

## Original Research Article

# Effect of Nucart VG (*Boswellia serrata* in combination with veg glucosamine sulphate) in comparison with glucosamine sulphate to improve quality of life of knee osteoarthritis patients: a randomized controlled trial

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## ABSTRACT

**Background:** *Boswellia serrata* has been proved to be an effective and safe herb for the treatment of osteoarthritis (OA). This study aims at assessing the synergistic effect of this herb with vegetarian glucosamine sulphate, a nutritional supplement, on knee osteoarthritis using quality of life indicators.

**Methods:** This was an open label, parallel group randomized trial of 12-week duration. Sixty-six subjects were equally randomized to two treatment arms: *Boswellia serrata* extract (600 mg) and glucosamine (750 mg) [Nucart VG]; and glucosamine sulphate (market comparator) 750 mg. Patients were administered 1 tablet twice-a-day post-meal for three months. Efficacy of treatment was measured on primary end-points like EuroQol-5D (EQ-5D) (health status indicator), visual analogue scale (VAS) and Western Ontario and McMaster Universities osteoarthritis index (WOMAC) scale (pain indicators), while safety was measured in terms of vital parameters. Both intention-to-treat (ITT) and per-protocol (PP) analyses were performed for comparing scores between the two groups.

**Results:** The baseline characteristics of patients between two groups were insignificantly different ( $p > 0.05$ ). In ITT analysis, the health status (EQ-5D score) of patients in Nucart VG group improved significantly than the comparator group at follow up 2 ( $p = 0.037$ ) and showed further improvement at follow up 3 ( $p = 0.012$ ). The pain indicators i.e. VAS and WOMAC scores were significantly lower in Nucart VG group right from follow up 1 till follow up 3 ( $p < 0.05$ ). Similar were the observations during PP analysis.

**Conclusions:** Nucart VG is beneficial for the treatment of mild to moderate knee OA, as inferred from the functional and health status assessment.

**Keywords:** *Boswellia serrata*, glucosamine sulphate, EQ-5D, VAS, WOMAC

## INTRODUCTION

Osteoarthritis (OA) is the most prevalent chronic rheumatic disease that causes pain and disability in adult individuals. It is the clinical and pathological outcome of a sequence of disorders that leads to structural and functional non-performance of synovial joints.<sup>1</sup> Usually,

OA increases slowly, typically in the middle-aged to elderly people. The cartilage between the bones in the joint breaks down, which causes the affected bones to slowly get bigger. The joint cartilage often breaks down due to mechanical stress or biochemical changes in the body, resulting the bone underneath to fail. OA can occur in conjunction with other types of arthritis such as gout or

rheumatoid arthritis. The prevalence of OA is 22% to 39% in India, and it is the most common rheumatologic problem and frequent joint disease.<sup>2,3</sup> The risk of developing OA increases dramatically with age, and it is more frequent in females compared to males.<sup>2,4,5</sup> Almost, 45% of females show symptoms and 70% of them have the radiological evidence.<sup>4,6</sup> The OA treatment usually aims at reducing the pain and improving the mobility in patients. Although there is no cure for the disease, some treatment strategy attempts to slow the disease progression. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for the treatment of pain and inflammation caused by the disease. However, long term use of NSAIDs shows adverse effect on kidneys, gastrointestinal and cardiovascular organs of patients.<sup>7-9</sup> Thus, clinicians are constantly in search of more effective treatment options other than NSAIDs, to reduce the pain and inflammation in OA with more bearable side effects. Many patients opt for dietary supplements as they are safer long term alternative for the treatment.<sup>10</sup>

*Boswellia serrata* has been found to be efficacious in the treatment of inflammatory disorders, especially arthritis. Further, glucosamine is a natural compound and found in healthy cartilage of human body, specifically in fluid around the joints. It is present in several chemical forms, but the most common is glucosamine sulphate, which is used in the treatment of OA. Various clinical trials and meta-analysis have shown that glucosamine sulphate has good effect in treating the symptoms and maintain a long term safety profile in patients in place of NSAIDs.<sup>11-15</sup> It is beneficial in increasing the proteoglycan and collagen synthesis, thereby improving the cartilage health. Nucart VG, a test drug, is a combination of *B. serrata* and glucosamine sulphate and till date no study showing the synergistic effect of these two ingredients has been reported. As the pathophysiology of OA is a combination of mechanical, cellular and biochemical processes, the interconnection of synergistic combination of phytomedicine and nutraceutical may result into a better improvement and correction of degenerative changes in articular cartilage.

Thus, the objective of study is to evaluate the efficacy and safety of this combination in reducing the joint stiffness, as well as maintaining and improving the joint health and functions in patients suffering from mild to moderate knee OA. An open-label randomized, comparative controlled trial was planned to test efficacy using EuroQol-5D (EQ-5D), visual analogue scale (VAS) and Western Ontario and McMaster Universities osteoarthritis index (WOMAC) scoring systems, while the safety was measured in terms of vital parameters.

## METHODS

The study drug Nucart VG tablet was supplied by Gufic Bioscience Ltd. for clinical trial purpose that contains *Boswellia serrata* extract (600 mg) along with glucosamine (750 mg), distributed as combo pack of 60

tablets, and constituted one treatment arm. The other treatment arm constituted only glucosamine sulphate (market comparator) 750 mg tablet (a pack of 60 tablets).

