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Role of homoeopathic mother tinctures in rheumatoid arthritis: An experimental study

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ABSTRACT

Objectives: The objective of present preliminary study was to assess the anti-inflammatory, analgesic and anti-arthritic effect of some homoeopathic mother tinctures viz. *Ricinus communis* (RCMT), *Rauwolfia serpentina* (RSMT), *Bellis perennis* (BPMT), *Curcuma longa* (CLMT), *Terminalia arjuna* (TAMT) and *Tribulus terresteris* (TTMT).

Materials and Methods: Paw oedema was induced by administration of 0.1ml 1% carrageenan in normal saline into right hind paw. Degree of inflammation was evaluated according to paw swelling. Arthritis was induced by Complete Freund's Adjuvant (CFA) injection in metatarsal footpad of Wistar albino rats.

Result: *Curcuma longa and Tribulus terresteris* mother tinctures reduced hind paw swelling decreased the paw volume in Carrageenan treated rats. Thus, revealed potent activity against inflammation. All homoeopathic mother tinctures showed peripheral analgesic activities in hot plate induced thermal algesia in mice.

Keywords: Analgesic, Anti-arthritic, anti-inflammatory, Bellis perennis, Carrageenan, Curcuma longa, Homoeopathic mother tinctures, Rauwolfia serpentina, Ricinus communis, Terminalia arjuna, Tribulus terresteris

INTRODUCTION

Rheumatoid Arthritis (RA) is a progressive, disabling, chronic multisystem disease which is characterized by pain, swelling and stiffness of the synovial joints, which is often worse in the morning and after periods of inactivity.[1] Although there may be a plethora of systemic manifestations, the characteristic feature of RA is persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. In inflammatory reaction, increased cellularity of synovial tissue and joint damage are the pathological hallmarks of RA.[2]

It has been known for centuries that homoeopathic remedy if prescribed carefully for RA can be of a great help in relieving pain and increasing the mobility of the joint. There are many medicines reported in the literature for RA but there are very less preclinical or clinical data for these mother tinctures. Considering arthritis as constitutional problem and especially in early stages, the cases of RA respond well to the homoeopathic treatment. The medicines can reduce the frequency, duration and severity of the attacks and delay the onset of complications. Through this treatment, the disease progress can be slowed down, significant reduction in joint stiffness and pain can be achieved and further complications of the disease can be prevented.[3]

In Homoeopathy, mother tinctures are routinely prescribed for the treatment of wide variety of ailments such as *Rauwolfia serpentina* is used for high blood pressure, fever, sedation, stomach pain, skin problems, and muscular problems.[4] *Ricinus communis* Mother tincture (RCMT) is used to relieve the symptoms of vertigo, burning sensation in stomach, diarrhoea and in inflamed anus.[5] Likewise the mother tincture of *Bellis perennis* (BPMT) is used for joint soreness, muscle soreness, soreness of abdominal wall and uterus, and in diarrhoea.[6] Similarly, the mother tincture of *Terminalia arjuna* (TAMT) is used in various diseases of heart, angina pectoris, suffocation vertigo and gonorrhoea.[7] These mother tinctures are prescribed for the treatment of analgesia and arthritis, but lacks scientific basis. Therefore, it was considered worthwhile to evaluate the analgesic, anti inflammatory and anti arthritic activities of these mother tinctures in experimental animal models in order to prevent scientific basis for its use in Homoeopathy.

These mother tinctures contain a number of compounds in complex matrices in which no single active constituent is responsible for overall therapeutic effect. The use of homoeopathic medicines as complements or alternatives to conventional medicines has been increasing worldwide. The reasons, which have given rise to this trend, include the availability, and accessibility of these medicines.

Objective

The objective of present preliminary study was to assess the anti-inflammatory, analgesic and anti-arthritic effects of some homoeopathic mother tinctures viz. *Ricinus communis* (RCMT), *Rauwolfia serpentina* (RSMT), *Bellis perennis* (BPMT), *Curcuma longa* (CLMT), *Terminalia arjuna* (TAMT) *and Tribulus terresteris* (TTMT).

