

EFFECTS OF *VITEX DONIANA* (SWEET) STEM BARK AQUEOUS EXTRACT ON KETAMINE ANAESTHESIA IN RABBITS**S. SANNI*, P.A. ONYEYILI AND J.G. THLIZA**Department of Veterinary Physiology and Pharmacology
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Abstract

The effects of *Vitex doniana* (sweet), black plum, stem bark aqueous extract alone on vital parameters (temperature, respiratory rate, heart rate), and sleeping time as well as the effects of the extract on the same parameters before and after ketamine anaesthesia in rabbits were investigated. Twenty rabbits were randomly separated into four equal groups and were administered 400, 600, 800 and 1200mg/kg-1 respectively of the aqueous extract of *Vitex doniana* (sweet) stem bark intraperitoneally. The temperature, respiratory and heart rates of the rabbits were taken before and after extract administration at 10th, 20th, 30th, 60th and 180th minutes. Fifteen other rabbits were randomly selected and separated into three groups of five each. Group I was administered 50mg/kg of ketamine alone intramuscularly. Groups II and III were administered 200 and 400mg/kg body weight respectively of the extract intraperitoneally 30 minutes prior to the administration of the same dose of ketamine as in group I. Temperature, heart and respiratory rates, as well as onset of, and recovery from, anaesthesia were measured prior to and after the administration of the agents. The administration of the extract alone to rabbits produced increase in temperature and decrease in respiratory rate and in heart rate. The increase in temperature and respiratory rates was associated with presence of reducing sugars in the extract and its analeptic/toxic effects respectively, while the decrease in all the parameters was associated with central nervous system depression. The administration of the extract prior to ketamine administration produced less significant ($P < 0.05$) decrease in respiratory rate and higher percentage decrease in heart rate but no significant ($P > 0.05$) effect on temperature compared with ketamine used alone. It is therefore concluded that the aqueous extract of *Vitex doniana* (sweet) stem bark used alone altered the vital parameters while it has a reversal action on respiratory rate and it intensifies the depression of heart rate when used prior to ketamine anaesthesia.

Introduction

Anaesthesia is defined as loss of sensation resulting from pharmacological depression of nerve function or from neurological dysfunction (Stedman, 1995). Many compounds have anaesthetic properties that demonstrate direct activity in modulating haemodynamics, myocardial blood flow and oxygenation and myocardial energy supply and utilization (Muir, 1977), all of which affect heart rate, respiratory rate and temperature of the subject.

The undesirable side effects such as the occurrence of hypothermia, which indicates depression (Irwin *et al.*, 1959; Hall and Clarke, 1991), vomiting, nausea, etc., associated with anaesthetics have necessitated the use of more than one agent to achieve ideal anaesthesia.

Ketamine (2-(0-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride is a dissociative anaesthetic which induces unconsciousness within 30 seconds of administration. It also does not induce hypoxia and hypercercbic stimulation of respiration in anaesthetic doses (Hirshman *et al.*, 1975). The undesirable side effects of ketamine which include poor muscle relaxation, increased heart rate and intracranial and intraocular pressure (Lawrence *et al.*, 1997), retention of pharyngeal, laryngeal, pain and palpebral reflexes (Bovill *et al.*, 1971) is a pointer to its combination with other agents. In animals, ketamine is used with other drugs like benzodiazepines and alpha 2 adrenoceptor agonists in order to reduce the dose of ketamine, improve muscle relaxation and to increase the effectiveness of the dissociative agent as an anaesthetic (Hall and Clarke, 1991).

Many plants and plant products have depressant properties and some have been shown to alter the effects of conventional drugs. Decoctions of *Lippia alba* leaf when inhaled promote sleep (Wong, 1976). *Ficus sycomorus* L

was shown to have sedative effect by increasing the amylobarbitone sleeping time in rats (Sandabe *et al.*, 2003).

Vitex doniana (sweet), black plum, is used among the Kanuri in the treatment of mental illness (Bolza and Keating, 1972). Sanni (2002) reported that the stem bark aqueous extract of *Vitex doniana* (sweet) causes depression and muscle weakness in rats. At present, not much has been done on the central nervous effects of the various extracts of the plant.

This study therefore aims at verifying the effects of the stem bark aqueous extract of *Vitex doniana* (sweet) on ketamine-induced anaesthesia in rabbits (*Oryctolagus cuniculi*).

