Research Journal of Pharmaceutical, Biological and Chemical Sciences

REVIEW ARTICLE

An overview of *Vitex negundo* linn. : Chemistry and Pharmacological profile.

B.B Zaware and Sunil A. Nirmal*

[1]Department of Pharmacognosy, Pravara Rural College of Pharmacy, Loni, M.S. India.

ABSTRACT

Vitex negundo Linn. is a commonly used herb in Ayurvedic medicine. This review supports all updated information on its phytochemical and pharmacological activities, traditional uses and scientific approach. The plant extract have been widely used for the treatment of a large number of human ailments. The chemical entities of this plant have been used as an antidiabetic, antibacterial, anti-inflammatory, antifungal, antinociceptive, anti androgenic, anticonvulsant, antioxidant, and anti-tumor agents. Scientifically proved activities are related with traditional concept. Scientific evidence exists with respect to their major and minor constituents. *V. negundo* is the most important controversial and effective natural origin that has a tremendous future for research. The novelty and applicability of *V. negundo* are hidden. Such things should be overcome through modern scientific concept.

Keywords:*Vitex negundo*, antidiabetic, Phytochemistry, Pharmacology.

*Corresponding author
Tel.: +91-09226564894
E-mail: nirmalsunil@rediffmail.com

INTRODUCTION

Vitex negundo Linn, of the family Verbenaceae is a large family of herb, shrubs and trees comprising of about 75 genera and nearly 2500 species [1, 2, 3]. *V .negundo* is distributed in east Asia, south west China, throughout India and cultivated in Pakistan [4,5]. Every part of this plant is valuable in medicine and various preparations of plant have been mentioned in indigenous system of medicine for various skin diseases, as antibacterial [6] anti inflammatory, and anti androgenic [7]. Different parts of *V. negundo* have been used in traditional Indian medicine as nervine sedative [8] and is of high value as constituents of Ayurvedic preparations such as *Vishagarbha thaila* is widely used to treat rheumatism in India [9]. The fresh aromatic leaves are useful for rheumatism and to relieve pain [10]. It is widely used in Chinese herbal medicine. It is second most important for treatment of chronic bronchitis and cold. The leaves of plant are astringent, febrifuge, sedative, tonic and vermifuge [11]. The leaves, in the form of a paste, are used for inflammatory swellings of the joints formed due to rheumatism, hydrocele and spleenic enlargement. They are also used in nervous disorders and leprosy. Oil prepared from leaves is useful for growth of hair and increases the function of brain. Roots are useful in rheumatism, dyspepsia, piles and as anthelmintic [12]. Chloroform extract of defatted seed of *V. negundo* showed anti-inflammatory activity [13]. It also possesses potent mosquito repelling activity against *Aedes aegypti* [14], anti-tumor [11] and analgesic activity [15].

PHARMACOLOGICAL ACTIVITY

Antifungal activity

In vitro antifungal activity of fruits of *V. negundo* was examined against 5 common fungal strains, *Candida albicans*, *C. glabrata*, *Aspergillus flavus*, *Microsporum canis* and *Fusarium solani.* Ethanol extract of fruit seeds showed significant activity against *F.solani* (90%) and moderate response against *M. canis* (60%) with no effect on *C. albicans*[1]. Both polar and nonpolar extracts viz. petroleum ether, chloroform, ethanol, methanol and aqueous extracts were prepared and studied for antibacterial activity using disc diffusion, agar cup and broth dilution methods. Results showed promising antibacterial activity of all the extracts of both leaf and bark against *Escheria coli*, followed by *Staphylococcus aureus*. Ethanol and methanol extracts of the leaf showed inhibition activity against both Gram-positive and Gram-negative bacteria where as petroleum ether and chloroform extracts of bark had better antibacterial activity against Gram-positive bacteria. MIC showed that 5% of the extracts were active in a concentration of 0.312 mg/ml; 27.5% in a concentration of 0.625 mg/ml and 88.75% in a concentration of 1.25 mg/ml; were active against different human pathogenic bacteria. At concentration about 2.5 mg/ml, 100% of inhibition was recorded against both Gram-positive and Gram-negative bacteria. The result obtained with ethanol and methanol extracts of leaves; petroleum ether and chloroform extract of bark exhibited significant antibacterial activity, a property that supports traditional use of the plant in the treatment of some diseases as broad spectrum antibacterial agents [16]. Ethanolic extracts of leaves of *V.negundo* were subjected to preliminary screening for antimicrobial activity .Ethanolic extracts exhibited significant anti-microbial activity comparable to the standard drug tetracycline [17].

