Evaluation of clinical efficacy and safety of RG-01 (Rumalaya gel) in management of chronic subacute inflammatory joint disorders

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ABSTRACT

Pain is an inevitable part of chronic subacute inflammatory disorders and although there are many analgesics available for chronic mild intermittent joint pain; topical gel are often preferred; being effective, safe, convenient and economical. These topical gel contain counterirritants and rubefacients, which had been well studied in terms of its pharmacological properties. This study was planned to evaluate the efficacy and safety of the RG-01 (Rumalaya gel) in chronic subacute inflammatory joint disorders.

Sixty-five ambulatory patients, of either sex were enrolled in the study and a written informed consent was obtained from all these patients. All included patients had clinical diagnosis of either of the following: Osteoarthroses, Polyarthritis, spondylosis, arthralgia, frozen shoulder, fibrofascitis, gout, neuralgia and low back pain over a period of 6 months prior to the study. Patients with established hypertension, renal, hepatic or cardiac failure, on long-term steroid treatment & suffering from autoimmune disorder; spastic condition or genetic disorders were excluded from the study. All patients were advised to apply Rumalaya ointment over the affected area, thrice daily for a period of 8-12 weeks. Statistical analysis of the observations was done according to intention-to-treat principles. Changes in various parameters from baseline values after the 5^{th} month were evaluated by paired 't' test. The minimum level of significance was fixed at 95% confidence limit and a 2-sided p value of less than 0.05 was considered significant.

In patients with arthralgia, spondylosis and polyarthritis there was significant reduction in joint tenderness, joint swelling, mobility restriction and early morning joint stiffness, at the end of the study. In patients with osteoarthritis of knees, there was moderate reduction in joint tenderness, joint swelling, mobility restriction and early morning joint stiffness at the end of the study. In patients with low back pain though there was reduction in severity of pain, yet spinal mobility & early morning joint stiffness did not improve. In patients with sprains there was appreciable reduction in tenderness and improvement in joint mobility. There was good compliance to the treatment and there were no adverse events reported or observed in the study patients, during the entire period.

INTRODUCTION

It has been proposed that pain to be divided into two entities: "physiological" and "pathophysiological (clinical)". "Physiological pain" describes the situation, in which a noxious stimulus activates peripheral nociceptors, which then transmit sensory information through several relays until it reaches the brain and is recognized as a potentially harmful stimulus. The pathophysiologic processes that occur after tissue injury result in a stimulus-response pattern that is quite different from that seen after physiological pain and therefore has been termed "pathophysiologic pain"[1].

The perception of pain is a complex interaction that involves sensory, emotional, and behavioural factors. The International Association for the Study of Pain has defined pain as: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Nociception, neuropathy, and psychological or environmental factors may singly, or in combination, contribute to the experience of pain and the person in pain always must be seen in the context of these interacting factors[1].

Pain is an inevitable part of chronic subacute inflammatory disorders and although there are many analgesics available for chronic mild intermittent joint pain; topical gel are often preferred being effective, safe, convenient and economical. These topical gel contain counterirritants and rubefacients, which had been well studied in terms of its pharmacological properties. Their pharmacological properties are thought to have a variety of mechanisms, including blocking effects on local nerve fibres, depletion of neurotransmitters, engagement of the "gate control" mechanism, and suggested placebo effects[2-6]. Various receptors (e.g. vanilloid receptor subtype 1), nonselective cation channels and thermal sensors are hypothesized as the target of these formulations[7]. Initial administration of topical counterirritants and rubefacients cause itching, pricking, and burning pain due to excitation of nociceptors and these initial effects may followed by a transient period of hyperalgesia[4,5].

Numerous drugs are used (alone or in combination) for analgesia in management of chronic, intermittent, mild pain of commonly encountered chronic subacute inflammatory diseases such as Ostoarthritis, Polyarthralgic non-articular rheumatism, spondylosis, arthralgia, frozen shoulder, fibrositis, gout, neuralgia, neuritis and sciatica. RG-01 (Rumalaya gel) is a polyherbal formulation and it contains extracts of *Vitex negundo, Cedrus deodara, Zingiber officinale, Boswellia serrata, Mentha arvensis, Cinnamomum zeylanicum, Pinus roxburghii* and *Gaultheria fragrantissima*. This study was planned to evaluate the efficacy and safety of RG-01 (Rumalaya gel) in chronic subacute inflammatory joint disorders.

