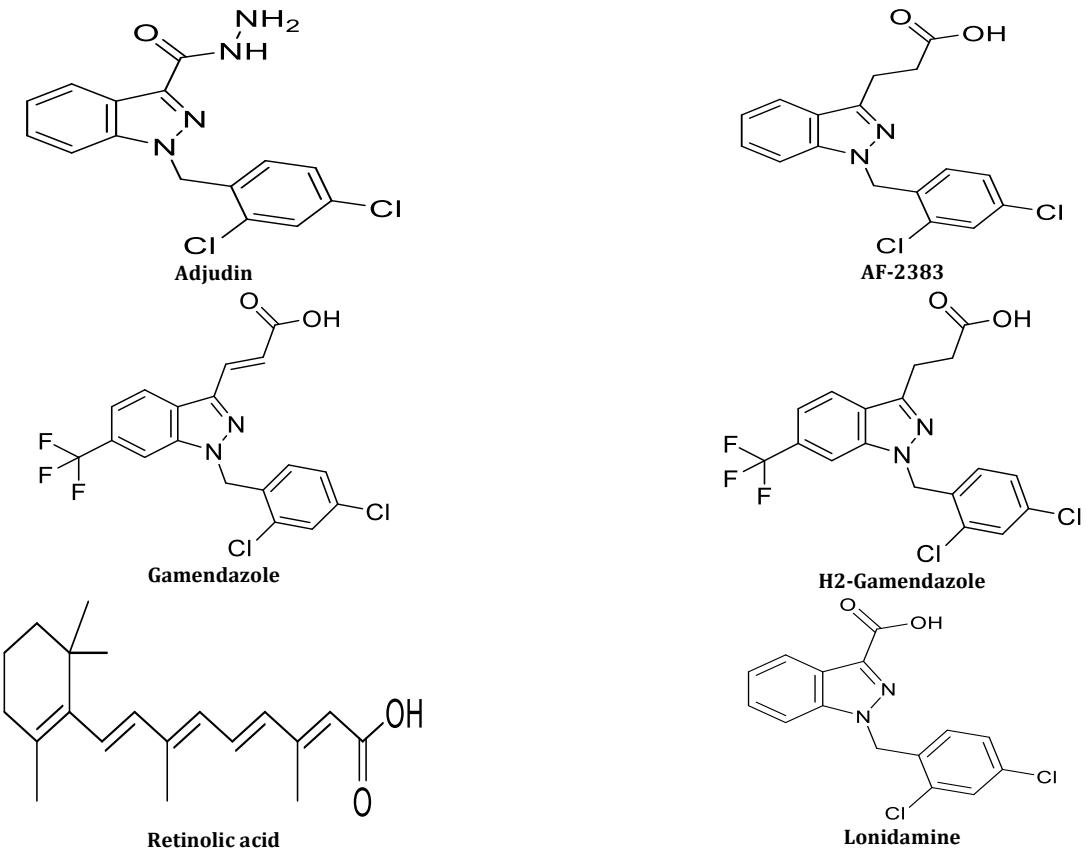

Fig. 2: Chemical structure of some contraceptives

H2-Gamedazole

H2-Gamendazole is a derivative of *lonidamine* as well as *Adjudin* that interferes in the maturation of spermatozoa. When a dose of 6 mg/kg is given for a w causes the arrest of spermatogenesis in rats. When given a high dose to rats, it will lead to their death [46]. Due to their high toxicity levels in rats, preclinical testing for humans must be needed.

Retinoic acid receptor antagonists

Vitamin A and its analogs (*retinoic acid*) are required for the spermatogenesis process [47, 48]. *Retinoic acid* binds to the *retinoic acid receptor* (RARs). Retinol is converted into *retinoic acid* in seminiferous tubules with the aldehyde dehydrogenase pathway. Deficiency and inhibition of *vitamin A* may be responsible for the arrest of spermatogenesis and termed as contraceptive agents. A RAR antagonist BMS-189453 when given by mouth to rat for 28 d causes inhibits fertility and recovery upon halted of treatment [49]. Liver inflammation can be observed as a side effect. A low dose of BMS-189453 1 mg/kg shows suppression of spermatozoa without toxicity to the liver. WIN 18,446 can be an advantageous male contraceptive that inhibits *retinoic acid* biosynthesis. Reversible oligozoospermia was observed in men when treated. Vomiting, mood changes, disulfiram reactions, nausea like side effects were noted, when taken with alcohol [50]. It inhibits sperm production with the help of the blocking of aldehyde dehydrogenase ALDH1A1 and ALDH1A2 [51, 52]. Research is ongoing on the development of such compounds which blocks *retinoic acid* biosynthesis without blocking alcohol metabolism [53]. Results are in under trials if possible it can be a great initiative for the contraceptive of men.