Laxative Activity

Crude aqueous extract of *V. negundo* leaves at doses of 100 and 200 mg/Kg was investigated for laxative activity according to Cappaso *et al*. in albino rats that were compared with standard drug agar-agar (300 mg/Kg, p.o.) in normal saline. The extract was found to produce significant laxative activity in dose dependant manner. The activity may be contributed to the phytoconstituents present [18].

Anti-inflammatory activity

Extract obtained from leaf of *V. negundo* having anti-inflammatory activity. Carrageenin induced hind paw edema and cotton pellet granuloma test in albino rats were employed to study the anti-inflammatory activity of *V. negundo* leaf extract. The extract was administered orally in graded doses (100, 250, 500 mg Kg^{-1}). The effects were compared with phenylbutazone (100 mg Kg^{-1}) orally in Carrageenin induced hind paw edema method and ibuprofen (200 mg Kg^{-1}.B.D×7 days) orally in cotton pellet granuloma test as standard controls,

respectively. *V.negundo* inhibited oxytocin induced contractions of rat uterus and plasma malondialdehyde levels significantly. These observations suggest that *V.negundo* possesses anti-inflammatory activity against acute and sub- acute inflammation [19].

Anti-convulsant activity

The ethanolic leaf extract of *V. negundo* was administered orally in graded doses (250, 500 and 1000 mg/Kg, p.o) in both the experimental models and the effects were compared with diphenylhydantoin in MES method and valporic acid in Pentylenetetrazole induced seizures method as standard control respectively. The *V. negundo* in the doses (250, 500 and 1000 mg/Kg, p.o) did not show protection against MES to any significant extent but significant post-ictal depression was observed in the dose of 1000 mg/Kg body weight in comparison to control. However, sub-protective dose of test drug (100 mg/Kg, p.o) potentiated the anticonvulsant action of diphenylhydantoin. The test drug in the dose (1000 mg/Kg, po) showed 50% protection in clonic seizures and 24-hour mortality against Pentylenetetrazole induced seizures. It also decreased number and duration of convulsions significantly. *V. negundo* potentiated anticonvulsant activity of valporic acid. The anticonvulsant activity of *V. negundo* has not been found equi-effective with standard drugs. These findings suggest that *V. negundo* possesses anticonvulsant activity particularly against Pentylenetetrazole induced convulsions [20].

Anxiolytic activity

The ethanolic extract prepared from the roots of *V. negundo* using the elevated plus maze and light-dark exploration test in mice. Male mice were either treated orally with the Vitex negundo extract or the positive control diazepam. Oral administration of 100 and 200 mg/Kg of *V. negundo* extract significantly increased the percentage time spent on and the number of entries in to the open arms of the elevated plus maze. The effect was comparable to that of the benzodiazepine diazepam (2mg/Kg p.o.). In light-dark exploration test, diazepam-treated rats significantly increased the time spent in light area and decreased the duration of immobility, *V.negundo* treated rats also showed significant increased the time spent in light area. These result indicate that *V.negundo* is an effective anxiolytic agent [21].

