Special Conference Edition, April, 2022
http://dx.doi.org/10.4314/bajopas.v13i1.22S

Bayero Journal of Pure and Applied Sciences, 13(1): 123 - 128
ISSN 2006 – 6996

ANTIPSYCHOTIC EVALUATION OF ETHANOL EXTRACT OF *Tapinanthus globiferus* A. RICH GROWN ON *Vitellaria paradoxa* HOST IN MICE

[1]*Abdullahi, M.H. and [2]Sani, I.H.
[1]Department of Pharmacology and Therapeutics, Bayero University, Kano
[2]Department of Clinical Pharmacology and Therapeutics, College of Health Sciences, Yusuf Maitama Sule University, Kano, Nigeria,
*Corresponding author; *E-mail:* mahuguma.pha@buk.edu.ng *Tel:* +234 08065541850

ABSTRACT
Tapinanthus globiferus has evolved to mimic the foliage of Vitellaria paradoxa as a host tree. It is used locally for the treatment of various diseases such as diabetes, stroke, headaches, insomnia, migraines, pains and schizophrenia. Though, patients with psychosis often use natural medicines and yet it is unclear whether these are safe and effective. This study aimed to evaluate the antipsychotic activity of ethanol extract of Tapinanthus globiferus grown on Vitellaria paradoxa in mice. Phytochemical screening and acute toxicity studies were carried out using standard methods. The antipsychotic activity of the extract was evaluated using haloperidol-induced catalepsy, apomorphine-induced climbing behaviour and tail suspension test in mice. The studies revealed that, the extract contained valuable biological active compounds with LD_{50} of 1,300 mg/kg i.p. which are slightly toxic. Tapinanthus globiferus offered significant effect in duration of haloperidol-induced catalepsy at 350 mg/kg, apomorphine-induced climbing behaviour at 87.5 and 175 mg/kg and no effect in duration of immobility in tail suspension in mice at all doses compared to control. The observed effect of the extract on haloperidol-induced catalepsy and significant reduction in climbing behaviour induced by apomorphine showed that the extract may have effect on dopamine receptors and antipsychotic agents antagonise dopamine D_2-receptors. The investigation revealed that extract of T. globiferus contained active constituents which have antipsychotic effect in mice.
Keywords: Tapinanthus globiferus, Vitellaria paradoxa, antipsychotic, apomorphine, haloperidol, imipramine

INTRODUCTION

Psychosis is a severe mental disorder in which a psychotic patient experiences a distortion or loss of contact with reality and blurring of consciousness. It is characterised by depression, delusion, hallucination, anxiety, sleep disturbance, thought disorder, social withdrawal and impaired role functioning (Ajao *et al.,* 2017). Antipsychotic drugs used in the treatment of schizophrenia act on dopamine D_2-receptor. However, haloperidol is widely used antipsychotic drug with a full antagonist at postsynaptic striatal D_2 and D_1 receptors (Bennett and Brown, 2008) and effective in the management of schizophrenia. Apomorphine is a derivative of morphine having structural similarities to dopamine and a full agonist at D_1 and D_2 receptors (Bennett and Brown, 2008) and it is a short-acting central and peripheral dopamine receptor agonist. Apomorphine has been used with limited success in ameliorating the symptoms of parkinson's disease and to induce emesis (Abiola *et al.*, 2019). Apomorphine induced emesis by acting directly on the chemoreceptor trigger zone (CTZ) or direct stimulation of postsynaptic striatal and mesolimbic dopamine receptors to induce stereotypic climbing behaviour (Jeong *et al.,* 2005). Imipramine is an effective drug for the treatment of depression and the most widely used tricyclic antidepressant in the management of panic disorder (Hashimoto, 2010). *T. globiferus* has been reported to contained alkaloids, flavonoids, saponins, tannins and cardiac glycosides (Bassey, 2012) and known to have various pharmacological activities on man and animals.