CatSper

CatSper is a calcium channel of sperm [54]. Inhibition of this protein can cause infertility in men because disrupts in calcium level in sperm leads to disrupts the quality of sperm [55]. No *in vivo* data was observed for this compound and *CatSper* antagonist to date. But few gatherings are in undertrials showing sperm ion channels as expected male contraceptive [56]. Also, there are some inventions of herbal products which are derived from raw plant or their parts. In this data like safety profile and toxicity value, their mechanism of actions, their effective doses, and their activity were included.

Some herbal products will be a promising approach in male contraception that is mentioned in table 1 and table 2. This table shows us all the related information about these herbal plants.

Table 1: Profile of some natural male contraceptives products

Plant extract	Dose	Model used	Duration	Recovery Period	Reference
Achyranthes aspera protein	25 mg/kg	Mice	5 w	N/A	[57]
Bergapten	75 mg/kg	Rats	8 w	N/A	[58]
Carica papaya fatty acid	50 mg/kg	Langur monkey	12 mo	After 60-120 d on withdrawal period	[59, 60]
	20, 40 mg/kg	Rats	21 w	After halted treatment 150 d	[61]
Cannabis sativa extract	3-6 g/kg	Mice	5 w	After halted treatment of 45 d and 100% recovery	[62, 63]
Camelliasaponin c1	100-400 mg/kg	Mice	42 d	N/A	[64]
Embelin	20 mg/kg	Rats	2-4 w	After 250 d on halt the treatment	[65, 66]
Lupeol acetate	50-60 mg/kg	Rats	8-9 w	N/A	[67]
NB-DNJ	5-2400 mg/kg	Mice	42 d	In 5 w on halted treatment	[68]
NB-DNJ	15 mg/kg	Mice	42 d	N/A	[69]
NB-DGJ	150-600 mg/kg	Mice	42 d	In 5 w on halted treatment	[70]
Oleanolic acid	16 mg/kg	Rats	4 w	After 14 d on halted treatment	[71]
	15-30 mg/kg	Rats	8 w	N/A	[72]
Piperine	10 mg/kg	Rats	8 w	After 60 d on withdrawal period	[73, 74]
Solasodine	100 mg/kg	Monkey	21 w	N/A	[65]
Tripterium wilfordii glycosides	10 mg/kg and 20 mg/kg	Rats	49-91 d and 28-70 d	After 20 d on halted treatment	[75]
	7.5-45 mg/kg	Rats	6 w	N/A	[76]
Triptolide	0.06 mg/kg	Rats	14 d	Complete recovery in 4-6 w on halt treatment	[77]
Xanthotoxin	150 mg/kg	Rats	56 d	N/A	[58]
Tetrahydrocannabinol [THC]	2 mg/kg	Rats	4 w	Complete recover Leydig cells after treatment in 63 d	[78]
ZNF 185 derived peptide	0.08 mg/kg	Mice as vaccine 4 times	7 d interval	N/A	[79]
β–sitosterol [pistia stratiotes]	50 mg/kg	Mice	7 w	N/A	[80]
β–Carophyllene	10 mg/kg	Rats	4 w	Reversible	[81]
α–Amyrin acetate	50-60 mg/kg	Rats	8 w	N/A	[82]
β–sitosterol	0.5-5 mg/kg	Rats	2-7 w	Later 30 d of withdrawal treatment	[83]

