DOI: https://doi.org/10.53555/nnmhs.v9i5.1664 Publication URL: https://nnpub.org/index.php/MHS/article/view/1664

CANNABIS AND MALE FERTILITY : A SYSTEMATIC REVIEW

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Abstract

Cannabis is a class of psychoactive substances derived from Cannabis sativa or Cannabis indica that can induce euphoria in the user. Cannabinoids are the term used to refer to the active component of cannabis, which contains 400 active compounds. DSM criterion 5 characterizes cannabis use disorder. Cannabis is the most commonly used illicit substance worldwide. The annual prevalence of cannabis abuse ranges from 2.9% to 4.3% of the global population aged 15 to 64. Cannabis sativa, Cannabis indica, and Cannabis ruderalis are the three varieties of cannabis. These three cannabis varieties contain varying amounts of tetrahydrocannabinol (THC). The THC content of Charas and hashish ranges between 7% and 14%. Cannabis and Sinsemilla are found in female shoots with an average THC concentration of 4-5% (rarely >7%). Low-grade Bhang preparations are derived from the 1% THC-containing residue of desiccated plants. Hashish oil, a concentrated liquid extracted from hashish distilleries, contains between 15 and 70 percent THC. Semen parameters provide the strongest evidence of cannabis-induced alterations in male fertility. Cannabis reduces sperm count and concentration, induces abnormalities in sperm morphology, reduces sperm motility and viability, and inhibits capacitation and fertilizing capacity, according to research.

Katakunci: *Cannabis; Fertility; Male; Spermatozoa; Testosteron*

INTRODUCTION

Cannabis is a group of psychotropic substances derived from the plant Cannabis sativa or Cannabis indica which can make the wearer experience euphoria. Cannabis has 400 active components, cannabinoids is the term used to designate the active component of cannabis. Cannabis use disorder is defined by DSM criterion 5.[1,2] Cannabis is the most widely used narcotic worldwide. The prevalence of cannabis abuse ranges from 2.9-4.3% per year of the world's population aged 15-64 years.[3,4]

Trends in the legalization of cannabis have been implemented by the United States in New York and Colorado, the Netherlands, Germany (possession of 6 grams), Argentina, Cyprus (15 grams), Ecuador, Mexico (5 grams), Peru (8 grams), Switzerland (4 bars), Belgium (3 grams), Brazil, Uruguay, Paraguay (10 grams), Colombia (20 grams), and Australia.[3,4] According to the World Health Organization (WHO), roughly 25 percent of the adult population around the world uses cannabis for recreational or other reasons. This number translates to 147 million people.[4–6]

When used for medicinal purposes, cannabis is considered an alternative and complementary medicine (CAM) because it is not a conventional therapy. About 40% of adults with epilepsy taking CAM improve due to lack of efficacy of standard therapies, because of side effects, or for other reasons.[4–6] As marijuana laws are changed and the number of people who use it is likely to rise, more needs to be known about how it might affect men's reproductive health.[7] Prior research on marijuana use and serum testosterone levels has produced contradictory results.[8–11]

While an early study found that marijuana users had lower testosterone levels than non-users, the majority of subsequent studies found no difference in testosterone levels between users and non-users. Recently, however, a large cohort study of young, healthy men in Denmark found that marijuana users have higher testosterone levels.[8–10,12] This article proved the association cannabis and male fertility.

METHODS

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist was used as the basis for the establishment of the criteria that govern the methodology of this particular systematic review. This systematic review was designed to evaluate papers on the relationship between cannabis and male fertility. These are the topics covered in the evaluated studies. To have your study evaluated, it must meet the following criteria: 1) Articles must be fully accessible online; 2) Articles must be written in English; and 3) Articles must have been published between 2015 and the time this systematic review was prepared.

The search for studies to be included in the systematic review was carried out from May 1st, 2023 using the PubMed and SagePub databases by inputting the words: “cannabis” and “male fertility”. Where *("cannabis"[MeSH Terms] OR "cannabis"[All Fields]) AND ("male"[MeSH Terms] OR "male"[All Fields]) AND ("fertility"[MeSH Terms] OR "fertility"[All Fields])* is used as search keywords.

