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EVALUATION OF ANALGESIC & ANTI-INFLAMMATORY PROPERTY OF POLYHERBAL FORMULATION IN WISTER RAT

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ABSTRACT: Introduction: Currently used analgesic agents are opioids & NSAID. All of these are associated with certain adverse effects, so research in new potent herbal formulations is urgently needed. Therefore a polyherbal formulation from seven well-known herbs that had been already individually tested for its analgesic & anti-inflammatory property was prepared, thinking that synergistically it would act better. **Aims & objective:** To evaluate the analgesic & anti-inflammatory properties of polyherbal formulation (PHF) in Wister rats. **Materials and Methods:** Analgesic activity was evaluated by using Eddy's hot plate method & acetic acid-induced abdominal writhing test. Anti-inflammatory activity was tested by using inj. carrageenan-induced hind paw edema test. 24 Wister rats were divided into four groups, *viz.* A to D. group A served as the control, B & C as test drug group & group D as standard. **Results:** PHF had shown a significant increase in the hotplate latency period ($p<0.01$) in a dose-dependent manner, indicating central analgesic property. PHF had also shown a significant reduction in acetic acid-induced abdominal writhes ($p<0.01$), indicating peripheral analgesic property in it. PHF in 600 mg/kg dose has significant central & peripheral analgesic property & results are comparable with modern drug diclofenac. PHF had also shown a significant reduction in hind paw edema induced by carrageenan injection, indicating anti-inflammatory action too. **Conclusion:** PHZ has potent analgesic & anti-inflammatory action, which supports its clinical use.

INTRODUCTION: International association for the study of pain defines pain as - 'Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [1]. The therapeutic agents currently available for the treatment of pain usually have limited effectiveness and safety [2].

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Analgesics relieve pain, without affecting its cause. Analgesics are divided into two groups, opioid analgesic and non-opioid analgesic [3]. None of the currently used analgesic agents *i.e.*, opioid & nonopioids fulfills the criteria for ideal analgesics.

Repeated use of non-steroidal anti-inflammatory drugs (NSAIDs) may induce several adverse effects, such as gastrointestinal lesions or renal and liver failure [4]. NSAIDs may cause or exacerbate gastrointestinal upsets, peptic ulcers, platelet dysfunction. It may cause bronchospasm resulting in exacerbation of bronchial asthma. Opioids are reserved for severe pain. Adverse effects of opioids include sedation, nausea, vomiting, constipation, physical dependence, tolerance, respiratory

depression & urinary retention. The use of conventional drugs for the treatment of pain and inflammation has largely resulted in various side effects. These challenges have triggered scientific researchers all over the world in search of alternative therapy [5]. Research into new effective and safe analgesic agents with satisfactory tolerability and proven efficacy is urgently needed [6]. Hence, analgesic drugs lacking these adverse effects are being searched all over the world as an alternative to NSAIDs and opiates.

During this process, the investigation of the efficacy of plant-based drugs used in traditional medicine has been paid great attention because they are cheap, have little side effects, and according to WHO, still about 80% of the world population rely mainly on plant-based drugs [7].

Recently, alternative agents, such as natural products, have been shown to contain richly diverse compounds, leading to the discovery of compounds with medical applications, particularly in the treatment of pain [8]. The use of herbal medicines worldwide has provided an excellent opportunity for India to look for therapeutic lead compounds from our ancient system of therapy, *i.e.*

Ayurveda, which can be utilized for development of new drug [9]. In extensive literature search we came to know that in many pharmaceutical institutes many animal experimentations established analgesic, anti-inflammatory & anti-pyretic properties of different herbs [10-16].

Sallaki (*Boswelia serrata*), nirgundi (*Vitex nigundo*), guduchi (*Tinospora cordifolia*), shigru (*Moringa oelifera*), yashtimadhu (*Glycerrhiza glabra*) *etc.* are some of these drugs. Promising results have been given in animal experimentations by these studies which are comparable with modern standard analgesics. Therefore it was thought to make a polyherbal formulation from these selected herbs thinking that synergistically it would work better & to evaluate its analgesic & anti-inflammatory property in animal experimentation so that it could be used in human beings.

Aims and Objective: To evaluate the analgesic & anti-inflammatory property of polyherbal formulation in Wister rat. To study effective fractional dose of polyherbal formulation.

