

# Efficiency of proteolytic enzymes in treating lumbar spine osteoarthritis (low back pain) patients and its effects on liver and kidney enzymes

Hira Naeem<sup>1\*</sup>, Syed Naim-ul-Hassan Naqvi<sup>1</sup>, Rehana Perveen<sup>1</sup>, Farhan Ishaque<sup>2</sup>, Raheela Bano<sup>3</sup>, Hina Abrar<sup>3</sup>, Adeel Arsalan<sup>4</sup> and Nousheen Malik<sup>1</sup>

<sup>1</sup>Department of Pharmacology, Baqai Medical University, Karachi, Pakistan

<sup>2</sup>Department of Physiotherapy, Dow University of Health Sciences, Karachi, Pakistan

<sup>3</sup>Department of Pharmaceutical Chemistry, Dow University of Health Sciences, Karachi, Pakistan

<sup>3</sup>Department of Pharmacology, Dow University of Health Sciences, Karachi, Pakistan

<sup>4</sup>Department of Pharmaceutics, Ziauddin University, Karachi, Pakistan

**Abstract:** Lumbar spine osteoarthritis with 40-85% prevalence, degeneration of spine with remarkable narrowing of disc space and osteophytes formation trigger pain in lower back. Pain in lower portion of back is now considered to be the second most commonly treated health issue in primary health care setups. This pain causes disability, functional loss and job absentees. Commonly pain is managed pharmacologically by NSAIDs but resulted in severe gastric side effects. The purpose of this trial was to appraise the properties of bromelain and papain, the vegetal proteolytic enzymes, in comparison with standard drug on LBP patients. Forty men and women with lumbar spine osteoarthritis were recruited and divided into group 1, received aceclofenac 100mg tablet b.i.d as standard treatment, group 2, patients treated with aceclofenac 100 mg tablet b.i.d and enzyme supplements 250 mg b.i.d for 6 weeks. All the participants were evaluated for their body mass index, vital signs and liver/ kidney enzymes before and after treatment. Moreover intensity of pain were also measured through visual analogue scale (VAS) and Oswestry low back pain questionnaire (ODI) before treatment (0 week), 3<sup>rd</sup> week and 6<sup>th</sup> week of treatment. The enzyme group patients showed significantly diminished pain scores VAS from 7.10±1.29 to 5.85±1.531\*\*\* (P= 0.001), ODI score from 56.2±8.70 to 51.6±8.125\*\*\* (P=0.000), significantly diminished enzymes; ALP from 210.00±55.24 to 196.90±51.02 (P=0.054\*) and serum creatinine from 0.97±0.153 to 0.87±0.139 (P= 0.035\*) and improved quality of life. Hence, this study suggested that the enzyme supplements for 6 weeks have prolonged beneficial carry-over effects in comparison to standard treatment without producing any change in BMI (P>0.05) and vital signs (P> 0.05).

**Keywords:** Lumbar spine osteoarthritis, low back pain, proteolytic supplements, bromelain, papain, visual analogue scale, Oswestry low back pain questionnaire.

## INTRODUCTION

*Osteoarthritis:* Lumbar spine Osteoarthritis (low back pain), a degenerated joint disease characterized by cartilage destruction (Deyle *et al.*, 2005) and the collective source of psychosocial and emotional distress in geriatric patients. Muscle toughness and gradual decrease in range of motion result in functional limitation of such patients (Koes *et al.*, 2006, Langworthy *et al.*, 2010). This painful condition affects more than 100 million of individuals and has negative impact on health care organizations because of its high incidence ratio (Ma *et al.*, 2014). This pain badly influence daily routine work due to decreased back flexibility (Wang and Ward, 2015). Non-steroidal anti-inflammatory drugs (NSAID) are among the principal therapies for pain management but with severe gastric problems. Among them aceclofenac 100mg bid is safe with high therapeutic index and minimum side effects (Lemmel *et al.*, 2002, Patel and Patel, 2017).

