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REVIEW

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A review of various types of male contraception

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Abstract

Birth control options for men are limited to only condoms and vasectomies. This review focuses on various types of male contraceptives for adequate fertility control and family planning by mutual understanding of couples (healthy family planning). Male contraceptive methods include hormonal and non-hormonal contraceptives, condoms, vasectomies, and using active ingredients from plants. Contraception in men is related to progesterone concentration, sperm count, sperm motility, sperm maturation and sperm viability. Studies are required on no side-effect-safe contraceptives for men that control serum progesterone levels, however do not increase oxidative stress. In conclusion, this article covers hormonal, non-hormonal, and plant-based male contraception in addition to the popular condoms and vasectomy. Furthermore, it includes partial description of the variety and mechanisms of male contraceptive methods available to men.

Keywords

Contraception; Male contraceptive method; Birth control; Progesterone

1. Introduction

Contraception for men is confined to condoms and vasectomies. As of 2020, the male contraception frequency before the age of 20 continues to increase, however limited to condoms [1]. Moreover, 40–66% unintended pregnancies result in abortion which leads to adverse health outcomes [2]. Pregnancy and abortion violate global equity in sexual and reproductive health rights [3]. Condoms are the only substantive male contraceptive method other than water loss. More than 98% men use this method however it has failure rate of above 10% [4]. Vasectomy once performed is irreversible which increases the infertility burden for men [5]. The need for safe, effective, and reversible male contraception thus continues to grow [6]. Among non-hormonal methods, reversible male contraception includes polymers' usage that block sperm transportation by reversible vaso-occlusive methods, the male pill, and long-acting injectables. They ensure reliability against failure and also consider side effects [7].

Efficient male contraception helps women in sharing their fears of unwanted pregnancy and thus avoid abortion [8]. Hormonal (androgen, combination of progestin and testosterone) or non-hormonal contraception, condom usage, and vasectomy are the only proven options for men. Other contraceptive methods require studies to improve efficacy while minimizing the usage risks [9]. This review article focuses on the male contraception for fertility control in men. The focus is placed on empirical studies—clinical trials, randomized controlled group trials—of useful and practical male contraceptive methods based on male reproduction. It can be employed as a resource to promote reliable family planning for men and create awareness of effective and practical contraceptive methods.

2. Mechanisms of male contraception

2.1 Hormonal male contraception

It is a natural hormonal contraceptive mechanism. It inhibits *Spermatogenesis* by interfering with the hypothalamic-pituitary-gonadal (HPG) axis. The gonadotropin-releasing hormone (GnRH) secreted by HPG stimulates pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In response, Sertoli cells in the testes are activated and Leydig cells stimulated by LH to produce abnormal testosterone [10]. These hormonal male contraceptives possess higher efficacy compared to condoms, which reduces the unintended pregnancy risk by 40% globally [11]. The control system of *Spermatogenesis* and androgen biosynthesis is based on the non-covalent interaction of FSH and LH through GnRH [12]. Progestins are related to exogenous androgens, both natural and synthetic progesterone. It puts negative feedback on hypothalamic-pituitary-testicular (HPT) axis and inhibits LH and FSH release. It has contraceptive role in *Spermatogenesis*, sperm motility, and transportation through vas deferens [13, 14]. This is demonstrated in Fig. 1.

A study on effective contraceptives for the couples finds that progestin, also called segesterone acetate, is the most efficient and preferred contraceptive method. "Pure progestin" is a transdermal gel for male contraception with no androgenic, estrogenic or glucocorticoid activity. It suppresses gonadotropin levels in above 80% men at the oral dose of 2–8 mg per day [15]. Progestins or physiologically administered testosterone for the combined contraceptive mechanism can lead to a series of side effects such as pain, acne, weight gain, mood and sex drive changes, depression and fatigue. Moreover, it has the potential for hormonal changes in serum