Materials and methods*Collection of plant materials*

The stem bark, twigs and flowers of *Vitex doniana* (sweet) was obtained from Auno areas of Borno state, Nigeria and was sent to the Biological Science Department, University of Maiduguri, for identification by a plant taxonomist. A voucher specimen was deposited in the Department of Veterinary Physiology and Pharmacology, University of Maiduguri.

Preparation of extract

The stem bark of *Vitex doniana* (sweet) was washed with distilled water to remove dust. It was sun dried and ground into powder using pestle and mortar. Eight hundred grams of the powdered bark was soaked for forty-five minutes into two liters of distilled water and was boiled for one hour then cooled and filtered. The filtrate was concentrated to 5.1mg/ml, and stored in a refrigerator at 4°C until used.

Experimental animals

Thirty-five rabbits (*Oryctolagus cuniculi*) of both sexes were used. They were kept in cages and were fed groundnut hay and vegetables and allowed access to water ad-libitum. The rabbits were administered amprolium at 5g/liter of clean drinking water approximately two weeks before the beginning of the experiment to control coccidia organisms.

Experimental procedures

Twenty rabbits were randomly separated into four (4) groups of five rabbits each. The groups were treated with 400, 600, 800 and 1200mg/kg of the water extract of the stem bark of *Vitex doniana* (sweet) intraperitoneally. The vital parameters measured were temperature, heart and respiratory rates. The parameters were obtained immediately before and after the administration of extract at different time intervals (10th, 20th, 30th, 60th and 180th minutes)

The effect of *Vitex doniana* (sweet) stem bark extract on ketamine anaesthesia

Three groups of five rabbits each were used. Group I was given 50mg/kg of ketamine alone while groups II and III were administered 200 and 400mg/kg body weight of the stem bark extract respectively 30 minutes prior to the administration of ketamine. All extract treatments were through intraperitoneal route, while ketamine was given intramuscularly. The vital parameters such as rectal temperature, heart rate (measured by the use of stethoscope) and respiratory rate (abdominal beats) were measured prior to, and after the administration of the agents. The periods of onset and recovery from anaesthesia were recorded.

Statistical analysis

Results were expressed as mean \pm standard deviation. Analysis of variance (ANOVA) and least significant difference (LSD) were used to compare the means, and the "null" hypothesis was rejected at 5% level of probability.

Results

Administration of *Vitex doniana* (Sweet) stem bark extract to rabbits at various doses resulted in temperature variations. At 600mg/kg, significant ($P<0.05$) decreases in body temperature were obtained for up to 180minutes post treatment. The 800 and 1200mg/kg extract doses produced a slight decrease in body temperature except at 10 minutes post extract treatment for 1200mg/kg dose where the temperature increased by 2.77%. The 400mg/kg dose only produced decreased body temperature at 30 and 60 minutes post extract treatment (Table 1).

The administration of various doses of *Vitex doniana* (sweet) to rabbits altered the respiratory rate. At lower doses (400 and 600mg/kg), the extract produced a dose dependent decrease in respiratory rate while at higher doses (800 and 1200mg/kg) increase in respiratory rate was produced when compared with the control. However, the increase in respiratory rates obtained was not dose dependant (Table 2).

The result of the effects of *Vitex doniana* (sweet) on heart rate of rabbit when compared to control indicated a significant ($P<0.05$) increase of 31.28, 32.94 and 26.07 percent at 20th, 60th and 180th minutes respectively for the group treated with 400mg/kg. The group treated with 600mg/kg of the extract showed decrease heart rate except at 20 minutes post treatment when there was 1.10% increase in heart rate. Treatment of rabbits with 800mg/kg

resulted in decreased heart rate (Table 3), while the animals treated with 1200mg/kg dose showed increased heart at 0 and 30min post treatment while at 20, 60 and 180 minutes after administration of the extract, the heart rate decreased by 0.51%, 14.8% and 12.0% respectively.

A significantly ($P<0.05$) higher temperature was recorded at zero hour (before administration of agents) for rabbits administered ketamine 30 minutes after administration of 200mg/kg of the extract of *Vitex doniana* (sweet) (Table 4) as compared to other doses. The absolute values showed that rabbits administered 200mg/kg extract 30 minutes before administration of 50mg/kg of ketamine, had a slight decrease in temperature while for those administered 400mg/kg of the extract, a slight increase in temperature was recorded (Table 4).

