ORIGINAL ARTICLE

AN EXPERIMENTAL COMPARATIVE STUDY OF ANALGESIC ACTIVITY OF CURCUMA: AMADA (MANGO-GINGER) WITH CONVENTIONAL NSAID ASPIRIN IN MALE ALBINO WISTAR RATS
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ABSTRACT: BACKGROUND: Mango ginger (Curcuma amada Roxb.) belongs to Zingiberaceae family has biological activities include antioxidant, antibacterial, antifungal, anti-inflammatory, antiallergic, CNS depressant and analgesic activity. The major chemical components include starch, phenolic acids, volatile oils, curcuminoids and terpenoids like difurocumenol, amadannulen and amadaldehyde. Pain is often the first indication of disease or injury and a major symptom in many clinical conditions and can significantly interferes with a person’s quality of life and general functioning. The standard and test drugs suppress the inflammatory mediators associated with pain. This article brings out the analgesic activity of C. Amada in comparison with aspirin. Therefore aqueous extract of C. amada was evaluated for analgesic activity in animal models of pain. OBJECTIVES: 1. To evaluate rhizomes of Curcuma Amada for analgesic activity in male albino wistar rats and to compare the analgesic activity with aspirin. 2. To Evaluate if combination of Curcuma Amada with aspirin is synergistic. MATERIALS AND METHODS: Albino rats are the proven models for analgesic studies. They were obtained from the animal house of DR.B. R. Ambedkar Medical College. Animals were maintained as per CPCSEA guidelines .The aqueous extract of Curcuma Amada was used. Aspirin (100mg/kg) was used as the standard analgesic drug. 4x4 groups of 6 Rats were used to ensure that results obtained were statistically significant using ANOVA test. Analgesic activity will be assessed with the help of following screening methods Acetic Acid Writhing Method using Acetic Acid, Tail Flick Method using the Analgesiometer, Tail Immersion Method using Hot Water (55°C) , Hot Plate method using Hot Plate. RESULTS: Aqueous extract of Curcuma Amada significantly suppressed the 1% acetic acid induced writhing response in rats when compared to standard drug aspirin. In the Tail flick and Hot plate test Curcuma Amada increases the latency period of pain (Reaction time). In the Tail immersion test the test drug significantly (P <0.001) reduced pain at 30 min when compared to the standard drug Aspirin at 60 min of oral administration. INTERPRETATION AND CONCLUSION: We can conclude that, Curcuma Amada possess analgesic activity which can be explained by animal models of pain. Probably, it acts by peripheral and central mechanisms. The combination of Curcuma Amada and Aspirin is synergistic. KEYWORDS: Acetic acid writhing; Tail immersion; Tail flick; Hot plate; pain; Curcuma Amada; Analgesic activity.

INTRODUCTION: “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”¹,²

Pain is often the first indication of disease or injury and a major symptom in many clinical conditions and can significantly interferes with a person’s quality of life and general functioning. It
ORIGINAL ARTICLE

may be physiological or pathological. Pain is a subjective experience and includes a strong affective component. The various types of pain in humans are somatic pain, visceral pain, referred pain, neuropathic pain, cancer pain etc.\(^3\) The IASP (International Association for Study of Pain) advocates that the relief of pain should be recognized as a human right, that chronic pain should be considered a disease in its own right, and that pain medicine should have the full status of a speciality.\(^4\) Perception of pain and response to analgesic drugs are complex processes that involve multiple biochemical pathways. Each of these pathways is influenced by significant genetic factors that may modify pain perception and/or response to analgesics. Indeed, there is a wide range of inter individual variability in the perception of pain, as well as in the dosage of analgesics that will provide pain relief.\(^5\) Analgesics relieve pain symptom, without affecting its cause. Opioid analgesics and NSAIDs are widely used in the management of pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce pain and edema by suppressing the formation of prostaglandins, by inhibiting the activity of the enzyme cyclooxygenase (COX-1 and COX-2). However, prostaglandins are key mediators of several components of GI mucosal defense, so suppression of synthesis of prostaglandins by NSAIDs greatly reduces the resistance of the mucosa to injury as well as interfering with repair processes. Use of Aspirin is also increasing because of its utility in reducing the incidence of a number of common disorders including stroke, myocardial infarction, Alzheimer’s disease and cancer.\(^6\) Drugs currently used for the management of pain are opioids and non-steroidal anti-inflammatory drugs, which carry many potential toxic effects. Opioids cause adverse effects such as sedation, mental clouding, blurring of vision, respiratory depression, constipation and urinary retention. NSAIDs cause the adverse effects involving several systems of the body such as gastrointestinal tract, kidneys, CNS, CVS, blood and skin. Studies suggest that risk of gastro intestinal bleeding is significantly associated with acute use of non-steroidal anti-inflammatory drugs like regular dose Aspirin.\(^7,8\) the rhizomes of Curcuma Amada have been proven to have many properties like anti-inflammatory, antipyretic, diuretic, emollient, expectorant and analgesic activites.\(^9\) If this rhizosome exhibits analgesic activity, it may prove very useful to mankind, as this herbal product can be used as a complementary alternative medicine for the treatment of pain. Hence this study was undertaken to evaluate the analgesic activity of Curcuma Amada, and to compare the analgesic activity with Aspirin. Also the two drugs are given together and the results obtained are compared to the other two groups to evaluate whether or not the combination of Aspirin and Curcuma Amada is synergistic.

