

# An open label, prospective, clinical study on a polyherbal formulation in osteoarthritis of knee

Sanjay U. Nipanikar, Manjit Saluja<sup>1</sup>, Vinod V. Kuber, Kalyan P. Kadhbane, Arvind Chopra<sup>1</sup>, Namdev R. Khade<sup>1</sup>

Department of Medical Services, R and D Center, Tulip Lab Pvt. Ltd., Ranjangaon, Shirur, Pune, <sup>1</sup>Center for Rheumatic Diseases (CRD), Hermes Elegance, Pune, India

## ABSTRACT

**Background:** Currently, though pharmacological, mechanical, and surgical interventions are used, there is no known cure for osteoarthritis (OA). **Objectives:** The main aim of the study was to assess the efficacy and safety of "TLPL/AY/03/2008," a polyherbal formulation on knee joint pain assessed on visual analogue scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). **Materials and Methods:** It was an open label, single center, prospective, clinical study conducted in 36 patients of OA Knee. Two capsules of 'TLPL/AY/03/2008' were given to all patients twice daily orally after meals for 180 days. **Results:** Data describing quantitative measures are expressed as mean  $\pm$  SD. Comparison of variables representing categorical data was performed using Chi-square test. The mean joint pain (as assessed on VAS) reduced significantly (59.85%;  $P < 0.05$ ) and the mean WOMAC combined score, WOMAC pain sub-score, WOMAC stiffness sub-score, and WOMAC difficulty sub-score also reduced significantly at the end of the study. The mean time taken by the patients to walk 50 feet too, was reduced significantly (25.26%) at the end of the study. At the end of 4 months of the treatment, no patient needed paracetamol as rescue medicine to control pain. Most of the patients had shown good overall improvement assessed by the physician and by the patients. Majority of the patients showed excellent tolerability to the study drug. No significant change in most of the safety laboratory parameters was observed at the end of the study. **Conclusion:** The study provides good evidence in support of the efficacy and safety of the 'TLPL/AY/03/2008' in OA of knee.

**Key words:** Efficacy, knee joint pain, osteoarthritis, polyherbal, quality of life, visual analogue scale, WOMAC osteoarthritis index

## INTRODUCTION

Osteoarthritis (OA) is a common, chronic, degenerative joint disorder characterized by joint pain, tenderness, limitation of movements, crepitus, occasional effusion, and variable degrees of local inflammation, without systemic manifestations.<sup>[1,2]</sup> The high prevalence rate, economic burden, and adverse implications on the quality of life

make OA a major public health issue.<sup>[3,4]</sup> The hypoxic conditions, elevation in the activities of proteolytic enzymes, biochemical stress, genetic factors, and trauma are main causes of OA. Obesity is a major risk factor for the disease affecting the knee.<sup>[1,4-6]</sup>

Currently, though pharmacological, mechanical, and surgical interventions are used, there is no known cure for OA.<sup>[7-9]</sup> Herbal remedies are widely used all over the world to treat the OA. Anti-arthritis herbs described in the Indian system of medicine are being used effectively in the management of the OA. Many permutations and combinations of the herbs mentioned in the classical texts of Indian system of medicine have been made and the formulations are being promoted as effective and safe remedies for the management of OA. Revalidation of the efficacy and safety of these formulations through clinical trials is a need of the hour.<sup>[10]</sup>

"TLPL/AY/03/2008" is an Ayurvedic proprietary polyherbal formulation, developed and manufactured by Tulip Lab Private Limited, India in capsule dosage form. The drug is approved by Food and Drug Administration, State of Maharashtra, India. All the herbs present in the

### Address for correspondence:

Dr. Sanjay U. Nipanikar, Department of Medical Services, R and D Center, Tulip Lab Pvt. Ltd., F-20/21, MIDC, Ranjangaon, Shirur, Pune - 412 220, India.  
E-mail: sanjay.n@tplindia.com

Received: 22-Aug-2012

Revised: 09-Nov-2012

Accepted: 19-Nov-2012

### Access this article online

Quick Response Code:



Website:

www.jaim.in

DOI:

10.4103/0975-9476.109549

formulation are being used for the treatment of OA since thousands of years. Anti-arthritis potential of individual herbs present in the formulation has been documented in many scientific studies.<sup>[11-26]</sup> The compositions of the drug are given in Table 1.

In acute oral toxicity study performed as per the Organization for Economic Co-operation and Development (OECD) guidelines for the testing of chemicals, "TLPL/AY/03/2008" was non-toxic up to and at 2000 mg/kg body weight and can be classified as globally harmonized system (GHS) category 5/unclassified according to the GHS for classification of chemicals. In repeated dose 90-day toxicity study, no observed adverse effect level of 'TLPL/AY/03/2008' when administered orally to Sprague Dawley rats for 90 consecutive days was found in 500 mg/kg body weight in males and 1000 mg/kg body weight in females. Based on the data available on "TLPL/AY/03/2008," a hypothesis was made that the drug is effective and safe in the treatment of OA. To test the hypothesis, the present clinical study was conducted.

