

Experimental Study on Sub-acute Testicular Toxicity of AMB-FUBINACA in Adult Male Albino Rats

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Abstract

Background: AMB-FUBINACA abuse was confirmed in case reports of a mass intoxication in the United States. Also it was reported that in New Zealand, there were at least 20 deaths related to the use of MMB-FUBINACA. **Aim of the Work:** To detect the toxic effect of synthetic cannabinoid (AMB-FUBINACA) with different doses on the testis of adult male albino rats histopathologically and Biochemically. **Methods:** the present work was conducted on 40 sexually mature male albino rats. Rats were divided into 5 groups 8 rats each as follow Group I: Negative control group, Group II: Positive control group where animals received ethanol 5%, Group III: Rats treated with AMB-FUBINACA at dose of 2.5 mg/kg dissolved in ethanol 5%, Group IV: Rats treated with AMB-FUBINACA at dose of 5 mg/kg dissolved in ethanol 5% and Group V: Rats treated with AMB-FUBINACA at dose of 10 mg/kg dissolved in ethanol 5% given by intraperitoneal injection for 4 weeks. **Results:** a significant decrease of testosterone level in AMB-FUBINACA treated groups compared to the control groups and degenerative changes in seminiferous tubules was also observed in treated groups. **Conclusion:** administration of AMB-FUBINACA for 4weeks was associated with toxic effects in testis

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Key words

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Introduction

AMB-FUBINACA is (methyl (2S)-2-({1-[(4-fluorophenyl)methyl]-1H-indazole-3-carbonyl} amino) - 3 - methyl butanoate) and it is a synthetic cannabinoid. It is also referred as MMB-FUBINACA and FUB-AMB (WHO, 2019).

On July 3, 2014 an ester analogue of AB-FUBINACA, (AMB-FUBINACA) was discovered in a product called “Train Wreck 2” in Louisiana and was immediately prohibited through emergency rule by the State of Louisiana. The synthetic cannabinoid AB-FUBINACA was developed by Pfizer and described as analgesic to patients in 2009 (Adams et al., 2017).

It was reported that in New Zealand, there were at least 20 deaths related to the use of AMB-FUBINACA as well as numerous hospitalizations. In the United States; the amounts of AMB-FUBINACA in confiscated products in New Zealand were found to be 2 to 25 times greater than those reported in the incident in the United States (WHO, 2019).

Four years later, the official spokesman for the Ministry of Health in Egypt announced that the five common types of synthetic cannabinoids(SCs) present in Strox have been added to the Egyptian list of highly addictive and dangerous narcotics (act No. 440 of 2018 under Law 182/1960, that prohibits the possession or trafficking of narcotics). These SCs are; AB-FUBINACA, AMB-FUBINACA, 5F-ADB, AB-CHMINACA, and XLR-11 (Zahraa and Hasnaa, 2020).

AMB-FUBINACA like other synthetic cannabinoids consumed by smoking. Products

containing synthetic cannabinoids include ready-to-smoke herbal mixtures (‘incense blends’) and liquids for e-cigarettes (‘cannabinoid liquids’). Also they are included in highly pure substances in powder form (‘research chemicals’) (Franz et al., 2020).

AMB-FUBINACA like other synthetic cannabinoids act by binding to cannabinoid receptors (CBRs). Cannabinoid receptors 1 (CBRs1) are found in central and peripheral nervous system, bone, heart, liver, lungs, vascular endothelium and reproductive system. Cannabinoid receptors 2 (CBRs2) are primarily found in the immune system and also in the central nervous system (Bilici, 2014; Wiley et al., 2014).

The most predominant symptom in a cluster of confirmed FUB-AMB overdose cases in New York City in July 2016 was severe CNS depression, resulting in slowed behavior and speech that was labeled as “zombielike” by the popular press (WHO, 2019).