MATERIALS AND METHODS

Animals

The study was carried out in the Department of Pharmacology with the approval of the Institutional Animal Ethics Committee, All India Institute of Medical Sciences (AIIMS), New Delhi (File No. 673/IAEC/12). After approval, animals were taken, weighed and distributed randomly into appropriate groups for conducting the study. The experiments were carried out in the premises of the Animal House, Department of Pharmacology, AIIMS, New Delhi. Animals were housed under standard laboratory conditions at 25 ± 2°C in groups of six with free access to food and water *ad libitum*. They were acclimatized to the laboratory conditions for a period of 5 days before the study.

Drugs and Chemicals

The homoeopathic drugs in the form of mother tinctures, on the request of Central Council for Research in Homoeopathy, Ministry of AYUSH, New Delhi were supplied by Dr. Willmar Schwabe India Pvt Ltd, Noida, U.P, India. Indomethacin was used as standard drug (Merck Chemicals, India). λ-Carrageenan was purchased from Sigma-Aldrich, USA and Complete Freund's adjuvant (CFA) from Difco Laboratories, USA.

Selection of Homoeopathic Mother Tinctures

Homoeopathic mother tinctures selected for evaluating anti-inflammatory, analgesic and anti arthritic activities were: RCMT (containing 94% v/v alcohol), RSMT (containing 77% v/v alcohol), BPMT (containing 65% v/v alcohol), CLMT (containing 60% v/v alcohol), TAMT (containing 82% v/v alcohol) and TTMT (containing 62% v/v alcohol) and were manufactured according to the Homoeopathic Pharmacopeia of India.[8]

Dose Calculation

Recommended dose given for rats is 20 μl/100 g body weight (200μl/kg body weight), per orally in de-ionized water (180μl) as vehicle for administration.

Carrageenan Induced Paw Oedema in Rats

Eight groups of male Wistar albino rats ($N = 6$) were used in this study (6 test drugs, one standard and one control group). The baseline paw volume was determined in the overnight fasted animals by using a plethysmometer. *Group I* received normal saline (0.1ml/10g p. o) and served as Control. *Group II* received Indomethacin (3mg/kg p. o) and served as standard group. *Group III* received BPMT, *Group IV* received CLMT, *Group V* received RSMT, *Group VI* received RCMT, *Group VII* received TTMT, and *Group VIII* received TAMT. After baseline paw volume measurement, paw oedema was induced by administration of 0.1ml 1% Carrageenan in normal saline into right hind paw.[9] Results were expressed as percentage of inhibition of oedema, calculated according to the following formula, percent inhibition = 100 × (Vc-Vt)/Vc), where Vc is the

volume of the oedema in control, Vt is the volume of oedema in animals treated with mother tinctures.

Eddy's Hot Plate Induced Thermal Algesia in Rats

Seven groups of male Swiss albino mice ($N = 6$) were used in this study (6 test drugs and 1 control). Grouping of animals and drug treatments were same as for carrageenan induced paw oedema. The animals were placed on the Eddy's hot plate (55°C) and the time until the animal either licked its paw or jumped was recorded by using a stop watch. This was the baseline time. Drugs/vehicle was then administered by gavage. Animals were then retested at 20, 60, and 90 minutes following drug/vehicle administration and the reaction latency was recorded. For evaluation of analgesic activity, the increase in latency of drug treated groups was compared against the vehicle treated group.[10] A cutoff reaction time of 15 seconds was chosen in order to avoid physical injury to the animal.

