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Evaluation of pharmacodynamic interactions of diclofenac sodium and indomethacin with aqueous extract of vitex negundo for anti-inflammatory and analgesic activity

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Abstract
The present study evaluates the pharmacodynamic interactions between herb and drugs for anti–inflammatory and analgesic activity. Anti–inflammatory activity of herb Vitex negundo and it's interactions with Diclofenac sodium and for analgesic activity were studied with Indomethacin. Inflammation was measured with plethysmometer while for analgesic activity by using acetic acid induced writhing test in mice. The further study is performed to evaluate the interactions as such effects of combined drugs for potentiation, additive, antagonistic and synergistic effects. Along with this it also gives information about the effects of combined drugs when taken together. These types of interactions get unnoticed because of this these interactions are clinically significant and also causes serious consequences. Many researcher have a lack of knowledge hence it becomes a part of study.

Keywords: pharmacodynamic interactions, herb vitex negundo, anti-inflammatory activity, analgesic activity

Introduction
Inflammation is a normal protective response to tissue injury that is caused by physical trauma, noxious chemicals or microbiological agents. Inflammation is result of concerted participation of large number of vasoactive, chemotactic and proliferative factors at different stages and there are many targets for anti-inflammatory action (Tripathi. K.D, 2004).
Algesia (pain) is an ill-defined, unpleasant bodily sensation, usually evoked by an external or internal noxious stimulus. Pain is a warning signal, primarily protective in nature. Analgesics relieve pain as a symptom, without affecting its cause. (Tripathi K.D 7th edition).
Pain stimuli is converted to electrical energy. This electrical energy is known as transduction. This stimulus send an impulse across the peripheral nerve fibre (nociceptor).Pain signal is transmitted to the spinal cord, hypothalamus and cerebral cortex. Pain is transmitted to spinal cord by A-delta fibers and C fibers. A delta fibers (myelinated) send sharp, localized and distinct sensations. C fibers (unmyelinated) relay impulses that are poorly localized, burning and persistent pain. Inhibitory neurotransmitters like endogenous opioids work to hinder the pain transmission. This inhibition of the pain impulse is known as modulation. Person is aware of pain –somatosensory cortex identifies the location and intensity of pain called as perception.
Herb-Drug interactions are the drug interactions that occur between herbs with conventional drugs. These types of interactions may be more common than drug-drug interaction. Sometimes these interactions get unnoticed because of this some such interactions are clinically significant, although most herbal remedies are not associated with drug interactions causing serious consequences. The mechanism of most herb-drug interactions are not yet fully understood, because of this it remains a part of study.
Depends upon the host defensive mechanism inflammation is classified as acute and chronic. While in case of analgesic the writhing response was considered as the visceral inflammatory pain model caused by release of pain mediators such as bradykinin, prostaglandins, histamine and serotonin in the peritoneal fluid of mice.

Materials and methods
Drugs and Chemicals
Carrageenan and all other required chemicals were obtained from SGRS College of Pharmacy which were laboratory grade.

Collection and preparation of plant extract
Dry powder of vitex negundo were purchaced from Div-Daman, India. Preparation of extract was done by weighing equivalent amount of dry powder and transferred to the sterile beaker containing distilled water, mixed thoroughly. Resulting aqueous extract was used for further experimental procedure.

Experimental animals
Female wistar rats and mice weighing 200 g and 20-25 g respectively were selected for animal activity. Animals were kept under standard housing conditions with free access to standard chow and water. Rats were kept in polypropylene cages with stainless steel lid and were exposed to 12 h darkness and light each. The bedding material of cages was changed everyday. Animals were fasted overnight prior to the acute experimental procedures. All experiments were approved by the institutional ethical committee and were carried out according to the CPCSEA (committee for the purpose of control and supervision of experiments on animals) guidelines for laboratory animal facility.

Experimental design

For anti-inflammatory activity: Animals were provided with 0.1ml of 1% Carrageenan by Sub plantar route in left hind paw.

- Group 1: Served as a normal.
- Group 2: Rats were received 0.1ml of 1% carrageenan into the subplantar surface in left hind paw.
- Group 3: Rats were received Diclofenac sodium.
- Group 4: Rats were received test drug vitex negundo.
- Group 5: Rats were received Diclofenac sodium and aqueous extract of Vitex negundo.

The paw volume was measured after 0, 30, 60, 120 and 180 minutes.

For analgesic activity

- Group 1: Served as a normal
- Group 2: Served as a disease control
- Group 3: Mice were received as a Indomethacin.
- Group 4: Mice were received aqueous extract of Vitex negundo.
- Group 5: Mice were received Indomethacin and aqueous extract of Vitex negundo.

The percentage inhibition in writhings was calculated.

Statistical analysis

On the basis of statistical analysis the Pharmacodynamics interactions between herb and drugs for anti-inflammatory and analgesic activity was done and percentage inhibition was calculated. Aqueous extract of vitex negundo showed interactions with drugs and calculated by Anova followed by Dunnet's t test.

