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EFFICACY OF AYURVEDIC MEDICINE *VITEX NEGUNDO* EXTRACT ON PAIN CONTROL BASED ON EXPERIMENTAL MODEL HAFFNER'S TAIL CLIP

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ABSTRACT

Years ago, narcotics have been used as strong analgesics in relieving severe acute or chronic pain. However high dose of narcotics leads to many side-effects like respiratory depression, apnea, nausea, vomiting, physical and mental dependence. Thus, narcotics along with other medicines known as nonsteroidal anti-inflammatory drugs (NSAIDs) are being increasingly used. The biggest risk with NSAIDs is severe and sometimes fatal gastrointestinal bleeding, increase in stomach acid, reduce the stomach's normal protective mucus layer, cause damage to the kidneys in people over 60 years; those with high blood pressure, heart disease, or pre-existing kidney disease. *Ayurvedic* medicines strengthen and enhance the body's own healing process. As all the ingredients are herbal, there is no fear of any adverse effects and hence effective results can be seen in relieving pain. The aim of our study was to evaluate the effectiveness of *Nirgundi (Vitex Negundo)* in providing efficient and adequate pain relief.

KEYWORDS: Alternative medicine, Ayurvedic medicine, Pain relief, *Vitex nigundo* extract (VNE).

INTRODUCTION

Pain is an unpleasant sensory and emotional experience due to a noxious stimulus associated with potential tissue damage. It is the most common and major symptom in most of the medical conditions affecting a person's quality of life.[1] To modulate the intensity and unpleasantness of pain, many other methods like distraction or excitement, hypnotic therapy, social support are practiced. Since many years narcotics have been used as strong analgesics in relieving severe acute pain but continuous use and high dose of these drugs lead to many side-effects like respiratory depression, apnea, nausea, and vomiting, physical and mental dependence. The nonsteroidal anti-inflammatory drugs (NSAIDs) are increasingly used for pain management. But these drugs also cause severe and sometimes fatal gastrointestinal bleeding, hyperacidity, which reduces the gastric normal mucus layer which acts as a protective layer, patients with hyper tension, cardiac disease or pre-existing kidney disease are also at risk of kidney damage. Since ancient times, *Ayurvedic* medicines have been used to treat various ailments including pain. *Ayurvedic* medicines are the nature's herbal products which strengthen and enhance the body's own healing process and do not have adverse effects, if given in appropriate doses. The aim of our study was to evaluate the effectiveness of the *Nirgundi* (*Vitex Negundo)* in providing efficient and adequate pain relief. When there is tissue destruction after trauma, the cell wall (cell membrane) undergoes lysis which leads to the production of arachidonic acid, a potent mediator for inflammation. The metabolic conversion of arachidonic acid through the lipoxygenase and the cyclo-oxygenese pathway produces leukotrines and prostaglandins which causes the pathological expression of inflammation, i.e. pain, erythema and edema. The allopathic analgesic drugs are mainly from the NSAIDs[2] group and the opioid[3] group, such as morphine and opium and para-acetylaminophenol group like paracetamol. Most commonly used drugs for postoperative pain management in oral and maxillofacial surgery are NSAIDs. These drugs are known to act by anti-inflammatory effect, analgesic effect, anti pyretic effect in one or more mechanisms. This is brought about by inhibition of arachidonic acid-cyclo-oxygenese pathway thus inhibiting the production of the prostaglandins and thromboxanes. Disadvantages of NSAIDs are due to adverse effects like nausea, vomiting, diarrhea or constipation, dyspepsia (impaired digestion), epigastric pain, bleeding, and ulceration (primarily gastric), rash, bronchospasm, rhinitis, edema, or an acute allergic reaction. Thus Cox-1 is a constitute engine expressed in most tissues including blood platelets and at any site of inflammation and promotes the production of natural mucus lining that protects the inner stomach. Cox-1 is involved in cell to cell signalling, tissue hemostasis, pain, clotting

and protecting the stomach, where as Cox-2 is involved in pain produced by inflammation. Whereas *Ayurvedic* medicines are effective in many diseases and also are effective in complicated ailments without any adverse effects. *Ayurvedic* treatment is nontoxic, so it can be used safely as an alternative therapy or alongside conventional therapies. Drugs useful in relieving pain are listed as *Shulahar (Vedanasthapana*) Drugs by *Bhav prakash.* The aim of the study was to prove the efficacy of the prepared *Ayurvedic* medicine as an analgesic based on Experimental model Haffner's tail clip.