METHODOLOGY

Aim of the study

The present study was aimed to evaluate the clinical efficacy and long-term safety of RG-01 (Rumalaya gel) in management of chronic subacute inflammatory joint disorders.

Study design

This study was an open clinical trial conducted in the Department of Orthopaedics, All India Institute of Medicine Sciences, New Delhi, for a period of 5 months (from February 2001 to June 2001) and institutional ethics committee approved the study.

Inclusion criteria

Sixty-five ambulatory patients, of either sex attending the Out Patient Department of Orthopaedics were enrolled in the study. A written informed consent was obtained from all these patients. All included patients had clinical symptoms of either of the following: Osteoarthritis, rheumatoid arthritis, Non-articular rheumatism, spondylosis (ankylosing, cervical and lumbar spondylosis), arthralgia, frozen shoulder, fibrositis, neuralgia, and low back pain & sprain over a period of 6 months prior to the study.

Exclusion criteria

Patients with established hypertension, renal, hepatic or cardiac failure, on long-term steroid treatment, patients suffering from autoimmune disorder; spastic condition or genetic disorders were excluded from the study.

Study procedures
A detailed medical history of all patients was recorded and symptomatic evaluation was done. The diagnosis of the concerned disease was confirmed by clinical and joint examination. All patients were advised to apply the RG-01 (Rumalaya gel) over the affected area, thrice daily for a period of five months. All patients were advised to apply hot saline water fomentation, along with a gentle massage with the RG-01 (Rumalaya gel). All patients were prescribed NSAIDs for the first week and physiotherapy was an essential part of the treatment.

Follow-up and assessment
The patients were followed up for 5 months and symptomatic evaluation was recorded after completion of each month. A complete clinical and joint evaluation was carried out at the end of the 5^{th} month.

Primary and secondary outcome measures
The predefined primary outcome measures for efficacy were decrease in the joint tenderness, joint swelling, and restoration of the joint mobility and prevention of the early morning joint stiffness. Secondary outcome measures were short and long-term safety assessed by incidence of adverse events and patient compliance to therapy.

Adverse events
All adverse events reported or observed by patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Relation of adverse events to study medication were predefined as "Unrelated" (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), "Possible" (follows a known response pattern to the suspected drug, but could have been produced by the patients clinical state or other modes of therapy administered to the patient), and "Probable" (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient's clinical state).

Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

Statistical analysis
Statistical analysis was done according to intention-to-treat principles. Changes in various parameters from baseline values after the 5^{th} months were evaluated by paired '*t*' test. The minimum level of significance was fixed at 95% confidence limit and a 2-sided *p* value of <0.05 was considered significant.

RESULTS

Total 65 patients were enrolled in the study and 5 patients were lost to follow up. There were 10 patients in the age group of 20 to 39 years, 34 patients in the age group of 40 to 59 years and 16 patients in the age group of 60 years and above (Table 1).

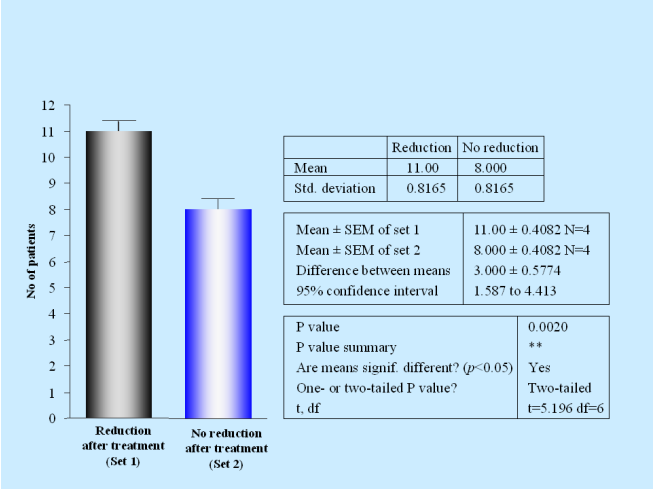
Table 1: Diagnosis/sex distribution

Diagnosis	Male		Female		Total	
	No. of patients	%	No. of patients	%	No. of patients	%
Osteoarthritis of knee	12	20.00	7	11.67	19	31.67
Lumbar & cervical spondylosis	10	16.67	9	15.00	19	31.67
Frozen shoulder	4	6.67	3	5.00	7	11.67
Gout	2	3.33	0	0.00	2	3.33
Polyarthritis	2	3.33	2	3.33	4	6.67
Arthralgia	2	3.33	1	1.67	3	5.00
Sciatica	2	3.33	1	1.67	3	5.00
Sprains	2	3.33	1	1.67	3	5.00
Total	**36**	**60.00**	**24**	**40.00**	**60**	**100.00**