## MATERIALS AND METHODS

### Study design

It was an open label, non-comparative, prospective, clinical study. The study protocol and related documents were reviewed and approved by institutional ethics committee at center for rheumatic diseases, 11, Hermes Elegance, 1988 Convent Street, Camp, Pune - 411 001, India. The study was conducted in accordance with Schedule "Y" of Drugs and Cosmetics Act, India, amended in 2005 and Indian Council of Medical Research (ICMR) ethical guidelines for biomedical research on human participants, adopted from World Medical Association (WMA)-Declaration of Helsinki.

### Primary and secondary outcome measures

Primary outcome measures of study were to evaluate efficacy of 'TLPL/AY/03/2008' in patients suffering from OA of knee by assessing knee joint pain on 100 mm visual

analogue scale (VAS), average change from baseline to the end of therapy visit using WOMAC pain sub-scale score, WOMAC physical function sub-scale score, and WOMAC stiffness sub-scale score. The secondary outcome measures were to evaluate the efficacy of 'TLPL/AY/03/2008' in patients with OA of the knee by assessing changes in the swelling of knee joint, global assessment for overall improvement by the physician and by the patient, and also to assess the safety of the drug on clinical as well as laboratory parameters such as liver function tests (LFT), renal function tests (RFT), lipid profile, Complete blood count (CBC), Erythrocyte sedimentation rate (ESR), Hemoglobin (Hb)%, and urine examinations.

### Sample size

The sample size calculation was based on the assumption that there will be decrease of 18.5% in Total WOMAC score from baseline to end of treatment. A sample size of 32 evaluable cases would provide an 80% power to estimate the reduction of total WOMAC score at 5% level of significance at the end of the study. Anticipating 25% dropouts, we enrolled 40 subjects to get 32 evaluable cases at the end of the study.

### Inclusion criteria

Subjects of both sexes of age group between 40 years and 70 years (both inclusive), having symptoms of OA for minimum 6 months and maximum 5 years (confirmed by radiographs and diagnosed as per American college of rheumatology (ACR) diagnostic Criteria for OA of the knee), and subjects without any knee joint deformity and having VAS pain score  $\geq 40$  mm on weight bearing activities were included in the study. All the patients included in the study were allowed to take paracetamol up to 2 g/day as a rescue medication in case of severe joint pain.

### Exclusion criteria

The patients having rheumatoid arthritis, gout, pseudo-gout, inflammatory arthritis, Paget's disease of bone, chronic pain syndrome, fibromyalgia, other major joint disorders, and patients having history of arthroscopy or major trauma to the joint in the previous 6 months before the screening visit were not included in the study. Patients requiring knee arthroplasty within 6 months of screening or anticipating any need for a surgical procedure on the index knee joint during the study were excluded. The patients with signs of clinically important active inflammation of knee joint at the screening visit and/or baseline visits were excluded. Patients taking any other investigational drug were not included in the study. The patients who were on systemic corticosteroids for past 2 months from screening visit or patients who used intra-articular visco-supplementation for the past 3 months from screening visit were excluded. The patients having major diseases, pregnant and lactating

**Table 1: Composition of investigational drug, i.e., 'TLPL/AY/03/2008' (each capsule contains extracts)**

| Ingredients | Botanical name                 | Quantity (mg) |
|-------------|--------------------------------|---------------|
| Kundur      | <i>Boswellia serrata</i>       | 130           |
| Guggulu     | <i>Commiphora mukul</i>        | 100           |
| Ashwagandha | <i>Withania somnifera</i>      | 75            |
| Nirgundi    | <i>Vitex negundo</i>           | 75            |
| Eranda      | <i>Ricinus communis</i>        | 60            |
| Parijata    | <i>Nyctanthes arbortristis</i> | 50            |
| Shunthi     | <i>Zingiber officinale</i>     | 15            |
| Excepients  | -                              | qs            |

Quantity sufficient (qs)

mothers, and persons having known hypersensitivity to ingredients used in study drug were excluded.