Table 2: Mechanism of action of above listed natural male contraceptives

Plant extract	Mechanism of action and their result	Reference
Achyranthes aspera protein	Spermatotoxicity manifests as sperm count motility and abnormalities. Significant differences in testicular actions such as HMG CoA reductase and serum testosterone.	[57]
Bergapten	Adult males who have been treated have pituitary glands that are significantly smaller and have low sperm per ejaculate. Elevated testosterone levels and testicular relative weight. Females bred to dosed adult males needed more time to become pregnant.	[58]
Carica papaya fatty acid	During 8 w of therapy, total suppression of sperm motility was determined, and this lasted for the whole 12 mo trial period. Following 4 w of treatment, sperm count, percentage viability, and percentage normal spermatozoa all showed a significant decrease. Following 30 d of treatment, sperm morphology indicated the predominance of midpiece anomalies. Sperm functional tests yielded infertile results. Sertoli cells and germ cells Vacuolization, After 12 mo, there was a loss of cytoplasmic organelles in	[59, 60]

Plant extract	Mechanism of action and their result	Reference
	spermatocytes and spherical spermatids.	
	Throughout 8 w, a total reduction of cauda epididymal sperm viability proportion was associated with a decline in the count of sperm and viability and an increased proportion of defective spermatozoa.	[61]
	For 8-21 w, few changes in germ cell proliferation into the prostate and vacuolization and pyknotic nuclei in a few epithelial cells of the cauda epididymis were seen.	
	Every month, a negative fertility test is performed.	
Cannabis sativa extract (Δ9-THC)	Restrictive changes in testicular weight dropped sperm count, viability, and motility by 14% and lowered the count of sperm, motility, and viability [all doses].	[62, 63]
	Because of a decrease in testicular enzyme activity, there is a significant decrease in the circulating testosterone stage.	
	A substantial improvement in the CB1 and CB2 receptors, as well as fatty acid amide hydrolase protein levels, was seen in mice testes as a result of GnRH inhibitory action.	
Camelliasaponin c1	Sperm counts diminished as the number of unusual spermatozoa continued to rise. As the dosage was increased to 400 mg/kg, the weight of the testicles and their seminiferous tube area steadily decreased. Germ cells were depleted and found to have an asymmetric distribution in seminiferous tubules at all doses.	[64]
	Necrosis can be used to suggest apoptosis in spermatocytes and spermatids. Enzymes involved, as well as superoxide dismutase, glutathione peroxidase, and total antioxidant capability, were drastically decreased, whereas malondialdehyde content was increased in the testicles.	
Embelin	In the epididymis, motile sperm count Suppression with some changes in the glycolysis activity and energy metabolism enzymes.	[65, 66]
Lupeol acetate	The weights of the testicles, seminal vesicle, epididymis, and ventral prostate all diminished.	[67]
	Sperm number and density were drastically decreased.	
	Secondary spermatocytes, germ cell pachytene preleptotene, and step-19 spermatid populations all showed a decrease in amount.	
	The nuclear region of the Leydig cell matures Leydig cell counts.	
	Sertoli counts and seminiferous tubular size cross-sectional surface region were drastically decreased.	
	The fructose content of seminal vesicular was also distorted, but the LDL cholesterol material in the testicles was markedly improved.	
NB-DNJ	15 mg of NB-DNJ and 150, 300, and 600 mg/kg/d of NB-DGJ caused the decline of spermatozoa with standard	[68]
NB-DGJ	nuclei and acrosomes but did not result in any epigenetic anomalies in the infants. The percentage of sperm	[69]
	cells that contain S-S-protamines is dramatically lower than in normal mice (caput). After mating among adult males and females, NB-DGJ and NB-DNJ are unable to fertilize oocytes *in vitro* and produce fewer offspring.	[70]
