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Evaluation of the Efficacy and Safety of Rumalaya Gel in the Management of Acute and Chronic Inflammatory Musculoskeletal Disorders: A Open, Prospective, Non-comparative, Phase III Clinical Trial

Abstract

Conventionally, chronic painful inflammatory conditions are treated with systemic NSAIDs, which have a substantial risk of adverse events, on gastro-intestinal, renal and cardiovascular systems. Various clinical reviews have proved that topical analgesics are useful in treating certain acute, and chronic painful inflammatory conditions, and offer short- and long-term safety. This clinical trial was conducted to evaluate the efficacy and safety of Rumalaya gel in the management of pain and inflammation associated with the musculoskeletal inflammatory disorders like RA, OA, sprains, spondylosis, post-traumatic stiffness and peri-shoulder arthritis.

This study was an open, prospective, non-comparative, phase III clinical trial and was conducted as per the ethical guidelines of Declaration of Helsinki. A total of 50 patients suffering from acute and chronic pain due to various musculoskeletal disorders were included in the study. All patients were advised to apply a small quantity of Rumalaya gel topically to the affected region, with gentle massage, twice daily. All the patients were assessed for pain relief, swelling, tenderness,

It may be concluded that Rumalaya gel is effective and safe in the management of pain and inflammation associated with the musculoskeletal inflammatory disorders like RA, OA, sports injuries, sprains, spondylosis, post-traumatic stiffness, peri-shoulder arthritis and other inflammatory musculoskeletal disorders like fibrositis, bursitis, synovitis, capsulitis and sciatica.

Abbreviations

OA	:	Osteoarthritis
RA	:	Rheumatoid arthritis
NSAID	:	Nonsteroidal anti-inflammatory drug
COX	:	Cyclooxygenase
DNIC	:	Diffuse noxious inhibitory control system
NF-κB	:	Nuclear factor-κB
NO	:	Nitric oxide
PG E1	:	Prostaglandin E1
PG E2	:	Prostaglandin E2
LOX	:	Lipoxygenase

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early morning joint stiffness, joint mobility and muscle cramps, and the treatment response was evaluated on a predefined score scale, from 0 to 5 (5 = maximum pain and 0 = no pain), and the symptom score evaluation was done during monthly follow-up visit. The predefined primary efficacy endpoint was a decrease in the symptom score for muscular pain, swelling, tenderness, early morning joint stiffness, muscular cramps and joint mobility, and the predefined secondary safety endpoints were short- and long-term safety, as assessed by the incidence of adverse events, and the patient compliance to therapy. All the adverse events either reported or observed by patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Statistical analysis was done according to intent-to-treat principles.

This study observed significant reduction in the mean symptom scores for joint tenderness, joint swelling, joint mobility, and a highly significant reduction in the mean symptom score for joint pain and early morning joint stiffness in the "OA patient group", in the "spondylosis patient group", there was a significant reduction in the mean symptom scores for joint pain and early morning joint stiffness. In the "muscular sprain patient group", there was highly significant reduction in the mean symptom scores for joint swelling and a highly significant reduction in the mean symptom score for early morning joint pain. In the "post-traumatic stiffness patient group", there was a highly significant reduction in the mean symptom score for joint stiffness. In the "peri-shoulder arthritis patient group", there was a highly significant reduction in the mean symptom score for pain. Also, there were no clinically significant adverse events and the overall compliance to the treatment was excellent. These excellent beneficial actions of Rumalaya gel might be due to the synergistic actions of its ingredients, which are well documented. Therefore, it may be concluded that, Rumalaya gel is effective and safe in the management of pain and inflammation associated with the musculoskeletal inflammatory disorders like RA, OA, sports injuries, sprains, spondylosis, post-traumatic stiffness, peri-shoulder arthritis and other inflammatory musculoskeletal disorders like fibrositis, bursitis, synovitis, capsulitis and sciatica.

Introduction

The "International Association for the Study of Pain" defines pain as "an unpleasant sensory and emotional experience associated with tissue damage". Conventionally, chronic painful inflammatory conditions are treated with systemic NSAIDs (mainly with COX-1 and -2 inhibitors), which carry a substantial risk of adverse events, on the gastro-intestinal[1,2] and renal system[3]. Although the incidence of gastro-intestinal complications is lower with COX-2-selective NSAIDs (than with non-selective NSAIDs)[4-6], an increased risk of cardiovascular complications[7] have been linked with the COX-2-selective NSAIDs. A randomized, controlled trial of rofecoxib versus naproxen revealed a significant increase in the rate of cardiovascular events with rofecoxib, with a relative risk of 1.89 (CI = 1.03-3.45)[4,7].