*Proteolytic enzyme:* Usually controlling of the arthritic pain is done pharmacologically through NSAIDs but due their unwanted effects other therapies with anti-inflammatory and pain combating effects are of great interest. Considering this point researchers swing towards natural remedies and found enzymatic treatment as significant method for damaged cartilage restoration, like bromelain and papain which possess anti-inflammatory and swelling combating properties as they showed significant pain reduction in osteoarthritis of the knee in comparison to diclofenac due to the inhibition of inflammation and direct effects on the nociceptors (Klein and Kullich, 1999, Hernandez-Diaz and Rodríguez, 2000). Food supplements derived from many herbs have significant anti-arthritic properties and appeared to be the substitute of NSAIDs for handling backache with better risk-benefit ratio (Maroon and Bost, 2006). Papain, the proteolytic enzyme, mined from papaya fruits (Puig *et al.*, 2008). Higher dose of *Carica papaya* extract does not produced toxic effects even at higher dose of 2000mg/kg (Goyal *et al.*, 2009). Papain reduces muscle soreness and side effects of radiation therapy and safe when taken by

\*Corresponding author: e-mail: dr.hiranaeem@gmail.com

mouth in appropriate medicinal volumes and when applied on the skin as a solution (Andrew and Robert, 2013) and used as raw material for food and pharmaceuticals (Boshra and tajul 2013).

Whole plant of papaya considered as a medicinal plant as its antioxidant beta-carotenes, various vitamins including vitamin C and vitamin E reduce the severity of osteoarthritis (Yogiraj *et al.*, 2014; Vyas and Shah, 2016). Papain has been evaluated for its bactericidal and neuroprotective effects moreover it collapse the fibrin cancer cell wall and breakdown protein into amino acid and has vital beneficial effects (oloyede, 2005, Aruoma *et al.*, 2010, Patil *et al.*, 2014, Kumar and Devi, 2017). Similarly Bromelain, a proteolytic enzymes found in pineapple plants exhibits fibrinolytic, antithrombotic, and anti-inflammatory, wounds healing properties and widely used in pharmaceutical and food industries (Arshad *et al.*, 2014, Sahbaz *et al.*, 2015, Ramli *et al.*, 2017).

Throughout the world approx. 159 plants were described to be used against arthritis significantly but only 6 plants have been evaluated in-vitro and 15 through in vivo (Sadia *et al.*, 2018). Bromelain and Papain, similar to human pepsin, increase natural killer cells, and bind with excessive immune complexes which cause autoimmune diseases like arthritis and hence proteolytic enzymes proved as immune boosters as they break down these complexes (Nutrition, 2019). These various effects believed to add the clinical worth of various proteolytic enzymes like bromelain and papain.

On the basis of these researches and reported mechanism of action of proteolytic enzymes this research work proposed to examine the efficacy and proficiency of natural auxiliary medicines like bromelain and papain enzyme supplement (250 mg) compared with standard drug therapy (aceclofenac 100 mg) in pain management moreover its effects on patient's vitals and liver/ kidney enzymes were also evaluated in order to report its safety profile as well.

## **MATERIALS AND METHODS**

### ***Population Dynamics***

This randomized control trial conducted under supervision of orthopedic surgeon of Fatima Hospital at Baqai Medical University (BMU) from August 2018-august 2019. Patients, both male and female, with age between 45-65 years having history of at least 3 months of lower back pain and radiological proven osteoarthritic signs (osteophytes formation and decreased cavity) but were non-hypertensive, non-traumatic and non-diabetic and related to different casts and professions. Patients were neither sensitive to aceclofenac nor received test medication prior their enrollment in trial.

Patient with metabolic diseases, neoplasms, rheumatoid arthritis, hypertension, hyper or hypothyroidism, joint replacement surgery, traumatic, diabetic, gastrointestinal disease, below 45 years were not included in this research work. For this trial 100 patients were recruited but 60 were excluded because of history of surgery, smoking, diabetes, trauma and only forty patients were enlisted according to the inclusion criteria as mentioned in fig. 1.

### ***Ethical conduct***

The study was approved by Ethics Committee of Baqai Medical University and all the recruited participants read and signed the approved informed consent form before the start of research work.

### ***Treatments/ dosing protocol***

Acenac (aceclofenac 100mg) from S.J. &G. Fazul Ellahie (Pvt.) Ltd. Karachi, Pakistan used as standard treatment. While Bromelain and Papain 250 mg capsule from Nature's Life<sup>®</sup>, NutraPure, Inc. USA (commercial product, size 100 vegetarian capsules) used as enzyme supplement. Dosing period of 6 weeks was selected from the previous research evaluated oral enzymes in comparison to NSAID in hip/knee osteoarthritis for 6 weeks (Farhan *et al.*, 2015, Klein *et al.*, 2006).

