Original Research Paper

Volume-7 | Issue-11 | November-2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

Physiology

THE ACUTE EFFECTS OF HYDRO-ALCOHOLIC KHAT (CATHA EDULIS FORSK) EXTRACT ON MESENTERIC BLOOD FLOW VELOCITY IN GUINEA PIGS.

Zewdu Minwuyelet Gebremariam	Biomedical department, college of medicine and health sciences, Dilla university, Ethiopia
Tesfaye Tolossa Dugul	Department of Physiology, College of Medicine and Health sciences, Addis Ababa University, Ethiopia
Diresbachew Haile Wendimu	Department of Physiology, College of Medicine and Health sciences, Addis Ababa University, Ethiopia
Vempati Poornodai	Biomedical department, college of medicine and health sciences, Dilla university, Ethiopia
Vulli Venkata Rao	Department of Biochemistry, Kampala International University- Health Sciences, Dar es Salaam, Tanzania
Suberu Safiu Adewale	Department of Biochemistry, Kampala International University- Health Sciences, Dar es Salaam, Tanzania

ABSTRACT This in vivo random experimental animal study was conducted to evaluate the acute effects of crude *Catha edulis* extract on mesenteric blood flow velocity in guinea pigs. A total number of 10 guinea pigs were used. Superior mesenteric blood flow velocity was measured by Ultrasound Doppler flow meter. This was tested by placing its flow meter probe (4 Hz) between 45 and 60 degrees on superior mesenteric blood vessels. Blood flow velocity was recorded digitally for half an hour following normal saline administration as baseline; while 0.2ml *Catha edulis* extract solution infusion as treatment and recorded for 1hour. Results showed significant increased systolic and diastolic blood flow velocities in response to Catha edulis extract infusion as compared to the base line. The significant increased systolic and diastolic blood flow velocities and the corresponding increase in resistance in superior mesenteric blood vessels in guinea pigs enable us to conclude that khat chewing could decrease the volume of blood flow to the gastrointestinal system.

KEYWORDS : *Catha edulis,* blood flow velocity,

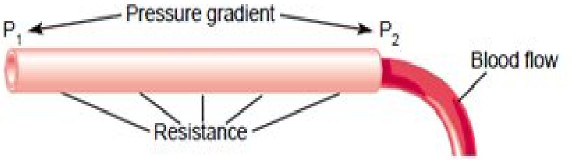
INTRODUCTION

The chemical constituents of khat have been studied since the late 19th century. Fluckiger and Gerok were among the first who found an alkaloidal fraction in this plant and called it "katin". This was followed by the isolation of many other substances and it was not known until the year 1975. 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 (United Nations Narcotic Laboratory, 1975).

The psycho stimulant component of khat which is Cathinone released within 15–45 min during chewing (Graziani *et al.*, 2008). Following this, the user can experience an increase in blood pressure and heart rate, anorexia, insomnia, alertness, elevated mood and loquacity (Al-Mamary *et al.*, 2002). Furthermore, chronic khat chewing for many years results in unpleasant effect of cognitive defects and psychosis associated with severe neurological illness.

Cathinone has a releasing effect on noradrenalin storage sites, which supports the conclusion that Cathinone facilitates noradrenalin transmission. Drake (1988) also proposed that Cathinone and Cathine cause inhibition of noradrenalin uptake. All abused central nervous system stimulants also stimulate the cardiovascular system. Chewing of khat has been associated with a transient rise in blood pressure and heart rate in experimental studies. Regular chewing of khat is associated with elevated mean diastolic blood pressure, which is consistent with the peripheral vasoconstrictor effect of Cathinone (Al Motarreb *et al.,* 2002; Kalix *et al.*, 1991; Hassan *et al.,* 2000). Cathinone (0.5 mg base/kg of body weight) has been associated with a transit increase in blood pressure which its effects coinciding with the presence of Cathinone in blood plasma (Brenneisen *et al.*, 1990; Kalix *et al.,* 1991). These effects could be blocked by the beta1-adrenoreceptor blocker atenolol, but not by the alpha1-adrenoreceptor blocker indoramine, indicating mediation through stimulation of beta1-adrenoreceptor (Hassan et al., 2005). Other studies have found the same increases in blood pressure but also significant increases in heart rate (Hassen *et al*., 2005).