Previous studies on *T. globiferus* revealed that, it's possess a number of therapeutic uses for managing a wide range of diseases such as diabetes mellitus and hypertension (Akanji *et al*., 2009; Ogbonnia *et al*., 2012), oxidative stress and inflammation (Adekunle *et al*., 2012; Adekunle, 2012) and trypanosomiasis (Abedo *et al*., 2013a). Comparative study on trypanocidal activity and phytochemical screening of *T. globiferus* and *Gongronema latifolium* were also reported (Abedo *et al*., 2013b). Most mistletoe species have evolved to mimic the foliage of their host tree and also their efficacy depending on the host tree. *Vitellaria paradoxa* commonly called shea butter, belongs to the family of Sapotaceae and has been used in traditional medicine in the treatment of epilepsy and diseases related to the brain like agitations, anxiety, dizziness, headaches, insomnia, migraines, pains and schizophrenia (Burkill, 2000). Animal models are used to screen the activity of neurochemical agents on the receptors. For example, schizophrenia involved mainly the neurotransmitters dopamine and glutamine hence antagonism of dopamine D2 receptors is a common feature of antipsychotic drugs (Lipska and Weinberger, 2000). Hence, this study aimed to evaluate the antipsychotic activity of ethanol extract of *Tapinanthus globiferus* in mice.

MATERIALS AND METHODS

Preparation and fractionation of the Plant Materials: Fresh *Tapinanthus globiferus* (whole mistletoe) grown on *Vitellaria paradoxa* was collected in June, 2021 from Huguma village, Takai Local Government Area, Kano State, Nigeria. *T. globiferus* was identified and authenticated at the Herbarium unit, Department of Botany, Ahmadu Bello University Zaria, Nigeria by comparing with existing voucher specimen number 1052. The plant material was dried under shade until constant weight, crushed and pounded into fine powder. The extraction was conducted with Ethanol (75% in water) using soxhlet extractor and the extract was concentrated on a water bath at temperature of 60^{o}C.

Drugs, Chemicals and Equipment: Drugs and chemicals were obtained from reputable scientific suppliers such as Sigma Aldrich Inc. USA (apomorphine, ethanol and imipramine), Sterop-Belgium (haloperidol) and Dana Plc Nigeria (Normal saline). Equipment used; Franz von Soxhlet apparatus (Soxhlet extractor).

Preparation of drug solutions: The ethanol extract of *Tapinanthus globiferus*, imipramine and apomorphine were prepared by dissolving the powder in normal saline prior to administration. Haloperidol was supplied in ampoule and appropriate dilutions were made with normal saline. The drug solutions were usually prepared fresh during the experiment to maintain stability of the drugs.

Experimental Animals: Albino Mice (19 – 25 g) of age between 7 – 9 weeks were obtained from Animal House, Department of Pharmacology and Therapeutics, Bayero University, Kano, Nigeria and kept in a well-ventilated room, fed with pelletized grower's mash (Vital feeds, Plc Jos) and water ad-libitum was provided throughout the period of the experiment. Mice were allowed to acclimatise prior to experiment. However, during the experiment they were grouped in a simple ratio.

Phytochemical screening: The phytochemical screening of the extract was conducted using standard method reported by Evans (2002).

Median lethal dose (LD_{50}): Determination of LD_{50} of the extract was conducted using the method reported by Lorke (1983).

Haloperidol-induced catalepsy in mice: Catalepsy was induced with haloperidol and assessed by means of a standard bar test at 30 minutes interval for 120 minutes. The study was conducted according to the reported method of Ferre *et al*. (1990) and modified by Salam (2011). Twenty-four adult mice were randomly divided into four groups of six each. The first group received 10 ml/kg body weight *i.p.* of normal saline while second, third and fourth groups received ethanol extract of *T. globiferus* at doses of 87.5, 175 and 350 mg/kg, body weight *i.p.* respectively. Thirty minutes after *i.p.* treatment, mice in all groups were treated with 1.0 mg/kg body weight of haloperidol *i.p*. The mice were positioned so that their hindquarters were on the bench and their forelimbs rested on 1 cm diameter horizontal bar that was 4 cm above the bench, this procedure was carried out 30 minutes after the administration of haloperidol. Mice were judged to be cataleptic if they maintained this position. The length of time for which the mouse maintained this position was recorded with a stopwatch with a maximum duration of 180 seconds and the end point of catalepsy was considered to occur when both front paws were removed from the bar.

Apomorphine-induced climbing behaviour in mice: Mice were selected and divided into four groups of six each. First group served as control and received normal saline (10 ml/kg body weight *i.p.*). The second, third and fourth groups were treated with graded doses of ethanol extract of *T. globiferus* (87.5, 175 and 350 mg/kg, body weight) *i.p.* respectively.

