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EVALUATION OF THE EFFICACY AND SAFETY OF NRL/2019/JC CAPSULES IN KNEE OSTEOARTHRITIS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED CROSSOVER CLINICAL STUDY

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ABSTRACT

Background: Osteoarthritis (OA) is a long-term chronic disease with deterioration of cartilage in joints which results stiffness, pain, and impaired movement. The most commonly prone joints are in the knees, hands, feet, and spine and is relatively common in knee and hip joints. Nutraceuticals developed for use in osteoarthritis have a role in the balance of anabolic and catabolic signals in joints. The antioxidant, anti-inflammatory and disease modifying capacity of nutraceutical blend can be considered for the management and prevention of osteoarthritis (OA). **Methodology:** The present clinical study was conducted in 101 subjects suffering from osteoarthritis of Knee(s). All the recruited subjects were provided with either placebo or NRL/2019/JC capsule for the period of 60 days and crossed over for 1 month i.e. till day 90. Subjects were asked to visit the study site every 30 days and changes in knee joint pain, stiffness, swelling, inflammatory markers, use of analgesic drug as rescue medicine, and quality of life of the subjects were assessed on every follow up visit. **Results:** After treatment with test drug, significant improvement in morning stiffness is observed from day 30 onwards and at the end of the study 12 (24%) subjects reported no morning stiffness while 38 (76%) reported mild morning stiffness. In test treated groups 87.5% subjects were dependent on analgesic as rescue medication which reduced significantly ($P < 0.05$) to 20% at day 60 in test group. There was significant reduction in pain in test treated group at day 60 from baseline. After day 60, placebo offered similar levels of markers but test treated group exhibited significant reduction in CRP and IL-6 levels with $p<0.05$. **Conclusion:** In the present study, use of NRL/2019/JC capsule in subjects suffering from OA is proved to be safe and effective. NRL/2019/JC capsule is significantly effective in reducing pain, swelling and stiffness of knee joint in subjects as well as in improving mobility of knee joints and quality of life. NRL/2019/JC capsule reduces elevated inflammatory cytokines thus confirms its anti-inflammatory activity. NRL/2019/JC capsule treatment led to reduction in dependency over NSAIDS as rescue medication.

KEYWORDS: *Osteoarthritis, nutraceutical, WOMAC, inflammation.*

INTRODUCTION

Osteoarthritis (OA) is a long-term chronic disease with deterioration of cartilage in joints which results stiffness, pain, and impaired movement. The most commonly prone joints are in the knees, hands, feet, and spine and is relatively common in knee and hip joints.[1]

OA is not only related to ageing, but also associated with a variety of both modifiable and non-modifiable risk factors, including: obesity, lack of exercise, sedentary lifestyle, genetic predisposition, low bone density, occupational injury, trauma, and gender.[2]

As per The National Institute of Health and Family Welfare (NIHFW) of India, Osteoarthritis is the most frequent joint disease with a prevalence of 22% to 39% in India. OA is more common in women than men.[3, 4]

Older patients with arthritis often represent comorbidity such as hypertension, cardiovascular disease, dyslipidemia, diabetes (14%), and mental health disorders including depression (12%).[5-7]

Pathogenesis of OA involve the accompanying biochemical, structural and metabolic changes in the joint cartilage which initiate a degenerative cascade resulting in alterations in the articular cartilage in

OA.[8,10] Hyaline cartilage is composed of chondrocytes embedded in extracellular matrix, type II collagen and proteoglycan. The cartilage experience active degeneration and regeneration occurring in equilibrium. Causative risk factors of OA lead to matrix and cartilage degeneration and active chondrocyte replication with enhanced biosynthesis, known as compensated OA with balanced repair and degeneration. If the degenerative process continues and reparative process gets exhausted, this leaves cartilage degradation unopposed leading to progressive OA affecting cartilage, synovial membrane, subchondral bone, ligaments and particular muscles.[11-12]

Very few drugs with significant disease modifying properties have emerged but still not in clinical practice so far. In the contemporary management of OA, oral agents are used primarily for analgesia. The side effects of the major class of analgesics can be significant and challenging. Natural product based treatment outcomes are more sustainable than conventional standard care in the treatment of OA. Nutraceuticals may provide preventive and therapeutic properties. Many nutraceuticals and herbal products have demonstrated effectiveness in treating chronic diseases of the musculoskeletal system. The goal of adjuvant OA treatment with nutraceuticals is not only to control symptoms but also prevent disease progression, minimize disability, and improve quality of life.[13]

By considering need of a safe and effective nutraceutical supplement in the management of OA, the current research depicts the efficacy and safety of the NRL/2019/JC capsules in patients suffering from knee OA.

