Management of chronic pain with Jalapragshhalana (water-wash) Shodhita (processed) Bhanga (Cannabis sativa L.) in cancer patients with deprived quality of life: An open-label single arm clinical trial

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Abstract

Introduction: Pain is a common and complex symptom of cancer having physical, social, spiritual and psychological aspects. Approximately 70%–80% of cancer patients experiences pain, as reported in India. Ayurveda recommends use of Shodhita (Processed) Bhanga (Cannabis) for the management of pain but no research yet carried out on its clinical effectiveness. Objective: To assess the analgesic potential of Jalapragshhalana (Water-wash) processed Cannabis sativa L. leaves powder in cancer patients with deprived quality of life (QOL) through openlabel single arm clinical trial. Materials and Methods: Waterwash processed Cannabis leaves powder filled in capsule, was administered in 24 cancer patients with deprived QOL presenting complaints of pain, anxiety or depression; for a period of 4 weeks; in a dose of 250 mg thrice a day; along with 50 ml of cow’s milk and 4 g of crystal sugar. Primary outcome i.e. pain was measured by Wong-Bakers FACES Pain Scale (FACES), QOL by FACT-G scale, performance status score like ECOG (ECOG), Hospital Anxiety and Depression Scale (HADS), OPA by Eastern Cooperative Oncology Group (ECOG) and Karnofsky score. Results: Significant reduction in pain was found on FACES Pain Scale ($P < 0.05$), OPA ($P < 0.05$), NPS ($P < 0.001$), HADS ($P < 0.001$), FACT-G scale ($P < 0.001$), performance status score like ECOG ($P < 0.05$) and Karnofsky score ($P < 0.01$). Conclusion: Jalapragshhalana Shodhita Bhanga powder in a dose of 250 mg thrice per day; relieves cancerinduced pain, anxiety and depression significantly and does not cause any major adverse effect and withdrawal symptoms during trial period.

Keywords: Anxiety, Bhanga, Cannabis sativa, cancer pain, depression, quality of life, Shodhana

Introduction

Despite all advancements in prevention, early detection, with newer and more effective treatment modalities, cancer remains one of the most debilitating and deadly diseases and is second leading cause of mortality.[¹] Sheer potential of suffering from cancer can be a horrifying experience for anyone bearing this diagnosis, while ‘pain’ is probably one of the most frightening symptoms of cancers which usually intensifies as the disease progresses in 50%–70% patients.[²] Less than half of patients get adequate relief of pain, which negatively impacts their quality of life (QOL).[³] Generally, pain is a subjective feeling that has not till date been easily and universally quantified.[⁴]

Patients with similar cancer types may experience different intensities of pain. Current WHO ladder method consistently failed to provide sufficient relief to 10%–20% of advanced cancer patients with pain and reported side effects of analgesics are the reasons for concern over these symptoms.[⁵] Bhanga

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(Cannabis) is a potent analgesic reported by folklore, Ayurveda as well as modern medical science and researches.[6] If used in Ashodhita (Unprocessed) form, may cause Madakari (Intoxicant) effects hence, Ayurveda classics have advised Shodhana (Purifying process) of Bhang before its therapeutic use.[7] Cannabis leaves processed with water-wash method has been advised for the management of pain.[8,9] As per ‘The 1961 Convention’, due to inclusion under narcotic category,[10] therapeutic as well as research use of Cannabis was stopped. In 19th century, again, the drug started gaining scientific attraction due to its significant therapeutic effects in palliative oncology care; as concurrent use of morphine is reported to causes many ill effects.[11] Various researches report positive results of Cannabis in managing symptoms cluster developed in cancer patients.

Objective
To assess the clinical effectiveness of water-wash processed Cannabis leaves powder in cancer patients having complaints of pain, anxiety, depression and deprived QOL.

Material
Preparation of trial drug (TD) by Jalaparakshalana (Water-wash) processing method
Leaves of female species of Cannabis sativa L. were tied in a muslin cloth; washed with water till greenish color stops oozing out from leaves, later shade dried,[12,13] finely powdered with mixer grinder and filled in red and white hard gelatine capsule of size “0” and dimension 21.04 ± 0.4 having capacity of 250 mg. Patients were selected by ‘purposive sampling’ (Non-random) method from outpatient department and in patient department section of Rama Ramdeo Anandiall Podar, Central Ayurveda Research Institute for Cancer (RRAP-CARIC), Worli, Mumbai; irrespective of specific region, religion country.

