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A Study of the Effect of Khat on the Bioavailability of Tadalafil (Ex-Vivo) Using Everted Sac Method

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Abstract:

Aims: This study aimed to knowledge and evaluation of the effect of presence of Khat in the GIT on the bioavailability and efficacy of Tadalafil. **Methods:** The present study was carried out in ex-vivo by using everted gut sac method, the rabbit was the experimental animal. In comparative studies for absorption of standard Tadalafil alone and stand. Tadalafil in presence of more than one type of khat (Hishishi and Arhabi) and confirm this study by comparative study for Tadalafil product (Saheal) alone and in presence of the more effective type of khat (Hishishi type). **Results:** In the proposed studies, by using the calibration curve equation (Regression equation) to calculation of Conc. %, the means of difference in Conc.% of stand. Tadalafil alone and stand. Tadalafil in presence of khat Hishishi and stand. sildenafil in presence of khat Arhabi, were 2.575 ± 0.866 and 1.572 ± 0.0104 respectively, and the mean of difference in Conc.% of Tadalafil product (Saheal) alone and Tadalafil product (Saheal) in the presence of khat Hishishi was 4.132 ± 0.008 . **Conclusion:** Based on the results obtained from this study, the Tadalafil bioavailability were significantly reduced in presence of khat (khat-chewing). The rate of reduction was effected by the type of khat, as Al-Hishishi khat was more effective than Al-Arhabi khat in reduction of bioavailability of Tadalafil.

Keywords: Bioavailability; Catha Edulis; Everted sac intestinal system; Ex-vivo; Khat; Tadalafil.

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Introduction

Catha Edulis is a plant from family of Celastraceae and known as Qat, Chat, *Khat*, Miraa Abyssinian tea, African tea, African salad and Quaatka ⁽¹⁾. This plant is widely cultivated in Arabian Peninsula and East Africa (e.g. Ethiopia and Kenya) ⁽²⁾.

Khat is a natural stimulant plant in which the most important parts are the young leaves and buds near the tip of the branch, and the most active substance are alkaloids with amphetamine like properties (Cathine and Cathinone) which have euphoric and excitatory effects ⁽³⁾.

In Yemen, chewing of *khat* is a widespread routine; approximately 80–85% of adult males and 50–60% of adult females in North of Yemen chew *khat* at least once a week. The simultaneous use of *khat* with standard drugs is anecdotally purported to be common using in Yemen ⁽²⁾. There are different types of *Khat* according to the region in which it is grown such as *Khat* hishishi, *Khat* Hamdani, *Khat* Arhabi, *Khat* Shami, Herari *Khat* (Ethiopian *Khat*), and so on. The quality of *Khat* based on the concentration of their components (alkaloids, flavonoids, tannins) ⁽⁴⁾.

Tadalafil is one of the important oral phosphodiesterase type 5 (PDE5) inhibitors that remain the standard pharmacologic therapy for erectile dysfunction (ED). ED, a prevalent disorder that is more common in men with old year more than 40 years, can have significant consequences for quality of life and self-esteem ⁽⁵⁾.

Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3-d] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate ⁽⁶⁾ with chemical structure showed in figure 1.

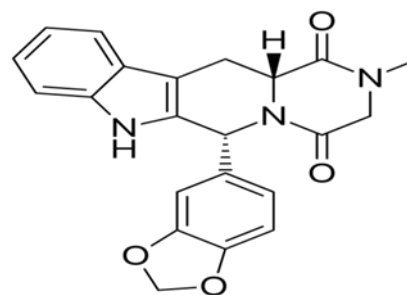


Figure 1: Structure of Tadalafil

Previous studies establish that among healthy Yemeni adults who chew *khat* significantly reduction in the bioavailability of some antibiotic drugs as ampicillin, amoxicillin, cephradine and ciprofloxacin ⁽⁷⁻⁹⁾, and antimalarial drug as chloroquine ⁽²⁾. Another study revealed significant reduction in the pharmacokinetics properties of tetracycline-HCl among healthy Yemeni adults who chew *khat* ⁽¹⁰⁾. Other studies found that *Khat* significantly increase bioavailability of some drugs (Clopidogrel, Sertraline, Clomipramine, Vilazodone, Aripiprazole) which might be attributed to inhibition of their metabolic enzymes ⁽¹¹⁻¹³⁾. Another study in healthy adults suggested that chewing of *khat* had an inferior effect on the bioavailability and other properties of aspirin as their antiplatelet activity ⁽¹⁴⁾. This study was carried out in ex-vivo by using everted gut sac intestinal permeability method according to previous studies ⁽¹⁵⁻²⁷⁾. This study aimed to investigate effect of chewing of *khat* on bioavailability of Tadalafil. In addition to determine the type of *khat* which have more effect on the bioavailability of Tadalafil.