Various clinical studies have proved that topical analgesics are useful in treating certain acute, and most chronic painful inflammatory musculoskeletal conditions[8,9]. Topical analgesics containing counterirritants are especially useful in treating neuropathic pain and pain associated with OA and RA[10,11]. Counterirritants, when applied externally cause a reversible, transient, mild inflammation and irritation of the skin, and thereby relieve the pain beneath the site of application. Counterirritants take advantage of the "pain paradox", (i.e., the induced pain reduce existing pain by distracting the nervous system). Furthermore, these agents offer short- and long-term safety, as the adverse events (burning, stinging, erythema), from topical applications are mainly limited to the site of application and the systemic adverse events are rare[11].

Rumalaya gel is a polyherbal topical formulation recommended for the management of pain and inflammation associated with the musculoskeletal inflammatory disorders. Each gram of Rumalaya gel contains *Mentha arvensis*, *Gaultheria fragrantissima*, *Pinus roxburghii*, *Cinnamomum zeylanicum*, *Cedrus deodara*, *Vitex negundo*, *Boswellia serrata* and *Zingiber officinalis*. This

clinical trial was conducted to evaluate the efficacy and safety of Rumalaya gel in the management of pain and inflammation associated with the musculoskeletal inflammatory disorders like RA, OA, sprains, spondylosis, post-traumatic stiffness and peri-shoulder arthritis.

Study aim

The present clinical trial was conducted to evaluate the efficacy and safety of Rumalaya gel in the management of pain and inflammation associated with the musculoskeletal inflammatory disorders like RA, OA, sprains, spondylosis, post-traumatic stiffness and peri-shoulder arthritis.

Materials and methods

Study design

This study was an open, prospective, non-comparative, phase III clinical trial and was conducted at Lifeline Hospital, Varanasi, India, as per the ethical guidelines of Declaration of Helsinki. The study protocol, case record forms, regulatory clearance documents, product related information and informed consent were submitted to the "Institutional Ethics Committee" and were approved by the same.

Inclusion criteria

A total of 50 patients suffering from acute and chronic pain, due to various musculoskeletal disorders like RA, OA, sprains, spondylosis, post-traumatic stiffness and peri-shoulder arthritis were included in the study.

Exclusion criteria

Patients with clinically active renal, hepatic or peptic ulcer disease, history of alcohol or drug abuse, concomitant skin disease or abrasions at the application site and those patients who were using any other topical product at the application site were excluded from the study. Pregnant and lactating women were also excluded from the study.

Study procedure

A total of 50 patients suffering from various musculoskeletal disorders (20 patients suffering from OA, 10 patients suffering from lumbar/cervical spondylosis, 8 patients suffering from acute sprains, 4 patients suffering from post-traumatic stiffness and 8 patients suffering from peri-shoulder arthritis were included in the study. All the patients were advised to apply a small quantity of Rumalaya gel topically to the affected region, with gentle massage, twice daily for a period of 3 months (in case of OA, spondylosis, post-traumatic stiffness and peri-shoulder arthritis) and for a period of 4 weeks (in case of sprains). All the patients were assessed for the pain relief, swelling, tenderness, early morning joint stiffness, joint mobility and muscle cramps. Response to the treatment was evaluated on a predefined score scale, from 0 to 5 (5 = maximum pain and 0 = no pain). All the patients were assessed for any local adverse reaction like irritation, burning/stinging sensation and erythema.

Follow-up and assessment

All the patients were followed at weekly and monthly intervals, and the symptom score evaluation was done during each monthly follow-up visit.

Primary and secondary endpoints

The predefined primary efficacy endpoint was a decrease in the symptom score for muscular pain, swelling, tenderness, early morning joint stiffness, muscular cramps and joint mobility. The predefined secondary safety endpoints were short- and long-term safety, as assessed by the incidence of adverse events and patient compliance to therapy.

Adverse events

All the adverse events either reported or observed by the 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 was 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 patient's 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

Table 1

Reduction in the mean symptom score in the "OA patient group"

Parameters	Joint pain		Tenderness		Swelling		Joint mobility		Early morning joint stiffness	
	Before treatment	After the 3rd month	Before treatment	After the 3rd month	Before treatment	After the 3rd month	Before treatment	After the 3rd month	Before treatment	After the 3rd month
Mean	2.64	2.224	2.5	2.38	2.7	2.6	2.7	2.56	2.48	1.76
Std. deviation	0.5628	0.7435	0.5803	0.6667	0.4629	0.5714	0.4629	0.644	0.6141	0.6247
Std. error	0.07959	0.1062	0.08207	0.09429	0.06547	0.08081	0.06547	0.09107	0.08685	0.08834
Lower 99% CI	2.427	1.94	2.28	2.127	2.525	2.383	2.525	2.316	2.247	1.523
Upper 99% CI	2.853	2.509	2.72	2.633	2.875	2.817	2.875	2.804	2.713	1.997
t value	5.754		2.585		2.333		2.824		9.498	
Df	48		49		49		49		49	
R^2	0.4082		0.12		0.1		0.14		0.648	
Mean of diff.	0.4082		0.12		0.1		0.14		0.72	
99% of CI	0.2176-0.5987		–0.004609-0.2446		0.01504-0.2150		0.006945-0.2731		0.5165-0.9235	
p value	$p < 0.0001$		$p < 0.0128$		$p = 0.0238$		$p = 0.0068$		$p < 0.0001$	
p value summary	HS		S		S		S		HS	