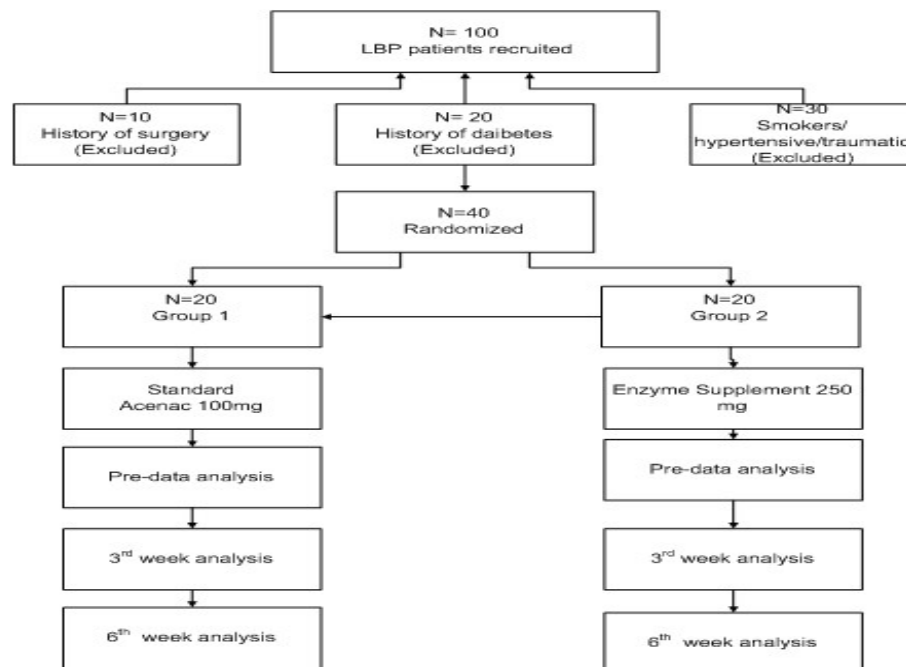
In this prospective, randomized, controlled clinical research work the subjects remained separated into 2 sets/groups, each consisting of 20 patients. *Group 1*: patients (n=20) were treated by standard drug (aceclofenac 100 mg bid) orally for 6 weeks (Patel & Patel, 2017). *Group 2*: patients (n=20) were treated by standard drug (aceclofenac 100mg bid) and enzymes supplement (papain 250 x 2 mg/day) orally for 6 weeks (Farhan *et al.*, 2015).

### ***Clinical assessments***

We assessed the effect of proteolytic enzymes on different parameters including:

Analysis of vital signs: General vital signs including body mass index, body temperature, pulse rate and respiratory rate were evaluated as according to Pahor *et al.* (1999) severe pain pointedly linked with various factors like higher body mass index (BMI), different position of osteoarthritis i: e osteoarthritis of hands, hips, or knees, higher creatinine clearance or to the diseases related to disk or spine.

Analysis of blood parameters (liver and kidney enzymes): Enzyme estimation of both groups were done to seek any specific change in the liver and kidney enzymes of osteoarthritis patients, for this purpose 5ml blood was taken before and after intervention of enzyme supplement. Different *liver enzymes* including SGPT, SGOT, ALP and *kidney enzyme* including serum creatinine were analyzed using kits through Micro lab 300 Semi Automated



**Fig. 1:** Enrollment of Patients

Clinical Chemistry Analyzer. ALAT (GPT) innoLine kit (for Alanine Amino Transferase), ASAT (GOT) innoLine kit (for Aspartate Aminotransferase analysis), ALP DGKC InnoLine kit, MartinDow (for Alkaline Phosphatase) while Creatinine Jaffé 1+1 innoLine kit, Martin Dow (for serum creatinine analysis) were used respectively. Cholinesterase was analyzed through spectrophotometer using Cholinesterase (CHE) kit (Randox laboratories).

Evaluation of the physical and functional status of osteoarthritic patients (LBP): intensity of pain was marked by two measuring tools; *visual analogue scale* (a straight vertical 10cm line with marking of 0-10 indicating one end with no pain and the other represents worst pain condition (Dixon and Bird., 1981, Olaogun *et al.*, 2004) and through *Low Back Pain Disability Questionnaire*. It is the form to evaluate patient's symptom status and pain-related infirmity (Fairbank *et al.*, 1980). Outcome measures of these tools were helpful in suggesting the effect of treatment in lowering pain intensity (Johnson, 2005). Analysis through VAS and ODI were done at pretreatment, 3<sup>rd</sup> week and 6<sup>th</sup> week to check the decrease in pain intensity.

