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Effect of Khat on Blood Coagulation

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Abstract

Catha edulis Forsk leaves " Khat " are chewed daily by a high proportion of the adult population in Yemen .The present study investigated the relationship between blood coagulation and khat chewing .In our study , we investigated the blood coagulation tests in two groups namely khat chewers group (n:30) and non– khat chewers group (n:60). The blood coagulation tests included bleeding time , clotting time , prothrombin time , partial thromboplastin time and platelets count. Statistical testing for data analysis included the student's t-test and chi 2 test. The results presented show the level of bleeding time , clotting time , prothrombin time , platelets count and platelets aggregation to be significantly different between khat chewers and non – khat chewers ($p< 0.05$) , we observed decrease in bleeding time , clotting time and prothrombin time in khat chewers less than normal values and we also observed enhance in platelets aggregation in khat chewers in comparison with non – khat chewers . The results presented show the level of partial thromboplastin time to be non -significantly different ($p > 0.05$) between both groups . The study concluded the khat chewing effects on blood coagulation physiology and consider as risk factor for blood coagulation system.

Keywords: *Khat , coagulation factors , Yemen.*

1. Introduction

Catha edulis Forsk leaves (khat) are chewed daily by a high proportion of the adult population in Yemen for the mild stimulant effect. The habit of khat chewing is widespread with a deep-rooted sociocultural tradition in Yemen and as such poses a public health problem. The consumption of khat has strongly increased in recent years, and the drug has also made its appearance in Great Britain. Khat chewing may have a negative effect on the central nervous system, cardiovascular, digestive and genitourinary systems, oral-dental tissues, diabetes mellitus and cancer. Khat chewing may be associated with increased risk of cardiovascular and blood coagulation disorders. It also may interfere with absorption , metabolism and mechanism action of some orally administered drugs [1-4]. Khat contains on glycosides and tannis in khat in addition to the alkaloids namely phenylalkaminens cathine (norpseudoephedrine) and cathinone {S(-)-alpha-aminopropiaphenone)}that have amphetamine like effect [6,7]. The chemical constitute of khat have been studied since the late 19th century. Fluckiger and Gerok were among the first who found an alkaloidal fraction in this plants [8] and called it "katin". This was followed by the isolation of many other substances and it was not until the year 1975 that the most important component of khat was isolated and named cathinone {S (-)-alpha-aminopropiaphenone)} at the United Nations Laboratories and it is considered the principle stimulant of the central nervous system (CNS) [9]. Determining the total contents of cathine and cathinone in fresh khat follows. It was found to range from 78–343 mg/100 g fresh khat from different khat samples. Khat contains two central nervous system (CNS) stimulants, namely cathinone and cathine. Cathinone (alpha-aminopriopiophenone), which is the principal active stimulant, is structurally similar to d-amphetamine and almost as potent as a CNS stimulant . Cathine, also called d-norpseudoephedrine [6]. Cathinone is currently believed to be the main active ingredient in fresh khat leaves . These effects were found to be maximum between 1.5–3.5 hours after starting to chew and they were progressively replaced by mild dysphoria , anxiety, reactive depression , insomnia and anorexia. Khat chewing increases plasma leptin concentration particularly in individuals who chew 400 g of khat leaves, triacylglycerol and none sterified fatty acids. The significance of increased plasma leptin is in explaining the underlying mechanism of the observed effects associated with khat chewing such as loss of appetite, decreased body weight. and hyperthermia. Also the plasma levels of triacylglycerol were significantly lower whereas plasma cholesterol levels were not affected [10]. Khat chewing effects on heart function whereas increases cardiac enzymes (CK-MB, aspartate transaminase, LDH) [11] . Finally The study highlights the possible