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 <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 intent-to-treat principles. Statistical analysis was done using "*Student's Paired 't' Test*" for assessment of mean symptom score in the "OA patient group" and in the "spondylosis patient group" and *"Repeated Measure One-Way ANOVA"*, followed by *"Bonferroni's Multiple Comparison Test"* was used for the assessment of mean symptom score in the "sprains patient group", the "post-traumatic stiffness patient group" and the "peri-shoulder arthritis patient group". The minimum level of significance was fixed at 99% confidence limit and a 2-sided '*p*' value of <0.001 was considered highly significant.

Results

In the "OA patient group", there was a significant reduction in the mean symptom scores for joint tenderness ($p < 0.0128$), joint swelling ($p = 0.0238$), joint mobility ($p = 0.0068$) and a highly significant reduction in the mean symptom score for joint pain ($p < 0.0001$) and early morning joint stiffness ($p < 0.0001$) (Table 1 and Fig. 1).

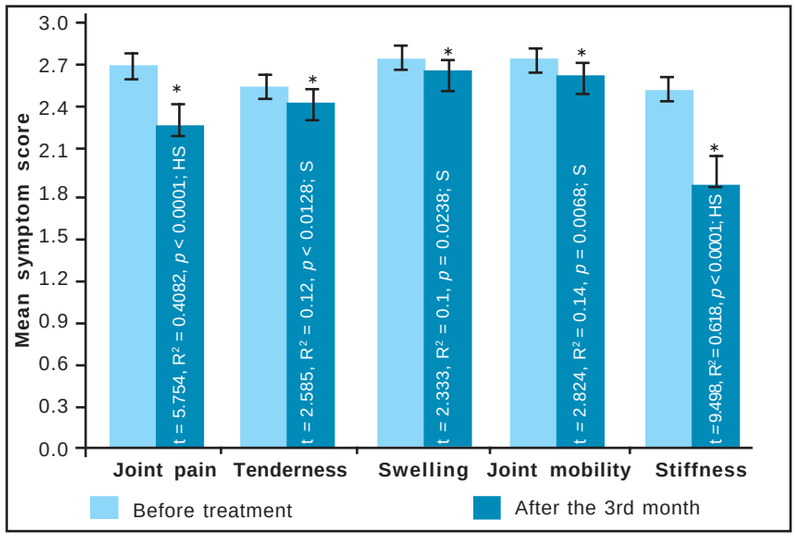

Figure 1. Reduction in the mean symptom score in the "OA patient group".

In the "spondylosis patient group", there was a significant reduction in the mean symptom scores for joint pain ($p < 0.0016$) and early morning joint stiffness ($p < 0.0238$) (Table 2 and Fig. 2).

In the "sprains patient group", there was highly significant reduction in the mean symptom scores for joint swelling ($p = 0.0262$) and a highly significant reduction in the mean symptom score for early morning joint pain ($p < 0.0001$) (Table 3 and Fig. 3).

In the "post-traumatic stiffness patient group", there was a highly significant reduction in the mean symptom score for joint stiffness ($p < 0.0001$) (Table 4 and Fig. 4).

In the "peri-shoulder arthritis patient group", there was a highly significant reduction in the mean symptom score for pain ($p < 0.0001$) (Table 5 and Fig. 5).

There were no clinically significant changes in any of the hematological and biochemical parameters. There were no clinically significant adverse reactions (either reported by patients, or observed by the investigators, and the overall compliance to the treatment was excellent.

Discussion

Counterirritants and rubefacients agents, when applied topically irritate the skin and provide pain relief to underlying tissues like muscles, ligaments and viscera[12]. The plausible explanations include stimulation of nociceptors (which inhibit the central neuronal response, which transmit the pain messages), the "gate theory"[13,14] and the release of endogenous opioid substances[15]. The subsequent changes are manifested as localized vasodilation, increase in microcirculation and increase in local tissue temperature[16-19].

LeBars, et al. proposed a skin stimulation mechanism that might engage a central integrative

Table 2
Reduction in the mean symptom score in the "spondylosis patient group"

Parameters	Joint pain		Early morning joint stiffness	
	Before treatment	After the 3rd Month	Before treatment	After the 3rd Month
Mean	2.64	2.42	2.46	2.36
Std. deviation	0.4849	0.6728	0.6131	0.6627
Std. error	0.06857	0.09515	0.08671	0.09372
Lower 99% CI	2.456	2.165	2.228	2.109
Upper 99% CI	2.824	2.675	2.692	2.611
t value	3.348		2.333	
df	49		49	
R^2	0.1862		0.1	
Mean of diff.	0.22		0.1	
99% of CI	0.04361-0.3964		–0.01504-0.2150	
p value	$p < 0.0016$		$p < 0.0238$	
p value summary	S		S	

