Cannabis is one of the most abused substances worldwide. The active component of cannabis is THC which has multiple effects in the endocrine system in both animal models and humans. The interest of scientific community in endocrine effects of cannabis is recent. We present a narrative review of endocrine effects of cannabis in different organ system along with description of possible mechanism both in the animal models and as well as in humans. We also highlight the need of research in this area especially in the population of South East Asia.

Keywords: Cannabis, THC, Endocrine system

BACKGROUND
Archeological and historical findings from China indicate that cannabis plant was cultivated for fibers since 4,000 B.C which might be the record of oldest use of cannabis. The great social importance of cannabis reached in the second half of the 20th century as there was explosion of its consumption for hedonistic and recreational purpose. The cannabis gained interest of the scientific community leading to growth in literature after Gaoni and Mechoulam identified the structure of $\Delta^9$ Tetrahydrocannabinol (THC) in 1964. This was then further intensified after the description and cloning of receptors specific for the cannabinoid in the nervous system and the isolation of an endogenous cannabinoid named anandamide subsequently.

On the basis of use in the past year it has been estimated that the prevalence of use of cannabis is as high as 4.9% and around 128 to 232 million people use cannabis worldwide. In India according to national survey the prevalence of cannabis use was 3% and ranked third common substance of abuse after alcohol and opioid to present in treatment setting. Cannabis is available in different names and form in our context; the dried leaves of cannabis plant known as “bhang”, female flowering tops known as “ganja” and the resinous form known as “charas”.

Apart from being a substance of abuse there are some clinical conditions where cannabis and its analogue could be of therapeutic help. Some of the potential conditions are spastic disorders, pain, emesis, loss of appetite, epilepsy, glaucoma, bronchial asthma and mood disorders.

The endocrine effects of cannabis have been a topic of interest from the last half of the century. It gained the light of research after Harmon and Aliapoulos provided the first description of marijuana-associated gynecomastia as an endocrine impact of cannabis use. Further investigation from the animal models has shown cannabis has widespread effects on multiple hormonal systems. Acute effects of cannabis is replicated in humans as well but the long term impact on the endocrine systems still remains unclear. This narrative review is aimed at looking into the endocrine effects of cannabis in different organ system along with description of possible mechanism both in the animal models and human.
**HPA axis:**
The main function of HPA axis is to maintain the homeostatic balance in response to stress. Somatic or psychogenic stresses initiate a neuroendocrine cascade resulting in the release of pituitary adrenocorticotropic hormone (ACTH) in the central nervous system which results in the synthesis and secretion of glucocorticoids from the adrenal cortex. The regulation of ACTH secretion is in turn regulated by corticotropin releasing hormone (CRH) which is synthesized in the hypothalamic parvocellular paraventricular nuclei. Apart from exerting effects on metabolic and reproductive processes and on the immune system the glucocorticoids secreted in response to ACTH provide a negative feedback for regulation of the hypothalamic-pituitary-adrenal axis by inhibiting CRH and ACTH release.

**Animal Studies:**
It has been seen in the animal model that an acute administration of Δ⁹ THC leads to increase in the glucocorticoid release within 30-60 min.\(^1\)
It was also found that administration of Δ⁹ THC leads to rapid increase in plasma levels of ACTH and corticosterone within 20 minutes in ovariectomized rats.\(^2\) This increase in ACTH and corticosterone release are most likely due to increase in CRF release and not a direct pituitary action. This hypothesis is supported by the studies done in in hypophysectomized male rats where the stimulation of corticosterone release by Δ⁹ THC does not occur.\(^3\) However, isolated pituitary slices or dispersed pituitary cells with either Δ⁹ THC or the CB agonist WIN55212-2 doesn’t have any effect on ACTH secretion, thus suggesting that there is no direct modulatory pathway of cannabinoids in ACTH release.\(^4\)