Oleanolic acid	The proportion of sperm motility was diminished. When the mated with treated male rats, no further pregnancy occurs.	[71]
Piperine	A massive decrease in the epididymis weight. Sperm concentration falls. At all levels, there is a massive reduction in sperm motility and viability. Significantly impairs sperm capacitation and maturation by decreasing the activity of superoxide dismutase and catalase. In all doses, groups ED and ED4 repressed the spermatozoa in tissues of the seminal vesicle and epididymis.	[73, 74]
Solasodine	Impairment with spermiogenesis in late spermatids at stage XI1. Spermatids had been reduced. Immature and mature Leydig cell activity has been reduced and a significant decrease in sperm count of the cauda region	[65]
	The epithelial size of the cauda epididymis was diminished. The cells atrophied. Total protein and sialic acid levels, as well as glycogen and acid phosphatase activity, have all dropped significantly in the cauda epididymis.	[66]
Tripterygium wilfordii glycosides	Spermatogenesis and initial nuclear protein synthesis turnover are significantly inhibited in post elongated spermatids. The sperm cells in the epididymis region were reduced, and surviving spermatozoa distorted, with head enlargement, separate head, tail, and curving of the middle portion.	[75]
	The rate of pregnancy declined as the dose and treatment time increased, reaching 0% at forty d in the 45 mg/kg group.	[76]
Triptolide	The cauda epididymis sperm concentration was diminished by 84.8 percent, and the proportion of sperm motility diminished. Extreme structural abnormalities were seen in epididymal sperm. Single-layer of cells that consist of Sertoli cells and spermatogonia, lines the flat seminiferous epithelium.	[77]
Xanthotoxin	Adult males who had been treated had a significantly small size of pituitary glands and less sperm ejaculation. Elevated testosterone levels and increased relative testis weight Females who were mated to injected adult males needed more time to become pregnant.	[58]
ZNF185-derived peptide	Peptide immunisation restricted the coupling and reproduction of mice, however, no noticeable differences in the number of offspring per litter due to a decrease in sperm count number and its motility, but the amount of unusual sperm was massively increased. There was no harm done to sex organs.	[79]
β-sitosterol saponin of Pistia stratiotes	Weight loss of reproductive organs such as the testicles, seminal vesicle, epididymis. Sperm count and viability, sperm abnormalities, and testosterone level of serum have all been significantly reduced. Alteration in the seminiferous tubules.	[80]
β-Caryophyllene	Significantly elevated in their weight of the body but does not affect the weight of sex organs. Sperm quantity of Cauda epididymal percentages of presented motile sperm and spermatozoa with normal form were significantly reduced. It has no effect on testicles or the epididymis.	[81]
α-Amyrin acetate	The weights of the testicles, epididymis, seminal vesicle, and ventral prostate all diminished.	[82]
	Sperm motility and density have both been diminished. There has been a drastic reduction in the populations of germ cell pachytene, preleptotene secondary spermatocytes, and spermatids.	
	The nuclear region of the Leydig cell grows Leydig cell counts. The diameter of the seminiferous, the amount of Sertoli cells, the cross-sectional surface areas were all diminished. The fructose level of seminal vesicular was also depleted, but the cholesterol quantity of the testicles was considerably increased.	
β-Sitosterol	The antifertility activity was shown by increasing daily dose, but there was a marked decline in the weight of testicles and sperm count after long-term treatment at higher and lower doses. The weights of all auxiliary sex organs, besides the caput epididymis, extended upon low doses, including the seminal vesicle, cauda epididymis, dorsolateral prostate, coagulating gland, ventral prostate. In a time-dependent manner, high dose reported decreased the weights of the testicle and auxiliary sex tissues such as the cauda epididymis.	[83]