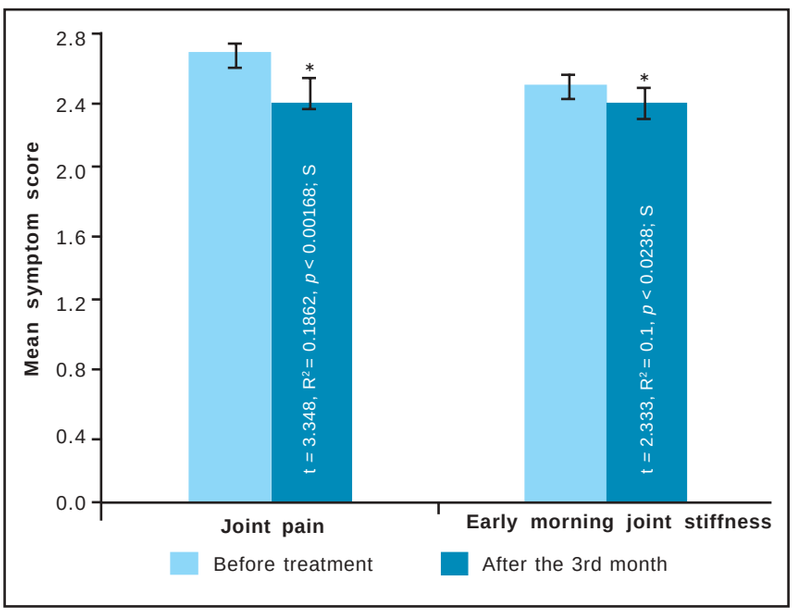

Figure 2. Reduction in the mean symptom score in the "spondylosis patient group".

mechanism (DNIC), which is activated by small diameter afferents[20,21]. Basbaum and Jessell described a pathway (implicated as a possible mediator of DNIC), which has been named as 'Periacqueductal Gray Endogenous Analgesia Circuit' and the activation of this endogenous analgesia system involves a supraspinal relay leading to the stimulation of lamina II of the spinal cord, with subsequent activation of the enkephalin-containing interneurons at spinal level[22]. Enkephalinergic interneurons cause pre- and postsynaptic inhibition of signals arising from A (delta) and C fibers within spinal cord lamina I and V[22,23]. Endogenous opiates are also centrally released locally in response to peripheral stimulation[24].

Dray, et al. offered another explanation, which emphasizes that counterirritants inflame and irritate the skin, increase cutaneous blood flow, stimulate/depress pain receptors and stimulate thermoreceptors[13,25]. By activating the nociceptors with a peripheral noxious stimulus, counterirritants inhibit the response of central neurons that transmit pain (these initial effects are followed by a period of "hyperalgesia") or nociceptor desensitization, which appears within a week (may last up to 3 weeks after stopping the application of counter irritants)[10,25].

Another speculation is that rubbing/massaging the analgesic topically onto the skin engages the "gate control" mechanism by activating A (b) fibers[26,27]. Finally, some researchers suggest that a placebo effect is the most likely source of the analgesic effects acting through the power of autosuggestion. The power of autosuggestion psychologically

Table 3

Reduction in the mean symptom score in the "sprains patient group"

Parameters	Swelling					Pain				
	Before treatment	1st week	2nd week	3rd week	4th week	Before treatment	1st week	2nd week	3rd week	4th week
Mean	2.58	2.5	2.42	2.42	2.42	2.5	2.26	2.16	2.14	2.04
Std. deviation	0.4986	0.5051	0.7309	0.7309	0.7584	0.5803	0.5997	0.7384	0.8084	0.9467
Std. error	0.07051	0.07143	0.1034	0.1034	0.1072	0.08207	0.0848	0.1044	0.1143	0.1339
Lower 99% CI	2.391	2.309	2.143	2.143	2.133	2.28	2.033	1.88	1.834	1.681
Upper 99% CI	2.769	2.691	2.697	2.697	2.707	2.72	2.487	2.44	2.446	2.399
ANOVA summary	F = 2.823; R^2 = 0.05447; p = 0.0262; S					F = 6.211; R^2 = 0.1125; $p < 0.0001$; HS				

Bonferroni's multiple comparison test

Parameters	Swelling				Pain			
	Mean diff.	t	p value	99% CI of diff.	Mean diff.	t	p value	99% CI of diff.
Before treatment vs 1st week	0.08	1.328	$p > 0.05$	–0.1045-0.2645	0.24	2.418	$p > 0.05$	–0.06403-0.5440
Before treatment vs 2nd week	0.16	2.656	$p < 0.05$	–0.02448-0.3445	0.34	3.425	$p < 0.01$	0.03597-0.6440
Before treatment vs 3rd week	0.16	2.656	$p < 0.05$	–0.02448-0.3445	0.36	3.627	$p < 0.01$	0.05597-0.6640
Before treatment vs 4th week	0.16	2.656	$p < 0.05$	–0.02448-0.3445	0.46	4.634	$p < 0.001$	0.1560-0.7640