### Study design

This was a randomized, open label, parallel group study of 12-week duration to assess the safety and efficacy of Nucart VG in comparison with glucosamine sulphate (750 mg) in the treatment of OA. The study was conducted during the period October 2019 to May 2020 at two centers namely PGIMER Chandigarh and Shatayu multispeciality hospital, Nagpur, India. During screening of subjects, routine laboratory tests, antero-posterior knee X-ray, physical and vital examinations, biochemistry were performed. The information about the concomitant medication was also sought. Concomitant medication like analgesics, muscle relaxant, antacids multivitamins and calcium supplements were administered to the patients during the study period.

### Inclusion criteria

Male and female (non-pregnant) aged 45 to 65 years with a clinical symptom of OA. Either unilateral or bilateral osteoarthritis for more than 3 months and symptoms for at least 6 months prior to screening. Patients with periarticular pain for 15 days of the preceding month.

### Exclusion criteria

Patients with recent injury in the area affected by OA of the knee (past 4 months) and expectation of surgery in the next 4 months. Patients with history of secondary OA, rheumatoid arthritis, grade IV OA, chronic inflammatory disease, hypersensitivity to non-steroidal anti-inflammatory drugs, abnormal liver or kidney function tests, history of peptic ulceration and upper gastrointestinal hemorrhage, congestive heart failure, hypertension, hyperkalemia and obesity were excluded. Also patients with history of gastrointestinal bleeding or peptic ulcer disease, hyperuricemia and/or past history of gout, major abnormal findings on complete blood count, history of coagulopathies, hematological or neurological disorders were excluded from the study.

### Efficacy and safety evaluations

#### Primary efficacy end points

EQ-5D score as a preference-based measure of health status, VAS and WOMAC scores measuring pain, stiffness and physical function. The measurements on these scales were obtained from baseline to follow up 3 on patients.

#### Safety end points

These included physical and vital examination parameters during each patient visit. The biochemical investigations at the end of study included: complete blood count (CBC),

serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), X-ray and rheumatoid arthritis (RA) factor.

#### *Study procedure and schedule*

A total of 82 patients were screened out of which 16 failed to meet the inclusion/exclusion criteria. The remaining 66 patients were enrolled in the study and randomized to one of the treatment arms in 1:1 ratio, following block randomization of size 4. In each group, patients were administered with the respective single tablet twice daily after meals, for 3 months. The patient did not undergo any special change in dietary habits, concomitant medication, lifestyle or exercise routine after being enrolled in the study, to avoid bias in the study intention. During the course of study, if patient suffered from any health issue, the medicine was administered after investigator's consultation and those records were maintained. The patient's visits were scheduled at day 0 (baseline), day 30 (follow up 1), day 60 (follow up 2) and day 90 (follow up 3). Moreover, telephonic assessments were done on day 15, day 45 and day 75 to ascertain the general wellbeing of patient. Each patient was asked for any adverse event (AE) or serious adverse event (SAE) experienced since last study visit. Last telephonic follow up to enquire about the incidence of adverse events was done 15 days after last visit. All the data were captured on hard copies (CRF) as well as on electronic data capturing system (eCRF system), following 21 CFR part 11 compliance. The drug dispensing and management was handled using an interactive web response system (IWRS). The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation and declaration of Helsinki (1975), as received in 2008. Informed consent was obtained from all the patient included in the study.

#### *Statistical analysis*

To determine the sample size, the success rate for the established glucosamine sulphate ranged from 48% to 55%. Assuming 55% success rate, a sample of 66 patients would be required to establish that the success rate prevails in the population with tolerable margin of 0.12 with type I error of 0.05 and type II error of 0.20.

The intention-to-treat (ITT) population was analyzed for efficacy endpoints, which consisted of all randomized patients, while per protocol (PP) population consisted of subset of ITT population attending all the follow ups and with observations on three efficacy endpoints. The safety population consisted of all patients receiving the allotted treatment. Categorical variables were expressed in terms of frequencies and percentages, while continuous parameters were summarized in terms of mean and standard deviation (SD). These descriptive statistics for various characteristics of patients were obtained at baseline and three follow-up visits in both the treatment arms. The continuous parameters were compared between

two arms using t-test for independent samples after ascertaining the normality assumption. The scores were compared using Mann-Whitney test for both ITT and PP populations. Also, the comparison of scores from baseline to each follow up time in each arm were performed using the same test. The categorical parameters like sex and OA grade were compared using Pearson's  $\chi^2$ -square test. All the statistical tests were two tailed and the level of significance was considered as 5%. The analyses were performed using statistical package for the social sciences (SPSS) version 20.0 (IBM Corp. ARMONK USA) software.

## **RESULTS**

Out of 82 screened patients, 16 patients could not fulfil one or more inclusion criteria, thus resulting into 66 eligible patients. After equal randomization in two treatment arms (33 each), there were 3 patients with loss to follow up in both the groups by the end of study (Figure 1).

#### *Demography and baseline clinical characteristics*

The mean age of ITT population in Nucart VG group was  $53.42 \pm 5.79$  years, while that of glucosamine sulphate group was  $55.61 \pm 6.12$  years, and the difference of means was statistically insignificant (Table 1). Further, the sex distribution in each group was also insignificantly different with female preponderance in both the groups. At baseline, body mass index (BMI) and all vital parameters were insignificantly different between two groups. The distribution of patients as per OA grades was also insignificantly different. Moreover, the score distributions were insignificantly different between the groups. Thus, both the treatment groups were matched with regard to demographic, vital parameters and score distributions.

