IMPEINDING 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 contraception and explores the management of male contraception. This 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 anti-fertility 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

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 population has been developing dramatically. 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.
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].

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 less effective in preventing conception of male partners conducted phase 2 clinical trials in four international sites with added progestin. Testosterone undecanoate (TU) 100 mg per d resulted in pregnancy was found during the trial [22]. In another study conducted as daily administration of medroxyprogesterone acetate (MPA) 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].

Vasectomy
Vasectomy is the surgery wherein the vas deference is cut and then ligated, to avoid 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 discontinuation 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 spermiotoxic 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-Dimethyacetamide

FDA approved excipient which is found as a male contraceptive agent named as N,N-Dimethyacetamide 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 BRDT, 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.

Immunococontraception

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 immunococontraception 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 Kuniz-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 definitive 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/threonine kinase substrate (TSSKs), serine/threonine kinase (STK), 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, STK, and TSSK5 are post-meiotic in action. As a result of this approach, they are potential targets for reversible contraception intermediate along with saving spermatogonia and spermatoocytes. 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 tests-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 recent a 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 action and the testis 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 androgenc, estrogen, and progesterone 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 weight gain, and mood change, increased appetite, etc. At present, a clinical trial is under-process 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 melanin 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-carboxyhydro-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-Gamedazole is a derivative of lonidamine as well as Adjutin that interferes in the maturation of spermatozoa. When a dose of 6 mg/kg is given for 4 weeks, it causes 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 is 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 alkaline 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 rats for 28 days causes inhibition of fertility and recovery upon halted 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 disruptions 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 under trials 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] |
| Cannabis sativ extract        | 3-6 g/kg | Mice          | 5 w      | After halted treatment 150 d | [61]      |
| Camelliasaponin c1            | 100-400 mg/kg | Mice | 42 d | N/A             | [62, 63] |
| 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-DGJ                        | 15 mg/kg | Mice          | 42 d     | N/A             | [69]      |
| Oleanolic acid                | 16 mg/kg | Rats          | 4 w      | After 14 d on halted treatment | [71]      |
| Piperine                      | 10 mg/kg | Rats          | 8 w      | N/A             | [72]      |
| Solasonine                    | 100 mg/kg | Monkey | 21 w | N/A             | [65]      |
| Tripterygium wilfordii        | 10 mg/kg and 20 mg/kg | Rats | 49-91 d and | After 20 d on halted treatment | [75]      |
| glycosides                    | 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]      |
| Tetrahydrcannabinol [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. Adult males who have been treated have pituitary glands that are significantly smaller and have low sperm per ejaculate. Elevated testosteron levels and testicular relative weight. Females bred to dosed adult males needed more time to become pregnant. | [57] |
| Bergapten                     |                                      | [58]      |
| Carica papaya fatty acid      | During 4 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] |
Spermatocyes 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. 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. A substantial improvement in the CB1 and CB2 receptors, as well as fatty acid amide hydrolase protein levels, was seen in mice tests as a result of GNRH inhibitory action. 

**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]. Because of a decrease in testicular enzyme activity, there is a significant decrease in the circulating testosterone stage. 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. The cauda epididymis sperm concentration was diminished by 84.8 percent, and the proportion of sperm viability, sperm abnormalities, and testosterone level of serum have all been significantly reduced. Weight unatural sperm was massively increased. There was no harm done to sex organs. The weights of the testicles, epididymis, seminal vesicle, and ventral prostate all diminished. The aorta 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, and 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.

**Embelin** In the epididymis, motile sperm count Suppression with some changes in the glycolysis activity and energy metabolism enzymes. 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. A substantial improvement in the CB1 and CB2 receptors, as well as fatty acid amide hydrolase protein levels, was seen in mice tests as a result of GNRH inhibitory action. 

**Lupeol acetate** The weights of the testicles, seminal vesicle, epididymis, and ventral prostate all diminished. 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. 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. The cauda epididymis sperm concentration was diminished by 84.8 percent, and the proportion of sperm viability, sperm abnormalities, and testosterone level of serum have all been significantly reduced. Weight unatural sperm was massively increased. There was no harm done to sex organs. The weights of the testicles, epididymis, seminal vesicle, and ventral prostate all diminished. The aorta 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, and 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.

**Solanidine** Impairment with sperm ligenosis in late spermatids at stage XI1. Spermatids had been reduced. Immature and mature Leydig cell activity has been reduced and a significant decrease in sper in count of the cauda region. The epithelial size of the cauda epididymis was diminished. The cells atrophied. Total protein and sialic acid levels, as well as glycolgen and acid phosphatase activity, have all dropped significantly in the cauda epididymis. 

**Tripterygium wilfordii glucosides** 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. The rate of pregnancy declined as the dose and treatment time increased, reaching 0% at forty d in the 45 mg/kg group. 

**Xanthotoxin** 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 spermatogon, lines the flat seminiferous epithelium. 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 with treated male rats, no further pregnancy occurs. 

**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. The cauda epididymis sperm concentration was diminished by 84.8 percent, and the proportion of sperm viability, sperm abnormalities, and testosterone level of serum have all been significantly reduced. Weight unatural sperm was massively increased. There was no harm done to sex organs. The weights of the testicles, epididymis, seminal vesicle, and ventral prostate all diminished. The aorta 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, and 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.

