Association between Cannabis sativa consumption, sperm indices and sex hormones among smokers in Suleja, Niger State, Nigeria

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Abstract

Background
Cannabis sativa use may be common among men presenting for fertility evaluation, and it's harmful effects on fertility may have been under-estimated. The objective of this study was to determine the effect of Cannabis sativa smoking on semen indices and sex hormones in apparently healthy male smokers.
Materials and Methods
Sperm characteristics and serum follicle stimulating hormone(FSH), luteinizing hormone (LH), testosterone were determined in 80 apparently healthy male Cannabis sativa smokers, mean age 38.0±9.6 years (range 20-60 years) and 40 apparently healthy non-smokers of Cannabis sativa and cigarette males with mean age 37.45±9.8 (range 20-60 years) (controls). Semen analysis was done according to the World Health Organization criteria while FSH, LH and testosterone were determined by Enzyme linked Immunosorbent Assay Technique using reagent supplied by Finecare FIA System, Guangzhou, China. Data was compared using unpaired Student's t-test, and analysis of variance while regression analysis was used to associate sperm parameters and sex hormones with duration of Cannabis sativa usage.
Results and Conclusion
Sperm concentration, percentage normal motility, normal morphology were significantly lower ($p<0.001$) among Cannabis sativa smokers than non-smokers, while percent asthenozoospermia, non-motile, teratozoospermia, spermatozoa were significantly higher ($p<0.05$) among Cannabis sativa smokers than non-smokers. Serum LH and testosterone were significantly lower ($p<0.001$) among Cannabis sativa smokers than non-smokers while the level of serum FSH even though was lower, the difference was insignificant. The concentrations of sperm count ($p<0.001$), serum FSH ($p<0.03$), serum LH ($p<0.001$) and serum testosterone ($p<0.001$) decreased with increasing duration of Cannabis sativa smoking among study participants. Clinicians should be aware of the effects of Cannabis sativa use on male reproductive potentials and detail clinical and Cannabis sativa use may be assessed in men investigated for infertility.

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Introduction

The consumption of Cannabis sativa is popular among young men and women in all over the world including Nigeria. It was estimated that over 219 million individuals were estimated in 2017 to use marijuana worldwide (NIDA, 2020). Nigeria being Africa's most populous nation with an estimation of over a 200 million inhabitants seems to have clandestine love affair with Cannabis sativa (marijuana), despite being an illegal commodity. In Nigeria, it is estimated prevalence of users among adults was 10.8% (18.8% among men and 2.6% of women) and the average age of initiation of Cannabis use among the general population

was 19years (UNODC, 2018). Despite the clampdown on Cannabis sativa usage in Nigeria, the number of individuals who crave for it has not abated. This has led to some groups calling for the legalization of its use citing some medical values of Cannabis. In fact, some supermarkets sell Cannabis containing confectionary and cookies and attempts has been by officers of the Drug Law Enforcement Agency to clampdown on their distributions. Also Cannabis sativa weed grows luxuriously in some parts of Nigeria.

The neurological effects of Cannabis sativa are well known (Scott et al., 2018). Experimental studies have indicated harmful effects of Cannabis on reproduction (Grimaldi et al., 2009; 2013). There is paucity of information on the harmful effects of Cannabis smoking on reproduction among Nigerians. Some authors elsewhere have assessed the reproductive effects of Cannabis smoking in men (Kasman et al., 2018; Henschke, 2019; Nassan et al., 2019; Alagbonsi et al., 2019), but the results have not been consistent. The incidence of male infertility is high in Nigeria and the main reason(s) is not known. The contribution of modifiable lifestyle to high incidence of male infertility has been reported (Emokpae and Brown, 2021). Moreover, recent study has indicated that men who had ever smoked marijuana had significantly higher sperm concentration than those who had never smoked marijuana (Nissan et al., 2019). This is contrary to previous studies that implicated marijuana use to declining sperm quality among human subjects (Kasman et al., 2018; Henschke, 2019). Others have associated the adverse effects of Cannabis on male reproductive potentials with the presence of endocannabinnoid receptors on several parts of the sex organs. Several aspects of the endocannabinoid system have been shown to play a role in male reproductive function (Dunne, 2019). Reproduction in male requires a functional hypothalamic- pituitary gonadal axis to produce spermatozoa and sex steroids. The secretion of gonadotropin- releasing hormone (GnRH) leads to FSH and LH production in the testes and this maintains spermatogenesis in the Sertoli cells and testosterone production in the Leydig cells. It is of public health importance to ascertain the effect of marijuana consumption on male fertility and the information may help to shape the lifestyle of many and reduce the incidence of infertility caused by the consumption of Cannabis sativa. This study seeks to determine the effect of Cannabis sativa smoking on semen indices and sex hormones in apparently healthy males in Suleja, Nigeria.