#### *Efficacy analysis*

The ITT and PP analyses were performed on the health status score (EQ-5D), pain scores (VAS, WOMAC) and vital parameters. The physical examination parameters for all the patients were within normal limits at all the follow up times. Table 2 gives the comparison of primary efficacy end points between groups at each follow up for ITT population. The EQ-5D score distribution differed significantly at follow up 2 ( $p=0.037$ ) as indicated by higher mean in Nucart VG group compared to glucosamine sulphate group. The trend continued at follow up 3, with a higher score in Nucart VG group than glucosamine sulphate group ( $p=0.012$ ). The VAS scores were significantly lower in Nucart VG group as compared to glucosamine sulphate at follow up 1 ( $p=0.047$ ). Further, at follow up 2 and 3, the scores in Nucart VG group continued to be significantly lower than glucosamine sulphate group with p values 0.019 and 0.011 respectively. Similarly, the WOMAC scores in Nucart VG group were significantly lower than glucosamine sulphate group at follow up 1 ( $p=0.019$ ). Subsequently, at follow up 2 and 3, the scores in the former group continued to be significantly

lower than the later, with p value of 0.003 each. Also, Table 2 provides the comparison of safety endpoints between two groups at each follow up for ITT population. It is evident that all the vital parameters differed insignificantly between two groups at all the three follow up times ( $p > 0.05$ ).

The PP analysis was performed on 60 patients (30 from each group) with complete information on efficacy parameters at all the follow ups (Table 3). As regards score comparison, the EQ-5D scores were significantly higher in Nucart VG group than glucosamine sulphate group at follow up 2 ( $p = 0.032$ ). Further, at follow up 3, the scores continued to be significantly higher in former group as compared to later ( $p = 0.012$ ). The VAS scores in Nucart VG group were significantly lower than glucosamine sulphate group, as indicated by their respective mean values ( $p = 0.043$ ). At subsequent follow ups, the scores continued to be lower in Nucart VG group compared to glucosamine sulphate group, with p values 0.035 and 0.011 respectively.

On similar lines, WOMAC scores were also significantly lower in Nucart VG group than glucosamine sulphate group at follow up 1 ( $p = 0.014$ ). The trend continued in follow up 2 and 3 with low scores in former group than later with p values 0.006 and 0.003 respectively. Further, the table provides the comparison of safety endpoints; and it is evident that all the parameters were insignificantly different between two arms at all the three follow up times ( $p > 0.05$ ).

As regards EQ-5D score, in both Nucart VG and glucosamine sulphate groups, the difference between baselines to follow up 1 were statistically insignificant. However, in the Nucart VG group, the difference of scores

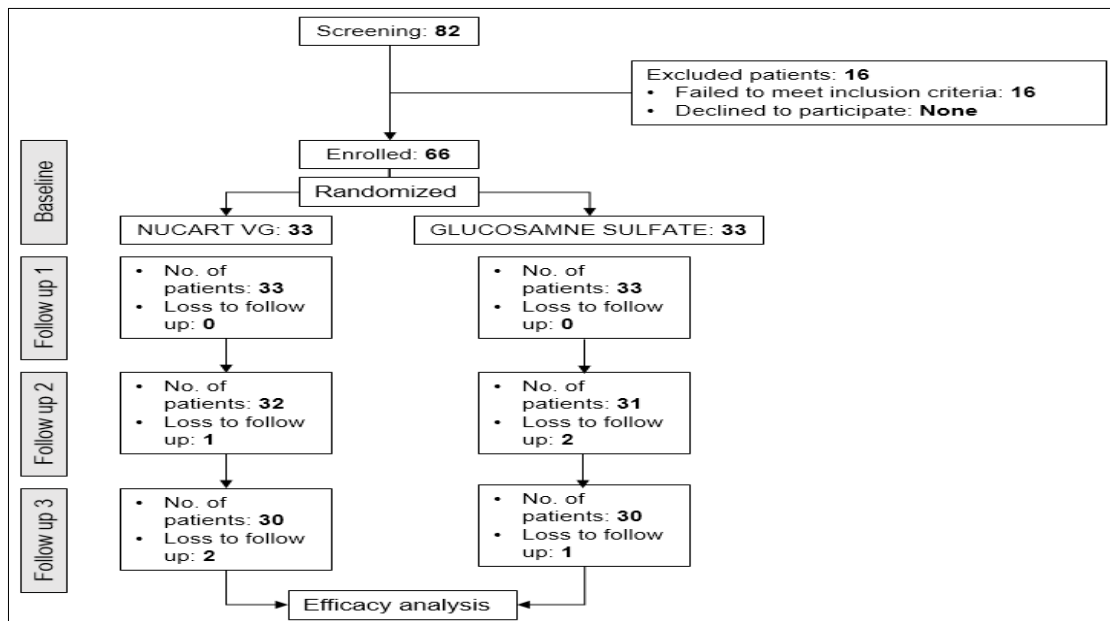
between baseline and follow up 2, as well baseline and follow up 3 were significant as indicated by p values 0.021 and 0.027 respectively. These differences were statistically insignificant in glucosamine sulphate group (Figure 2). The percent change of scores at follow up times with respect to baseline were obtained as shown graphically in Figure 3. In absolute sense, the reduction at follow up 3 in Nucart VG group was more (15.86%) than that of glucosamine sulphate group (7.54%).