Toxic effects reported from these incidents involving FUB-AMB have included: Nausea, persistent vomiting, agitation, altered mental status, seizures, convulsions, loss of consciousness, and cardiotoxicity (Rule and Authority, 2018)

It has been known that synthetic cannabinoids (SCs) are agonists of endocannabinoid system (ECS), ECS agonists like marijuana acts via releasing of cannabinoid compounds that compete with endocannabinoids for binding on the cannabinoid. Endocannabinoids and CBRs exist in Sertoli cells, Leydig cells and spermatozoa which thought to play a

role on hypothalamus–pituitary–gonadal (HPG) axis that CBRs1 receptors are expressed in the anterior pituitary, SCB-receptor agonists for CBRs may play a role in disturbing HPG axis which can affect Gonadotropin Releasing Hormone (GnRH) release that stimulates the release of Luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary, which reduce LH secretion and that affect Leydig cells which cause decrease in testosterone hormone level (Martinotti et al., 2017; Mutluay et al., 2019).

So this study was done to determine the effect of exposure to AMB-FUBINACA on rat testis.

Materials and Methods

Animals

The present work was conducted on 40 sexually mature male albino rats. Animals were purchased from animal house, faculty of medicine Assiut University. They were about 10 weeks old, their weight ranged from (200:220) gm at the beginning of the experiment.

The animals were housed in stainless metal cages in a ventilated animal room under ambient temperature, 21 ± 3 °C. They were fed with standard pellet feed and water. They were acclimatized to the laboratory condition for one week before starting the treatment protocol. The protocol of ethics and husbandry conditions of animal research were considered according to the guide of care and use of laboratory animals approved by the Ethical Committee of Faculty of Medicine, Sohag University.

The duration of sub-acute toxicity is 14-28 days (Denny and Stewart, 2017).

The doses of AMB-FUBINACA treated groups were selected as Group III received the lowest dose 2.5mg/kg which was confirmed to occupy all cannabinoid receptors with no or little clinical effect according to (Wilson et al., 2019; Trexler et al., 2020), Group V received the highest dose 10 mg/kg which cause confirmed toxicity and tolerated by animals according to (Mousa et al., 2021; Wilson et al., 2019) and Group IV received dose 5mg/kg midway between the lowest and the highest dose according to (Hsin-Hung Chen et al., 2016).

Chemicals

Synthetic cannabinoid (AMB-FUBINACA) powder was purchased from the Cayman chemical company.

1. Solvents and vehicle substance (ethanol) was purchased from Sigma Aldrich company.
2. Kits for estimation of total testosterone level were purchased from Biocheck, inc. Company.
3. Hematoxyline and Eosin (H&E) stains were purchased from ALPHACHEMIKA Company.

Animal groups

The AMB-FUBINACA was in the form of powder. The powder of AMB-FUBINACA was dissolved by 100% ethanol and saline solution (1:19) to give 5% ethanol solution (Safont et al., 2022) and rats were divided into 5 groups 8 rats each as follow:

Group I: Negative control group, where animals received normal diet only.

Group II: Positive control group where animals received ethanol 5% at a dose of 625 μ l /rat/ day by intraperitoneal injection for 4 weeks.

Group III: Rats treated with AMB-FUBINACA at dose of 2.5 mg/kg dissolved in ethanol 5% at a dose of 625 μ l /rat/ day by intraperitoneal injection for 4 weeks.

Group IV: Rats treated with AMB-FUBINACA at dose of 5 mg/kg dissolved in ethanol 5% at a dose of 625 μ l /rat/ day by intraperitoneal injection for 4 weeks.

Group V: Rats treated with AMB-FUBINACA at dose of 10 mg/kg dissolved in ethanol 5% at a dose of 625 μ l /rat/ day by intraperitoneal injection for 4 weeks.

Collection of blood samples

Six (6) ml of blood were drawn from each rat cervical blood vessels by cervical decapitation under anesthesia by ether into clean dry tubes. Blood samples then centrifuged [4000 Revolutions per minute (Rpm) for 5 minutes]. The serum was separated and transferred to sterile screw capped vials for measurement of Testosterone hormone level.