Anti-oxidant activity

The effect of the oral administration of *V. negundo* leaf extract on the levels of enzymic and non-enzymic antioxidants were studied in the adjuvant induced arthritic rats. The levels of antioxidant enzymes such as SOD, CAT, GPx, G6PD, GSH and Vit-C were estimated in various groups of the experimental rats. It was observed that the antioxidant enzyme levels in the adjuvant induced arthritic were significantly low when compared to normal rats. A significant decrease in enzymic antioxidant – SOD, CAT, GPx, G6PD and non-enzymic antioxidant – GSH,Vit-C were observed in the liver of adjuvant induced arthritic rats compared to the normal rats. These results suggest that the leaf extract of *V.negundo* possesses antioxidant activity [22]. A new phenyldihydronaphthalene-type lignan, vitexdoin A , a new phenylnaphthalene-type lignan alkaloid, vitedoamine B , four new phenylnaphthalene-type lignans, vitexdoins B-E and four known lignan derivatives were isolated from *V. negundo* seeds. The ability of the isolates to prevent nitric oxide production by LPS-stimulated RAW 264.7 macrophages in a concentration-dependent manner was also studied. Which are compounds 5, 6, and 9 were among the most potent nitric oxide production inhibitors, with IC (50) values of 0.13, 0.15, and 0.11 µM, respectively. The introduction of free hydroxy groups plays a vital role in the potency of these compounds [23].

Hepatoprotective activity

Hepatoprotective activity of *V. negundo* leaf ethanolic extract was investigated against hepatotoxicity produced by administering a combination of three anti-tubercular drugs isoniazid -7.5 mg/Kg, rifampin -10 mg/Kg and pyrazinamide -35 mg/Kg for 35 days by oral route in rats. *V. negundo* leaf ethanolic extract was administered in three graded doses of 100, 250 and 500 mg/Kg orally, 45 min prior to anti-tubercular challenge for 35 days. Hepatoprotective effect of *V. negundo* leaf ethanolic extract was evident in the doses of 250 and 500 mg/Kg as there was a significant decrease in TB, AST, ALT and ALP levels in comparison to control.

Histology of the liver section of the animals treated with the *V. negundo* leaf ethanolic extract in the doses of 250 and 500 mg/Kg further confirms the Hepatoprotective activity [24].

Analgesic activity

The analgesic activity of *V. negundo* leaf extract [500 and 1000 mg/Kg] was studied using acetic acid induced writhing test in mice for assessing peripheral analgesic effect and tail immersion test in mice for assessing central analgesic effect. The hydroalcoholic extract of *V. negundo* leaves significantly increased the reaction time and decreased the writhing movements in mice in acetic acid-induced writhing test. There was a significant increase in the reaction time in tail immersion test. The phytochemical study reveals that bioflavonoid is present in extract which may be responsible for analgesic activity [25].

Anti-asthmatic Activity

Ethanol extract and various fractions like petroleum ether, aqueous and ethyl acetate of leaves of *V. negundo* were prepared. The antiasthmatic activity of AE, PF, AF and EAF was evaluated by various experimental models like mast cell degranulation by compound 48/80, passive cutaneous anaphylaxis, and egg-albumin induced asthma. Dexamethasone (5mg/Kg) was used as a reference standard. Present study concluded that AE, EAF, and AF of leaves of *V. negundo* are found to be effective in various experimental models of asthma. Stabilization of mast cells, inhibitory effects on immediate hypersensitivity reactions and antieosinophilic activity appear to be involved in its mode of action [26].

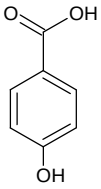
Anti-snake venom activity

The methanolic root extract of *V. negundo* were explored for the first time for antisnake venom activity. The plant extract significantly antagonized the *Vipera russellii* and *Naja kaouthia* venom induced lethal activity both in in vitro and in vivo studies. *V. russellii* venom-induced haemorrhage, coagulant, defibrinogenating and inflammatory activity was significantly neutralized by plant extract. No precipitating bands were observed between the plant extract and snake venom. The above observations confirmed that the plant extract possess potent snake venom neutralizing capacity and need further investigation. The root extract of *V.negundo* effectively antagonised the Viper venom-induced defibrinogenating activity. In in vitro studies, the plant extract (2 mg) gave protection upto 125 MDD against venom-induced defibrinogenating. In in vivo studies, venom-induced defibrinogenating was antagonised by the plant extract. The fold of protection was always higher in in vitro studies. The effective doses were found to be 0.12, 0.12 mg in in vitro and 1.4, 1.2 mg in in vivo, respectively. A modified plaque assay was used for the neutralization of *V. russellii* venom-induced fibrinolytic activity. The minimum fibrinolytic dose was defined as the amount of venom that produced fibrinolytic halos of 10 mm diameter. The Viper venom-induced fibrinolytic effect was effectively antagonized by the plant extract (*V. negundo*). The ED_{50} of *V. negundo* were found to be 0.6 and 0.5 mg, respectively [27].