The VAS scores showed significant lowering of scores at follow up 1, 2 and 3 with respect to baseline in both the study arms, as indicated by p values  $< 0.0001$  (Figure 2). However, percent change of scores from baseline revealed that the effect was more in Nucart VG group (38.14%) than glucosamine sulphate group (24.61%) at follow up 3 (Figure 3). On similar lines, the WOMAC scores at follow up times were significantly lower than baseline ( $p < 0.0001$ ) in both the groups (Figure 2). However, the percent change of scores from baseline showed that the effect was more in Nucart VG group (42.88%) as compared to glucosamine sulphate group (29.93%).

### Safety analysis

The safety endpoints viz. physical and vital parameters were assessed at all the follow up times and were within the normal limits for all the patients throughout the study period. Also, the comparison of biochemical parameters differed insignificantly between screening and end of study, especially in the Nucart VG group (data not shown).

Figure 2 provides the line plots for each scoring system in two groups according to time. The change of score from baseline to each follow up time point was tested for statistical significance with the results shown in Table 4.



All the drop outs from either group were due to COVID-19 pandemic and refused to visit hospital for further follow ups

**Figure 1: Sample flow in each treatment arm.**



**Table 1: Descriptive statistics for various patient characteristics in two treatment groups.**

Patient characteristics	Group		P value
	Nucart VG (n=33)	GS (n=33)	
Age in years (mean±SD)*	53.42±5.79	55.61±6.12	0.140
Sex N (%)‡			
Male	12 (36.4)	13 (39.4)	0.999
Female	21 (63.6)	20 (60.6)	
BMI (kg/m <sup>2</sup> )	23.2±1.98	23.6±2.01	0.312
BP diastolic (mmHg) (mean±SD)*	79.39±4.96	80.15±5.04	0.540
BP systolic (mmHg) (mean±SD)*	120.85±8.65	120.64±6.19	0.909
Heart rate (bpm) (mean±SD)*	78.52±6.38	78.15±3.63	0.777
Pulse rate (bpm) (mean±SD)*	78.52±6.38	78.15±3.63	0.777
Respiratory rate (per min) (mean±SD)*	18.73±1.26	18.67±1.31	0.849
OA grade (Kellgren and Lawrence classification)‡			
Grade II	13	18	0.3239
Grade III	20	15	
EQ-5D (mean±SD)‡	59.42±16.37	57.06±19.21	0.643
VAS pain (mean±SD)‡	6.82±1.01	6.94±1.03	0.712
WOMAC (mean±SD)‡	41.21±8.32	41.36±8.11	0.888

\*P value obtained using t-test for independent samples; ‡p values obtained using Wilcoxon rank sum test; †p value obtained using Pearson's Chi-square test; GS: glucosamine sulphate; and SD: standard deviation

**Table 2: Descriptive statistics for patient characteristics according to follow ups–intention to treat population.**

Patient characteristics (mean±SD)	Follow up 1			Follow up 2			Follow up 3		
	Nucart VG (n=33)	GS (n=33)	P value	Nucart VG (n=32)	GS (n=31)	P value	Nucart VG (n=30)	GS (n=30)	P value
<b>Primary end points‡</b>									
EQ-5D	63.09±9.59	59.85±14.28	0.552	67.59±8.94	61.45±12.24	0.037	69.17±7.67	63.2±9.57	0.012
VAS	5.82±0.92	6.33±1.08	0.047	5.19±1.38	6.03±1.56	0.019	4.33±1.15	5.3±1.8	0.011
WOMAC	30.97±5.18	34.55±6.29	0.019	27.72±5.38	32.13±7.13	0.003	23.8±6.85	29.27±6.98	0.003
<b>Safety end points*</b>									
BP diastolic (mmHg)	79.06±4.33	80.58±4.83	0.197	79.52±4.62	79.04±5.94	0.749	77.37±4.18	78.58±5.2	0.325
BP systolic (mmHg)	119.45±7.03	121.42±5.87	0.237	119.85±9.83	123.33±7.06	0.157	117.4±6.99	118.93±7.55	0.418
Heart rate (bpm)	77.73±3.88	77.85±4.85	0.607	76.7±2.97	76.58±2.87	0.884	75.93±3.53	77.3±3.05	0.114
Pulse rate (bpm)	77.73±3.88	77.85±4.85	0.607	76.7±2.97	76.58±2.87	0.884	75.93±3.53	77.3±3.05	0.114
Respiratory rate (/min)	18.94±1.37	18.94±1.39	0.844	18.81±1.49	18.63±1.13	0.615	19.13±1.33	18.97±1.03	0.590

‡P value obtained using Mann-Whitney test; \*p value obtained using t-test for independent samples; bold values indicate statistical significance; GS: glucosamine sulphate; SD: standard deviation

**Table 3: Descriptive statistics for patient characteristics according to follow ups – per protocol population.**

Patient characteristics (mean±SD)	Baseline			Follow up 1			Follow up 2			Follow up 3		
	Nucart VG (n=30)	GS (n=30)	P value	Nucart VG (n=30)	GS (n=30)	P value	Nucart VG (n=30)	GS (n=30)	P value	Nucart VG (n=30)	GS (n=30)	P value
<b>Primary end points‡</b>												
EQ-5D	59.7±17.11	58.77±19.35	0.844	63.76±9.72	61±14.47	0.395	67.93±8.92	61.83±12.26	0.032	69.17±7.67	63.2±9.57	0.012
VAS pain	7.00±0.83	7.03±1.03	0.891	5.93±0.87	6.45±1.07	0.043	5.23±1.41	6.07±1.57	0.035	4.33±1.15	5.3±1.8	0.011

Continued.