MATERIALS AND METHODS:

Preparation of Formulation: 500 mg of the tablet was prepared to contain extract of each herb in the following concentration-

Sallaki (*Boswellia serrata*)	:	hydroalcoholic Gum-resin extract - 125 mg
Nirgundi (*Vitex nigundo*)	:	Hydroalcoholic leaf extracts-125 mg
Yashtimadhu (*Glycerrhiza glabra*)	:	hydroalcoholic stem extract- 50 mg
Sariva (*Hemidesmos indicus*)	:	hydroalcoholic root extract-50 mg
Shigru (*Moringa oleifera*)	:	hydroalcoholic leaves extract -50 mg
Guduchi (*Tinospora cordifolia*)	:	aqueous stem extract -50 mg
Tagar (*Velleriana wellichii*)	:	aqueous root extract - 50 mg

Drug was prepared in GMP certified Unijules life sciences pharmaceutical company located at Kalmeshwar, Nagpur (India). Drug standardization was done in research laboratory of the same pharmaceutical company.

Extract of the individual herb was procured from Bhagvati herbal & healthcare Pvt. Ltd Vapi, dist. Valsad, Gujrat state, India. Extract of each herb was mixed in the above-mentioned proportion to prepare 500 mg tablet.

Chemicals: Carrageenan powder was procured from Hi media laboratories Pvt. Ltd. Mumbai, acetic acid was procured from the local market (Ranbaxy laboratories).

The experimental design and research plan along with animals handling and disposal procedures was placed before the institutional animal ethics committee at Datta Meghe institute of medical sciences, Savangi, Wardha (India).

The Work was started after Clearance from the institutional animal ethics committee in accordance with guidelines formulated by CPCSE, India. (Institutional animal ethics committee approval letter ref no. DMIMS (DU)/IAEC/2018-19/06) 30 Wister rats weighing 150-200 gm of either sex were selected randomly from the animal house at Datta Meghe Institute of medical sciences at Wardha.

Husbandry Condition: The animals were housed under a standard condition of temperature at 22 ºC (± 3 ºC) with humidity 50 % to 60% and were exposed to 12 h light & 12 h dark cycle. The animals were kept in a polypropylene mice cage labeled according to the group as per institutional animal house protocol. Animals were fed with Amrut brand rat pellet feed supplied by Pranav Agro Ltd. throughout the study period.

Drinking water was given *ad libitum* in a polypropylene bottle with a stainless steel sipper tube. All animals were kept under acclimatization for seven days before experimentation. All animals were marked on the tail one by one with marker pain as I to VI roman numbers for identification.

Grouping of Rats: Animals were equally divided into four groups viz. A, B, C & D (each group had six animals)

Group A: Served as control group & received 0.9% NS

Group B: Served as a test drug group I & received polyherbal formulation (PHF) in a dose of 400 mg/kg body weight.

Group C: Served as test drug group II & received PHF in a dose of 600 mg/Kg body weight.

Group D: Served as a standard group & received diclofenac sodium 50 mg + paracetamol 375 mg combination in a dose of 9 mg/Kg body weight.

Standard drug used was procured from the local market which is manufactured by Troika pharmaceuticals marketed by the name dynapar.

Route of Drug Administration: All animals of each group received the respective drug of that group as per body weight by oral route with the help of gastric catheter sleeved to syringe nozzle & pushed to stomach with the help of 2cc syringe. Test drug & standard drug was dissolved in 0.9% NS

Acute Oral Toxicity Study: Acute oral toxicity study was done as per OECD 425 guideline [17]. As ingredients of this polyherbal formulation (PHF) are herbal & individually tested for its toxicity, this formulation is supposed to be nontoxic. First, a female Wister rat weighing 200 gm was given a polyherbal formulation (PHF) in a limited dose of 2000 mg/Kg body weight after overnight fasting. It was observed for any toxic effects like convulsions, tremors, diarrhea, salivation & lethargy. As it didn't die in 24 h. Another 4 rats (2 males & 2 females) were given polyherbal formulation in a same limit dose of 2000 mg/Kg body weight next day. All these animals were observed for two weeks for the incidence of any toxic effect. None of the animals showed any changes in the respiratory, circulatory or nervous system. As none of the animal died LD 50 is considered to be more than 2000 mg/kg body weight.

Analgesic Activity Study: Analgesic activity study of test drug was done by using acetic acid-induced writhing test & Eddy's hot plate method.

Acetic Acid-Induced Writhing in Mice: This method is useful for the evaluation of the peripheral analgesic activity of the drug. All animals fasted overnight. Dose calculation of drug for each animal according to body weight in the respective group was done. One hour before inducing writhes with acetic acid, all animals received their respective drug as per body weight [18].

One hour after dosing, writhing was induced in mice by intraperitoneal injection of 0.6% acetic acid in a dose of 10 ml/kg body weight [19]. Numbers of writhes were counted for 10 min beginning from 5th min. after the acetic acid injection. Writhing is a response consisting of contraction of an abdominal wall, pelvic rotation followed by hind limb extension [20]. Percentage inhibition of writhing response in each group was calculated by using the following formula.

$$\text{Percentage inhibition} = N - N_t / N \times 100$$

N: Average no. of writhes of the control group

N_t: average no. of writhes of the test group (or standard group)

After this experiment, all animals were put for a wash out period of 14 days.