Achyranthes aspera protein

- A protein is isolated from the alcoholic extract of the root of *Achyranthes aspera.*
- *Achyranthes aspera* posse various activities like anti-arthritic, anti-microbial, anti-oxidant, anti-depressant, anti-bacterial, etc [84].
- Home administration orally which protein has a dose of 25 mg per kg for 5 w. causes alteration in spermatogenic level and testicular activities and also a reduction in testosterone level [57].

Bergapten and xanthotoxin

- *Bergapten and Xanthotoxin* are the main examples of *psoralens*.
- These are given in the treatment of many diseases like *psoriasis and vitiligo* [85].
- A dose of 75 and 150 mg per kg per d for 8 w orally of both *psoralen* can induce alteration in the pituitary gland and the epididymis of testis and vasa deference [58].

Camelliagenin C

- This component was isolated from the defatted *Camellia oleifera* plant and had pharmacological activities [86].
- Suggesting the result that *sasanguasaponin* has been given to adult rats 100-400 mg/kg for 42 d cause [64].

Carica papaya fatty acids

- It belongs to *Caricaceae* family [87].
- Seeds and leaves are given as a remedy for any type of disease [88].
- On administration daily has a dose of 50 mg per kg of chloroform extract of *Carica papaya* seeds can cause an alteration in the motility of sperm and density and viability [59, 60].
- It can be our natural male contraceptive but it has its minor testicular toxicity.
- Apoptosis of spermatogenesis by inducing oxidative stress in it [89].

Cannabinoids

- A phytocannabinoids found in the cannabis plant and other *cannabinoids* is tetrahydrocannabinol [90].
- The effect of *cannabinol* on chronic uptake of bhang 3-6 mg per kg per d for 5 w causes major changes in the structure of a testis and can be suppressed the sperm density and its motility [63].
- Oral administration of *cannabis* extract as a dose of 2 mg per kg for 30 d to mice can produce toxicity levels in mice and can induce oxidative stress in it.
- In males, because of its increased toxicity, *Cannabis sativa* is not commonly utilized as a natural infertility inducer [91].

Embelin

- *Embelin* is one of the benzoquinone natural compounds which is isolated from the plant species of *Embelia ribes* barries [92].
- Administration of *embelin* as a dose of 20 mg per kg for 2-4 w altered the epidermal sperm and its motility and some of the activity of an enzyme associated with glycolysis [65, 66].

Gossypol

- *Gossypol* is a polyphenol isolated from the seed, roots, and stem of *Gossypium species* found in cottonseed oil [93].
- Administered as *gossypol acetate* at 20 mg/kg dose for forty d causes a reduction in the spermatogenesis process [94].
- Another trial of *gossypol* in which around 10-12.5 mg/adult for 4 mo can cause azoospermia in men [95].

Lupeol acetate and α-Amyrin acetate

- These are the main component of *Alstonia scholaris* leaves of its benzene fraction [96].
- *Alstonia scholaris* known to possess various activities like analgesic, anticancer, hepatoprotective, anti-inflammatory, anti-bacterial, wound healing. These can be used in arthritis, diabetic conditions [97].
- For contraceptive effects, both components were given to rats orally at a dose of 50-60 mg/kg for 8-9 w cause lowered sperm count and motility condition. It is also a reduction in the weight of reproductive organs [67].
- *Thevetia peruviana* extracts when given to rats at a dose of 400-500 mg/kg/d administered orally showing the content of *lupeol acetate* and *amyrin acetate* triterpenes [98].

N-butyldeoxynojirimycin (NB-DNJ) and N-butyldeoxygalactonojirimycin (NB-DGJ)

- *NB-DNJ* is glucose mimetic and can be utilized in *Gaucher* disease (type1) which is a genetic disorder [99].
- On oral administration of this extract has a dose of 15 mg per d for 42 d, two mice can cause a tidal spermatozoa alteration as in abnormal head shapes and reduction in sperm motility [69].
- Both compounds do not alter the reproductive system of males and the reproductive organ except when given in high dose and recover completely from their effects presented on the reproductive system of males occurred in 5 w after halted the treatment.

Oleanolic acid

- *Oleanolic acid* is a glucuronide compound which is an active compound of *Sesbania sesban* roots [100].
- For contraceptive effects, on oral administration of extract as a dose of 16 mg/kg for 4 w causing lowered in spermatozoa levels [71].
- *Oleanolic acid* can be a safe natural component that is used in health drinks.

Ursolic acid

- It is pentacyclic *triterpenes* identified in plant species of *Alstonia macrophylla* [101].
- The plant species of *Terminalia chebula* extract when given to male albino mice in a dose of 100-500 mg/kg for 35 d showing the content of ursolic acid present in it [102].
- It has anti-inflammatory and antipyretic activity.
- It is an irreversible and toxic contraceptive for men for daily usage.

Piperine

- *Piperine* is extracted from the natural alkaloid plant *Piper nigrum* [103].
- The anti spermatogenic effect on administration daily of *piperine* compound as 10 mg per mg for 8 w altered the spermatogenesis process which was associated with a decrease in motility of sperm and its viability and count [73].