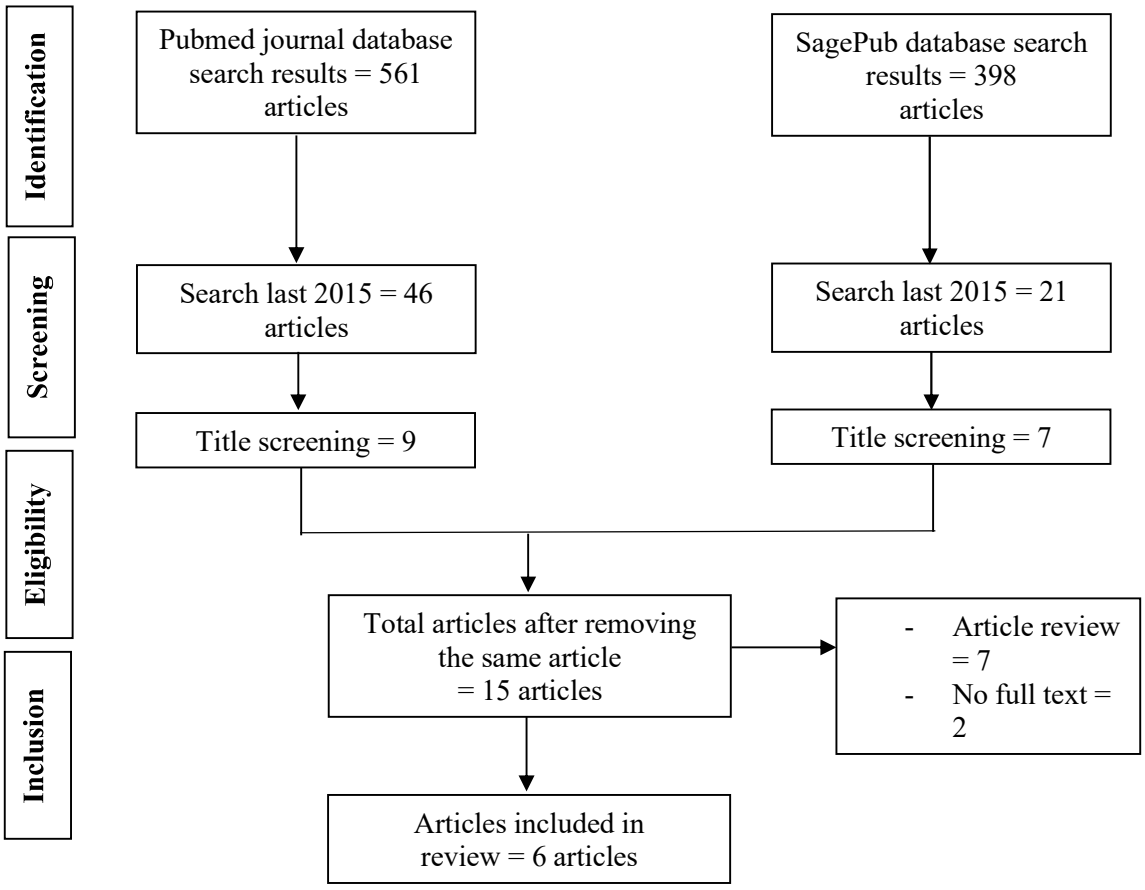

Figure 1. Article search flowchart

Following a comprehensive literature review, the researcher modified the inclusion and exclusion criteria for the study based on an analysis of the titles and abstracts of previously published research. In the process of conducting the systematic review, only those research endeavors that fulfilled all of the requisite criteria were included. The identification of a distinct research study is contingent upon several key factors, including but not limited to the title, authorship, date of publication, location of origin, research design, and variables under investigation.

The given information has been presented in a particular format for the purpose of your critical evaluation and contemplation. The authors conducted individual evaluations of a subset of research works identified in the titles and abstracts of the papers to determine the eligibility of the studies for inclusion. The comprehensive texts of the studies meeting the criteria for incorporation in the systematic review will subsequently undergo assessment to determine the papers that are suitable for definitive inclusion in the review.

RESULT

Gundersen,, et al (2015)[8] conducted a study with 1,215 Danish men. After adjusting for confounders, weekly marijuana use was associated with a 28% (95% confidence interval [CI] = -48 – [-1]) lower sperm concentration and a 29% (95% CI = -46 - [-1]) lower total sperm count. The combined use of marijuana and other recreational substances decreased sperm concentration by 52% (95% CI= -68 – [-27-) and total sperm count by 55% (95% CI = -71 - [-31]).

