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Efficacy of *Varunadi Ghritha* (polyherbal compound) in treated head and neck cancer cases as a biological response modifier

Divya Ravindran, Indhu Hariharan[1], Richard Muwonge[2], Rejnish R. Kumar, M. Radhakrishna Pillai[1], Kunnambath Ramadas

Department of Radiation Oncology, Regional Cancer Centre, Thiruvananthapuram, [1]Integrated Cancer Research Program, Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, Kerala, India, [2]Early Detection and Prevention Section, International Agency for Research on Cancer, Lyon, France

Abstract

Background: Persistent immune suppression is reported in Head and Neck Cancers (HNC) even after treatment and a higher recurrence rate was observed in patients with poor CD3 count. Loco regional recurrences and second primary tumours are the common forms of failure in head and neck cancers. Several agents have been tried to overcome this problem without much benefit. In Ayurveda, several plant based products have been reported to have anti-tumour and immunomodulatory properties. **Aim:** To test the role of *Varunadi Ghritha,* as an immunomodulator in apparently healthy, treated and controlled HNC patients and to evaluate its effectiveness in preventing locoregional relapses and development of second primary tumours. **Materials and Methods:** Total 78 patients of treated head and neck cancers were randomly selected for intervention and control group. Patients in the intervention group (*n* = 38) received *Varunadi Ghritha,* 5gms twice daily for one year and followed up to two years. Patients in the control group (*n* = 40) were followed up at regular intervals. Immune parameters were assessed in the peripheral blood at base line and at the end of administration of the study compound. **Results:** In the intervention group, mean percentage increase in CD3, CD19 and CD16 positive cells were significantly higher after the administration of the study compound compared to the control group indicating an immunomodulatory effect of the study compound. A non-significant improvement in disease control was observed in patients with advanced stage of disease in the intervention group. **Conclusion:** Administration of *Varunadi Ghritha* resulted in an increase in T cell counts in patients with treated HNC.

Key words: Ayurveda, head and neck cancer, immunomodulation, loco-regional control, second primary tumour

Introduction

Head and Neck Cancer (HNC) is a major health problem world over and especially in India. The incidence of this cancer varies from 22.8–28.6 per 100,000 populations among males and 6.9–11.2 per 100,000 females in various cancer registries in India. In Thiruvananthapuram, it is estimated to be 21.4 and 9.1 per 100,000 among men and women respectively.[1] The 5-year survival after treatment is poor, mainly due to residual disease following treatment or development of loco-regional recurrences or Second Primary Tumours (SPT). Most loco-regional recurrences develop during the first two years following treatment. Even among successfully treated patients with early-stage disease, about 15-20% develops SPT over a five years period.[2-4] The clinical manifestations of carcinogenesis occurring in head and neck region support the field cancerization concept. The high frequency of SPT in treated HNC patients are attributed to field cancerization, which assumes that the index tumour and second primaries result from progression of commonly initiated premalignant lesions.[5-7]

In Ayurveda, there are several plant based products which have reported anti-tumour properties and the ability to improve the immune system of patients.[8] The study compound *Varunadi Ghritha* has traditionally long been used by Ayurvedic physicians in the management of tumours of the head and neck; both benign and malignant.[9,10] It is reported to be free of any side effects and no toxicity has been reported for this compound

Address for correspondence: Dr. K. Ramadas,
Medical Superintendent & Prof. of Radiation Oncology,
Regional Cancer Centre, Medical College P.O.,
Trivandrum- 695 011, Kerala, India.
E-mail: ramdasrcc@rediffmail.com

so far. *Varunadi Ghritha* is also frequently advised for cancer patients who have completed radiation and chemotherapy for preventing the recurrence of the disease by general practitioners of Ayurveda. Though no scientific study with *Varunadi Ghritha* has been reported yet many of the individual components used for the preparation of this compound [Table 1] have been studied separately for their anti-tumour properties.