OBJECTIVES:
1. To Evaluate rhizomes of Curcuma Amada for analgesic activity in male albino wistar rats and to compare the analgesic activity with aspirin.
2. To Evaluate if combination of Curcuma Amada with aspirin is synergistic.

MATERIALS AND METHODS:

MATERIALS:
I. Chemicals: Gum Acacia, Aspirin, Curcuma-amada aqueous extract, 1 % acetic acid.
II. Animals: Male Albino wistar rats weighing 100 - 150 gms.
III. Equipments: Tuberculin Syringe (1 ml), Analgesiometer, Thermometer, Temperature controlled organ bath, Hot Plate.
Gum Acacia: Gum-Acacia is the dried gummy exudation from the stems and branches of acacia senegal or other African species of Acacia. It is an inert substance used as a suspending agent for the oral administration of the test compound and the standard compound, the concentration being 2%.

Acetic Acid: In our study, intraperitoneal injection of 1% acetic acid has been used to induce pain.

SOURCE OF ANIMALS: Albino rats are proven models for analgesic studies. In this study, male albino wistar rats weighing 100-150gms were used. Animals were obtained from the animal house, Dept. of Pharmacology, DR. B. R. Ambedkar Medical College, K. G. Halli, Bangalore-560045.

Animals were maintained as per Committee for the purpose of control and supervision on Experiments on Animals [CPCSEA] guidelines with food and water.

Number of rats used was 96, in order to provide statistically significant results using ANOVA test.

METHOD OF COLLECTION: The aqueous extract of Curcuma Amada was used for the process of evaluation, as by this method the chemical composition of the biologically active components of Curcuma Amada will not be disturbed. The rhizomes of Curcuma Amada were deskinned, and weighed. 250 grams of deskinned Curcuma Amada rhizomes were put in a mixer-grinder at 1,850 RPM for 5 minutes. The aqueous extract thus obtained was diluted with distilled water so as to make up the volume to 100 ml. Thus, the extract has strength of 2500 mg/ml. Aspirin (100mg/kg) was used as the standard analgesic drug. The volume of drug suspension was 1 ml/100 gms of the body weight of the rat. The drug treated groups received Aspirin and Curcuma – Amada extract in the dose of 100 mg/kg body weight in 2% gum acacia suspension orally. The untreated group received 2% plain gum acacia suspension (without drug) orally. The animals used were 4x4 groups of 6 Male Albino Wistar Rats to ensure that the results obtained were statistically significant using ANOVA test.

METHODOLOGY:
Inclusion Criteria: Male albino wistar rats, 100 days old weighing 100-150grams.

Exclusion Criteria:
- Pregnant or female rats.
- Rats weighing more than 150grams.
- Diseased rats.
- Study has been approved by Institutional Animal Ethics Committee (IAEC), and CPCSEA Delhi.

METHODS: The Methods employed here in to study the analgesic activity are
- Acetic acid writhing method using acetic acid.10
- Tail flick method using the Analgesiometer.11
- Tail immersion method using hot water (550C).12
- Hot plate method using hot plate.13
Acetic acid writhing method using acetic acid

**Principle:** Acetic acid induces a painful reaction on intra peritoneal injection (I.P.).

**Requirements:** 6x4=24 male albino wistar rats (100-150gm), test drugs (CA, Aspirin, Gum acacia, combination of Aspirin + CA), 2ml syringe, acetic acid 1% (0.1 ml/10g body weight).

**Procedure:**
Rats are pretreated (with control and test drugs 1 hour before)

1 ml of 1% acetic acid I.P.

**Response:** No of writhes occurring for next 30 min were observed.

**WRITHE:** A stereotyped behaviour in rats characterised by constriction of the abdomen, twining of the trunk and extension of hind limbs is called as writhe.