Materials and Methods

This is a cross sectional study of 80 male smokers of Cannabis sativa who were recruited in Suleja Niger State. They were consecutively recruited from smokers' joints between June, and December, 2020. The study population was apparently healthy male Cannabis sativa smokers, mean age 38.0±9.6 years (range 20-60 years) residing in Suleja, Niger State. Also 40 apparently healthy non-smokers of Cannabis sativa and cigarette mean age 37.45±9.8 (range 20-60 years) were used as controls.

Ethical clearance for the study was obtained from the Ethics committee of Hospital Management Board, Minna, Niger State, with reference number STA/495/Vol/150 and issued on 5th June, 2020.

The sample size was determine using the sample size determination formula (N=Z2pq/d2) by Lwanga and Lemeshow, 1991 and using 5% prevalence of Cannabis sativa smokers in Suleja Niger state (Adamson et al., 2015). Therefore, 80 subjects were recruited for the study and 40 non-consumers of Cannabis sativa were used as controls.

Sample Collection and Analysis

Semen was collected in the morning after 3-5days of sexual abstinence by self or assisted masturbation without the use of condom in to wide-mouth universal container and submitted to the laboratory within one hour. On the same day, 5mL of venous blood was collected into a plain tube for sex hormones determination. Semen analysis was done after liquefaction using microscopic technique according to World Health Organization criteria while follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone were determined using Enzyme linked Immunosorbent assay technique and reagents supplied by Finecare diagnostic products, Dhaka, Bangladesh.

Quality control
Each Finecare TM LH Rapid quantitative test cartridge contains internal control that satisfies routine quality control requirement. This internal control was performed each time a test sample is done. The control test cartridge was inserted and read by Finecare TM FIA System. An invalid result from the internal control causes an error message on Finecare TM FIA System indicating that the test should be repeated.
Statistical Analysis

Data from the study are presented as mean±standard deviation (minimum-maximum, 95% confident interval). Statistical Package for Social Science SPSS version 20 was used for the data analysis while Duncan Multiple Range Test was used for the comparison and correlation studies. A p-value 0.05 was considered as statistically significant.

Results

The results from this study are presented in Tables 1-4. Table 1 shows the comparison of measured sperm characteristics among Cannabis sativa smokers and non-smokers. It indicates that sperm concentration, percentage normal motility, normal morphology were significantly lower ($p<0.001$) among Cannabis sativa smokers than non-smokers. Conversely, Percent asthenozoospermia, non-motile, teratozoospermia, spermatozoa with head defect, midpiece defects, principal piece concentration and excess residual cytoplasm concentration were significantly higher ($p<0.05$) among Cannabis sativa smokers than non-smokers.

Serum LH and testosterone were significantly lower ($p<0.001$) among Cannabis sativa smokers than non-smokers while the level of serum FSH even though was lower, was insignificant (table 2). Table 3 shows the comparison of sperm concentration and measured sex hormones among Cannabis sativa smokers based on duration of smoking. The concentrations of sperm count ($p<0.001$), serum FSH ($p<0.03$), serum LH ($p<0.001$) and serum testosterone ($p<0.001$) decreased with increasing duration of Cannabis sativa smoking among study participants. Similarly the duration of Cannabis sativa use correlated inversely with sperm count ($r=-0.457, p<0.001$), motility ($r=-0.341, p<0.001$), morphology ($r=-0.341, p<0.002$), FSH ($r=-0.255$, $p<0.023$), LH($r=-0.616, p<0.001$) and testosterone ($r=-0.639, p<0.001$).

