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Analgesic Activities of *Chirabilvadi Yoga*: An Ayurvedic Compound Formulation

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ABSTRACT

BACKGROUND: Analgesics are agents which selectively relieve pain by acting in the CNS and peripheral pain mediators without changing consciousness. NSAIDs are most commonly used to control pain. But due to their adverse effects, there uses are limited. Many herbal or herbo-mineral preparations are commonly used for the treatment of pain in alternative medicine. *Chirabilvadi Yoga*, a combination of four classical *Ayurvedic* dried herbs i.e. leaves of *Chirabilva (Holoptelia integrifolia)*, bark of *Arjuna* (*Terminalia arjuna*), leaves of *Jyotishmati* (*Celastrus paniculatus*) and leaves of *Kakanasa* (*Pentatropis capensis*) in powder form is used in this study to evaluate and compared the analgesic activity profile of this *Yoga* before and after trituration with juice of *Chirabilva leaves* .

METHODS: Charles Foster albino rats (200 ± 20 g) of either sex divided in to four groups, six in each were used to evaluate the analgesic effect by using Formaline induced hind paw licking and Eddi's hot plate methods. Solution of *Chirabilvadi Yoga* and *Bhavita Chirabilvadi Yoga* were made with deionized water freshly with the dose of 900 mg /kg body weightorally.

RESULTS:A decrease in the number of paw licking response were seen in the second phase (10-20) of formalin induced paw licking response in both the test drugs groups, which indicates the presence of mild analgesic activity in the drug mediated through modulation of neuropeptides. In eddy's hot plate method test rug *Bhavita Chirabilvadi Yoga* shows non-significant decrease at 120,180 and 240 min as compare to initial and control group.

CONCLUSION: This study suggested that *Chirabilvadi Yoga* and *Bhavita Chirabilvadi Yoga* possessed mild and similar analgesic activity. Hence, it can be used in the management of mild pain conditions.

Key Words *Analgesic effect, ChirabilvadiYoga, Eddy's hot plate method, NSAIDs*

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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. An analgesic (also known as a painkiller) is any member of the diverse group of drugs used to

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relieve pain (achieve analgesia). Multiple formulations of analgesics are available in the market containing different drug molecules. It is reported that, among patients who seek treatment for pain, 50% are reported to be dissatisfied with the available pharmacological options[1]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment for a variety of painful conditions[2]. But these drugs cause side effects mainly related to gastrointestinal (bloating, dyspepsia, nausea, vomiting, bleeding, diarrhoea, and peptic ulceration[3]) and renal (decreased blood flow, interstitial nephritis, papillary necrosis) effects[4]. Thus to combat these hazardous side effects, there is need to search a safe remedy with less side-effects and herbal drugs. Since ancient times, *Ayurvedic medicines* have been used to treat various ailments including pain. In *Ayurveda*, more than one herb is used in formulations, they are known as polyherbal formulations. Four herbal drugs i.e. leaves of *Chirabilva (Holoptelia integrifolia Planch*)[5], bark of Arjuna (Terminalia arjuna Roxb.)[6], leaves of *Jyotishmati (Celastrus paniculatus Willd.*)[7], leaves of *Kakanasa* (*Pentatropis capensis* Linn.)[8], were reported individually for their analgesic effect on experimental models. According to *Ayurvedic* pharmaceutics, *Bhavana* (trituration) with organic juices improves the bioavailability of the drugs thereby enhances their rate of absorption[9]. Keeping these facts in view the pharmacology study was planned on suitable animal models, to evaluate and compare the analgesic activity profile of *Chirabilvadi yoga* and *Bhavita Chirabilvadi yoga.*

MATERIALS AND METHODS

TEST FORMULATIONS

Chirabilvadi Yoga (CY) composition was the combination of the four herbal ingredients of equal part (As seen in Table 1) and *Bhavita Chirabilvadi Yoga* (BCY) along with these ingredients three times triturated with the juice of *Chirabilva* leaves. Drugs like bark of *Arjuna*, leaves of *Chirabilva* and leaves of *Jyotishmati* were procured from the campus of I.P.G.T&R.A, Jamnagar and *Kakanasa* leaves were collected from periphery of Jamnagar, Gujarat. Random samples of the collected drugs were subjected to pharmacognostical studies with an attention to check their identity and genuineness. After establishing proper identity, individual drugs were deposited institute laboratory for further reference. After that individual ingredients were shade dried and made into fine powder separately with the help of mechanical grinder, sieved through 120# and mixed together mechanically in equal proportion to get homogenous mixture. For the preparation of *Bhavita* (triturated) *Chirabilvadi yoga***,** the prepared powder of CY was triturated with juice of *Chirabilva* leaves, three times in end runner. In each *Bhavana* sufficient amount of juice made from leaves of *Chirabilva* was added to the powder of CY, allowed to well soaked and then triturated for 4-5 hours daily till the *Bhavana* given to the powder