MATERIALS AND METHODS

Materials: *Vitex Negundo* whole plant was collected from herbal garden of National Institute of *Ayurveda* (NIA), Jaipur. Whole plant was identified taxonomically as well as macroscopic and microscopic examination were performed by expert botanist. Diclofenac sodium (DIS) injections were used. Solvents and chemicals used for experimental work were of AR grade.

Preparation of the extract: Plant was collected, shade-dried and powdered mechanically. About 60 gm of whole plant part powder were extracted with 600 ml of distilled water with vigorous shaking for 6 hr after 24 hr filtered it. The extract was obtained by vacuum distillation and dried at 40º C. For pharmacological screening VNE was then dissolved in distilled water to prepare fresh drug solution in desired concentration just before use.

Phytochemical investigation: Specific qualitative tests were performed for the presence or absence of phyto-chemicals viz., alkaloids, tannins, flavonoids, saponins and glycosides in aqueous extract of VN to identify the constituents by the methods described by Kokate.[4]

Animals: Swiss albino mice (20-25 g) of either sex were used for analgesic studies, respectively. They were divided in 4 groups of six animals each. The animals were housed in polypropylene cages in central animal house, facility with food and water freely available ad libitum. The rooms were maintained at the, temperature of 24 ± 2ºC with 12 hour light/dark cycles. All the animal experiments were carried out according to the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India, guidelines. The animals were fasted overnight prior to the experiment and given water ad libitum. The study was approved by Institutional Animal Ethics Committee (IAEC), of Institute of Biomedical and Industrial research, Jaipur (Rajasthan) CPCSEA Approval No: 1737/PO/C/14/CPCSEA prior to study. IAEC approval number:- IBIR/IAER/2014/ I/2 and the work was conducted at the Institute of Biomedical and Industrial research, Jaipur

(Rajasthan). As per OECD guidelines acute toxicity study was done in female mice.[5] The animals were observed for any gross behavioral changes, sedation, morbidity and mortality. Based on this preliminary study doses of 300 and 2000 mg/kg were selected for further experiments.

Analgesic studies: Analgesic activity in mice was assessed in pressure induce pain using Haffner's tail clip model.[6]

Haffner's Tail Clip Model: Total of 24 mice were randomly divided in 4 groups (n = 6). The groups were treated as control (distilled water, p. o.) and standard (DIS 40 mg/kg, p.o.) while test - VNE-45, and VNE-90 received VNE (45 and 90 mg/kg, p.o, respectively). An artery clip was applied to the root of the tail of mice and the reaction time is noted. Groups of 4 mice of either sex with an initial weight of 18 to 22 g are used for each dose. The test compounds are administered orally. The drug was administered 60 min prior testing. An artery clip was applied to the root of the tail (approximately1 cm from the body) to induce pain. The animal quickly responds to these noxious stimuli by biting the clip or the tail near the location of the clip. The time between stimulation onset and response was measured by a stopwatch in 1/10 seconds increments. The prolongation of the latency times comparing the values before and after administration of the test compounds or the values of the control with the experimental groups and Standard Group were used for statistical comparison using the ANOVA.

RESULTS

Phytochemical investigation Qualitative phytochemical analysis showed presence of alkaloids, glycosides, tannins, Flavonoids and saponins in the aqueous extract of VN (Table 1).

Table No. 1. Primary Qualitative Phytochemical Analysis.

Qualitative test for Test	Reagent	Result
1. Alkaloids Hager's test	Wagner's test	+ +
2.Glycosides (on acid- hydrolysis)	Fehling's test Molisch's test	+++ +++
3. Tannins	Ferric chloride test	+++
4. Saponins	Froth test	++
5. Flavonoids	Ammonia, conc. H2SO4	+++
6. Steroids	Conc. H2SO4	-

