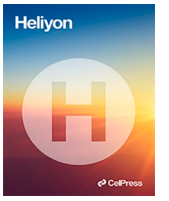
Heliyon 9 (2023) e20691

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



# Benefits of basil tea for patients with differentiated thyroid cancer during radioiodine therapy: A randomized controlled trial

Kenta Nomura, Michihiro Nakayama *, Atsutaka Okizaki

*Department of Radiology, Asahikawa Medical University, Hokkaido, Japan*

ARTICLE INFO

*Keywords:*
Radioactive iodine therapy
Thyroid cancer
Acute sialadenitis
Basil tea

ABSTRACT

*Background:* Acute sialadenitis is one of the major physical complications of radioactive iodine therapy (RAIT) for differentiated thyroid cancer (DTC). It is considered necessary to pay attention to the psychological impact on the patient as well as the physical influence during RAIT.
*Objective:* To find evidence of the benefits of Basil tea on the psychological and physical side effects of RAIT.
*Methods:* Forty-four DTC patients after total thyroidectomy were randomly divided into Group A (Basil tea group, n = 22) and Group B (Control group, n = 22). Subjects in Group A drank 180 mL of Basil tea prepared from 2.0 g of Holy basil (*Ocimum tenuiflorum Linn.*) leaves after each meal for four days, starting on the day RAIT was performed. Those in Group B drank the same amount of distilled water after each meal for the same period as those in Group A. The State-Trait Anxiety Inventory (STAI) was used to assess anxiety, while the saliva component test, and salivary gland scintigraphy were used to assess the oral cavity.
*Results:* The rate of change of the STAI score (both State Anxiety and Trait Anxiety) was significantly lower in Group A than in Group B ($P < 0.05$). The rates of change of cariogenic bacteria, ammonia, protein, and occult blood were significantly lower in Group A than in Group B ($P < 0.05$). The rate of change of the washout ratio for salivary gland scintigraphy was significantly lower in Group B than in Group A ($P < 0.05$).
*Conclusions:* Basil tea consumption not only protected against oral mucosal conditions and salivary gland disorders but also significantly relieved the patient's RAIT-related anxiety. Therefore, it was suggested that this tea could be useful for the maintenance of patients' QOL during RAIT.

## 1. Introduction

The number of patients diagnosed with differentiated thyroid cancer (DTC) has increased due to an increase in the number of opportunities for medical investigations in recent years [1]. Despite the increasing number of incidentally diagnosed patients with DTC, the 5-year survival rate was approximately 98 %, and the age-adjusted mortality rate associated with DTC remains stable (approximately 100.0 per 50,000 persons per year) [2]. Thus, the post-treatment follow-up period tended to be longer. Therefore, serious adverse events associated with therapy for DTC impair the patient's long-term quality of life (QOL) and should be prevented.

Radioactive iodine therapy (RAIT) has been an effective treatment for many years and a postoperative option for DTC [3]. RAIT is known to prolong survival in patients after total thyroidectomy via the ablation of residual cancer cells and metastases [4]. Patients

* Corresponding author. Asahikawa Medical University, Midorigaoka-higashi 2-1-1-1, Asahikawa, Hokkaido 078-8510, Japan.
*E-mail address:* m-naka@asahikawa-med.ac.jp (M. Nakayama).

https://doi.org/10.1016/j.heliyon.2023.e20691
Received 28 May 2023; Received in revised form 4 October 2023; Accepted 4 October 2023
Available online 5 October 2023

receiving high-dose RAI often require inpatient treatment in radiation-shielded rooms [5]. Physical contact with family members and healthcare workers is restricted to a minimum for some time after RAIT, as the patients themselves can be a source of radiation exposure. It is presumed to be an unusual environment that induces feelings of anxiety and loneliness, unlike normal hospitalization wards. In addition, hypothyroidism associated with pre-RAIT thyroid hormone withdrawal can cause mood changes, lack of concentration, and emotional instability [6]. Therefore, it is considered necessary to pay attention to the psychological impact and mental health burden on the patient, as well as the physical impact of RAIT [7].

On the other hand, salivary gland disorders following acute sialadenitis are major physical complications of RAIT [8]. Multiple RAIT sessions may be performed within the dose limit [9], and the patients should be treated immediately clinical manifestations are observed. There have been some reports of the administration of lemon candies and vitamin C lozenges as methods of protecting salivary gland function from RAIT [10]; however, no consensus has been reached yet on the optimal strategy [11]. Regarding the administration of lemon candies and vitamin C lozenges during RAIT, there are also reports that salivary gland function decreases if their timing and dosage are not appropriate [12]. Currently, it is difficult to think that lemon administration alone is a sufficient method of preserving salivary gland function. In addition, since iodine intake restriction, and thyroid hormone replacement are performed before RAIT, some patients temporarily experience anorexia and nausea due to RAIT-associated hypothyroidism. Thus, what a patient can ingest during RAIT is different for each individual, and it is preferable to prepare multiple options for the preservation of salivary gland function.