Adjuvant Induced Arthritis

Thirteen groups of male Wistar albino rats ($N = 6$) were used in this study (Test drugs along with their respective control). The baseline paw volume was determined in the overnight fasted animals by using micrometer screw gauge. Thereafter, *Group I* received Indomethacin (3mg/kg p. o) and served as standard, *Group II* received BPMT, *Group III* received same percentage of alcoholic solution as of mother tincture (65% v/v) which served as respective control for BPMT and indomethacin, *Group IV* received CLMT, *Group V* received same percentage of Alcoholic solution as of mother tincture (60% v/v) which served as respective control for CLMT and indomethacin, *Group VI* received RSMT, *Group VII* received same percentage of Alcoholic solution as of mother tincture (77% v/v) which served as respective control for RSMT and Indomethacin, *Group VIII* received RCMT, *Group IX* received same percentage of alcoholic solution as of mother tincture (94% v/v) which served as respective control for RCMT and indomethacin, *Group X* received TTMT, *Group XI* received same percentage of alcoholic solution as of mother tincture (62% v/v) which served as respective control for TTMT and Indomethacin, *Group XII* received TAMT, *Group XIII* received same percentage of alcoholic solution as of mother tincture (82% v/v) which served as respective control for TAMT and Indomethacin. 30 minutes after administration of the vehicle/drug, arthritis was induced by sub-plantar administration of 0.1ml of Complete Freund's Adjuvant (CFA) (0.05% w/v *Mycobacterium butyricum* in mineral oil) into the left hind paw of all the rats. This was designated as day 0. After immunization with CFA, all the groups were maintained on vehicle/drug treatment for 20 more days. Joint diameter of the injected paw was again measured on 3, 7, 14 and 21 days, after 30 minutes vehicle/drug administration.[11]

Statistical Analysis

Statistical analysis was performed using graph pad Instat software. All values are Mean ± SE ($N = 6$). Statistical analysis was performed by one-way analysis of variance followed by Dunnette's Multiple Comparisons. $^{*}P < 0.05$, $^{**}P < 0.01$ as compared with control.

RESULTS

Anti-inflammatory Activity

Administration of BPMT, RSMT, RCMT and TAMT did not produce any effect on hind paw swelling, thus indicates lack of anti-inflammatory activity in tested dose. However CLMT and TTMT produced a significant reduction in paw oedema at 3 and 6 hours post carrageenan administration [Figure 1]. Maximum percentage of paw oedema was seen in Indomethacin (41%), CLMT (39.70%) and TTMT (36.76%) groups, revealed potent activity against inflammation [Figure 2].

Analgesic Activity

Evaluation of analgesic activity of test drugs using eddy's hot plate induced thermal algesia demonstrated an increase in reaction latency

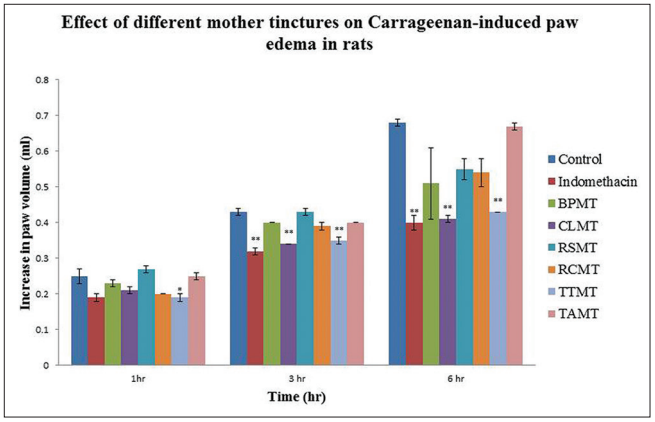

Figure 1: Effect of administering different mother tinctures on Carrageenan-induced paw oedema model in Wistar rats. Difference between initial paw volume and paw volume at observation points post-carrageenan administration was considered to be the increase in paw volume (depictive of paw edema). Each bar represents the mean ± SE of 6 animals. Statistical analysis by one-way ANOVA followed by Dunnette's multiple comparisons. $^{*}P < 0.05$, $^{**}P < 0.01$

(paw licking and jumping behavior) in drug treated animals. This increase in reaction latency was statistically significant ($P < 0.05$) in all drug treated groups as compared to control animals. These observations suggest the involvement of higher centres in development of analgesia [Figure 3].

Anti-arthritic Activity

Maximum joint swelling was observed in all the groups on day 3. However, in the control treated groups, after the initial decrease in joint diameter, from day 7–14 there was a slight increase in the joint diameter up to day 21. Maximum reduction of joint swelling was produced by groups CLMT and TTMT on day 21, whereas the groups RCMT and TAMT showed slight increase in joint diameter on day 21. BPMT and RSMT groups showed initial decrease in joint diameter from 7–14 days and there was an increase in joint diameter on day 21 [Figures 4-9].