Selection of patients
Inclusion criteria
Clinically diagnosed patients of all type of cancer; irrespective of their gender; between age 18 to 70 years; who were receiving possible available treatment(s) for the management of cancer or terminally ill patients with any Eastern Cooperative Oncology Group (ECOG) score; presenting ‘pain’ as a chief symptom and willing to participate in clinical trial after getting information about drug and treatment protocol were included.

Exclusion criteria
Patients suffering from systemic diseases such as uncontrolled hypertension/diabetes, cardiac/pulmonary/hepatic or renal dysfunctions, HIV/VDRL, pregnant or breast-feeding women, patients with inability to comprehend and complete proposed course of intervention were excluded.

Ethical and legal approval
The study was approved by the Institutional Ethics Committee of IPGT and RA, Gujarat Ayurved University, Jamnagar (PGT/7/-A/ethics/2015-16/2625) and RRAP, CARIC, CCRAS, Worli, Mumbai (CARIC/Ref. No. 03/16-17). ‘Clinical Research Proforma’ (CRP) was designed exclusively for cancer palliative care focusing on patient’s symptoms and related details. ‘Patient’s consent form’ (according to the guidelines of the CCRAS) and ‘drug compliance form’ was developed which was presented and approved through IEC-CARIC and Departmental Research Committee meeting at IPGT and RA, Jamnagar. Trial drug was procured through the pharmacy of Gujarat Ayurved University, Jamnagar after taking due approval of the state excise authority. Records were maintained as per the present rules and regulations.

Trial registration
Study was registered in Clinical Trials Registry of India. (CTRI/2016/02/006658).

Methods
Study design
An open labelled single arm clinical trial of sample size 40 (Dropout rate of 25%) was conducted at RRA Podar CARIC, CCRAS, Worli, Mumbai, of duration 1 month with four follow-up at interval of a week and last one follow-up for assessment of withdrawal symptoms after trial drug was stopped. Before treatment (BT) and after treatment (AT), laboratory investigations namely complete blood count, urine test, biochemistry parameters such as total- direct- indirect bilirubin, albumin: globulin ratio, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, triglycerides, total cholesterol (TC), high-density lipoproteins (HDL), low-density lipoproteins (LDL), very LDL, TC: HDL ratio, serum urea, serum uric acid, serum creatinine, fasting and post prandial blood sugar level and ECG were done to check the safety aspects after 1 month of administration of trial drug and to check any biochemical parameter disturbance after TD administration. Recommended dose of water-wash processed cannabis leaves as per Ayurvedic pharmacopoeia of India is 250 mg[14] which was given to patients thrice a day (9 am, 3 pm and 9 pm) orally with 50 ml of cow’s milk mixed with 4 g of crystal sugar as an adjuvant; for the period of 4 weeks. Patients were asked to discontinue any type of analgesic drug during trial period. However if patient had intolerable pain, then they were advised to inform and report trial center or nearby clinic and rescue medicine advice was kept in protocol. Patients were given ‘drug compliance form’ to fill the details of consumption of medicine capsules.

Telephonic follow-up was maintained with patients who failed to attend follow-up every week due to continuation of their chemotherapy or radiation cycles or due to long distance as some patients in trial were from other states.

Case report form
Data filled in ‘Case Report Form’ (CRF) was also entered in electronic format designed in Microsoft Excel. After trial completion, CRFs along with laboratory investigations reports were submitted to IEC for evaluation.
Outcome measures
For assessment of pain, Wong -Baker FACES Pain Rating Scale for pain (FACES),[15] Objective Pain Assessment (OPA)[16] and Neuropathic Pain Scale (NPS) were used.[17] Anxiety and depression were assessed by Hospital Anxiety and Depression Scale (HADS).[18] Associated complaint’s scoring was evaluated by WHO-DFC project guidelines for developing clinical research methodology in Ayurveda.[19] For estimation of QOL in cancer patients, FACT-G scale was adopted.[20] Performance status of a cancer patient was evaluated by ECOG and Karnofsky score.[21] All the above parameters scorings were recorded at baseline and after every week of assessment. ‘Post withdrawal effects assessment scale’[22] and ‘adverse drug reaction (ADR) reporting forms’ were noted at the end of 5th week.