Histopathological examination

The dissected testes of rats were fixed in Bouin's solution immediately after animals were sacrificed. After fixation the testicular specimens, the specimens were processed and paraffin embedded. Sections were done at 5 microns thickness and stained by (H&E) stain. Sections of testis were examined then photographed as required (Bancroft and Marilyn, 2008).

Statistical Analysis

Data was recorded using Microsoft Excel program (Microsoft Co, USA) and presented in the form of tables and graphs. Statistical Package for the Social Science (SPSS) program (version 22) was used for data analysis. As our data is continuous nonparametric variables were presented as median (25th percentile, 75th percentile) and compared using Kruskal-Wallis test. Statistical significance was considered when two-tailed P value < 0.05 . A post-hoc test was used whenever a P value is significant to investigate the position and magnitude of significance among study groups.

Results

A- Testosterone level:-

The present study showed that there was non-significant changes in median values of testosterone hormone level between the negative control group (group I) on one side and the positive control (group II) as shown in table (1).

The median values of testosterone hormone level in AMB-FUBINACA treated groups (groups III, IV and V) showed a significant decrease as compared to negative control group (group I) and positive control group (group II) as shown in table (1).

There were non-significant changes in median values of testosterone hormone level between AMB-FUBINACA treated groups (group III, IV and V) as shown in table (1).

Table (1): Statistical analysis of the median values of Testosterone (ng/ml) level in all groups and comparing them using Kruskal-Wallis test:

Group	Group I	Group II	Group III	Group IV	Group V
Median (25 th percentile, 75 th percentile)	2.22 (1.84-0.31)	2.31 (1.61-3.11)	0.94 (0.47-1.08)	0.835 (0.332-1.075)	0.43 (0.282-0.500)
Group I: p-value	—	1.000NS	0.030*	0.026*	0.012*
Group II: p-value	1.000NS	—	0.049*	0.048*	0.021*
Group III: p-value	0.030*	0.049*	—	1.000 NS	0.068NS
Group IV: p-value	0.026*	0.048*	1.000 NS	—	0.302NS
Group V: p-value	0.012*	0.021*	0.068NS	0.302NS	—

P values are shown as: *P < 0.05 (significant), **P < 0.01 (highly significant), NS: Non significant, ***P < 0.001 (very highly significant), SD: Standard deviation

B- Histopathological findings of testis:-as shown in figure (1)

