The Journal of Medical Research 2024; 10(1):12-19

The Journal of Medical Research

Research Article

JMR 2024; 10(1):12-19
January- February
ISSN:2395-7565

www.medicinearticle.com
Received:13-01-2024
Accepted:01-03-2024
DOI: 10.31254/jmr.2024.10104

Evaluating benefits of a polyherbal oral formulation PRA-5 in patients with head and neck cancer undergoing chemoradiotherapy: Results of a pilot study

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Abstract

Background: Radiotherapy/chemoradiotherapy (RT/CRT) causes widespread cellular damage leading to undesirable side-effects in patients with cancer. With other comorbidities, these patients are highly susceptible to infections. This pilot study assessed the benefits of an innovative oral polyherbal formulation (PRA-5) in patients with head and neck cancer (HNC) undergoing RT/CRT. Materials and methods: In this randomized, controlled, proof-of-concept study, 21 patients with HNC undergoing RT/CRT were randomized 1:1 to receive thrice daily tablets of PRA-5 (n=10) or placebo (n=11) up to 52 days. Patients were monitored weekly for acute toxicities and their various clinical, biochemical, and hematological parameters were evaluated at prespecified timepoints. Data were analyzed using 't' test; a P-value of < 0.05 was considered as significant. Results: Overall, the baseline characteristics were well-balanced between the treatment groups. PRA-5 group showed 3% increase in malonaldehyde post RT/CRT compared with a 24% increase in the placebo group. Total antioxidant status, white blood cells, and platelet count decreased in patients receiving placebo whereas these parameters increased in patients receiving PRA-5. There was no significant difference in other biological and hematological parameters between the two groups. Skin reactions and oral mucositis of various grades were noted in both groups. PRA-5 showed beneficial effects in reducing oral mucositis post-RT/CRT. Conclusions: PRA-5 was well-tolerated in patients with HNC receiving RT/CRT. Compared with placebo, PRA-5 supplementation showed considerable protection from radiation-related cellular damage. The pilot study showed that PRA-5 could be used as a safe and effective supplement to reduce the RT/CRT related side-effects in patients with HNC.

Keywords: Radiotherapy, Chemotherapy, Chemoradiotherapy, Head and neck cancer, Polyherbal oral formulation, Standardized herbal extracts.

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INTRODUCTION

According to the World Health Organization (WHO), cancer is responsible for almost 13% of all fatalities. By 2030, it is predicted that this figure might reach to 45% [1]. Each year, millions of individuals are diagnosed with cancer, and more than 50% of those lose their life due to cancer [2]. Squamous cell carcinoma is the most common type of head and neck cancer (HNC), which arises from the mucosal epithelium of the oral cavity, larynx, and pharynx [3]. HNC accounts for around 3% of all malignant tumors in the Western countries. The oral cavity accounts for nearly 48% of tumor cases, with squamous cell carcinoma representing 90% of these occurrences [4].

Radiotherapy (RT) and/or chemoradiotherapy (CRT) are commonly used methods for the treatment of cancer and are able to destroy remaining cancer cells after surgery [5]. Although the goal of RT/CRT is to harm only the cancerous cells, it also damages the normal tissues by direct deposition of energy into essential macromolecules or by reactive free radical generation that interacts with biomolecules and causes oxidative damage [6]. Various radiation-induced side-effects include loss of taste, mucositis, xerostomia, and severe dentition degradation that can result in loss of masticatory function [7]. Radiation may cause myelosuppression and immunosuppression [8,9]. Antioxidants, such as glutathione peroxidase, catalase, and superoxide dismutase, protect normal cells against radiation damage through a variety of enzymatic systems [10].

Over the last few decades, researchers have screened and tested synthetic and natural compounds in the hopes of discovering effective drugs that can reduce radiation damage. Radioprotectants are categorized into various classes including antioxidants, immunomodulators, and bio-stimulants depending on how

they work [11]. Radio sensitizing properties are also shown by the plant-derived (herbal-based) polyphenolic chemicals [10]. Medicinal herbs are known to possess anti-inflammatory, immunomodulatory, and antioxidant activities and could be evaluated for their potential use in mitigating/preventing radiation-related toxicities [12]. There are plenty of studies pointing to the benefits of various herbs in cancer patients undergoing RT/CRT. However, duly approved, well-defined dosage forms of herbal extracts with clinically proven safety and efficacy are rare.