### Study procedures

On screening visit, patient's voluntary written informed consent was taken and general and systemic examinations were done. Patient's blood and urine samples were collected and sent to the laboratory for investigations viz., CBC, Hb%, ESR, Random Blood Sugar level, Rheumatoid factor, Anti-streptolysin O (ASO) Titer, C-reactive protein (CRP), Serum Calcium, RFTs, LFTs, Lipid Profile, Urine examination, HIV-I and II, and Urine Pregnancy Test (in Female Subjects). The diagnosis of OA knee joint was confirmed by clinical evaluation and radiographs of knee joint (ACR diagnostic Criteria for diagnosis of OA Knee).<sup>[27]</sup> Wash out period of 3 days was given and during wash out period and the entire study period, all patients were advised to refrain from Non-steroidal anti-inflammatory drugs (NSAIDs) or any other topical or systemic analgesics (except paracetamol up to 2 g/day).

On baseline visit, 40 patients were enrolled, who met the inclusion and exclusion criteria. All enrolled subjects were assigned in a single group and were given 'TLPL/AY/03/2008' a polyherbal formulation in a dose of 2 capsules twice daily orally after meals for 180 days. Recruited patients were advised to carry on their daily activities and exercises that they had been doing before the enrollment and also advised to continue the same till the end of study period. Patient's pain (preceding 48 h during weight bearing activities) was recorded on 100 mm VAS. WOMAC Index (Version Likert 3.0) containing 24 questions (Q) was used to grade pain (Q. 1-5), stiffness (Q. 6-7), and physical function difficulty (Q. 8-24) pertaining to the knee joint. The patient's answers were graded on a quantitative scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = extreme). The maximum possible WOMAC score was 96 (pain = 20, stiffness = 8, and difficulty = 68). The source WOMAC was modified for Indian use and validated primarily through a consensual approach and pilot testing in the community and patients before this trial by the principal investigator. The knees were examined for the swelling/synovitis (grades: 0 = none, 1 = detectable synovial thickening without loss of bony contours, 2 = synovial thickening with loss of bony contours, and 3 = bulging synovial proliferation with cystic characteristics). On baseline visit and on every follow-up visit (except 6<sup>th</sup> visit), patients were provided with two containers each containing 70 Capsules of 'TLPL/AY/03/2008' for 1-month duration (120 capsules for 30 days and 20 additional capsules for delayed follow-up, maximum by 5 days). Patients were advised to return empty containers on every follow-up visit in order to check drug compliance.

### Follow-up assessment

Patients were called for follow-up visits on day 30 (Visit 1), day 60 (Visit 2), day 90 (Visit 3), day 120 (Visit 4), day 150 (Visit 5), and day 180 (Visit 6). On each follow-up visit, patient's general and systemic physical examinations were done. Assessment of the symptoms of OA was done on VAS and WOMAC OA index. Global assessment of overall efficacy of the study treatment was also done by the investigator and by the patient on every follow-up visit. Laboratory investigations (CBC, Hb%, ESR, RFTs, LFTs, Lipid Profile, and Urine examination) were repeated on 3<sup>rd</sup> and 6<sup>th</sup> visits. Drug tolerability was assessed by the patient and by the investigator on day 180.

### Statistical analysis

Consultant statistician performed the analysis of the data using statistical software SPSS 10.0. Data describing quantitative measures are expressed as median or mean  $\pm$  SD or SE or the mean with range. Qualitative variables are presented as counts and percentage. Comparison of variables representing categorical data was performed using Chi-square test. All *P* values are reported based on two-sided significance test and all the statistical tests are interpreted at 5% level of significance.

## RESULTS

Out of 40 patients included in the study, 11 (27.5%) were males, whereas 29 (72.5%) were females. The mean age of patients was  $57.35 \pm 10.58$  years. Out of 40 recruited patients, 36 completed the study, whereas 4 subjects dropped out prematurely due to their personal reasons (other than the adverse events). All the 36 patients, who completed the study, had shown good compliance to the study medicine.

No significant change from baseline to end of therapy values in any of the vital signs (pulse rate, body temperature, respiratory rate, and systolic and diastolic blood pressure), appetite, and body weight was observed. At the end of the treatment (180 days), a statistically significant improvement in the sleep pattern was observed; all the patients had sound sleep.

At baseline visit, the mean knee joint pain score assessed on VAS was  $51.89 \pm 07.85$ . The mean knee joint pain score (VAS) reduced significantly from baseline to  $43.71 \pm 09.06$  (15.8%) after 1-month treatment with "TLPL/AY/03/2008." The mean pain score further reduced significantly from baseline to  $38.14 \pm 08.60$  (26.5%),  $35.22 \pm 10.71$  (32.12%),  $31.25 \pm 11.47$  (39.77%), and  $24.79 \pm 09.86$  (52.22%) on days 60, 90, 120, and 150, respectively. At the end of the treatment, the mean knee joint pain score reduced significantly from baseline to  $20.83 \pm 08.35$  (59.85%) [Figure 1].