Patient characteristics (mean±SD)	Baseline			Follow up 1			Follow up 2			Follow up 3		
	Nucart VG (n=30)	GS (n=30)	P value	Nucart VG (n=30)	GS (n=30)	P value	Nucart VG (n=30)	GS (n=30)	P value	Nucart VG (n=30)	GS (n=30)	P value
<b>WOMAC</b>	41.67±7.65	41.77±8.28	0.961	30.97±4.41	34.6±6.49	0.014	27.4±5.04	32.03±7.23	0.006	23.8±6.85	29.27±6.98	0.003
<b>Safety end points*</b>												
<b>BP diastolic (mmHg)</b>	79.73±4.83	80.57±4.92	0.510	79.23±4.18	80.87±4.32	0.142	79.56±4.8	79.09±6.07	0.765	77.37±4.18	78.58±5.2	0.325
<b>BP systolic (mmHg)</b>	120.6±8.92	121.37±5.83	0.695	119.73±7.16	121.8±5.76	0.223	119.84±10.23	123.48±7.18	0.164	117.4±6.99	118.93±7.55	0.418
<b>Heart rate (bpm)</b>	77.97±5.29	77.9±3.67	0.955	77.7±4.04	77.07±4.89	0.587	76.52±4.8	76.61±2.93	0.918	75.93±3.53	77.3±3.05	0.114
<b>Pulse rate (bpm)</b>	77.97±5.29	77.9±3.67	0.955	77.7±4.04	77.07±4.89	0.587	76.52±4.8	76.61±2.93	0.918	75.93±3.53	77.3±3.05	0.114
<b>Respiratory rate (/min)</b>	18.6±1.25	18.53±1.31	0.841	18.83±1.39	18.83±1.42	0.999	18.72±1.51	18.57±1.12	0.691	19.13±1.33	18.97±1.03	0.590

‡P value obtained using Mann-Whitney test; \*p value obtained using t-test for independent samples; bold values indicate statistical significance; GS: glucosamine sulphate; SD: standard deviation

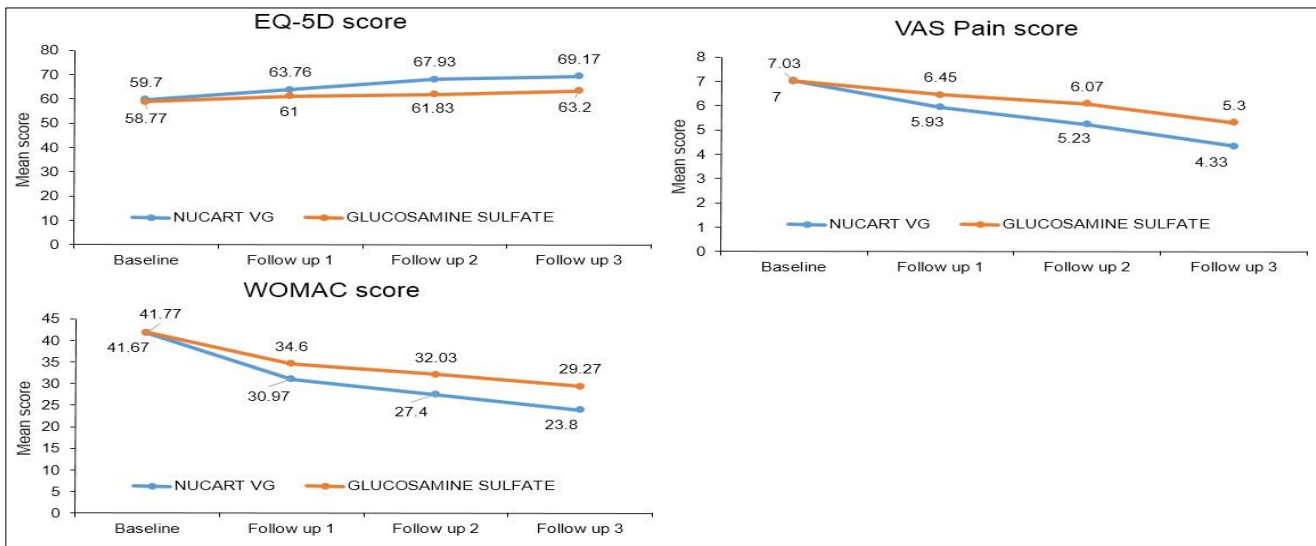


Figure 2: Line chart showing trend of various scores with time in two study groups (per protocol sample).