Eddy's Hotplate Method: This method is useful for evaluating the central analgesic activity of a drug. For this experiment, animals of each group were tested for paw lick or jump response after placing them on eddy's hot plate, and only those

that reacted in the range of 3 to 5 sec (up to 15 sec) were used for the experiment. Those who didn't show a response within 15 sec were removed from the experiment. Time interval from placing animals on the surface of the hot plate to licking of hind paws or jumping is termed as hot plate latency period [21].

This is called a basal hot plate latency period. After recording the basal hot plate latency period of each animal in all four groups, selected animals of each group received their respective drug as per body weight [22].

30 min after dosing, animals of each group were placed on Eddy's hot plate analgesiometer one by one, which was maintained at 55 ± 1 ºC temperature. Hot plate latency period for each animal was noted by using stopwatch at 0, 30, 60, 90 & 120 min. after dosing. The mean hot plate latency period for each group was calculated. Cut-off time was 45 sec. As after dosing response time increases, those who did not react till 45 sec were removed from hot plate to reduce chances of burn.

Anti-inflammatory Activity Evaluation: For this study carrageenan-induced paw edema test was done.

Carrageenan Induced Paw Edema: A phlogistic agent, Kappa carrageenan was used for inducing paw edema. It is a water-soluble powder.

1% of carrageenan solution was prepared by adding 1 gm of carrageenan to 100 ml of distill water. The animals were starved overnight. Dosing of all animals as per the group and body weight was done. The left hind paw was marked with ink at the level of the lateral malleolus.

Thirty minutes later, the rats were challenged by subcutaneous injection of 0.05 ml of 1% solution of carrageenan into the plantar side of the left hind paw [23].

The paw volume was measured plathysmo-graphically before carrageenan injection & at 1, 3, 6, 12, and 24 h after carrageenan injection.

Orchid Scientifics Company's digital plathismo-meter PLM-01 Plus model was used. It measures the displacement of the volume of water due to the immersion of the paw. The left hind paw of each animal was immersed in the water chamber of plathismometer up to the ink mark at the level of lateral malleolus for measurement of paw volume.

Statistical Analysis: Results obtained are expressed as Mean + SEM for each treatment group. Results are analyzed using a one-way analysis of variance (ANOVA) test followed by Dunnett's test. The difference between the means of the treatment group and the control group is considered to be significant at $p<0.01$ & $p<0.05$.

OBSERVATIONS AND RESULTS:

TABLE 1: EFFECT OF POLYHERBAL FORMULATION ON ACETIC ACID INDUCED WRITHING TEST

Groups	Drug	Dose (mg/kg)	Number of writhes in 10 min	% inhibition of writhing
A	Control		37.66±1.36	--
B	PHF	400	23±2.41**	38.92%
C	PHF	600	18.33±0.88**	51.32%
D	Diclofenac50+ paracetamol 375	09	11.50±1.12**	69.46%

Values are expressed as Mean ± SEM, N=6 **P<0.01 When compared with control (ANOVA followed by Dunnet's t-test).

TABLE 2: RESULT SEEN IN ALL FOUR GROUPS ON EDDY'S HOT PLATE METHOD

Group	Drug	Dose (mg/kg)	Reaction time in sec at time in min.				
			0	30	60	90	120
A	Control(normal saline)	1.44 ml/200 gm	8.66 ±1.20	8.66 ±0.84	7.16 ±0.94	6.66 ±0.84	5 ±0.68
B	PHF	400	9.16 ±1.44	12* ±0.99	16..16* ±1.01	16.16 ±0.79	9.83 ±0.30
C	PHF	600	9.33 ±1.45	16.83* ±0.70	20.66** ±1.08	19** ±0.63	14 ±0.85
D	Diclofenac 50+ Paracetamol375	09	11.16 ±1.07	19.16** ±1.01	26.16** ±1.24	25** ±0.73	24** ±0.84

Values are expressed as Mean ± SEM, N=6 *P<0.05**P<0.01 When compared with control (ANOVA followed by Dunnet's t-test).

Table 1 shows that Group B & Group C had shown significant inhibition of writhes compared to control group A. Standard group D showed the best result (69.46% inhibition of writhing) followed by group C (51.32% inhibition of writhing). The result of group C is comparable with the result of standard group D. **Table 2** shows that group B has significant central analgesic activity at 30 & 60 min. Compared to the control group, group C showed a significant increase in reaction time at 30, 60 & 90 min. as compared to control group A. Group D showed a long-lasting significant increase in reaction time from 30 to 120 min. Result of group C & group D is comparable at 60 & 90 min. Among the four groups, group D performed best, followed by group C.