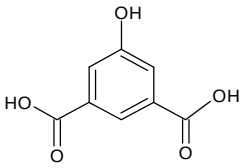
Table 1: Chemical constituents of *V. negundo*

Sr No	Parts	Chemical constituents
1	Leaves	glucononitol, p-hydroxybenzoic acid (1), 5-hydroxyisophthalic acid (2), 3,4-dihydroxybenzoic acid (3), vitamin C, carotene[28,29,30], casticin (4), orientin (5), isoorientin (6), luteolin (7), luteolin-7-0-glucoside (8), corymbosin, gardenins A and B, 3-0-desmethylartemetin, 5-0-des-methylnobiletin, 3',4',5,5',6,7,8-heptamethyoxyflavone[31,32], 3',5-dihydroxy-4',7,8-trimethoxyflavanone (9), 3',5-dihydroxy-4',6,7-trimethoxyflavanone[33] (10), iridoid- agnuside, aucubin (11), nishindaside, negundoside (12), 6'-p-hydroxybenzoyl-mussaenosidic acid, 4,4'-dimethoxy-trans-stilbene (13), fructose. Essential oil contains terpenes (14), α-pinene, camphene (15), citral and β-caryophyllene [28] (16), d-guaiene, epoxide, ethyl-hexadecenoate [34], sabinene (17), linalool (18), terpinen-4-ol, α-guaiene and globulol.
2	Seed	casticin, artemetin (19), 3',5,7-trihydroxy-4',6',8-trimethoxyflavone, diterpenoid, 5β-hydro-8,11,13-abietatrien-6-α-ol, triterpenoids, 2α,3α-dihydroxyoleana-5,12-diene-28-oic acid, 2β,3α-diacetoxyoleana-5,12-dien-28-oic acid, 2α,3β-diacetoxy-18-hydroxyoleana-5,12-diene-28-oic acid, lanostan-8,25-diene-3β-ol, 3β-acetoxyolean-12-en-27-oic acid, lignin, n-alkanes (mainly containing C_{27}-C_{37}) long chain fatty alcohols, β-sitosterol (20), benzoic acid derivatives and glucose. amino acids- glycine (21), alanine (22), valine (23) and leucine (24). The seed oil contains fatty acids viz oleic, linoleic and palmitic acids [28].
3	Fruit	Fruit oil - β-selinene, a-cedrene, germacrene D and hexadecanoic acid [34].
4	Bark	Flavone glycosides- 6- β-glucopyranosyl-7-hydroxy-3',4',5',8-tetramethoxyflavone-5-O-α-L-rhamnopyranoside, 3',7-dihydroxy-4',6,8-trimethoxyflavone-5-O-(6"-O-acetyl-β-Dglucopyranoside), 3,3',4',6,7-pentamethoxyflavone-5-O-(4"-O-β-D-glucopyranosyl)-α-L-rham-nopyranoside, 4',5,7-trihydroxyflavone-8-(2"-caffeoyl-β-D-glucopyranoside), 3',5,5',7-tetrahydroxy-4-methoxyflavone-3-O-(4"-O-β-D-galactopyranosyl) galactopyranoside. Leucoanthocyanidines, leucodelphindin methyl ether, leucocyanidin-7-O-rhamnoglucoside, luteolin, acerosin [28] (25), terpenes, sterols, phenolic compounds, alkaloids, organic acid, β-sitosterol, glucosides, anthocyanines, and p-hydroxybenzoic acid[35].
5	Root	furanoeremophilane[36], 2β,3α-diacetoxyoleana-5,12-dien-28-oic acid, 2α, 3α-dihydroxyoleana-5,12-dien-28-oic acid, 2α,3β-diacetoxy-18-hydroxyoleana-5, 12-dien-28-oic acid, vitexin (26), and isovitexin[37] (27).
6	Flowers	Flowers oil contains a-selinene, germacren-4-ol, carryophylene epoxide, (E)-nerolidol, p-cymene, and valencene[34].