association of long-term use of khat and abnormal seminal fluid analysis profiles [12]. and almost as potent as a CNS stimulant . Cathine, also called d-norpseudoephedrine [6]. Cathinone is currently believed to be the main active ingredient in fresh khat leaves . These effects were found to be maximum between 1.5–3.5 hours after starting to chew and they were progressively replaced by mild dysphoria , anxiety, reactive depression , insomnia and anorexia. Khat chewing increases plasma leptin concentration particularly in individuals who chew 400 g of khat leaves, triacylglycerol and none sterified fatty acids. The significance of increased plasma leptin is in explaining the underlying mechanism of the observed effects associated with khat chewing such as loss of appetite, decreased body weight. and hyperthermia. Also the plasma levels of triacylglycerol were significantly lower whereas plasma cholesterol levels were not affected [10]. Khat chewing effects on heart function whereas increases cardiac enzymes (CK-MB, aspartate transaminase, LDH) [11] . Finally The study highlights the possible association of long-term use of khat and abnormal seminal fluid analysis profiles [12]. Khat extract without alkaloids was used as suitable media for bacterial growth in vitro [13] and alkaloids was used as antimicrobial activity against gram negative bacteria [14].Coagulation is a complex process by which blood forms solid clots. It is an important part of haemostasis (the cessation of blood loss from a damaged vessel) whereby a damaged blood vessel wall is covered by a platelet- and fibrin-containing clot to stop bleeding and begin repair of the damaged vessel. Disorders of coagulation can lead to an increased risk of bleeding and/or clotting and embolism [15]. Many substances may stimulate or inhibit coagulation factors and khat chewing may interfere blood coagulation physiology. In our study will determine the correlation between khat chewing and blood coagulation**.**

2. Materials and methods

2.1. Materials

The materials of our study included kit of prothrombin time estimation [Plasmascann reagent] , kit of partial thromboplastin time estimation [Hemoscann reagent, CaCl2] ammonium oxalite, tube with sodium citrate , tube with EDTA , tube without anticoagulant [QCA Company , Aspain] , microscope , [Olyompus , Japan] , slide , cover slide , platelets count cha ber [Brand , Germany] , sphygmomanometer , Balance , Meter [China Brand] , incubation [Memert , German] , syringe , Tourniquet , lancets , Gaemsa´s stain ,

2.2. Methods

2.2.1. Study design

90 blood samples from 90 volunteers were prepared and classified into two groups. Chronic khat chewers group (n : 30) and non – khat chewers (n : 60) . The personal data age , sex , Body Mass Index (BMI) , heart rate , blood pressure and risk factors were recorded .

2.2.2. Blood coagulation tests

Blood coagulation tests were estimated in both groups , bleeding time , clotting time , prothrombin time , partial thromboplastin time , platelets count and aggregation. Blood samples were collected in three tubes ; (1) tube contains anticoagulant (sodium tricitrate) to estimate PT and PTT , (2) tube contains anticoagulant (EDTA) to estimate PC and Blood Film , (3) : tube without anticoagulant to estimated CT [16].

2.2.3. Data Analysis

Differences between cases and controls were confirmed using Descriptive analysis , Student's t-test and Chi2 test and were used explore the effects of khat on the blood coagulation .

3. Results

3.1. Subjects

The background information on the 90 samples in the all groups is summarized in table [1].

Table [1]: Personal data and blood coagulation parameters of volunteers

Parameters	Khat Chewers Group (n :30)	Non – Khat Chewers Group (n :60)	*p*-value
Age	20 – 40 Year	20 – 40 Year	NA
Sex	Males	Males	NA
Blood Pressure mm Hg	95/140	75/116	NA
Heart Rate	99.23 / minute	68.93 / minute	NA
BMI **Weight** **Length**	19.01 53,13 167,20	20,60 59,53 169,47	NA
Bleeding Time (BT)	42 second	143.16 second	$p < 0.05$ *
Clotting Time (CT)	201.13 second	249.46 second	$p < 0.05$ *
Prothrombin Time (PT)	9,10 seconds	12,11 seconds	$p < 0.05$ *
Partial Thromboplastin Time (PTT)	35 seconds	34 seconds	$p > 0.05$
Platelets Count	213000 /mm3	204000 /mm^3	$p < 0.05$ *
*** Significant ($p < 0.05$)**			

3.2. Khat Effect on Blood Coagulation

In the first study , the effect of regular khat chewing on BT , CT , PT , PTT , PC and BF levels were investigated in both khat chewers (n:30) and non – khat chewers " Negative Control (n:60) ".