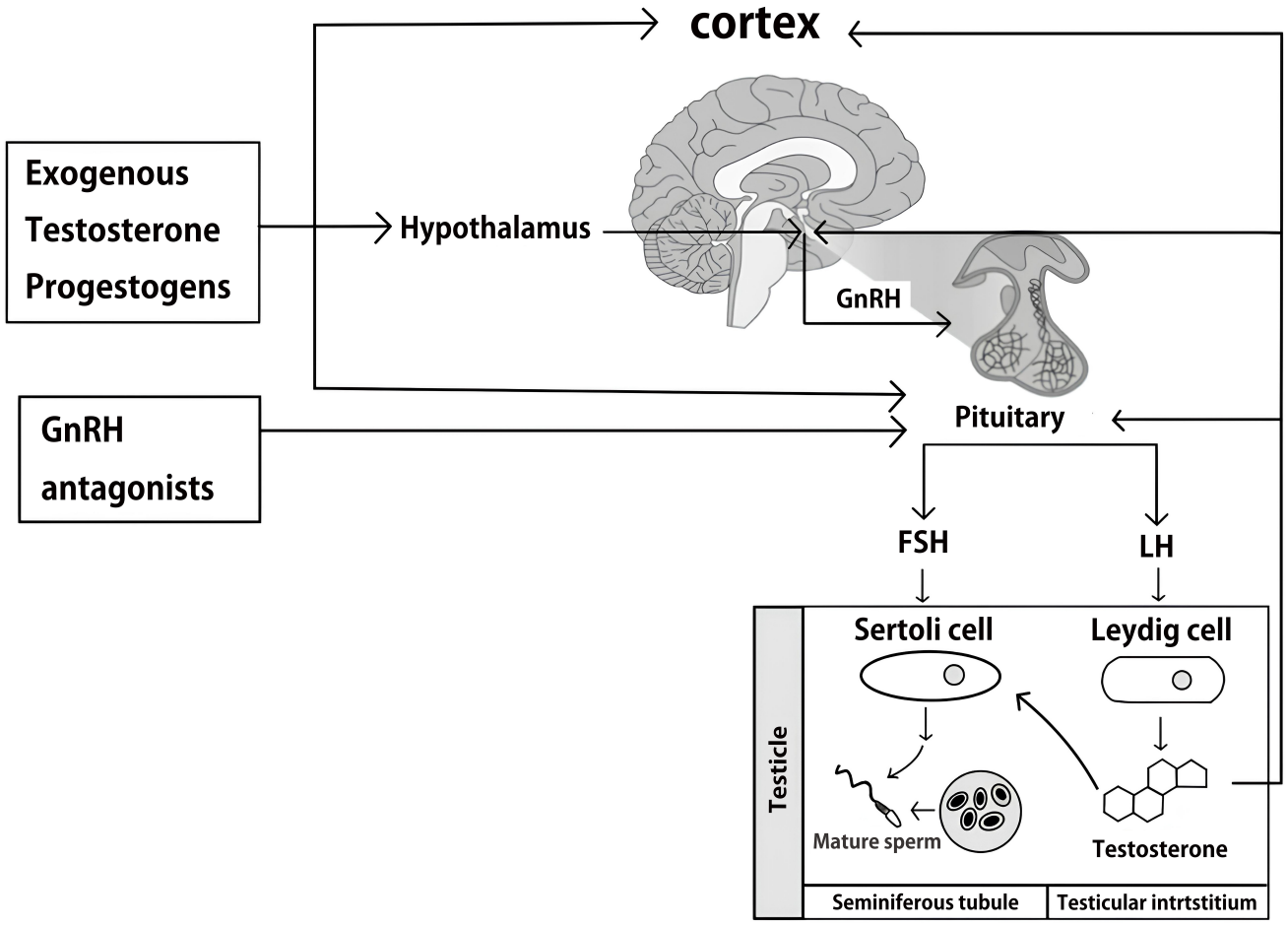

FIGURE 1. Hormonal regulation of testicular function. GnRH: gonadotropin-releasing hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone.