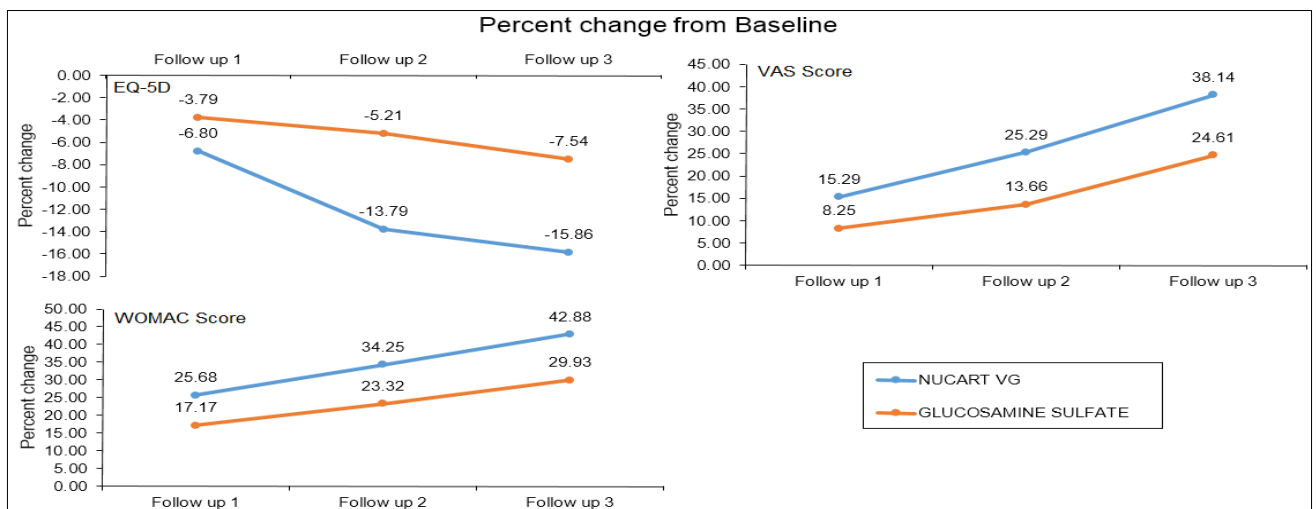


Figure 3: Line chart showing trend of percent change with time in two study groups (per protocol sample).

**Table 4: Probability values for comparison of scores between baseline and each follow up time in two treatment groups.**

Score	Comparison (baseline–follow-up)	Group	
		Nucart VG (n=30)	GS (n=30)
EQ-5D	1	0.151	0.126
	2	<b>0.021</b>	0.47
	3	<b>0.027</b>	0.417
VAS	1	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
	2	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
	3	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
WOMAC	1	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
	2	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
	3	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>

P values obtained using Mann-Whitney test; GS: glucosamine sulphate; bold values indicate statistical significance

## DISCUSSION

Osteoarthritis (OA) is one of the most common musculoskeletal disorders, affecting approximately 15% of the population. The condition is characterized by irreversible destruction of articular cartilage as well as bone erosion, and is triggered by pro-inflammatory cytokines such as IL-1, IL-6, and TNF- $\alpha$ . These mediators increase the synthesis of collagenase or matrix metalloproteinase (MMP) and degradation of collagen type II, as well as decrease the synthesis of collagenase inhibitors such as collagen and proteoglycans.

### *Boswellia serrata*

Due to serious side-effects encountered with standard drugs in OA, recent years have witnessed renewed interest in medicines of botanical origin. In an animal model of collagen-induced arthritis, an extract of *B. serrata* was shown to suppress pro-inflammatory mediators and enhance the levels of antioxidant enzymes. In a bovine serum albumin-induced arthritis model, oral or local administration of BAs had been associated with reduced infiltration of leucocytes into the knee joint and amelioration of the electrophoretic pattern of the synovial fluid proteins.<sup>16</sup>

Clinical evidence from double-blind, randomized, placebo-controlled studies conducted on patients with knee OA had revealed that *B. serrata* gum resin lowered pain and elevated functionality within a few days (a week or so at most) with no serious adverse effects. *B. serrata* based therapy was found to improve the functional status and symptoms. It also accelerated functional recovery, and decreased pain, as well as signs of inflammation in persons with OA.

The potent anti-inflammatory and anti-arthritis activities of the gum resin extract from *B. serrata* are related to biologically/pharmacologically active compounds

boswellic acids.<sup>17</sup> Boswellic acids have been shown to inhibit 5-lipoxygenase, an enzyme that catalyzes the formation of pro-inflammatory leukotrienes from arachidonic acid. In addition to this mechanism, boswellic acids also decrease the activity of the enzyme, Human leukocyte elastase (HLE). *B. serrata* extract prevents TNF- $\alpha$  induced expression of matrix metalloproteinase (MMP) and mediators of apoptosis. Unlike, NSAIDs, which are well known to disrupt glycosaminoglycan synthesis, thus accelerating articular damage in arthritic conditions, boswellic acids have been shown to significantly reduce glycosaminoglycan degradation.