Materials and Instrumentations

Materials:

Tadalafil standard (99.5%) were purchased from Shiba Pharma-Yemen. Distilled water, Methanol, Medium of stomach (The TC 199 solution containing 145 Millimolar (mM) NaCl, 4.56 mM KCl, 1.25 mM CaCl₂.2H₂O and 5 mM NaHPO₄. From Pure Chemical Co. India and UNI-CHEM.Co. Naslovna strana), CHCl₃ (Pure Chemical Co. India), all materials were purchased from the market. *Khat* were purchased from the market. Tadalafil product (Saheal tablet-Shaphaco-Pharmaceutical Ind. Yemen) were purchased from the market.

UV spectrophotometer (Lasany international, India). Electric balance (Radwag, Poland), Mixture (JJ-1 mixer, China). Water bath (HH-4, China), Centrifuge (China).

Rabbit intestinal permeability test system was constructed in our lab as described in the literatures (15-27).

Methods

Standard calibration curve:

Procedure:

Dissolve 100 mg of Tadalafil standard in 100 ml volumetric flask with 50 ml methanol and complete the volume to 100 ml with the methanol to prepare standard stock solutions of concentration (1 mg/ml). Take 10 ml of stock solution to another 100 ml volumetric flask and complete the volume to 100 ml with methanol to prepare solutions of 100 µg/ml concentration, take to six 10 ml volumetric flask 0.5 ml, 1 ml, 1.5 ml, 2 ml, 2.5 ml, and 3 ml of (100 µg/ml) concentration, and complete all to 10 ml with TC 199 solution to prepare 6 solutions of the following concentration 5 µg, 10 µg, 15 µg, 20 µg, 25 µg, 30 µg. Measure the UV spectrophotometric absorbance at 260 nm for six concentrations and repeat each conc. three times and write the absorbance data.

Everted gut sac test:

The test was carried out based on adopted methods described in literatures (15-27).

Animal models:

Twenty male rabbits (800 -1200 g) were used as models in this test. The animals were incubated in appropriate cage. Prior to test, they were fastened overnight with free excess to water. The animals were anesthetized by chloroform. The intestine section included duodenum and jejunum of 15 cm and a range of surface area of (1 cm²) was excised. The animal was sacrifice by excess dose of chloroform.

The intestine of the animal was exposed by abdominal incision and 15 cm of jejunum (starting 20 cm below the pylorus) was excised and was immediately chilled and clean it by D.W, then placed in 37 °C oxygenated TC199 buffer solution. The segment was everted over using a glass rod. The lower end was tied with a ligature.

Test apparatus

The apparatus consisted of a volumetric beaker (1000 ml) placed on a water bath at 37.5 °C. The beaker contained 500 ml of buffer. The buffer was

Instrumentations:

prepared in volumetric flask by mixing (2.12 g of 145 mM NaCl, 0.084 g of 4.56 mM KCl, 0.0347 g of 1.25 mM CaCl₂.2H₂O and 0.177 g of 5 mM NaHPO₄), and the volume was made up to 1000 ml with distilled water, this solution known as TC 199 buffer solution. The everted gut sac was filled with 10 ml of a buffer solution (for testing the intestinal permeability). The sac was incubated for 45 minutes in the buffer medium which was kept oxygenated and stirred all over the experiment at a rate of 85 rpm.

In Ex-Vivo Procedures:

The experiment was carried out as described in the literatures (15-27), with appropriate modification. Prior to intestinal permeability test, it was necessary to carry out standard calibration curve of the drug in the incubation medium used in the experiment. Therefore, a stock solution (100 µg/ml) of Tadalafil acetate standard in TC 199 solution was prepared. Serial dilution of stock solution was made to prepare 6 diluted standard solutions of concentrations (5-30 µg/ml). The UV absorbance of those solutions at 260 nm were measured and calibration curve was then constructed, from which the regression equation was determined.