Blood flow around the circulation is driven by a difference in pressure between the arteries and the veins. The amount of blood flow produced for a given pressure gradient depends on how much resistance to flow is offered by the vascular system (Silverthorn, 2009). Blood is an incompressible fluid, and its volume cannot decrease when the ventricles contract. Instead, blood is pressurized, creating the potential energy for blood flow. Blood pressure decreases over distance as potential energy is lost through friction between blood and blood vessel walls and between blood cells. The difference in pressure between the two ends of the vessel, not the absolute pressure in the vessel that determines rate of flow (Guyton and Hall, 2006).



Physiologic control of vascular resistance is achieved by altering the blood vessel diameter through vasoconstriction and vasodilatation. The sympathoadrenal system is active to a certain degree (even when at rest) helps to set the "tone" of vascular smooth muscles. Adrenergic sympathetic fibers (release nor epinephrine) activate alpha-adrenergic receptors to cause a basal level of vasoconstriction. Thus, Stimulation of the sympathoadrenal system increases the total peripheral resistance. Parasympathetic endings in arterioles are always cholinergic and promote vasodilation. Parasympathetic innervations of blood vessels are limited to the digestive tract, external genitalia, and salivary glands. Net vascular tone in the mesenteric vasculature is under the influence of several key factors. These factors include locally acting and circulating hormones, intrinsic myogenic properties of the vessel, as well as neurotransmitters released from perivascular post-ganglionic sympathetic neurons. In general, the arteries and veins of the splanchnic circulation are richly innervated with sympathetic nerves that act to constrict these vessels. Maximal activation of the sympathetic constrictor nerves can produce an 80% reduction in blood flow to the splanchnic region. On the other hand, an adequate amount of blood supply is necessary for the proper functioning of all body organs as blood carries all the nutrients and oxygen that our body needs to stay healthy. Various conditions including drugs may cause an impaired supply of blood to the organs due to a direct or indirect action of drugs on the controlling systems of the body. Thus, the primary purpose of this study is to evaluate and present available information about the acute effect of Catha edulis extract on GIT blood flow in guinea pigs.

MATERIALS AND METHODS

Fresh khat collection

Six bundles of fresh khat of "Aweday" type were purchased at a local market from one retailer in Bole, Addis Ababa, who received daily supply from Aweday, its natural habitat, 525 km South of Addis Ababa, Ethiopia. Then these fresh materials of Khat were wrapped in a plastic bundle as chewers do and taken to Ethiopian food and nutrition research institute, for extraction. The fresh materials were washed to remove dust and debris with distilled water.

Extraction

Shoot leaves were collected, and chopped/ crushed with pestle and mortar on a glass plate and weighted (500 grams) by electronic digital balance and placed in Erlenmeyer flasks (≤200g per flask) wrapped with aluminum foil to avoid light induced decomposition. And then ethanol (70%) was added to cover the minced leaves in ratio of 4mL: 1g. Then, put in to rotary /orbital shaker (DS-500) for 24 hrs at the speed of 120rpm at ambient temperature under dark condition. Then filtered the filtrates with Whatman filter paper # 1 and collected and kept in another flask. Rotary evaporator (RE300) is used to remove all traces of ethanol which was used for extraction at a digital water path (RE300DB) at a speed of 3 rotations per second, 40^0c temperature and 70kpa vacuum pump (RE3022C) pressure. Finally, the fraction was left overnight in a deep freezer and then lyophilized using freeze dryer (Christ 100400 Bio block Scientific, France) and approximately 40 gram of crude khat extract was yield.

Experimental animals

Experimental animals (10 guinea pigs) were obtained from Ethiopian food and nutrition research institute, department of Laboratory animal breeding. The animals were housed in mice cages in physiology lab, Department of Physiology, Black Lion Specialized Hospital, Addis Ababa University.

