International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1559-1566 www.ijprajournal.com ISSN: 2456-4494

Formulation and Evaluation of Nasal Niosomes of venlafaxine HCL forbrain targeting

P. Samba Siva Rao[1], A. Sanjay[2], B. Navya[3], I. Manasa[4], K. Pavani[5], M. Rajesh kumar[6]

1.Associated professor Dhanvanthari institute of pharmaceutical sciences, Sujatha Nagar, Kothagudem. 2,3,4,5,6. 4thYear 2ndSemester Pharmacy Students of Dhanvanthari institute of pharmaceutical sciences, Sujatha Nagar, Kothagudem, Telangana, India, 507120.

Date of Submission: 15-02-2025 Date of Acceptance: 25-02-2025

ABSTRACT: venlafaxineHcl, a newer antidepressant.The intranasal venlafaxine Hcl Niosomes are effective in the delivery of venlafaxine Hcl to the central nervous system.

Non-ionic surfactant vesicles containing venlafaxine Hcl were prepared using drugSpan60 and cholesterol in the ratios(by weight) of 1:1:1, 1:2:1,1:3:1,1:4:1, and 1:5:1 by using four different methods. The prepared vesicles were characterized for the shape, size, entrapment efficiency, and in-vitro drug release. The particle size distributions were carried out by optical microscopic techniqueand sphericalshape observedby SEMstudies. The drug encapsulation efficiencies varied from 63.25 % to 97.42%. Invitro skin permeation studies were carried out by using PBS (pH: 7.4) as a dissolution medium for 2 hours. From the invitro skin permeation studies the niosomes formulated by sonication method was found to be more satisfactory whichexhibitaencapsulation efficiency of 97.42%, compared than other methods

Keywords: venlafaxine Hcl, Non-ionic surfactant, Entrapment efficiency.in vitro skin permeation studies, Anti-depressant action.

I. INTRODUCTION:

Depression is the most common of the affective disorders, defined as disorders of mood rather than disturbances of thought or cognition; it may range from a very mild condition, bordering on normality, to severe (psychotic) depression accompanied by hallucinations and delusions. Worldwide, depression is a major cause of disability and premature death. In addition to the significant suicide risk, depressed individuals are more likely to die from other causes, such as heart disease or cancer[1].

In order to treat CNS diseases such as depression, anxiety etc., it is necessary to overcome the blood brain barrier. It is well known that the blood–brain barrier (BBB) restricts the transport of most substances from the systemic circulation to the central nervous system (CNS) in order to maintain a stable environment. However, this barrier is also the main obstacle for the delivery of therapeutic substances to the brain, preventing many drugs from reaching thereat therapeutic concentrations. As a result, treatment of some CNS diseases including depression, anxiety by oral or intravenous (i.v.) administration still remains difficult. Therefore, brain-targeting delivery has been a challenging topic in brain diseases therapy in recent years. In the past decade, the use of the nasal cavity as a route for drug delivery has been an area of great interest, especially for systemically acting drugs that are difficult to deliver via routes other than injection, because it is an attractive noninvasive route that can offer advantages such as rapid absorption, avoidance of liver first-pass metabolism, ease of convenience, and self-mediation[2].

Recently it has also been reported that a direct anatomical connection exists between the nasal cavity and the CNS that makes it possible to deliver some substances into the CNS by circumventing the BBB instead of penetrating it, which provides the basis for the development of therapeutic agents for intranasal (i.n.) administration. Many substances, including tracer materials, heavy metals, low molecular weight drugs and peptides have been shown to reach the CSF, the olfactory bulb (OB) and in some cases other parts of the brain, after nasal administration[3]. Drugs have been shown to reach the CNS from the nasal cavity by a direct transport across the olfactory region situated at the loft of the nasal cavity. It is the only site in the human body where the nervous system is in direct contact with the surrounding environment. The nasal route could be

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1559-1566 www.ijprajournal.com ISSN: 2456-4494

important for drugs that are used in crisis treatments, such as for pain, and for centrally acting drugs where the putative pathway from nose to brain might provide a faster and more specific therapeutic effect[4]. The nasal route, therefore, offers a potential for drugs targeting the brain.