PRA-5 is a polyherbal formulation (patented formula; Indian Patent 301192) that contains a synergistic combination of hydroalcoholic extracts of five herbs (ashwagandha, giloy/guduchi, behada, turmeric, and holy basil) [13, 14]. PRA-5 was found effective in protecting gamma radiation-induced deoxyribonucleic acid (DNA) strand breaks [13]. It also shows antimicrobial, antioxidant, and anti-inflammatory activity [14,15]. In this pilot study, we assessed the benefits of PRA-5 in patients with HNC undergoing RT/CRT. The study also assessed various clinical, biochemical, and hematological parameters along with skin, oral, gastro intestinal toxicities and adverse reactions.

MATERIALS AND METHODS

This was a single-center, randomized, controlled, proof-of-concept study. Patients with HNC undergoing RT/CRT were randomized 1:1 to receive thrice daily (TID) tablets of PRA-5 or placebo (Figure 1). The primary objective of the study was to see the effect of PRA-5 on various hematological and biochemical parameters which are affected by RT/CRT in patients with HNC. The study also assessed the safety of PRA-5 in these patients.

Patients who met the inclusion criteria – histopathologically proven stage I, II, III and IV A HNC, age between 30–75 years, normal hematological and biochemical functions, Karnofsky performance status more than 80% were included in this study. Patients who had previously received RT and/or CRT, stage IV B HNC, age more than 75 years, had other comorbidities, and pregnant and lactating women were excluded from the study. Patients were enrolled on a first come first serve basis. Randomization was done by lottery method both for placebo and test groups. The randomization process was impacted due to COVID-19; patients who were COVID-19 positive were excluded so as to avoid contact with people and equipment in the radiation room.; Placebo group had one patient more than the PRA-5 group.

The study was conducted in accordance with the Declaration of Helsinki. All patients provided a signed informed consent before being enrolled in the study. The study was approved by the Institutional Ethics Committee (PIMS/IEC/DR/2018/16) and has been registered in the Clinical Trial Registry of India (CTRI/2019/02/017414).

All patients received external beam radiotherapy (EBRT) by 3-dimensional conformal radiotherapy (3D-CRT) on the 6 mega-voltage (MV) linear accelerator (Clinac DBX: Varian Medical System, Palo Alto, CA, USA). Planning computed tomography (CT) scan of the head and neck region was done with mold to maintain the patient positioning and immobilization during each treatment on Siemens Healthcare, Erlangen, Germany CT scan machine, for all patients. Planning CT scan images were transferred to the Eclipse version 15.03 treatment planning system (TPS) contouring stations using the Digital Imaging and Communications in Medicine (DICOM) protocol. Planning was done on the Eclipse TPS.

EBRT treatment was delivered five days a week for an average of 52 days, with a fraction size of 1.8–2 Gy/day to the total dose of 60-66 Gy in 30–35 fractions (reduced field after 44–46 Gy for spinal cord preservation) to the head and neck region with concurrent weekly cisplatin 40 mg/m^2 in concurrent CRT plan.

Patients in the test group received a 600 mg tablet of PRA-5 three times a day, morning (half an hour before RT/CRT), after lunch, and after dinner along with water for a duration of 52 days or completion of the RT/CRT course, whichever was earlier. Each tablet of PRA-5 comprised of hydroalcoholic extracts of-

Withania somnifera (Ashwagandha) (root)- 100 mg
Tinospora cordifolia (Giloy or Guduchi) (stem)- 100 mg
Terminalia bellirica (Behada) (fruit)- 100 mg
Curcuma longa (Turmeric) (rhizome)- 100 mg
Ocimum sanctum (Holy basil) (leaf)- 100 mg
Piper nigrum (Black pepper) (fruit)- 2.5 mg and
Excipients quantity sufficient to make- 600 mg.

Other group received placebo tablets as per the above schedule. The tablets were supplied in a high-density polyethylene bottle containing 60 tablets.