**Human Studies:**
In the human subjects, a similar effect of increased cortisol release is seen in response to the intravenous use of cannabis. Δ-9-THC when given intravenously; raised the plasma cortisol levels and this raise in levels was dose-dependent in both cannabis dependent individuals and controls, however, in case of frequent users, blunted response is seen as compared to healthy controls.\(^5\)\(^6\)\(^7\) In other studies it is seen that there is no change in the cortisol or ACTH level after the oral administration of cannabis in chronic users, new users or in the placebo group.\(^8\)\(^9\) There is some evidence that there is HPA axis hypo-activity at the time of morning awakening in adolescents who have early onset of cannabis use compared to late onset users. This finding might indicate an increased risk for early users of seeking stimulation to restore arousal levels by using substances which is an indirect way of saying that cannabis increases the cortisol level.\(^10\)

**Thyroid Hormone:**
The thyroid hormone has major contribution in the cellular metabolism. The secretion of thyroid hormone is regulated by Thyroid Stimulating Hormone (TSH) which ultimately is controlled by thyrotropin-releasing hormone (TRH). It is seen that there are functional CB1 cannabinoid receptors organized along the central and peripheral thyroid hormone axis.\(^11\)

**Animal Studies:**
The first report of action of cannabis in thyroid hormone was collected as early as 1965 where there was decrease of iodine accumulation in thyroid gland.\(^12\) The levels of thyroxin and TSH are significantly decreased for a short duration after acute administration of THC in rodents. Similarly, cannabis extract has shown to decrease the release of radioactive iodine from the thyroid. When exogenous TSH is administered, these effects are reversed suggesting a pituitary site of action. When THC is chronically administered the depressant effect of cannabinoids in thyroid is lost suggesting some amount of tolerance.\(^13\)\(^14\) Intraperitoneal injection of THC in rats also leads to significant decrease in TSH, T3 and T4 hormone, however, the pituitary or thyroid response to exogenous thyrotropin releasing hormone given exogenously is not affected by THC.\(^15\)\(^16\) The available evidence points towards the pituitary gland as only site of action for THC.

**Human Studies:**
Research on human have shown subtle lower levels of T4 in chronic cannabis users compared to other users and control subjects; but all of these values were within the standard range.\(^17\) In another study involving 39 cannabis dependent individual it was seen that the thyroid hormones was within the population range and it didn’t correlate with the level of THC, THC-OH or THC-COOH in serum.\(^18\) The action of cannabis on thyroid hormone in human is yet to be concluded.
**Growth Hormone:**
Apart from growth, the growth hormone helps in many aspects of metabolism and general well-being. It is secreted by anterior pituitary and is stimulated by growth hormone releasing hormone (GHRH) whereas, somatostatin inhibits its release.

**Animal Studies:**
In the animal model it is seen that the administration of Δ-9-THC lead to decrease in GH level acting as a stressor in the neuroendocrine system. The decrease in the growth hormone seems to be of differential nature on administration of different cannabinoids. Similarly a synthetic cannabinoid, HU-120, when administered in rats leads to dose dependent inhibition of the growth hormone.

**Human Studies:**
There are very few studies investigating the effect of cannabis on GH secretion in humans. In one of the studies by Benowitz et al, it was seen that that 4 days of oral THC in individuals with insulin-induced hypoglycemia lead to blunting of the normal GH response. A study done in four male revealed increase in growth hormone level after cannabis use. Use of cannabis during pregnancy leads to impaired fetal growth which might be an indirect evidence for the effect on growth hormone.

**Male reproductive hormones:**
Testosterone secreted by Leydig cells is under the control of LH and it has multiple actions including maintenance of secondary sex characters, whereas FSH acts on sertoli cells to regulate spermatogenesis.

**Animal Studies:**
In animal studies administration of THC leads to significant decrease in testosterone concentration as evidenced from the studies in rhesus monkey. There is decreased weight and decreased testosterone formation by rat testis. It was later hypothesized it may be the result of THC’s effects on the hypothalamo-hypophyseal area. THC reduces gonadotropin levels causing reduction in cytochrome P-450 of interstitial cell microsomal system which is needed for the synthesis testosterone. The effects on the testosterone level in animal studies seem to have tolerance which is explained on the basis of down regulation of CB1 receptors after multiple exposures. In animal models it is also seen that the CB1 receptors are also present in testes. Not only has this, cannabis (THC) also inhibited the binding of dihydrotestosterone to the androgen receptors. Thus, these evidences conclude that the action of THC is not only at the central level but also at the testicular level.