MATERIALS AND METHODS

This was a randomized, double blind, placebo controlled, crossover clinical trial.

Male and/or female volunteers aged between 40 to 60 years both inclusive were included in the study with BMI $\geq$ 24 Kg/m^2 and $\leq$38 Kg/m2 and willing to come for regular follow-up visits. Patients diagnosed with osteoarthritis of the knee based on the American College of Rheumatology (ACR) criteria were recruited. Patients with congenital arthropathy, rheumatoid arthritis, active gout, other type of arthritis with/without inflammation e.g. septic, fibromyalgia or collagen vascular disease were excluded. Patients with known history of coagulopathies, patients with history of major trauma or surgery in the knee joint were excluded. Patients with uncontrolled diabetes and hypertension, any severe cardiac, renal and hepatic disease were excluded. Patients who participated in any clinical trial within 30 days before enrollment into the study. Any other condition which the Principal Investigator thinks may jeopardize the study were excluded together with subjects in vulnerable group. We intended to complete 100 subjects (50 in each group) at the end of the study. Additional subjects were recruited to complete the required number (100) of completed subjects for analysis. As per computer generated randomization list, subject was either be randomized to NRL/2019/JC (Test) or Placebo Group in 1:1 ratio. Subjects were advised to take given medication in a dose of 1 capsule BD after meals with lukewarm water for 90 days.

After getting approval from the ethics committee, the study was registered on CTRI website. Patients were enrolled in the study only after registration of study on CTRI website. The Registration details of study are-CTRI/2020/02/023199. Male and female subjects of age between 40 to 60 years of age (both inclusive) attending outpatient department of study site(s) were screened for eligibility criteria. On screening visit, a written informed consent was obtained from subjects for their participation in the study. Subject's demographic details were collected. Subject undergone clinical examination. Subject's medical, surgical and treatment history was taken. Subject's current medication if any was noted in the case record from (CRF). Subject's vitals were recorded. The subject was considered for further evaluation as per the inclusion and exclusion criteria. The BMI of the subject is assessed. During screening visit and the entire study duration subjects was advised to refrain from nutraceutical, herbal or Ayurvedic medication. Laboratory testing i.e. CBC, liver function tests, renal function test and urine routine along with the inflammatory markers like CRP, IL etc. was performed at screening and at end of study. All the subjective questionnaire scores like, SF-36 Health Survey score, VAS scale, WOAMC questionnaire were assessed from baseline at every follow up i.e. day 30, 60 and 90. Subjects were scored on their symptoms like morning stiffness, tiredness, tenderness, and muscle spasms on every visit. At baseline visit and at every follow up visit (except last follow up visit), as per computer generated randomization list, subjects were provided with containers each containing either a test drug or placebo. Subject were advised to consume given product in a prescribed dosage i.e. 1 capsule BD after meals. Subject were advised to continue his/ her concomitant medication other than antioxidant agents, weight loss management, vitamins, anti-inflammatory drugs, hormones, Nutraceutical, Ayurvedic, Siddha, Unani, herbal /homeopathic medicines etc. Subjects who continuously missed dosing for >3 consecutive days or total missed dose > 9 during the study period were treated as drop outs. There was no compliance failure in the study. All subjects were advised to follow their exercise and diet routine as it is during the entire study period. Rescue medication details were recorded in CRF. At day 60, the crossover was performed i.e. subjects from placebo treatment group received test and subjects from test group received placebo treatment for next 30 days i.e. till day 90. Subjects were strictly monitored for presence of any adverse events during study period.