cholesterol, blood pressure, fat, muscle, and bone mass which require caution [16, 17]. There are also oral contraceptive substances available for hormone-based male contraception. 7α-Methyltestosterone (7α-MT) and 7α-ethyltestosterone (7α-ET) show resistant effect on 5α-reductase activity. T analogs, 7α-MT and 7α-ET, consequently become helpful in long-term male contraception by reducing prostate growth and maintaining mineral density [18]. Dimethandrolone (7α, 11β-dimethyl-19-nortestosterone) undecanoate (DMAU) is currently used as male hormonal contraceptive which is metabolized to dimethandrolone (DMA) in the body through administration of ester form. It reduces plasma LH and *Spermatogenesis* of testosterone-producing stromal cells of testes 28 days after oral administration. It affects male fertility by regulating testosterone levels via FSH stimulation. It is thus responsible for increasing androgen-binding protein (ABP) production. This is shown in the clinical trials where DMA from castor oil was ingested [19, 20]. DMA also suppresses gonadotropins and testosterone as revealed in 28-day placebo-controlled trial of male contraception. The hormonal bioavailability of orally administered DMAU as the male contraceptive is ensured by taking with a meal containing 25–30% fat, or by the co-administration of drug with breakfast [21]. 11β-Methyl-19-Nortestosterone-17β-dodecylcarbonate (11β-MNTDC) is another oral contraceptive inducing hormone-based male contraception. It is an ester based prodrug converted *in vivo* into the active substance 11β-Methyl-19-Nortestosterone. It binds to androgens and progesterone like the DMA and inhibits androgens' secretion. However, the long-term usage can cause side effects like erectile dysfunction and decreased libido. It may also expose them to cardiovascular diseases which require adjustments in concentration and dosage [22, 23].

2.2 Non-hormonal male contraception

Hormone-based male contraception is constituted of oral, injectable, and transdermal hormonal contraceptives. The non-hormonal alternatives may have side effects. It is thus imperative to test them through clinical trials. The non-hormonal male contraception removes mature sperm from ejaculate, or removes sperm cells, and precursor cells forming the sperm. World Health Organization has recognized the need for sperm removal. Efficient non-hormonal contraception is thus being debated [24, 25]. These methods of contraception are being developed and yet not available. If the hormonal male contraception focuses on restrictive action mechanism inhibiting the early stages of sperm production, the non-hormonal contraception can be a targeted method to achieve the short-term contraception goal [26]. EP055, a protease targeting epididymal protease inhibitor (EPPIN), is an oral non-hormonal con-

traceptive which inhibits prostate-specific antigen (PSA) based on protein-protein interactions [27]. Testis-specific serine kinase (TSSK) is a drug target for developing non-hormonal male contraceptives against *Spermatogenesis* and male fertility. This stems from the unique characteristics of TSSKs. Inhibition of TSSK activity by specific drugs can reversibly inhibit *Spermatogenesis* and sperm fertilization. TSSK has the ability to find specific small molecule inhibitors and may regulate their development during *Spermatogenesis* [28]. Cation channel of sperm (CatSper) is the validated target for non-hormonal male contraception. The calcium ion channel CatSper is developed as the non-hormonal agent to target testes, epididymis and sperm. It is only expressed in male contraceptive sperm and thus lead to complete sterilization. It only works with semen-positive sperm as it blocks CatSper. It has the efficiency of preventing sperm and treating vaginismus. It also prevents cytotoxicity towards human sperm by blocking CatSper and makes it a male contraceptive from reproductive and biological perspective [29]. Progesterone indirectly stimulates CatSper activity. The 2-acrachidonylglycerol (2-AG) of abhydrolase domain containing 2 (ABDH2) boosts inhibition and suppresses progesterone activity as depicted with CatSper [30, 31]. The process efficacy of this non-hormonal male contraception provides access to certain enzymes, Specifically *the catSper channels, transmembrane transporters* (sNHE), *solute carrier family 26 member 8* (SLC26A8), A *TPase Na+/K+ transporting subunit alpha 4* (ATP1A4), protein phosphatase 1, catalytic subunit gamma 2 (PP1γ2) including surface proteins (EPPIN), *glyceraldehyde-3-Phosphate dehydrogenase, Spermatogenic* (GAPDHS), *soluble adenylyl cyclase* (sAC), *etc*. This is an immunological strategy to induce non-hormonal contraception through gene mutation. It is active in preclinical trials these days. Small organic ligands such as drugs have been identified in this regard [32].