Solasodine

- It is a nitrogenous analog of *diosgenin*.
- This compound is extracted or isolated from the plant species of *Solanum xanthocarpum* berries.
- Its part can be known as four medicinal uses in sore throat, pain-relieving, dysurea, etc.
- For contraceptive effects in monkeys as daily administration of *solasodine* as a dose of 100 mg per kg for 21 w resulted in antisperm at organic effect with lowered the production level of ladies cell and spermatids [65].

Triptolide

- It is a bioactive diterpene epoxide compound of *Tripterygium wilfrodii* extracts [77].

- Oral bioavailability is high leads to high systemic toxicity. So a transdermal controlled release formulation is preferred [104].
- The controlled release formulations of *Triptolide* recover completely from toxicity levels sign after halted its treatment [105].

Tripterygium wilfordii glycosides

- *Tripterygium wilfordii* species are used in the inhibition of spermatogenesis in rats as a fixed dose of 10 mg per kg for 49-91 d [75].
- This can lead to a reduction in epididymis sperm and further reaction.
- These *glycosides* can be a promising contraceptive for a male due to their high safety to reproductive organs and rapid reversibility on the use of oral microemulsion formulation.

ZNF185

- *Zinc-finger protein* consists of a group of a molecule that proceeds with the various biological function of the body.
- *Zinc finger protein* includes *ZNF300, ZNF105, ZNF185*, etc involved in the spermatogenesis process [79,106].
- This type of peptide may be a potential contraceptive utilized as a safe vaccine for male contraception after their clinical trial.

β sitosterol saponin Pistia straiotes

- A *sitosterol saponin* present in *Pistia stratiotes*. A dose of 50 mg/kg for 7 w to mice causes antispermatogenic activities and reduction in weight of reproductive organs [80].
- Also reduce the levels of testosterone, sperm count, motility, and viability.
- More *saponins* were used as antispermicidal such as *Nonoxynol N-9*.
- Poor bioavailability of *saponin* can be cause for not likely used as a male contraceptive.
- Some reasons for the reduction of systemic absorption of *saponin* are solubility, permeability, stability, dehydration, protein binding, and another similar factor [80].
- At given in high dose it causes toxicity in the male system and can be avoided as oral administered.

β sitosterol

- It is one of the *phytosterols* extracted from the plant *Alstonia macrophylla*.
- In the rat, when given subcutaneously as a dose of 0.5 and 5 mg/kg 2-7 w causes no complete reversibility from its effects and has poor bioavailability [83, 107].

Why we have not received the male birth control pill yet?

The male birth control pill is seen as a new era in contraception terms. But it is not like that. Keep this in mind; many researchers have examined the different types of drugs as birth control. In 1960, FDA approved the birth control pill for females in which the hormone estrogen and progestin combine that comes like a revolutionary product in the world. But manufacturing a male birth control pill in this mist seems like a waste. However, this year, numerous scientists said that assembling a male contraception pill is a stage towards the counteraction of accidental pregnancy and lessen the burden of conception in females. Promising another examination has been exhibited the efficacy of a few new details of male contraception. The first is the *dimethandrolone undecanoate [DMAU]* pill passed through the clinical assessment comparatively a pill *11-beta-MNTDC* a novel medication is still in undertrial [36]. Second is *NET/T*, as an effective gel with a blend of progestin and testosterone which is in progress to analyze the adequacy as a prophylactic in a long manner [37].

But there can be a possibility of a breakthrough in male contraception. Hormonal contraception for men is highly effective and also reversible. There are lots of men who are willing to participate in it and want to share the burden of contraception. Still, options for men are like years away because any drug to be marketed would first have to go through large scale testing. Contraceptives are having longer time action and work continually that why a drug needs to be used for years before it can be proved as effective. And we think it will be a decade that goes toward the male contraception methods and more work to do.