The tricyclic antidepressants which are used for the depression have many sideeffects. These include anticholinergic effects such as tachycardia, urinary retention, reduced gut motility, and visual problems. Antihistamine mediated side effects include sedation and decreased gastric acid secretion. One of the potentially most dangerous sideeffects is orthostatic hypotension. This is probably mediated by alpha-1 adrenergic blockade [5]. Venlafaxinehydrochloride(EffexorT)is a structurally novel antidepressant that is chemically unrelated to tricyclic, tetracyclic, or otheravailableantidepressants. Pharmacologically, venlafaxine inhibits reuptake of 5-hydroxytryptamine and noradrenaline [6]. Unlike the older antidepressants, venlafaxine is devoid of antimuscarinic effects, and does not have any affinity for brain histamine binding sites. It is also without affinity for alpha-1 adrenergic, alpha-2 adrenergic, beta adrenergic, benzodiazepine, 5HT-1, 5HT-2, dopamine-2 and opiate receptors. This profile is predictive of a lack of side-effects common to older antidepressants, and thus may potentially be better tolerated.

VEN exerted anti-depressant action even after single administration which may have been related to prolonged nor- adrenergic desensitization of the neural system[7.8].

To apply venlafaxine hydrochloridefor neurological function, it is necessary to overcome the limitations of venlafaxine hydrochloride: poor absorption and very low distribution to the brain after oral administration due to both rapid metabolism and difficulties in the penetration through the blood-brain barrier (BBB). An effective dose of venlafaxine hydrochloride to exert certain neurological activities could be relatively high because of first-pass metabolism.

Niosomes, the surfactant vesicles, are spherical lipid bilayers capable of entrapping water soluble solutes within an aqueous domain or alternatively lipid molecules within the lipid bilayers. Niosomes have been prepared from several classes of non-ionic surfactants. Niosomes may be unilamellar or multilamellar depending on the method used to prepare them. In recent year, noisome have been extensively studied for their potential to serve as carrier for delivery of drugs, antigen, hormone and other bioactive agents. The basic aim in developing delivery system is controlling the release of drugs from the carrier system, in order to achieve an extended uptake in the body. Encapsulation of a drug in vesicular structure can be predicted to prolong the existence of the drug in the systemic circulation and thus enhance penetration into target tissue and reduce toxicity.

Niosomes similar to liposomes are biodegradable, biocompatible andnon-immunogenicin nature and exhibit flexibility in their structural characterization[9].

In addition, handling and storage of noisome require no special conditions[10,11]. Niosomes are now widely studied as an alternative to liposome because they alleviate the disadvantages associated with liposome such as chemical instability, variable purity of phospholipids and high cost[12].

II. METHODS

Materials

VenlafaxineHcl (Reddy's laboratories, Hyderabad),Cholesterol (Kiran light laboratories,Mumbai) Span 60 (oxford laboratories,Mumbai),Soyalecithin 30% (Dr.Reddy′slaboratories,Hyderabad),Diethyl ether.

Fourier transform infrared spectroscopy (FTIR)

In order to get evidence on the possible interaction of drug with excipients of the carrier at molecular level, FTIR study by disc method was carried. Physical mixtures of Venlafaxine HCL individually with excipients were subjected to InfraRed(IR) spectral analysis (FTIR 8400 Spectrophotometer). The disc of KBr were prepared by palletization method containing1 part of drug to 100 partof KBr and subjected for interpretation. The scanning range was from 450 cm^{-1} to 4000 cm^{-1} and the resolution was 1 cm^{-1}. The FTIR spectrum of the formulation was then analyzed in comparison with the spectrum of standard Venlafaxine HCl for evidence of any drug degradation.

Calibration curve of Venlafaxine Hcl:

A stock solution of Venlafaxine Hcl (1 mg/ml) was prepared by dissolving 100 mg ofVenlafaxine Hcl in Water. Aliquot volumes of stock solution were diluted to give standard curve concentrations range 1-10 µg/ml.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1559-1566 www.ijprajournal.com ISSN: 2456-4494

Preparation methods for venlafaxine Hcl Niosomes

For the preparation of venlafaxine Hcl Niosomes four methods were used.They are

1. Ether Injection method

Niosomes with different concentrations of span 60 were prepared according to the method described by P.K. Lakshmi et al,.(2009) [13].In this method In this method lipid solution in diethyl ether is slowly introduced into warm water. Surfactant (span 80) and cholesterol was dissolved in diethyl ether then the lipid solution was slowly injected into warm water containing the drug maintained at 55-65^{0}C. Vaporization of ether leads to the formation of single layered vesicles (SLVs).