Discussion

Cannabis sativa use may be common among men presenting for fertility evaluation, and may have a harmful effect on semen quality and sex hormone levels. Detail probing on lifestyle behaviour of subjects being evaluated may go a long way in assisting in diagnosis and management of the infertile subjects. Cannabis sativa is the most popular drug of abuse in Nigeria by about 18.8% men and 2.6% women and the average age of initiation of Cannabis sativa use among the general population was estimated to be 19years (UNODC, 2018). The situation is worrisome because the weed grows luxuriously in the some parts of the country. Only few studies on the effects of Cannabis sativa on reproductive health of smokers have been conducted in Nigeria. Studies elsewhere on the effects of Cannabis sativa use on reproduction have yielded conflicting results among men, with some of the studies using different species of the weeds which contain little quantity of the major active ingredient of Cannabis sativa (tetrahydrocannabinol). It will be of public health advantage to ascertain the effect of Cannabis sativa consumption on male fertility using the specie of the weed grown in Nigeria. Also, the information may help to shape the lifestyle of many users in order to avoid the harmful effects the hemp on male infertility.

In this study, sperm concentration, percentage normal motility, normal morphology were significantly lower ($p<0.001$) among Cannabis sativa smokers than non-smokers. Conversely, Percent asthenozoospermia, non-motile, teratozoospermia, spermatozoa with head defect, midpiece defects, principal piece concentration and excess residual cytoplasm concentration were significantly higher ($p<0.05$) among Cannabis sativa smokers than non-smokers. These findings were consistent with previous studies (Huang et al., 1978; Benerjee et al., 2011; Gundersen et al., 2015). In a study among young Danish men, it was reported that participants who belong to the highest frequency of Cannabis sativa use had 28% lower sperm concentration than non-smokers (Gundersen et al., 2015). Similarly, harmful effects at high

Table 1: Comparison of measured sperm parameters between smokers and non-smokers of Cannabis sativa (mean±SD)

PARAMETERS	CANNABIS SMOKERS (min-max) (n=80)	NON-CANNABIS SMOKERS (min-max) (n=40)	p-VALUE
Sperm concentration count ($x 10^6$/ml)	57.5±2.18 (14 - 96)	108±3.08 (60 - 141)	0.001
Total motility			
Normal (≥40%)	71.9± 1.83 (41- 92)	86.1± 1.37 (64-98)	0.001
Asthenozoospermia(1-39%)	13.22± 0.89 (2-36)	6.9±0.59 (2-18)	0.001
Non-motile (0%)	6.7± 0.5 (1-22)	4.3± 0.53 (1-15)	0.004
Sperm morphology			
Normal(>40%)	43.0±2.07 (9.8- 89.3)	101.1±3.57 (46.8-140.0)	0.001
Teratozoospermia(0-39%)	15.8±1.15 (3.5- 89.3)	6.8±0.657 (0.00- 17.8)	0.001
Types of sperm defect			
Head defect concentration Count	7.1±0.44 (0.5-23.8)	3.3±0.36 (0.0- 7.5)	0.001
Midpiece defect concentration count	1.6±0.16 (0.0- 6.5)	0.86±0.18 (0.0-3.8)	0.005
Principal piece concentration count	5.0±0.3 (0.9-12.8)	2.0±0.29 (0.0-8.8)	0.001
Excess residual cytoplasm concentration count	1.1±0.12 (0.0-5.2)	0.6±0.16 (0.0- 3.27)	0.026
Volume(ml)	2.58±0.035 (1.5-2.9)	2.64± 0.041 (1.7-3.2)	0.270

Table 2: Comparison of measured sex hormones between Cannabis sativa smokers and non-smokers (mean±SD)

SEX HORMONES	CANNABIS SMOKERS (MIN-MAX) (N=80)	NON-CANNABIS SMOKERS (MIN-MAX) (N=40)	p-VALUE
Follicle Stimulating Hormone (mIU/mL)	6.0±0.74 (4.2- 6.4)	7.8±0.21 (4.9-9.9)	0.085
Luteinizing hormone (mIU/mL)	3.9±0.18 (0.0-6.8)	6.5±0.15 (4.3-7.7)	0.001
Testosterone (ng/mL)	3.1±0.17 (0.1- 6.0)	5.4±0.33 (0.5- 7.3)	0.001

Table 3: Comparison of sperm concentration and measured sex hormones among Cannabis sativa smokers based on duration of smoking