Thirty minutes after *i.p.* treatment, mice in all groups received 3 mg/kg body weight of apomorphine *s.c*. Mice were placed individually in a wire mesh stick cage and the climbing behaviour was scored at 10 minutes interval for a period of 30 minutes. The scoring system used was as follows: 0 = when the four paws are on the floor, 1 = when the two paws are holding the vertical bars and 2 = when the four paws are holding or climbing the vertical bars (Costall *et al*., 1978).

Tail suspension test in mice: The study was conducted according to the methods of Steru *et al.* (1985). Adult mice were randomly divided into five groups of six each. Mice in the first and second groups received normal saline (10 ml/kg) and imipramine (4 mg/kg) respectively (*i.p.*). Third, fourth and fifth groups received graded doses of the ethanol extract of *T. globiferus* (87.5, 175 and 350 mg/kg, body weight) *i.p.* respectively. Thirty minutes after *i.p.* treatment, each mouse was suspended by the tail on the edge of a shelve 58 cm above a table top and length of immobility were recorded for a period of 6 minutes after discarding activity in the first 2 minutes during which the mouse tried to escape. Mouse was considered immobile when hung passively and remains motionless.

Statistical Analysis

Statistical analysis was carried out using SPSS software (version 20). Data were analysed using One Way Analysis of Variance (ANOVA) and values of $p \leq 0.05$ were considered statistically significant. Results were presented as Mean ± Standard Error of the Mean (Mean ± SEM) in tables.

RESULTS AND DISCUSSION

Phytochemical study of the ethanol extract of *T. globiferus* revealed the presence of valuable chemical constituents such as alkaloids, flavonoids, saponins, tannins, steroids and terpenoids (Table 1), some of which have been reported to have sedative, analgesic and antipsychotic properties (Iniaghe *et al*., 2015; Sharma *et al*., 2016; Sapkota *et al.,* 2020). The LD_{50} of the ethanol extract of *T. globiferus* was found to be 1,300 mg/kg *i.p.* in mice, which shown that the extract was slightly toxic in mice. According to Lorke (1983), values of LD_{50} between 1,000 to 5,000 mg/kg are slightly toxic and substance with LD_{50} values greater than 5,000 mg/kg are practically non-toxic.

The ethanol extract of *T. globiferus* offered significant ($p \leq 0.05$) potentiation in the duration of haloperidol-induced catalepsy in mice at dose of 350 mg/kg compared to control group that received 10 ml/kg normal saline (Table 2). The potentiation of haloperidol-induced catalepsy in mice revealed that, the extract has antipsychotic property. Haloperidol is a neuroleptic compound which is observed to act as a D_2 receptor antagonist in the mesolimbic-mesocortical and nigrostriatal pathways (Pathan *et al*., 2009), agents that increase dopamine transmission would inhibit neuroleptic-induced catalepsy (Yadav and Nade, 2008). An agent would induce catalepsy when it can antagonise more than 80% of D_2 receptors (Wadenberg *et al.,* 2001) in the nigrostriatal pathway.

Table 1: Phytochemical Constituents of Ethanol Extract of *Tapinanthus globiferus*

Constituents	Inference
Alkaloids	+
Anthraquinones	+
Carbohydrates	+
Flavonoids	+
Cardiac glycosides	+
Saponins	+
Steroids	+
Tannins	+
Terpenoids	+

Keys: + = Present

Table 2: Effect of Ethanol Extract of *Tapinanthus globiferus* on Haloperidol-induced Catalepsy in Mice

Treatment (mg/kg)	Time spent on the horizontal bar (sec)			
	30	60	90	120
NS 10 ml/kg	84.83 ± 26.15	115.17 ± 25.82	106.83 ± 33.01	139.33 ± 26.80
TgE (87.5)	81.33 ± 32.00	113.83 ± 27.06	129.67 ± 28.85	114.67 ± 34.70
TgE (175)	94.83 ± 38.12	145.17 ± 24.61	143.17 ± 28.33	133.17 ± 21.76
TgE (350)	137.17 ± 21.21 [a]	143.50 ± 26.26	167.17 ±12.83 [a]	180.00 ± 0.00 [a]

[a] $p \leq 0.05$ compared to NS and no significant difference over time–repeated measure ANOVA followed by Bonferroni *post-hoc* test. n = 6, Data = Mean ± SEM, Haloperidol (1.0 mg/kg), route of administration = intraperitoneal, TgE = *Tapinanthus globiferus* Ethanol Extract, NS = Normal saline.