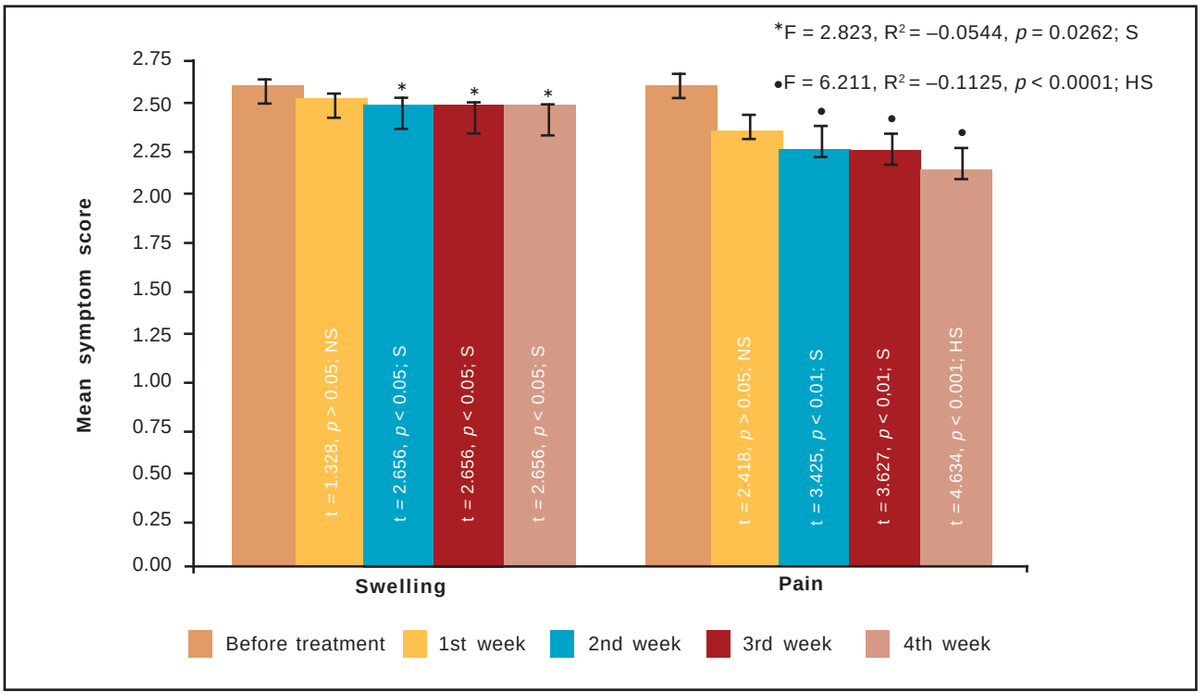

Figure 3. Reduction in the mean symptom score in the "sprains patient group".

stimulates the nervous system, alternatively the topical or subcutaneously applied analgesics could be depleting the nerve terminals of substance P, which is a nociceptive neurotransmitter[28].

Increased oxidative stress (associated with advancing age), makes chondrocytes more susceptible to oxidant-mediated cell death, through the dysregulation of the glutathione antioxidant system. This represents an important contributing factor to the development of OA in older adults[29]. Nuclear factor-κB plays a key role in immune and inflammatory responses, and NF-κB activation leads to enhanced expression of pro-inflammatory cytokines, chemokines, inflammatory enzymes (inducible NO synthase [iNOS] and COX-1 and -2 and adhesion molecules) and receptors. Therefore, modulation of NF-κB activation may provide a direct way of inhibiting inflammatory mediators[30-33].

This study observed significant reduction in the mean symptom scores for joint tenderness, joint swelling, joint mobility and a highly significant reduction in the mean symptom score for joint pain and early morning joint stiffness in the "OA patient group", in the "spondylosis patient group", there was a significant reduction in the mean symptom scores for joint pain and early morning joint stiffness. In the "muscular sprain patient group", there was highly significant reduction in the mean symptom scores for joint swelling and a highly significant reduction in the mean symptom score for early morning joint pain. In the "post-traumatic stiffness patient group", there was a highly significant reduction in the mean symptom score for joint stiffness. In the "peri-shoulder arthritis patient group", there was a highly significant reduction in the mean symptom score for pain. Also, there were no clinically significant adverse events and the overall compliance to the treatment was excellent. These excellent beneficial actions of Rumalaya gel might be due to the synergistic actions of its ingredients, which are well documented.