Statistical analysis
Obtained data were analyzed statistically using SigmaStat 3.5 version for Windows (Systat Software, Inc., 501 Canal Blvd., Suite E, Point Richmond, California). Statistical analysis was done by applying ‘paired t-test’ to BT and AT assessment scores. \( P < 0.05 \) was considered statistically significant.[23] Percentage difference of change in relief of each symptom at every week period to achieve 50% relief in respective symptom was calculated. Overall improvement in signs and symptoms. Percentage improvement of every symptom per week for each patient was calculated by the formula \( \text{Percentage improvement} = \frac{\text{After Treatment value} - \text{Before Treatment value}}{\text{Before Treatment value}} \times 100 \). Average of the percentage improvement was calculated. Obtained results were measured according to the grades as cure/complete remission 75%≥100%, marked Improvement 51% ≥74%, moderate improvement 26%–50%, mild Improvement 1% ≥25% and unchanged 0%.

Observations and Results
Status of enrolled patients
Total 37 (100%) patients were enrolled in trial out of which 24 (64.86%) have completed treatment while 13 (35.14%) patients dropped out due to reasons such as conventional therapy settings and inconvenience in long distance travelling to reach trial center.

Demographic profile
Demographic data of enrolled patients \( n = 37 \) viz. distribution of patients according to age, gender, marital status, educational status, past and present occupation, habitat and religion are depicted in Table 1.

Treatment modalities opted by patients for symptoms management
Conventional treatment like chemotherapy and radiation therapy were received (ing) by 40.54% and 18.92% patients respectively whereas 37.83% patients were undergoing treatment from Complementary and Alternative Medicine pathies and 40.54% patients were found suffering from various side effects of conventional treatment for cancer.
Distribution of patients according to types of cancer

Patients presenting ‘pain’ as chief complaint having various nineteen different types of cancer are depicted in Graph 1, out of which cancer of breast (16.21%), buccal mucosa (13.51%), cervix (8.10%) and esophagus (8.10%) were found in most patients.

Chief and associated complaints (n = 24)

Pain (100%) was the chief complaint presented by all patients followed by anxiety (79.17%), depression (83.33%), fatigue (70.83%), exhaustion (62.5%), loss of appetite (54.17%), insomnia (45.83%), tastelessness (45.83%), dryness of skin (29.17%), fever (16.67%), dyspnea (16.67%), constipation (8.33%), hair loss (8.33%) and diarrhea (4.16%). Score-wise distribution of enrolled patients complaining pain on Wong-Baker FACES Pain Rating Scale score between ‘6’ and ‘8’ BT while after treatment (AT) no patients had score above ‘6’ [Tables 2-4].

Before treatment, OPA score of 87.5% and 12.5% patient’s was ‘3’ and ‘2’ respectively while AT 95.83% patients had OPA score ‘1’ [Table 5].

On NPS, BT assessment, patients showed ‘pain score >5’ on parameters like intensity (91.68%), sharpness (70.84%), hot (20.84%), dull (79.17%), cold (4.17%), sensitive (91.66%), itchy (20.84%), unpleasant (95.83%), deep (87.49%) and surface (50%) types of pain which was reduced below ‘5’ in AT assessment in 100% patients [Table 6].

On HADS, at BT, in anxiety assessment; borderline abnormal score was shown by 16.67% and 62.5% patients respectively which reduced up to 16.67% and 4.17% respectively thus in to 58.33% of patients were relieved from abnormal score. AT, no patients had score above ‘0’ of anxiety [Table 7].

