ijpbs 2020; doi 10.22376/ijpbs.2020.11.4.p75-80

International Journal of Pharma and Bio Sciences

Review Article

Pharmacology for Better Drug Screening

Multi-Faceted Effects of Cannabis and Cannabinoids on the Male Reproductive System: A Review

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Abstract: *Cannabis sativa* is a hallucinating drug used in different parts of the world from ancient time. This is used as a part of various religious and social practices. Cannabis is a special type of Marijuana which can provide temporary relief from analgesia, body pain, and some other clinical conditions. Thus, importance of Cannabis is mostly described as a narcotic analgesic agent. But, the impacts of Cannabis on the reproductive health of females and males are multi-faceted and differentially fatal. Current researches suggest that cannabis may negatively impact male and female fertility conditions. In females, Cannabis can reduce female fertility by disrupting the hypothalamic release of gonadotropin-releasing hormone (GnRH), leading to reduced estrogen and progesterone production and an ovulatory menstrual cycles. In males, cannabis can cause changes in different ways in the reproductive system. At the tissue level, under chronic administration testicular morphology is changed which can exert its effect on sperm quality. Sperm quality is marked by different parameters like semen quality, sperm morphology, sperm mortality, and sperm motility. Upon chronic cannabis treatment, it was noted that almost all of the sperm parameters are significantly reduced. Reduced sperm parameters, eventually affect male reproductive hormones i.e. testosterone, Interstitial Cell Stimulating Hormone (ICSH), Luteinizing Hormone (LH), and Follicle Stimulating Hormone (FSH). These physiological and hormonal parameters finally cause reduced libido which may even lead to oligospermia and infertility. Till date, studies delineating cannabis effect on the male reproductive system is mostly centered on rodent models and it is mostly lacking in human and in sub-human primates. Considering the primate male reproductive system, these kinds of studies are haphazard and scanty. Thus, the lacunas of previous studies were identified and the present review focuses on the effects of cannabis on the male reproductive system in a systematic manner considering human and sub-human primates in particular.

Keywords: Cannabis, Effects, Hormones, Male, Marijuana, Reproduction, Reproductive potentiality, sperm parameters.

Article History	Date of Receiving	27 July 2020	Date of Revision	11 September 2020
	Date of Acceptance	16 September 2020	Date of Publishing	03 October 2020

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Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

CItation Dr. Somenath Ghosh , Multi-faceted effects of cannabis and cannabinoids on male reproductive system: A state of art review..(2020).Int J Pharm Sci.11(4), P75-80 http://dx.doi.org/10.22376/ijpbs.2020.11.4.p75-80

Int J Pharma Bio Sci., Volume11., No 4 (Oct) 2020, pp P75-80

1. INTRODUCTION

Cannabis, which is a type of marijuana has been used by the people of the Indian subcontinent from time unknown for different social, ritual and entertainment purposes.[1] They not only use this herb as a part of the holy practice but also use it for recreational purposes[2]. Irrespective of sex, this hallucinogenic agent is used by most parts of the world particularly by the populations of South America, India, Bangladesh, and Pakistan from a long time ago[3]. Reports suggesting the roles of *Cannabis* causing systemic neuropathy[4], neuronal disability[5], impaired fetal development[6,] and mal-functioning of male reproductive system[7-10] are documented. But, no reports available depicting the effects of marijuana in the female reproductive system. The main causative agent of the effects of marijuana/cannabinoids is the endocannabinoid. This is a neutral lipid and highly conserved molecule throughout evolutionary history[11]. They are having different derivatives like anandamide[12], 2-arachidonoylglycerol[13,] and Δ^9-tetrahydrocannabinol (THC)[14]. However, among all of the fatty acid derivatives of cannabinoids or endocannabinoids (eCBs) the THC has now been established as the most important hallucinogenic agent of this molecule[15]. There is a literature suggesting the role of this THC in the regulation of functions of the central nervous system and thus regulating the reproductive functions by affecting/ modulating hypothalamic-pituitary-gonadal axis (HPG-axis)[16]*via* its receptor CB1 and CB2[17]. Now it has been reported that CB1 receptors are localized mostly in the whole vertebrate central nervous system (CNS) and some peripheral tissues, whereas CB2 receptors are mostly expressed in peripheral tissues and immune cells, however, they have recently been found also in the CNS[18]. But, with all the advancement in psycho-neuro-endocrine research, to date, it is a matter of debate on how THC is going to regulate the reproductive system at the peripheral level. Some literatures suggest that there is a general agreement on the inhibitory effect exerted by cannabinoids and eCBs on GnRH release[19] Thus, it is affecting the subsequent FSH and LH release and impairing both male and female reproduction[20]. In the area of male fertility, cannabis use has been linked to reproductive hormone changes, altered semen parameters, and reduction in libido and sexual performance[21]. A detailed review of how marijuana affects male fertility at each point along the fertility axis is needed for clinicians to assess the potential risks that patients incur when using this substance. Although men are more likely to use drugs[22] and have a substance use disorder[23], drug abuse can seriously impact even women's health. After alcohol and heroin, marijuana is the most common primary drug of abuse for women entering treatment for substance abuse[24]. Females appear to be more sensitive to the behavioral and physiological effects of marijuana and marijuana-like substances[25], and treatment-seeking women endorse more severe marijuana withdrawal symptoms than treatment-seeking men[26]. After tobacco and alcohol, marijuana is the most commonly abused substance by women of childbearing age[22]. According to the 2013 NSDUH, 5.4 percent of pregnant women and 11.4 percent of non-pregnant women ages 15 to 44 are currently illicit drug users[22], with marijuana representing 64 to 79 percent of female drug use[22, 27-29]. As marijuana becomes more widely legalized, marijuana used by women will likely increase[22]. Thus, with this brief introduction, it is evident that any form of marijuana can cause a detrimental effect on both male and female reproductive health. We have gone through several literatures from Pubmed/Pubmed Central (PMC) and MedLine and with the results procured from our previous experiments on the impact of Cannabis on female reproduction [as published elsewhere][30] the present article is designed. However, the present article is restricted to elucidate the roles of cannabis on male reproduction since the role of cannabis on female reproduction is a matter for another full-length chapter. This article may throw some light and put forward some recent knowledge on the impacts of marijuana and Cannabis in particular on reproductive impairment in males.