The active constituents of *Mentha arvensis* are menthol, monooterpene and sesquiterpene hydrocarbons (which include alcohols, aldehydes, esters, ethers, ketones, phenols and oxides)[34,35]. Methyl salicylate, an ester of salicylic acid, is the principle

Table 4

Reduction in the mean symptom score in the "post-traumatic stiffness patient group"

Parameters	Before treatment	1st month	2nd month	3rd month
Mean	2.32	2.14	2.12	2.06
Std. deviation	0.7126	0.7001	0.7183	0.7931
Std. error	0.1008	0.09902	0.1016	0.1122
Lower 99% CI	2.05	1.875	1.848	1.759
Upper 99% CI	2.59	2.405	2.392	2.361
ANOVA summary	F = 7.601; R^2 = 0.1343, p < 0.0001; HS			

Bonferroni's multiple comparison test

Parameters	Mean diff.	t	p value	99% CI of diff.
Before treatment vs 1st month	0.18	3.134	p < 0.01	0.008640-0.3514
Before treatment vs 2nd month	0.2	3.483	p < 0.01	0.02864-0.3714
Before treatment vs 3rd month	0.26	4.527	p < 0.001	0.08864-0.4314

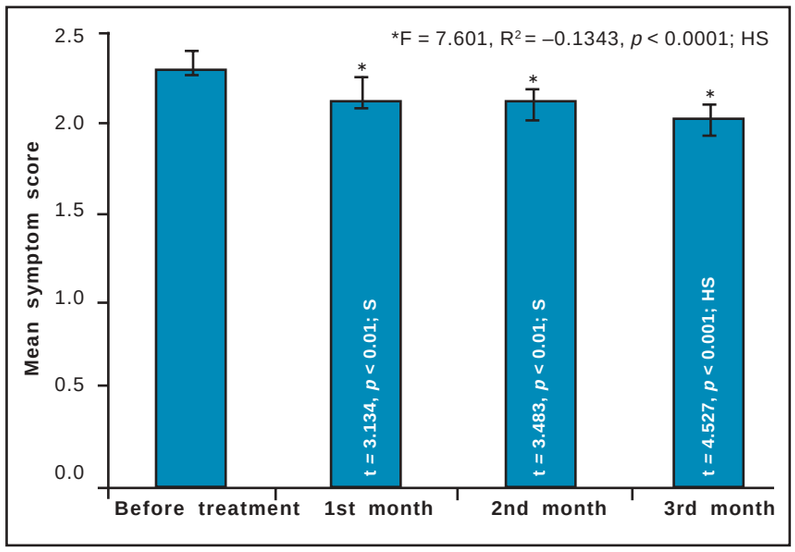

Figure 4. Reduction in the mean symptom score in the "post-traumatic stiffness patient group".

ingredient of *Gaultheria fragrantissima* (which is also known as 'oil of wintergreen'). *Mentha arvensis* and *Gaultheria fragrantissima* have analgesic, anti-inflammatory and antioxidant properties. Methyl salicylate is a counterirritant, and hence has analgesic and anti-inflammatory properties. *Mentha arvensis* and *Gaultheria fragrantissima* also contain menthol, which acts as a cooling agent (which counteracts the feeling of warmth generated by methyl salicylate), and as a penetration enhancer. Furthermore, *Mentha arvensis* also possess NO scavenging, and tumor necrosis factor-α inhibiting properties[36,37].

The active constituents of *Pinus roxburghii* are α-pinene, β-pinene, camphene 3-carenea, terpinene, limonene, phellandrene, α-terpinene, terpinolene, longipinene, longicyclene, sativene, longifolene, caryophyllene and terpinyl acetate. Martin, et al. investigated the anti-inflammatory activity of α-pinene against carrageenin and PG-E1-induced inflammation, and observed potent anti-inflammatory activity of *Pinus roxburghii*[34,38]. Zhou, et al. observed that α-pinene inhibits NF-κB nuclear translocation, induced by lipopolysaccharides, therefore stabilizing the degradation and nuclear translocation of NF-κB, blocks the gene regulatory effects of NF-κB, which represents one of

Table 5

Reduction in the mean symptom score in the "peri-shoulder arthritis patient group"

Parameters	Before treatment	1st month	2nd month	3rd month
Mean	2.46	2.44	2.26	2.1
Std. deviation	0.6455	0.644	0.6328	0.8631
Std. error	0.09129	0.09107	0.08949	0.1221
Lower 99% CI	2.215	2.196	2.02	1.773
Upper 99% CI	2.705	2.684	2.5	2.427
ANOVA summary	F = 8.268; R^2 = 0.1444; p < 0.0001; HS			

Bonferroni's multiple comparison test

Parameters	Mean diff.	t	p value	99% CI of diff.
Before treatment vs 1st month	0.02	0.2403	p > 0.05	–0.2283-0.2683
Before treatment vs 2nd month	0.2	2.403	p > 0.05	–0.04834-0.4483
Before treatment vs 3rd month	0.36	4.326	p < 0.001	0.1117-0.6083