Patients were monitored weekly for acute toxicities; their clinical and hematological parameters were analyzed at the baseline, during the treatment, and end of treatment. However, data are presented only for baseline and end of treatment. A single physician assessed general health criteria and toxicity symptoms. Blood samples were collected every week for biochemical and hematological analysis. Biochemical analysis of the blood samples was performed using VITROS 5600 dry technology. Unicell DxH 800 Coulter Cellular Analysis system was used for hematological analysis. Serum malonaldehyde (MDA) was determined by the method described by Satoh (1978) [16] and serum total antioxidant status (TAS)/power was determined by the method described by Benzie and Strain (1996) [17].

This was a proof-of-concept study, therefore, a sample size of 20 participants was considered sufficient. A Student's t-test was used to analyze the data, and a *P*-value lower than 0.05 was considered as significant.

RESULTS

A total of 21 patients met the eligibility criteria and were enrolled in the study (PRA-5, n=10; placebo, n=11). One patient from the PRA-5 group did not adhere to the treatment protocol and was excluded from the final analysis. Overall, the baseline characteristics were comparable between the PRA-5 and placebo groups (Table 1). Majority of the patients (>80%) were male and received RT/CRT for HNC.

In the placebo group, patients experienced a significant increase in serum MDA level (24%), and a significant decrease in TAS level (10%). On the other hand, patients receiving PRA-5 had a marginal increase of 2.5% in serum MDA level and contradictory to the placebo group, TAS level increased by 5.3% (Table 2). In the placebo group, there was a significant decrease in hemoglobin level (10%), platelets (21%), and white blood cell (WBC) count (19%). Whereas, in the PRA-5 group, there was an increase of 5%, 11%, and 17% in hemoglobin level, platelets, and WBC count, respectively (Table 2).

There were no substantial differences in serum glucose and serum amylase levels between patients in the placebo and PRA-5 groups (Table 2). Post-treatment, serum biochemical parameters related to kidney function (urea, creatinine, and electrolytes like serum Na+ and K+) remained unchanged in the placebo and PRA-5 groups. RT/CRT increased the serum uric acid levels in the placebo group whereas administration of PRA-5 did not alter the serum uric acid levels. There was no significant difference in various liver function tests (serum total bilirubin and alanine aminotransferase) between the placebo and PRA-5 groups post-RT. Total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels did not differ between the placebo and PRA-5 groups post-RT/CRT (Table 2).

PRA-5 was well-tolerated and there were no serious adverse events reported during the study. Skin reactions and oral mucositis of various grades were noted in both the groups (Table 3). None of the patients in the PRA-5 group developed any infections during the study.

Table 1: Baseline characteristics

Characteristics, n (%)	Placebo (N=11)	PRA-5 (N=9)
Age at disease		
≤ 40 years	1 (9.1)	2 (22.2)
41- 50 years	5 (45.4)	2 (22.2)
51- 60 years	5 (45.4)	2 (22.2)
61-75 years	0 (0)	3 (33.3)
Gender		
Male	9 (81.8)	8 (88.9)
Female	2 (18.2)	1 (11.1)
Histopathology		
Squamous cell carcinoma	10 (90.9)	9 (100.0)
Adenocarcinoma	1 (9.1)	0 (0)
Diagnostic sites		
Oral cavity	6 (54.5)	5 (55.5)
Oropharynx	2 (18.2)	1 (11.1)
Hypopharynx	2 (18.2)	2 (22.2)
Larynx	1 (9.1)	1 (11.1)
Stages of Disease:		
Stage I	2 (18.2)	1 (11.1)
Stage II	0 (0)	3 (33.3)
Stage III	4 (36.4)	3 (33.3)
Stage IV A	5 (45.4)	2 (22.2)
Treatment:		
Radiation alone	3 (27.3)	1 (11.1)
Chemoradiotherapy	8 (72.7)	8 (88.9)

N, number of patients in a group; n, number of patients with a particular characteristic