The respiratory rate of rabbits administered ketamine 30 minutes after administration of 200 and 400mg/kg *Vitex doniana* (sweet) stem bark aqueous extract significantly ($P<0.05$) increased when compared to those of rabbits administered 50mg/kg ketamine alone. All the doses however, showed a significant ($P<0.05$) decrease compared to controls (Table 5). However, while those treated with 50mg/kg ketamine alone showed about 80% decrease in respiratory rate, the administration of same dose of ketamine to rabbits 30 minutes after the administration of 200 and 400mg/kg of extract resulted in only 60 and 50% decrease in respiratory rates respectively.

There were significant ($P<0.05$) decrease in heart rates of rabbits administered 50mg/kg of ketamine alone and its combination with 200 and 400mg/kg of *Vitex doniana* (sweet) extract (Table 6). Decreases of 20, 22 and 38% in heart rates were recorded for ketamine alone, ketamine plus 200mg/kg and ketamine plus 400mg/kg of extract of *Vitex doniana* (sweet) respectively (Table 6). The decrease in heart rates appear to be dose dependant with the combination with the highest extract dose (400mg/kg) producing highest heart rate depression (Table 6).

The administration of ketamine alone and its combination with various doses of *Vitex doniana* (sweet) to rabbits resulted in decreased respiratory rates. Prior to administration of agents the respiratory rates were 142.4 ± 10.69 , 157.6 ± 10.69 and 164.8 ± 10.69 cycles per minute respectively in groups treated with ketamine alone, ketamine plus 200mg/kg extract and ketamine plus 400mg/kg extract. However, following the administration of various combinations of extract and ketamine, the respiration significantly ($P<0.05$) decreased to 32.00 ± 3.75 cycles per minute in animals treated with ketamine alone, 62.00 ± 7.35 cycles per minute in rabbits treated with ketamine plus 200mg/kg *Vitex doniana* extracts and 78.20 ± 7.35 cycles per minute in animals treated with ketamine plus 400mg/kg extract. The result indicates that the higher the extract dose used the lesser the respiratory depression (Table 5).

All the rabbits irrespective of dose or agents combinations showed appreciable length of anaesthesia (Table 7). However, while 50mg/kg of ketamine alone produced 26 minutes of anaesthesia, rabbits treated with 50mg/kg of ketamine 30 minutes after administration of 200 and 400mg/kg of the aqueous extract of *Vitex doniana* (sweet) stem bark produced 15 and 21 minutes of anaesthesia respectively (Table 7).

Table 1: Effects of *Vitex doniana* (sweet) stem bark aqueous extract on temperature (°C, Mean± SD) of rabbits

Extract dose (mg/kg)	n†	Time post-administration (minutes)					
		*0	10	20	30	60	180
400	5	38.32±0.31	39.04±0.39 ^b (+1.88)**	38.84±0.47 (+1.36)	37.80±0.59 (-1.36)	37.92±0.35 (-1.04)	39.14±0.53 ^b (+2.14)
600	5	39.78±0.31 ^a	39.78±0.31 ^a (-5.28)	37.68±0.39 ^y (-4.12)	37.12±0.59 ^y (-6.69)	37.96±0.35 ^y (-4.58)	36.78±0.53 ^y (-7.54)
800	5	37.92±0.31	37.61±0.39 (-0.82)	38.20±0.47 (+0.74)	37.22±0.59 (-1.85)	36.90±0.35 (-2.69)	37.02±0.53 (-2.37)
1200	5	38.78±0.31	39.28±0.39 ^b (+2.77)	37.98±0.47 (-0.58)	37.66±0.59 (-1.41)	37.65±0.35 (-1.44)	37.76±0.53 (-1.15)

†Sample size

*Control

**Figures in bracket represent percent (%) increase (+) or decrease (-) as compared to control

^a Significantly (P<0.05) higher than other doses^b Significantly (P<0.05) higher than control^y Significantly (P<0.05) lower than control**Table 2:** Effects of *Vitex doniana* (sweet) stem bark aqueous extract on respiratory rate (cycles/minute, Mean± SD) of rabbits