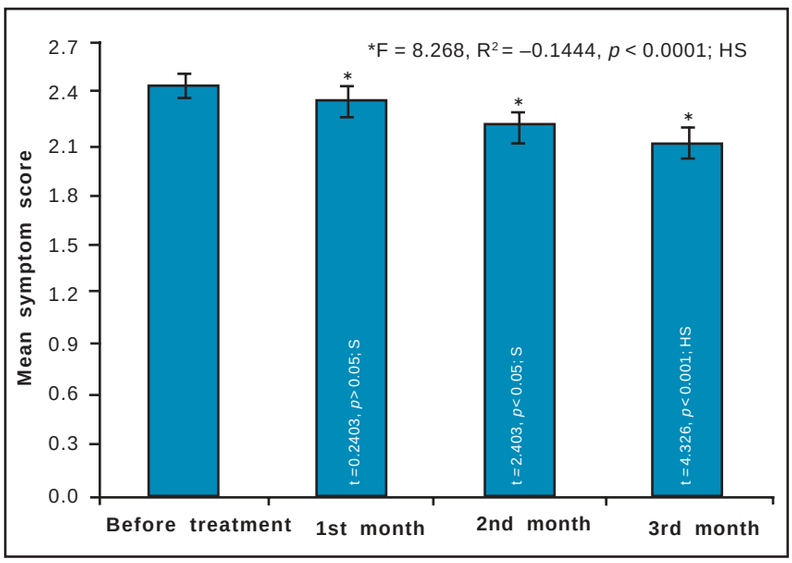

Figure 5. Reduction in the mean symptom score in the "peri-shoulder arthritis patient group".

the anti-inflammatory mechanisms of α-pinene, obtained from *Pinus roxburghii*[39].

The active ingredients of *Cinnamomum zeylanicum* are *l*-arabino-d-xylan, d-glucan, diterpenes, cinnzeylanin, cinnzeylanol, tannin (cinnamm and tannin B1), terpene hydrocarbons, oxygenated terpenoids, α-bergamotene, α-copaene, menthol, menthone, menthyl acetate, neomenthol, isomenthone, menthofuran limonene, pulegone, α and β pinenes, and trans-sabinene hydrate[40]. Atta, et al. observed antinociceptive and anti-inflammatory effects of *Cinnamomum zeylanicum*[41]. Fleming, et al. showed that *Cinnamomum zeylanicum* had an anti-inflammatory effect on intraleukin-1 β production[40]. *Cinnamomum zeylanicum* also has potent antioxidant activities[35,42-44].

The active ingredients of *Cedrus deodara* are matairesinol, nortrachelogenin, and a dibenzylbutyrolactollignan (4,4′, 9-trihydroxy-3, 3′-dimethoxy-9, 9′-epoxylignan)[45]. The anti-inflammatory activity of *Cedrus deodara* is attributed to the mast cell stabilizing activity, and to the inhibition of leucotriene synthesis. Shinde, et al. reported the analgesic activity of *Cedrus deodara*[46], and in another study by Shinde, et al., *Cedrus deodara* produced significant inhibition of

both exudative-proliferative and chronic phases of inflammation[47].

The principal constituents of *Vitex negundo* are casticin, isoorientin, chrysophenol D, luteolin, p-hydroxybenzoic acid, D-fructose, lignans (negundins A and B), diasyringaresinol, lyoniresinol, vitrofolal E, vitrofolal[48], a vitexicarpin[45] and anti-inflammatory triterpenoids (3-beta-acetoxyolean-12-en-27-oic acid, 2-alpha-3-alpha-dihydroxyoleana-5-12-dien-28-oic acid, 2-beta-3-alpha-diacetoxyoleana-5-12-dien-28-oic acid, and 2-alpha-3-beta-diacetoxy-18-hydroxyoleana-5, and 12-dien-28-oic acid[49]. Dharmashri, et al. observed that *Vitex negundo* has anti-inflammatory and analgesic activities, which were possibly mediated via PG synthesis inhibition, antihistaminic action, and by membrane stabilization[50], along with antioxidant activities[51,52].

The principle constituents *Boswellia serrata* are acetyl 11-keto-beta boswellic acid, 11-keto beta-boswellic acid, acetyl beta-boswellic acid and beta-boswellic acid[53,54]. *Boswellia serrata*blocks the synthesis of pro-inflammatory 5-LO products (i.e., 5-hydroxyeicosatetraenoic acid and LTB4)[55,56]. Boswellic acids from *Boswellia serrata* inhibit the leukotriene biosynthesis by a non-redox, non-competitive inhibition of 5-LOX[57]. In another study by Ammon, et al., *Boswellia serrata* decreased 5-LOX mediated metabolisation of AA, to leucotriene B4 and 5-hydroxy eicosotetrachoic acid[58]. Boswellic acids from *Boswellia serrata* have anticomplementary activity, which inhibits C3-convertase of the classical complement pathway[59]. *Boswellia serrata* has been shown effective in the treatment of RA, and it has a disease modifying effect, is well-tolerated and safe for long-term therapy.

Glycosaminoglycans and proteoglycans are the building blocks of cartilage, and in degenerative conditions like OA and RA, the cartilage is primarily affected. Reddy, et al. observed reduced degradation of glycosaminoglycans and proteoglycans, with *Boswellia serrata* pre-treatment[60]. *Boswellia serrata*has been recommended by various researchers for long-term management of OA[61,62].