3.1.2. Bleeding Time (BT)

The results presented show the level of BT to be significantly different between khat chewers and non – khat chewers " Negative Control " (Figure 1) .The mean of BT in khat chewers was 0.42 minute while the mean of BT in negative control group was 2.30 minutes . Significant decrease was observed in BT in khat chewers in comparison with non – khat chewers ($p< 0.05$). We observed a decrease of BT in khat chewers less than the normal value whereas the normal range of BT is between 2 – 9 minutes . The results presented show the level of BT in khat – smoking combination was zero minute , the Figure 2 shows the comparison between khat chewers and khat – smoking combination.

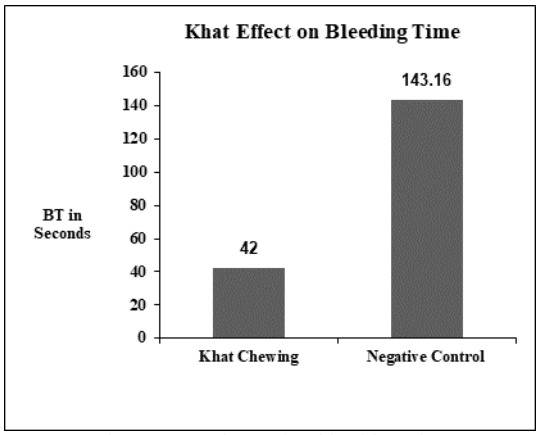

Figure [1] The BT was determined in khat chewers [n:30] while the BT in non – khat chewers [n:60]

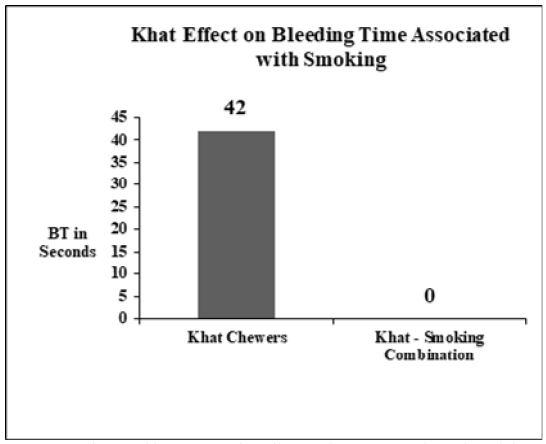

Figure [2] Khat Effect on Bleeding Time associated with smoking (n : 5 mean: Zero)

3.2.2. Clotting Time (CT)

We used the CT as second test to estimate the blood coagulation function and the CT was determined by lee and white method .The results were observed in khat chewers and non – chewers (See Figure 3) . The mean of CT was 3.23 minutes in khat chewers while the mean of CT in negative control was 4.10 minutes . Significant reduce was observed in CT in khat chewers in comparison with non – khat chewers ($p< 0.05$) . We observed decrease of CT in khat chewers less than the normal value whereas the normal range of clotting time is between 4 – 9 minutes .

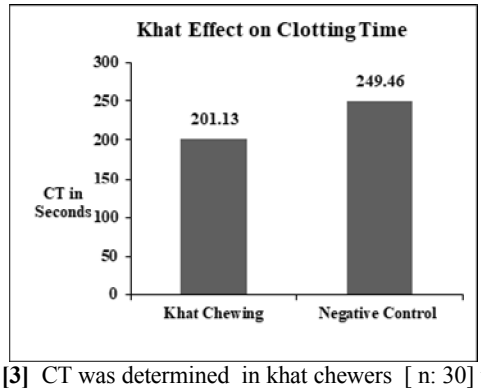

Figure [3] CT was determined in khat chewers [n: 30] whereas in non – khat chewers [n:60]

3.2.3. Prothrombin Time (PT)

The normal range of PT is between 10 – 14 seconds but the results showed a decrease of the mean of PT in khat chewers which was 9 seconds while the mean of PT in non – khat chewers was 12 seconds ($p< 0.05$) . Significant difference between khat chewers and non – khat chewers (See Figure 4).