METHODS

Study Design: Laboratory based experiment involving quantitative and descriptive analysis of data.

Study Area: Laboratory of Department of Physiology, Faculty of Medicine, Addis Ababa University; Ethiopian Health and Nutrition Research Institute, Addis Ababa, Ethiopia.

RESULTS

The response of *Catha edulis* extract on superior mesenteric blood vessels in guinea pigs

As shown in table 1, infusion of 0.2ml of *Catha edulis* extract solution had significantly (p<0.05) increased mean systolic and diastolic blood flow velocities both in superior mesenteric arteries and veins. The mean systolic blood flow velocity had shown an increment from the base line of 33.44 ± 4.82 cm/s flow velocity to 57.24 ± 3.40 cm/s; while the diastolic from16.66 ± 2.43cm/s to 36.26 ± 7.02 cm/s in arteries. Similarly in veins, the mean systolic blood flow velocity had shown an increment from the base line of 16.65 ± 3.14 cm/s flow velocity to 36.94 ± 11.03 cm/s; while the diastolic blood flow velocity altered from 12.55 ± 3.73cm/s to 27.64± 13.34 7.02 cm/s.

Table 1: The effects of *Catha edulis* extract solution on superior mesenteric artery and vein blood flow velocities (cm/s) in male guinea pigs (n=10). Data are presented as Mean ± SE.M.

Variables	Mean ± SE. Mean		Minimum		Maximum		Level of Significance
Artery	Baseline	After	Baseline	After	Baseline	After	
SysV (cm/s)	33.44 ± 4.82	57.24 ± 3.40 *	27	51.8	44	62.6	P<0.05
DiaV (cm/s)	16.66 ± 2.43	36.26 ±7.02 *	13	22	22	43.7	P<0.05
RI	0.36 ± 0.14	0.54 ± 0.27 *	0.17	0.21	1.00	0.69	P=0.2
PI	1.99 ± 2.01	0.79 ± 0.59 *	0.66	0.62	5.59	1.93	P= 0.05
Vein							
SysV (cm/s)	16.65 ± 3.14	36.94 ± 11.03 *	12	14	20.33	57.2	P<0.05
DiaV (cm/s)	12.55 ± 3.73	27.64 ± 13.34 *	7	16.33	14.14	50.72	P<0.05
RI	0.24 ± 0.16	0.24 ± 0.16	0.10	0.10	0.55	0.46	None
PI	0.56 ± 0.22	0.55 ± 0.56	0.30	0.12	0.90	1.63	None

*Significant; SysV (cm/s) = Systolic blood flow velocity, DiaV (cm/s) = Diastolic blood flow velocity, RI= Resistive index, PI= Pulsatile index.

Figure 1: An invasive single record of superior mesenteric artery blood flow measurement by Doppler blood flow meter in guinea pig before *Catha edulis* extract infusion.

Figure 2: An invasive single record of superior mesenteric artery blood flow measurement by Doppler blood flow meter in guinea pig after 20 minutes of Catha edulis extract solution (0.2ml i.v.) infusion. A marked increase in systolic blood flow velocity from 36 to 58cm/s and diastolic blood flow velocity from 27 to 45cm/s.

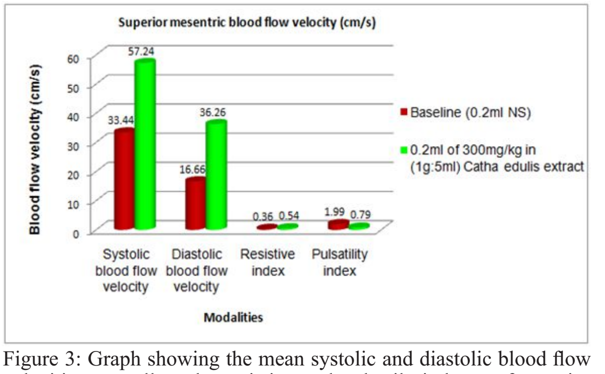


Figure 3: Graph showing the mean systolic and diastolic blood flow velocities as well as the resistive and pulsatile indexes of superior mesenteric artery in male guinea pigs (n = 10). Intravenous infusion of 0.2ml of Catha edulis extract solution prepared from a dose of 300mg/kg body weight in the concentration ratio of 1mg: 5ml had significantly (p< **0.05**)increased the mean systolic and diastolic blood flow velocities. Correspondingly the resistance had increased while the pulsatile index decreased significantly.