Before treatment, patient’s showed scoring of severity of associated symptoms like Agnimandya (Loss of appetite) (41.67%; ‘3’), Hrillasa (Nausea) (20.83%; ‘2’), Aruchi (Tastelessness) (45.83%; ‘4’), Atisara (diarrhoea) (4.17%; ‘3’), Vibhandha (Constipation) (8.33%; ‘1’), Jwara (Fever) (16.67%; ‘1’), Shrama (Exhaustion) (29.17%; ‘1’, 16.67%; ‘2’ and 16.67%; ‘3’) and Shwasa (Dyspnea) (16.67%; ‘1’). AT the scoring changes were found as loss of appetite (8.33; ‘1’), Hrillasa (Nausea) (20.83; ‘0’), Aruchi (Tastelessness) (41.67%; ‘0’), Atisara (diarrhoea) (4.17; ‘1’), Daurbalya (weakness) (37.5; ‘1’), Twakrakshata (Dryness of skin) (71.43; ‘0’), Keshapatana (Hair fall) (8.33; ‘2’), Jwara (Fever) (16.67; ‘1’), Shrama (Exhaustion) (29.17; ‘1’, 16.67; ‘2’ and 16.67; ‘3’) and Shwasa (Dyspnea) (16.67; ‘1’). AT the scoring changes were found as loss of appetite (8.33; ‘1’), Hrillasa (Nausea) (20.83; ‘0’), Aruchi (Tastelessness) (41.67%; ‘0’), Atisara (diarrhoea) (4.17; ‘1’), Daurbalya (weakness) (37.5; ‘1’), Twakrakshata (Dryness of skin) (71.43; ‘0’), Keshapatana (Hair fall) (8.33; ‘2’), Jwara (Fever) (16.67; ‘0’), Shrama (Exhaustion) (37.5; ‘1’) and Shwasa (Dyspnea) (8.33; ‘0’) [Table 4].

Performance status

Before treatment, scorings of ECOG scale were found in 4.17% (4), 4.17% (3), 20.83% (2), 54.17% (1) and 16.67% (0). AT, ECOG score of patients was reflected as 4.17% (4), 4.17% (3), 75.0% (1) and 16.67% (0) [Table 7]. BT, Karnofsky score was found as 25% (90), 37.5% (80), 8.33% (70), 12.5% (60), 8.33% (50) and 8.33% (40). AT, it was reflected as 66.67% (90), 20.83% (80), 4.17% (70), 4.17% (60), and 4.17% (40) [Table 8].

Drug compliance

Duly signed ‘drug compliance form’ showing records of per week consumption of total capsules by each patient was collected during follow-up.

Effect of therapy

Assessment of percentage difference in relief per week

Fifty percent relief was observed between 2nd and 3rd weeks of trial period on FACES scale and NPS while between 3rd and 4th weeks on OPA scale. After completion of trial, 84.10% relief was found on FACES scale and OPA scale. 100% relief was found in cold pain while 92.02%, 74.79%, 79.3%, 78.38% and 66.64% relief was observed in itchy, intensity, unpleasant, deep and hot type of pain respectively as compared to initial status of pain score. TD relieved pain in 8.33%, 16.67% and 33.33% of patients at the end of first, second and third week respectively thus in to 58.33% of patients were relieved from pain while 46.67% patients still complained pain but of reduced intensity [Table 9].

Associated symptoms

Patients suffering from fever got relief during 2nd week. Fifty percent relief in symptoms such as loss of appetite, nausea and insomnia was achieved within a week while in tastelessness, diarrhea, dryness of skin, fatigue and dyspnea; relief was achieved within 2 to 3 weeks. AT, relief found in loss of appetite, tastelessness, insomnia and nausea was 94.87%, 90.91%, 90.91% and 78.57% respectively. More than 75% relief was found in diarrhea and fatigue while 50% relief was found in...
general debility after the completion of trial [Table 10].

Statistical significance and overall effect of therapy

Pain
Statistically reduction in pain was analyzed on FACES pain scale ($P < 0.05$), OPA scale ($P < 0.05$) and NPS. ($P < 0.001$) [Table 9] during and AT with TD except in two patient’s where analgesic was used as a rescue medicine. ‘Complete remission’ was found in 41.67% patients while ‘marked improvement’ was found in 54.17% patients and ‘moderate improvement’ was found in 4.17% patient on cancer pain.

Pain and associated complaints
Statistically significant result was obtained in loss of appetite, nausea, tastelessness, general debility, dryness of skin, fever, fatigue and insomnia [Table 10]. No significant relief was found in diarrhea and hair loss. Diarrhea was presented due to metastatic carcinoma of rectum and hair loss was due to side effect of chemotherapy. However, TD has not created any negative impact on respective symptoms.