There was a male preponderance in the study population (Males: Females: 3:2). Majority of patients were suffering from OA of knees (31.67%), lumber and cervical spondylosis (31.67%) and frozen shoulder (11.67%). The remaining patients were suffering from polyarthritis (6.67%), gout (3.33%), arthralgia (5.00%), sciatica (5.00%) and sprains (5.00%).

In patients with arthralgia there was total reduction in joint tenderness, joint swelling, mobility restriction and early morning joint stiffness at the end of the study. In patients with spondylosis there was significant reduction (t=5.196, p=0.0020), in joint tenderness, joint swelling, mobility restriction and early morning joint stiffness at the end of the study (Figure 1). In patients with polyarthritis there was significant reduction (t=7.201, p = 0.0004), in joint tenderness, joint swelling, mobility restriction and early morning joint stiffness at the end of the study (Figure 2).

Figure 1: Spondylosis: Reduction in joint tenderness, joint swelling, mobility restriction and joint stiffness



In patients with osteoarthritis of knees, there was moderate reduction (63.16%) in joint tenderness, joint swelling, mobility restriction and early morning joint stiffness at the end of the study (Figure 3). In patients with low back pain there reduction in severity of pain following application, but there was no appreciable improvement in spinal mobility and early morning stiffness. In patients with sprains there was reduction in joint tenderness & swelling & subsequently improvement in joint mobility.

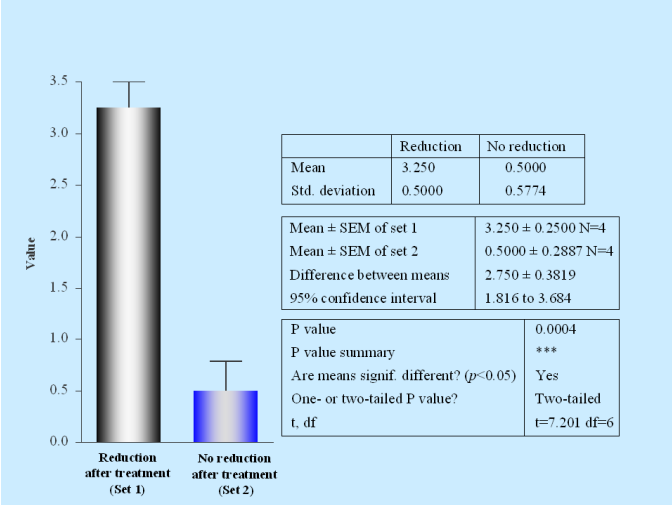
There was good compliance to the treatment and there were no adverse events reported or observed in the study patients, during the entire study period.

DISCUSSION

The primary afferent nociceptor is the initial structure involved in nociceptive processes. Nociceptors respond to chemical, mechanical, and thermal stimuli and depending on the response characteristics of the nociceptor, stimulation results in propagation of impulses along the afferent fiber toward the spinal cord. Two main fiber types, the faster conducting myelinated A fibers and the slower-conducting unmyelinated C fibers, are involved in the transmission of noniception[8].

Recent studies have shown that damage to a peripheral nerve results in a number of physiologic, morphologic, and biochemical changes that act as a focus of pain in them. It also has been demonstrated that reduction in blood supply to myelinated fibers results in demyelination, which results in the production of ectopic impulses that may be perceived as the sharp, shooting, or burning pain in conditions such as diabetic neuropathy[8].

Figure 2: Polyarthritis : Reduction in joint tenderness and joint swelling, mobility restriction and early morning stiffness