At baseline visit, the mean WOMAC combined score was  $35.38 \pm 11.21$ , which was reduced significantly to  $13.56 \pm 06.89$  (61.67%) at end of the study. The mean WOMAC pain sub-score reduced significantly from baseline value  $08.56 \pm 02.78$  to  $03.13 \pm 01.96$  (63.43%) at the end of the study. The mean WOMAC stiffness sub-scores reduced significantly from baseline value  $02.81 \pm 01.72$  to  $00.75 \pm 00.77$  (73.3%) at the end of the study. At baseline visit, the mean WOMAC difficulty sub-score was  $24.00 \pm 08.3$ , which was reduced significantly from baseline value to  $09.69 \pm 04.78$  (59.6%) at the end of the study [Figures 2-5].

At baseline visit, the mean time taken by the patients to walk 50 feet was  $16.31 \pm 01.70$  s. The mean time to walk 50 feet was reduced significantly from baseline value to  $12.19 \pm 02.04$  (25.26%) s at the end of the study [Figure 6].

At baseline visit, 19 (52.8%) out of 36 patients used paracetamol as rescue medicine for pain management. From day 120 onwards till the end of the study, no single subject used paracetamol as a rescue medication [Table 2].

As per the global assessment for overall improvement done by the physician, 18 (50%) patients had good improvement,

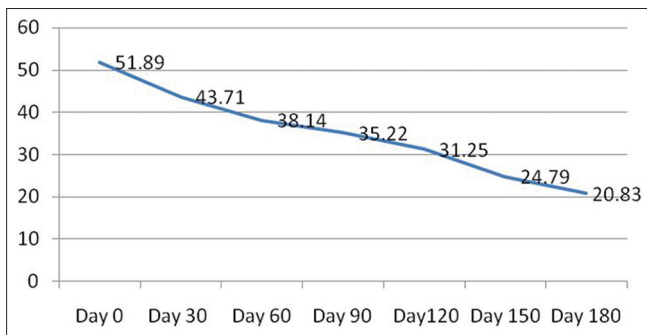
whereas 18 (50%) patients had satisfactory improvement at the end of the study. As per the global assessment for overall improvement done by the patient, 23 (63.9%) patients had good improvement, whereas 13 (36.1%) patients had satisfactory improvement at the end of the study.

As per the global assessment of drug tolerability done by the physician, no adverse events (Excellent tolerability) were reported in 29 (80.5%) patients [Table 3].

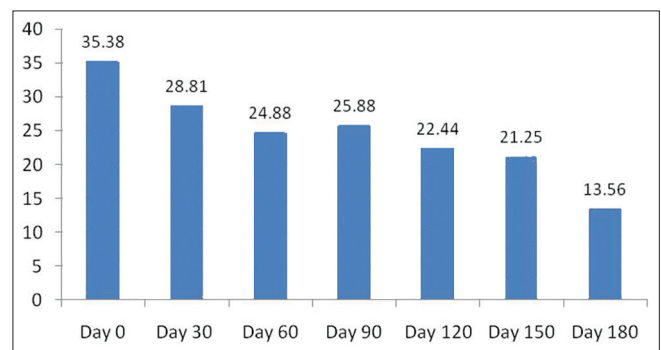
**Adverse effects**

As per the global assessment of drug tolerability done by the patient, no adverse events were reported in 27 (75%) patients, mild adverse events were reported in 8 (22.2%) patients such as insomnia, proctitis, reduced appetite, which subsided without medication, and one patient (2.8%) had experienced mild to moderate adverse event (mouth ulcer), which subsided with medication and did not necessitate stoppage of study medication. According to the study physician, casual relationship between adverse events and the study drug was not established.

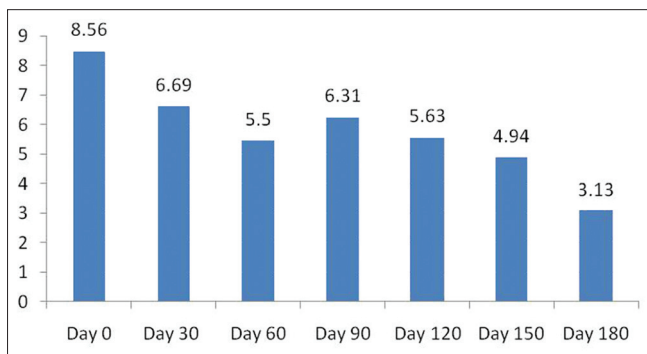
At baseline visit, the mean value of total cholesterol in study patients was  $147.31 \pm 33.69$ , which was increased