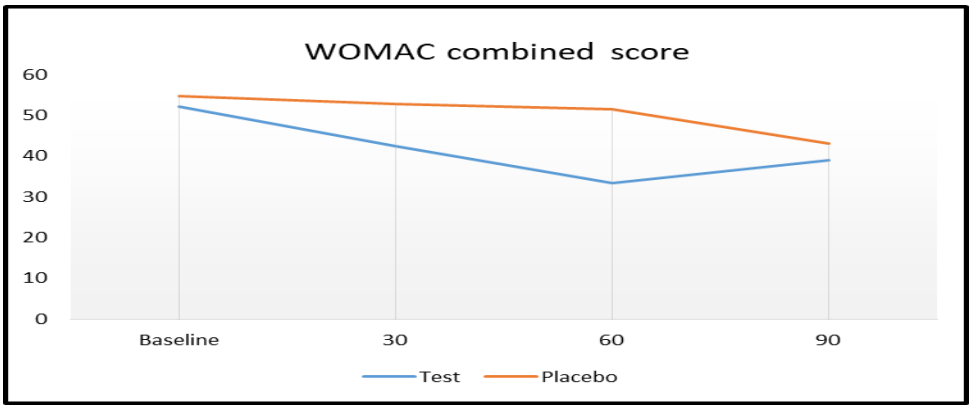
RESULTS AND DISCUSSION

In the present study, 115 subjects were screened. 03 subjects were screened failure as per the decision of investigator as were having uncontrolled diabetes. Out of 112 subjects, 11 lost to follow up in the study. 101 subjects were considered evaluable cases at the end of the study 50 in test and 51 in Placebo treated group. The mean age of Test group subjects were 48.5 ± 5.75 years and the mean age of Placebo group subjects was 49.2 ± 6.06 years. The ratio of approximately 1:1 for male and female was decided and maintained during recruitment of the study.

Assessment of pain, stiffness and difficulty in movement by Western Ontario & Mcmaster osteoarthritis index (WOMAC) score between the groups

The mean WOMAC combined score at baseline in test group was 52.14 which reduced by 18.72% from baseline on day 30 and 36.00% on day 60. At day 90, the crossover in treatment was performed and test group subjects received placebo which led to mean WOMAC combined score 39.08. The reduction in score in comparison to baseline was 25.05%.

The mean WOMAC combined score at baseline in placebo group was 54.66 which reduced by 3.37 from baseline on day 30 and 5.71 % on day 60. At day 90, the crossover in treatment was performed and placebo group subjects received test product which led to mean WOMAC combined score 43.16. The reduction in score in comparison to baseline was 21.04%. The details are depicted in graph 1.



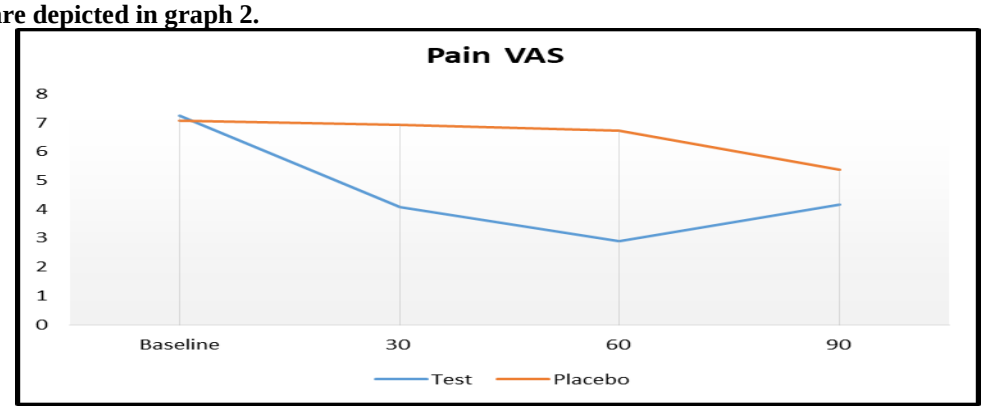
Graph 1: assessment of WOMAC combined score between the groups.