**Interpretation:**
- Analgesics decrease the total number of writhes when compared to control groups.

\[
\text{Percentage of Inhibition} = \frac{\text{No. of writhes in control group} - \text{No. of writhes in treated group}}{\text{No. of writhes in control group}} \times 100
\]

The results obtained are indicated in Table 1.

**Tail Flick Method Using the Analgesiometer:**

**Principle:** The application of thermal radiation to the tail of an animal provokes the withdrawal of the tail by a brief vigorous movement. It is the reaction time of this movement that was recorded.

**Requirements:** 24 male albino wistar rats (100-150gms), Test drugs (C.Amada, Gum acacia), equipment- Analgesiometer.
Procedure:
- N=6 rats were weighed and numbered.
- Animal was held in a restrainer in such a way that the tail lies over the nichrome wire of the Analgesiometer.
- Strength of current used is 4 ampere.
- Basal reaction time to radiant heat was taken by placing the tip of tail (last 1-2 cm) on the radiant heat source.
- Tail withdrawal from heat (flicking response) was taken as the end point.
- A rat withdraws its tail within 3-5 sec.
- Reaction time 10 sec is considered as maximal analgesia and tail is removed from the source of heat to avoid tissue damage.
- Index of analgesia was calculated by percentage increase in reaction time at each time interval.
- Reaction time was taken at 0, 30, 60, 90 minutes.
- The results obtained are indicated in Table 2.

Tail immersion method using hot water (55 °C):

**Principle:** Analgesics prolong reaction time of tail-withdrawal reflex in rats induced by immersing the end of the tail in warm water of 55°C.

**Requirements:** 24 male albino wistar rats (100-150gms), test drugs (C.Amada, Gum acacia), Organ bath with temperature controlled at 55°C.

Procedure:
- N=6 rats were weighed and numbered.
- Lower 5 cm portion of the tail is marked.
- Marked part of the tail was immersed into the organ bath with water maintained at 55°C.
- Within few seconds the rat reacts by withdrawing the tail.
- The reaction time was recorded in 0.01s units by a stopwatch.
- After each determination the tail was carefully dried.
- The reaction time was determined before and periodically after oral administration of the test and standard substance.
- The cut off time was 15 sec.
- Observations were recorded at time intervals of 0, 30, 60, 90, 120 min.
- The results obtained are indicated in Table 3.

Hot Plate Method using hot plate:

**Principle:** Heat is used as a source of pain (Thermal stimulus), the paws of rats are sensitive to heat at temperatures of 55-56 0°C.
Requirements: 24 male albino wistar rats (100-150gms), Test drugs (C. Amada, Gum acacia), Eddy’s hot plate.

Procedure:
- N=6 rats were weighed and numbered.
- Animals were placed on hot plate
  
  Temperature of hot plate was maintained at 55-56 °C
  
  Response: hind paw licking and jump response.
  - The basal reaction time was 6-8 seconds.
  - Cut-off period was 15 sec. to avoid damage to rats.
  - Reaction time taken for licking for paws or jumping was recorded.
  - Percentage increase in reaction time was calculated.
  - Observations were recorded at time interval of 0, 30, 60, 90, 120 min.
  - The results obtained are indicated in Table 4.

STATISTICAL ANALYSIS: Results were expressed as mean ± SEM. Differences among data were determined by one way ANOVA. P value <0.001 was considered statistically significant.

RESULTS: Acetic Acid Writhing Test: Curcuma Amada at a dose of 100mg/kg significantly suppressed the 1% acetic acid induced writhing response. The standard analgesic drug Aspirin produced increasing inhibition of writhing when compared to the control and test group. Pain inhibition percentage (PIP) is maximum with combination group (CA + Aspirin), PIP of test drug and standard drug is almost similar.

Acetic acid induced writhing: Number of writhing in 30min.

| Treatment Group                        | Dose (mg/kg) | No. of writhes in 30 min (Mean±SEM) | Inhibition (%) |
|----------------------------------------|--------------|------------------------------------|----------------|
| Control group (Gum acacia)             | 100mg/kg     | 63.7±1.054                         | -              |
| Test group (CA)                        | 100mg/kg     | 21.2±0.307                         | 66.76 %        |
| Standard group (Aspirin)               | 100mg/kg     | 20.2±0.477                         | 68.33 %        |
| Combination group (CA + Aspirin)       | 50 mg/kg+50mg/kg | 18.8±0.477                        | 70.42 %        |