‘Complete remission’ was found in 66.67% of patients while ‘marked improvement’ was observed in 33.33% of patients when pain and associated symptoms were assessed together.

Anxiety and depression
Statistically significant reduction in anxiety and depression was found AT on HADS assessment ($P < 0.001$) [Table 11].

Quality of life
Statistically significant improvement was found on FACT-G scale except on social well-being parameter.[Table 11]. Social well-being parameter consists questionnaire of personalized relationship aspects influencing patients mind and eventually health. TD reported for creating positive impact on patient’s psyche.[46] but during this trial period, score of social well-being parameter was unchanged.
Table 6: Effect of Shodhita Bhanga therapy on Neuropathic Pain Scale

| Symptom | TOA | Score (%) |
|---------|-----|-----------|
|         | BT  | AT        |         |
|         | 0   | 1         | 2       | 3       | 4       | 5       | 6       | 7       | 8       | 9       | 10      |
| Intensity| 0   | 0         | 0       | 4.17    | 4.17    | 4.17    | 0       | 4.17    | 4.17    | 41.67   | 37.5    | 4.17    |
|         | 4.17| 37.5      | 25      | 25      | 8.33    | 0       | 0       | 0       | 0       | 0       | 0       |
| Sharpness| 25  | 0         | 4.17    | 0       | 0       | 16.67   | 12.5    | 12.5    | 12.5    | 12.5    | 4.17    |
|         | 54.17|16.67      | 16.67   | 12.5    | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| Hot     | 66.67|0          | 8.33    | 0       | 8.33    | 4.17    | 4.17    | 4.17    | 4.17    | 0       | 0       |
|         | 83.33|4.17       | 4.17    | 0       | 8.33    | 0       | 0       | 0       | 0       | 0       | 0       |
| Dull    | 8.33 | 0         | 4.17    | 12.5    | 8.33    | 16.67   | 8.33    | 29.17   | 12.5    | 4.17    |
|         | 29.17|45.83      | 20.83   | 4.17    | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| Cold    | 91.67|4.17       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 4.17    | 0       |
|         | 95.83|4.17       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| Sensitive| 4.17|0          | 0       | 4.17    | 0       | 4.17    | 8.33    | 8.33    | 37.5    | 20.83   | 12.5    |
|         | 20.83|37.6       | 29.17   | 4.17    | 8.33    | 0       | 0       | 0       | 0       | 0       | 0       |
| Itchy   | 62.5 | 4.17      | 0       | 4.17    | 8.33    | 4.17    | 0       | 3.33    | 4.17    | 0       | 4.17    |
|         | 83.33|16.67      | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| Unpleasant| 4.17|0          | 0       | 0       | 0       | 4.17    | 0       | 8.33    | 37.5    | 33.33   | 12.5    |
|         | 16.67|29.17      | 25      | 16.67   | 8.33    | 0       | 0       | 0       | 0       | 0       | 0       |
| Deep    | 0    | 0         | 0       | 0       | 12.5    | 8.33    | 8.33    | 20.83   | 25      | 25      | 0       |
|         | 16.67|45.8       | 16.67   | 16.67   | 4.17    | 0       | 0       | 0       | 0       | 0       | 0       |
| Surface | 16.67|0          | 20.83   | 4.17    | 8.33    | 16.67   | 12.5    | 8.33    | 8.33    | 0       | 4.17    |
|         | 50   | 41.67     | 4.17    | 0       | 4.17    | 0       | 0       | 0       | 0       | 0       | 0       |

BT: Before treatment, AT: After treatment, TOA: Time of assessment

Table 7: Effect of Shodhita Bhanga therapy on eastern cooperative oncology group performance score

| TOA | Score % |
|-----|---------|
|     | 0       | 1       | 2       | 3       | 4       | 5       |
| BT(%) | 16.67   | 54.17   | 20.83   | 4.17    | 4.17    | 0       |
| AT(%) | 16.67   | 75      | 4.17    | 0       | 4.17    | 0       |