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was completely absorbed. On completing the three *Bhavana*, the obtained powder was dried and filtered through 120# sieve mesh and stored as BCY.

ANIMALS:

Charles Foster albino *rats* of either sex, weighing 200 ± 20 g were used for the study. The animals were obtained from the animal house attached to Institute for Post Graduate Teaching and Research in Ayurveda (IGPT and RA), Gujarat Ayurved University, Jamnagar. Six animals were housed in each cage and were maintained on 'Amrut' brand animal pellet feed of Pranav Agro Industries and tap water was given *ad libitum*. The temperature (22 ± 03º C) and humidity (50 to 70%) were kept at optimum and the animals were exposed to natural day-night cycles. The experiments were carried out in conformity with the guidelines of the Institutional Animal Ethics Committee after obtaining its permission (approval number IAEC/12/2016/05) in accordance with the guideline formulated by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India.

DOSE CALCULATION

Dose of the drug was fixed by extrapolating the human dose to laboratory animals on body surface area ratio as per Paget and Barnes (1964)[10].The adult human dose (10 gm/day) was converted in to the animal dose, (900 mg/kg) for both the formulations. The test drugs were suspended in distilled water by making a uniform suspension with a suitable concentration depending upon the body weight of the animals and administered orally with the help of a gastric catheter sleeved to a syringe. The drugs were administered to overnight-fasted animals.

EXPERIMENTAL PROTOCOLS

Analgesic activity

Eddy's hot plate method[11]*:*

Charles Foster albino rats of either sex weighing 200 ± 20 g were randomly divided in to four groups each comprised of six rats. First group received distilled water (10 ml/kg, po) and served as normal control group. The second and third group received *Chirabilvadi yoga* (900 mg/kg, po) and *Bhavita Chirabilvadi yoga* (900 mg/kg, po) respectively. Pentazocine (20 mg/kg, ip) was used as a reference standard drug to the fourth group.

The temperature of incremental hot/cold plate was fixed at 55±0.2°C. Mean initial reading was noted for each rat for paw licking or jump response. The test drugs were administered to respective groups and distilled water to control group. One hour after test drug administration, each animal was placed on hot plate kept at a temperature of 55±0.5ºC. A cut off period of 15 sec. was observed to avoid damage to the paw. Reaction time was recorded when animals licked their fore or hind paws, or jumped at 30, 60,120,180 and 240 min. after the administration of the drug. Results were expressed as an increase the time interval in the onset of reaction as compared to initial and control group.

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Formalin-induced hind paw licking response[12]:

The test conditions, test drugs and groupings were similar to Eddy's hot plate method, except the fourth group which was taken as standard and administered with the standard drug Diclophenac sodium (5mg/kg/po, Novartis India Limited).

The test drugs and distilled water were administered to respective groups once daily for five consecutive days. On fifth day, one hour after the drug administration, pain response was induced by injecting 0.1 ml of 2% v/v formalin in distilled water in sub plantar region of right hind paw. Immediately after the injection animals were placed in a transparent plastic chamber (30 x 30 x 30 cm). Onset time of paw licking and number of licking of formalin injected paw were considered as an index of pain or nociception. The number of paw licking was noted as an index of nociception at different time intervals periods of 0-10 min. (early phase), 11-20 min. and 21-30 min. (Late phase). Results were expressed as the decrease in number of the paw licking in comparison to initial and control group.

Statistical Analysis:

The obtained data has been presented as Mean ± SEM, difference between the groups, statistically determined by student't' test for paired and unpaired data to assess the statistical significance between the groups. The value $P< 0.05$ is considered as statistically significant.

RESULTS

ANALGESIC ACTIVITY

Eddy's Hot plate method

The summarized data related to effect of test drugs on radiant heat induced pain method at different intervals in rats mentioned in Table 2 to Table 6.