## STATISTICAL ANALYSIS

Analysis was done at three points i.e., at 0 week (pretreatment), 3<sup>rd</sup> week and 6<sup>th</sup> week in order to evaluate results at different time intervals. One-way analysis of variance (ANOVA) used to relate baseline (pre-treatment) characteristics with 3<sup>rd</sup> week and 6<sup>th</sup> week clinical changes. Additionally, over all variations during the whole study period of 6 weeks (before and after the

treatment) were analyzed through paired *t*- test. Analyses were performed using SPSS software, version 23 and the data was represented as mean  $\pm$  standard deviation (SD).

## RESULTS

### *Patient response and study progress*

Over-all 100 patients were screened but 60 patients were disqualified as they were not appropriate for the study and remaining 40 recruited (20 in each group; 1 and 2) randomized and treated. Patient's response between the two treatment groups did not reveal any significant differences in basic demographic data but major significant improvements were reported in functional status and pain scores in group 2 (enzyme supplement) patients.

### *Treatment response*

Various baseline demographic parameters including body mass index, body temperature, pulse rate, respiratory rate were analyzed before and after supplement administration and reported no significant variation ( $P= 0.33$ ,  $P= 0.099$ ,  $P= 0.604$  and  $P= 0.670$  respectively) as listed in table 1. Supplement administration significantly reduced alkaline phosphatase enzyme ( $210.00 \pm 55.24$  to  $196.90 \pm 51.02$ ,  $P=0.054$ ) and serum creatinine ( $0.97 \pm 0.153$  to  $0.87 \pm 0.139$ ,  $P=0.035$ ) of liver and kidney respectively as listed in table 2 while standard treatment don't reported any significant change.

Disability level, intensity of pain and serviceable status of backache patients were assessed through VAS and ODI and the data were collected at baseline (pre-treatment), 3<sup>rd</sup>

**Table 1:** Demographic data (baseline characteristics of 40 patients analyzed through paired *t*-test (SPSS, version 23)

Parameters	Pre-standard (n=20)	Post-standard (n=20)	Sig.	Pre-Enzyme (n=20)	Post-Enzyme (n=20)	Sig.
Age n=20	50.45±5.44	50.45±5.44	NS	50.30±5.48	50.30±5.48	NS
Gender (M/Fc)	12/08	12/08	NS	11/09	11/09	NS
BMI	20.10±2.22	20.20±2.21	0.330	19.75±1.51	19.93±1.55	0.33
B.T	97.98±0.44	97.80±0.000	0.083	98.07±0.581	97.86±0.26	0.099
P.R	65.45±5.99	68.05±7.42	0.091	68.05±7.423	67.25±5.893	0.604
R.R	14.70±2.922	14.70±2.536	1.000	15.20±2.46	14.80±3.287	0.670

BMI: Body mass index, B.T: body temperature, P.R: pulse rate, R.R: respiratory rate, NS: not significant, (M/Fc): Male/Female Values are expressed as mean along with Standard Deviation (mean ± SD), n =20 for each group. Level of significance P<0.05\*, P<0.01\*\*, P< 0.001\*\*\* with respect to control, P-values <0.05 is considered significant

**Table 2:** Statistical Analysis of standard and enzyme supplement on liver and kidney enzymes through *t*-test (SPSS, version 23)

Parameters	Pretreatment	Post-treatment	Sig.
Standard (n=20)			
ALP	243.15±55.01	247.45±79.48	0.706
SGPT	46.35±22.24	43.55±24.237	0.105
SGOT	41.55±10.99	39.95±9.451	0.107
Sr. Cr.	0.99±0.129	0.93±0.138	0.062
ACHE	5551.10±886.277	5650.60±930.77	0.170
Enzyme (n=20)			
ALP	210.00±55.24	196.90±51.02	0.054*
SGPT	56.60±18.68	53.80±19.60	0.640
SGOT	35.50±11.97	35.00±11.20	0.580
Sr. Cr.	0.97±0.153	0.87±0.139	0.035*
ACHE	5712±865.8	5601±869.88	0.341

ALP: alkaline phosphatase. SGPT: Alanine Amino Transferase (ALAT), SGOT: Aspartate Aminotransferase (ASAT), Sr. Cr: Serum Creatinine, ACHE: Acetyl Choline Esterase, Values are expressed as mean along with Standard Deviation (mean± SD), n =20 for each group. Level of significance P<0.05\*, P<0.01\*\*, P< 0.001\*\*\* with respect to control, P-values <0.05 is considered significant.