DISCUSSION

In this study, the effect of six homoeopathic mother tinctures viz. RCMT, RSMT, BPMT, CLMT, TAMT, and TTMT were investigated in inflammatory disorders. Scientific literature review on these homoeopathic mother tinctures indicates that these mother tinctures were used clinically for the treatment of arthritis and analgesia. So, it has been designed to scientifically revalidate these mother tinctures for analgesic and anti arthritic effects using experimental models. The present study demonstrates that mother tinctures prepared according to homoeopathic pharmacopeia in alcohol and water, attenuates the synovial proliferation in rats suffering from RA. The major findings of study were that CLMT and TTMT possess significant disease modifying activity as compared to control.

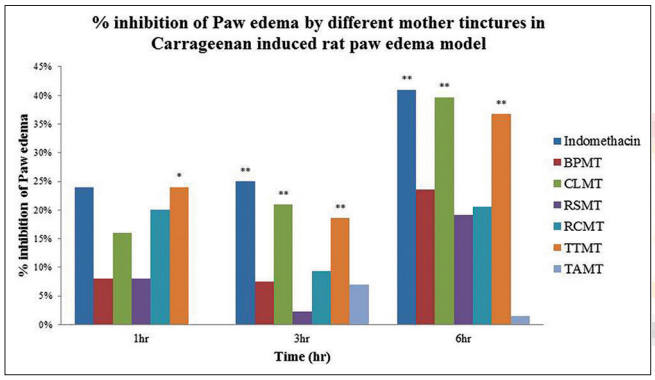

Figure 2: Percentage Inhibition of Paw oedema by different mother tinctures in Carrageenan-induced rat paw edema model in Wistar rats. Each bar represents the mean ± SE of 6 animals. Statistical analysis by one-way ANOVA followed by Dunnette's multiple comparisons. *$P < 0.05$, **$P < 0.01$

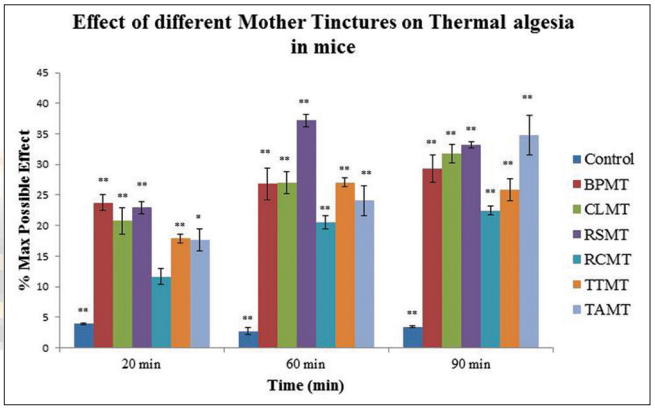

Figure 3: Effect of administering different mother tinctures on Eddy's hot plate induced thermal algesia in swiss albino mice. Each bar represents the mean ± SE of six animals. Statistical analysis by one-way ANOVA followed by Dunnette's multiple comparisons. *$P < 0.05$, **$P < 0.01$

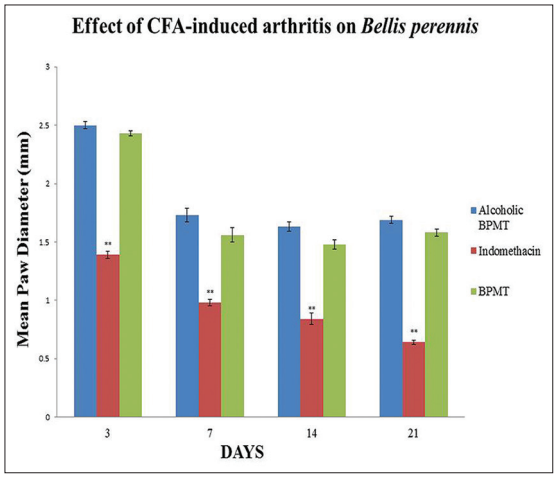

Figure 4: Effect of *Bellis perennis* on Complete Freund's adjuvant (CFA) induced arthritic model in Wistar rats. Each bar represents the mean ± SE of six animals. Statistical analysis by one-way ANOVA followed by Dunnette's multiple comparisons. *$P < 0.05$, **$P < 0.01$