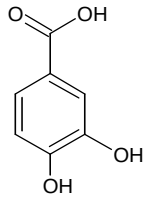
Figures 1: Chemical structures of various phytoconstituents from *V.negundo*



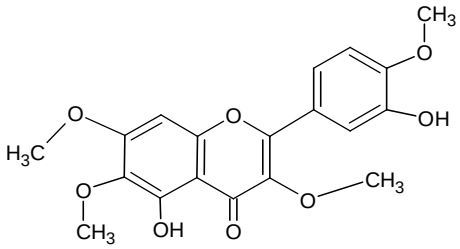
(1) p-hydroxybenzoic acid



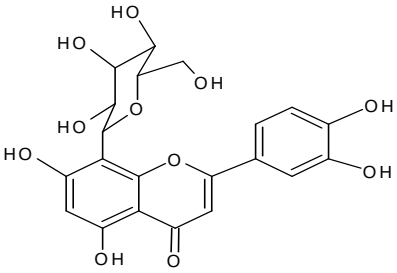
(2) 5-hydroxyisophthalic acid



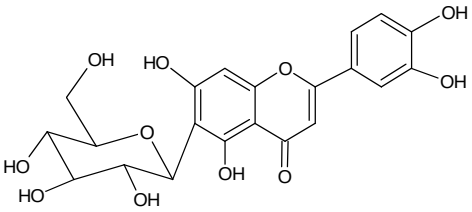
(3)3,4 dihydroxybenzoic acid



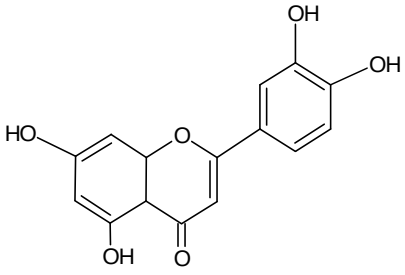
(4) casticin



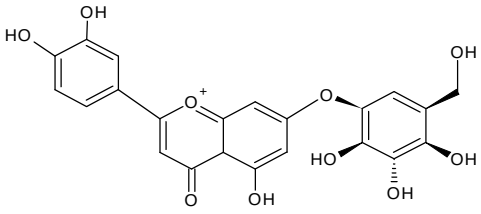
(5) orientin



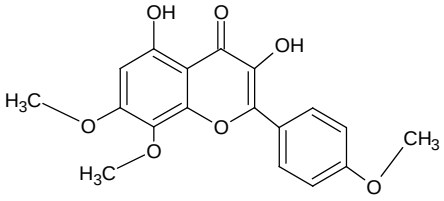
(6) isoorientin



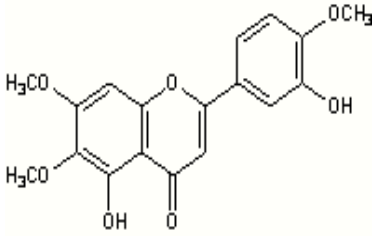
(7) luteolin



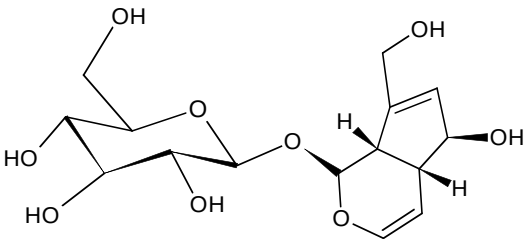
(8) luteolin-7-o-glucoside



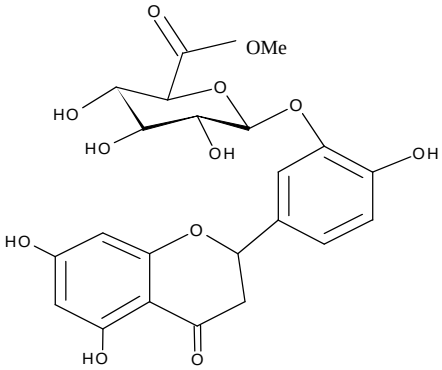
(9) 3',5-dihydroxy-4',7,8-trimethoxyflavanone