Results and discussion

Carrageenan induced inflammation

The anti-inflammatory effect was studied by Carrageenan induced left hind paw edema method, the edema was induced by 0.1ml of 1% of carrageenan in left hind paw of the rat by subplantar region and right paw served as a control. Inflammation was measured by Plethysmometer.

Measurement was carried out by immediately after the standard and test drug. Inflammation was measured after the 0, 30, 60, 120 and 180 minutes. Percentage inhibition was calculated according to the formula:-

$$\frac{[(V_T - V_0)\ \text{control} - (V_T - V_0)\ \text{treated}] \times 100}{(V_T - V_0)}$$

Where

V_T is the average volumes for each group after 30, 60,120and 180 min

V_0 the average volume obtained for each group at 0 min after carrageenan injection

Table 1

Sr. No.	Groups	0 min	30 min	60 min	120 min	180 min
1.	Control group	0.395+_0.129	1.717+_0.0091	1.745+_0.0099	1.773+_0.006	1.80+_0.0057
2.	Diclofenac sodium	1.685+_0.2527	2.407+_0.0133	2.355+_0.015	2.29+_0.019	2.123+_0.020
3.	Vitex negundo	1.145+_0.034	2.722+_0.036	2.603+_0.034	2.515+_0.035	2.407+_0.050
4.	Diclofenac sodium+Vitex negundo	1.652+_0.014	2.078+_0.0147	2.043+_0.0152	1.993+_0.0236	1.923+_0.0332

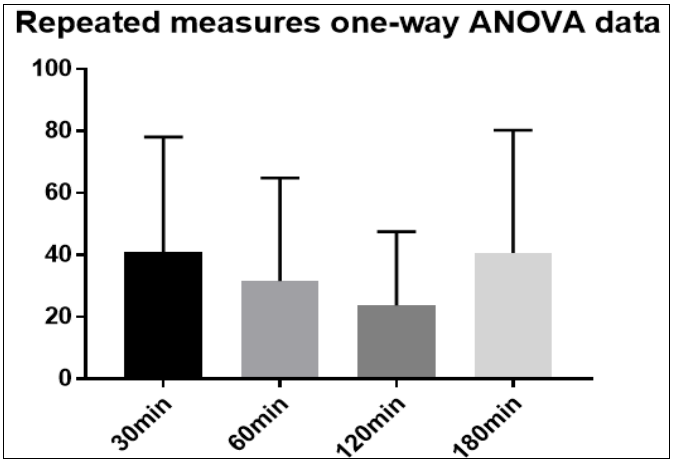

Fig 1

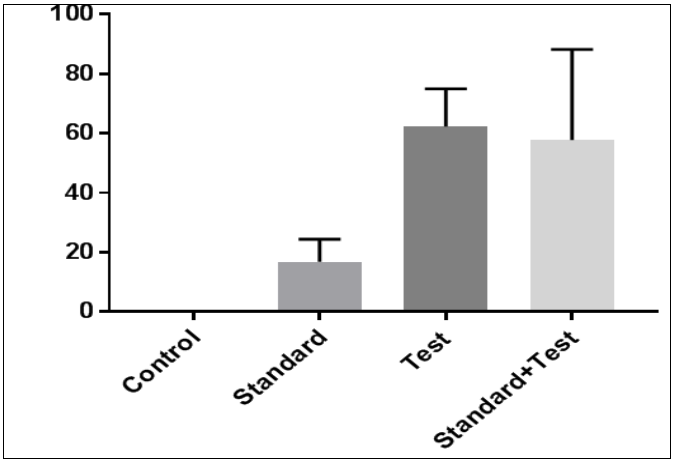

Fig 2

Table 2: Percentage edema inhibition in rats

Groups	Dose mg/kg	30min	60min	120min	180min
Control	Vehicle	0.0	0.0	0.0	0.0
Diclofenac Sodium	2.5mg/kg	76.92%	48.46%	55.7%	68%
Vitex negundo	100mg/kg	19%	8%	26%	14%
VNAE+Diclofenac Sodium	2.5+100mg/kg	67.6%	70%	13%	80.7%

Table 3: Acetic acid induced writhing test in mice

Sr. No.	Body wt. (in gm)	Treatment	No. of writhes in 15 minutes
1.	30	Acetic acid	43
2.	29	Indomethacin	17
3.	21	Vitex negundo	20
4.	24	Indomethacin+Vitex negundo	9

$$\% \text{ inhibition of writhing} = \frac{N - N^t \times 100}{N}$$

Where
N= is average number of stretching of control per group
N^t = is average number of stretching of test per group

Table 4: Percentage inhibition in writhings

Sr. No.	Treatment	No.of writhings in 10 minutes	Percentage inhibition in writhings
1.	Acetic acid	42.83+-0.945	0%
2.	Indomethacin	16.50+_1.118	63.27%
3.	Vitex negundo	18.83+_0.9098	57.21%
4.	Indomethacin+Vitex negundo	8.50+_0.7638	81.54%