The anti - cancer activity and cytotoxic activity as well as immunomodulatory effect of *Semecarpus anacardium* Lf. fruit nuts has been demonstrated.[11-13] Extracts of *S. anacardium* have been found to induce programmed cell death.[14] Extracts from *Aegle marmelose* L. (Correa) have been found to inhibit *in vitro* proliferation of human tumour cell lines and its anticancer effect has also been shown *in vivo*.[15-16] Niazimicin (3) isolated from the ethanol extract of *Moringa oleifera* Lam. has anti tumour properties.[17,18] *Ferula assa-foetida* L. extracts inhibited two stage chemical carcinogenesis.[19] The anti oxidant and anticarcinogenic potential of *F. assa-foetida* has also been studied.[20] The effect of *Plumbagin* isolated from *Plumbago rosea* L., on mouse Ehrlich ascites carcinoma *in vivo* exposed to gamma radiation showed significant micronuclei induction with the drug or radiation alone. However the combination of the two further enhanced this effect.[21] The tumour growth inhibitory and radio sensitizing effects of the alchoholic root extract of *Plumbago rosea* on experimental mouse tumours suggest that it may be a good product for use with radiation to enhance tumour-killing effect; the anticancer mechanism of plumbagin also has been studied.[22,23] *Terminalia chebula* Retz. another ingredient in *Varunadi Ghritha* has immunomodulatory, anti-oxidant and free radical scavenging activities.[24,25] Studies also reveal that *T. chebula* extract increased cell viability, inhibited cell proliferation and induced cell death.[26] Another ingredient, *Asparagus racemosus* Willd. was found to inhibit mammary carcinogenesis and have immunomodulatory action as well as antioxidant properties.[27-31] The indications of *Varunadi Ghritha* as mentioned in Ashtangahrudaya.[10]

Table 1: Ingredients of *Varunadi Ghritha*

Botanical Name of Plants used	Sanskrit name	Parts used
Crataeva nurvala Buch.-Ham.	*Varuna*	Bark
Barleria prionitis L.	*Sairyaka*	Dried root
Barleria cristata L.	*Sairyaka*	Dried root
Asparagus racemosus Willd.	*Sathawari*	Root tuber
Plumbago rosea L.	*Dahana*	Dried root
Chonemorpha fragrans (Moon.) Alton.	*Morada*	Dried root
Aegle marmelose L. (Corrrea)	*Bilwa*	Dried root
Vallaris solanacea (Roth.) Kuntze.	*Vishanika*	Dried root
Solanum xanthocarpum Schrad.	*Brihathy*	Dried root
Solanum indicum L.	*Brihathy*	Dried root
Pongamia pinnata	*Karanja*	Dried root
Holoptelia integrifolia (Roxb.) Planch.	*Karanja*	Dried root
Premna serratifolia L.	*Jaya*	Dried root
Terminalia chebula Retz.	*Jaya*	Fruit pericarp
Moringa oleifera Lam.	*Bahala pallava*	Leaf
Desmostachya bipinnata (L.) Stapf.	*Darbha*	Dried root
Semecarpus anacardium L.f.	*Rujakara*	Nut
Ferula assa-foetida L.	*Hingu*	Resin

In Ayurveda, *Varunadi Ghritha* is indicated in the management of internal tumours both benign and malignant and has been used since several years without any reported toxicity. However; no proper scientific evaluation of this drug has been carried out so far. The aim of this study is to test the role of *Varunadi Ghritha*, as an immunomodulator in apparently healthy, treated and controlled HNC patients and to evaluate its effectiveness in preventing locoregional relapses and development of second primary tumours.

Material and Methods

Selection of patients

Between November 2005 and December 2006, 78 patients of HNC who were in complete remission on two consecutive follow up visits following primary treatment were randomly selected into the intervention and control group after getting informed consent. All these patients received radiotherapy, 13 patients in the intervention arm and 11 patients in the control arm received additional chemotherapy. Randomization was done using a computer generated randomization chart. This study was approved by the Institutional Review Board and the Institute Ethics Committee (IEC) of Regional Cancer Centre, Thiruvanathapuram.

Methods

Patients in the intervention group received 5 gms of *Varunadi Ghritha* twice daily orally for one year and were followed up at three monthly intervals during the second year. Patients in the control group were followed up at 3 monthly intervals for two years without any medication. During each visit patients were examined for loco-regional recurrence, measurement of body weight and blood samples collected for estimation of haemoglobin, liver and renal function tests and cholesterol levels to monitor for any toxicity for the study compound. Chest X – ray was taken at 6 monthly intervals. Blood was taken for assessment of immune function parameters at baseline, 6 months and 12 months or at the time of failure, whichever was earlier. Failure was defined as loco-regional recurrence or development of metastasis or second primary tumour. The study was completed on 31st December 2008. However, follow up data regarding the occurrence of second primary tumour and loco-regional recurrence were collected up to December 2010.