BT: Before treatment, AT: After treatment, TOA: Time of assessment

Table 8: Effect of Shodhita Bhanga therapy on Karnofsky score

| TOA | Score (%) |
|-----|-----------|
|     | 0         | 10      | 20      | 30      | 40      | 50      | 60      | 70      | 80      | 90      | 100     |
| BT(%) | 0         | 0       | 0       | 8.33    | 8.33    | 12.5    | 8.33    | 37.5    | 25      | 0       |
| AT(%) | 0         | 0       | 0       | 4.17    | 4.17    | 4.17    | 20.83   | 66.67   | 0       |

BT: Before treatment, AT: After treatment, TOA: Time of assessment

Performance status
Significant improvement in ECOG ($P < 0.05$) and Karnofsky score ($P < 0.01$) was found. Thus, TD helps in improving performance status QOL in cancer patients [Table 10].

Adverse drug reaction and Cannabis withdrawal scale
No ADR were noted during the trial period. No withdrawal symptoms were noted after completion of trial. Precautions had been taken while prescribing TD for Pitta predominant Prakriti (constitution) patients and those who were reported to have chronic addiction(s) of any form. Patients ($n=1$) who reported burning sensation after TD administration were dropped out from trial.

Discussion
Prevalence of cancer and associated symptoms did not find parallel with any studied parameter of demographic data [Table 1].

Fifty percent relief was found on all the three scales used for assessment of pain within 2–3 weeks of trial period. Relief on pain scales was statistically significant when compared to baseline score [Table 9]. Bhanga; due to its Ushna [24] (Hot) Veerya (Potency) helps in relieving Sheeta (Cold) completely as excess Sheeta Guna (Property) alleviates Vata and hence increases pain. [23] Being Vyavayi [24] (Potent in action) and analgesic in nature, drug helps in instant pain reduction. Due to potency of creating pleasurable effects, helps in achieving feeling of accomplishment of mind’s objects by creating state of euphoria thus, helps in reducing unpleasant pain. Hot pain was relieved less as compared to other parameters, may be due to hot potency and acidic nature of drug. [24] Recent researches reports significant analgesic activity of Cannabis in cancer pain is due to presence of phytoconstituents like tetra-hydrocannabinol (THC) and Cannabidiol (CBD) [26-29] Water-wash processed Cannabis contains 65% THC and low traces of CDB in comparison with unpurified one. [6]

Associated symptoms
Cancer patients often experience cluster of symptoms, which can independently predict changes in patient’s function,
Table 9: Assessment of percentage difference in relief per week and statistical significance on pain

| Interval         | n  | Percentage relief during treatment period | AT | Avg. 50% relief | Statistical significance (AT and BT) |
|------------------|----|------------------------------------------|----|-----------------|-------------------------------------|
|                  |    | BT-1 week | BT-2 weeks | BT-3 weeks | BT-AT | Week | Mean±SEM | t  | P          |
| Scale            |    |           |            |            |       |      |               |    |            |
| Wong-Baker FACES Pain Rating | 24 | 26.39     | 48.54      | 74.10     | 84.10 | 2-3  | 6.42±0.32  | 20.176 | <0.001     |
| Objective Pain Assessment | 24 | 26.39     | 48.54      | 74.10     | 84.10 | 2-3  | 1.83±0.08  | 23.592 | <0.001     |
| Neuropathic Pain Scale |    |           |            |            |       |      |               |    |            |
| Intensity        | 24 | 26.37     | 42.79      | 62.54     | 74.79 | 2-3  | 6.00±0.36  | 16.849 | <0.001     |
| Hot              | 7  | 38.11     | 38.11      | 69.68     | 66.64 | 2-3  | 1.08±1.08  | 2.522  | 0.019      |
| Dull             | 22 | 25.5      | 47.98      | 48.74     | 82.45 | 2-3  | 5.21±0.47  | 11.081 | <0.001     |
| Cold             | 2  | 50        | 50         | 100       | 100   | At 2 | 0.33±0.34  | 0.984  | <0.001     |
| Sensitive        | 23 | 25.67     | 44.18      | 65.99     | 80.32 | 2-3  | 6.04±0.46  | 13.015 | <0.001     |
| Itchy            | 9  | 92.02     | 77.29      | 84.6      | 92.02 | At 1 | 1.88±0.60  | 3.110  | 0.005      |
| Unpleasant       | 9  | 23.48     | 43.95      | 75.28     | 79.3  | 2-3  | 6.58±0.35  | 18.780 | <0.001     |
| Deep             | 24 | 32.91     | 45.2       | 68.52     | 78.38 | 2-3  | 3.50±0.51  | 6.806  | <0.001     |
| Surface          | 20 | 33.33     | 59.83      | 66.34     | 85.98 | At 2 | 3.46±0.50  | 6.918  | <0.001     |