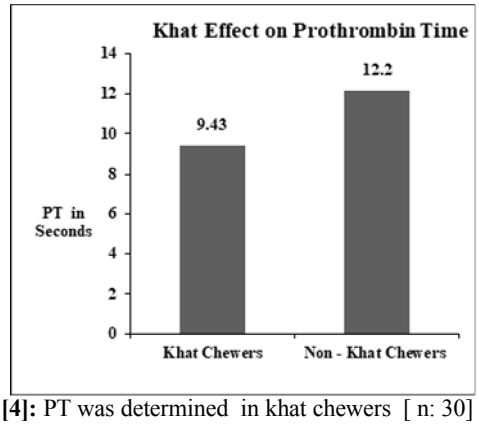

Figure [4]: PT was determined in khat chewers [n: 30] whereas in non – khat chewers [n:60]

3.2.4. Partial Thromboplastin Time (PTT)

PTT was determined and the results were recorded in Figure5. These proved non significant difference between the khat chewers group and non – khat chewers group ($p> 0.05$) but the results of two groups fall within the normal rang whereas normal rang of PTT is between 30 – 42 where the mean of khat chewers PTT was 35 seconds whereas the mean of no-khat chewers PTT was 34 seconds . We observed some of khat chewers (2 volunteers) has increased in PTT more than normal value PTT = 50 – 52 seconds but the PTT value decreases spitting the leaves out into normal value seconds .

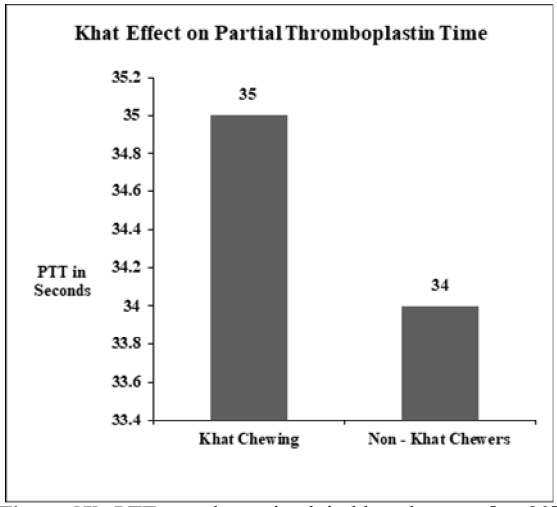

Figure [5]: PTT was determined in khat chewers [n: 30] whereas in non – khat chewers [n:60]

3.2.5. Platelets Count

According to manual method , we determined the platelets count in khat chewers and non – khat chewers. The results were showed in Figure 6. These results proved the existence of a significant difference between the khat chewers and the negative control ($p< 0.05$) but the results of two different groups fall within the normal rang whereas normal rang of Platelets count is between 150000 – 400000 /mm^3. The means of platelets count in khat chewers and non – khat chewers were 213000 and 204000 /mm^3 respectively.

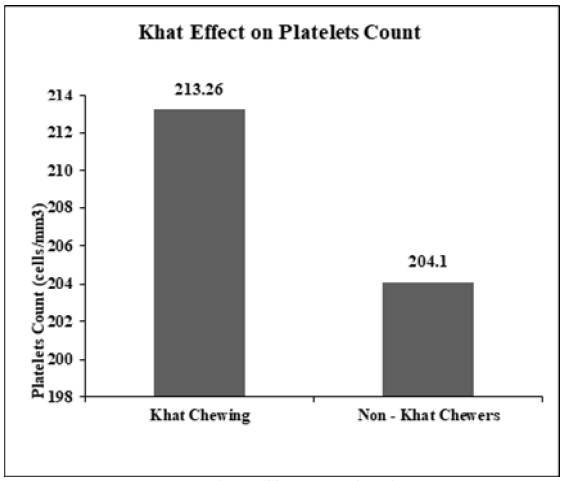

Figure [6]: Khat effect on platelets count

3.2.6. Platelets aggregation

The platelets aggregation was observed in blood film and the results presented show complete platelets aggregation 56 % , partial platelets aggregation 20 % and no platelets aggregation 34 % in khat chewers while the results were observed in non – khat chewers where complete platelets aggregation was 16% , partial

platelets aggregation 10% and no platelets aggregation 74% (Figure 7). These proved significant difference between the khat chewers group and non – khat chewers (p<0.05) .