### Glucosamine

Glucosamine is a type of glycosaminoglycan (GAG), an amino saccharide, and the preferred substrate for the biosynthesis of proteoglycans, such as aggrecans, which maintain cartilage integrity and function.<sup>18</sup> The positive effects of glucosamine on patients with OA have been established in numerous clinical trials. Glucosamine decreases pain, enhances joint function and mobility, and reduces cartilage deterioration in patients with OA. Glucosamine supplementation for 2 years and 6 months reduced the risk of radiographic knee OA by preventing the narrowing of joint spaces.<sup>19</sup> Glucosamine is an agent that has beneficial effects on the joint structure and maintains joint health by preventing the degradation of cartilage, reducing the inflammation and oxidative stress of the joint, improving the autophagy response of the chondrocytes, and increasing the chondrogenic potential of stem cells. Thus, glucosamine functions as a building block of the cartilage matrix and has multifaceted roles in promoting joint health.<sup>20</sup> Glucosamine reduces proteoglycan loss, delays cartilage degeneration and joint-space narrowing and improves osteoarthritic pain in OA animals and patients.<sup>21</sup> In vitro studies showed that glucosamine can reduce the expression of MMPs in chondrocytes and osteoblasts cultures and upregulate the expression of collagen type 2A1 and sirtuin-1 (SIRT1) in chondrocytes.<sup>22</sup>

In a study by Sawitzke et al the authors evaluated the efficacy and safety of glucosamine and chondroitin sulphate combination versus placebo, but could not find significant synergistic effect over placebo.<sup>23</sup> However, subsequently, Zeng et al, Hochberg, Lomonte et al and Truong et al observed the synergistic effects of the combination on pain relief and functional parameters.<sup>24-27</sup>

The present trial aimed at determining the synergistic effect of *B. serrata* and glucosamine sulphate on patients with mild to moderate knee OA using Nucart VG. The combination helps in improving cartilage health, reduce stiffness and intensify joint mobility, and pain relief at the end of study. It was observed that the primary end points like EQ-5D, VAS score and WOMAC score were more favorable in the Nucart VG group as compared to only Glucosamine sulphate group at the end of 12 week. The improvement in the health quality status (EQ-5D) was

significantly better in test group as compared to only glucosamine sulphate group. The reduction in VAS score was significant in Nucart VG group as compared to only glucosamine sulphate group at the end of study. Further, the overall WOMAC score, measuring the pain, function and stiffness, also reduced significantly in Nucart VG group than those who received only glucosamine sulphate. To understand which aspects of WOMAC improved

significantly, a question wise analysis at each time point between groups, and within groups across time points, were performed (Table 5). The analysis revealed that the activities like going up or down stairs, ascending stairs, rising from bed, getting on off toilet and light domestic duties showed significant improvement in Nucart VG group as compared to only glucosamine sulphate group at the end of 12-week.