week (post-treatment) and at 6<sup>th</sup> week (post-treatment) and analyzed statistically table 3. Pain scores through VAS in group 1 was (7.50±1.10 to 6.95±0.998, P= 0.012) and group 2 score was (7.10±1.29 to 5.85±1.531, P=0.001) during 6 weeks analysis and represented gradual significant decrease in pain score from baseline values. ODI scores of both groups were characterized by significant increase in functional status of group 1 patients from 54±8.07 to 51±8.491 (P=0.005) but more noticeable in group 2 patients from 56.20±8.70 to 51.60±8.125 (P=0.000) respectively as shown in table 4. Intensity of pain remarkably reduced in group 2 low back patients receiving enzyme supplement as their VAS and ODI significantly reduced as compare to the standard.

## DISCUSSION

Low back pain (LBP) mentioned as 2<sup>nd</sup> most communal disability in United States (Ricci 2006) but in a survey of 54 countries researchers suggested that LBP has become foremost worldwide problem which is seen more in

females of 40-80 years with 11.9±2.0% mean ± SEM prevalence (Hoy *et al.*, 2012). Through statistical analysis this study suggested, that 6 week therapy with bromelain and papain enzyme supplement has valuable residual effects in lowering low back pain due to lumbar spine osteoarthritis. Many scientists clinically evaluated oral proteolytic enzymes for 3 weeks as an alternative way to treat knee arthritis pain in comparison of marketed diclofenac and reported great statistical reduction in bone degeneration, muscle tenderness and pain in enzyme treated group (Gert and Kullich., 2000; Singer *et al.*, 2001).

Proteolytic enzymes has anti-inflammatory efficacy similar to ibuprofen and has immunomodulatory effects to delay destructive arthritis (Chintalacheruvu *et al.*, 2001) as Rakhimov (2001) reported that papain has comparable anti-inflammatory effects as that of butadion and indomethacin. In light of these clinical researches, proteolytic enzyme supplement containing bromelain and papain was evaluated for low back pain and found

**Table 3:** Mean Changes in Clinical Variables during 0 week, 3<sup>rd</sup> week and 6<sup>th</sup> week Follow-Up In Each Group analyzed through ANOVA, SPSS (version 23)

Groups:	Parameters	
Group 1 (standard)	VAS	ODI
Pretreatment	7.50±1.10	54±8.07
3 <sup>rd</sup> week	6.65±1.039	53.45±8.09
6 <sup>th</sup> week	6.95±0.998**	51±8.491**
Group 2 (enzyme)		
Pretreatment	7.10±1.29	56.2±8.70
3 <sup>rd</sup> week	6.90±1.11	55.0±8.8
6 <sup>th</sup> week	5.85±1.531***	51.6±8.125***

Values are expressed as mean along with Standard Deviation (mean ± SD), n =20 for each group. Level of significance P<0.05\*, P<0.01\*\*, P< 0.001\*\*\* with respect to control, P-values <0.05 is considered significant, VAS: visual analogue scale, ODI: oswestry disability index

**Table 4:** Mean Changes in Clinical Variables during 6 week (pre and post) treatment analyzed through *t*-test

Outcomes	Pretreatment	Post-treatment	Sig. (P- values)
VAS(standard, group 1)	7.50±1.10	6.95±0.998	0.012
VAS(enzyme, group 2)	7.10±1.29	5.85±1.531	0.001
ODI(standard, group 1)	54±8.07	51±8.491	0.005
ODI(enzyme, group 2)	56.2±8.70	51.6±8.125	0.000

Values are expressed as mean along with Standard Deviation (mean± SD), n =20 for each group, Level of significance P<0.05\*, P<0.01\*\*, P< 0.001\*\*\* with respect to control, P-values <0.05 is considered significant, VAS: visual analogue scale, ODI: oswestry disability index

significant pain reduction on visual analogue scale from 7.10±1.29 to 5.75±1.51\*\* and in oswestry disability index from 56.2±8.70 to 50.5±7.50\*\*\* with significant reduction of ALP (210.00±55.24 to 196.90±51.02, P=0.054\*) and serum creatinine (0.97±0.153 to 0.87±0.139, P=0.035\*) values towards normal range without producing any change in body mass index (P=0.33) and vital signs (P >0.05).