Vitamin A (retinol) deficiency yields active metabolite. It was first studied and recognized in male rats. Antagonists inhibiting the pathway of retinoic acid (RA) towards male retinoic acid receptor α (RARα), interfere with RA synthesis and disrupt *Spermatogenesis* [33]. WIN 18,446 is a bis-dichloroacetyldiamine analog of RA pathway which inhibits *Spermatogenesis* in more than 60 men, as found out in a clinical trial of over 1 year [34]. The bromodomain testis-specific proteins (BRDTs) are the non-hormonal targets. They are a subgroup of bromodomain and are the *in vitro* (BET) proteins, and include bromodomain (BRD)2, BRD3, BRD4 and BRDT. Testis-specific BRDT has a role in chromatin remodeling during the *Spermatogenesis*. It is reversibly contraceptive through small molecule inhibitor JQ1 [35, 36]. CDB-4022 being an indenopyridine is another example. It attaches to the sperm cells and releases immature sperm from vas deferens epithelium. It is a potential contraceptive inhibiting the mature sperm production. Sperm production resumes without the side effects once medication is stopped. The same happens for non-hormonal oral contraceptive H2-gamendazole which targets *Neisseria gonorrhoeae*. Clinical trials on animal models depict reversible contraceptive effects at low doses, however irreversible reproductive impact at higher doses [37, 38]. Other non-hormonal contraceptives are thus developed which target testicular germ cell-sertoli cell junction in combination with FSH [32].

3. Male condoms

The first male condom was produced in 1855 and employed for centuries to prevent pregnancy and sexually transmitted infections (STIs). It was the most popular male birth control in the West in 19th century. It was mass-produced in 1930 from the cemented rubber using liquid latex. It is directly obtained from rubber tree by emulsifying the tiny rubber particles in water. It has since changed from cemented wooden condoms to latex condoms [39]. Condoms are the most classic male contraceptive method with the recognition of 98% men [40]. In addition to providing simple protection, they reduce STI transmission including human immunodeficiency virus (HIV), gonorrhea, human papillomavirus, chlamydia, herpes simplex, syphilis and trichomonas. However, they may break, slip, leak and cause erection problems. They thus require proper fit, replacement, and safe disposal [41, 42]. There are two main types of condoms, *i.e.*, latex and polyurethane. The randomized controlled clinical trials (RCTs) have shown that polyurethane condoms are more likely to fail compared to latex, especially with breakage and slippage because of crushing [43]. Condoms have a failure rate of 13%. However, failure rate is 2% when employed correctly. Consistent usage improves contraceptive rates [44, 45]. Orgasmic disorder prevalence among the users of ill-fitting condoms is higher compared to those of properly sized condoms. Condoms fitting too tightly can cause erection problems, pain, condom breakage and slippage. Delayed ejaculation (DE) caused by the inadequate condom creep can contribute to acquired patient etiology which includes psychological, biological and other multiple factors [46]. In addition, this includes condom size and the acquired or situational patient's drug use status [47].

4. Surgical contraception: vasectomy

Increased awareness and education about vasectomy has reduced the disproportionate contraceptive burden on women and has provided healthy family planning options for men. However, hygiene-related fears were the main reason in couples not opting for vasectomy [48]. Vasectomy as a potentially irreversible surgery has few complications. It is available through a variety of access routes. However, the vasectomy failure rate is also a consideration with ~3–6% requiring reperfusion efforts [49].