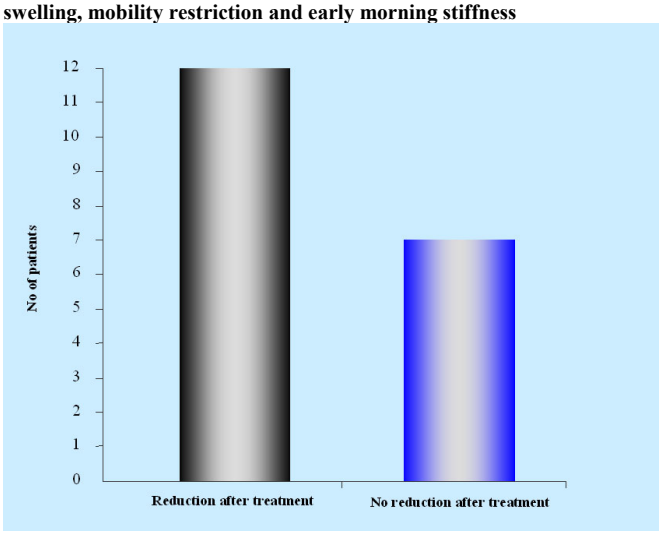
	Reduction	No reduction
Mean	3.250	0.5000
Std. deviation	0.5000	0.5774

Mean ± SEM of set 1	3.250 ± 0.2500 N=4
Mean ± SEM of set 2	0.5000 ± 0.2887 N=4
Difference between means	2.750 ± 0.3819
95% confidence interval	1.816 to 3.684

P value	0.0004
P value summary	***
Are means signif. different? (p<0.05)	Yes
One- or two-tailed P value?	Two-tailed
t, df	t=7.201 df=6

In chronic subacute inflammatory conditions there is continuous release of inflammatory chemomediators such as potassium, serotonin, bradykinin, substance P, histamine alongwith products of arachidonic acid metabolism. These chemicals then act to sensitise high-threshold nociceptors and after sensitisation, low-intensity stimuli that normally would not cause pain are perceived as painful. This series of events that occur after tissue injury is termed peripheral sensitisation and it is characterized by an increased responsiveness to thermal stimuli at the site of injury. It has been found that there is a class of unmyelinated primary afferent fibers that normally do not respond to excessive mechanical or thermal stimuli. In the presence of inflammation and chemical sensitization, however, they become responsive and discharge vigorously, even during ordinary movement. The properties of these receptors still require characterization, but they have been identified in a number of different tissues and species and are termed “silent” nociceptors. Arthritis pain that occurs with flexion and extension may be a result of activation of these normally “silent” nociceptors[9.10].

Figure 3: Osteoarthritis of knee: Reduction in joint tenderness, joint swelling, mobility restriction and early morning stiffness



The sympathetic nervous system also has an important role in the generation and maintenance of chronic pain states. Nerve damage and even minor trauma can lead to a

disturbance in sympathetic activity that leads to a sustained condition termed a “complex regional pain syndrome;” this now replaces the previously used term “reflex sympathetic dystrophy.” Complex regional pain syndromes are associated with features of sympathetic dysfunction, including vasomotor and pseudomotor changes, abnormalities of hair and nail growth, osteoporosis, and sensory symptoms of spontaneous burning pain, hyperalgesia, and allodynia. It has been demonstrated that, after peripheral nerve injury, the nerve sprouts and becomes hypersensitive to alpha-adrenergic agonists. It also has been demonstrated that alpha adrenoreceptors are formed on the dorsal root ganglion and the ganglion becomes innervated by sympathetic efferent terminals, which means that, activity in sympathetic efferent fibers can lead to abnormal activity or responsiveness of the primary afferent fiber[11].

Counterirritants and rubefacients inflame or irritate the skin, increase cutaneous blood flow, stimulate or depress pain receptors, and stimulate thermoreceptors. By activating nociceptors with a peripheral noxious stimulus, counterirritants and rubefacients inhibit the response of central neurons that transmit pain[2.5].

Another speculation is that rubbing or massaging counterirritants and rubefacients onto the skin during application may engage the “gate control” mechanism by activating A fibers. A psychologist, Ronald Melzack and anatomist, Patrick Wall first proposed the gate control theory in 1965 and they suggested that there is a "gating system" in the central nervous system that opens and closes to let pain messages through to the brain or to block them. According to the gate control theory of pain thoughts, beliefs, and emotions may affect how much pain we feel from a given physical sensation[2,12,13].