Under such circumstances, we thought that the ingestion of herbal tea might be expected to improve the physical adverse events and psychological burden associated with RAIT. Herbs, including Holy basil (*Ocimum tenuiflorum Linn.*), have long been used not only as spices but also as therapeutic agents for diseases, and the administration of these herbs is considered safe [13–15]. Furthermore, basil has also been shown to exhibit anticancer activity [16]. Holy basil (*Ocimum tenuiflorum Linn.*) has long been reported to have mucosa-protective, antibacterial, and antioxidant effects. It has also been reported to preserve the oral condition [15,17]. In addition, it has also been reported that one of the representative effects of basil is to relieve anxiety and stress [14,18]. Holy basil contains eugenol, linalool, cineol, α-terpineol, and saponins as biologically active ingredients [19]. Eugenol, which has digestive and appetite-stimulating properties [20], might effectively alleviate loss of appetite [21]. Linalool, which emits a sweet scent similar to that of a lily flower, also possesses stress-reducing and appetite-stimulating properties [22,23]. Eugenol and linalool exhibit anti-inflammatory and antibacterial properties [24], α-terpineol exhibits anti-inflammatory properties [25], and saponin exhibits antioxidant and blood flow-promoting activity in peripheral tissues [26]. Therefore, we hypothesized that holy basil would reduce physical and psychological side effects in patients undergoing RAIT. Basil can be ingested in powder or tea form. Given that swallowing function might be adversely impacted after thyroidectomy in some patients, basil tea might be easier to ingest than its powder form. Therefore, we focused on Holy basil (*Ocimum tenuiflorum Linn.*) tea in the current study.

In this study, we aimed to objectively evaluate RAIT-related anxiety, stress, salivary gland function, and oral mucosal conditions, providing evidence that Basil tea protects salivary gland function, preserves the oral condition, and reduces anxiety during RAIT.

## 2. Materials and methods

In this study, we included DTC patients who were undergone $^{131}$I treatment after total thyroidectomy at Asahikawa Medical University hospital from September 2020 to September 2021. The therapeutic dose of $^{131}$I was 3.70–5.55 GBq. All patients underwent at least two weeks of thyroid hormone withdrawal before RAIT. Patients with autoimmune diseases, those with previous salivary gland diseases, or those who just underwent external-beam radiotherapy to the head and neck were excluded from the study. Those with a history of neurological or psychiatric disorders were also excluded. All patients with thyroid cancer were treated according to the

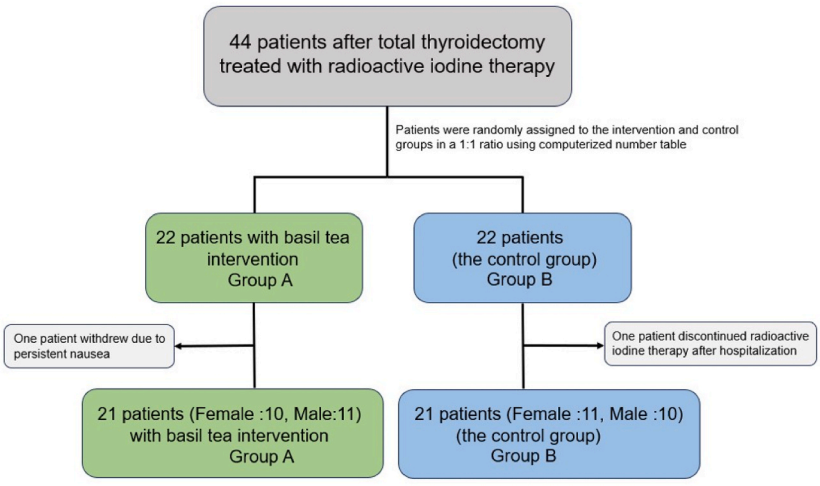



**Fig. 1.** Study flow chart showing randomization Group A, basil tea intervention group; Group B, control group.

management guidelines of the American Thyroid Association [27]. This study was a randomized controlled trial registered with the University Hospital Medical Information Network (UMIN) (ID = UMIN000041411) clinical trials registry and conducted following the Consolidated Standards of Reporting Trials guidelines.