Table 1: Acetic acid Writhing Method

Each value is the mean±S. E.M. p<0.001 for all the parameters, data were analyzed by using ANOVA.
**Original Article**

**Tail Flick Method:** In the tail flick test the CA extract 100 mg/kg exhibited increase in the tail flick latency in rats. The increase was significant (P <0.001) at 60 min for test drug. Standard drug and combination group (P <0.01) at 60 and 90 min.

| Treatment group | Reaction time in seconds |
|-----------------|--------------------------|
|                 | 0 min | 30 min | 60 min | 90 min |
| Control group (Gum acacia) | 5.01±0.46 | 5.34±0.56 | 5.40±0.38 | 5.31±0.38 |
| Test group (Curcuma Amada) | 5.22±0.30 | 5.73±0.37 | 7.83±0.26<sup>c</sup> | 7.31±0.41<sup>b</sup> |
| Standard group (Aspirin) | 5.56±0.37 | 6.83±0.29<sup>a</sup> | 7.63±0.48<sup>b</sup> | 7.67±0.43<sup>b</sup> |
| Combination group (Curcuma Amada + Aspirin) | 5.72±0.20 | 7.15±0.55<sup>a</sup> | 9.30±0.76<sup>b</sup> | 8.60±0.73<sup>b</sup> |

**Table 2: Tail Flick Method**

Each value are the mean±S.E.M.  <sup>a</sup> P <0.05,  <sup>b</sup> P <0.01,  <sup>c</sup> P <0.001. Data were analyzed by using ANOVA.

**Tail Immersion Method:** In tail immersion method all the test and standard drugs significantly (P< 0.001) reduced the pain as compare to the control group. The test drug and combination group showed analgesic activity at 30 mines where as standard drug showed analgesic activity at 60min.

| Treatment group | Reaction time in seconds |
|-----------------|--------------------------|
|                 | 0 min | 30 min | 60 min | 90 min | 120 min |
| Control group (Gum acacia) | 0.78±0.07 | 1.24±0.09 | 1.15±0.12 | 1.08±0.05 | 0.96±0.04 |
| Test group (Curcuma Amada) | 0.77±0.03 | 1.76±0.07<sup>c</sup> | 1.99±0.03<sup>c</sup> | 2.44±0.14<sup>c</sup> | 2.49±0.16<sup>c</sup> |
| Standard group (Aspirin) | 0.77±0.05 | 1.60±0.11<sup>a</sup> | 2.68±0.13<sup>c</sup> | 3.27±0.18<sup>c</sup> | 4.43±0.18<sup>c</sup> |
| Combination group (Curcuma Amada + Aspirin) | 0.85±0.03 | 1.95±0.05<sup>c</sup> | 2.90±0.14<sup>c</sup> | 3.36±0.13<sup>c</sup> | 5.01±0.05<sup>c</sup> |

**Table 3: Tail Immersion Method**

Each value are mean±S. E. M.  <sup>a</sup> P <0.05,  <sup>b</sup> P <0.01;  <sup>c</sup> P <0.001. Data were analyzed using ANOVA.

**Hot Plate Method:** CA at a dose of 100 mg/kg produced an increase in the latency period of pain induced by heating of the plate. The significant (P <0.001) analgesic activity was noticed at 90 and 120 min for test drug, standard drug and combination group.

| Treatment group | Reaction time in seconds |
|-----------------|--------------------------|
|                 | 0 min | 30 min | 60 min | 90 min | 120 min |
| Control group (Gum acacia) | 4.08±0.38 | 3.85±1.00 | 3.89±1.76 | 3.98±0.85 | 4.46±0.58 |
| Test group (Curcuma Amada) | 4.24±0.51 | 5.19±0.48 | 6.41±0.34 | 7.66±0.51<sup>c</sup> | 7.66±0.51<sup>c</sup> |
| Standard group (Aspirin) | 4.24±0.62 | 5.49±0.29<sup>a</sup> | 6.78±0.20<sup>a</sup> | 7.99±0.49<sup>c</sup> | 8.48±0.42<sup>c</sup> |
Each value are mean±S. E. M.  a P <0.05,  b P <0.01,  c P <0.001. Data were analyzed using ANOVA.

DISCUSSION: In the present study the analgesic activity of Curcuma Amada has been studied and subjected to preliminary screening for its Analgesic activity and is compared with the prototype NSAID Aspirin. The results obtained indicate that Curcuma Amada possess analgesic activity, evident in all the models, signifying that it possess both central and peripherally mediated activities. The analgesic effect of Curcuma Amada was evaluated in different experimental models of pain such as Acetic acid writhing method, Tail flick method, Tail immersion method, Hot plate method. The observed analgesic activity was found to be significant with P <0.001 when compared with the control group, almost similar to Aspirin (P<0.01) and the combination was synergistic (P<0.001).