PARAMETERS	1-5 YEARS (MIN-MAX) (N=24)	6-10 YEARS (MIN-MAX) (N=21)	11-15 YEARS (MIN-MAX) (N=18)	16-20 YEARS (MIN-MAX) (N=17)	p-VALUE
Sperm Concentration Count (cells/mL) x 10^6	82.9±2.79 (59-96)	56.8±2.68 (14 - 83)	49.2±2.87 (14 - 81)	44.6±5.49 (16- 58)	0.000
Follicle Stimulating Hormone (FSH) mIU/mL	10.9±4.43[a] (4.8- 64.0)	5.3±0.20[b] (0.0- 6.8)	4.9±0.19[b] (3.1 -6.4)	4.4±0.37[C] (3.0- 5.8)	0.031
luteinizing hormone (LH) mIU/mL	5.7±0.22[a] (4.5- 6.8)	4.2±0.22[b] (0.05.80)	3.0±0.34[c] (0.0- 5.6)	2.7±0.59[c] (0.0- 5.0)	0.000
Testosterone ng/mL	4.9±0.17[a] (3.5 - 6.0)	3.3±0.17[b] (0.5- 4.8)	2.5±0.27[b] (0.2 - 4.7)	1.1±0.54[c] (0.1 -3.3)	0.000

Table 4: Association between duration of Cannabis sativa use and sperm parameters and sex hormones

CORRELATION	r-VALUE	p-VALUE
Duration of smoking/Sperm concentrations	-0.457	0.001
Duration of smoking/Motility	-0.376	0.001
Duration of smoking/Morphology	-0.341	0.002
Duration of smoking/FSH concentration	-0.255	0.023
Duration of smoking/LH concentration	-0.616	0.001
Duration of smoking/Testosterone concentration	-0.639	0.001

levels of Cannabis sativa use were reported by earlier studies (El-Gothamy and El-Samahy, 1992; Vescovi et al., 1992). Humans who smoke Cannabis sativa at least 4days a week for 6months, 10 or more times per week, and others who smoke 5-9 Cannabis sativa cigarettes per week had similar significantly lower mean sperm concentrations (Kolodny et al., 1974). The finding from the latter study indicated that the effect of Cannabis on sperm quality and quantity is independent of frequency of smoking. Harmful effects of Cannabis sativa use on spermatogenesis have also been reported in experimental studies (du Plessis et al., 2015; Alagbonsi et al., 2016; Di Giacomo et al., 2016). Among rats exposed to 16puffs per day of Cannabis sativa, a decreased epididymal sperm concentration was reported compared to the recreational levels in humans for 75 days (Huang et al., 1978). Also, in male rats exposed to 3 to 6mg/kg Cannabis sativa derived bhang had a significant decreased concentration of sperm count (Benerjee et al., 2011). Similar observation was reported in dogs administered daily with 12.5mg/kg Cannabis sativa for 30days and a complete spermatogenesis arrest was observed (Dixit et al., 1977). The suggested mechanisms whereby Cannabis sativa harm spermatogenesis, hormonal secretion and reproduction are via its effect on cannabinoid receptors. It was reported that in cannabinoid receptor 1(CB-1) knock-out mice, exposure to exogenous Cannabis sativa did not have significant effect on hormone secretion, spermatogenesis and reproductive potential of the animals (Cacciola et al., 2008; 2013).

Our data revealed that Cannabis sativa use may have induced considerable morphological alterations in spermatozoa. This aligns with previous studies in animal models (Zimmerman et al., 1978; Huang et al., 1978). Male mice treated for 5 consecutive days with intraperitoneal injections of Cannabis sativa demonstrated significantly higher teratozoospermia (Zimmerman et al., 1978). Some of the abnormalities observed in that study were banana-shaped, amorphous, folded or hookless heads. Other authors reported detachment of sperm heads from tails in rats administered inhaled Cannabis sativa (Huang et al., 1978). In a large prospective study involving 1,700 subjects who had used Cannabis sativa in the last 3months prior to collection of semen specimen had abnormal sperm morphology (Payne et al., 2020).