The ethanol extract of *T. globiferus* at doses of 87.5 and 175 mg/kg produced significant ($p \leq 0.05$) reduction in the climbing score in mice induced by apomorphine (10 minutes after administration) compared to control (Table 3). The extract initiate reduction in climbing behaviour induced by apomorphine which revealed the antagonistic effects of the extract on apomorphine receptor. The climbing behaviour observed in mice after apomorphine administration is attributed to activation of D_1 and D_2 receptors (Sapkota *et al.,* 2020). Apomorphines induce climbing behaviour by direct stimulation of postsynaptic striatal and mesolimbic dopamine receptors (Jeong *et al.,* 2005). Antipsychotic drugs antagonise dopamine D_2-receptors and are clinically more effective against hallucinations and delusions (Gardner *et al*., 2005). Reduction in apomorphine-induced stereotypic climbing behaviour in rodents is one of the properties of antipsychotic that might act as dopamine D_1 and D_2 receptor blockade (Pandy *et al*., 2012).

Table 3: Effect of Ethanol Extract of *Tapinanthus globiferus* on Apomorphine-induced Climbing Behaviour in Mice

Treatment (mg/kg)	**Climbing behavioural scores**		
	10	**20**	**30**
NS 10 ml/kg	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00
TgE (87.5)	0.83 ± 0.40[a]	1.33 ± 0.42	1.00 ± 0.37
TgE (175)	0.17 ± 0.17[a]	1.33 ± 0.42	0.33 ± 0.33[a]
TgE (350)	1.00 ± 0.45	1.33 ± 0.42	1.17 ± 0.40

[a]$p \leq 0.05$ compared to NS, non-parametric test; Kruskal-Wallis followed by Duni's test. n = 6, Data = Mean ± SEM, route of administration = intraperitoneal, TgE = *Tapinanthus globiferus* Ethanol Extract, NS = Normal saline, Apomorphine (3 mg/kg s.c).

The ethanol extract of *T. globiferus* at doses of 87.5, 175 and 350 mg/kg did not exhibit any significant ($p \geq 0.05$) effect on duration of immobility in mice suspended by tail. Imipramine (4 mg/kg) used as positive control significantly ($p \leq 0.05$) reduced the duration of immobility in mice compared to control (Table 4). The tail suspension test is one of the most commonly used animal models for screening antidepressant compounds (Vogel, 2008). Many antidepressant compounds are able to reduce immobility as well as to promote the occurrence of escape related behaviour as observed in tail suspension test in mice (Steru *et al*., 1985; Taqa, 2013). The observed decrease in the immobility time at lower dose of 87.5 mg/kg may lead to the conclusion that, ethanol extract of *T. globiferus* has little or no antidepressant activity in mice. However, the increase in the duration of immobility at higher doses may be due to sedative property of the extract. Moreover, luteolin from lemon has been reported to increase immobility time by inducing sedation and calming effect in mice (Terry *et al*., 2009). However, compound that possess effective antidepressant activities significantly reduce the immobility time displayed by rodents after active and unsuccessful attempts to escape when suspended by the tail (Taqa, 2013). Potentiation of catalepsy induced by haloperidol and increased immobility time in tail suspension tests in mice showed an indication of CNS depression activity which was supported by reduction in climbing behaviour induced by apomorphine.

Table 4: Effect of Ethanol Extract of *T. globiferus* on Immobility Time in Tail Suspension Test in Mice

Treatment (mg/kg)	**Immobility (sec)**
NS 10 ml/kg	123.17 ± 8.67
TgE (87.5)	119.50 ± 8.34
TgE (175)	161.83 ± 13.15
TgE (350)	162.17 ± 14.55
IMP (4)	35.33 ± 9.64[a]

[a]$p \leq 0.05$ compared to NS, One way ANOVA followed by Dunnett's *post-hoc* test, n = 6, Data = Mean ± SEM, route of administration = intraperitoneal, TgE = *Tapinanthus globiferus* Ethanol Extract, NS = Normal saline, IMP = Imipramine.

The observed effect of the extract on haloperidol and apomorphine revealed that the extract might have effect on dopamine receptors. Haloperidol is a dopamine receptor antagonist while apomorphine is a short acting central and peripheral dopamine receptor agonist and they are antipsychotic agents. Antipsychotics have variable antagonist actions at dopaminergic, muscarinic, α-adrenoceptors and histaminergic receptors in brain and peripheral tissue (Vogel, 2008) and probably the extract produced effect via dopaminergic pathway.