Extract dose (mg/kg)	n†	Time post-administration (minutes)					
		*0	10	20	30	60	180
400	5	135.2±9.68	123.8±13.81 (-8.43)**	134.4±16.73 (-0.60)	120±16.72 (-10.90)	129.2±14.93 (-4.44)	35.6±16.99 (+0.30)
600	5	203.2±9.68 ^a	162.0±13.81 ^y (-20.28)	164.4±16.73 ^y (-19.09)	173.6±16.72 ^y (-6.69)	135.2±14.93 ^y (-33.46)	41.4±16.99 ^y (-30.41)
800	5	132.8±9.68	158.0±13.81 (+19.00)	148.4±16.73 (+11.75)	152.4±16.72 (+14.76)	133.6±14.93 (+0.06)	119.2±16.99 (-10.24)
1200	5	146.8±9.68	160.4±13.81 (+9.26)	169.2±16.73 (+15.26)	160.8±16.72 (+9.54)	148.8±4.93 (+0.82)	165.6±16.99 (+12.81)

†Sample size

*Control

**Figures in bracket represent percent (%) increase (+) or decrease (-) as compared to control

^a Significantly (P<0.05) higher than other doses^y Significantly (P<0.05) lower than control**Table 3:** Effects of *Vitex doniana* (sweet) stem bark aqueous extract on heart rate (beats/minute, Mean± SD) of rabbits

Extract dose (mg/kg)	n†	Time post-administration (minutes)					
		*0	10	20	30	60	180
400	5	168.8±11.92	166.4±16.15 (-1.42)	221.6±15.61 ^a (+31.28)	219.2±17.30 (+29.86)	224.4±16.49 ^a (-4.44)	212.8±11.84 ^a (+26.07)
600	5	1164.0±11.92	155.4±16.15 (-5.24)	165.8±15.61 (+1.10)	157.4±17.30 (-4.02)	155.6±16.49 (-5.12)	131.0±11.84 (-20.12)
800	5	164.0±11.92	146.8±16.15 (-10.49)	150.4±15.61 (-8.29)	157.2±17.30 (-4.15)	152.0±16.49 (-7.32)	154.4±11.84 ^b (-5.85)
1200	5	156.8±11.92	188.6±16.15 (+20.28)	156.0±15.61 (-0.51)	157.6±17.30 (+0.51)	133.6±16.49 (-14.80)	138.0±11.84 (-12.0)

†Sample size

*Control

**Figures in bracket represent percent (%) increase (+) or decrease (-) as compared to control

^a Significantly (P<0.05) higher than other doses^b Significantly (P<0.05) higher than control

Table 4: Effects of *Vitex doniana* (sweet) stem bark aqueous extract on temperature (°C, Mean± SD) of rabbits induced with ketamine anaesthesia

Drug/Extract dose	n†	*Time post-administration of extract/ketamine (minutes)	
		0	30
50mg/kg ketamine	5	38.82 ± 0.25	38.58 ± 0.42 (-0.62)
50mg/kg ketamine plus 200mg/kg extract	5	39.02 ± 0.25 ^a	38.38 ± 0.42 (-1.64)
50mg/kg ketamine plus 400mg/kg extract	5	38.48 ± 0.25 ^a	38.62 ± 0.42 (+0.36)

^a Significantly (P<0.05) higher than other doses

†Sample size

*Ketamine was administered 30 minutes after extract administration

Table 5: Effects of *Vitex doniana* (sweet) stem bark aqueous extract on respiratory rate (cycles/minute, Mean± SD) of rabbits induced with ketamine anaesthesia

Drug/Extract dose	n†	*Time post-administration of extract/ketamine (minutes)	
		0	30
50mg/kg ketamine	5	142.4 ± 10.69	32.00 ± 7.35 ^y (77.53)**
50mg/kg ketamine plus 200mg/kg extract	5	157.6 ± 10.69	62.00 ± 7.35 ^y (60.66)
50mg/kg ketamine plus 400mg/kg extract	5	164.8 ± 10.69	78.20 ± 7.35 ^{ay} (52.55)

†Sample size

*Ketamine was administered 30 minutes after extract administration

**Figures in bracket represent percent (%) decrease compared to control

^a Significantly (P<0.05) higher than other doses^y Significant (P<0.05) decrease compared to control**Table 6:** Effects of *Vitex doniana* (sweet) stem bark aqueous extract on heart beat (beats/minute, Mean± SD) of rabbits induced with ketamine anaesthesia