Significantly lower percentage sperm motility was observed in the ejaculates of Cannabis sativa smokers compared with non-smokers in this study. Again this is consistent with earlier studies. Spermatotoxic effects of tetrahydrocannabinol (THC) was reported in spermatozoa incubated with THC at therapeutic

doses normally used to relieve pain or reduce spasticity in human for 3 hours as measured by computer assisted semen analysis (Whan et al., 2006). A decreased progressive motility was also observed therapeutic and recreational THC concentration was administered. Similarly, decreased sperm motility was observed among 16 apparently healthy chronic Cannabis sativa users after 4 weeks of high dose Cannabis sativa usage (Hembree, 1978). The decreased in sperm motility was attributed to harmful effect of Cannabis sativa via CB-1 receptor and mitochondrial activity (Barbonetti et al., 2010). The incubation of sperm with the CB-1 agonist met-AEA resulted in a significant reduction in mitochondrial transmembrane potential. But when the sperm cells were placed under glycolysis blockage, it caused the spermatozoa to switch to oxidative phosphorylation for energy metabolism, but the addition of met-AEA to the medium halted sperm motility. This finding indicated that the inhibitory effect of THC on CB-1 receptor on spermatozoa mitochondrial dysfunction. Other authors extended the above study by the addition of THC to semen and measured oxygen concentration as a marker of respiration and observed a decline of oxygen in a concentration dependent manner (Badawy et al., 2009).The above findings suggest that Cannabis sativa acts via the CB-1 receptor on the mitochondrial activity to significantly reduce sperm motility.

The finding from this study is not consistent with some other studies. Nassan et al.,(2019) reported that men who had ever smoked Cannabis sativa had higher sperm concentration and total sperm count, fewer sperm abnormalities below the World Health Organization reference range than men who had never smoked marijuana. Their findings suggest a direct pro-spermatogenic testicular effect and secondary compensation in FSH secretion. The reported association between Cannabis sativa smoking with sperm count was stronger among past smokers than current smokers. The longer the duration since last Cannabis sativa use, the higher the concentrations of sperm count (Nassan et al., 2019). Alagbonsi et al.,(2019) reported that the administration of Benin Republic hemp ethanol extract which has no cannabichromene and tetrahydrocannabinol but very small amount of cannabinol and higher quantity of fatty acids resulted in increased sperm count, morphology and viability but not motility. The authors suggested that Benin Republic Extract may have beneficial effects because of the deficiency in the gonadotoxic phytocannabinoids (Alagbonsi et al., 2019).

Studies have reported that over 500 different compounds are found in Cannabis sativa including about 100 varieties of cannanoids. Of all these, tetrahydrocannabinol (THC) is the most harmful or inducing compound in Cannabis sativa (Dunne, 2019). Interestingly, spermatozoa possess both CB-1 and CB-2 receptors and exposure to cannabinoid in-vivo may lead to alteration in the sperm count and motility.

It was observed from this study that the duration of Cannabis sativa use correlated inversely with sperm count ($r=-0.457, p<0.001$), motility ($r=-0.341, p<0.001$), morphology ($r=-0.341, p<0.002$), FSH ($r=-0.255$, $p<0.023$), LH($r=-0.616, p<0.001$) and testosterone ($r=-0.639, p<0.001$). This is an indication that the longer the duration of Cannabis sativa use the more it impacts negatively on sperm indices. Those authors who had reported that Cannabis sativa use is safe have not provided sufficient evidence to buttress their claim. Apart from the Benin Republic variant of Cannabis sativa which does not contain high concentration THC, the Nigeria variant of Cannabis sativa appears to be harmful to reproductive health. An author opined recently that until high-quality evidence of safety of Cannabis use is provided, healthcare givers would not succumb to the assumption that Cannabis is safe and cannot reassure users that consumption will not affect their fertility or their offspring. Hehemann et al.,(2021) reported that marijuana consumption had a mixed impact on sperm quality in reproductive-age male participants who presented for infertility evaluation. They concluded that the findings of deleterious effects on sperm indices are of critical importance especially in settings where the use of marijuana has been widely legalized.
It was observed from this study that Serum LH and testosterone were significantly lower ($p<0.001$) among Cannabis sativa smokers than non-smokers but the change in the level of serum FSH was insignificant. This is consistent with some previous studies in both animal and human studies (Wenger et al., 1987; Vescovi et al., 1992; Martin-Calderon et al., 1998). The lowering effect of Cannabis on LH level was

demonstrated by the use polyclonal antibodies against CB1 and CB2 to localize cells that express cannabinoid receptors (Wenger et al., 1999). It was revealed that those cells expressing CB-1 receptors secreted lower level of LH in the wild-type mice but no alteration was observed in LH levels in the CB1 knockout mice (Wenger et al., 2001). On the contrary this result did not align with that of Kolodny et al., (1974), who did not observe any significant change in plasma LH levels between men who smoked 5 to 9 Cannabis sativa per week and men who smoked 10 or more per week.