Preparation of study drug

The ingredients of *Varunadi Ghritha* are depicted in Table 1. All the ingredients were used for the preparation of the *Ghritha* after confirming their identities by typical morphological features. The drug was prepared strictly under the supervision of an Ayurvedic physician as per the method of preparation mentioned in the Ayurvedic Formulary of India.[9]

Assessment of immune cells

Peripheral blood was obtained for analysis of immune cells. Blood was drawn into heparin containing vacutainer tubes, diluted 2:1 with 1X PBS and then separated by centrifugation over a Histopaque-10771 (Sigma, St. Louis, MO) density

gradient for 20 min at 1000 × *g* at room temperature. Peripheral blood mononuclear cells (PBMCs) were collected, washed and analysed by flow cytometry to determine cell type. Immunopheno type was determined by CD3 PE, CD19 FITC, CD16 Clone NKP15 FITC (BD Biosciences, San Jose, CA). Briefly, the cells were pelleted down, washed in 1XPBS, treated with antibodies (1: 100 dilution) in 1% BSA in 1X TBST and incubated for 3 h in 37^{0}C water bath. At the end of the incubation period, the cells were pelleted, washed with 1XPBS, filtered using a cell strainer and analyzed by flow cytometer (BD Facs ARIA). The results obtained were stored as percentage of antibody positive cells.

Data management and statistical analysis

Data were entered in Epi Info and analyzed using STATA 10.0 software package. Demographic, clinical and pathological characteristics and recurrence rates of subjects were compared between the intervention and control groups using Chi - squared (χ^2) or Fisher's exact test. The effect of the intervention on loco-regional recurrences and second malignancies were estimated with hazard ratios (HRs) and their 95% confidence interval (CIs), derived from Cox proportional hazards regression analysis. Because of the small sample size, statistical adjustment to measure the effect of the intervention was done in separate regression models for each of the following variables: age (categorized into <50 and ≥50 years), gap between treatment and recruitment (categorized into <6 and ≥6 m), histology {categorized into Early/Well differentiated squamous cell carcinoma (WDSCC), moderately and poorly differentiated squamous cell carcinoma (MDSCC/PDSCC) and squamous cell carcinoma (SCC)}, N stage (categorized into negative and positive), T stage (categorized into stages T1 - T2 and T3 - T4), composite stage (categorized into stages I - II and II I-IV) and site (categorized into oral cavity, oropharynx, hypopharynx, larynx).

The number of person-years in the intervention and control groups was estimated from the date of recruitment to date of recurrence or last follow-up visit, whichever came first. Changes in percentage of antibody positive cells were obtained by taking the difference between the values at the end of the study and the baseline values. Mean percentage change in CD3, CD19 and CD16 were calculated and compared using the *t*-test. The disease free survival was estimated using Kaplan – Meier method.

Observations and Results

There were 38 patients in the intervention group and 40 in the control group. One patient in each group was later found to be HbsAg positive and excluded from the study. Another patient in the control group did not come for follow up after randomization. The baseline characteristics of patients in both groups were similar as shown in Table 2.

There were no significant difference in the mean change in hemoglobin, cholesterol and weight at the beginning and end of the study in both groups, although the trial drug was a lipid based preparation. No major toxicity for the study compound was observed. None of patients in the intervention group had any derangement of liver and renal functions. Unlike control group, patients in the intervention group experienced lesser side effects of radiotherapy such as intolerance to spicy food and difficulty in swallowing which is usually found in patients who undergo external radiotherapy for HNCs. Patients in the intervention group also had good appetite and better taste sensation. The compliance to the study medication was good.

At the end of the follow-up, 674 months and 671 months were accrued in the intervention and control groups, respectively.