The fundamental basis for this theory is that, psychological and physical factors guide the brain's interpretation of painful sensations and the subsequent response. Although the physical cause of pain may be identical, the perception of pain is dramatically different. First, sensory messages travel from stimulated nerves to the spinal cord and there, they are reprocessed and sent through open gates to the thalamus. Once the nerve signal reaches the brain, the sensory information is processed in the context of the individual's current mood, state of attention, and prior experience. The integration of all this information influences the perception and experience of pain, and guides the individual's response. If the brain sends a message back down to close the gate, the pain signals to the brain are blocked and the person experiences lower pain and this message (may be carried by endorphins). If the brain orders the pain gates to open wider, the pain signal intensifies and the person feels debilitating pain. The gate-control theory predicts that massaging a particular area stimulates large diameter nerve fibres and these fibres have an inhibitory input onto T cells leading to depressed activity of T cells and pain relief follows (whereas, conversely, small diameter nociceptive nerve fibres have an excitatory input)[14].

Finally, many researchers had suggested a placebo effect as the most likely source of the analgesic effects acting through the power of suggestion and the power of suggestion psychologically stimulates the nervous system[2,15]. Price and colleagues used heat induced experimental pain and a placebo analgesic gel to analyse factors that contribute to the magnitude of placebo analgesia. Although placebo effects are closely associated with expectancy, they found that no relationship exists between placebo effects and the desire for relief**.** This suggests that any analgesic effect experienced from counterirritants and rubefacients is not primarily due to psychological factors[16].

Chronic conditions like arthritis, non-articular rheumatism, spondylosis, arthralgia, frozen shoulder, fibrositis, gout, neuralgia, neuritis, and sciatica are a result of chronic subacute

inflammation. These conditions lead to a compromised quality of life and chronic, mild, intermittent joint pain with joint swelling are the cardinal features of these disorders. Commonly prescribed systemic NSAIDs are causally associated with various short and long term adverse events and there is a felt need for a safer topical effective, economical formulation for long-term use.

In this study, it was observed that, at the end of the study, there was significant reduction in joint tenderness, joint swelling alongwith restorement of joint mobility and relief from early morning joint stiffness. These finding suggest the synergistic action of all ingredients of the RG-01 (Rumalaya gel).

The principal constituents of *Vitex negundo* are casticin, isoorientin, chrysophenol D, luteolin, p–hydroxybenzoic acid and D-fructose, which exhibit anti-inflammatory and analgesic activities. *Vitex negundo* contents bioflavonoids, which are known to act through inhibition of prostaglandin biosynthesis resulting in both central and peripheral analgesic action. The antiinflammatory activity of *Vitex negundo* was found to be more pronounced on subacute rather than on acute inflammation[17].

Telang *et al.,* examined the details of analgesic and antiinflammatory action of hydroalcoholic extract of *Vitex negundo* leaves using "acetic acid induced writhing test" in mice for assessing peripheral analgesic effect and "tail immersion test" in mice for assessing central analgesic effect. The antiinflammatory activity was studied by using the models of "carrageenin induced rat paw edema" and "carrageenin induced granuloma pouch in rats" for assessing the effect on acute and subacute inflammations, respectively. Isolated rat uterus was also used to study the involvement of prostaglandins in the analgesic and antiinflammatory activities. It was observed that, there was significant increase in the reaction time and decrease in the writhing movements in mice in acetic acid-induced writhing test. There was a significant increase in the reaction time in tail immersion test. *Vitex negundo* significantly decreased the rat paw oedema volume at higher dose and also significantly decreased the formation of granuloma pouch in rats. *Vitex negundo* also had inhibitory action on oxytocin-induced contractions in isolated horns of uterus primed with oestradiol[17].

Shinde *et al.,* examined the volatile oil extracted by steam distillation of the wood of *Cedrus deodara* for its anti-inflammatory and analgesic activity and observed a significant inhibition of carrageenan-induced rat paw edema. The oil was also tested in both (exudative proliferative and chronic) phases of inflammation in arthritic rats and was found to possess analgesic activity against acetic acid-induced writhing and hot plate reaction[18].

The principal constituents of *Zingiber officinale* are *Zingiberene* (a and b), and zingiberol. Penna et al, investigated the effects of the crude hydralcoholic extract of ginger rhizomes on the classical models of rat paw and skin edema. It was observed that, the intraperitoneal administration of ginger extract a hour prior to serotonin injections reduced significantly the serotonin induced rat skin edema. They also demonstrated that crude extract of Zingiber officinale was able to reduce rat paw and skin edema induced by carrageenan compound and the antiedematogenic activity was thought to be due to the antagonism of the serotonin receptor[19].