2. Rotary evaporation

Niosomes with different concentrations of span 60 were prepared according to the method described by Pandey Shivanand et al,.(2010)[14] .In this method Soya lecithin/cholesterol mixture was dissolved in diethyl ether in a round bottom flask and ether was removed at room temperature under reduced pressure, in a rotary evaporator. The dried lipid film was hydrated with aqueous phase containing drug at 50 - 60°C with gentle agitation; this method produces multilamellar vesicles (ML V) with large diameter.

3. Sonication Method

Niosomes with different concentrations of span 60 were prepared according to the method described by F. Alhaique et al,.(1998)[15] and Tianqing Liu et al,.(2007)[16].In this method Accurately weighed quantities of the respective span 80 and cholesterol were transferred to a 50 ml round bottom flask and the contents dissolved using diethyl ether. Aqueous phase containing the venlafaxine HCL was added to the organic phase and a w/o emulsion was subsequently formed by high energy transfer provided by a bath sonicator for 3-4 min.

4. Reverse phase evaporation

Niosomes with different concentrations of span 60 were prepared according to the method described by Shubhini A Saraf et al,.(2011)[17] .In this method Accurately weighed quantities of the respective span 80 and cholesterol were transferred to a 50 ml round bottom flask and the contents dissolved using diethyl ether. Aqueous phase containing the venlafaxine HCL was added to the organic phase and a w/o emulsion was subsequently formed by high energy transfer provided by a bath sonicator for 3-4 min. The organic solvent was then removed from the emulsion in a rotary evaporator, the water bath maintained at 30^o C, until a smooth suspension of unilamellar liposomes was formed.

Physicochemical characterization of venlafaxine Hcl Niosomes

SEM (scanning electron microscope) and optical microscopy was used to determine the particle size distribution. The mean size of the particles was measured by an optical microscope fitted with a camera. The particle size distributionof each formulation was evaluated by determining the size of 100 randomly selected Niosomes.

The morphology of the niosome was studied by scanning electron microscopy. Noisome samples were prepared by air-drying on an aluminum stub. The stubs were then coated with gold to a thicknessof 200 to 500 A^0 under argon atmosphere using a gold sputter module in a high vacuum evaporator. The coated samples were randomly scanned by SEM.

Determination of entrapment efficiency

The determination ofVenlafaxine Hclentrapment was performed by an indirect method. TheVenlafaxine Hcl liposomes were ultracentrifuged at a speed of 10,000 rpm. The supernatant was collected for UV analysis to quantify the nonentrappedVenlafaxine Hcl. The entrapment efficiency was calculated by using the following equation[18]:

$$\%EE = \frac{Ctotal - Cfree}{Ctotal} \times 100$$

Nasal mucosa permeability measurement

The release studies were carried out in 25 ml beaker containing 10 ml of phosphate buffer. Phosphate buffer pH 7.4 (10 ml) was placed in a 25 ml beaker. The beaker was assembled on a magnetic stirrer and the medium was equilibrated at 37±5^0 C.

The nasal mucosa of cattle was collected from local slaughter house. The nasal mucosa was dissected from the nasal septum of the posterior nasal cavity by cutting off the nasal bone and the dorsal parietal cartilage. After rinsing with PBS twice, the excised nasal mucosa was tied to the one end of the open ended diffusion cell. The mucosal surface of the nasal mucosa faced the donor compartment and the serosal surface faced the receptor compartment. venlafaxine containing Niosomes were placed in the donor compartment,

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1559-1566 www.ijprajournal.com ISSN: 2456-4494

and PBS was placed in the receptor compartment. A mixture of O –CO (95:5) was bubbled through the PBS at 378C for 10 min before being added to the compartments. Continuously bubbling the same gas mixture at a rate of three to five bubbles was carried out throughout the experiment to maintain the viability of the nasal mucosa. The area of the nasal mucosa for drug permeation between the donor and receptor compartment was 0.64 cm. The cell was thermostatically controlled at 37.8^0C. Samples were withdrawn from the receptor compartment at intervals for a 6 h period, and an equal amount of PBS was filled back to the receptor compartment. The concentration of venlafaxine Hcl in the receptor compartment was determined by UV[19].