In this study an insignificant change in FSH level was observed which is consistent with that reported elsewhere (Cone et al.,1986). The authors failed to observe significant change in 4 healthy subjects with history of frequency Cannabis sativa use. A similar finding was reported among adult male rats injected with THC in the third cerebral ventricle (Wenger et al., 1987). A no alteration in serum FSH level was reported upon gonadotropin-releasing hormone stimulation in 10 male chronic Cannabis sativa users, who were given gonadotropin releasing hormone intravenously (Vescovi et al., 1992). Conversely, significantly lower FSH was however observed among 11 men who use 10 or more Cannabis cigarettes per week but not in those who use 5 to 9 Cannabis sativa per week, when compared with the normal controls (Kolodny et al., 1974).

Serum testosterone was significantly lower ($p<0.001$) among Cannabis sativa smokers than non-smokers and the concentration decreased with increasing duration of Cannabis sativa smoking. This finding does not entirely align with previous study (Thistle et al., 2017). The authors stated that there was no difference in serum testosterone levels between individuals who had used Cannabis sativa (adjusted mean = 3.69 ng/mL, 95% CI: 3.46, 3.93) and those who had never used Cannabis sativa (adjusted mean = 3.70 ng/mL, 95% CI: 3.45, 3.98) upon multivariable analysis. They however stated that serum testosterone was negatively associated with duration since last regular use of Cannabis sativa, a relationship that was strengthened among users age between 18-29years which is similar to the age range evaluated in our study. The authors also stated that recency of use, and not duration or frequency, had the strongest association with testosterone levels. In our study, only recent users and not those who had ever used were evaluated. Testosterone is the major hormone of adult males which plays principal roles in male reproductive development and has important behavioral manifestations. Cannabis sativa may be related to reproductive health due to alterations in circulating hormones via the actions of tetrahydrocannabinol the principal active component of Cannabis sativa (du Plessis et al., 2015). The finding from this study disagree with that reported in a large population study among young healthy men in Denmark and significantly higher testosterone concentrations were reported among marijuana users (Gundersen et al., 2015). Previous studies have reported inconsistent results of serum testosterone levels among users of Cannabis sativa. Whereas earlier study reported significantly lower levels of serum testosterone among users of Cannabis sativa (Kolodny et al., 1974), others observed significantly lower serum testosterone levels among marijuana users, and some have reported no significant difference in serum testosterone levels between users and non-users (Mendelson et al., 1974; Schaefer et al., 1975; Cushman, 1975;Coggins et al., 1976).
The mechanism by which Cannabis sativa modulate the concentrations of circulating testicular hormone level in the body may be via the cannabinoid receptors, CB1 and CB2, to THC. These receptors are present in the male reproductive sex organs, including the Leydig cells of the testis which produces testosterone in men. It is known that Leydig cell testosterone production declines with age, but testosterone production may also be affected by changes in the intracellular redox environment (Beattie et al., 2015; Thistle et al., 2017). The redox environment may lead to oxidative stress, damage to cellular components and decreased testosterone concentrations.

Conclusion

Semen characteristics, serum LH and testosterone were adversely affected by Cannabis sativa among apparently healthy smokers in this study. Sperm concentration, percentage normal motility, normal morphology were significantly lower while percent asthenozoospermia, non-motile, teratozoo-spermia, spermatozoa with head defect, midpiece defects, principal piece concentration

and excess residual cytoplasm concentration were significantly higher among Cannabis sativa smokers than non-smokers. Serum LH and testosterone were significantly lower among Cannabis sativa smokers than non-smokers while the level of serum FSH was not significantly changed. The concentrations of sperm count, serum FSH, serum LH and serum testosterone decreased with increasing duration of Cannabis sativa smoking. Clinicians should be aware of the effects of Cannabis sativa use on male reproductive potentials and detail clinical and lifestyle behaviour of males investigated for infertility may be assessed.

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