Thistle, et al (2017)[10] 26.6% of the weighted study group used marijuana, and 66.2% had used it. Multivariable analysis showed no difference in serum testosterone between ever users (adjusted mean = 3.69 ng/mL, 95% CI = 3.46-3.93) and never users (3.70 ng/mL, 3.45-3.98). However, serum testosterone decreased with time since last regular marijuana use ($p = 0.02$). When restricted to men aged 18–29 years, this relationship strengthened ($p < 0.01$) and serum testosterone was inversely associated with time since last use, indicating that recency of use, not duration or frequency, had the strongest relationship with testosterone levels.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Gundersen, 2015[8]	Denmark	Cross sectional	1,215 young Danish men	In the same range as cigarette users, people who smoked marijuana had greater levels of the male hormone testosterone. They findings are of public significance due to the prevalence of marijuana use, which has been hypothesized to be a factor in recent reports of poor sperm quality.
Thistle, 2017[10]	United State of America	Cross sectional	1,577 men	Men who had used weed more recently had more testosterone in their blood. Studies are needed to find out how much testosterone levels in the blood affect the link between marijuana use and male reproductive results.
Lotti, 2015[13]	Italy	Cross sectional	426 subjects seeking medical care for couple infertility	They report an apparent paradox in current smokers (CS): a decrease in SV volume despite an increase in testosterone levels. The fact that the difference between CS and non-smokers remained significant after adjusting for confounding variables such as testosterone suggests that smoking may negatively impact seminal vesicles (SV) volume in an independent manner. This is the first investigation to report ultrasound evidence of this nature. The impact of this new smoking-related change and limited semen volume on male fertility requires additional research.
Belladelli, 2022[14]	USA	Cross sectional	112 men	There were no consistent relationships found between cannabis usage and any of the characteristics of sperm in Asian-American men, according to our findings. Additional research in this area is required to investigate the racial and ethnic differences in factors affecting the quality of sperm and lifestyle factors.
Hehemman, 2021[15]	USA	Retrospective study	409 patients	Marijuana use is frequent among males who arrive for fertility examination. Marijuana use may have a negative influence on sperm quality, especially in terms of morphology and volume, although it may protect against aberrant sperm motility. Large-scale, prospective studies examining both the quality of the sperm and the fertility of this expanding population at risk are necessary.
Lee, 2020[16]	USA	Cross sectional	12 men	This is the first study that has successfully identified and quantified THC in human sperm, which demonstrates that THC is able to penetrate the blood-testis barrier in certain people. It was discovered that there was a moderate correlation between seminal THC and serum THC as well as THC metabolites.

In comparison to the rest of the sample, the CS had a lower ejaculate volume (P <0.01) and a higher prevalence of normal sperm morphology (P <0.02). When total testosterone was added as a covariate to the multivariate model, only the difference in ejaculate volume between CS and nonsmokers was confirmed (-0.61 ± 0.23 ml, P <0.01). Finally, even after controlling for confounders, CS had lower total SV volume before and after ejaculation (P = 0.02 and 0.01, respectively). When the reported number of cigarettes smoked or the number of pack-years were considered separately, similar results were observed.[13]

Other study with 112 men in they study, 51 had used cannabis at least once in their lifetime, 30 had used it at least once in the previous 12 months, and 26 had used it at least once in the previous 30 days. Cannabis usage in the previous 30 days was associated with lower sperm morphology (β: -0.45, p=0.025) and sperm motility (β: -1.64, p=0.016) in adjusted linear regression models. When stratified by subfertile semen quality (i.e., WHO criteria), no link between semen quality and cannabis use was found. Lower sperm morphology and motility are connected with recent cannabis use, but none of the other sperm metrics are.[14]

Other study showed current and former users were more likely to have aberrant sperm strict morphology than never-users (33.1% versus 50.7% and 53.4%, respectively; p < 0.001). However, sperm motility was more likely to be less than WHO reference values in never-users than current and past-users (38.3% versus 21.1% and 27.2%, respectively; p = 0.01). In multivariate logistic regression analyses, current use was associated with increased odds of abnormal strict morphology (odds ratio [OR] 2.15, 95% CI = 1.21-3.79) and semen volume less than WHO reference value (OR = 2.76, 95% CI = 1.19-6.42), while odds of less than WHO reference value sperm motility were reduced (OR = 0.47, 95% CI = 0.25-0.91).[15] Lee, et al (2020)[16] showed the median concentration, motility, and morphology of sperm were 75,5 million/mL, 69.5 percent, and 5.5 percent, respectively. THC-COOH was detected in the urine of all 12 participants, and at least one THC metabolite was present in the serum of 10 of the 12 participants. Two sperm samples lacked adequate volume for analysis. Two participants' sperm contained THC concentrations above the 0.50 ng/mL threshold for reporting. Serum concentrations of THC, 11-OH THC, and THC-COOH were moderately correlated with seminal THC (r = 0.66), 0.57, and 0.67, respectively. There was no correlation between seminal delta-9 THC and urinary cannabinoid levels or semen analysis parameters.