**Female Reproductive System:**
LH and FSH secreted from anterior pituitary control the female reproductive system. At the end of menstruation, the level of progesterone and estrogen wanes leading to increase of FSH level which in turn stimulates growth and development of ovarian follicle. The rising estrogen after that has negative feedback on both LH and FSH. Peak estrogen causes LH
surge and ovulation subsequently. The corpus luteum produces estrogen and progesterone under the influence of LH. The discussion about the effects of cannabis in the reproductive system and hormone production was a matter of great interest in 70s and 80s as evidenced by the literature.

**Animal Studies:**
Administration of THC have led to decrease in progesterone level in female rat during the luteal phase of estrous cycle.48 49 Many studies demonstrated that there is decrease in the secretion of LH and FSH acutely after the administration of THC and would delay the ovulation in female rats.50 51 52 Even the low dose of THC delays the onset of puberty and the post pubertal reproductive functions in female rats and this effect of THC seems to be of long-term and irreversible nature.53 The same finding was seen even in the ovariecctomized rats suggesting the central endocrine mechanism.54 Apart from this the studies in the rhesus monkey have also shown decrease in the level of LH and FSH after the administration of single dose of THC and the effect seems to be of central action.55 There is evidence of presence of CB1 receptors in ovary as well.56 The crude marijuana extract, condensed marijuana smoke competes with estradiol for binding to the estrogen receptor, but pure delta 9-tetrahydrocannabinol doesn’t not interact with the estrogen receptor. Among many common cannabinoids tested, only cannabidiol had some binding with the estrogen receptor.57 These few findings lead a credence to the concept of some peripheral action of cannabis at ovary. It has also been said that the female of many species are more sensitive to the effects of THC than male.58 However, tolerance develops in the disruptive effect of THC in estrous cycle in female primates.59 60

**Human Studies:**
The effect of THC in human female population is not as clear as in the animal model. A single dose of cannabis (1g) induces a 30% suppression in LH level during luteal phase.61 A study done in 16 female have shown small but statistically significant decrement in LH level, however, all LH levels were within the normal range for healthy adult women and biologically insignificant. In the same study there was no evidence of any dose-related suppression of ovulation or change of luteal phase function in women with heavy, moderate or occasional marijuana smokers. This indicate that smoking cannabis at the dose levels observed for 21 days doesn’t disturb the menstrual cycle in healthy adult women.62 Another study has shown increase in LH level as well.63 Yet another study by the same author has shown no change in LH level after smoking of cannabis in menopausal women.64 However, the direct action of cannabis in the ovary haven’t been demonstrated.

**Reproduction:**

**Animal Studies:**
Postnatal mortality is increased and neonatal weight decreased at 21 days after treatment with cannabis in female rats.65 TLC administration in prepubertal rats when given in small doses too have long term irreversible alteration in reproductive function.66 Abortion and still birth in rats and rhesus monkey was also seen in few cases when THC was administered in early pregnancy.67 68 Apart from that it also has teratogenic and embryocidal property in animals.68 At a genetic level sex steroids control the expression of the CB1 gene in the anterior pituitary gland of both male and female rats. So, we can speculate that a regulatory mechanism is operational in the reproductive organ.69