Assessment of physicians global Assessment of performance of patient on pain VAS scale between the groups

The mean VAS score at baseline in test group was 7.24 which reduced by 43.64% from baseline on day 30 and 60% on day 60. At day 90, the crossover in treatment was performed and test group subjects received placebo which led to mean VAS score 4.16. The reduction in score in comparison to baseline was 42.56%.

The mean VAS score at baseline in placebo group was 7.08 which reduced by 2.26% from baseline on day 30 and 5.08 % on day 60. At day 90, the crossover in treatment was performed and placebo group subjects received test product which led to mean VAS score 5.38. The reduction in score in comparison to baseline was 24.01%.

The details are depicted in graph 2.



Graph 2: assessment of pain VAS scale between the groups.

Assessment of Improvement in SF-36 Health Survey score between the groups

Quality of life of recruited subjects was assessed using SF-36 Questionnaire limitation of activities was measured along with general health and energy status. These parameters altogether were considered to reflect the overall quality of life of the individual on following parameters.

Effect of on general health

The subjects were asked to rate their health status as excellent, very good, good, fair or poor on every visit. In test group, on baseline visit, 6% subjects rated their health as Very good, 14% rated their general health as Good whereas 24% subjects were found to have rated their general health as fair and 56% as Poor. After treatment of 60 days when the subjects reported their general health, it was found that 4% had excellent health, 20% had very good health, 56% had good health and only 20% reported their health as fair. Results are depicted in table 1.

Table 1: Changes in general health status.

Assessment	Test (N = 50)				Placebo (N = 51)			
	Day 0		Day 60		Day 0		Day 60	
	No	%	No	%	No	%	No	%
Excellent	-	-	*02	04.0	-	-	-	-
Very good	03	06.0	*10	20.0	05	9.80	06	11.76
Good	07	14.0	*28	56.0	06	11.76	05	09.80
Fair	12	24.0	10	20.0	15	29.41	20	39.21
Poor	28	56.0	-	-	25	49.00	20	39.21

By Chi – Square test
**P < 0.05, Significant*

Changes in proportion of cases with limitation of daily moderate activities due to health status

Recruited subjects were asked about the level of limitation faced by them while performing moderate activities like moving a table, pushing a vacuum cleaner, carrying groceries, climbing one to several flights of stairs etc. When asked to rate the limitation as limited a lot, limited a little or not limited at all; in test group, 30% subjects reported lot of limitation, 50% subjects reported little limitation and 20% subjects were known to face no limitation in activities at all. At the end of 60 days period 4% faced lot of limitation, 70% faced little limitation and 26% subjects reported moderate activities to be not limited at all. Results are depicted in table 2.

Table 2: Changes in proportion of cases with limitation of doing moderate activities.

Assessment	Test (N = 50)				Placebo (N = 51)			
	Day 0		Day 60		Day 0		Day 60	
	No	%	No	%	No	%	No	%
Limited a lot	15	30.0	*02	04.0	13	25.5	15	29.4
Limited a little	25	50.0	*35	70.0	28	54.9	26	51.0
No limited at all	10	20.0	13	26.0	10	19.6	10	19.6

By Chi – Square test
*P < 0.05, *Significant*

Energy and Emotions

In test group, on baseline visit, no subject felt like having lot of energy while 26% felt lot of energy most of the times. The improvement was observed at day 60. After day 60, 2% subjects informed that they had lot of energy all the time and 46% informed to had lot of energy most of the time. In placebo group there was no significant changes in number of subjects reporting their energy status. Results are depicted in table 3.

Table 3: Changes in Proportion of Cases with Lot of Energy.