Table 3: List of various contraceptives patents

Patent no.	Patent name	Inventor/Assignee
DE10027378B4	Procreation prevention	Schooo, Andreas, 80686 Munchen DE
DE102012005379A1	Contraception method for men, involves applying heat to epididymis in regular time spacing for fixed duration on fixed increased temperature so that maturity process of sperm is disrupted and sperm die	Anmelder Gleich
EP1488784B1	Male contraceptive implant	Saleh I. Saleh, Alfred J. Moo-Young
EP1666044B1	Male contraceptive formulation comprising norethisterone	A. Rubig, UF. Habeeicht, A. Kamischke, E. Nieschlag, M. Oettel, E. Schillinger
JPH07289576A	Lubricant jelly encapsulation condom and its production	Tsuguto kaieda
JP4029359B1	Men's birth control device	Kiyoji Sawada
JP3053331U	Condom fall prevention ring	Seiki Yamanaka
US4972849A	Condom (sanitary contraception device)	Yong-Yeon Park, Weol-Seon Suh
US20150320586A1	Condom having a form tip	KC Nguyen, C. Ngowprasert, C. Netrung, C. Pongthanomsak
US3536066A	Human birth control appliance	Reginald O Ludwig
US5733565A	Male contraceptive implant	Alfred J. Moo-Young, Saleh I. Saleh
US20100089406A1	Method and device for male contraception	Elena Kachiguina
US5888543	Oral contraceptives	Michael J. Gast
US5858405	Oral contraceptive	Michael J. Gast
US5063064	Method for inhibiting and destroying spermatozoa	Pierre Bourbon, Pierre Lagny, Pierre Billot
WO2008062858A1	Dropping preventive device for male contraceptive device	Seji Sawada
WO1997031921A1	Immunosuppressive compounds and method	You Mao Qi, John H. Musser, John M. Fidler
WO2014127682A1	Blocking ring type condom	Lan Qingtian
WO2009113108A2	*Styrene maleic anhydride* based formulation for male contraception and prostate cancer	Kumar Guha Sujoy
WO2016205539A1	Non hormonal male contraceptive agents and method using same	Wei Yan

Acceptance of male contraceptives

Why the production of contraceptives is not continued? One reason for this is that the development of male contraceptives at this time may raise questions regarding their acceptability. However, demand is increased toward the male contraceptive and women forum and other population conferences clear-cut called for recent male contraceptives. In the global population, one-quarter of couples are based totally on practicing male contraception methods. But along with different preferences practicing male contraception is notably grown in Netherland. The proportion of vasectomized men whose better halves were in reproductive age rose from 2%-10.5% in 1975-2008 and 8%-12% in the USA. Higher numbers of vasectomized men were found in the United Kingdom, New Zealand. Comparatively, the uses of condoms in different countries for contraception have an average of 5-6%. According to a survey, 10 y ago in Shanghai and Hong Kong, half of the population of men were willing to use contraceptive pills as daily intake, and in Cape town around 2/3 of men do so [108, 109]. After 50 y of oral female contraceptives, the posture of male contraceptives has been changed. A different survey conducted worldwide showed the willingness to use contraceptive methods [110].

There are some contraceptives patents listed in below table 3.

CONCLUSION

In developing countries, population growth is the major cause of poverty and pollution. Over the years, several different ways of infertility induction have been investigated. These contraceptives can provide options for men and women who have difficulty or do not have access to modern contraceptives, particularly in rural parts of developing countries with a large population, such as India. However, due to insufficient inhibition of fertility or adverse effects, the hunt for an oral, safe, and effective contraception remains important for fertility regulation. From this study, it is clear these contraceptives can play a vital role in the prevention of unplanned pregnancy. These contraceptives may impact the male reproductive system has been studied in animals by way of commentary of changes in weight, histology, and endocrine functions. The researchers have advised that it may additionally be due to the inhibition of synthesis or the release of gonadotropin from the pituitary gland, a direct inhibitory impact of the testis or hormonal activity. The overview consequences confirmed that the above-mentioned contraceptives possess anti-fertility activity in dose based manner. Hence, it is concluded that this assessment may additionally focus the researcher's interest in medical research which ought to be of fantastic scientific contribution to society.

ABBREVIATIONS

FSH: Follicle-stimulating hormones, LH: Luteinizing hormones, DMSO: Dimethyl sulfoxide, EDTA: Ethylenediaminetetraacetic acid, PEG: Polyethylene glycol, ALDH: Aldehyde dehydrogenase

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CONFLICT OF INTERESTS

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