Drug/Extract dose	n†	*Time post-administration of extract/ketamine (minutes)	
		0	30
50mg/kg ketamine	5	136.4 ± 14.84	107.4 ± 12.71 ^y (21.26)**
50mg/kg ketamine plus 200mg/kg extract	5	167.8 ± 14.84	132.0 ± 12.71 ^y (21.33)
50mg/kg ketamine plus 400mg/kg extract	5	188.0 ± 14.84	136.0 ± 12.71 ^y (27.66)

†Sample size

*Ketamine was administered 30 minutes after extract administration

**Figures in bracket represent percent (%) decrease compared to control

^y Significant (P<0.05) decrease compared to control**Table 7:** Effects of *Vitex doniana* (sweet) stem bark aqueous extract on time of onset and recovery from ketamine-induced anaesthesia in rabbits

Drug/Extract dose	n†	*Time post-administration of extract/ketamine (minutes)	
		0	30
50mg/kg ketamine	5	2.80 ± 1.10	28.20 ± 4.17
50mg/kg ketamine plus 200mg/kg extract	5	6.40 ± 1.10	21.40 ± 4.17
50mg/kg ketamine plus 400mg/kg extract	5	4.20 ± 1.10	25.40 ± 4.17

†Sample size

*Ketamine was administered 30 minutes after extract administration

Discussion

The administration of the aqueous extract of *Vitex doniana* (sweet) stem bark alone and its combination with ketamine anaesthetic has been shown to have effects on the vital parameters (temperature, respiratory and heart rates), as well as on the sleeping time of rabbits.

There was an increase in temperature when the extract was used alone which may be attributed to the presence of reducing sugar in the extract as earlier reported (Sanni,

2000). The metabolism of sugars produces energy (Strove, 1989, Guyton, 1997), which increases the temperature of the body. The decrease in temperature noticed may be due to central nervous system depression. Irwin *et al.* (1959) reported that the presence of hypothermia when plant extract is used is an indication of central nervous system depression. However, the combination of the extract with ketamine did not produce an appreciable effect on the

temperature as opposed to the hypothermia normally associated with ketamine alone.

The decrease in respiratory rate noticed at lower doses when the extract was used alone may be an indication of central nervous system depression while the increase in the same parameter at higher doses indicate analeptic or toxic effect which may be compensatory to the depressant effect. Irwin *et al.* (1959) reported that respiratory rate may be accelerated by toxic extracts or respiratory analeptic and may be decelerated by respiratory depressants or agents. The combination of the extract with ketamine however produced less decrease (between 50-60%) in respiratory rate than the decrease (80%) produced by ketamine alone.

The decrease in heart rate when the extract was used alone may be attributed to the saponin content of the extract. Sage-Saka, (1995) reported that antihypertensive saponin isolated from the methanolic extract of tea leaf reduced blood pressure for 2 to 24 hours. The increase in heart rate in some of the groups may be due to compensatory erythropoietic activity of the extract. Increased erythropoietic activity, which may increase blood pressure, was reported (Sanni, 2002) and it was associated with the saponin content of the extract. However, in combination with ketamine, higher percentage decrease in heart rate was recorded. The decrease may indicate its sympatholytic or its ganglion blockage activity. Sofowora, (1984) reported that if an extract causes a brief decrease in blood pressure it may have a sympatholytic activity and if a prolonged decrease beyond 5 minutes a ganglion blocking activity. The administration of the extract reduced the anaesthetic period of ketamine. This may probably be due to the saponin content of the extract that may be an inducer of liver microsomal enzyme thereby reducing the concentration of the anaesthetic agent. Xing, *et al.*, (1995) reported that gingseng flower bud saponins increased the superoxide dismutase (SOD) enzyme content in myocardium, lung and liver of dogs. This may also have contributed to the action of the extract seen in temperature and respiratory rate.

Conclusion

The aqueous extract of *Vitex doniana* (sweet) stem bark altered the temperature, respiratory and heart rates. The decrease was associated with lower doses and increase associated with higher doses. The extract could be said to have a central nervous system depressant / stimulatory as well as cardiovascular effects.

The extract reduced the respiratory effect of ketamine; potentiate its effect on heart rate, with no appreciable effect on its hypothermic property. It also reduced the anaesthetic period of ketamine.

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