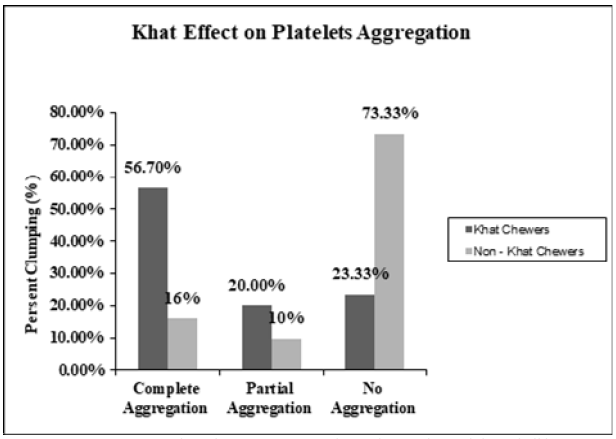

Figure [7]: Platelets aggregation based on blood film

4. Discussion

In our research , khat effect on blood coagulation , through personal data collections such as names , BMI, blood pressure , heart rate and risk factors , we found increase in blood pressure (moderate hypertension) and heart rate that have been observed in human volunteers after khat chewing process .This increase can be attributed to the existence of the cathinone . The peak effect on the arterial blood pressure and pulse rate was reached 3 hours after starting to chew, followed by a decline 1 hour after spitting the leaves out. These observations support the suggestion that cathinone is the constituent that is mainly responsible for the increase in arterial blood pressure and pulse rate during khat chewing [17]. Similar blood pressure changes have also been observed in smaller numbers of subjects when pure cathinone in gelatin capsules was taken orally . A mechanism is the release of catecholamines from presynaptic storage sites. The elevation of blood pressure and increase in pulse rate suggesting these effects are mediated by the stimulant effect of cathinone in khat on β 1 adrenoceptors in the heart and α1 adrenoceptor [17,18]. Cathine and cathinone are released and absorbed through the mucous membranes of the mouth and the lining of the stomach. The action of cathinone on the reuptake of epinephrine and norepinephrine has been demonstrated in human body [18]. We observed decrease in BT in khat chewers attributed to khat's alkaloids through adrenaline and noradrenaline (norepinephrine) release from peripheral neurons and serotonin and dopamine in the central nervous system [19].Adrenaline at low concentration to cause aggregation of human platelets aggregation and noradrenaline has the same effect but is less active than adrenaline [20].In addition , the khat's alkaloids release serotonin and dopamine in the centralnervous system. The marked increase in serotonin concentration observed in the latter stages of thrombus formation strongly suggests that platelet aggregation is a significant factor in the evolution of an occlusive coronary thrombus [21]. In addition , dopamine induces platelet aggregation and enhances ADP-induced aggregation [22]. The khat chewing has been reported to shorten the clotting time of the blood attributed to adrenergic effect . The results suggested an increase in the activity of clotting factor V [23]. Bleeding time less in khat chewers associated with smoking attributed to synergic effect between khat and cigarette whereas the khat acts as platelets aggregation stimulate and some substance in cigarette smoke promotes aggregation of adenosine diphosphate and platelet adhesiveness [24]. Cathinone and cathine decrease PT through adrenaline and noradrenaline release from peripheral neurones and serotonin in the central nervous system . The adrenaline causes increase activity in factor V and the action of serotonin is postulated as an antagonist of an antithrombin which blocks the fibrinogen to fibrin reaction [25,26,23] . Many factors that may prolong PTT test values include antihistamines , ascorbic acid " Vitamin C " , chlorpromazine , heparin ... etc [27]. Prolong PTT test in 2 volunteers of khat chewers attributed to other factors or un clear mechanism but this increase in PTT temporary whereas the PTT values declines after spitting the leaves out. Also catecholamines namely adrenaline has not effect on plasma thromboplastin time [28].

5. Conclusion

Khat chewing has a negative effect on blood coagulation system . It is associated with an increased risk of cardiovascular and blood coagulation disorders. The negative effect on blood coagulation factors " extrinsic and intrinsic factors due to the presence of the alkaloids cathinone and cathine in the leaves.

Data Availability

No data were used to support this study**.**

Conflicts of Interest

The authors declare that they have no conflicts of interest**.**

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Ethical Approval

The studies involving human participants were reviewed and approved by Ethics Committee ofLaboratory of Pharmacology and Physiology and Environment, Health, Department of Biology, Faculty of Sciences Dhar Mehraz, Sidi Mohamed Ben Abdellah University, 30000 Fez, Morocco **.**

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