CONCLUSION

The effects of the ethanol extract of *Tapinanthus globiferus* on haloperidol and apomorphine induced catalepsy and climbing behaviour respectively, indicated that the extract possesses antipsychotic property in mice which may possibly produce its effects via dopaminergic pathway. Hence, the extract might have potential active phytochemical constituents in the management of psychotic disorder.

REFERENCES

Abiola, L.A., Ayofe, M.A., Adedoyin, A. (2019) Neurobehavioural Mechanism of Antidepressant Effect of Methanol Stem Bark Extract of *Adansonia digitate* (*Linn*) in Tail Suspension Test in Mice. *Journal of Advances in Pharmacology and Pharmacy*, **7(1),** 5 – 13. DOI: 10.13189/app.2019.070102

Abedo, J. A., Jonah, O. A., Abdullahi, R. S., Mazadu, M. R., Idris, H.Y., Muhammed, H., Shettima, F. T., Ombugadu, S., Dauda, M., Garba, J., Abdulmalik, U., Kugu, B. A. and Usman, A. O. (2013a). Evaluation of Trypanosomal Activity of *Tapinanthus globiferus* and *Gongronema latifolium* on *Trypanosoma congolense. Bioscience Research,* **10(1):** 20 - 28.

Abedo, J. A., Jonah, A., Abdullahi, R., Mazadu, M., Idris, H., Muhammed, H., Shettima, F., Ombugadi, S., Dauda, M., Garba, J., Abdulmalik, U. and Kagu, B. (2013b). Comparative Studies of *In vitro, In vivo* Trypanocidal Activity and Phytochemical Screening of *Tapinanthus globiferus* and *Gongronema latifolium. International Journal of Animal and Veterinary Advances,* **5(3):** 120 - 124.

Adekunle, A. S., Oyewo, B. E. and Afolabi, O. K. (2012). Therapeutic Efficacy of *Tapinanthus globiferus* on Acetaminophen-induced Nephrotoxicity, Inflammatory reactions and oxidative stress in albino rats. *International Research Journal of Biochemistry and Bioinformatics*, **2(2):** 41 - 45.

Adekunle, A. S. (2012). Increased Inflammatory Activities and Oxidative Stress inHepatotoxicity due to Acetaminophen Administration: Ameliorative Effects of *Tapinanthus globiferus.* http://www.sciencepub.net/report

Ajao, A.A., Afolakemi A.A., Olatunji, O.A., Balogun, F.O & Saheed, S.A. (2017). A synopsis of antipsychotic medicinal plants in Nigeria, Transactions of the Royal Society of South Africa, DOI: 10.1080/0035919X.2017.1386138 http://dx.doi.org/10.1080/0035919X.2017.1386138

Akanji, M. A., Ayorinde, B. T. and Yakubu, M. T. (2009). Anti-lipidaemic Potentials of Aqueous Extract of *Tapinanthus globiferus* Leaves in Rats. *Ethnopharmacology, Chemistry and Medicinal Values,* **25:** 1 - 8.

Bassey, M. E. (2012). Phytochemical Investigations of *Tapinanthus globiferus* (*Loranthaceae*) from two Hosts and Taxonomic implication. *International Journal of Chemical, Environment and Pharmaceutical Research,* **3(2):** 174 - 177.

Bennett, P. N. and Brown, M. J. (2008). Clinical Pharmacology, 10th edition. Churchill Livingstone, Elsevier. pp. 353 - 356.

Burkill, H. M. (2000). *Useful Plants of West Tropical Africa*, Vol. 5, (6th ed.) Royal Botanic Gardens, Richmond, Survey, England, pp. 448 – 460.

Costall, B., Naylor, R. J. and Nohria, V. (1978). Climbing behaviour induced by apomorphine in mice. A potent model for the detection of neuroleptic activity. *Psychopharmacology,* **50(2):** 39 - 50.

Evans WC. (2002) *Phytochemistry*. In: Trease, G.E. and Evans, W.C. (Eds). Pharmacognosy Text book, 15th Ed. Saunders W.B. Pp 233 - 336.

Ferre, S., Guix, T., Prat, G., Jane, F. and Casas, M. (1990). Is experimental catalepsy property measure? *Pharmacology, Biochemistry and Behaviour,* **35(4):** 753 - 757.

Gardner, D. M., Baldessarini, R. J. and Waraich, P. (2005). Modern antipsychotic drugs: A critical overview. *Journal of Canadian Medical Association.,* **172(13):** 1703 - 1711.