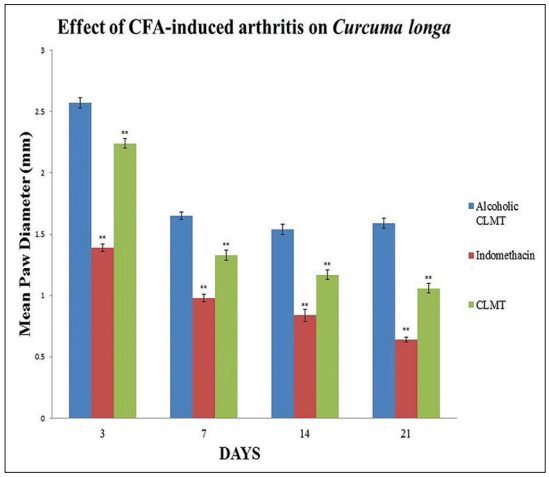

Figure 5: Effect of *Curcuma longa* on CFA induced arthritic model in Wistar rats. Each bar represents the mean ± SE of six animals. Statistical analysis by one-way ANOVA followed by Dunnette's multiple comparisons. *$P < 0.05$, **$P < 0.01$

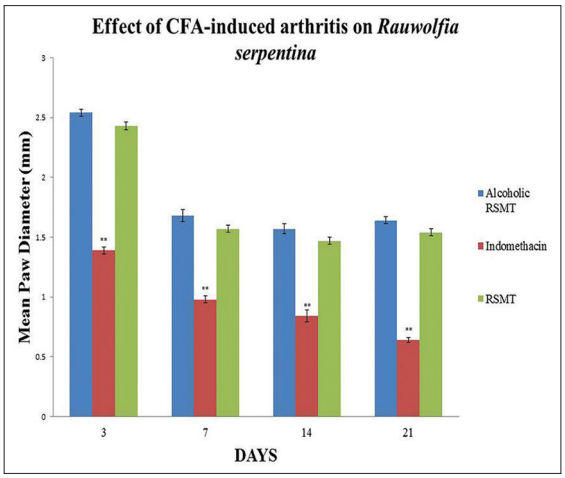

Figure 6: Effect of *Rauwolfia serpentina* on CFA induced arthritic model in Wistar rats. Each bar represents the mean ± SE of six animals. Statistical analysis by one-way ANOVA followed by Dunnette's multiple comparisons. **P* < 0.05, ***P* < 0.01

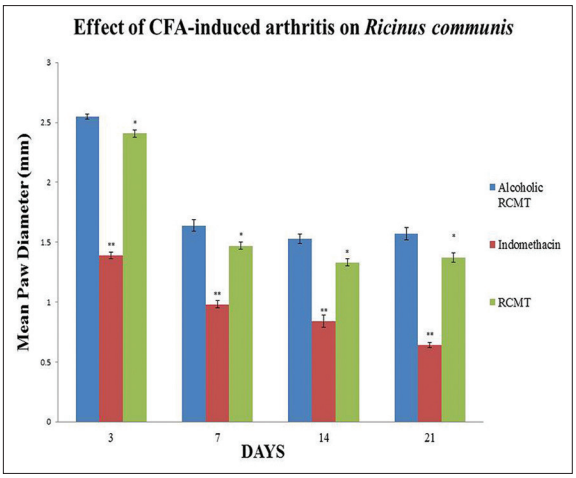

Figure 7: Effect of *Ricinus communis* on CFA induced arthritic model in Wistar rats. Each bar represents the mean ± SE of six animals. Statistical analysis by one-way ANOVA followed by Dunnette's multiple comparisons. **P* < 0.05, ***P* < 0.01