III. RESULTS

Table no.1 Formulations of Niosomes containingVenlafaxine Hcl with different ratios of surfactant prepared by Ether injection method
surfactant prepared by Ether injection method

Surfactants used	Formulation code	Drug: Surfactant: Cholesterol Ratio	Drug: Surfactant: Cholesterol Weighed(mg)
Span 80	F1	1:1:1	20:20:20
Span 80	F2	1:2:1	20:40:20
Span 80	F3	1:3:1	20:60:20
Span 80	F4	1:4:1	20:80:20
Span 80	F5	1:5:1	20:100:20

Table no.2 Formulations of niosomes containingVenlafaxine Hcl with different ratios of surfactant prepared bySonication method

Surfactants used	Formulation code	Drug:Surfactant: Cholesterol Ratio	Drug:Surfactant: Cholesterol Weighed(mg)
Span 80	F6	1:1:1	20:20:20
Span 80	F7	1:2:1	20:40:20
Span 80	F8	1:3:1	20:60:20
Span 80	F9	1:4:1	20:80:20
Span 80	F10	1:5:1	20:100:20

Table no.3 Formulations of niosomes containingVenlafaxine Hcl with different ratios of surfactant prepared by Rotary evaporation method

Surfactants used	Formulation code	Drug:Surfactant: Cholesterol Ratio	Drug:Surfactant: Cholesterol Weighed(mg)
Span 80	F11	1:1:1	20:20:20
Span 80	F12	1:2:1	20:40:20
Span 80	F13	1:3:1	20:60:20
Span 80	F14	1:4:1	20:80:20
Span 80	F15	1:5:1	20:100:20

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1559-1566 www.ijprajournal.com ISSN: 2456-4494

Table no.4 Formulations of niosomes containingVenlafaxine Hcl with different ratios of surfactant prepared byReverse phase evaporation method

Surfactants used	Formulation code	Drug:Surfactant: Cholesterol Ratio	Drug:Surfactant: Cholesterol Weighed(mg)
Span 80	F16	1:1:1	20:20:20
Span 80	F17	1:2:1	20:40:20
Span 80	F18	1:3:1	20:60:20
Span 80	F19	1:4:1	20:80:20
Span 80	F20	1:5:1	20:100:20

Table no.5 Particle size and entrapment efficiency of Niosomes containing Venlafaxine Hcl

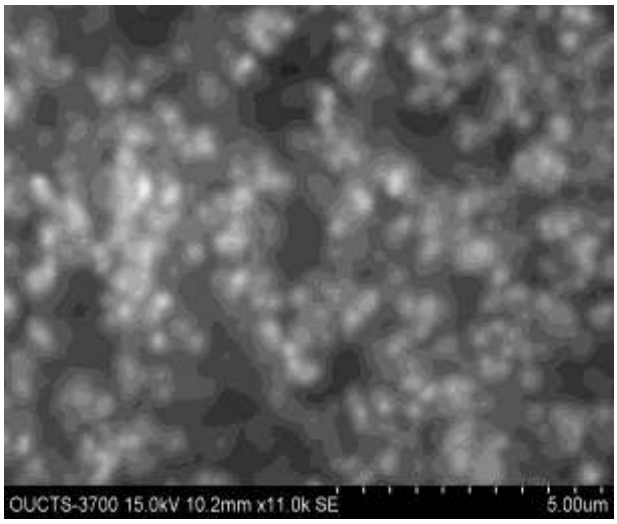
Method used	Formulation code	Average particle size (µm)	%Entrapment efficiency
Ether injection	F1	2.76	73.2
	F2	3.8	74.4
	F3	4.92	71.2
	F4	4.7	72
	F5	4.12	70
Sonication	F6	1.8	97.42
	F7	2.04	91
	F8	3.28	96.75
	F9	3.28	94.2
	F10	4.36	93.75
Rotary evaporation	F11	2.04	65.26
	F12	3.4	62.05
	F13	3.72	69.92
	F14	3.92	66.57
	F15	5.5	69.25
Reversephase evaporation	F16	4.4	67
	F17	3.4	68.7
	F18	2.8	69.5
	F19	3.6	63.25
	F20	4.5	66.5