Hashimoto, K. (2010). Novel Therapeutic Drugs for Neuropsychiatric Disorders. *Medicinal Chemistry Journal,* **4:** 1 – 4.

Iniaghe, O.L., Magaji, G.M., and Nmeka, O. (2015). Evaluation of Antipsychotic Properties of Aqueous Extract of *Lophira alata* (*Ochnaceae*) and *Afzelia Africana* (*Leguminosae*) Stem Barks in Rats. *Nigerian Journal of Pharmaceutical and Applied Science Research,* **4(3):** 19 – 25.

Jeong, S. H., Kim, J. Y., Kim, E. and Chung, I. W. (2005). Effects of Newer Antipsychotic Drugs on Apomorphine-induced Climbing Behavior in Mice. *Korean Journal of Psychopharmacology*, **16(6):** 455 – 461.

Lipska, B. K. and Weinberger, D. R. (2000). To model a psychiatric disorder in Animals: Schizophrenia as a reality test. *Neuropsychopharmacology*, **23(3):** 223 – 239.

Lorke, D. (1983): A new Approach to Practical Acute Toxicity Testing. *Archives of Toxicology Journal*, **54**: 275 -287.

Ogbonnia, S. O., Anyika, E. N., Mbaka, G. O., Utah, P., Ugwu, D., Nwakakwa, N. and Ota, D. A. (2012). antihyperglycaemic and antihyperliplDaemic effects of aqueous ethanol extract of *Tapinanthus globiferus* leaves and *Treculia africana* root bark and their mixture on alloxan diabetic rats. *Agriculture and Biology Journal of North America,* **3(6):** 237 – 246.

Pandy, V., Narasingam, M. and Mohamed, Z. (2012). Antipsychotic-like activity of Noni (*Morinda citrifolia* Linn.) in mice. *Journal of Traditional, Complementary and Alternative Medicine,* **19(12):** 186 – 192.

Pathan, A. A., Kasture, S. B. and Mahalaxmi, M. (2009). Residue of *Mucuna Pruriens* Potentiates Haloperidol and Clonidine-induced Catalepsy in Mice. *Pharmacologyonline,* **3(1):** 652 – 658.

Salam, A. O. and Nada, S. (2011). Piracetam reverses haloperidol-induced catalepsy in mice. *Turkish Journal of Medical Science*, **41(4):** 693 – 699.

Sapkota, B., Acharya, A., Dangi, B. and Annegowda, HV. (2020). Evaluation of Antipsychotic Activity of Ethanolic Bark Extract of *Myrica Esculenta* in Rats. *Pharmaceutical Sciences and Research,* **7(3):** 153 – 158.

Sharma, K., Parle, M. and Yadav, M. (2016). Evaluation of Antipsychotic Effect of Methanolic Extract of *Ocimum Sanctum* Leaves on Laboratory Animals. *Journal of Applied Pharmaceutical Science,* **6(5):** 171 – 177.

Steru, I., Chermat, R., Thierry, B. and Simon, P. (1985). Tail suspension test: A new method for screening antidepressants in mice. *Psychopharmacology,* **85(3):** 367 – 370.

Taqa, G. A. (2013). Evaluation of Antidepressant Activity of Diphenhydramine in Mice. *Innovare Journal of Medical Sciences*, **1(2):** 15 – 18.

Terry, R., Paul, J., Naomie, M., Robert, D., Suzanne, M. and Thomas, C. (2009). Investigation of the Anxiolytic Effect of Luteolin, a Lemon Balm Flavonoid in the Male Sprague-Dawley Rat. *Journal of American Association of Nurse Anesthesiology,* **77:** 33 – 36.

Vogel, G. H. (2008). Psychotrophic and neurotrophic activity In: Vogel, G. H. (Ed) *Drug discovery and Evaluation: Pharmacological Assays,* Springer-Verlag Berlin Heidelberg New York, pp. 566 – 874.

Wadenberg, M. I., Soliman, A., VanderSpek, S. C. and Kapur, S. (2001). Dopamine D_2receptor occupancy is a common mechanism underlying animal models of antipsychotics and their clinical effects. *Neuropsychopharmacology,* **25(5):** 633 – 641.

Yadav, A. V. and Nade, V. S. (2008). Anti-dopaminergic effect of the Methanolic Extract of *Morus alba* L. leaves. *Indian Journal of Pharmacology*, **40(5):** 221 – 226.