Table 2: Serum biochemical and hematological parameters

Parameters	Placebo (N=11)			PRA-5 (N=9)		
	Baseline	EOT*	Difference	Baseline	EOT*	Difference
Malonaldehyde (nmole/dl)	160.5 ± 30.2	199.2 ± 34.1 ☹	▲38.7; *P*<0.01	169.7 ± 24.3	174.1 ± 23.7 ☺	▲4.4; *P*<0.72
TAS	90.2 ± 13.1	81.2 ± 9.8 ☹	▼-9; *P*<0.04	95.2 ± 14.2	100.2 ± 15.1 ☺	▲5; *P*<0.4
Hemoglobin (g/dl)	12.5 ± 1.53	11.3 ± 1.55 ☹	▼-1.2; *P*<0.03	12.3 ± 1.35	12.88 ± 1.44 ☺	▲0.58; *P*<0.41
Platelets (10^3 / ml)	222 ± 53	175 ± 33 ☹	▼-47; *P*<0.04	249 ± 59	276 ± 47 ☺	▲27; *P*<0.3
WBC (10^3 / ml)	7.07 ± 1.26	5.70 ± 1.01 ☹	▼-1.37; *P*<0.01	7.17 ± 0.9	8.41 ± 1.17 ☺	▲1.24; *P*<0.02
Amylase (IU/L)	101.3 ± 12	98.7 ± 28 ☹	▼-2.6; *P*<0.79	110.2 ± 46	115.1 ± 41 ☺	▲4.9; *P*<0.8
Glucose (mg/dl)	86.2 ± 7.3	90.2 ± 8.00	▲4; *P*<0.6	92.6 ± 8.8	90.2 ± 9.5	▼-2.4; *P*<0.3
Urea (mg/dl)	23.4 ± 5.8	25.5± 6.1	▲2.1; *P*<0.43	23.6 ± 7.6	26.1 ± 7.1	▲2.5; *P*<0.6
Creatinine (mg/dl)	0.66 ± 0.11	0.79 ± 0.16	▲0.13; *P*<0.5	0.75 ± 0.19	0.65 ± 0.15	▼-0.1; *P*<0.8
Sodium (meq/L)	136.1 ± 2.9	137.2 ± 3.9	▲1.1; *P*<0.5	138.5 ± 4.3	140.1 ± 4.8	▲1.6; *P*<0.9
Potassium (meq/L)	4.40 ± 0.7	4.2 ± 0.4	▼-0.2; *P*<0.4	4.1 ± 0.5	4.3 ± 0.6	▲0.2; *P*<0.9
Total cholesterol (mg/dl)	169.2 ± 30	165.4 ± 25	▼-3.8; *P*<0.7	175.8 ± 29	169.4 ± 23	▼-6.4; *P*<0.6
HDL (mg/dl)	33.6 ± 9.8	32.4 ± 4.1	▼-1.2; *P*<0.8	37.7 ± 6.1	35.2 ± 4.3	▼-2.5; *P*<0.4
Triglycerides (mg/dl)	132.1 ± 25.5	168.2 ± 28.1	▲36.1; *P*<0.05	125.7 ± 25.1	165.3 ± 33.1	▲39.6; *P*<0.03
Total bilirubin (mg/dl)	0.55 ± 0.11	0.60 ± 0.13	▲0.05; *P*<0.36	0.51 ± 0.14	0.53 ± 0.1	▲0.02; *P*<0.38
SGPT (IU/L)	16.2 ± 4.9	16.6 ± 5.2	▲0.4; *P*<0.9	18.7 ± 5.0	20.3 ± 6.4	▲1.6; *P*<0.59
Uric acid (mg/dl)	4.18 ± 0.35	4.82 ± 0.73 ☺	▲0.64; *P*<0.02	3.83 ± 0.8	4.58 ± 0.6 ☺	▲0.75; *P*<0.06

*At day 52; ☺ Positive outcome; ☹ Negative outcome; ▼ Reduction; ▲ Increase
Unless otherwise stated, the results are reported as Values ± SD.
P values are based on t-test, *P*<0.05 was considered significant.
HDL, high density lipoprotein; SD, standard deviation; SGPT, Serum Glutamic Pyruvic Transaminase; TAS, total antioxidant status; WBC, white blood cells