One of the principal constituents in the gum resin of *Boswellia serrata* is boswellic acid, which exhibits anti-inflammatory activity. Boswellic acid, which is the principle ingredient of *Boswellia serrata*, is known to block the synthesis of pro-inflammatory chemomediators like 5-Lipooxygenase (including 5-hydroxy-eicosa tetraenoic acid) and leukotriene[20,21]. Further,

Boswellia serrata also reduces glycosamino glycan degradation, which is essential to prevent articular damage[22-24]. Menon and Kar have reported potent sedative and analgesic effects for *Boswellia serrata*[25].

The bark of *Cinnamomum zeylanicum* contains a significant amount of a mucilaginous substance, which consists mainly of water extractable L-arabino-D-xylan and an alkali-extractable D-glucan. The bark also contains the diterpenes, cinnzeylanin and cinnzeylanol besides tannin. Cinnamon bark contains 0.5 to 1.0 % of volatile oil, with tannin and mucilage. Powdered cinnamon bark is carminative and antiseptic, by virtue of its volatile oil, and astringent owing to the tannin[26].

Mentha arvensis on steam-distillation yields a volatile oil having menthol as the principle constituent, which is useful in treating pain and inflammation of muscles and joints due to its counterirritant actions. *Katya et al.,* had reviewed the potential uses of essential oils from temperate aromatic plants and they demonstrated the constituents of the oils as monoterpene and sesquiterpene hydrocarbons. Oxygenated compounds derived from these hydrocarbons included alcohols, aldehydes, esters, ethers, ketones, phenols and oxides[27].

The turpentine oil obtained from Pinus roxburghii is rubefacient. The chief constituents of the oil are hydrocarbons (principally the two isomeric bodies d- and l-pinene) and other constituents are resin acids, camphene, and fenchene, while dipentene (the optically inactive form of limonene) and polymeric terpenes. The action of oil of turpentine is representative of that of a large number of volatile oils and when applied to the skin they produce irritation and rubefaction, due to dilatation of the superficial vessels. Oil of turpentine is employed externally as a counter-irritant and rubefacient, in the form of Linimentum Terebinthinae and Linimentum Terebinthinae Aceticum, in chronic rheumatism[27].

The volatile oil obtained from Gaultheria fragrantissima is identical to Wintergreen oil and the principal constituent of the oil is methyl salicylate. Ichiyama and colleagues showed that methyl salicylate attenuated the pressor response at 20 min and 40 min post application. Salicylates have been shown to penetrate the dermis and work subcutaneously over time. It seems likely that the salicylate portion had some effect on sensory nerve endings through both local penetration and blood borne routes, presumably on prostaglandin metabolite formation[22,28].

In present study, the favourable effect to the RG-01 (Rumalaya gel) might have been due to the synergistic actions of all above ingredients. The good compliance to the treatment and absence of any adverse events indicate the excellent safety profile of the RG-01 (Rumalaya gel).

CONCLUSION

From the present study results it can be concluded that, this RG-01 (Rumalaya gel) is an effective and safe topical formulation symptomatic management of sprains & chronic subacute inflammatory joint disorders.

REFERENCES

1. Woolf, C.J. Recent advances in the pathophysiology of acute pain. *Br. J. Anaesth.* 1989; 63: 139-146.
2. Barone, J.N. Topical analgesics: how effective are they? *Physician Sportsmed*, 1989; 17: 162–166.