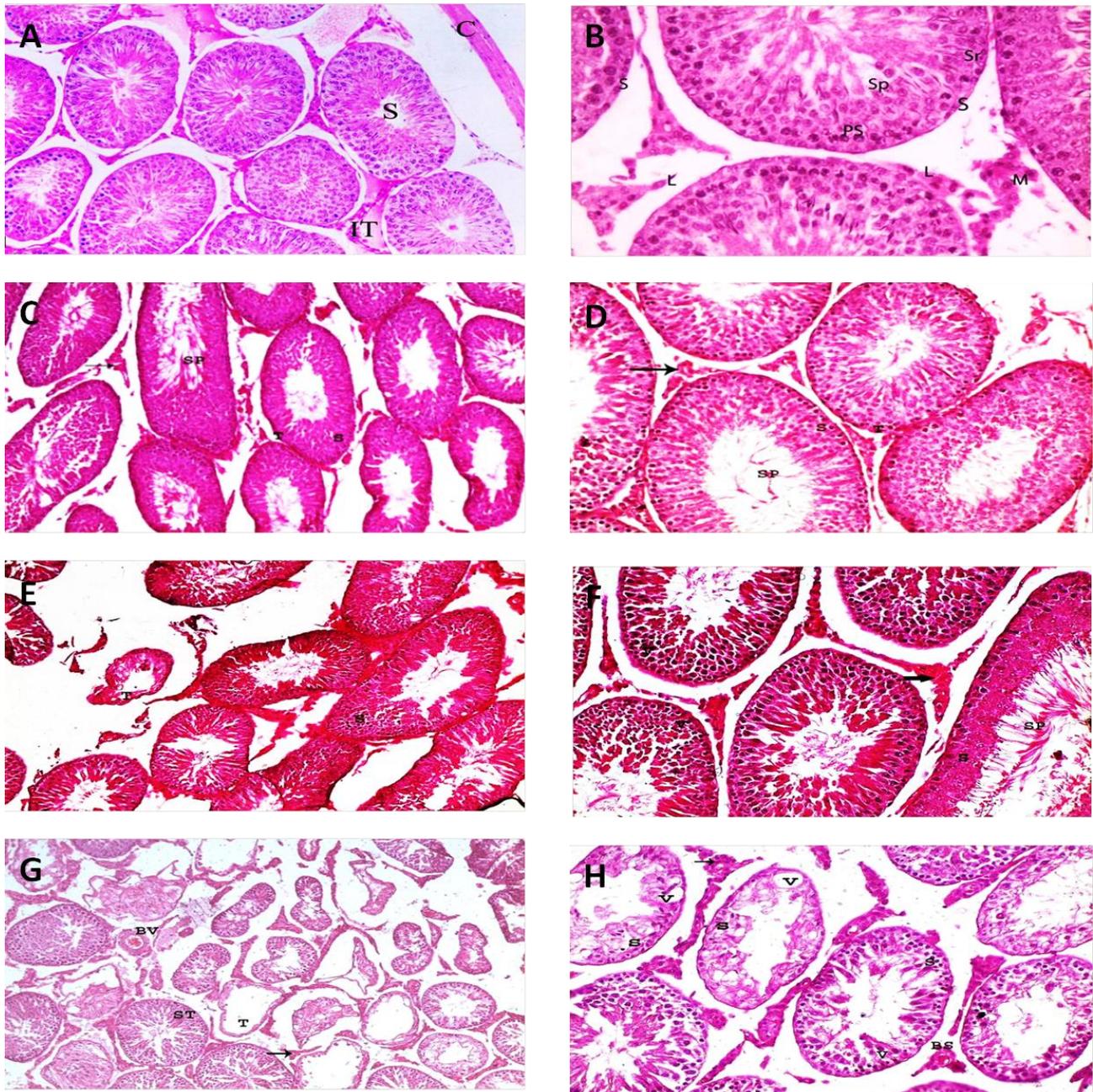


Fig. (1): Photomicrographs of cross section in rat testis of:

(A) The control group showing seminiferous tubules with regular outlines (S) and there are lumina full of sperms. Interstitial tissue (IT) Note: capsule of the testis (C) H&E X 200.

(B): A magnified part of the previous section showing seminiferous tubules lined with spermatogenic cells as follow spermatogonia (S), primary spermatocytes (ps), rounded spermatid (sp) and sperms. Interstitial tissue showing leydig cells (L) and macrophages (M). Note sertoli cells (Sr) H&E stain X 400.

(C): AMB –FUBINACA treated group (III) showing closely packed tubules (T) with many layers of germ cells(S) up to spermatids. The interstitial tissue appears more or less similar to the control group (SP) H&E stain X 200.

(D): A magnified part of the previous section in the testis of the AMB –FUBINACA treated group (III) showing closely packed tubules (T) with many layers of germ cells up to sperms (Sp) ,The interstitial tissue appear more or less similar to the control group (arrow) H&E stain X 400.

(E): AMB –FUBINACA treated group (IV) showing most of the tubules (arrow) have many layers of germ cells up to spermatids(S). Few tubules appear shrunken irregular with few germ cells (T) H&E stain X 200.

(F): A magnified part of previous section in the testis of AMB–FUBINACA treated group (IV) showing most of the tubules(S) have many layers of germ cells up to spermatids (sp). Few tubules appeared shrunken irregular with few germ cells (F). The interstitial tissue (arrow) showing congestion of blood vessels H&E stain X 400.