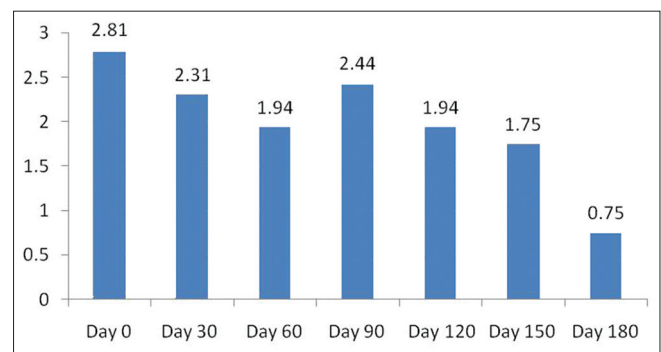
**Figure 1:** Changes in the mean knee joint pain assessed on visual analogue scale



**Figure 2:** Changes in the mean WOMAC combined score



**Figure 3:** Changes in the mean WOMAC Pain sub-score



**Figure 4:** Changes in the mean WOMAC Stiffness sub-score

**Table 2: Assessment of the rescue medication (paracetamol) used (n=36)**

| Duration            | Screening visit | Day 0 to 30 | Day 30 to 60 | Day 60 to 90 | Day 90 to 120 | Day 120 to 150 | Day 150 to 180 |
|---------------------|-----------------|-------------|--------------|--------------|---------------|----------------|----------------|
| Number of cases (%) | 19 (52.8)       | *04 (11.1)  | *02 (05.6)   | *01 (02.8)   | - (-)         | - (-)          | - (-)          |

\*P<0.05 significant by Chi-square test



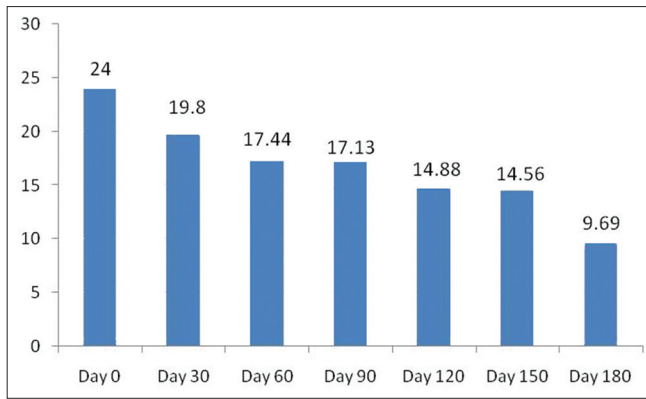


Figure 5: Changes in the mean WOMAC difficulty sub-score

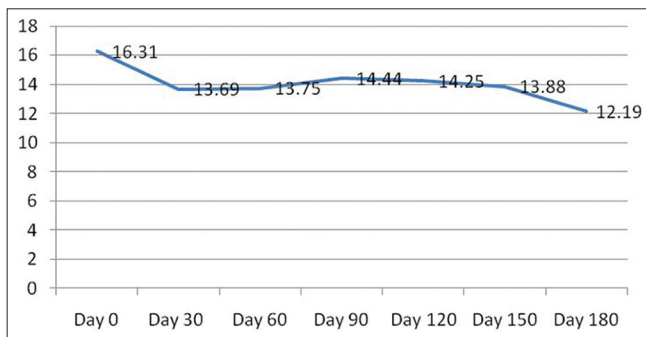


Figure 6: Changes in the mean time (s) taken to walk 50 feet distance

Table 3: Global assessment of drug tolerability done by the physician and by the patient

| Tolerability | Number of cases (n=36)          |                               |
|--------------|---------------------------------|-------------------------------|
|              | Assessment by the physician (%) | Assessment by the patient (%) |
| Excellent    | 29 (80.5)                       | 27 (75.0)                     |
| Good         | 06 (16.7)                       | 08 (22.2)                     |
| Fair         | 01 (02.8)                       | 01 (02.8)                     |
| Poor         | -                               | -                             |

significantly to  $191.72 \pm 49.93$  at the end of the study. The mean low density lipoprotein (LDL) cholesterol value at baseline was  $74.89 \pm 34.71$ , which was also increased significantly to  $115.64 \pm 24.65$  at the end of the study. The mean very low density lipoprotein (VLDL) value at baseline was  $26.56 \pm 11.84$ , which was increased to  $31.19 \pm 9.45$  (statistically not significant) at the end of the study. Though there was increase in total cholesterol, LDL, and VLDL values after treatment, the increased values at the end of the treatment were within normal limits (clinically insignificant).

The mean serum alkaline phosphate value at the beginning of the trial was  $148.97 \pm 53.15$ , which was increased significantly to  $189.25 \pm 61.03$  at the end of the study. After 1 month post-study period, the value again came down to  $156.85 \pm 53.35$ . No significant changes in rest of

the safety laboratory investigations were observed at the end of the study.