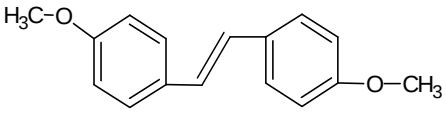
(10) 3',5-dihydroxy-4',6,7-trimethoxyflavanone



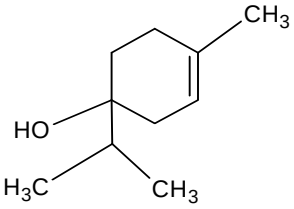
(11) aucubin



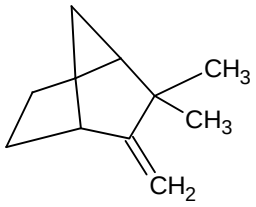
(12) negundoside



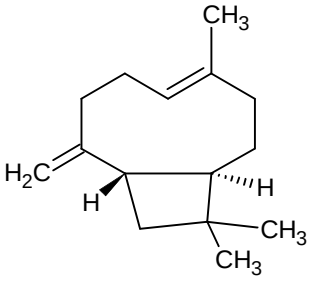
(13) 4,4'-dimethoxy-trans-stilbene



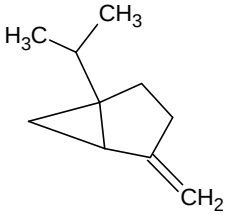
(14) terpene



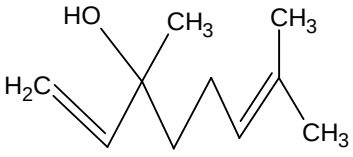
(15)camphene



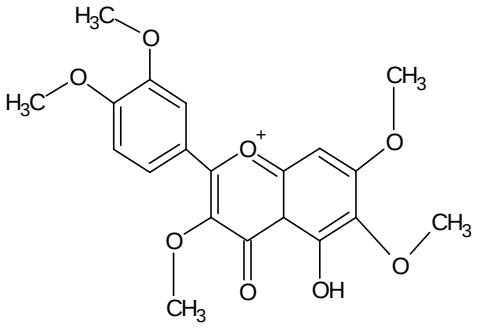
(16)beta-caryophyllen



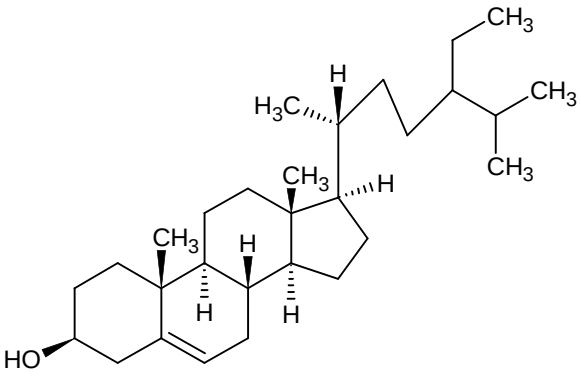
(17) sabinene



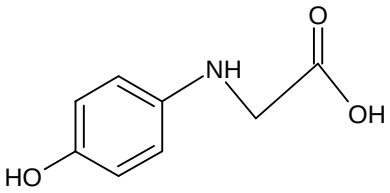
(18) linalool



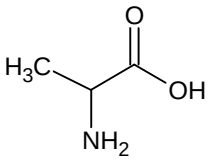
(19) artemetin



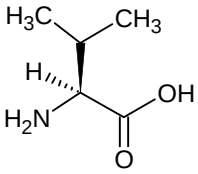
(20)Beta Sitosterol



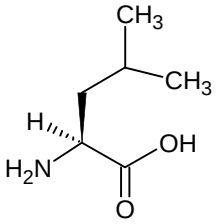
(21) Glycin



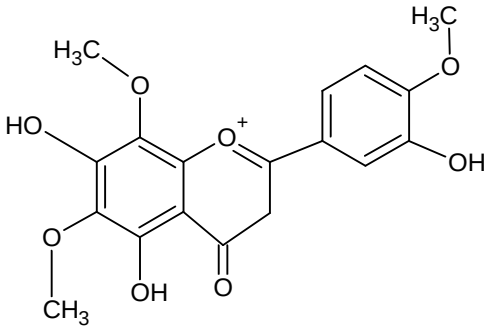
(22)Alanine



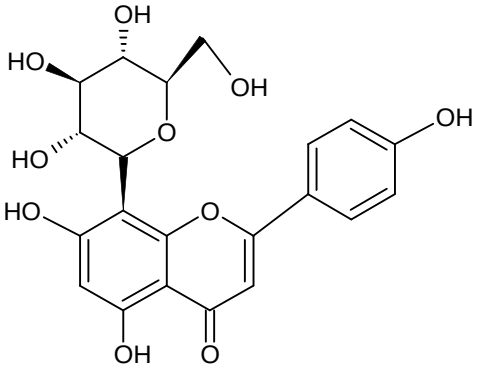
(23)Valine



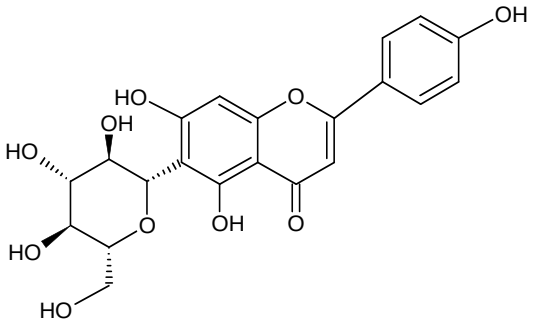
(24)leucine



(25) acerosin



(26) vitexin



(27) isovitexin

CONCLUSION

V. negundo is traditionally very important herb having many important pharmacological activities like analgesic, antidiabetic, anti-inflammatory antifungal, antimicrobial, defibrinogenating, antiasthmatics and antioxidant property. Many important phytoconstituents responsible for the