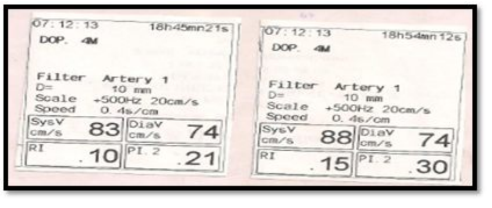


Figure 4: An invasive record of superior mesenteric artery blood flow by Doppler blood flow meter in guinea pigs after 0.2ml i.v infusion of *Catha edulis* extract. It had revealed peak increment of both systolic (83,88 cm/s) and diastolic (74,74 cm/s) blood flow velocities; while a marked decrease pulsatile indexes (0.21, 0.30) respectively.

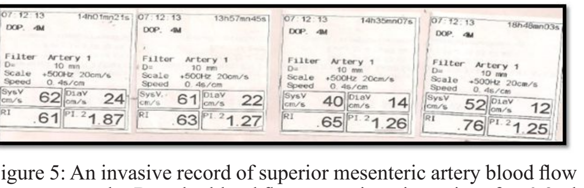


Figure 5: An invasive record of superior mesenteric artery blood flow measurement by Doppler blood flow meter in guinea pigs after 0.2ml i.v infusion of *Catha edulis* extract. It had revealed a relative decreased in systolic (62, 61, 40, 52 cm/s) and diastolic blood (24,22,14,12) flow velocities, which was occurred in some cases when there had marked increase in pulsatile indexes (1.87

,1.27,1.26,1.25) greater than 1.00 respectively.

DISCUSSIONS

Catha edulis extract solution had significantly increased mean systolic and diastolic blood flow velocities both in superior mesenteric arteries and veins in guinea pigs. Correspondingly the resistance had increased while the pulsatile index decreased significantly. Interestingly, even though there had significant ($p< 0.05$) increased in blood flow velocity in veins during systolic phase (from 16.65 ±3.14 to 36.94 ± 11.03) and diastolic phase (from 12.55 ±3.73 to 27.64 ± 13.34), there had been no change at all in mean resistive index (0.24± 0.16) in both baseline/before (0.2ml i.v. N.S) and treated/after (0.2ml i.v. *Catha edulis* extract solution) infused guinea pigs. This result confirms the scientific fact that, venous system has high capacitance, low pressure reservoir and resulting little resistance to flow while arteries are the site of greatest vascular resistance in the circulation. This result is also strengthened by a reduction in pulsatlity index from 1.99 ± 2.01 to 0.79± 0.59 and increment in resistive index value from 0.36 ± 0.14 to 0.54 ± 0.27 of arteries (n=10).

As the resistance index had increased the blood flow velocity increased. This finding agreed with the studies of Al Motarreb, *et al*. (2002); Kalix *et al*. (1991) and Hassan et al. (2000) on the effect of khat on the cardiovascular system that khat chewing is associated with elevated mean diastolic blood pressure, which is consistent with the peripheral vasoconstrictor effect of Cathinone. Khat chewing leads to a significant increase in systolic and diastolic blood pressures persisting for 3 to 4 hours after the onset of chewing (Toennes et al., 2003; Widler *et al*., 1994). According to Al Motarreb *et al*. (2010), these effects of Cathinone occur by two mechanisms. Primarily Cathinone can act as an indirect sympathomimetic amine (ISA mechanism) that inters into sympathetic neurons and cause a release of noradrenaline on to α-adrenoreceptor. Secondly it can also act via a sympathomimetic-independent mechanism by directly acting on trace amine-associated receptors (TAAR mechanism) results in vasoconstriction. Kalix and Braenden (1985) also identified that khat chewing is associated with constipation, probably caused by a combination of the astringent properties of the khat tannins and the sympathomemetic properties of Cathinone. The sympathomemetic properties of Cathinone overwhelm the function of cholinergic innervations of the gut; resulting a decrease gut motility. This may be the reason for a decreased blood flow rate (i.e. an increased flow velocity) through vasoconstriction behind Khat chewing/or oral administration of Cathinone.