Vasectomy is performed in two different stages. It is a method of separating vas deferens by passing and exposing the vas deferens from outside scrotum and closing the vas deferens. Alternatively, a standard incisional approach is used to expose the vas deferens. The no-scalpel vasectomy (NSV) technique is based on the isolation of vas deferens. NSV is preferred because of the reduced hematoma or blood loss, reduced infection, shorter operative time, and less pain [50]. Questions are raised about vasectomy as a risk factor for prostate cancer (PCa). However, vasectomy does not increase PCa risk in its safe and sterilized form [51]. It is also shown that prostatitis causing PCa is not associated with urethritis, orchitis and epididymitis [52]. Studies have shown that changes in

semen bacterial flora can be reversed and kept similar. This is contrary to the claims that vasectomy alters bacterial flora of semen, and changes the relative abundance of bacterial species in microbiome [53]. Vasectomy also has positive impact on sperm quality. Y chromosome microdeletions causing abnormal sperm quality are not associated with vasectomy [54]. Numerous reports have demonstrated that vasectomy is safe, reliable and low-complication method for fertility control in men. No increased risks of autoimmune disease, prostate cancer, cardiovascular disease, or sexual dysfunction exist pertaining to vasectomy [55]. Vasectomy blocks the vas deferens to eliminate the sperm delivery. On the other hand, castration is a method divided into chemical and surgical castration [56]. These vasectomies are the healthy surgical contraception as they are reversible compared to the castration and do not affect the hormone levels, and thus no increase in oxidative stress [57–59]. Chemical castration involves the chemicals' injection into shins, epidermis and bladder for inhibiting the *Spermatogenesis*. Surgical castration requires the testicles removal as it is the primary testosterone production site [60].

5. Potential plant-based contraceptives

Botanicals include glycosides, alkaloids, saponins, steroids, flavonoids, tannins and terpenoids. They have pharmacological characteristics suitable for developing oral contraceptives. Currently available oral contraceptives for men are proven safe in clinical trials, however, they have some complications and side effects. Nonetheless, contraception through natural plant-based ingredients is emerging [61, 62]. The contraceptive impact of M. longifoli leaf extract has been demonstrated via an animal model of male rats. They are treated with M. longifoli leaf extract to attain decreased sperm motility and sperm viability, especially at high doses. This suggests that the *Spermatogenesis* pathway is impaired to result in decreased fertility. Reduction in sperm maturation and fertilization indicates anti-fertility with the highest reduction in clinical trials of animals treated at the dose of 100 mg/kg. It demonstrates that the plant extract crosses testicular barrier and interferes with the normal sperm production and motility [63]. Stinging nettle leaf extract reduces fertility in the animal models of male rats. P2X1-purinceptor is the compound obtained from stringing nettle leaf extract. Its oral administration reduces fertility in male rats to indicate that fertility is pharmacologically blocked by α1A-adrenoceptors and P2X1-purinoreceptors. This enables the usage of non-hormonal oral male contraceptives. Purinoreceptors do not harm male characteristics or sperm viability, and induce contraception by reducing fertility at ejaculation, decreasing vas contractility, and interfering with sperm transport [64]. These pharmacological activities of medicinal plants are traditionally used for contraception. They are employed as contraceptive because of the high activity and low toxicity of active constituents [65]. Two most popular herbal male contraceptives are Terminalia Chebula Retz and Musa balbisiana Colla extract. This is confirmed from an animal model study showing decrease in the sperm levels and androgenic parameters of male rats [66]. This is because the phenolic compounds from plants have contraceptive activity. Strong contraception can be expected, especially from the leaves and plant extracts. This is demonstrated in inbred experiments on albino male rats [67]. The methanolic leaf extract of Hedera nepalensis is a natural anti-androgenic contraceptive. It increases antioxidant activity and oxidative stress, and interferes with the male fertility by causing hormonal imbalances, as observed in a clinical trial of adult male rats [68]. Ingredients in plant-based contraceptives include β-caryophyllene, embelin, oleanolic acid, tryptone and N-butyldeoxynojirimycin (NB-DNJ). They are the naturally derived compounds for male contraception, as proven through clinical trials [69].