(G): AMB –FUBINACA treated group (V) showing many tubules have few germ cells with irregular outlines (T).Other tubules have numerous spermatogenic cells (ST). The interstitial tissue (arrow) shows congestion of blood vessels (BV) H&E stain X 200.

(H) A magnified part of the previous section showing many tubules (S) have few degenerated germ cells with vacuoles (V), congestion blood vessels(BS) and some degenerated leydig cell (arrow) H & EstainX400.

Discussion

A-Testosterone hormone level :

AMB-FUBINACA is a synthetic cannabinoid that is also referred to as MMB-FUBINACA and FUB-AMB. AMB-FUBINACA is available as a powder, in solution or sprayed on plant material that mimics the appearance of cannabis. It is sold as herbal incense or branded products under a variety of different names (WHO, 2019).

The study was performed to evaluate the sub-acute toxicity of AMB-FUBINACA on testis of adult male albino rats. Biochemical and histological changes were investigated for assessment of its toxicity.

Testicles as a part of the male reproductive system are responsible for production and nutrition of spermatozoa on puberty and synthesis of testosterone that is the main male sex hormone. In each lobule of testis, there are seminiferous tubules where sperm are produced and stroma-containing leydig cells which are responsible for production of testosterone (Abdelkader et al., 2021).

In the current study there was a statistically significant difference between testosterone levels of AMB-FUBINACA treated groups and control groups, but there was no statistically significant difference between testosterone level of AMB-FUBINACA treated groups.

The present results go on harmony with Mutluay et al. (2019) who found a statistically significant decrease in the mean of testosterone level between mice treated with synthetic cannabinoids (JWH-018) with dose 0.3mg/kg for 9 days and control groups.

Also Mandal and Das (2010) reported decrease in mean values of testosterone hormone levels of mice treated by intraperitoneal injection of cannabis extract for 20, 30 and 40 days.

Synthetic cannabinoids affect testosterone level by binding to Cannabinoid receptors which present in Sertoli cells, spermatozoa and Leydig cell which is responsible for testosterone hormone production as reported by Mutluay et al. (2019).

B-Histopathological results of Testis:

The synthetic cannabinoids (SCs) marked as ‘K2,’ ‘Spice,’ ‘Black Mamba,’ ‘Synthetic Marijuana,’ ‘Dream,’ and ‘Mr. Nice Guy’ especially used by adolescents and young adults have serious short- and long-term effects on male reproduction system (Lewis et al. 2012).

The current study showed tubular degeneration with congestion of interstitial blood vessels with degeneration in some leydig cells with varying degrees in different doses compared to control groups. These observations go in hand with biochemical changes of the testosterone level in the study.

The present results go on harmony with Mutluay et al. (2019) who reported that histopathological changes of the testis where in the form of predominantly vacuolar degeneration, disorganized epithelium, exfoliated germ cells and multi- nucleated germ cells in their experimental study.

Similar observations were also reported by Banerjee et al. (2011) after using cannabis, the histopathological changes of the testis were in the form of tubular degeneration which is characterized by germinal epithelium degeneration, Sertoli cell vacuolation, increased residual bodies and/or intraluminal syncytial “giant cells” and widening of the intertubular space and absence of spermatozoa in the tubules.

Also Yassa et al. (2010) using cannabis leaves on male albino rats reported disruption and irregularity of the basement membrane, appearance of giant cells in the lumen of some seminiferous tubules. The spermatogenic cells showed degenerated and vacuolated cytoplasm and small dense nuclei.

Ozor et al. (2015) found cellular damages in the spermatogenic area of the seminiferous tubules of the testis of adult wistar rats and sertoli cell population was reduced in the germinal epithelium of the seminiferous tubules after using cannabis for 14 days.

Also Mandal, & Das (2010) reported degenerated germ cells, damaged lamina propria of

germinal epithelium and degenerative changes of seminiferous tubules of mice treated by Intraperitoneal injection of cannabis extract for 20, 30 and 40 days.

Testicular changes could be attributed to oxidative stress. Payne et al. (2019) found direct damage to the seminiferous tubules, which may be mediated by oxidative stress as there was significant decrease in the antioxidant enzymes in the testis of rats received cannabis.