## DISCUSSION

In this clinical study, 6-month treatment with 'TLPL/AY/03/2008' significantly decreased the mean joint pain score (assessed on VAS). On day 90, slight increase in WOMAC combined score, all the three WOMAC sub-scales, and 50 feet walking time were observed from last follow-up visit (i.e., day 60), but when compared to baseline values, these values reduced on day 90. At the end of the study, WOMAC combined score, all the three WOMAC sub-scales, and 50 feet walking time decreased significantly from their baseline values. We are unable to explain the slight increase in these scores on day 90. A detailed experimental study can be planned to know the precise reason behind it.

The need of rescue medicine for pain management was reduced as study progressed. These findings highlighted that 'TLPL/AY/03/2008' reduced joint pain and joint stiffness and improved physical function in patients suffering from OA knee. Most of the patients had shown good overall improvement as per the assessment of the overall improvement done by the physician and by patient himself/herself. No patient reported the worsening of any sign or symptom of the OA knee during and at the end of the study.

The results of this clinical study are in line with the results of the earlier clinical studies conducted on Ayurvedic Proprietary Medicines for various types of OA more or less similar (with respect to the ingredients used in the formulation) to "TLPL/AY/03/2008".<sup>[10-11,28-32]</sup> The formulation "TLPL/AY/03/2008" was developed by Tulip Lab Private Limited, containing seven herbal ingredients, which are being used since antiquity for the treatment of various types of arthritis. The formulation was developed keeping in mind that synergistic action of the seven ingredients will lead to a better formulation for the management of arthritis. Majority of the ingredients in 'TLPL/AY/03/2008' have anti-inflammatory and analgesic activities.<sup>[11-18,20-21,23,33]</sup> Plants such as *Nyctanthes arbortristis*, *Withania somnifera*, and *Boswellia serrata* possess immunomodulatory activity.<sup>[14,23-24]</sup> Plants also reported anti-oxidant activity,<sup>[18,20,25]</sup> chondroprotective activity,<sup>[25,34]</sup> and anti-pyretic activity.<sup>[20]</sup> It was observed from results of this clinical study that the synergistic effect of the herbs present in the formulation has contributed to the overall anti-inflammatory and analgesic activities of the formulation "TLPL/AY/03/2008".

In acute and sub-chronic (90 days) toxicity studies, we demonstrated that 'TLPL/AY/03/2008' is safe and non-toxic in rats. In this clinical study, according to the global assessment of drug tolerability assessed by the physician, 97.2% subjects had feeling of good to excellent tolerability of drug, whereas 2.8% of the subjects had fair tolerability. The similar outcomes, as that of global assessment of tolerability assessed by the physician, were observed by subjects also. One subject had proctitis which was mild to moderate in nature and resolved after treatment. Mild to moderate mouth ulcer was observed in one subject, which also resolved after treatment. A significant increase over baseline to end of the study value was observed in safety laboratory parameters, such as serum alkaline phosphatase, total cholesterol, LDL cholesterol, and VLDL. Though there was significant increase in the above-mentioned values post-treatment, the increased values were within normal limits. To check whether the increase in the serum alkaline phosphatase continues even after the stoppage of the treatment, we performed serum alkaline phosphatase in most of the cases 1 month after discontinuation of the treatment. It was observed that serum alkaline phosphatase value came down near to its baseline value. Taken together, these observations further demonstrate that 'TLPL/AY/03/2008' is safe in the treatment of OA in humans.

It is evident from the data that total cholesterol, LDL, VLDL, and serum alkaline phosphatase values increased at the end of the study treatment. After reviewing literature on the individual ingredient of the formulation, it is observed that most of the ingredients possess hypolipidemic activity. Also majority of the herbs present in the formulation have hepatoprotective activity. In spite of having hypolipidemic and hepatoprotective herbs in the formulation, post-treatment increase in TC, LDL, VLDL, and serum alkaline phosphatase values cannot be explained with the available data. Clinical studies in large population and experimental studies on the formulation are needed to find out the suitable answers for the same. This study also lacks in ruling out the "placebo effect."

The sample size on which the drug has been tested though enough to show statistically significant effect, but a randomized, double blind, multi-centric clinical study with large sample size to evaluate the efficacy and safety of 'TLPL/AY/03/2008' is indicated.

## CONCLUSION

In summary, this study provides the evidence in support of the potential efficacy and safety of the herbal formulation 'TLPL/AY/03/2008' in subjects suffering from OA of

knee. Six months of treatment with 'TLPL/AY/03/2008' significantly reduced joint pain, improved joint function and mobility in subjects suffering from OA knee. Hence, it can be concluded that the 'TLPL/AY/03/2008' is a safe and effective for treatment of OA.