Assessment	Test (N = 50)				Placebo (N = 51)			
	Day 0		Day 60		Day 0		Day 60	
	No	%	No	%	No	%	No	%
All of the time	-	-	*01	02.0	02	04.9	02	04.9
Most of the time	13	26.0	*23	46.0	13	25.5	13	25.5
A good bit of time	05	10.0	*10	20.0	05	9.8	05	9.8
Some of the time	05	10.0	*08	16.0	05	9.8	05	9.8
A little bit of time	22	44.0	*08	16.0	20	39.2	23	45.0
None of the time	05	10.0	-	-	06	11.76	03	6.1

By Chi – Square test
*P < 0.05, *Significant*

Assessment Levels of inflammatory mediators
Table 4 depicts the changes in inflammatory mediators from baseline to day 60. At baseline all the mediator levels i.e. CRP, IL-6 and TNF-alpha were comparable with no significant difference. After day 60, placebo offered similar levels of markers but test treated group exhibited significant reduction in CRP and IL-6 levels with p<0.05. There was no significant reduction observed in TNF-alpha levels in test treated group at day 60 though the levels were reduced magnitude wise.

Table 4: Assessment Levels of inflammatory mediators: CRP, IL-6 and TNF-alpha.

Duration (Days)	(Mean± SD)			
	Baseline		Day 60	
	Placebo (N = 51)	Test (N = 50)	Placebo (N = 51)	Test (N = 50)
Serum CRP (mg/l)	4.30± 2.11	4.19± 1.28	4.22± 2.35	2.15± 1.12*
IL-6 (pg/mL)	4.32± 0.11	4.38± 0.88	4.61± 0.64	2.81± 0.74*
TNF- Alpha (pg/mL)	3.38± 1.01	3.22± 0.66	3.51± 0.64	2.76± 0.47

*By ANOVA multiple comparison Test: P > 0.05 Not Significant; significant p< 0.05**

Assessment of symptom improvement like morning stiffness, tiredness, tenderness, and muscle spasms in the group based on duration and between the groups:
Morning stiffness
In test group, significant improvement in morning stiffness is observed from day 30 onwards and at the end of the study 12 (24%) subjects reported no morning stiffness while 38 (76%) reported mild morning stiffness. In placebo treated group there was no significant changes in proportion of patients informing grades of morning stiffness till day 60 but as at Day 60 there was crossover of treatment executed, the placebo treated group received test drug for one month which led to the significant movement of proportion of patients reporting severe stiffness moving towards moderate and 9.8% subjects reported no stiffness. The details are presented in table 5.

Table 5: Assessment proportions of subjects with Morning stiffness.

Assessment	Proportion of cases with morning stiffness															
	Test (N=50)								Placebo (N=51)							
	Baseline		Day 30		Day 60		Day 90		Baseline		Day 30		Day 60		Day 90	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
None	-	-	3	6	**35	70	12	24	-	-	-	-	-		*5	9.8
Mild	1	2	**38	76	14	28	38	76	5	9.8	5	9.8	4	7.8	6	11.7
Moderate	21	42	**9	18	1	2	0	0	25	49	25	49	26	51	25	49
Severe	28	56		0	0	0	0	0	21	41.1	21	41.1	21	41.1	*15	29.4

By Chi – Square test
P<0.05, P < 0.001, **Significant*

Tiredness
In test group, at baseline visit 23(46 %) subjects reported moderate tiredness, 27 (54%) reported severe tiredness. Significant improvement in morning tiredness is observed from day 30 onwards and at the end of the study 8 (16%) subjects reported no tiredness while 40 (80%) reported mild tiredness and 2 (4%) reported moderated tiredness. In placebo treated group there was no significant changes in proportion of patients informing grades of morning stiffness till day 60 but as at Day 60 there was crossover off treatment executed, the placebo treated group received test drug for one month which led to the significant movement of proportion of patients reporting severe tiredness moving towards moderate. The details are presented in table 6.

Table 6: Assessment proportions of subjects with tiredness.

Assessment	Proportion of cases with tiredness															
	Test (N=50)								Placebo (N=51)							
	Baseline		Day 30		Day 60		Day 90		Baseline		Day 30		Day 60		Day 90	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
None	-	-	*1	2	**23	46	8	16	-	-	-	-	-	-	-	-
Mild	-	-	**37	74	*23	46	**40	80	-	-	10	20	10	20	20	39
Moderate	23	46	12	24	4	4	2	4	25	49	15	29	15	29	15	29
Severe	27	54	0	0	0	0	0	0	26	51	26	51	26	51	16	32