activity were isolated. This proves therapeutic importance of the plant. Such type of systematic information about the plant is useful for the researchers. This review of *V. negundo* is hopeful induce the advance research about the benefit of this plant for human life.

REFERENCES

[1] Mahmud S, Shareef H, Farrukh U, Kamil A ,Rizwani GH. Pak J Bot 2009; 41 (4): 1941-1943.

[2] Nasir E, Ali SI. Flora of West Pakistan.Verbenaceae, No.77 complied by Jafri SMH. Ghafoor A, Herbarium, Department of Botany, University of Karachi 1974.

[3] Sastri BN. The Wealth of India. A Dictionary of Raw Material and Industrial Products. Publication and information directorate,CSIR New Delhi,1950, pp. 285-293.

[4] Khan UG, Hannan A, Shafique F, Aslam M. Cultivation of Medicinal Plants. Published by Ministry of Food Agriculture and Livestock, Ajab printing press, Karachi, 2007, pp. 293-294.

[5] Khare CP. Indian Medicinal Plants. An illustrated Dictionary, Springer Science and Business Media, 2007, pp.710.

[6] Kustrak DS, PepelJnak KA, Antolic A, Balzevic N. Pharm weeklal (sci. Ed) 1987; 9 (4): 238-239.

[7] Bhargava SK. J Ethnopharmacol 1989; 27(3): 327-339.

[8] Perry LM. Medicinal Plants of East and South East Asia. Attributed properties and uses, MIT Press, London, 1980.