2. CANNABIS EFFECT ON MALE REPRODUCTION

Impacts of Cannabis consumption on male reproduction is multi-dimensional and can be exerted at many levels. Thus, it can be discussed under different sub headings.

2. 1. CANNABIS EFFECT ON SPERM PARAMETERS

2.1.1. SPERM COUNT AND CONCENTRATION

Cannabis use is strongly associated with reductions in sperm count and concentration in animal and human studies. Decreased epididymal sperm concentrations were observed in mature male rats exposed to 16 puffs per day of marijuana, comparable to the recreational level in humans, for 75 days[31]. This effect was replicated in a study, in which, 3 to 6 mg/kg of the *Cannabis sativa* derivative bhang was administered in adult male mice. The results of the study demonstrated a significantly depressed sperm count[32]. Human studies have shown similar findings. A Danish cohort study on marijuana use in 1,215 participants revealed similar changes[33]. Men who reported using marijuana more than once per week had a 28% lower sperm concentration and a 29% lower sperm count than men who had never used marijuana. In a study in which 16 chronic marijuana smokers were exposed to 4 weeks of high dose marijuana the time to a reduced sperm count was 5 to 6 weeks after initiating marijuana use[34]. In human and animal models cannabis has shown strong links to reduced sperm count and concentration which may be linked to arrested spermatogenesis. Future work is needed to elucidate causal mechanisms.

2.1.2. MORPHOLOGY

Cannabis use also appears to induce considerable morphological changes in sperm. In a 1978 study, Zimmerman *et al* treated male mice for 5 consecutive days with intraperitoneal injections of the marijuana components THC, cannabinoid, or cannabinol[35]. On microscopy, 35 days after exposure mice treated with THC and cannabinol had a significantly higher incidence of abnormal morphology than the control group, such as banana-shaped, amorphous, folded, or hookless heads. Despite morphological changes the research suggests that cannabis does not induce chromosome breakage in sperm. Generoso *et al*[36] administered 50 mg/kg THC 5 times per week for 6 weeks in 498 male mice[36]. After mating them with females no increase was observed in fetal dominant lethal mutations or heritable translocations over those in controls. These findings were supported by a study by Berryman *et al*, who found no THC induced increase in preimplantation loss, fetal mortality, or the mutation index in fetuses fathered by male mice chronically dosed with THC[37]. In animal and human models

evidence suggests that cannabis induces morphological changes in sperm while genetic material is preserved.