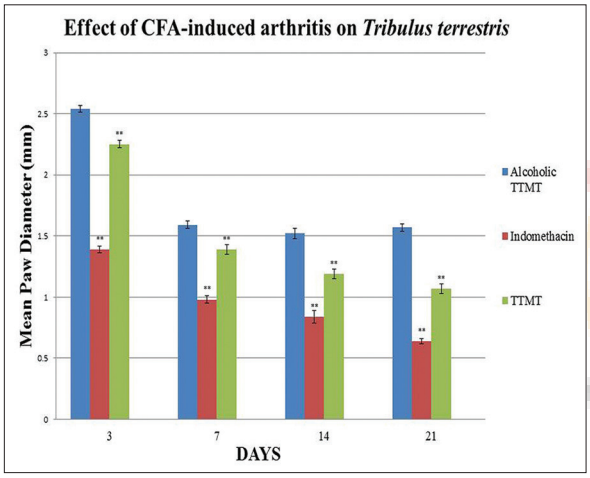

Figure 8: Effect of *Tribulus terrestris* on CFA induced arthritic model in Wistar rats. Each bar represents the mean ± SE of six animals. Statistical analysis by one-way ANOVA followed by Dunnette's multiple comparisons. **P* < 0.05, ***P* < 0.01

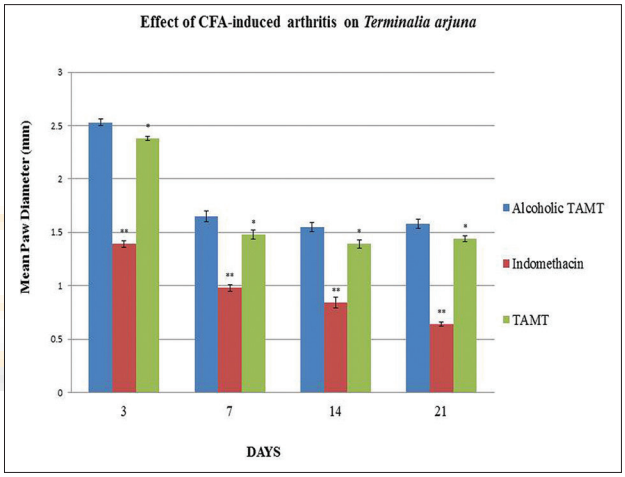

Figure 9: Effect of *Terminalia arjuna* on CFA induced arthritic model in Wistar rats. Each bar represents the mean ± SE of 6 animals. Statistical analysis by one-way ANOVA followed by Dunnette's multiple comparison. **P* < 0.05, ***P* < 0.01

Some of medicinal plants have already been evaluated for their anti-inflammatory and anti- arthritic activity. Root extract of RCMT has been shown to be effective in reducing inflammation in carrageenan induced paw edema and cotton pellet granuloma model.[12] Leaf extract of *Terminalia arjuna* had shown to be effective in carrageenan induced paw edema, histamine and dextran induced paw edema model in Wistar rats.[13] It has been reported that *Curcuma longa* possesses significant anti-inflammatory activity in endotoxin induced uveitis model in rabbits.[14] *Tribulus terresteris* showed *in-vitro* activity against inflammation in cultured mouse macrophage cells.[15] However, despite the presence of a large number of active principles, the antiarthritic and anti-inflammatory activity of these plants has not been assessed in homoeopathic system of mother tincture.

Therefore, the present study was carried out to scientifically evaluate the analgesic, anti inflammatory and anti arthritic effect of mother tinctures using different animal models. Eddy's hot plate induced thermal algesia was used to assess the analgesic action of mother tinctures. Carrageenan induced paw edema was used to evaluate the anti-inflammatory activity and complete freund's induced arthritis model was used to evaluate the antiarthritic efficacy of mother tinctures.

To evaluate the effect of mother tinctures on autacoid system, carrageenan induced paw edema

model is widely used.[9] This model has three distinct phases of autocoid involvement. During first phase (1–2 hr after carrageenan administration) the primary involvement of histamine in inflammation, in second phase (2–3 hours. after carrageenan administration) Serotonin and kinin are the primary mediator for inflammation and the last third phase (3 hour onwards) the primary mediators are prostaglandin and leukotriens. Anti inflammatory activity of different mother tinctures was evaluated using carrageenan paw edema model, reveals significant reduction of paw oedema in CLMT and TTMT.