[9] Jayaweera DM. Medicinal Plants (Indigenous and Exotic) used in Ceylon. Part 2 A Publication of the Natural Sciences Council of Sri Lanka, Colombo, 1980.

[10] Nadkarni KM.1976. Indian Materia-Medica with Ayurvedic, Unani Product and Home Remedies Mitewiez AE, Gejdal H, Sworen K, Sien Kiewiez, Jedrze J, Popular Prakasham, Bombay, *Drug Res*., vol. 1, 1993,43: pp. 752-758.

[11] Horowitz RM, Gentili B. Long range proton shielding in C-glycosyl compoundsstructure of some new C-glycosyl flavones. Chemistry & Industry, London, United Kingdom, 1966; (15): 625-7.

[12] Daniel M. Medicinal plants, Chemistry and Properties. Oxford and IBH Publishing co.pvt. Ltd, New Delhi, 2006, pp. 79.

[13] Gupta GS. 1973. Telang RS, Chatterjee S, Varshneya C. Ind J Pharmacol 1999;31: 363-366.

[14] Asaka Y. Rana AC. Arch Pharm Res 1973; 14(1): 96-98.

[15] Gupta M, Mazumder UK Bhawal SR. Ind J Exp Biol 1999; 37(2): 143-146.

[16] Panda SK, Thatoi HN, Dutta SK. J Med Plants Res 2009; 3(4): 294-300.

[17] Rastogi T, Ghorpade DS, Deokate UA, Khadabad SS. Res J Pharmacog Phytochem 2009; 1(1):75-77.

[18] Adnaik RS, Pai PT, Mule SN, Naikwade NS, Magdum CS. Asian J Exp Sci 2008; 22(1): 159-160.

[19] Tandon VR, Gupta RK. Intern J Pharmacol 2006; 2(3):303-308.

[20] Tandon VR, Gupta RK. Indian J Physiol Pharmacol 2005; 49 (2): 199–205.

[21] Adnaik RS, Pai PT, Sapakal VD, Naikwade NS, Magdum CS. International Journal of Green Pharmacy July-September 2009; 243-247.

[22] Renuka P, Devi S, Kumari K, Kokilavani C. Ind J Clin Biochem 2007; 22 (1): 143-147.

[23] Zheng CJ, Huang BK, Han T, Zhang QY, Zhang H, Rahman K, Qin LP. J Nat Prod 2009; 72(9):1627-30.

[24] Vishal R, Tandon V, Khajuria B, Kapoor D, Kour, Gupta S. Fitoterapia December 2008; 79(7-8): 533-538.

[25] Telang RS, Chatterjee S, Varshneya C. Ind J Pharmacol 1999; 31: 363-366.

[26] Patel J, Shah S, Deshpande S, Shah G. Asian J Pharm Clin Res 2009; 2(1): 81-86.

[27] Alam MI, Gomes A. J Ethnopharmacol 2003; 86(1):75-80.

[28] Das B, Das R (nee Chakrabarti). Indian Drugs 1994; 31(9): 431-435.

[29] Itikawa N, Yamasita T. J Chem Soc Jap 1940; 61:787-793.

[30] Basu NM, Ray GK, De NK. J Ind Chem 1947; 24: 358.

[31] Sirait LM, Rimpler H, Haensal R. Experientia 1962; 18, 72.

[32] Banerji J, Das B, Chakrabarti R, Jha H. Ind J Chem 1988; 27B: 597.

[33] Achari B, Chowdhury US, Dutta PK, Pakrashi S. Phytochemistry 1984; 23:703.

[34] Khokra SL, Prakash O, Jain S, Aneja KR, Dhingra Y. Ind J Pharm Sci 2008; 70(4): 522-526.

[35] Dhakal RC,Rajbhandari M, Kalauni SK, wale SA, Gewali MB. J Nepal chem 2008-09; 23: 89-92.

[36] Chawla AS, Sharma AK, Handa SS, Dhar KL. J Nat Prod 1992; 55: 163.

[37] Srinivas K, Rao SS, Rao MEB, Raju MBV. Ind J Pharm Sci 2001; 63 (5): 422-424.