2.1.3. MOTILITY AND ENERGY METABOLISM

The most extensive body of evidence for cannabis related alterations to sperm is for sperm motility. Whan *et al*[38]noted spermatotoxic effects of THC by incubating sperm with THC at therapeutic doses, similar to concentrations shown to relieve pain or reduce spasticity in humans with multiple sclerosis (0.032 mM) and recreational concentrations (4.8 and 0.32 mM) for 3 hours, and then measuring motility by computer-assisted semen analysis[38]. Therapeutic and recreational THC concentrations also resulted in reduced straight-line velocity. A similar decrease in sperm motility was seen in an analysis of semen samples from 16 healthy, chronic marijuana users after 4 weeks of high dose marijuana[34]. Barbonetti *et al* elucidated the mechanism of these findings by establishing a link between CB1 and sperm mitochondrial activity[39]. In sperm incubated with the CB1 receptor agonist Met-AEA a significant reduction was observed in mitochondrial trans-membrane potential. When the sperm was placed under glycolysis blockade, causing them to switch oxidative phosphorylation, the introduction of Met-AEA abolished sperm motility. The link between cannabis and sperm mitochondrial dysfunction was furthered by Badawy *et al*[40], who added THC to semen and measured the oxygen concentration as a marker of respiration. Upon the addition of THC mitochondrial respiration immediately declined and was concentration-dependent in effect. The results were much more pronounced in washed sperm than in neat semen, suggesting that seminal plasma contains some protective factors. These various investigations suggest that through the action of cannabis on the CB1 receptor the mitochondrial activity of sperm is reduced and as a result motility is significantly impaired. Although Met-AEA and THC administration in the laboratory has helped map potential pathways, to our knowledge it is not known whether these effects are fully replicated in the male testes. Future testing should be done to explore whether mitochondrial impairment is present in the semen of chronic cannabis users.

2.1.4. VIABILITY

Cannabis also has a detrimental effect on sperm viability. Rossatoet al[41] incubated semen samples with the endocannabinoid AEA at varying concentrations and found that viability was decreased in a manner at supraphysiological AEA concentrations. Reduced sperm viability related to cannabis has also been investigated using the highly specific CB1 receptor antagonist rimonabant (SR141716). Cobelli*et al*[42] found that adding a micromolar concentration of rimonabant induced a small but significant increase in the number of viable spermatozoa. Aquila et al[43] reported similar findings with 1 and 10 nM concentrations of rimonabant increasing sperm viability with no further viability changes observed at higher concentrations. While the cannabinoid system has clear links to sperm viability, future work should be done to confirm these findings with exogenous cannabinoids as well as in the *in vivo* setting.

2.1.5. FERTILIZATION CAPACITY

Research suggests that the cannabinoid signaling pathway may be involved in inhibiting sperm capacitation and activation. Using high performance liquid chromatography Schuel*et al*[44] observed that high levels of AEA are present in seminal plasma and in progressively decreasing amounts in oviductal and follicular fluid, indicating that sperm are exposed to progressively decreasing AEA levels along the entire fertilization path[45]. The authors speculated that high AEA levels maintain sperm in a quiescent state and the decrease in AEA levels which occurs in the fertilization environment enables sperm to become activated. These data suggest that increase in cannabinoid levels may interfere with sperm activation and may be especially pertinent in the female reproductive tract, where the sperm depend on for tightly regulated AEA levels to maintain proper function. Rossato *et al* reported that AEA inhibits the capacitation induced acrosome reaction of human sperm after incubation in capacitating medium[41]. Using boar sperm Maccarrone et al found that Met- AEA reduced sperm capacitation in a time dependent manner[46]. They also noted that this effect was mediated by the CB1 receptor since when rimonabant, which blocks CB1, was added, Met-AEA produced no change in capacitation. Schuelet al[44] used the cannabinoid agonist AM-365 to identify concentration-dependent stimulation and inhibition of sperm hyperactivated motility, which is a state needed for sperm to reach the egg surface and which assists with penetration of the zonapellucida. Current work suggests that the endocannabinoid system is intimately linked to the fertilization process in the male and female reproductive tracts. Given the well described inhibitory effects, cannabis is likely to have negative impacts on fertilizing potential.

3. CANNABIS EFFECTS ON REPRODUCTIVE HORMONES:

3.1. FOLLICLE STIMULATING HORMONE

Relatively few studies have focused on cannabis and FSH levels, and most have observed no effect. Cone et al found no significant change in FSH levels in 4 healthy males with a history of frequent marijuana use before and after 2 marijuana cigarettes per day for 3 consecutive days[47]. Vescovi et al observed that cannabis did not alter the response of FSH to gonadotropin-releasing hormone in 10 male chronic marijuana users given gonadotropin-releasing hormone intravenously[48]. A depression in FSH levels was observed only by Kolodny *et al*, who compared plasma hormone levels among 11 men who used 5 to 9 marijuana cigarettes per week, 9 who used 10 or more marijuana cigarettes per week, and normal controls[29]. Based on current studies, FSH may not be affected by cannabis except perhaps in the limited case of heavy chronic use. Human studies to date have been limited in suggestive power due to the small cohort sizes, leaving considerable room for further validation with larger sample size investigations.