Table 3: Acute toxicities post-RT/CRT as per CTCAE grading (Version – 5.0)

Toxicities, n	Placebo (N=11)			PRA-5 (N=9)		
	Day 0	Day 21	Day 52	Day 0	Day 21	Day 52
Skin Reaction						
Grade 0: Nil	11			9		
Grade 1: Faint erythema or dry desquamation		6			7	
Grade 2: Moderate to brisk erythema		4	6		2	5
Grade 3: Moist desquamation		1	4			4
Oral Mucositis						
Grade 0: Nil	11			9		
Grade 1: Asymptomatic or mild mucositis		6			5	
Grade 2: Moderate fibrinous / cough / dysphagia		4	8		4	5
Grade 3: Severe mucositis/dysphagia		1	3			4
Gastro-intestinal						
Grade 0: Nil	11	4	2	9	4	1
Grade 1: Mild nausea/vomiting/diarrhea		7	9		5	8

CRT, chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients in a group; n, number of patients experiencing acute toxicity; RT, radiotherapy

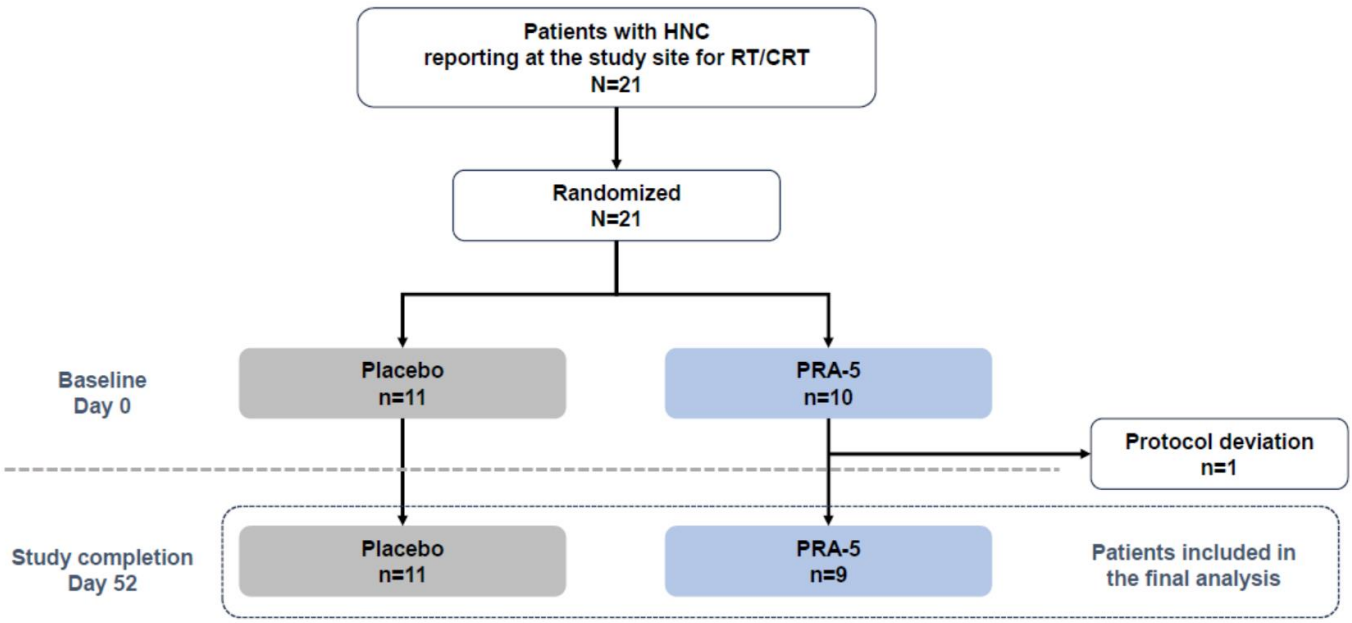

Figure 1: Study design and patient disposition

CRT, chemoradiotherapy; HNC, head and neck cancer; N, total number of patients; n, number of patients in each group; RT, radiotherapy