CONCLUSION

From the results of acute hemodunamic response, we conclude that *Catha edulis* extract solution (0.2ml i.v. infusion) had significantly increased the mean systolic and diastolic blood flow velocities both in superior mesenteric arteries and veins in guinea pigs. Correspondingly the resistance had increased while the pulsatile index decreased significantly. As the resistance index had increased the blood flow velocity increased (i.e. flow rate/volume decreased). Therefore, khat chewing (*Catha edulis*) could decrease the blood flow volume to the gastrointestinal tract. So, it may aggravate stomatitis, oesophagitis and gastritis diseases condition of the gastrointestinal tract as well as cardiovascular diseases such as hypertension and myocardial infarction and even may lead to fatal condition in chronic higher dose oral administration of *Catha edulis*.

REFERENCES

[1]. Al Motarreb A, Al Kebsi M, Al Adhi B, Broadley KJ. (2002) Khat chewing and acute myocardial infarction. Heart 2002; 87:279-280.

[2]. Al-Motarreb, A.L, Al-Habori M, Broadley KJ. (2010). Khat chewing, cardiovascular diseases and other internal medical problems: The current situation and directions for future research. J Ethnopharmacology. vol. 132: 540-548.

[3]. Brenneisen R, Fisch HU, Koelbing U, Geisshusler S, Kalix P. (1990) Amphetamine-like effects in humans of the khat alkaloid cathinone. Br J Clin Pharmacol; 30:825-828.

[4]. Drake, P.H. (1988). Khat chewing in the Near East. Lancet, i, 532-533.

[5]. Graziani, M., M.S. Milella and P. Nencini (2008). Khat chewing from the pharmacological point of view: An update. Sub. Use Misuse, 43: 762-783. DOI: 10.1080/10826080701738992

[6]. Guyton and Hall. (2006). Text book of medical physiology: 11th edition, PP., 163-164, 771-778.

[7]. Hassan, N.A., Gunaid, A.A., El Khally, F.M. and Murray-Lyon, I.M. (2000). The effect of khat chewing on blood pressure and heart rate in healthy volunteers. Tropical doctor, 30: 107-8.

[8]. Hassan, N.A., Gunaid, A.A., El Khally, F.M. and Murray-Lyon, I.M. (2002).The subjective effects of chewing Qat leaves in human volunteers. Ann Saudi Med; 22 (1-2): 34-7.

[9]. Hassan, N.A., Gunaid, A.A., El Khally, F.M. and Murray-Lyon, I.M. (2005). Khat chewing and arterial blood pressure. A randomized controlled clinical trial of selective α1 and β1 adrenoceptor blockades. Saudi medical journal, 26:537-41.

[10]. Kalix P. (1991). The pharmacology of psychoactive alkaloids from ephedra and catha. J. Ethnopharmacol. 3: 201–208.

[11]. Kalix, P. and Braenden, O. (1985). Pharmacological aspects of the chewing of khat leaves. Pharmacol Rev vol. 37:149-164.

[12]. Silverthorn, D.U. (2009). Physiology (in German: Physiologie). Pearson Studium

[13]. Toennes S.W., Harder, S., Schramm, M., Niess, C. and Kauert, G.F. (2003). Pharmacokinetics of cathinone, cathine and norephedrine after the chewing of khat leaves. Br J Clin Pharmacol; 56(1):125-30.

[14]. United Nations Narcotic Laboratory. Studies on the chemical composition of khat. (1975)

[15]. Widler, P., Mathys, K., Brenneisen, R., Kalix, P. and Fisch, H. (1994). Pharmacod ynamics and pharmacokinetics of khat: a controlled study. Clinical Pharmacology & Therapeutics 55, 556–562.