3.2. LUTEINIZING HORMONE

In human and animal models LH is consistently lowered by cannabis[49, 50]. In the single exception,Kolodny*et al*[29] did not observe any significant difference in plasma LH levels between men who smoked 5 to 9 marijuana cigarettes per week and men who smoked 10 or more per week.12 However, the variation in marijuana use levels in this study may have been insufficient to induce LH variations. The relationship between cannabis and LH was strengthened in a study by Wenger *et al*, who used polyclonal antibodies against CB1 and CB2 to localize individual cells expressing

cannabinoid receptors[51]. The CB1 receptor was found in the anterior pituitary in LH secreting gonadotrophic cells. Wenger *et al* reaffirmed these results after administering AEA to wild-type and CB1 knockout mice, which revealed decreased LH secretion in the wildtype mice but unchanged LH levels in the CB1 knockout mice[32] As is the case with FSH related investigations, understanding how cannabis impacts LH would be improved by larger randomized, controlled trials in human subjects.

3.3. TESTOSTERONE

The reported effect of cannabis on serum testosterone levels is widely variable across current studies. In early work in 20 chronic marijuana users, Kolodny *et al* found a significant reduction in testosterone levels between chronic and never marijuana users[29]. The evidence that cannabis depresses testosterone levels relies heavily on animal studies. In contrast to findings in animals, most human studies support the conclusion that testosterone levels are not significantly changed by cannabis use. A 1974 study by Mendelson et al in 27 chronic marijuana users who were administered marijuana for 21 days showed no significant changes in plasma testosterone levels[52]. In a 1986 study of 4 male chronic marijuana users given 2 marijuana cigarettes per day depressed free testosterone levels were observed but the levels did not significantly differ from baseline[47]. In a later study, free testosterone levels were compared in 41 normal controls, and in 66 Pakistani men who smoked cannabis daily or regularly consumed cannabis tea [35]. No significant difference was observed in plasma testosterone levels between the cannabis users and the normal controls. Although the sample size was limited in these early human studies, they suggest that cannabis consumption does not significantly alter testosterone levels. It is only recently that large cohort studies of cannabis users have been possible. To date, these studies have continued the trend of presenting conflicting or inconclusive evidence on the link between cannabis use and testosterone levels. The first large cohort study on the effects of cannabis use was performed by Gundersen *et al* in 2015 using a registry of 1,215 Danish men undergoing a compulsory medical examination to determine fitness for service[33]. Testosterone levels were 7% higher in self-reported marijuana smokers than in nonusers. This was within the same range of testosterone elevation observed in cigarette smokers in the cohort. The authors cautioned that increased testosterone levels in marijuana users could not be separated from the effect of tobacco smoking alone. A second major cohort study was done in 2017 by Thistle *et al*[53]. They used data on 1,577 American men using data from the 2011to2012 United States National Health and Nutrition Survey with several novel outcomes. No difference was observed in serum testosterone levels between ever and never users of marijuana. However, serum testosterone levels showed an inverse association with time since the last regular use of marijuana, and since the last marijuana use. This indicated that decency rather than frequency of use may have the strongest relationship with serum testosterone levels. Additional large, population-based samples are needed to clarify currently conflicting reported effects of cannabis on testosterone levels.

4. CONCLUSION

As cannabis increasingly gains legalized status across the United States, the popularity and prevalence of use continue to grow. Although medically it demonstrates therapeutic promise in some areas such as multiple sclerosis and chronic neuropathic pain, the potential adverse effects remain widely under studied. Current research shows that cannabis likely has negative impacts at several points along the male fertility pathway. Human sperm express cannabinoid receptors, suggesting that they are directly impacted by alterations in the balance of the end cannabinoid system. The effect of cannabis on testosterone levels is largely undetermined while LH levels appear to be lowered and FSH levels are unchanged. The strongest evidence for the deleterious effects of cannabis on male reproductive capacity is its impact on semen parameters. Studies demonstrate reduced sperm count and concentration, morphological changes, reduced motility and viability, and decreased fertilizing capacity in animals and humans exposed to marijuana or cannabis derivatives. Furthermore, animal studies suggest that cannabis has a role in testicular atrophy. While cannabis may increase libido in the short term, chronic use may diminish erectile function in men. The evidence presented to date largely depends on animal models, *in vitro* studies of endogenous cannabinoid compounds and retrospective analyses. The ethical and legal complications of an *in vivo*, controlled study drive the limited amount of data presented in human subjects, a limitation which is unlikely to abate going forward. Future studies should focus on gathering large cohort data in national surveys, similar to the voluntary, cannabis related data collection done with compulsory military fitness examinations in different countries. These types of studies are needed to confirm that animal models can be translated into human experience.

5. CONFLICT OF INTEREST

Conflict of interest declared none.

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