Table 2: Comparison of baseline characteristics of patients in both groups

Characteristics	Intervention *n* (%)	Control *n* (%)	*P**
Age (in years)			
<50	7 (18.9)	7 (18.4)	0.96
50+	30 (81.1)	31 (81.6)	
Interval between primary treatment and randomization			
<6 months	13 (35.1)	17 (44.7)	0.40
6+ months	24 (64.9)	21 (55.3)	
Mean (SD)	8.7 (6.4)	7.6 (4.5)	0.40
Histology			
Early/WDSCC[1]	16 (43.2)	21 (55.3)	0.43
MDSCC[2]/PDSCC[3]	16 (43.2)	11 (28.9)	
SCC[4]	5 (13.5)	6 (15.8)	
N Status at diagnosis			
Negative	18 (48.6)	23 (60.5)	0.30
Positive	19 (51.4)	15 (39.5)	
T Status at diagnosis			
T1-T2	25 (67.6)	30 (78.9)	0.27
T3-T4	12 (32.4)	8 (21.1)	
Composite stage at diagnosis			
I-II	14 (37.8)	21 (55.3)	0.13
III-IV	22 (62.2)	17 (44.7)	
Site			
Oral cavity	19 (51.4)	21 (55.3)	0.85
Oropharynx	8 (21.6)	6 (15.8)	
Hypopharynx	4 (10.8)	3 (7.9)	
Larynx	6 (16.2)	8 (21.1)	
Haemoglobin level (mean (SD))	12.8 (1.8)	13.0 (1.2)	0.59
Cholesterol (mean (SD))	202.0 (27.7)	197.6 (35.2)	0.55
Weight (mean (SD))	52.9 (9.5)	51.8 (11.1)	0.64
CD3 (mean (SD))	50.2 (5.5)	49.0 (6.7)	0.46
CD19 (mean (SD))	11.4 (1.6)	11.0 (2.0)	0.40
CD16 (mean (SD))	11.9 (2.0)	11.8 (2.6)	0.82
IL2 (mean (SD))	1.3 (0.6)	1.4 (0.7)	0.63

*Chi square test for categorical and t-test for continuous variables; n: Number; SD: Standard deviation. [1]Well differentiated squamous cell carcinoma; [2]Moderately differentiated squamous cell carcinoma; [3]Poorly differentiated squamous cell carcinoma; [4]Squamous cell carcinoma. WDSCC: Well differentiated squamous cell carcinoma, MDSCC: Moderately and poorly differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma

The number of failures were almost identical in both groups, 10 out of 37 (27.0%) in the intervention group and 11 out of 38 (28.9%) in the control group. In the intervention group all failures were loco- regional (primary alone 3, node alone 6 and primary + node 1). None of the patients in the intervention group developed distant metastasis or second primary tumour. Total 03 out of 10 failures in the intervention group were immediately following recruitment into the study (within two months). In the control group, 01 patient developed distant metastasis, 03 patients developed second malignancy and 07 had loco-regional recurrence (primary alone 4, node alone 2 and primary + node 1). The proportions of failures under various host and disease related parameters are shown in Table 3. Table 4 shows the effect of intervention on loco-regional recurrences and second malignancies compared to the control group obtained from the different adjusted regression models. All adjusted models did not show significant reductions in failure in the intervention group compared to the control group. However, a 29% non significant reduction was obtained after adjustment for composite stage (HR = 0.71, 95% CI = 0.30-1.71), followed by a 23% reduction after adjustment for N stage (HR = 0.77, 95% CI = 0.32-1.83). Other non significant reduction observed was 20% from the regression model after adjustment for histology type. The disease free survival was almost similar in both groups [Figure 1].

The mean percentage change in the CD3, CD19 and CD 16 values at the end of the study and the baseline values are presented in Table 5. Significant mean percentage increases in CD3, CD19 and CD16 were observed in the intervention group compared to the control group.

Discussion

Immune system plays an important role in tumour growth and regression. Human lymphocytes are classified into three major populations based on their biological function and cell-surface antigen expression: T lymphocytes, B lymphocytes and Natural Killer (NK) lymphocytes. T lymphocytes express the cell surface antigen CD3; B lymphocytes express cell surface antigen CD 19 and NK cells CD16. Patients with HNC have significantly lower absolute number of CD3+, CD4+, CD8+ cells. Several investigators have observed that the decreased T cell count remain as such and never come back to normal levels even in patients who remain disease free following treatment.[32-34] It was