P<0.05, P<0.02, P<0.01, P<0.001 when compared with initial value (paired ttest). SEM: Standard error of mean, BT: Before treatment, AT: After treatment.

Table 10: Assessment of percentage difference in relief per week and statistical significance on associated symptoms

| Symptoms         | n  | Percentage relief during treatment period | 50% relief In week | Statistical significance (AT and BT) |
|------------------|----|------------------------------------------|-------------------|-------------------------------------|
|                  |    | BT-1 week | BT-2 weeks | BT-3 weeks | BT-AT | Mean±SEM | t  | P          |
| Daurbalya (weakness) | 17 | 18.63     | 25.49      | 42.16      | 50    | 4        | 0.83±0.21 | 3.890 | <0.001     |
| Shrama (Exhaustion)  | 15 | 22.22     | 37.79      | 55.56      | 65.56 | 2-3      | 0.63±0.15 | 4.307 | <0.001     |
| Agnimandya (Loss of appetite) | 13 | 50        | 67.95      | 85.90      | 94.87 | 1        | 1.42±0.28 | 5.027 | <0.001     |
| Nidralpata (Insomnia) | 11 | 53.03     | 83.33      | 90.91      | 90.91 | 1        | 0.17±0.08 | 2.145 | 0.043      |
| Aruchi (Tastelessness) | 11 | 0         | 34.09      | 84.09      | 90.91 | 2-3      | 0.42±0.16 | 2.632 | 0.015      |
| Hrillasa (Nausea) | 7  | 57.14     | 71.43      | 85.71      | 78.57 | 1        | 1.67±0.41 | 4.053 | <0.001     |
| Twakrukshata (Dryness of skin) | 7  | 14.29     | 28.57      | 57.14      | 50    | 2-3      | 0.25±0.09 | 2.769 | 0.011      |
| Jwara (Fever) | 4  | 75        | 100        | 100        | 100   | 1        | 0.17±0.08 | 2.145 | 0.043      |
| Shwasa (Dyspnea) | 4  | 0         | 75         | 75         | 100   | 2        | 0.17±0.08 | 0.08  | 0.043      |
| Vibandha (Constipation) | 2  | 8.33      | 8.33       | 100        | 100   | 3        | 0.08±0.058 | 1.446 | 0.162      |
| Keshapatana (Hair fall) | 2  | 0         | 0          | 25         | 25    | -        | 0.04±0.04 | 1.000 | 0.328      |
| Atisara (diarrhoea) | 1  | 33.33     | 33.33      | 66.67      | 66.67 | 2-3      | 0.08±0.08 | 1.000 | 0.328      |

P<0.05, P<0.02, P<0.01, P<0.001 when compared with initial value (paired ttest). SEM: Standard error of mean, BT: Before treatment, AT: After treatment, n: Number of patients suffering from treatment failures and post-therapeutic outcomes. Bhanga being antipyretic reduces fever effectively. Statistically significant effect was obtained in symptoms like loss of appetite, tastelessness, nausea, general debility, dryness of skin, fever, fatigue and dyspnea. More than 90% relief was found in loss of appetite, tastelessness and insomnia. After administration of TD, 50% relief was achieved within seven days in symptoms like loss of appetite, nausea, fever and insomnia while it took four weeks for improvement in fatigue symptom. Anti-pyretic action of Bhanga is due to its Tikta (Bitter) Rasa (Taste) and Swedajanana (hyperhidrosis) nature.
Table 11: Statistical significance for anxiety, depression, quality of life and performance status on respective scales