6. Future direction

Hormonal regulation of male fertility is the male contraception underlying mechanism where titanium dioxide (TiO_2) generates ROS or cleaves spermine analog-tetrakis (3-aminopropyl) cyclen (SA-tK). The hormonal effect on 5α reductase activity of 7α-MT, 7α-ET [70], bioavailability and targeted bioavailability of non-hormonal preparations via DMAU oral administration [19, 21], condom usage [40], vasectomy [58], and botanical compounds are the multiple options of male contraception. These male contraception are supported by the clinical trials and randomized controlled trials. A summary of relevant studies are given in Table 1. Condom usage and vasectomy are the proven and popular male contraceptive methods. Herein, the hormonal and non-hormonal methods have been included which are still in clinical phase. Moreover, the potential contraceptive methods using botanical active ingredients from nature are discussed as future male contraceptives.

A new male contraceptives' source is coming from rodents. Rodents are involved in the self-renewal of human sperm stem cells and the undifferentiated sperm. They go through mitosis in *Spermatogenesis* and meiosis in differentiation and transformation into spermatocytes. It can be used as the non-hormonal male contraceptive. It is available in the signaling pathway of mammalian target of rapamycin complex 1 (mTORC1)/ribosomal protein S6 (rpS6)/AKT serine/threonine kinase 1 (Akt1)/AKT serine/threonine kinase 2 and p-FAK-Y407 and can be employed as the selective inhibitors [71]. Testosterone being an essential sex hormone is involved in male fertility and toxicity. It has role in *Spermatogenesis* and thus make it a starting point for male contraceptive strategies. Therefore, 17-hydroxyprogesterone (17-OHP) and insulin-like factor 3 (INSL3) are evaluated as the biomarkers [72]. Testosterone thus becomes a natural and essential steroid hormone in PCa which is an androgenic signaling factor in tumor cell growth. They are monitored to assess their resistance towards treatment and potential utility in clinical trials [73]. A variety of potential long-term strategies for male contraception based on hormonal, chemical, and immunologic interventions through plants are emerging. Traditional contraceptives based on medicinal plant preparations are being tested in clinical trials for their efficacy and safety to screen for plant-specific toxicity and side effects. It can thus be used as an effective alternate oral fertility regulator for men and has also been recognized as a potential contraceptive [74]. The development of plant-based oral contraceptives for men is ongoing. The identification and validation of specific targets based on transcriptomics and

TABLE 1. Summary of the studies on clinical male contraception.

Reference	Subjects	Male contraceptive methods	Findings
Wang *et al.* [17]	Human	Hydrogel contraception	Single intra-vasal injection, converts to hydrogel from liquid in less than 160 seconds. Safe and reversible male contraceptive strategy to control male fertility. TiO_2 generates ROS by non-invasive ultrasound which cleaves SA-tK to destroy hydrogel network. Fertility rate can be restored to 100%.
Lee *et al.* [70]	Human T-47D cells, Rabbits	PA molecules: 7α-MT and 7α-ET	Mitigate negative effects on bone density with long-term usage of androgen receptors and progesterone receptors. Reduced metabolism of T-analogs reduces prostate growth concerns. Demonstrate progesterone activity in a rabbit model to indicate safety of male contraception.
McNeil *et al.* [19]	Rat	Castor seed oil	*Spermatogenesis* and sperm motility inhibited by 6 weeks of castor oil seed extract treatment. Ricinus communis-linn as a potent male contraceptive with significant antimotility.
Nguyen *et al.* [21]	Human	11β-MNTDC	Higher satisfaction with the pill compared to placebo. Pills (90%) are preferred over topical gels and injections as they do not interfere with daily routine. About one-third of participants experience side effects but will use again as it does not interfere with daily routine.
D'Francisco *et al.* [40]	Cat	Hemiorchiectomized	Reduction in volume of all seminal cell components except spermatozoa. Reproductive epithelium recovers quickly. Interferes with *Spermatogenesis*.
Sancak *et al.* [58]	Rat	Vasectomy	Vasectomy does not affect hormone levels with no increase in ROS compared to tubal ablation and castration, making it a healthier male birth control.
David *et al.* [63]	Rat	ML	A decrease in number of spermatozoa, sperm maturation, seminiferous bodies, seminiferous tubules diameter, lumen diameter, and epithelial height with a contraceptive effect.
Eise *et al.* [64]	Rat	Stinging nettle root and leaf extracts	Role as an antagonist of P2X1-purinoceptors. Reduce urogenital smooth muscle levels. Pharmacologic blockade of P2X1-purinoceptors blocks sperm transport. Biological male contraceptive strategies.
Ain *et al.* [68]	Rat	Methanolic leaf extract of *H. nepalensis*	Decreases antioxidant activity and increases ROS. Plasma LH and FSH levels increase at high dose. Decrease in testosterone concentration. ROS, hormonal imbalances interfere with male fertility.