Eddy's hot plate is a test of pain response in animals.[10] Analgesic activity of different mother tinctures was evaluated using eddy's hot plate induced thermal algesia, resulting in increase in reaction latency of mother tinctures treated animals as compared to control animals.

The CFA-induced arthritis model is widely used for evaluating the antiarthritic activity of drugs. It shares number of clinical and immunological features with human arthritis. Therefore, CFA model has high degree of validity.[11] In this model, measurement of joint inflammation (joint diameter) is used for evaluating the disease modifying activity of mother tinctures. In our study, CLMT and TTMT indicate significant reduction in joint diameter at all observation points.

Positive results if obtained in animal models (rats), it could be extrapolated in meaningful and convincing manner for their possible human use in Homoeopathy. The results will induce further research in exploring the usefulness of specific compounds responsible for antiarthritic effects.

The exact mechanism by which mother tinctures exert their anti-inflammatory and analgesic activity is not determined yet and need further investigation to elucidate the active compounds and underlying mechanism (s).

CONCLUSION

From the results observed from the current investigation, it is concluded that the homoeopathic mother tinctures of plants viz *Ricinus communis, Rauwolfia serpentina, Bellis perennis, Curcuma longa, Terminalia arjuna and Tribulus terresteris* possesses potentially useful analgesic activity. *Curcuma longa* and *Tribulus terresteris* groups showed potent activity against Carrageenan induced paw edema model and adjuvant induced arthritic model. Based on our results, we conclude that these mother tinctures (CLMT and TTMT) have potential to be used as anti-inflammatory in the treatment of RA and could be further explored as safer alternative in treatment of RA.

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रूमेटाइड संधिशोथ में होम्योपैथिक मातृ टिंक्चरों की भूमिका: एक प्रायोगिक अध्ययन

सार

उद्देश्य: वर्तमान प्रारंभिक अध्ययन का उद्देश्य कुछ होम्योपैथिक मातृ टिंक्चरों यथा एरंड पादप (RCMT), सर्पगंधा (RSMT), बेलिस परेनिस (BPMT), कुरकुमा लोंगा (CLMT), टर्मिनिलिआ अर्जुन (TAMT) और ट्राइब्यूलस टरेस्टेरिस (TTMT) के शोथरोधी, वेदनाहर तथा संधिशोथरोधी प्रभावों का आकलन करना था।

सामग्री व विधि**:** सामान्य लवण विलयन में 1% कैरागीनन की 0.1 ml मात्रा देकर दाहिने पश्च पंजे में पंजा शोथ प्रेरित किया गया। शोथ की मात्रा का आकलन पंजे की सूजन के आधार पर किया गया। विस्टर एल्बीनो चूहों के प्रपद तलवे में पूर्ण फ्रायन्ड सहऔषध (CFA) इंजेक्शन लगाकर संधिशोथ प्रेरित किया गया।

परिणाम: कुरकुमा लोंगा तथा ट्राइब्यूलस टरेस्टेरिस मातृ टिंक्चर द्वारा कैरागीनन उपचारित चूहों के पश्च पंजे के सूजन में कमी आई और पंजे का आयतन घटा। यह शक्तिशाली शोथरोधी सक्रियता को दर्शाता है। सभी होम्योपैथिक मातृ टिंक्चरों ने चूहों में उष्ण पट्टिका प्रेरित तापीय वेदना में परिधीय वेदनाहर सक्रियता दर्शाई।

मुख्य शब्द: वेदनाहर, संधिशोथरोधी, शोथरोधी, बेलिस परेनिस, कैरागीनन, कुरकुमा लोंगा, होम्योपैथिक दवा, होम्योपैथिक मातृ टिंक्चर, सर्पगंधा, एरंड पादप, टर्मिनिलिआ अर्जुन, ट्राइब्यूलस टरेस्टेरिस