| Parameter/scale (n=24) | Mean±SEM | SD | t | P       |
|------------------------|----------|----|---|---------|
| Anxiety and depression (Hospital Anxiety and Depression Scale) | | | | |
| Anxiety                | 7.167±0.996 | 4.878 | 7.197 | <0.001 |
| Depression             | 4.292±0.797 | 3.906 | 5.382 | <0.001 |
| QOL (FACT-G scale)    | | | | |
| Physical well being   | 8.208±0.849 | 4.160 | 9.667 | <0.001 |
| Social                | 0.0417±0.185 | 0.908 | 0.225 | >0.05   |
| Emotional             | 3.458±1.077 | 5.275 | 3.212 | 0.004   |
| Functional            | 3.250±0.615 | 3.011 | 5.288 | <0.001 |
| Performance status    | | | | |
| ECOG                  | 0.250±0.109 | 0.532 | 2.304 | 0.031   |
| Karnofsky             | 11.25±3.47  | 17.020 | 3.238 | 0.004   |

P<0.05, P<0.02, P<0.01, P<0.001 when compared with initial value (Paired t test). ECOG: Eastern Cooperative Oncology Group, QOL: Quality of life.

Bhanga imparts Deepana (Appetizer), Pachana (Digestive) action thus improves loss of appetite, fever, nausea. Due to Grahi (Withholdings secretions) action; it helps to reduce diarrheal frequency. Being Balya (tonic) in nature, it helps in replenishment of Dhatu (Body elements) and decreases fatigue. According to Ayurveda, Dhatuparinamana (Formation of new body constituents/elements) is a sustainable process and takes time of whole month. Thus, achieving 50% result in fatigue within a month; in patients suffering from cancer; patients already gets deteriorated by the disease and its treatment modalities like chemotherapy and radiation.

Cannabis is well established medicine for chemotherapy induced nausea and vomiting, loss appetite, weight loss, pain, depression, pain with depression, anxiety, sleep disorders, asthma and diarrhea due to its constituents like THC and nabilone.

Anxiety and depression
Anxiety and depression, commonly co-exist in cancer patients. TD showed significant reduction in complaint of anxiety and depression. Bhanga creates pleasure and pleasantness, thus; calms patient. Being Medhya (memory enhancer) and Uttejaka (Stimulant) in nature helps to improve intellect and alertness of mind respectively.

Clinical researches report effectiveness of constituents of Cannabis such as nabilone and cannabidiol for the management of both anxiety and depression simultaneously.

Quality of life
Statistically significant improvement in FACT-G scale’s parameters confirms the processed herbal form of Cannabis possess role in improving QOL in cancer patients by combating multiple symptoms, similarly like its extract. Impact of TD on social behaviour is difficult to co-relate from this study. Clinical researches report, analgesic potential and improvement of QOL by Cannabis is due to its constituent nabilone.

Performance status
Disease cancer has negative impact on all systems of body. TD has showed significant improvement in performance status, i.e., functioning status of a patient. Cannabis is well reported for aphrodisiac, adaptogenic and immune-modular actions. It helps in nourishing and improvement of body tissue and immunity. Cannabis being appetizer, digestive, tonic, antipyretic, analgesic, aphrodisiac, adaptogen, quick acting, memory tonic etc., helps in skirmishing pain along with associated cluster of symptoms which eventually helps in improving QOL in patients.

Use of Cannabis helps to reduce consumption of opioids. Clinically it is proved effective as adjunctive of morphine and found helpful in decreasing morphine induced side effects. Still, when administered in unprocessed form Cannabis has risk of habit formation and other cognitive impairments. The fundamental behind purification of Cannabis is to reduce its ill effects. With consumption of processed Cannabis for a month, no withdrawal symptoms was noted, thus, proves a promising drug in the field of palliative oncology care cancer.

Conclusion
Administration of Jalaprakshalana Shodhita Bhanga (water-wash processed Cannabis) leaves powder in dose of 250 mg thrice a day with 50 ml of cow’s milk and 4 g sugar as an adjuvant, for a period of 1 month; significantly relieves pain, anxiety and depression of cancer patients without creating any major side effects, dependency and withdrawal symptoms. Processed Cannabis is significantly effective for improvement in QOL of a cancer patient.

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Conflicts of interest
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