3. Ledoux, J.F. and Wilson, L.B. Neuronal application of capsaicin modulates somatic pressor reflexes. *Am. J. Physiol*.2001; 281: R868–R877.
4. Nolano, M., Simone, D.A., Wendelschafer-Crabb, G., Johnson, T., Hazen, E. and Kennedy, W.R. Topical capsaicin in humans: parallel loss of epidermal nerve fibers and pain sensation. *Pain* 1999; 81: 135–145.
5. Dray, A. Mechanism of action of capsaicin-like molecules on sensory neurons. *Life Sci*. 1992; 51: 1759–1765.
6. Ghersetich, I., Bianchi, B. and Lotti, T. Capsaicin: therapeutic activities on itch by depleting sensory neuropeptides fibers in the skin. *J. Invest. Dermatol*., 1999; 12: 608.
7. Caterina, M.J., Schumacher, M.A., Tominaga, M., Rosen, T.A., Levine, J.D. and Julius, D. The capsaicin receptor: a heat-activated ion channel in the pain pathway, *Nature* 1997; 389: 816–824.
8. Devor, M. The pathophysiology of damaged peripheral nerves; In: Wall PD, Melzack R, (Eds.) Textbook of Pain, 2nd Edition, Churchill-Livingstone, London, 1989, pp. 63-81.
9. Stein, C., Millanm M.J., Shippenbergm T.S. Peripheral opioid receptors mediating antinociception in inflammation: Evidence for involvement of mu, delta, and kappa receptors. *J. Pharmacol. Exp. Ther.* 1989; 248: 1269-1275.
10. McMahon, S., Koltzenburg, M., The changing role of primary afferent neurons in pain. *Pain* 1990; 43: 269-272.
11. McMahon, S.B. Mechanisms of sympathetic pain. *Br. Med. Bull.* 1991; 47: 584-600.
12. Denegar, C.R. Therapeutic Modalities for Athletic Injuries. Champaign, IL: Human Kinetics, 2000, pp. 63–68; 115–117; 120.
13. Prentice, W.E. Therapeutic Modalities for Allied Health Professional, New York: McGraw Hill, New York, 1998, pp. 48; 202–203; 293.
14. Melzack, R., Wall, P.D. The challenge of pain, 2nd edition, Li Wan Po A and Pharm J., (Eds.), Penguin Books, London, 1996.
15. Winocur, E., Gavish, A., Malachmi, M., Eli, I. and Gazit, E. Topical application of capsaicin for the treatment of localized pain the temporomandibular joint area. *J. Orofac. Pain*. 2000; 14: 31–36.
16. Price, D.D., Milling, L.S., Kirsch, I., Duff, A., Montgomery, G.H. and Nicholls, S.S. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain* 1999; 83: 147–156.
17. Telang, R.S., Chatterjee, S., Varshneya, C. Studies on analgesic and anti-inflammatory activities of *Vitex negundo* Linn. *Indian Journal of Pharmacology* 1999; 31: 363-366.
18. Shinde, U.A., Phadke, A.S., Nair, A.M., Mungantiwar, A.A., Dikshit, V.J., Saraf, M.N. Studies on the anti-inflammatory and analgesic activity of *Cedrus deodara* (Roxb.) Loud. Wood oil. *Journal of Ethnopharmacology* 1999; 65(1): 21-27.
19. Penna, S.C., Medeiros, M.V., Aimbire, F.S., Faria-Neto, H.C., Sertie, J.A., Lopes-Martins, R.A. Anti-inflammatory effect of the hydralcoholic extract of *Zingiber officinale* rhizomes on rat paw and skin edema. *Phytomedicine* 2003; 10(5): 381-385.
20. Keuttner, K.E., Goldberg, V.M. Introduction, In: Kuettner, KE, Goldber, V M (Eds.), *Osteoarthritis disorders Rosemont IL*, American Academy of Orthopedic Surgeons, 1995, pp. XXI-XXV.
21. Meulenbelt, I., Bijker, K.C., Medema, H.S. *et al*. A genetic association study of the IGF-I gene and radiological osteoarthritis in a population based cohort study. *An. Rheum. Dis.* 1998; 57: 371-374.
22. Reddy, G.K., Chandraksan, G., Dhar, S.C. Studies on the mechanism of the metabolism of glycosaminoglycans under the influence of new herbal anti-inflammatory agents. *Biochem. Pharm*. 1989; 38: 3527-3534.

23. Brandt, K.D., Plmoski, M.J. Effect of salicylates and other non-steroidal anti-inflammatory drugs on articular cartilage. *Am. J. Med.* 1984; 77: 65-69.
24. Rastogi, R.P., Mehrotra, B.N. Compendium of Indian Medicinal Plants. Rastogi RP (Ed.), Pub & Information Directorate, New Delhi, India, 1991, pp. 204-205.
25. Menon, M.K., Karr, A. Analgesic and psychopharmacological effect of the gum resin of Boswellia serrata. *Planta medica* 1971; 4: 332-341.
26. The British Pharmaceutical Codex, Published by The Council of the Pharmaceutical Society of Great Britain, 1911
27. Ravid, U., Putievsky, E., Katzir, I. Enantiomeric distribution of piperitone in essential oils of some Mentha spp., *Calamintha incana* (Sm.) Heldr. and *Artemisia judaica* L. *Flav. Fragr. J.* 1994; 9: 85-87.
28. Singh, P. and Roberts, M.S. Skin permeability and local tissue concentrations of non-steroidal anti-inflammatory drugs after topical application. *J. Pharmacol. Exp. Ther.,* 1993; 268: 144–151.

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