DISCUSSION

Patients with cancer need RT/CRT either for curative or palliative purposes; however, it is well-known that RT/CRT is associated with side-effects [18]. There is a need for treatment with supplemental products which can mitigate radiation-induced cellular damage. Compared with placebo, the polyherbal formulation, PRA-5, showed promising results in this pilot study in patients with HNC. Use of PRA-5 as a supplement was found to reduce serum MDA levels and increase TAS levels. Patients undergoing RT/CRT show a reduction in the levels of hemoglobin, platelets, and WBC which results in compromised immunity and hence more susceptibility of patients to bacterial, fungal and viral infections. The increase in parameters such as platelet and WBC count is strong evidence of the immuno-protective and immuno-boosting properties of PRA-5. There was no significant difference between the PRA-5 and placebo groups for other clinical, biochemical and hematological parameters tested in the study, indicating safety of the formulation. None of the patients reported any drug-related or serious adverse events.

MDA is one of the markers of free radical-mediated lipid peroxidation and is responsible for tissue injury. A significant correlation exists between elevated serum MDA levels and decreased antioxidant properties [19]. Compared with placebo, supplementation with PRA-5 showed lower levels of MDA and increased TAS, thus indicating a protective effect of PRA-5 in preventing radiation-related cellular damage. The antioxidant action of PRA-5 could be attributed to the synergistic effect of the individual herbal components of the formulation. Free radical scavenging and antioxidant properties of *Withania somnifera*, [20] antioxidant and DNA-protective activities of *Terminalia bellirica* extracts, [21,22] metal chelation and free radical scavenging of *Tinospora cordiofollia*, [23] antioxidant and radio-protective activity of *Curcuma longa* [6] have been previously reported in the literature. According to several studies, patients receiving oral antioxidant treatment after RT had significant reduction in MDA level compared with patients who did not receive any antioxidant supplement [24-26]. Our results are in line with the outcomes of these studies. We have previously reported the radioprotective, antimicrobial, antioxidant, and anti-inflammatory activities of PRA-5 [13-15]. The results from this proof-of-concept study further substantiate the results from our previous studies.

The immune system is suppressed after RT/CRT in cancer patients, making them more prone to bacterial, viral and fungal infections [27]. Clinicians prescribe various antioxidants and vitamin supplements to overcome these effects but patients are still prone to infections. PRA-5 shows a broad spectrum of beneficial effects in a single formulation. It acts as an antioxidant and immune booster, it helps in managing mucositis, and exerts strong anti-infective properties.

Various flavonoids and polyphenols in herbs have been associated with antibacterial, anti-inflammatory, antioxidant, hepato-protective, and other pharmacological actions [28]. PRA-5 is rich in various flavonoids, flavanols, alkaloids, glycosides, polyphenols and their derivatives. It has also demonstrated protective effects against radiation [14]. The unique combination of five herbs in the formulation seems to have a synergistic effect that might help to protect and stimulate the hemopoietic system. Despite exposure to radiations, patients in the PRA-5 showed an increase in hemoglobin, platelets, and WBC levels, indicating protection of natural immunity against radiation induced damage. There were no significant changes in levels of monocytes, eosinophils, and basophils in patients receiving PRA-5, indicating safety of the product.

Patients with oral precancerous conditions and oral cancers experience a reduction in the serum lipid profile (total cholesterol, LDL, HDL, and LDL) [29]. This decrease could be due to an increase in lipid peroxidation of cellular membranes of these cells [30]. These lipids are derived by cells from circulating lipoproteins, and the breakdown of these main lipoprotein components can lower serum lipid levels. In our study, a decrease in total cholesterol, HDL, and LDL was observed; however, serum triglycerides increased slightly at the end of RT. This could be due to stressful conditions causing lipolysis. In case of steroid treatment, increase in blood glucose levels is a common side-effect owing to effect on pancreas. Serum glucose levels were unaffected during RT/CRT and PRA-5 supplementation, indicating no negative effect of the formulation on the pancreas.