Another explanation is affection of hypothalamus-pituitary-gonadal axis. It was reported that synthetic cannabinoids are agonist of endocannabinoid system which act as marijuana via releasing of cannabinoid compound that compete with endocannabinoid on cannabinoid receptor (Martinotti et al., 2017; Du Plessis et al., 2015)

Synthetic cannabinoids may play a role in disruption of hypothalamo pituitary gonadal axis that affect the release of GnRH, FSH and LH which affect testosterone secretion from leydig cells that relatively affect male fertility (Mutluay et al., 2019)

Conclusion

Administration of AMB-FUBINACA for 4 weeks in rats was associated with functional and pathological changes in the testis in non-dose dependent manner.

Recommendations

1. Improving the availability of advanced laboratory resources to improve our ability to detect synthetic cannabinoids and their metabolites in different types of samples especially urine.
2. Appropriate legislation is necessary to assist in limiting availability as well as efforts to educate local communities, physicians, and those working within the judicial system.
3. Further studies should be carried out on AMB-FUBINACA for longer duration, in different doses to show their effects on different body organs and studying if its effects are reversible or not.
4. Further studies should be carried out on AMB-FUBINACA including seminal analysis with measuring the levels of Luteinizing hormone (LH) and follicle stimulating hormone (FSH) together with testosterone hormone level.
5. Studying the effect of antioxidants should be conducted specially those found naturally in food in reducing AMB-FUBINACA toxic effects.

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دراسة تجريبية عن السمية تحت الحادة على الخصيتين لمادة AMB-FUBINACA على ذكور الجرذان البيضاء البالغة

مصعب محمود رشوان^١ و مها عبد الحميد هلال^١ و هدى محمد السيد^٢، خالد مسعود محمد^٣ و ولاء أحمد السيد^١

الملخص العربي

المقدمة: استخدام AMB-FUBINACA تم التأكيد منه في بعض تقارير حالات التسمم الجماعي في الولايات المتحدة. وأفيد أيضا أنه في نيوزيلندا كان هناك ما لا يقل عن ٢٠ حالة وفاة مرتبطة باستخدام مادة AMB-FUBINACA.

الهدف من الدراسة: الكشف عن التأثير السام لمادة الحشيش المصنع الجديدة (AMB-FUBINACA) بجرعات مختلفة على خصيتين ذكور الجرذان البيضاء من الناحية النسيجية والكيمياء الحيوية.

طريقة البحث: اجريت الدراسة على ٤٠ من ذكور الجرذان البيضاء. تم تقسيم الجرذان إلى ٥ مجموعات ٨ فئران لكل منها على النحو التالي المجموعة الأولى: المجموعة الضابطة السلبية، المجموعة الثانية: المجموعة الضابطة الايجابية حيث تلقت الحيوانات الإيثانول ٥٪، المجموعة الثالثة: الجرذان التي تلقت مادة AMB-FUBINACA بجرعة ٥ مجم / FUBINACA بجرعة ٢,٥ مجم / كجم مذاب في الإيثانول ٥٪، المجموعة الرابعة: الجرذان التي تلقت مادة AMB-FUBINACA بجرعة ٥ مجم / كجم مذاب في الإيثانول ٥٪ والمجموعة V: الجرذان التي تلقت مادة AMB-FUBINACA بجرعة ١٠ مجم / كجم مذاب في الإيثانول ٥٪ يعطى عن طريق حقنها في غشائها البريتوني لمدة ٤ أسابيع.

نتائج البحث: لوحظ انخفاض كبير في مستوى هرمون التستوستيرون في المجموعات المعالجة بمادة AMB-FUBINACA مقارنة بالمجموعات الضابطة والتغيرات التنكسية في الأنايب المنوية.

الخلاصة: ان تناول مادة AMB-FUBINACA لمدة ٤ أسابيع قد تصاحبه تأثيرات سامة على الخصيتين.

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