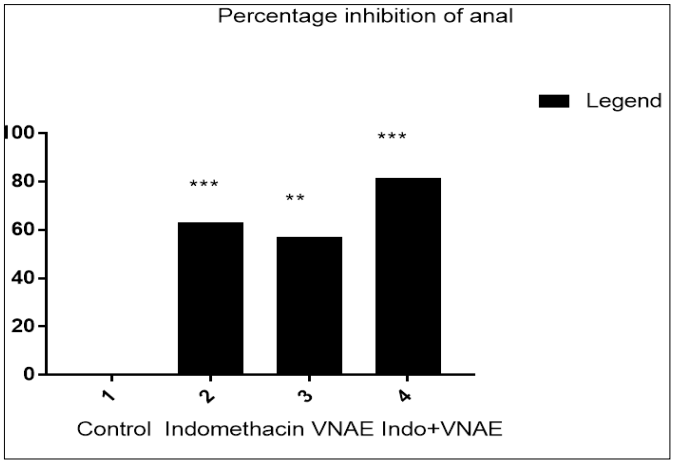

Fig 3

Discussion

We have evaluated the aqueous extract of Vitex negundo in models of inflammation and pain in rats and mice for interaction study between herb and drugs.

Carrageenan-induced paw edema as an in vivo model of inflammation has been frequently used to assess the anti-edematous effect of natural products and their interactions with synthetic drugs. Carrageenan-induced paw edema is a useful model in assessing the contribution of mediators involved in vascular changes associated with acute inflammation. It is also suitable for assessing the anti-oedematous effect of natural products and is believed to be biphasic. In the early hyperemia, 0-2 hrs after carrageenan injection, there is a release of histamine, serotonin, and bradykinin on vascular permeability. The inflammatory edema reached its maximum level at the third hour and after that it started declining. The late phase of the inflammatory response has been shown to be due to the potentiating effect of bradykinin on mediator release and prostaglandins, producing edema after mobilization of the leukocytes. The second phase is more sensitive to clinically used anti-inflammatory agents [1, 2, 3].

Nitrous oxide (NO) is a potent vasodilator and is also involved in carrageenan induced paw edema, which may be related to its ability to increase vascular permeability and edema through changes in local blood flow [4].

Carrageenin induces inflammation by enhancing PGE2 release and leukocyte migration. The carrageenin-induced paw oedema model in rats is known to be sensitive to cyclooxygenase (COX) inhibitors and has been used to evaluate the effect of non-steroidal anti-inflammatory agents. The significant reduction as well as inhibitory effect of the extract and reported interactions on the carrageenin-induced oedema paw volume is an indication of the anti-inflammatory potentials of the plant. The VNAE at 100 mg/kg p.o. doses shows inhibition after the third hour indicating an effect on the inhibition of prostaglandin release or biosynthesis. While diclofenac sodium shows significant activity from the first hour indicating an effect on both phases of inflammation.

The acetic acid-induced writhing model is a chemical stimulus widely used for the evaluation of peripheral antinociceptive activity [5, 6]. In this model, pain is generated indirectly via endogenous mediators like bradykinin, serotonin, histamine, substance P and prostaglandins, all acting by stimulating peripheral nociceptive neurons. These fibers are sensitive to narcotics such as morphine and non-steroid anti-inflammatory drugs (NSAIDs) [7]. Intraperitoneal injection of acetic acid can produce the peritoneal inflammation (acute peritonitis) which causes the response characterized by contraction of the abdominal muscle accompanied by an extension of the forelimbs and elongation of the body. This writhing response is considered as a visceral inflammatory pain model [8]. This method has been associated with the increased levels of prostaglandins in the peritoneal fluids [9]. The results in this study revealed that VNAE significantly reduced the acetic acid-induced writhing responses similar to that of the reference drug Diclofenac sodium (10mg/kg) and shows interactions with herb.

Herbs interact with drug through several mechanisms:-

1) Pharmacodynamics interactions
2) Pharmacokinetic interactions

Some examples

1. Bleeding when Warfarin is combined with ginkgo or garlic.
2. Mild serotonin syndrome when S.J.W. is taken with serotonin reuptake inhibitor.
3. Induction of mania in depressed patients with neoleptic drugs, are taken with betel nut.
4. Increased risk of hypertension when tricyclic anti-depressants combined with Yohimbin.

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Herbal medicine is the oldest and the still most widely used system of medicine in the world today. Besides, the World Health Organization has estimated that over 75% of the world's population still relies on plant derieved medicines, for basic healthcare needs. Many indigenous drugs have been claimed to have anti-inflammatory effect in Ayurvedic system of medicine but they are not properly investigated. Still there is a need to search effective and safe drugs.

Conclusion

Further study on herb drug interactions shows synergistic effect for anti-inflammatory activity and for analgesic activity it also shows the synergistic effect.

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