Anesthetizing the rabbit using chloroform, the rabbit is weighed and the autopsy started by making an incision in the skin of the rabbit from the chest to the lower abdomen using a surgical scalpel. The piece of intestine starting from the duodenum was taken from the jejunum as it is the main part of absorption because it contains many large circular folds in the mucosa called circular folds that increase the surface area of absorption by about 15 cm. It is washed and cleaned with distilled water well. The intestine is turned from the outside to the inside in order for the absorption pills to form from the outside and the materials are absorbed inside after tying them from the bottom and adding 10 ml of Buffer and then tying them from the top using a surgeon's thread. Then put the inverted intestine piece in beaker with 1000 ml and fix it from the bottom with a cymbal weighing 100 grams, as well as fix it from the top in a rod clamp at a height of 4 centimeters and a distance of 2 cm from the head of the beaker, then the beaker is placed in a water bath to shatter at a temperature of about 37.5 °C, then add 500 ml of Buffer to the beaker, then fix the mixer device in order to move the medium by setting it to 7 cycles in 5 seconds, equivalent to 84 rotations per minute, then the solution was transferred to an Erlenmeyer flask and was oxygenated (O₂:CO₂=95:5) throughout the experiment time. The medium was completely

covered with tin to maintain the temperature and this process lasts 45 minutes. After that, the intestine was taken out of the medium and the solution in intestine was transferred into a beaker

was carried out for standard alone, for standard with Hishishi khat, for standard with Arhabi khat, for brand product (Saheal) alone and for product (Saheal) with hishishi khat. Their UV absorbance were also measured at 260 nm. The averages of their UV absorbance were calculated and

and then measured and filtered. The UV absorbance of the liquid was measured by UV spectrophotometer at 220 nm. The test was performed in triplicates. Similarly, the test

introduced into the calibration regression equation to calculate practical concentration (Cp µg/ml) of the drug in everted intestine and calculate concentration % from which the percentage of reduction of bioavailability was calculated.

Results and Discussion

Figure 2 shows the UV standard calibration curve, at 260 nm, of Tadalafil in TC 199 solution for everted intestinal sac experiment. The calibration curve has optimum linearity of 0.9998 and their regression equation that was used to calculate practical concentration of the drug in the sample was ($y = 0.0159x + 0.0198$).

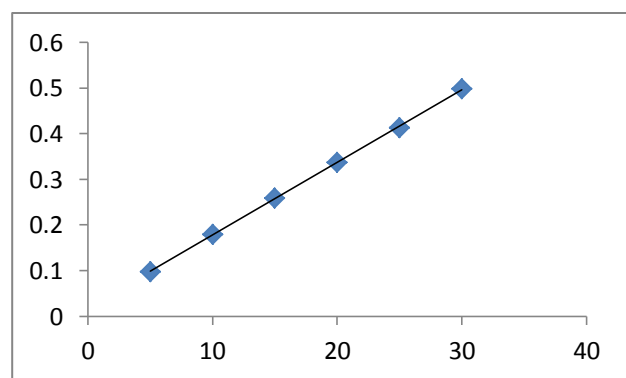


Figure 2: Calibration curve of Tadalafil in TC 199 solution measured by UV spectrophotometer at 260 nm.

From the present study, the presence of or co-administration of Tadalafil with khat was found to significantly affect the pharmacokinetics of Tadalafil in *Ex-vivo* study. This was comparable to reported reductions in the low bioavailability of chloroquinone, ampicillin, amoxicillin and the pharmacokinetic activity of tetracycline hydrochloride when co-administered with *khat* (2, 7-10). A possible drug-plant

Tadalafil-*khat* interaction exists, as indicated by the significantly reduced Tadalafil AUC and recovery percentage of concentration values observed without and with *khat* that used in the present study. The mechanisms underlying this interaction are unknown; however, one possible mechanism may relate to the interaction of the drug with some of *khat's* components-tannic acid, cathinone and cathine which are known to cause the formation of insoluble complexes and non-absorbable compounds (7-10).

In the present study, comparing the result of the standard Tadalafil concentration% alone and those from Tadalafil with *khat* (Hishishi) and *khat* (Arhabi) as showed in table 1 and the difference between them with *khat* (Hishishi) and with *khat* (Arhabii) as showed in table 1, this reduction in concentration of drug mean reduction in bioavailability of tadalafil by *khat* (Hishishi) more than by *khat* (Arhabi) as showed in table 1. Also confirmed this results, the results obtained from comparing between conc.% of Tadalafil tablets (Saheal) alone and their conc.% in presence of *khat* (Hishishi) and the difference between them as showed in table 1. So there was significance reduction in bioavailability of drug.

In this study, Tadalafil conc. levels were significantly reduced in presence of *khat* in comparison to absence of *khat* and this affect differ from *khat* type to another type, where the *khat* (Hishishi) have more affect than *khat* (Arhabi), and this attributed to the difference in the percentage of their conc. components.