Acetic Acid Writhing Method: The abdominal constriction response induced by acetic acid is a sensitive procedure to evaluate peripherally acting analgesics. Acetic acid causes pain by liberating endogenous substances such as serotonin, histamine, prostaglandins, bradykinins and substance P. Local peritoneal receptors are postulated to be involved in the abdominal constrictions response.

The method has also been associated with prostanoids in general that is, increased levels of PGE2 and PGF2α in peritoneal fluids as well as lipooxygenase products.

Curcuma Amada at a dose of 100mg/kg significantly reduced the number of writhes (P<0.001) in comparison to the control group. The standard drug Aspirin 100mg/kg significantly (P<0.001) inhibited the number of writhes at all the time intervals. Among all the treatment groups, the highest pain percentage inhibition of writhing was shown by a combination group of Curcuma Amada + Aspirin (50mg/kg+ 50mg/kg).

Recent findings suggest that aqueous and alcoholic (ethanol) extracts of Curcuma Amada contains active phytoconstituents which showed analgesic activity by inhibiting either synthesis, release of inflammatory mediators. These observations provide a possible basis for the peripheral analgesic action of CA.

Tail Flick Method: In the tail flick test Curcuma Amada extract exhibits increase in the tail flick latency in rats. The increase was significant (P <0.001) at 60 minute post treatment time point compared to control group. Aspirin 100mg/kg elicited a significant (P <0.01) increase in the tail flick latency at 60 and 90 min post treatment time point. The combination group (CA+Aspirin) also shows significant (p<0.01) increase in tail flick latency at 60 and 90 min post treatment.

Time point. Tail flick test is most sensitive to centrally acting analgesics. Increase in tail flick latency by CA indicated possible involvement of a higher center and it is spinally mediated reflex. The effectiveness of analgesic agents in the tail-flick pain model is highly correlated with relief of human pain perception.
Tail Immersion Method: Tail immersion test useful in elucidating centrally mediated antinociceptive responses, which focuses mainly on changes above the spinal cord level. The analgesic activity of the extract of CA and standard drug Aspirin significantly (p < 0.001) reduces pain as compared to the control group. The test drug CA, combination group (CA + Aspirin) produced significant effect after 30 min of oral administration whereas as standard group (Aspirin) produces significant effect after 60 min of oral administration.

Hot Plate Method: The treatment with CA 100mg/kg showed significant (P<0.001) analgesic activity in the hot plate method at 90 and 120 min. Aspirin and the combination group (Aspirin + CA) also showed significant (P<0.001) analgesic activity at 90 and 120 min. The hot plate method was useful in elucidating centrally mediated analgesic responses, which focuses mainly on changes above the spinal cord level. Prolongation of the reaction time in the hot plate method indicates the involvement of supraspinal mechanisms. These findings indicate that CA may contain opioids-like compounds which are responsible for the analgesic activity of the plant.

Centrally acting analgesic drugs increase pain threshold of animals to heat and pressure.

Aspirin has peripheral analgesic activity, only inhibit the late phase of pain. However many studies suggest that it also has central action through suprasegmental action. Aspirin exhibits its analgesic action by two components—a peripheral one due to a local sensitizing action and a central one, following the release of prostaglandins (PGE2, PGI2) in the CNS which lowers the threshold of the central pain circuit.

The anti-nociceptive activity of the test drug was evaluated using both chemical and thermal methods of nociception in rats. These methods are used to detect central and peripheral analgesic activity.

Acetic acid induced writhing test was used for detecting peripheral analgesia, whereas hot plate and tail flick tests are most sensitive to centrally acting analgescics. Studies done by Mujumdar et al. Policegoudra RS et al. also suggest that CA has analgesic activity thus supporting our study.

CONCLUSION: Considering that the relief of painful symptoms typically involves pharmacotherapy and the constituents of CA have been assessed in various acute and chronic pain models. The chemical constituents of CA exhibit antinociceptive activity via central and peripheral mechanisms. CA shows significant analgesic activity in the test group as well as treatment group aspirin. The combination of Curcuma Amada and Aspirin is synergistic. Drugs currently used in the treatment of pain are associated with potential toxic effects including GI bleeding. Therefore, Curcuma Amada can be used as a complementary alternative medicine for the treatment of acute somatic pain.

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