TABLE 3: RESULT SEEN IN ALL FOUR GROUPS IN CARRAGEENAN INDUCED PAW EDEMA

Group	Drug	Dose	Paw volume in ml at time (hr)					
			0	1	3	6	12	24
A	Control		0.491 ±0.0009	0.489 ±0.008	0.518 ±0.007	0.510 ±0.009	0.491 ±0.0010	0.470 ±0.008
B	PHF	400	0.435 ±0.003	0.485 ±0.001	0.499* ±0.001	0.494* ±0.001	0.484 ±0.001	0.464 ±0.001
C	PHF	600	0.434 ±0.001	0.465* ±0.003	0.184* ±0.004	0.480** ±0.004	0.159** ±0.003	0.457 ±0.003
D	Diclofenac+ Paracetamol	09	0.428 ±0.003	0.449** ±0.003	0.464** ±0.003	0.456** ±0.003	0.448** ±0.003	0.139** ±0.003

Values are expressed as Mean ± SEM, N=6 * P <0.05**P<0.01 When compared with control (ANOVA followed by Dunnet's t-test).

In carrageenan-induced paw edema test, group B showed a significant reduction in paw volume at 3 & 6 hrs compared to control ($p<0.05$), group C also showed a significant reduction in paw edema at 1, 3, 6 & 12 h, compared to control group. Among all groups, group D performed best. Significant reduction in paw edema was seen from 1 h to 24 h, best time among 6 timings of observation (0, 1, 3, 6, 12 & 24 h) is 24 h to reduce paw volume. Paw volume of group C at 24 h is comparable to that of paw volume at 6 & 12 h in group D, indicating that the performance of group C is satisfactory followed by a performance of group D.

DISCUSSION: Hot plate method & acetic acid-induced writhing test method are commonly used rapid & reliable methods to evaluate central & peripheral analgesic activity of any drug, respectively. In the present study, polyherbal formulation showed to have both the central & peripheral analgesic action in the experimental model in a dose dependant manner. In Eddy's hot plate method mean hot plate latency period was increased in test drug group B & C, which was significant compared to the control group at $p<0.05$ level of significance & highly significant in standard group D ($p<0.01$). The result of group C is comparable with that of group D. This shows that polyherbal formulation has good central analgesic property in higher doses & is comparable with standard drug. From **Table 2** it is clear that significant analgesic activity is not seen for a longer duration in group B & C (*i.e.*, at 120 min.), whereas analgesia lasts for a longer duration in group D till 120 min. In the acetic acid-induced abdominal writhing test, animals treated with polyherbal formulation showed significant inhibition of writhes. This shows that polyherbal formulation has peripheral analgesic action. The result of group C is comparable with group D.

Carrageenan induced hind paw edema test was done to evaluate anti-inflammatory action of polyherbal formulation because of its sensitivity in detecting orally active anti-inflammatory agents, particularly in the acute phase of inflammation [24], Intraplanter injection of carrageenan results in hind paw edema due to inflammation. Its first phase (0-2.5 h after injection of carrageenan) results from the concomitant release of mediators: histamine, serotonin, and kinins on the vascular permeability. The second phase is correlated with leukotrienes [25]. The oral administration of different fractions of PHF might have suppressed inflammation during the second phase, possibly due to inhibition of inflammatory mediators like prostaglandins.

Polyherbal formulation under study is made up of seven herbs containing sallaki, nirgundi, shigru, sariva, yashtimadhu, guduchi & tagar.

PHF contains B-boswelik acid, malik acid, hexacosane, glycerrhizine, flavonoids, saponins. Coumarin, hemidesmin, barberin tinosporin, valetric acid & many more. Analgesic effect mediated through central mechanism indicates the involvement of endogenous opioid peptides and biogenic amines like 5-HT. The ability of the PHF to prolong the reaction time to pain induced thermally in rats suggests central analgesic activity [26]. The activity may be attributed due to the presence of flavonoids and other bioactive compounds like saponins.

PHF as it inhibits the acetic acid-induced writhes, it's the mechanism of action is supposed to inhibit prostaglandin synthesis by acting on cycloxygenase & lipoxygenase enzyme [27]. Results PHF seen in animal experiments definitely encourages researchers to see its results in humans to establish this formulation as a potent analgesic. It could be a better alternative to NSAID.

CONCLUSION: From this animal experimentation, it can be concluded that polyherbal formulation has both central & peripheral analgesic action. It also has anti-inflammatory property too. Polyherbal formulation shows better results in a dose of 600mg/kg body weight. Thus experiment supports its clinical use.

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