By Chi – Square test *P<0.05*, P < 0.001, **Significant*

Changes in proportion of cases with use of analgesic drug as rescue medicine

During entire study period, patients were allowed to take tab Paracetamol (up to 2 gm./day) or any standard analgesic drug in case of severe joint pain and the details of use of this medication were recorded as rescue medication. In test and placebo treated groups proportion of cases requiring use of rescue medication during washout period was 87.5% and 90% respectively which reduced significantly ($P < 0.05$) to 20% had to use rescue medication for severe knee joint pain at day 60 in test group. In placebo group at day 60, 75% subjects reported to consume rescue medication at least once a month. From day 60 to day 90, crossover in treatment was being conducted so placebo received test product and test group received placebo. At end of day 90, 80% of subjects required rescue and 72% from placebo group required rescue analgesic.

Comparison of Safety Parameters between The Groups

To evaluate safety of the study interventions, following biochemical tests were performed- lipid profile, liver profile, renal profile and complete blood count etc. Vitals like BP, HR etc were also assessed from baseline to end of study in both groups. In the present study it was observed that there were no significant changes in the above cited biochemical tests and vitals in both the groups.

Profile of adverse events

Amongst 101 subjects enrolled in the study, 26 subjects had suffered at least one adverse event. Total 48 adverse events were recorded throughout the study period. As per the investigator, the adverse events were not associated with the study medication. The adverse events were headache, hyperacidity, loose motions, cough and cold etc. which resolved with rescue medication and there was no need to discontinue the treatment.

DISCUSSION

A crossover study design has two advantages over a parallel study and single arm study. First, the influence of confounding covariates is reduced as a result of a patient serving their own control. Second, optimal crossover designs are statistically efficient, and so precise and sure results can be expected by minimizing biases due to psychological variants.[14]

The ACR clinical criteria was employed to confirm the established OA in knee joints. The very first clinical sign of OA being pain in joints. It can be easily measured as a Visual analog score (VAS) reported by subject himself or herself. In the present study, significant reduction in knee joint pain (on VAS) was seen with NRL/2019/JC treatment right from day 30 and continued till day 60. There was 48.90% reduction in the knee joint pain (on VAS) at day 60 of treatment. At day 90, the crossover in treatment was performed and test group subjects received placebo which led to mean VAS score 5.16. The reduction in score in comparison to baseline was 28.73%.

WOMAC combined score is the sum of the pain subscore, stiffness subscore and physical function subscore assessed on WOMAC Index. The mean WOMAC combined score at baseline in test group was 52.14 which reduced by 18.72% from baseline on day 30 and 36.00% on day 60. At day 90, the crossover in treatment was performed and test group subjects received placebo which led to mean WOMAC combined score 39.08. The reduction in score in comparison to baseline was 25.05%.

Commiphora mukul (guggul) present in test product is proven for reduction of pain, stiffness, and improved joint function in a clinical trial of OA of the knee[15] From a study published earlier, *Boswellia serrata* which is key component of test product has significantly increased the pain threshold and pain tolerance force and time compared to placebo in mechanical pain model in human volunteer.[16] VAS and WOMAC score reduction could be attributed to the analgesic and anti-inflammatory activity of *Commiphora mukul* and *Boswellia serrata*.

The 36-item short form of the Medical Outcomes Study questionnaire (SF-36) was designed as generic indicator of health status. It can also be used in conjunction with disease-specific measures as an outcome measure in clinical practice and research. This questionnaire takes care of many aspects of the quality of life such as vitality, physical functioning, general health perceptions, emotional role functioning, social and mental health.

OA is characterized by limitation of daily moderate activities. Subjects experiencing lot limitation were shifted towards no limitation and little limitation after treatment with test product. The subjects were asked about their energy and emotional status at every visit as part of assessment of their quality of life assessment. Subjects experiencing no energy throughout day got shifted to the subjects experiencing energy for good bit of time, most of time to all of time after test product treatment.