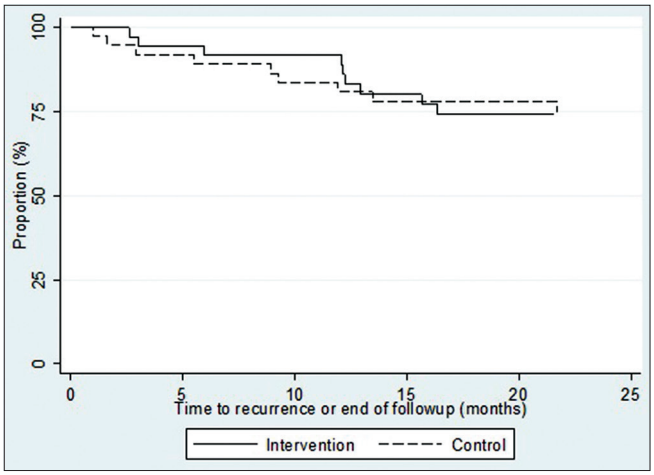

Figure 1: Kaplan-Meier disease-free survival to recurrence by study group

Table 3: Proportion of failures under various categories by group

	Intervention		Control	
	Total number	Failure *n* (%)	Total number	Failure* *n* (%)
Age (years)				
<50	7	2 (28.6)	7	4 (57.1)
50+	30	8 (26.7)	31	7 (22.6)
Interval between primary treatment and randomisation				
<6 months	13	6 (46.2)	17	7 (41.2)
6+ months	24	4 (16.7)	21	4 (19.0)
Histology				
Early/WDSCC[1]	16	1 (6.3)	21	6 (28.6)
MDSCC[2]/PDSCC[3]	16	7 (43.8)	11	4 (36.4)
SCC[4]	5	2 (40.0)	6	1 (16.7)
N status at diagnosis				
Negative	18	3 (16.7)	23	4 (17.4)
Positive	19	7 (36.8)	15	7 (46.7)
T status at diagnosis				
T1-T2	25	7 (28.0)	30	8 (26.7)
T3-T4	12	3 (25.0)	8	3 (37.5)
Composite stage at diagnosis				
I-II	14	2 (14.3)	21	3 (14.3)
III-IV	23	8 (34.8)	17	8 (47.1)
Site				
Oral cavity	19	4 (21.1)	21	6 (28.6)
Oropharynx	8	4 (50.0)	6	2 (33.3)
Hypopharynx	4	1 (25.0)	3	1 (33.3)
Larynx	6	1 (16.7)	8	2 (25.0)

WDSCC: Well differentiated squamous cell carcinoma, MDSCC: Moderately and poorly differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma

Table 4: Effect of intervention on failure using cox regression

	Hazard ratio (95% CI)	
Control group	1.00	
Intervention group		
Crude	0.94	(0.40-2.21)
Adjusted for*		
Age	0.95	(0.40-2.25)
Gap	1.04	(0.44-2.48)
Histology	0.80	(0.33-1.92)
N stage	0.77	(0.32-1.83)
T stage	1.10	(0.42-2.86)
Composite stage	0.71	(0.30-1.71)
Site	0.91	(0.38-2.15)

*Effect estimate shown is that of the intervention compared to the control group after adjustment for each variable separately. CI: Confidence interval

Table 5: Mean change in CD3, CD19 and CD16

	Mean change (SD)				*P*
	Intervention (*n*=29)		Control (*n*=25)		
CD3	4.71	(3.6)	−0.39	(2.7)	<0.001
CD19	0.75	(1.2)	−0.25	(0.8)	0.001
CD16	0.76	(1.1)	−0.27	(0.9)	0.001

SD: Standard deviation

also observed that the decrease in the T cell count progresses with increase in stage of the disease.[34] A higher recurrence rate was observed among those who had poor CD3 count.[35] A lower peripheral blood lymphocyte NK activity has also been reported in patients with HNC.[36] A lower NK cell activity has been observed in patients with recurrence when compared to those who remained disease-free.[37]

Loco-regional recurrence and second primary tumours are major determinants of survival in the HNC patients. Several agents with antioxidant and anti-proliferative properties have been evaluated in improving disease-free survival.[38-40] However, results have not been encouraging.

The ingredients of *Varunadi Ghritha* is indicated in the management of *Anthar Vidradhi* (internal tumours both benign and malignant).[10] Therefore; by administering this compound to patients who are treated and cured of primary cancer, it is anticipated that it can prevent the development of recurrence and second primary tumours in these patients by preventing the tumorigenesis at the celluar level. *Varunadi Ghritha*, a polyherbal Ayurvedic compound has several ingredients with immunomodulatory, anti-proliferative and anti-carcinogenic properties.[13,15,19] The present study showed a significant increase in the CD3, CD19 and CD16 positive cells in patients with treated HNCs in remission, following administration of *Varunadi Ghritha*, indicating a possible immunomodulatory effect of the Ayurvedic compound. The mean change in CD3, CD19 and CD16 cell count was slightly lower in the control group indicating the persistently lower lymphocyte count in HNCs as observed by several other investigators.[32,33]

The disease failure was similar in both groups. However, three out of 10 failures in the intervention group were immediately following the recruitment into the study (within two months) compared to none in the control group. The failure in these 3 patients immediately following the recruitment may be due to the presence of subclinical disease at the time of recruitment. Advanced stage at presentation and node positivity are the two important prognostic factors in HNC.[41,42] The Cox regression analysis of the data in the present study showed lower failure rate in patients with advanced stage and nodal disease after adjustment for other variables in the intervention group compared to the control group. This indicates a better tumour control in patients with poor prognostic factors. Although a notable fact, this was not statistically significant may be due to the small number of patients in the study groups.