## ACKNOWLEDGMENT

The authors sincerely thank Mr. Kailas Gandewar, Biostatistician, Soham Consultancy, Dadar, Mumbai for his kind help in sample size calculation and data analysis for the study. The authors sincerely thank to Dr. Vijayanti V. Lagu-Joshi, MD, Consulting Rheumatologist, Center for Rheumatic Diseases (CRD) for her contribution in the trial. The authors also thank to Dr. Anuradha Venugopalan, incharge, R and D Lab, CRD and the team for doing the investigations of all the patients in time.

## REFERENCES

1. Mahajan A, Verma S, Tandon V. Osteoarthritis. *J Assoc Physicians India* 2005;53:634-41.
2. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, *et al.* Guidelines for the medical management of osteoarthritis. Part I. Osteoarthritis of the hip. *American College of Rheumatology. Arthritis Rheum* 1995;38:1535-40.
3. Felson DT, Lawrence RC, Hochberg MC, McAlindon T, Dieppe PA, Minor MA, *et al.* Osteoarthritis: New insights. Part 2: Treatment approaches. *Ann Intern Med* 2000;133:726-37.
4. Peat G, Duncan RC, Wood LR, Thomas E, Muller S. Clinical features of symptomatic patellofemoral joint osteoarthritis. *Arthritis Res Ther* 2012;14:R63.
5. Holderbaum D, Haqqi TM, Moskowitz RW. Genetics and osteoarthritis: Exposing the iceberg. *Arthritis Rheum* 1999;42:397-405.
6. Felson DT, Neogi T. Osteoarthritis: Is it a disease of cartilage or of bone? *Arthritis Rheum* 2004;50:341-4.
7. Papaioannou NA, Triantafillopoulos IK, Khaldi L, Krallis N, Galanos A, Lyrithis GP. Effect of calcitonin in early and late stages of experimentally induced osteoarthritis. A histomorphometric study. *Osteoarthr Cartilage* 2007;15:386-95.
8. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, *et al.* Osteoarthritis: New insights. Part 1: The disease and its risk factors. *Ann Intern Med* 2000;133:635-46.
9. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, *et al.* Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. *American College of Rheumatology. Arthritis Rheum* 1995;38:1541-6.
10. Chopra A, Lavin P, Patwardhan B, Chitre D. A 32-week randomized, placebo-controlled clinical evaluation of RA-11, an Ayurvedic drug, on osteoarthritis of the knees. *J Clin Rheumatol* 2004;10:236-45.
11. Sharma JN, Sharma JN. Comparison of the anti-inflammatory activity of *Commiphora mukul* (an indigenous drug) with those of phenylbutazone and ibuprofen in experimental arthritis induced by mycobacterial adjuvant. *Arzneimittelforschung* 1977;27:1455-7.
12. Manjula N, Gayathri B, Vinaykumar KS, Shankernarayanan NP, Vishwakarma RA, Balakrishnan A. Inhibition of MAP kinases by crude extract and pure compound isolated from *Commiphora mukul* leads to down regulation of TNF-alpha, IL-1beta and IL-2. *Int Immunopharmacol* 2006;6:122-32.
13. Francis JA, Raja SN, Nair MG. Bioactive terpenoids and guggulsteroids from *Commiphora mukul* gum resin of potential