Progressive OA shows elevated levels of a number of pro-inflammatory mediators like C-reactive protein, Interleukin-6 and TNF- alpha. In rodent models of traumatic joint injury studies earlier, TNF-alpha expression induced joint space narrowing.[17]

Increased circulating levels of CRP and IL-6 have been found to be predictors of reduced physical mobility and incident mobility limitation in OA. Moreover, there is a substantial evidence, obtained mostly from cross-sectional studies, suggesting that CRP levels are elevated in OA.[18]

In present study, the inflammatory cytokines were analyzed. At baseline all the mediator levels i.e. CRP, IL-6 and TNF-alpha were comparable with no significant difference. After day 60, placebo offered similar levels of markers but test treated group exhibited significant reduction in CRP and IL-6 levels with $p<0.05$. There was no significant reduction observed in TNF-alpha levels in test treated group at day 60 though the levels were reduced magnitude wise.

Clinical evaluation of *Boswellia serrate* in a clinical trial of OA reduced elevated levels of CRP levels. **[19]** The curcuminoids from *Curcuma longa* which is a key ingredient in test product, is known to exhibit actions at different locations in the pathogenesis of OA as anti-inflammatory, down-regulating enzymes as phospholipase A2, cyclooxygenase-2, and lipoxygenases, and reducing tumor necrosis factor-alpha-and interleukins such as interleukin-1β (IL-1β), IL-6, and IL-8. It induces of apoptosis in synoviocytes, decreasing the inflammation process through its strong antioxidant activity.[20]

From an earlier research it is evident that *Cissus quadrangularis* which is present in test product, is reported to alleviated IL induced cell toxicity and up-regulated cell growth and proliferation in OA. It helped inhibited gene expression of cytokines and matrix metallo-proteinases, known to aggravate cartilage and bone destruction. *Cissus quadrangularis*, together with *Withania somnifera*, enhanced alkaline phosphatase and cartilage tissue formation in animal models as compared to untreated.[21]

Aqueous extracts of *Withania somnifera* which is present in test product,is reported as chondroprotective by inhibition of the gelatinase activity of collagenase type 2 enzyme in vitro. It is one of the key ingredient of test product. *Withania somnifera* is reported having potential as anti-inflammatory, analgesic, and chondroprotective in experimental studies of OA. It has demonstrated blockage of the cyclo-oxygenase (COX) pathway and has analgesic effects.[22]

Test product has blend of herbs that are having potent antioxidant potential. The immunomodulatory activity of Ashwagandha, Curcumin together with Zingiber officinale leads to adaptogenic activity in test product. This may help in improving symptomatology. There was improvement in symptoms like morning stiffness, tiredness which ultimately leads to improved energy and quality of life in patients of OA.

The main purpose of any of the adjuvant therapy is to halt the progression of disease and reduce dependency on conventional medication. In present study, use rescue medication in test treated group was markedly reduced. This result is suggestive of potential of test product to decrease events and doses of NSAIDs for management of pain, as pain gets better managed with treatment of test product. This is very crucial in order to achieve gastro protection. The natural anti-inflammatory agents being used in test product are not irritating on gastric mucosa and fairly managing pain hence the conventional NSAIDs can be spared.

OA is a heterogeneous multi-faceted joint disease with multi-tissue involvement of varying severity. Current therapeutic regimens for OA are insufficient and offer significant associated toxicities. There are no disease-modifying drugs approved by the regulatory bodies. Some of the phytoconstituents like curcumin from *Curcuma longa*, withanoloids from *Withania Somnifera* and ketosterones from *Cissus quadrangularis* are effective in modifying root cause of OA like cytokine mediated inflammation, inhibiting metalloproteinase, chondro-regenerative activity.**[23]** NRL/2019/JC capsule possesses selective blend of herb which can modify disease and work at root cause level.

CONCLUSION

In the present study, use of test product (NRL/2019/JC capsule) in subjects suffering from OA is proved to be safe. Test product is significantly effective in reducing pain, swelling and stiffness of knee joint in subjects with OA. It reduced elevated inflammatory cytokines thus confirms its anti-inflammatory activity. Test product treatment led to reduction in dependency over NSAIDS as rescue medication. It confirms adjuvant potential of test product. Thus, NRL/2019/JC capsule is safe and effective in the management of Osteoarthritis when compared to placebo.

CONFLICT OF INTEREST

There is no conflict of interest.

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