**Human Studies:**
In human studies it is seen that cannabis use has been correlated with low birth weight and prematurity.70 71 There is a negative impact of cannabis intake in the mid-gestational fetal growth after adjusting for maternal use of other substance.72 Further, in chronic cannabis user dose dependent lower gestational age is seen.73 There is an emerging body of evidence indicating that marijuana may cause problems with neurological development, resulting in hyperactivity, and poor cognitive function.74 Current understanding suggests that endogenous and exogenous cannabinoids may be critical in the areas of embryo implantation and miscarriage. It is clear that cannabis-based substances and compounds that might interact with endocannabinoid synthesis are contraindicated during pregnancy.75 A meta-analysis is planned to assess the effects of prenatal exposure to cannabis on pregnancy outcomes; after which a clear evidence can be presented in this font.76
Erectile/Sexual Function:
Cannabis is regarded as one of the important causes of erectile dysfunction. However, the recent studies have failed to find any association between frequency of cannabis use and problems in erection as evidenced in 8656 Australians where 754 had cannabis use and also from a population based study from Morocco. Similar findings were seen in the study by Johnson and colleagues where there was no association between lifetime cannabis use and lack of erection in men or lack of arousal for women. However, there was some relation between cannabis use and inhibited orgasm; a history of cannabis use was associated with a reporting of an inability to orgasm Other studies too support that high doses of cannabis might lead to “inability to perform” and that this may be related to changes in plasma testosterone level; modest doses lead to increase in plasma testosterone level but high doses lower testosterone below baseline. It is also seen that cannabis use being associated with an increased duration of intercourse and decreased number of orgasms. A study by Aversa et al. has shown that endothelial dysfunction as a result of chronic cannabis use might be the marker of vasculogenic erectile dysfunction. So, overall speaking there is some effect of cannabis in male sexual function but the studies are limited in both quality and quantity and the results are conflicting and contradictory.

Prolactin:
Prolactin is initially regarded as anterior pituitary hormone is also synthesized within the central nervous system, the immune system, the uterus and its associated tissues of conception, and even the mammary gland itself has a major function of stimulating milk production and maintaining lactation in human after child birth. It also controls the variety of behaviors and even the homeostasis. It is inhibited by dopamine. Animal Studies: The studies in animal models have demonstrated acute reduction in prolactin level after administration of THC. The decrease in the prolactin level are not consistent in all studies. This decrease seem to be dependent on the stage of ovulatory cycle. Apart from this, in one of the studies, it was seen that there was biphasic response showing initial increment in the prolactin level followed by significant decrease after administration of THC. This study concluded a direct effect on hypothalamic structures having cannabinoid receptors small in quantity but very active. More recently it has been shown that the effect on prolactin is due to direct action on CNS rather than on the pituitary gland as evidenced by the failure of THC to alter tonic PRL secretion in hypophysectomized/pituitary-autografted rats or PRL release from pituitary tissue in vitro. However, some evidence of no change in the prolactin level with administration of THC are also present. Human Studies: In human female it has been seen the prolactin level decreases acutely on administration of THC but in the luteal phase of menstrual cycle as evidenced in the study of 16 healthy females. But both acute and chronic smoking of cannabis in male had no effect in the prolactin level when compared to healthy male. Same findings have been replicated in female as well. The frequent users have lower baseline plasma prolactin levels relative to healthy controls as evidenced from the pooled data in which intravenous Δ9-THC was given in 36 healthy controls and 40 frequent cannabis users. One of the large studies in both male and female have shown no significant change in prolactin level.

Obesity/Weight Gain and glucose metabolism:
Animal model: The review of studies published between 1965 to 1975 by Abel have found that, out of 25 experiments only three studies showed increase in the weight after cannabis intake. However, after the discovery of cannabinoid receptors, most research has shown hyperphagic action of THC. This hyperphagic action of THC seems to be mediated by CB1 cannabinoid receptors as evidenced by the THC induced hyperphagic feeding being reversed by the selective CB1 antagonist rimonabant, but not by the CB2-selective antagonist SR144258. Anandamide and 2AG when administered into the shell of nucleus accumbens and hypothalamic nuclei leads to increased appetite in animal models.
suggesting the effect on the eating motivation\textsuperscript{99} \textsuperscript{100}. Hence, it can be said that use of cannabis in animals lead to obesity as evidenced from the hyperphagia. Colombo et al. (1998) have shown that that daily administration of rimonabant, an inverse agonist of CB1 receptor, suppresses intake of lab chow and induces weight loss in rats in persistent manner.\textsuperscript{101} Vickers et al. (2003) also demonstrated that oral treatment with rimonabant decreases food intake along with gain in body weight (both in lean and genetically obese Zucker (fa/fa rats) in dose-dependent manner. Reduction in body weight is more in case of obese rats.\textsuperscript{102} This an indirect evidence to the relationship of cannabis and feeding as well as weight gain. Similarly, it is a known fact that the cannabinoid receptors and their endocannabinoid ligands play a significant role in regulating glucose hemostasis, appetite, insulin sensitivity and pancreatic \(\beta\)-cell function.\textsuperscript{14} Cannabis intake in different dosage leads to increase in the blood glucose level and decrease in the glucose tolerance in animal models.\textsuperscript{103}

