**INTRODUCTION**

The chemical constituents of khat have been studied since the late 19th century. Fleckiger 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-aminopropiophenone) 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 release. 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 transient 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 (Hassan 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 sympathetic nervous 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. Stimulation of the sympathetic nervous system increases the total peripheral resistance. Parasympathetic endings in arterioles are always cholinergic and promote vasodilatation. 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 postganglionic 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.
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 from 16.66 ± 2.43 cm/s flow velocity 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 ± 3.73 cm/s to 27.64 ± 13.34 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 ± S.E.M.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>After</th>
<th>Level of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artery</td>
<td></td>
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<tr>
<td>SystV (cm/s)</td>
<td>33.44 ± 4.82</td>
<td>57.24 ± 3.40</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>DiastV (cm/s)</td>
<td>16.66 ± 2.43</td>
<td>36.26 ± 7.02</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>RI</td>
<td>0.36 ± 0.11</td>
<td>0.54 ± 0.27</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>PI</td>
<td>0.56 ± 0.22</td>
<td>0.53 ± 0.60</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Vein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SystV (cm/s)</td>
<td>16.65 ± 3.14</td>
<td>36.94 ± 11.03</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>DiastV (cm/s)</td>
<td>12.55 ± 3.73</td>
<td>27.64 ± 13.34</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>RI</td>
<td>0.46 ± 0.10</td>
<td>0.52 ± 0.19</td>
<td>None</td>
</tr>
<tr>
<td>PI</td>
<td>0.42 ± 0.23</td>
<td>0.36 ± 0.38</td>
<td>None</td>
</tr>
</tbody>
</table>

*Significant: SystV (cm/s) = Systolic blood flow velocity, DiastV (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 decrease in systolic (62, 61, 40, 52 cm/s) and diastolic (24, 22, 14, 12) flow velocities, which was occurred in some cases when there had marked increase in pulsatile indexes (1.87
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 (26.94 ± 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. NS) 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 pulsatility index from 1.99 ± 2.01 to 0.79± 0.39 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 interst in sympathetic neurons and cause a release of noradrenaline on to α-adrenoreceptors. 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 sympathomimetic properties of Cathinone. The sympathomimetic 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 hemodynamic 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