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1559-1566 www.ijprajournal.com ISSN: 2456-4494

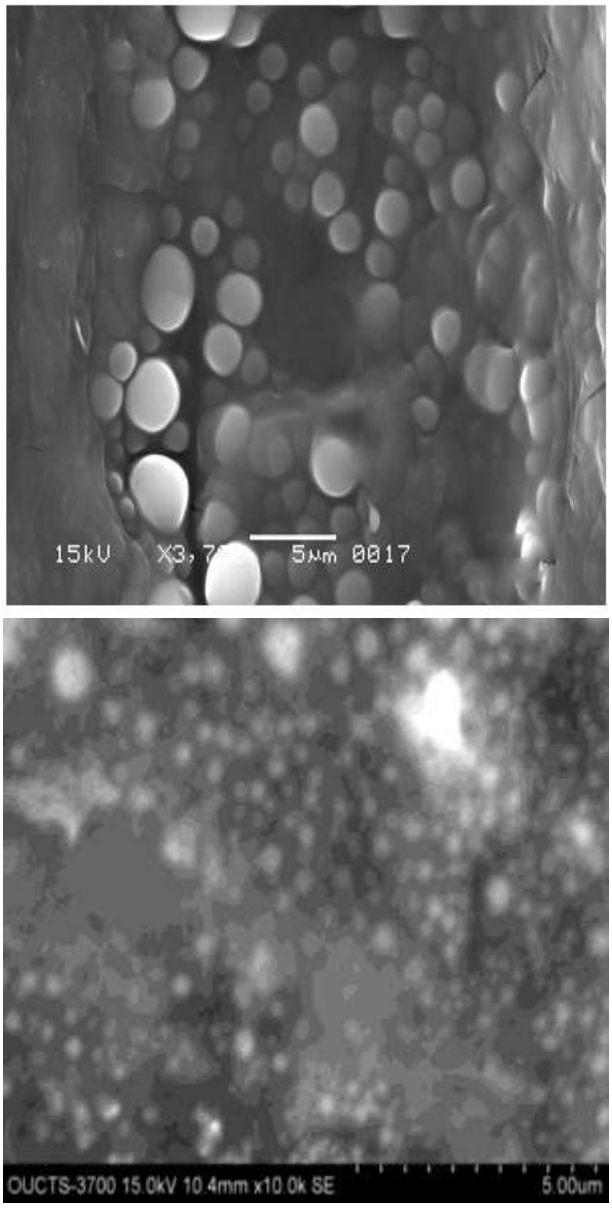
Table no.6 In-vitro drug release study of Niosomes containing Venlafaxine Hcl

Formulation code	% Drug release in 2 Hours
F1	96.69
F2	85.36
F3	96.016
F4	95.86
F5	94.88
F6	94.55
F7	88.66
F8	78.55
F9	78,98
F10	88.66
F11	53.619
F12	62.08
F13	56.8
F14	76.5
F15	90.57
F16	77.77
F17	68.66
F18	67.66
F19	68.66
F20	69.66

Pictures of Niosomes



International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1559-1566 www.ijprajournal.com ISSN: 2456-4494



REFERENCES:

[1]. Lalit Lakhwani , Sudheer K. Tongia, Veerendra S. Pal, Rajendra P. Agrawal1, Prem Nyati and Pradeep Phadnis, Omega-3 Fatty acids have Antidepressant Activity in Forced Swimming test in wistar rats,Acta Poloniae Pharmaceutica- Drug Research 2007; 64: 271-276,.

[2]. Behl CR, Pimplaskar HK, Sileno AP et al Effects of physicochemical properties and other factors on systemic nasal drug delivery. Adv Drug Deliv Rev 1998; 29:89–116

[3]. Illum L Transport of drugs from the nasal cavity to the central nervous system. Eur J Pharm Sci 2000;11:1–18.

[4]. Illum L Nasal drug delivery: new developments and strategies. Drug Discov Today 2002; 7:1184–1189.

[5]. Haddox, D.J,, Neuropsychiatric dmg use in pain management. In: P.P. Raj (Ed.), Practical Management of Pain 1992; 2: 636-659.