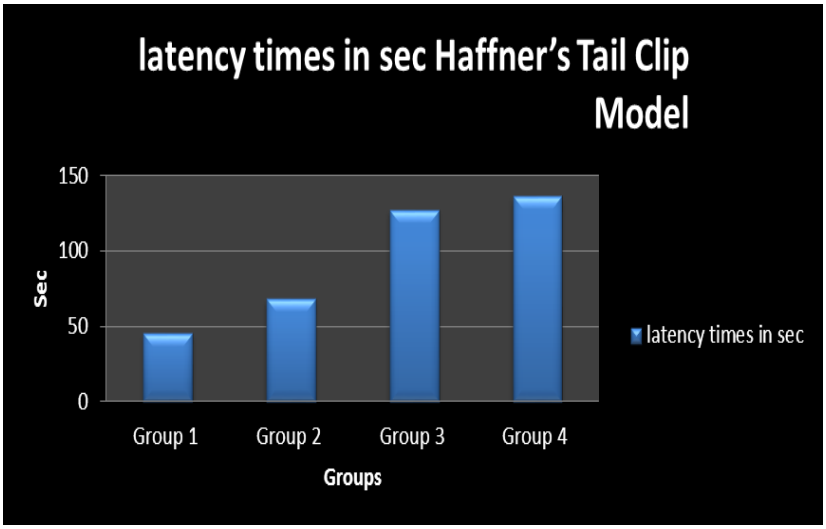
+ = mild positive, ++ = moderate positive, +++ = strong positive, - = nil

Preclinical investigations: Acute toxicity screening of VNE was carried out in mice for 300 and 2000 mg/kg, administered orally and indicated no gross behavioral changes, sedation, morbidity and mortality at this dose. Therefore, 300 and 2000 mg/kg dose was considered as a safe dose for oral administration. VNE indicated significant and dose dependent analgesic activity against Heffner's tail clip model. Pressure induces pain in Heffner's tail clip model standard (DIS 40 mg/kg, p.o.) and VNE (45, and 90 mg/kg p.o.) treated animals showed significantly reduced pain respectively when compared to that of control group ($P < 0.0001$). However, analgesia produced by VNE was not found to be higher than that produced by standard, diclofenac sodium at any of the employed doses (Table 2). Extract of Nirgundi at dose 90 mg/kg and 45 mg/kg found significant changes comparison with negative control group. Extract at dose 90mg/kg able to increase time of pain sensation in pressure pain induce on rat tail.

Table No- 2. Analgesic Effect of Vitex Negundo Extract in Haffner's Tail Clip Model

Observation	Group 1 Negative Control	Group 2 Test Group (45 mg/kg)	Group 3 Test Group (90 mg/kg)	Group 4 Standard Group	P Value
latency times in sec (Mean±SEM)	45±3.5653	68±3.5024	127±4.1425	136±9.3832	<0.0001

Dunnett's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Summary	Adjusted P Value
Group A vs. Group B	-23.33	-43.83 to -2.836	Yes	*	0.0238
Group A vs. Group C	-82.17	-102.7 to -61.67	Yes	****	0.0001
Group A vs. Group D	-91.67	-112.2 to -71.17	Yes	****	0.0001



Graph No. 1: Result of Haffner's Tail Clip Model.

DISCUSSION

Thus, in the present studies, VNE was studied for its analgesic potential in both peripheral (non-narcotic) and central (narcotic) type of pain models. Diclofenac sodium (40 mg/kg, p.o.) were used as standard drugs for comparing analgesic effects at peripheral and central levels, respectively. VNE pretreatment markedly reduces the painful response produced by pressure induced pain, manifested as writing at the employed doses. Pain is a complex process mediated by many physiological mediators e.g. prostaglandins, bradykinin, substance P. In the Haffner's tail clip model It was highly significant ($p<0.001$) with the dose of 90 mg/kg body weight when compared to the control group indicating antinociceptive activity of VNE. In one of the studies, the extract of *Vitex Negundo* shows a significant suppression of nociceptive response when compared to the control. In the Group 2 (45 mg/kg *Nirgundi* extract) the increase in reaction time is significant. The maximum increase in the reaction time ($p<0.001$) in the Group 3 (90 mg/kg *Nirgundi* extract). According to the results obtained increase in reaction time with 90 mg/kg *Nirgundi* extract is greater when compared to DIS. As already quoted previously the tail clip method is used primarily to evaluate analgesics acting through central mechanism (DIS). The test animals treated with VNE in this test have shown positive response. It can be thus inferred that the VNE has central mechanism of antinociceptive activity analogous to DIS as represented in the Table No. 2. The present study support that the potential active principle is a polar compound(s) present in the aqueous extract of VN.

CONCLUSION

On the basis of experimental study it is found that *Nirgundi Extract* has significant result in analgesic Haffner's tail clip model. Therefore, further isolation and purification of aqueous *Vitex nigundo* extract may develop a potential new lead compound with analgesic and anti-inflammatory action from herbal origin. In addition further exploration is also required to understand its influence on various pain and inflammatory mediators.

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