A favourable symptomatic improvement in the late effects of radiotherapy such as dryness of mouth, intolerance to spicy food, discomfort in the throat and difficulty in swallowing were observed in the intervention group and the patients in the intervention group had good quality of life, although this study was not primarily designed to evaluate quality of life issues. The compliance to medication was also good.

Immune surveillance in cancer is a complex process in which T cells and tumour cells influence each other in several ways. The present study clearly showed an immunomodulatory effect following administration of *Varunadi Ghritha*. Considering the fact that most of the failures in the intervention group were in the regional lymph nodes, it is possible that the T cells identified in the peripheral blood may not have the potential to migrate to the regional nodes because of the effects of previous irradiation. However, since this is a small pilot study, further investigations with more number of patients and functional studies with migratory pattern of T cell responses are needed.

Conclusion

Administration of *Varunadi Ghritha* resulted in an increase in CD3, CD19 and CD16 cells in the study subjects indicating an immunomodulatory effect of the study compound. Although the survival and disease failure were similar in both groups, a trend in better disease control was observed in patients with advanced stage disease in the intervention group. A significant increase in CD3 count, a pan T cell marker, was found in patients after treatment for HNCs which has probably never been reported elsewhere. The long term significance of the immunomodulatory properties of the study compound and its role in preventing loco regional recurrence and development of second malignancy in treated HNCs need to be investigated further in a larger study with longer follow up.

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हिन्दी सारांश

चिकित्सा प्राप्त शिर एवं कण्ठगत अर्बुद (कैंसर) में वरुणादि घृत के प्रभाव का बायोलोजिकल रिस्पॉन्स मोडिफायर के रूप में अध्ययन

दिव्या रविन्द्रन, इन्दु हरिहरण, रिचर्ड मुवोंगे, रजनिश आर. कुमार, एम. राधाकृष्ण पिल्लै, कुन्नामभट रामदास

शिर एवं कण्ठगत अर्बुद(कैंसर) के आतुरों में व्याधि क्षमत्व का निरन्तर ह्रास चिकित्सा प्राप्त होने के बाद भी होता है, साथ ही व्याधि का पुनरागमन भी न्युन उञ्ज गणना वाले आतुरों में देखा गया है। लोको रिजनल पुनरागमन एवं सेकण्ड प्राइमरी अर्बुद (ट्युमर) शिर और कण्ठगत अर्बुद में विफलता का सामान्यतः रूप है। आुयर्वेद जो एक परम्परागत चिकित्सा पद्धति है, जिसमें अनेक औषधियाँ अपने अर्बुद–रोधी (एण्टी ट्युमर) और प्रतिरक्षा संस्थापन (इम्युनो मोडुलेटरी) प्रभाव के लिए प्रमाणित हैं। इस अध्ययन में कुल–७८ आतुर जो कि शिर एवं कण्ठगत अर्बुद (कैंसर) की चिकित्सा प्राप्त कर चुके थे, उनको अविधिपूर्वक(रेण्डमाइझड) चिकित्सा और नियन्त्रण समूह में विभाजित किया गया। चिकित्सा समूह के आतुरों (प=३८) में वरुणादि घृत ५ ग्राम प्रतिदिन दो बार एक वर्ष के लिए एवं निरीक्षण अवधि २ वर्ष तक रखी गयी। नियन्त्रण समूह के आतुरों (प=४०)का समयावधि अनुसार परीक्षण किया गया। दोनों समूहों में प्रतिरक्षा सम्बन्धी सभी मापदण्डों का अध्ययन किया गया। वरुणादि घृत की चिकित्सा प्राप्त आतुर समूह में मढफ सेल गणना में वृद्धि पायी गयी, जो कि शिर एवं कण्ठगत अर्बुद (कैंसर) में पूर्व में किसी भी अध्ययन में ज्ञात जानकारी के अनुसार नही पायी गयी है।