The principal constituents of *Zingiber officinalis* are zingiberene (A and B), gingerols and zingiberols[63]. The gingerols are agonists of the capsaicin-activated vanilloid (VR1) receptor, and 6- and 8-gingerol evoke intracellular Ca2+ and ion currents in neurons, which can be blocked by capsazepine (the VR1 receptor antagonist). Thus, gingerols represent a novel class of naturally occurring VR1 receptor agonists that contribute to the analgesic property of *Zingiber officinalis*[64]. Mustafa, et al. demonstrated that topical application of *Zingiber officinalis* extract inhibits the activities of COX and LOX in the AA cascade. Therefore, the anti-inflammatory effects of *Zingiber officinalis* might be due to the decrease in the formation of PGs and LTs[65]. Srivastava, et al. observed that *Zingiber officinalis* was a potent inhibitor of thromboxane synthase, and it increases prostacyclin levels without a concomitant rise in PG E2.[66] Mascolo, et al. and Sharma, et al. reported that oral administration of *Zingiber officinalis* decreases induced edema, *in vitro*with a comparable potency of acetylsalicylic acid[67,68]. Suekawa, et al. also observed that 6-shogaol from*Zingiber officinalis* inhibits carrageenin-induced edema by COX inhibition[69]. Recently, Kawakishi, et al. demonstrated that labdane type diterpene dialdehydes from *Zingiber officinalis* inhibits 5-LO, *in vitro*[70]. Ghazanfar, et al. conducted a clinical trial amongst 113 patients with RA and injected *Zingiber officinalis*extract into the painful points/reaction nodules and reported that all the participants experienced full or significantly partial relief from pain, decrease in joint swelling and improvement or significant recovery in joint function[71]. Srivastava, et al. observed that, the oral administration of *Zingiber officinalis* to patients with rheumatism and musculoskeletal disorders provided varying degrees of relief from pain and swelling[72].

Therefore, it can be summarized that the beneficial effects of Rumalaya gel are due to analgesic activities (of *Mentha arvensis, Gaultheria fragrantissima, Cedarus deodara, Vitex negundo* and *Boswellia serrata*), anti-inflammatory

activities (of *Mentha arvensis, Gaultheria fragrantissima, Pinus roxburghii, Cedrus deodara, Vitex negundo, Boswellia serrata* and *Zingiber officinalis*), antioxidant activities (of *Mentha arvensis, Gaultheria frangantissima, Pinus roxburghii, Cinnamomum zeylanicum, Vitex negundo* and *Zingiber officinalis*), glycosaminoglycan building activity (of *Boswellia serrata*) and the cartilage healing property (of *Cinnamon zeylanicum*). Rumalaya gel also induces cutaneous vasculature vasodilatation, which produces increased blood circulation and a feeling of warmth. Consequently, cutaneous receptors are stimulated for thermal sensations, which serve to distract deep-seated pain sensations, from the distant areas from the skin's surface like joints, ligaments and muscles.

Conclusion

Conventionally, chronic painful inflammatory conditions are treated with systemic NSAIDs. However, these agents carry a substantial risk of adverse events, particularly on the gastro-intestinal, renal and cardiovascular systems. Various clinical reviews have provided the evidence that these topical analgesics are useful in treating certain acute and chronic painful inflammatory conditions. The counterirritants take advantage of the "pain paradox", and offer short- and long-term safety. This clinical trial was conducted to evaluate the efficacy and safety of Rumalaya gel in the management of pain and inflammation associated with the musculoskeletal inflammatory disorders like RA, OA, spondylosis, sprains, post-traumatic stiffness, peri-shoulder arthritis and other inflammatory musculoskeletal disorders.

This study observed significant reduction in the mean symptom scores for joint tenderness, joint swelling, joint mobility, and a highly significant reduction in the mean symptom score for joint pain and early morning joint stiffness in the "OA patient group", in the "spondylosis patient group", there was a significant reduction in the mean symptom scores for joint pain and early morning joint stiffness. In the "muscular sprain patient group", there was highly significant reduction in the mean symptom scores for joint swelling and a highly significant reduction in the mean symptom score for early morning joint pain. In the "post-traumatic stiffness patient group", there was a highly significant reduction in the mean symptom score for joint stiffness. In the "peri-shoulder arthritis patient group", there was a highly significant reduction in the mean symptom score for pain. Also, there were no clinically significant adverse events and the overall compliance to the treatment was excellent. These excellent beneficial actions of Rumalaya gel might be due to the synergistic actions of its ingredients, which are well documented. Therefore, it may be concluded that Rumalaya gel is effective and safe in the management of pain and inflammation associated with the musculoskeletal inflammatory disorders like RA, OA, sports injuries, sprains, spondylosis, post-traumatic stiffness, peri-shoulder arthritis and other inflammatory musculoskeletal disorders like fibrositis, bursitis, synovitis, capsulitis and sciatica.

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