Oral mucositis, inflammation or ulceration of the oral mucosa, is one of the most prevalent side-effects of RT/CRT in patients with HNC. Ulcers in the oral cavity affect ability to ingest food, thus depriving patients of essential nutrition. Studies have shown that the frequency of oral mucositis progressed from grade 2 to grade $\geq$ 3 in patients who did not receive any supplementary treatment along with RT [31,32]. Studies have reported the beneficial outcomes of turmeric-based oral rinse [33] and *Glycyrrhiza glabra* [34] in managing oral mucositis. In our study, moderate to brisk erythema grade 2 was noted in both placebo and PRA-5 treated groups, while moist desquamation was observed in a smaller number of patients receiving PRA-5 vs placebo. Grade 2 moderate fibrinous/cough/dysphasia was observed in ~55% of patients in the PRA-5 group versus ~72% in the placebo group. None of the patients had Grade 2 gastrointestinal symptoms in both the groups. It is reported that medicinal plant extracts improve oral mucositis via immunomodulatory, anti-inflammatory, antiseptic, wound healing, and antioxidant activities resulting from various alkaloids, flavonoids, terpenes, etc. present in the medicinal plants [28]. It can be concluded that PRA-5 is effective in reducing the intensity of oral mucositis but cannot totally prevent its occurrence at the existing dosage of 3 tablets/day. Increase in dosage to 6 tablets/day is likely to be beneficial and further reduce incidence of oral mucositis and cough. The PRA-5 formulation is non-toxic and did not cause any other undesired/untoward effects.

Being a single center study, the study had its own limitations. This was a proof-of-concept study and hence the number of patients included in this study was small. The study did not include patients suffering from associated and comorbid conditions which might impact the outcomes in real-life situation. Additional studies in larger patient population in clinical and/or real-world settings at different centers could substantiate and strengthen the outcomes of PRA-5 observed in this pilot study.

CONCLUSION

To the best of our knowledge, PRA-5 is the first patented, legally approved, and clinically tested polyherbal formulation developed as a well-defined oral dosage form of standardized herbal extracts to reduce side-effects of RT/CRT in cancer patients. PRA-5 acts as a natural radioprotective, antioxidant, anti-infective, and immune booster formula that protects normal cells against cellular and DNA damage caused by ionizing radiations locally as well. PRA-5 was found to be beneficial in patients with oral mucositis. These results nominate PRA-5 as a supplementary agent to attenuate radiation-induced damage in cancer patients undergoing RT/CRT. The phytochemicals that provide beneficial effects of the formulation in patients with HNC could also prove beneficial in all other types of cancer sites in patients undergoing RT/CRT**.**

Author Contributions

Suresh Jangle: writing, reviewing, editing, and data curation. Vandana Jain: data review and clinical inputs. Rahul Kunkulol: data review and analysis. Parikshit Bansal: manuscript revisions and formulation related aspects. All authors had complete control over the content of the manuscript and they have critically reviewed and approved all drafts of the manuscript. All authors take complete ownership of accuracy and integrity of the data presented in this manuscript.

Acknowledgments

The authors are thankful to Orthodiagnostics for the supply of reagent kits for biochemical investigations. The authors would like to acknowledge medical writing support by Lakshya Untwal (M. Tech.) in accordance with GPP 2022 guidelines (https://www.ismpp.org/gpp-2022).

Conflict of Interest

The authors declare no conflict of interest.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Institutional Ethics Committee (PIMS/IEC/DR/2018/16) and has been registered in the Clinical Trial Registry of India (CTRI/2019/02/017414).

Informed Consent

All patients provided a signed informed consent before being enrolled in the study.

Data Availability Statement

All study data are described within the manuscript. Anonymized patient-level data could be requested from the corresponding author.

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ABBREVIATIONS

CRT- Chemoradiotherapy
CT- Computer tomography
DICOM- Digital Imaging and Communications in Medicine
DNA- Deoxyribonucleic acid
EBRT- External beam radiotherapy treatment
HDL- High-density lipoprotein
HNC- Head and neck cancer
LDL- Low-density lipoprotein
MDA- Malonaldehyde
MV- Mega-voltage
RT- Radiotherapy
TAS- Total antioxidant status
TID- Thrice daily
TPS- Treatment planning system
WBC- White blood cells
WHO- World Health Organization

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