[6]. Muth, E.A., Haskins, J.T., Moyer, J.A,, Husbands, G.E., Nielsen, S.T.and Sigg, E.B., Antidepressant biochemical profile of the novel bicyclic compound Wy-

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1559-1566 www.ijprajournal.com ISSN: 2456-4494

45,030, an ethyl cyclohexanol derivative, Biochem. Pharmacology 1986; 35: 4493-4497.

[7]. Muth E.A., Moyer J.A., Haskins J.T., Andree T.H., Husbands G.E.M.: Biochemical, neuropsychological and behavioural effects of Wy-45-233 and other identified metabolites of the antidepressant venlafaxine. Drug Develop. Research 1991; 23: 191–199.

[8]. Nalepa I., Vetulani J.: β-Down-regulation induced by repeated vasopressin treatment. Eur. J. Pharmacology 1990; 178: 375–376.

[9]. Oommen E., Tiwari S.B., Udupa N., Kamath R., Umadevi P., Niosome entrapped b-cyclodextrin methotrexate complex as a drug delivery system, Indian J. Pharmacology 1999; 31: 279-284.

[10]. Azmin M.N., Florence A.T., Handjani-vila R.M., Stewert J.F., Vanlerberghe G., Whittaker J.S., The effect of nonionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice, J. Pharm. Pharmacology 1985; 37: 237-242.

[11]. Baillie A.J., Florence A.T., Hume L.R.,Muirhead G.T., Rogerson A., The preparation and properties of niosome nonionic surfactant vesicles. J .Pharm. Pharmacology 1985; 37: 863-868.

[12]. Vora B., Khopade A.J., Jain N.K., Proniosome based transdermal delivery of levonorgestrel for effective contraception, J. Control. Rel.,1998; 54:149-165.

[13]. P.K. Lakshmi ,Shyamala Bhaskaran and, Comparative evaluation of niosome formulations prepared by different techniques, Acta Pharmaceutica Sciencia 2009; 51:27-32.

[14]. Pandey Shivanand,Development and Characterization of Cefpodoxime Proxetil Niosomes,International Journal of Pharma World Research 2010;1:1-11.

[15]. F. Alhaique, M. Carafa , E. Santucci, T. Coviello , E. Murtas , F.M. Riccieri G. Lucania, M.R. Torrisi,Preparation and properties of new unilamellarnon-ionic:ionic surfactant vesicles,International Journal of Pharmaceutics 1998;160: 51–59.

[16]. Tianqing Liu ,Wei Hua,Preparation and properties of highly stable innocuous niosome in Span 80/PEG 400/H2O system,Colloids and Surfaces A: Physicochem. Eng. Aspects 2007; 302: 377–382.

[17]. Shubhini A Saraf ,GyanendraSingh,Harinath Dwivedi, Shailendra K Saraf , Niosomal Delivery of Isoniazid - Development and Characterization, Tropical Journal of Pharmaceutical Research April 2011; 10 (2): 203-210.

[18]. Aroonsri Priprem, PhD,,JintanapornWatanatorn,PhD,SaengraweeSutthiparinyanont, MSc,WathitaPhachonpai, MSc,SupapornMuchimapura, PhD, Anxiety and cognitive effects of quercetin liposomes in rats, Nanomedicine: Nanotechnology, Biology, and Medicine 2008; 4 :70–78.

[19]. S.L. Law , K.J. Huang, H.Y. Chou, Preparation of desmopressin-containing liposomes for intranasal Delivery, Journal of Controlled Release 2001;70: 375–382.

[20]. Abraham Zangen,Roman Gersner, Michal Gordon-Kiwkowitz,Automated behavioral analysis of limbs' activity in the forced swim test,Journal of Neuroscience Methods 2009; 180: 82–86..

[21]. Vimal Kant Sharma , Nagendra Singh Chauhan , Santram Lodhi , A.K. Singhai,Anti-Depressant Activity of Zizyphusxylopyrus,International Journal of Phytomedicine 2009;1: 12-17.

[22]. Hanka Hertmanowska,Elzbieta Nowakowska, Krzysztof Kus, Teresa Bobkiewicz-Kozowska,Role of Neuropeptides in antidepressant and Memory improving effects of Venlafaxine, Polish journal of pharmacology 2002;54, 605-613,2002.