Table 2 Effect of test drugs on radiant heat response of rats after 30 minutes of drug administration

Group	Dose (mg/kg)	Reaction time in minutes at time			
		Initial	30 minutes	% change to initial	% change to control
Control	Q.S.	3.47 ± 0.12	4.06 ± 0.26	17.05↑	-----
CY	900.0	3.65 ± 0.25	4.18 ± 0.14	14.50↑	2.95↑
BCY	900.0	3.62 ± 0.31	4.095 ± 0.36	12.98↑	0.86↑
Pentazocine	100.0	4.13 ± 0.26	6.17 ± 0.49*#	49.62↑	51.97↑

Table 3 Effect of test drugs on radiant heat response of rats after 60 minutes of drug administration

Group	Dose	Reaction time in minutes at time			
		Initial	60 minutes	% change to initial	% change to 60 min
Control	Q.S.	3.47 ± 0.121	4.26 ± 0.239	22.7↑	-----
CY	900mg/kg	3.65 ± 0.247	4.49 ± 0.440	23.01↑	5.39↑
BCY	900mg/kg	3.62 ± 0.309	4.32 ± 0.356	19.33↑	1.40↑
Pentazocine	100.0	4.13 ± 0.26	7.66 ± 0.63**#	85.65↑	79.81↑

Table 4 Effect of test drugs on radiant heat response of rats after 120 minutes of drug administration

Group	Dose	Reaction time in minutes at time			
		Initial	120 minutes	% change to initial	% change to control
Control	Q.S.	3.47 ± 0.121	3.52 ± 0.279	1.44↑	-----
CY	900mg/kg	3.65 ± 0.247	3.70 ± 0.280	1.36↑	5.11↑
BCY	900mg/kg	3.62 ± 0.309	2.79 ± 0.341	22.92↓	20.73↓

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Pentazocine	100.0	4.13 ± 0.26	6.24 ± 0.63*#	51.27↑	77.27↑

Table 5 Effect of test drugs on radiant heat response of rats after 180 minutes of drug administration

Group	**Dose**	**Reaction time in minutes at time**			
		Initial	**180 minutes**	**% change to initial**	**% change to control**
Control	Q.S.	3.47 ± 0.121	2.70 ± 0.365	22.19↓	----
CY	900mg/kg	3.65 ± 0.247	2.83 ± 0.183	22.46↓	4.81↑
BCY	900mg/kg	3.62 ± 0.309	2.45 ± 0.238	32.32↓	9.25↓
Pentazocine	100.0	4.13 ± 0.26	6.05±0.39*#	46.54↑	124.07↑

Table 6 Effect of test drugs on radiant heat method of rats after 240 minutes of drug administration

Group	**Dose**	**Reaction time in minutes at time**			
		Initial	**240 minutes**	**% change to initial**	**% change to control**
Control	Q.S.	3.47 ± 0.121	2.97 ± 0.247	14.40↓	----
CY	900mg/kg	3.65 ± 0.247	3.00 ± 0.241	17.80↓	1.01↑
BCY	900mg/kg	3.62 ± 0.309	2.78 ± 0.388	23.2↓	6.39↓
Pentazocine	100.0	4.13 ± 0.26	4.23±0.25#	2.44↑	42.42↑

Data:QS: Sufficient quantity, Mean±SEM; ↓= Decrease, ↑= Increase
*P<0.01, **P<0.001 compared with initial (Paired 't'test)
#P<0.01 when compared with control group (Unpaired't' test)

After 30 and 60 min., there was increase in the reaction time to radiant heat induced pain in all the groups compared to initial reading including control group. At 120 min. there was no any effect on reaction time to radiant heat induced pain in comparison to initial and control group. After 180 minutes, there was decrease in the reaction time to radiant heat induced pain in all the groups compared to initial reading including control group. Both test drugs produced almost similar fashion of effects as shown in control group against thermal-induced pain in rats. Standard drug produced significant analgesic effects at all time-intervals in comparison to initial reaction time and control group.