**Human Studies:**

The first systematic study published as early as 1976 by Greenberg et al. has shown that there is increase in both energy intake and weight after the intake of cannabis. It was also shown that body weight continued to increase even after energy intake was stabilized.\textsuperscript{104} In other studies too it was seen that cannabis increased total food intake. The food components that had significant increments were sweet solid snack items such as candy bars, cookies and cakes.\textsuperscript{105} The probable mechanism of increased food intake is CB1 receptor mediated as the CB1 cannabinoid receptor antagonist SR141716 (rimonabant) reduces food intake after systemic administration in animals and the same molecule also leads to the reversal of most of the psychological and physiological effects of cannabis.\textsuperscript{107} This has also been tested in humans in the conditions involving wasting and severe appetite loss like cancer cachexia and AIDS where the treatment with THC (synthetic form, Dronabinol) leads to improvement in both ratings of appetite and actual consumption level of food. However, the trials are hampered by the serious nature of illness.\textsuperscript{108} In a recent study by Strat and Le Foll where the authors took the data from 2 representative epidemiologic studies of US adults aged 18 years or older namely the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; 2001–2002) and the National Comorbidity Survey–Replication (NCS-R; 2001–2003), and estimated the prevalence of obesity as a result of cannabis use. They found that prevalence of obesity to be lower in cannabis users than in nonusers.\textsuperscript{109} This study was in contrast to the other studies of the similar nature which had shown frequent use of cannabis to be associated with obesity in girls taking nationally representative sample (\(n=7885\)).\textsuperscript{110} Another study showed that use of cannabis is associated with a higher intake of calories but is not associated with a higher BMI suggesting no role in obesity.\textsuperscript{111} Thus, the role of cannabis as an associated factor in obesity is still controversial. It is a known fact that the cannabinoid receptors and their endocannabinoid ligands play a significant role in regulating glucose hemostasis, appetite, insulin sensitivity and pancreatic \(\beta\)-cell function.\textsuperscript{14} It is seen that in healthy human volunteers, the acute treatment with cannabis leads to impaired intolerance.\textsuperscript{112} In a study with a sample of 4657, in multivariable adjusted models it was seen that current marijuana use was associated with 16\% lower fasting insulin levels and 17\% lower homeostasis model assessment of insulin resistance. There was also significant association marijuana use and smaller waist circumferences. This result is in contrast to the other physiological effects like weight gain and impaired glucose tolerance. However, the authors do not comment on the mechanism.\textsuperscript{114} In another study of 30 cases and 30 controls it was seen that chronic cannabis smoking had association with visceral adiposity and insulin resistance of adipose tissue but no association was seen with insulin insensitivity, impaired pancreatic \(\beta\) cell function or glucose intolerance.\textsuperscript{115} The CARDIA, 15 years of longitudinal study too didn’t find any significant change in the glucose level in the patients who took cannabis.\textsuperscript{111} These finding has also been supported by other studies that found the lower prevalence of diabetes in the cannabis users. The authors have postulated that there could be a role of anti-inflammatory properties of cannabinoids of marijuana that modify inflammation probably through the
inhibitory actions on prostaglandins and COX-2.\textsuperscript{116}

**CONCLUSION:**
Cannabis as well as its active component THC has multiple effects in the endocrine system in both animal models as well as in humans. Most of the effect can be summarized as depressant of almost all hormones; however, some inconspicuous reports have been seen. Like other effects the tolerance has been seen to develop with chronic administration. Variation in study designs, stage of human development, and clear cut lack of a definite cohort has produced inconsistent results in human population. The clinical consequences and a long-term effect seem to be subtle. The research from South East Asia is limited in this regard and further studies are warranted from this part of the world.

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**CONFLICT OF INTEREST:** None

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