Leipner *et al.*, (2001) clarified the use of plant and animal based supplements containing bromelain, papain, trypsin and chymotrypsin in rheumatic complaints. These oral supplement preparations showed significant analgesic and anti-inflammatory effects in patients suffering from rheumatic pain in comparison with standard NSAIDS. This study statistically proved the reported claim by reducing pain and improving functional grade of patients suffering from LBP after 6 weeks of treatment with enzymes.

The result of this study suggests that range of motion, functional status and disability in life due to pain recovers maximum in enzyme supplementation group (2) which may be due to the attenuation of inflammatory process, edema and reduced pain receptor recruitment as protease enzymes decreases the biosynthesis of pro-inflammatory agents, facilitates restructuring of damaged area by increasing permeability of tissues and decreasing pressure due to edema with no side effects as that of NSAIDS as Brien *et al.*, (2004) reported different anti-inflammatory

pathways of various proteolytic enzymes (bromelain) through clinical trials. According to them proteolytic enzymes augment fibrinolytic action, reduce plasma fibrinogen and reduce levels of bradykinin, vascular permeability and resulting in reduced swelling and pain.

Inflammation cause swelling, pain and restriction of movement while proteolytic enzymes work as modulator of these inflammatory responses by improving humoral immunity (Sadek, 2012), rising macrophages, destroy pathogenic complexes and remove them through lymphatic system. Moreover it also enhanced the potency of natural killer (NK) cells, dropped the mucous membrane swelling, reduced capillary permeability, liquefied blood clot/fibrin deposits and resolved pain and swelling (Nutrition Review Archive 2013). Papain significantly inhibits production of tissue necrotic factor (Sagnia *et al.*, 2014) while same response was found in papaya leaf extract (5 mg/ml) (Salim *et al.*, 2014). Bromelain and Papain significantly decreased cells migration, inhibiting cell growth and proved to be effective antitumor agent (Müller *et al.*, 2016). According to Ashok and Mol (2017) papain, a phyto-constituent of papaya used to treat arthritis pain.

Papaya when given to the rabbits at the dosage of 250-500 mg/day orally do not disturbed SGPT, SGOT, ALP, WBC, neutrophil count and significantly increased platelets count similarly papaya seed used in pain management of arthritis and toothache (Ahmed and Jehan, 2017, Ahmed

*et al.*, 2017; Panda *et al.*, 2018). In African culture papaya ric in papain enzyme used in treating different painful conditions and reported significant reduction in elevated lipid profile in experimental rats (Ojo *et al.*, 2018).

In the light of above discussed literature this study evaluated the significant reduction in pain, inflammation and improved functional status of low back pain patients. Currently very little clinical work has been done to evaluate dietary supplements base on natural products for LBP, as only 6 plants have been evaluated in-vitro and 15 through *in vivo* against arthritis (Sadia *et al.*, 2018). The effect of bromelain and papain as assessed through pain scale and disability questionnaire functional performance at 3<sup>rd</sup> and 6<sup>th</sup> week represents highly significant differences from baseline values. Typically LFTs found irregular in arthritis but in this research work enzymes reduced liver enzymes towards normal (Fahmy *et al.*, 2018, Radovanović-Dinić *et al.*, 2018).

Osteoarthritis is a diverse ailment commonly treated by NSAIDS to control pain but their long term use end up with various adverse events which divert patient's interest towards other natural based alternatives like nutraceuticals for clinical improvement with reduced drug intake.

This study suggested that lumbar spine osteoarthritis (LBP) can be well managed by plant produced bromelain and papain enzyme supplement as its administration do not produced any alteration in body mass index (BMI), and vital signs (P.R, B.T, R.R) with no side effect which are specially associated with NSAIDS. Pain, quality of life and work restoration with significant carry over effects were observed during six weeks study however, a detailed weekly analysis also suggested the gradual improvement in health status.

## CONCLUSION

Systemic use of enzyme therapy (proteolytic supplement) significantly resolved inflammatory condition with speedy healing of pain and better resolution of symptoms. This research work may oblige as preliminary standard for the use of enzymatic supplementation in treating low back pain as bromelain and papain was first time evaluated for lumber spine osteoarthritis. Further studies are necessary to authorize the findings to evaluate the proteolytic enzymes in the field of rheumatology to appraise further comprehensive clinical properties. This research, worked as window to upraise the use of natural products as first line of treatment in pain management with minimum or no side effects and high patient's compliance and require further intense and more detailed clinical evaluation to promote the consumption of proteolytic enzymes in the management of low back pain.

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