DISCUSSION

Cannabis is the abbreviated name for the plant Cannabis sativa. The term cannabis generally refers to the leaves, flowers and stems of the plant which are cut, dried and chopped and usually shaped into cigarettes. Other names for the cannabis plant are marijuana, grass, weed, pot, tea, Mary Jane and its products hemp, hashish, charas, bhang, cannabis, dagga and sinsemilla. This annual plant can reach two meters in height. Finger leaves with male and female flowers are on different plants. Cannabis only grows in tropical mountains with elevations above 1,000 meters above sea level.[4,5]

There are three types of cannabis namely Cannabis sativa, Cannabis indica, and Cannabis ruderalis. These three types of cannabis have different levels of tetrahydrocannabinol (THC). The THC content in Charas and hashish is around 7-8% in the range to 14%. Cannabis and Sinsemilla originate from the dry matter and are found in female shoots, where the average THC content is around 4-5% (rarely >7%). Low grade Bhang preparations are taken from the dried residue of plants with a THC content of about 1%. Hashish oil, a concentrated liquid from hashish distilleries, contains about 15-70% THC.[4,5] Gundersen *et al*.[8] conducted the first large cohort study on the effects of cannabis use in 2015 using a registry of 1,215 Danish men undergoing mandatory medical examination for military fitness.13 Self-reported marijuana consumers had 7% higher testosterone levels than nonusers. This was within the same range of elevated testosterone levels observed in the cohort of cigarette smokers. The authors cautioned that the elevated testosterone levels among marijuana consumers could not be distinguished from the effect of tobacco smoking alone.

Using marijuana was associated with an elevation in serum testosterone to the same level as that brought on by smoking cigarettes. There is no way for us to rule out the potential that the guys who used marijuana had generally unhealthy lifestyles and health behaviors, both of which could have an effect on the quality of their sperm and the hormone levels in their bodies. On the other hand, we accounted for recognized aspects of lifestyle.

In 2017, Thistle *et al*.[10] conducted a second significant cohort study.36 Using data from the 2011-2012 United States National Health and Nutrition Examination Survey, they gathered information on 1,577 American men with novel outcomes. Marijuana users and non-users had similar testosterone levels. However, serum testosterone levels decreased with time since the last marijuana use and regular marijuana use. Serum testosterone levels may be most correlated with recency. Cannabis' contradictory effects on testosterone require population-based studies.[17]

Sperm concentration, motility, and morphology were all at 75.5 million/mL, 69.5%, and 5.5%, respectively. Urinary THC-COOH was found in all 12 subjects, and at least one serum THC metabolite was found in 10 of the 12. Two sperm samples were too little to be examined. THC levels in the sperm of two of the remaining subjects were higher than the reporting standard of 0.50 ng/mL. Seminal THC levels were marginally linked with serum THC levels (r = 0.66), serum 11-OH THC levels (r = 0.57), and serum THC-COOH levels (r = 0.67). Seminal delta-9 THC levels were not connected to urine cannabis levels or the parameters of sperm analysis.[16]

Marijuana affects hormones and sperm quality through unknown molecular pathways. Δ9-tetrahydrocannabinol (THC), the active component of cannabis, binds to the human cannabinoid receptors CB1 and CB2.[18] When engaged, CB1 receptors in the testis, vas deferens, and human sperm cells decrease sperm motility and mitochondrial activity. Marijuana affects hormones, spermatogenesis, and mature sperm. In vitro investigations showed that THC hyperactivated spermatozoa and inactivated them like anandamide. THC may alter anandamide levels, affecting semen quality.[19,20]

Marijuana may impact semen quality through affecting the testis and hypophyseal hormones, which affect spermatogenesis. Marijuana lowers testosterone and LH. Previous studies ignored cigarette smoking and other potential factors. Unlike other studies, marijuana usage increased testosterone in this study. This increase could not be separated from tobacco smoking, which has been shown to enhance testosterone levels, making it impossible to distinguish the harmful effects of marijuana and cigarette smoking in this investigation.[21]

THC levels in sperm were found to have some correlation with levels of THC metabolites and blood THC, but not with urinary THC-COOH. We were unable to find an association between frequency of marijuana use or dosage and levels of THC in the seminal fluid of any of the participants since they all used marijuana at least four times per week. Both of the participants who had detectable levels of THC in their sperm had a regular marijuana use history ranging from 5–10 years.[16]

There were five additional chronic marijuana users whose sperm did not test positive for THC despite having the same amount of time spent using marijuana.The vast majority of individuals smoked marijuana at least eight hours before producing their ejaculated sample (just one person smoked it two hours earlier), and all participants refrained from ejaculating for forty-eight hours prior to their study visit.[16] Marijuana's effect on human gametes and fertilization is unknown. One prospective study of 221 patients undergoing assisted reproductive technology discovered that marijuana users had a 28% reduced fertility rate.[22]

CONCLUSION

The category of semen parameters is where we find the most compelling evidence that cannabis use can cause changes in male fertility. Cannabis may play a role in the reduction of sperm count and concentration, the induction of defects in sperm morphology, the reduction of sperm motility and viability, and the inhibition of capacitation and fertilizing capacity, according to research that has been conducted.

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