- anti-inflammatory interest. *Chem Biodivers* 2004;1:1842-53.
14. Banno N, Akihisa T, Yasukawa K, Tokuda H, Tabata K, Nakamura Y, *et al.* Anti-inflammatory activities of the triterpene acids from the resin of *Boswellia carteri*. *J Ethnopharmacol* 2006;107:249-53.
  15. Ammon HP. Boswellic acids in chronic inflammatory diseases. *Planta Med* 2006;72:1100-16.
  16. Das S, Sasmal D, Basu SP. Anti-inflammatory and antinociceptive activity of arbortrioside-A. *J Ethnopharmacol* 2008;116:198-203.
  17. Saxena RS, Gupta B, Saxena KK, Singh RC, Prasad DN. Study of anti-inflammatory activity in the leaves of *Nyctanthes arbor tristis* Linn. – An Indian medicinal plant. *J Ethnopharmacol* 1984;11:319-30.
  18. Ilavarasan R, Mallika M, Venkataraman S. Anti-inflammatory and free radical scavenging activity of *Ricinus communis* root extract. *J Ethnopharmacol* 2006;103:478-80.
  19. Ojewole JA. Analgesic, antiinflammatory and hypoglycaemic effects of ethanol extract of *Zingiber officinale* (Roscoe) rhizomes (Zingiberaceae) in mice and rats. *Phytother Res* 2006;20:764-72.
  20. Dharmasiri MG, Jayakody JR, Galhena G, Liyanage SS, Ratnasooriya WD. Anti-inflammatory and analgesic activities of mature fresh leaves of *Vitex negundo*. *J Ethnopharmacol* 2003;87:199-206.
  21. Saxena RS, Gupta B, Saxena KK, Srivastava VK, Prasad DN. Analgesic, antipyretic and ulcerogenic activity of *Nyctanthes arbor tristis* leaf extract. *J Ethnopharmacol* 1987;19:193-200.
  22. Singh BB, Mishra LC, Vinjamury SP, Aquilina N, Singh VJ, Shepard N. The effectiveness of *Commiphora mukul* for osteoarthritis of the knee: An outcomes study. *Altern Ther Health Med* 2003;9:74-9.
  23. Rasool M, Varalakshmi P. Immunomodulatory role of *Withania somnifera* root powder on experimental induced inflammation: An *in vivo* and *in vitro* study. *Vascul Pharmacol* 2006;44:406-10.
  24. Puri A, Saxena R, Saxena RP, Saxena KC, Srivastava V, Tandon JS. Immunostimulant activity of *Nyctanthes arbor-tristis* L. *J Ethnopharmacol* 1994;42:31-7.
  25. Rasool M, Varalakshmi P. Protective effect of *Withania somnifera* root powder in relation to lipid peroxidation, antioxidant status, glycoproteins and bone collagen on adjuvant-induced arthritis in rats. *Fundam Clin Pharmacol* 2007;21:157-64.
  26. Nurtjahja-Tjendraputra E, Ammit AJ, Roufogalis BD, Tran VH, Duke CC. Effective anti-platelet and COX-1 enzyme inhibitors from pungent constituents of ginger. *Thromb Res* 2003;111:259-65.
  27. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al.* Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986;29:1039-49.
  28. Singh D, Aggarwal A, Maurya R, Naik S. *Withania somnifera* inhibits NF-kappaB and AP-1 transcription factors in human peripheral blood and synovial fluid mononuclear cells. *Phytother Res* 2007;21:905-13.
  29. Srivastava RN, Sharma VD, Kolhapure SA. Evaluation of the clinical efficacy and safety of rumalaya forte and glucosamine and chondroitin combination, in patients suffering from osteoarthritis of the knee. *Med Update* 2005;12:43-50.
  30. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)* 2006;45:50-2.
  31. Mathur HH, Khurana A, Mathur D, Kolhapure SA. Evaluation of the efficacy and safety of JT-2000\* in Osteoarthritis: A comparative clinical trial. *Med Update* 2004;11:31-7.
  32. Chopra A, Lavin P, Patwardhan B, Chitre D. Randomized double blind trial of an ayurvedic plant derived formulation for treatment of rheumatoid arthritis. *J Rheumatol* 2000;27:1365-72.
  33. Paul BN, Saxena AK. Depletion of tumor necrosis factor-alpha in mice by *Nyctanthes arbor-tristis*. *J Ethnopharmacol* 1997;56:153-8.
  34. Sumantran VN, Kulkarni A, Boddul S, Chinchwade T, Koppikar SJ, Harsulkar A, *et al.* Chondroprotective potential of root extracts of *Withania somnifera* in osteoarthritis. *J Biosci* 2007;32:299-307.

**How to cite this article:** Nipanikar SU, Saluja M, Kuber VV, Kadbhane KP, Chopra A, Khade NR. An open label, prospective, clinical study on a polyherbal formulation in osteoarthritis of knee. *J Ayurveda Integr Med* 2013;4:33-9.

**Source of Support:** The clinical study was funded by Tulip Lab Pvt. Ltd. Also, the study drug was manufactured and supplied by Tulip Lab Pvt. Ltd., **Conflict of Interest:** The authors 1 and 3 are the employees of sponsor company and the author 4 is a former employee of the sponsor company i.e., Tulip Lab Pvt. Ltd. The authors 2, 5 and 6 have no conflicts of interest.

## Staying in touch with the journal

### 1) Table of Contents (TOC) email alert

Receive an email alert containing the TOC when a new complete issue of the journal is made available online. To register for TOC alerts go to [www.jaim.in/signup.asp](http://www.jaim.in/signup.asp).

### 2) RSS feeds

Really Simple Syndication (RSS) helps you to get alerts on new publication right on your desktop without going to the journal's website. You need a software (e.g. RSSReader, Feed Demon, FeedReader, My Yahoo!, NewsGator and NewzCrawler) to get advantage of this tool. RSS feeds can also be read through FireFox or Microsoft Outlook 2007. Once any of these small (and mostly free) software is installed, add [www.jaim.in/rssfeed.asp](http://www.jaim.in/rssfeed.asp) as one of the feeds.