Table 7 Effect of test drugs on formalin-induced paw licking response in rats

Groups	**Dose (mg/kg)**				
		On set of paw licking	% change	Numbers of paw lickings (0-10 mins)	% change
Control	Q.S.	16.66 ± 2.09	----	14.66 ± 2.09	----
CY	900.0	30.66 ± 1.45	11.04↑	10.83 ± 1.44	26.12↓
BCY	900.0	14.33 ± 5.44	13.98↓	16.00 ± 2.22	9.14↑
Diclofenac	5.0	20.83 ± 4.39	25.03↑	6.33 ± 0.49*	56.82↓

Data**:** QS: Sufficient quantity,Mean ± SEM, ↑ - Increase, ↓ - Decrease,
*P<0.01when compared with control group (Unpaired 't' test)

Formalin-induced hind paw licking response:

Table 7 showed the effects of test drugs on the onset of paw licking and numbers of paw licking responses in the rats. In group CY, the time of onset of paw licking is increased by 11.04% but in group BCY the time onset of the paw licking is decreased by 13.98% as compared to the control group. Number of paw licking was non-significantly decreased in CY treated group (26.12%) while increased in the BCY treated group in comparison to control group. Standard drug produced non-significant increase in onset

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of paw licking and significant decrease in number of paw licking during initial phase in comparison to control group.

Table 8 Effect of test drugs on formalin-induced paw licking response in rats

Groups	Dose (mg/kg)	Numbers of paw lickings			
		10-20 mins	% change	20-30 mins	% change
Control	Q.S.	8.83 ± 2.12	----	20.33 ± 4.88	----
CY	900.0	8.00 ± 2.39	9.96↓	16.50 ± 3.02	18.83↓
BCY	900.0	8.16 ± 2.91	7.58↓	19.50 ± 4.48	4.082↓
Diclofenac	5.0	1.83 ± 0.65*	79.27↓	2.83 ± 0.79*	86.07↓

Data**:** QS: Sufficient quantity, Mean ± SEM, ↑ - Increase, ↓ - Decrease,
*P<0.001when compared with control group (Unpaired 't' test)

Table 8 showed the effects of test drugs on the onset of paw licking responses in the rats. At 10-20 min, numbers of paw licking responses were non-significantly decreased by 9.96% and 7.58% in CY and BCY treated groups respectively. At 20-30 minutes numbers of paw licking responses were non-significantly decreased by 18.83% and 4.02 % in both the group CY and BCY treated groups respectively in comparison to control group. Standard drug produced significant decrease in number of paw licking during late phase in comparison to control group.

DISCUSSION

The models investigating anti-nociception were selected based on their capacity to investigate both centrally and peripherally mediated effects. The Formaline-induced hind paw investigate central as well as peripheral but Eddy's hot plate method investigates only central activity.

Formalin injection to plantar aponeurosis of rats shows pain response in two phase's viz., initial and late phase. The initial phase lasts for 0-10 minutes of formaldehyde injection; it is supposed to be mediated through modulation of neuropeptides[13]. The second phase, which is observed 20-30 minutes of formaldehyde injection, is supposed to be mediated through release of inflammatory mediators like prostaglandin etc.

Test drug CY shows statistically insignificant increase in latency of onset whereas BCY shows statistically insignificant decrease in latency of onset for inhibiting formalin-induced pain response. In the first phase (0-10 minutes) both test drug groups failed to exhibit a significant decrease in the number of paw licking response. However, in the second phase (10-20) both CY and BCY groups exhibit a decrease in the number of paw licking response which indicates the presence of mild analgesic activity in the drug mediated through modulation of neuropeptides. While, in the second phase of reading season, i.e. 20-30 minutes non-significant decrease was observed in both test drug groups. Though, the result found in is not statistically significant but the percentage wise decrease in number of paw licking is suggestive that both the test drugs have mild inhibitory activity against inflammatory pain.

Eddy's hot plate model, which is thermal induced nociception, indicates narcotic involvement,

which is sensitive to opioid μ receptors (Abbott and Young, 1988)[14]. Both the test drug treated groups did not show any significant increase in response in hot plate model as compared to initial reading and control group. Both test drugs produced almost similar fashion of response as shown in control group against thermal-induced pain in rats which suggests that, both the test drugs have devoid of any central analgesic effects in animal model. Standard drug produced significant analgesic effects at all time-intervals in comparison to initial reaction time and control group.

CONCLUSION

Both the formulations, *Chirabilvadi Yoga* and *Bhavita Chirabivadi Yoga* are statistically insignificant but the percentage wise decrease in number of paw licking is suggestive that both the test drugs have mild inhibitory activity against at the studied dose level. However, human physiology differs from animal physiology, further study requires for substantiating the tribal claims at different dose levels with different proportion of ingredients.

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