TiO_2: titanium dioxide; ROS: reactive oxygen species; SA-tK: sodium alginate conjugated with reactive oxygen species-cleavable thioketal; PA: progesterone and androgen; 7α-MT: 7α-methyltestosterone; 7α-ET: 7α-ethyltestosterone; 11β-MNTDC: 11β-methyl-19-nortestosterone 17β-dodecylcarbonate; ML: Mentha longifolia L; LH: luteinizing hormone; FSH: follicle-stimulating hormone.

proteomics using the knockout mice may discover new non-hormonal contraceptives. The ubiquitous expression of protein sequences has identified the targets with high sequence similarity to protein. This has prompted research and development (R&D) and commercialization of male contraceptives which also consider potential side effects [75].

7. Conclusions

This review article exhibits that hormonal and non-hormonal contraceptive methods, condom usage, vasectomy, and male contraception with natural plant active ingredients are available with potential utility. Clinical trials are ongoing for oral contraceptives, injectables, and gene pathway and targeted therapies in male contraception. This review analyzes current

and upcoming male contraceptive methods including but not limited to the condoms and vasectomies. However, it is important in the longer run to study the development of male contraceptives which are free of side effects and complications. The development of a male contraceptive based on these findings is thus recommended which has no side effects such as depression, loss of libido, pain and complications.

ABBREVIATIONS

TiO_2, titanium dioxide; ROS, reactive oxygen species; SA-tK, sodium alginate conjugated with reactive oxygen species (ROS)-cleavable thioketal; HPG, hypothalamic-pituitary-gonadal; GnRH; gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; HPT, hypothalamic-pituitary-testicular; 7α-MT, 7α-methyltestosterone; 7α-ET, 7α-ethyltestosterone; DMA, dimethandrolone; ABP, androgen-binding protein; DMAU, dimethandrolone undecanoate; 11β-MNTDC, 11β-methyl-19-nortestosterone 17β-dodecylcarbonate; EPPIN, epididymal protease inhibitor; TSSK, testis-specific serine kinase; CatSper, cation channel of sperm; ABDH2, abhydrolase domain containing 2; 2-AG, 2-acrachidonylglycerol; RARα, retinoic acid receptor α; RA, retinoic acid; ALDH-2, aldehyde dehydrogenase-2; BRDT, bromodomain testis-specific protein; BET, bromodomain and extraterminal; STIs, sexually transmitted infections; HIV, human immunodeficiency virus; RCT, randomized controlled clinical trials; DE, delayed ejaculation; PCa, prostate cancer; BPH, benign prostate hyperplasia; NB-DNJ, n-butyldeoxynojirimycin; mTORC1, mammalian target of rapamycin complex 1; rpS6, ribosomal protein S6; 17-OHP, 17-hydroxyprogesterone; INSL3, insulin-like factor 3; R&D, research and development; sNHE, specifically the catSper channels, transmembrane transporters; SLC26A8, solute carrier family 26 member 8; ATP1A4, ATPase Na+/K+ transporting subunit alpha 4; PP1γ2, protein phosphatase 1, catalytic subunit gamma 2, GAPDHS, glyceraldehyde-3-Phosphate dehydrogenase, spermatogenic; sAC, soluble adenylyl cyclase; BRD, bromodomain.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

YP and KHK—conceptualization, validation, writing-review. YP—methodology, software, formal analysis, investigation, resources, data curation, writing-original draft preparation, editing, visualization. KHK—supervision. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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