**NB-DNJ** The proportion of sperm motility was diminished. When the mated with treated male rats, no further pregnancy occurs. 

**NB-DGJ** 15 mg of NB-DNJ and 150, 300, and 600 mg/kg/d of NB-DGJ caused the decline of spermatozoa with standard nuclei and acrosomes but did not result in any epigenetic anomalies in the infants. The percentage of sperm cells that contain 5-S-protanines 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.

**Oleanolic acid** The proportion of sperm viability was diminished. When the mated with treated male rats, no further pregnancy occurs. 

**Embelin** In the epididymis, motile sperm count Suppression with some changes in the glycolysis activity and energy metabolism enzymes. 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. 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. The cauda epididymis sperm concentration was diminished by 84.8 percent, and the proportion of sperm viability, sperm abnormalities, and testosterone level of serum have all been significantly reduced. Weight unatural sperm was massively increased. There was no harm done to sex organs. The weights of the testicles, epididymis, seminal vesicle, and ventral prostate all diminished. The aorta 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, and 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.
**Achyranthes aspera protein**
- A protein is isolated from the alcoholic extract of the root of Achyranthes aspera.
- *Achyranthes aspera* possess various activities like anti-arithmetic, 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 *sasangusaponin* 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 phytocannabinoid found in the cannabis plant and other cannabinoids is tetrahydrocannabinol [90].
- The effect of *cannabinoil* 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* berries [92].
- Administration of embelin as a dose of 20 mg per kg for 2-4 w altered the epididymal 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 also is a reduction in the weight of reproductive organs [67].
- *Thevetia peruviana* extracts when given to rats at a dose of 400-500 mg/kg administrated orally showing the content of *lupeol acetate* and *amyrin acetate* triterpenes [98].

**N-butyldiexojnojirimycin (NB-DNJ) and N-butyldiexojgalactonjirimycin (NB-DGJ)**
- NB-DNJ is glucose mimetic and can be utilized in Gaucher disease (type 1) 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 *Sebania seban* roots [100].
- For contraceptive effects, on oral administration of extract as a dose of 1.6 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].

**Solosodine**
- It is a nitrogenous analog of *diogenin*.
- 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, dysuria, etc.
- For contraceptive effects in monkeys as daily administration of *solosodine* 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 wilfordii* 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 stratiotes**

- A sistorol 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 antispermical such as Nonoyonol 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, dehydrogenation, 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.

**Tripterygium wilfordii species**

- 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 mix 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 exhibited the efficacy of a few new details of male contraception. The first is the diethylstilbestrol undecanoate (DMSU) 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 need more time to do.

**Table 3: List of various contraceptives patents**

| Patent no. | Patent name | Inventor/Assignee |
|------------|-------------|-------------------|
| DE10207378B4 | Procreation prevention | Schoo, Andreas, 80686 Munchen DE |
| DE10201205379A1 | Contraception method for men, involves applying heat to epididymis in regular time spacing for fixed duration on increased temperature so that maturity process of sperm is disrupted and sperm die | Amneller Gleich |
| EPI488784B1 | Male contraceptive implant | Saleh I. Saleh, Alfred J. Moo-Young |
| EPI666044B1 | Male contraceptive formulation comprising norethisterone | A. Rubig, UF. Habeeb, A. Kaura, A. Kurschke, E. Nieschlag, M. Oettel, E. Schillinger |
| JPH0728957A6 | Lubricant jelly encapsulation condom and its production | Tsuguto kaieda |
| JP4029359A1 | Men’s birth control device | Kiyoji Sawada |
| JP3053331U | Condom fail prevention ring | Seki Yamanaka |
| US4972849A | Condom (sanitary contraception device) | Yong-Teun Park, Weol-Seon Suh |
| US20150320586A1 | Condom having a form tip | KC Nguyen, C. Ngowprasert, C. Nethungr, C. Pongthanomsak |
| US3536066A | Human birth control appliance | Regnald O Ludwig |
| US7333565A | Male contraceptive implant | Alfred J. Mow-Young, Saleh I. Saleh |
| US20100089406A1 | Method and device for male contraception | Elena Kachigina |
| US5888545 | Oral contraceptives | Michael J. Gast |
| US5858045 | Oral contraceptive | Michael J. Gast |
| US563064 | Method for inhibiting and destroying spermatogenesis | Pierre Bourbon, Pierre Layn, Pierre Billot |
| WO2008082538A1 | Dropping preventive device for male contraceptive | Seji Sawada |
| WO1997031921A1 | Immunosuppressive compounds and method | You Mao Qi, John H. Musser, John M. Fidler |
| WO2014127682A1 | Blocking ring type condom | Lan Qiantang |
| WO2009113108A2 | Sperone 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 the Netherlands. The proportion of vasectomized men whose better mates 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 years 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 years 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 conclusions 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, DMOS: Dimethyl sulfoxide, EDTA: Ethylenediaminetetraacetic acid, PEG: Polyethylene glycol, ALDH: Aldehyde dehydrogenase

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All the authors have contributed equally.

CONFLICT OF INTERESTS

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