Table 1: The results of Tadalafil conc.% alone and with khat obtained in Ex-vivo using everted sac methods

Sample	Standard Tadalafil	Tadalafil with <i>khat</i> Hishishi	Difference	Standard Tadalafil	Tadalafil with <i>khat</i> Arhabi	Difference	Tadalafil tab (Saheal)	Saheal with <i>Khat</i> Hishishi	Difference
1	21.95	20.455	1.495	21.95	20.36	1.59	29.35	25.67	3.68
2	22.1	18.255	3.845	22.1	20.51	1.59	29.44	25.17	4.27
3	22.03	19.825	2.205	22.03	20.42	1.61	29.57	25.33	4.24
4	21.95	19.195	2.755	21.95	20.42	1.53	29.82	25.48	4.34

Mean	22.008	19.433	2.575	22.008	20.435	1.573	29.545	25.413	4.133
SD	0.0723	0.938	0.866	0.072	0.062	0.0104	0.204	0.213	0.009
SE	0.0361	0.469	0.433	0.036	0.031	0.0052	0.102	0.107	0.0045
Bioavailability-reduction %			11.71			7.15			13.96

Stand: Standard, Conc: Concentration, SD: Standard deviation, SE: Standard Error.

Statistical analysis:

Statistical analysis of the results obtained by the suggested methods for the comparison study of recovery conc. % of standard Tadalafil, Tadalafil tablet (Saheal) with and without *khat* was carried

out using Student's t-test and variance ratio F-test at $P=0.05$. As shown in Table 2, calculated t and F values were more than the tabulated ones, indicating significant difference between them.

Table 2: Statistical analysis between the results of Tadalafil conc.% alone and with khat obtained in Ex-vivo using everted sac methods

Statistical term	Standard Tadalafil	Tadalafil with <i>khat</i> Hishishi	Standard Tadalafil	tadalafil with <i>khat</i> Arhabi	Tadalavil tab (Saheal)	Saheal with <i>khat</i> Hishishi
Mean	22.008	19.433	22.008	20.435	29.545	25.413
SD	0.072	0.939	0.072	0.062	0.204	0.213
SE	0.036	0.469	0.036	0.031	0.102	0.107
N	4	4	4	4	4	4
*F(0.108)		0.593		0.732		0.918
*t(2.447)		5.471		33.22		27.98
P		0.00156		0.00005		0.000014

SD; Standard deviation. SE Standard Error. N: Number of samples

*Figures in parentheses are the theoretical t and F values at ($p=0.05$).

Conclusion and recommendations

Based on the results obtained from the present study, the Tadalafil bioavailability were significantly reduced in presence of *khat* (*khat*-chewing). The ratio of absorption was in the product (Saheal) more

than the standard Tadalafil, but also the presence of *khat* decrease the bioavailability of drug product as the standard with the same percentage. The rate of reduction was effected by the type of *khat*, as al-Hishishi *khat* was more effective than Al-Arhabi *khat* in reduction of bioavailability of Tadalafil.

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دراسة تأثير القات على التوافر البيولوجي لتادالافيل (خارج الجسم) باستخدام طريقة الكيس المقلوب.

الأهداف: هدفت الدراسة إلى معرفة وتقييم تأثير وجود القات في الجهاز الهضمي على التوافر البيولوجي وفعالية تادالافيل. **الطرق:** أجريت الدراسة الحالية خارج الجسم باستخدام طريقة الكيس المقلوب للأمعاء، وكان الأرنب هو الحيوان التجريبي. في الدراسات المقارنة لامتناس تادالافيل القياسي بمفرده وتادالافيل القياسي في وجود أكثر من نوع من القات (الحشيشي والأرحبي) وتأكيد هذه الدراسة بدراسة مقارنة لمنتج تادالافيل (ساهيل) بمفرده وفي وجود النوع الأكثر فعالية من القات (الحشيشي). **النتائج:** في الدراسات المقترحة، باستخدام معادلة منحنى المعايرة (معادلة الانحدار) لحساب نسبة التركيز، كانت متوسطات الفروق في نسبة التركيز لتادالافيل القياسي بمفرده وتادالافيل القياسي في وجود القات الحشيشي وتادالافيل القياسي في وجود القات الأرحبي 0.866 ± 2.575 و 1.572 ± 0.0104 على التوالي، ومتوسط الفرق في نسبة التركيز لمنتج تادالافيل (ساهيل) بمفرده ومنتج تادالافيل (ساهيل) في وجود القات الحشيشي 4.132 ± 0.008 . **الاستنتاجات:** بناءً على النتائج المستخلصة من هذه الدراسة، تبين أن التوافر البيولوجي لتادالافيل انخفض بشكل كبير في وجود القات. كان معدل الانخفاض متأثراً بنوع القات، حيث كان القات الحشيشي أكثر فعالية من القات الأرحبي في تقليل التوافر البيولوجي لتادالافيل.