**Table 5: Comparison of WOMAC scores on each question item between two groups and across time points in each group.**

Question	Baseline			Follow-up 1			Follow-up 2			Follow-up 3		
	Mean±SD (median)		P value *	Mean±SD (median)		P value *	Mean±SD (median)		P value *	Mean±SD (median)		P value *
	Nucart VG (n=30)	GS (n=30)		Nucart VG (n=30)	GS (n=30)		Nucart VG (n=30)	GS (n=30)		Nucart VG (n=30)	GS (n=30)	
1	1.27±0.72 (1)	1.55±0.67 (2)	0.0843	1.12±0.7 (1)	1.3±0.59 (1)	0.2006	1.06±0.62 (1)	1.06±0.57 (1)	1.0000	0.9±0.66 (1)	0.83±0.59 (1)	0.7096
2	2.48±0.71 (3)	2.58±0.61 (3)	0.6810	1.97±0.59 (2)	2.06±0.56 (2)	0.5171	1.64±0.63 (2)	1.84±0.52 (2)	0.2071	1.52±0.57 (2)	1.73±0.58 (2)	0.0030
3	1.55±0.75 (2)	1.61±0.79 (2)	0.6357	1.15±0.57 (1)	1.36±0.6 (1)	0.2364	1.19±0.4 (1)	1.26±0.44 (1)	0.5040	0.97±0.49 (1)	1.17±0.65 (1)	0.1661
4	1.73±0.63 (2)	1.85±0.76 (2)	0.4308	1.48±0.57 (1)	1.48±0.67 (2)	0.8401	1.31±0.59 (1)	1.19±0.6 (1)	0.4304	1.1±0.66 (1)	1.2±0.55 (1)	0.5719
5	1.55±0.67 (2)	1.76±0.83 (2)	0.2316	1.12±0.55 (1)	1.55±0.62 (2)	0.0019	1.09±0.69 (1)	1.16±0.52 (1)	0.5634	0.93±0.52 (1)	1±0.45 (1)	0.5891
6	2.21±0.82 (2)	2.03±0.88 (2)	0.4166	1.85±0.67 (2)	1.76±0.71 (2)	0.6634	1.66±0.55 (2)	1.19±0.6 (1)	0.0036	1.33±0.48 (1)	1.2±0.44 (1)	0.2122
7	2.64±0.65 (3)	2.7±0.53 (3)	0.8675	2.18±0.53 (2)	2.33±0.48 (2)	0.2588	1.92±0.51 (2)	2.06±0.57 (2)	0.4361	1.73±0.52 (2)	1.97±0.56 (2)	0.0020
8	2.12±0.65 (2)	1.97±0.73 (2)	0.3812	1.73±0.57 (2)	1.64±0.65 (2)	0.4617	1.53±0.67 (1.5)	1.55±0.62 (2)	0.8301	1.43±0.73 (1)	1.57±0.63 (1.5)	0.4802
9	1.76±0.66 (2)	1.64±0.82 (2)	0.5312	1.12±0.6 (1)	1.36±0.7 (1)	0.1797	1.09±0.64 (1)	1.16±0.64 (1)	0.6733	0.97±0.41 (1)	0.9±0.48 (1)	0.5524
10	1.94±0.75 (2)	2.09±0.95 (2)	0.3124	1.45±0.61 (1)	1.73±0.67 (2)	0.0435	1.34±0.65 (1)	1.23±0.67 (1)	0.4747	1.27±0.69 (1)	1.4±0.72 (2)	0.3994
11	1.09±0.58 (1)	1.36±0.74 (1)	0.1184	0.97±0.64 (1)	1.09±0.58 (1)	0.3033	0.97±0.65 (1)	0.9±0.47 (1)	0.8046	0.8±0.48 (1)	0.8±0.48 (1)	1.0000
12	1.7±0.77 (2)	1.61±0.66 (2)	0.8650	1.27±0.52 (1)	1.39±0.7 (1)	0.3666	1.19±0.64 (1)	1.32±0.7 (1)	0.3317	1.02±0.62 (1)	1.13±0.73 (1)	0.1780
13	1.76±0.79 (2)	2.03±0.88 (2)	0.1600	1.48±0.67 (1)	1.61±0.61 (2)	0.3228	1.38±0.79 (1)	1.32±0.75 (1)	0.8256	1±0.53 (1)	1.23±0.68 (1)	0.1558
14	2.12±0.93 (2)	1.91±0.91 (2)	0.3767	1.42±0.66 (1)	1.39±0.79 (1)	0.7349	1.31±0.69 (1)	1.35±0.91 (1)	0.8304	1.13±0.68 (1)	1.07±0.69 (1)	0.4589
15	1.7±0.64 (2)	1.79±0.6 (2)	0.5137	1.33±0.54 (1)	1.52±0.51 (2)	0.1811	1.13±0.66 (1)	1.19±0.54 (1)	0.5464	1.00±0.52 (1)	1.17±0.46 (1)	0.0130
16	2.09±0.91 (2)	2±0.9 (2)	0.7786	1.45±0.67 (1)	1.45±0.75 (1)	0.9944	1.31±0.69 (1)	1.16±0.86 (1)	0.3911	0.97±0.61 (1)	1.1±0.71 (1)	0.5952
17	1.58±0.71 (2)	1.36±0.6 (1)	0.2725	1.15±0.36 (1)	1.27±0.45 (1)	0.2320	1.03±0.54 (1)	1.13±0.43 (1)	0.4486	0.87±0.57 (1)	0.83±0.53 (1)	0.8352
18	1.73±0.84 (2)	1.79±0.6 (2)	0.6353	1.48±0.62 (1)	1.3±0.64 (1)	0.3049	1.28±0.52 (1)	1.32±0.6 (1)	0.6950	0.93±0.58 (1)	1.03±0.61 (1)	0.1890
19	2.03±0.59 (2)	1.64±0.74 (2)	0.0184	1.73±0.57 (2)	1.64±0.6 (2)	0.6334	1.75±0.51 (2)	1.68±0.6 (2)	0.6892	1.5±0.57 (2)	1.6±0.62 (2)	0.5330
20	2.33±0.74 (2)	2.12±0.93 (2)	0.3788	1.82±0.58 (2)	1.79±0.65 (2)	0.9459	1.29±0.55 (2)	1.58±0.67 (2)	0.0411	1.12±0.52 (1)	1.27±0.52 (1)	0.0310

Continued.



Question	Baseline			Follow-up 1			Follow-up 2			Follow-up 3		
	Mean±SD (median)		P value *	Mean±SD (median)		P value *	Mean±SD (median)		P value *	Mean±SD (median)		P value *
	Nucart VG (n=30)	GS (n=30)		Nucart VG (n=30)	GS (n=30)		Nucart VG (n=30)	GS (n=30)		Nucart VG (n=30)	GS (n=30)	
21	2.21±0. 78 (2)	2.42±0. 61 (2)	0.207 5	1.97±0. 64 (2)	2.03±0. 68 (2)	0.588 4	1.81±0. 47 (2)	1.81±0. 65 (2)	0.844 2	1.67±0. 61 (2)	1.87±0. 68 (2)	0.32 14
22	1.64±0. 65 (2)	1.58±0. 71 (2)	0.750 1	1.36±0. 6 (1)	1.48±0. 62 (1)	0.367 0	1.21±0. 54 (1)	1.23±0. 5 (1)	0.187 9	1.02±0. 57 (1)	1.17±0. 53 (1)	0.04 10

\*Using Mann-Whitney test; bold p values show statistical significance

Safety profile of patients revealed that the physical and vital parameters were within normal limits in either group throughout the study period. Also, the biochemical parameters were normal and insignificantly different between groups. There were no serious events and no need of any rescue medications to any patient in either group during the study. This finding was consistent with that of systemic quality assessment and meta-analysis.<sup>15</sup>

This was a preliminary study to evaluate the role of Nucart VG. A larger study with long term follow up may lower WOMAC scores further as well as improve the health status (EQ-5D) of patients in the test group. Relief of symptoms and improved functional capacity may help in delaying knee joint surgery.

## CONCLUSION

In conclusion, for patients with mild to moderate knee osteoarthritis, a fixed daily dose of Nucart VG tablet twice a day, after meals, is efficient for the treatment of knee OA, as inferred from the functional and health status assessment. Moreover, a favorable safety profile makes the combination as a preferred option for the treatment of knee osteoarthritis.

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