The minimum sample size for this study was determined based on a previous study on anxiety in patients with thyroid cancer [6] since no previous studies that used the same method were found. Using the formula for sample size calculation size for two independent groups, taking into account a significance level of $\alpha = 0.05$, a confidence level of 95 %, an effect size of 0.92 and a statistical power of 80 %, the total sample size was 44 patients (22 in each group). Fig. 1 shows the study flow chart for patient selection by randomization. Study participants were randomly assigned to the intervention and control groups in a 1:1 ratio using a computerized number table.

## 3. Ethics

All procedures in this study were approved by the ethics review board of Asahikawa Medical University, Japan (no. 20083). Informed consent was obtained from all subjects for the current study, and the latter was conducted per the principles of the 2013 revised Declaration of Helsinki.

### 3.1. Basil tea intervention

The basil tea used a molded teabag (Holy Basil Herb Teabag, ITANSE Co., Ltd., Osaka, Japan) filled with 2.0 g net of dried and shredded basil (*Ocimum tenuiflorum Linn.*) leaves (Fig. 2). Although some commercially available basil tea products contain additives such as citric acid, which are incorporated during the manufacturing process, a product made only from basil leaves was used in the present study. This teabag was soaked in 180 ml of boiling water for 5 min and then cooled to 40 °C. These processes were carried out in a uniform procedure. Patients in Group A (the basil tea intervention group) drank this tea three times a day for four days after every meal, starting from the day of RAI ingestion (the day of admission to the radiation isolation room). Since there were no reports that could be a guideline for the ideal period of basil tea administration, the intervention period was set to four days when radioactivity was often below the threshold for exiting the radiation isolation room. Participants in Group B (the control group) ingested the same amount of distilled water as the intervention group after each meal for four days (in addition to the amount of water they would normally drink during RAIT).

### 3.2. State-Trait Anxiety Inventory

All participants underwent the State-Trait Anxiety Inventory (STAI, Japanese version). The STAI is the most commonly used self-

**Fig. 2.** Teabag (Holy Basil Herb Teabag, ITANSE) filled with 2.0 g net of dried and shredded basil leaves *(Ocimum tenuiflorum Linn.*).

administered test in objectively assessing anxiety [28]. The test consists of two independent questionnaire-based assessments of State Anxiety and Trait Anxiety. The first is state anxiety (STAI-S), in which transient life events are currently believed to cause stress. The second is the anxiety tendency (STAI-T), which involves personal predispositions, and is assessed as a relatively stable aspect that includes a general state of calmness, self-confidence, and security [29]. Each of the two STAI subscales has 20 items, for a total of 40 items. Composed of subscales scored on a 4-point Likert scale from 1 (rarely) to 4 (almost always), scores on this test range from low (20) to high (80) anxiety. Higher scores indicate higher levels of anxiety. A previous study described scores of $>39$ as the high-anxiety category and scores of $\leq 39$ as the low-anxiety category on the STAI [30]. All subjects performed STAI before and after RAIT (the day before the start of treatment and the 5th day after treatment). Test scores were compared quantitatively. Analyses were performed using the rate of change in scores. The change rate was calculated using the following formula: (Score after RAIT − Score before RAIT)/Score before RAIT × 100.

### 3.3. Saliva component test

Since it is necessary to minimize radiation exposure (including exposure to the saliva of patients who just underwent RAIT), the components of saliva must be measured rapidly and easily. In this study, we used the SillHa (ARKRAY, Inc., JAPAN) saliva test device. With this device, the results can be calculated within 5 min. This device does not measure the density directly; rather, it measures the color tone of the material as the rate of reflection by reflectance photometry. It has been shown that the magnitude of this measured value (reflectance, %) is strongly correlated with the magnitude of the actual measured value [31]. The measurement was performed by having the patients rinse their mouths with 30 ml of distilled water for 10 s, sucking the liquid with a dedicated dropper, and dropping 1 mL onto exclusive test papers for analysis. This device quantitatively calculates the number of cariogenic bacteria, the densities of ammonia, leukocytes, protein, and the amount of occult blood in saliva. Cariogenic bacteria, occult blood, and leucocytes are used for assessing the risk of periodontal disease, and the amounts of ammonia and protein indicate the degree of oral hygiene [32]. Increments in these parameters suggest that the oral condition is deteriorating. Saliva samples from participants in both groups were measured on the day before RAI ingestion and on the 5th day after its ingestion. In this study, statistical analyses were performed by calculating the rate of change in each measurement before and after RAIT. This rate of change is calculated as follows: (reflectance after RAIT - reflectance before RAIT)/reflectance before RAIT x 100.

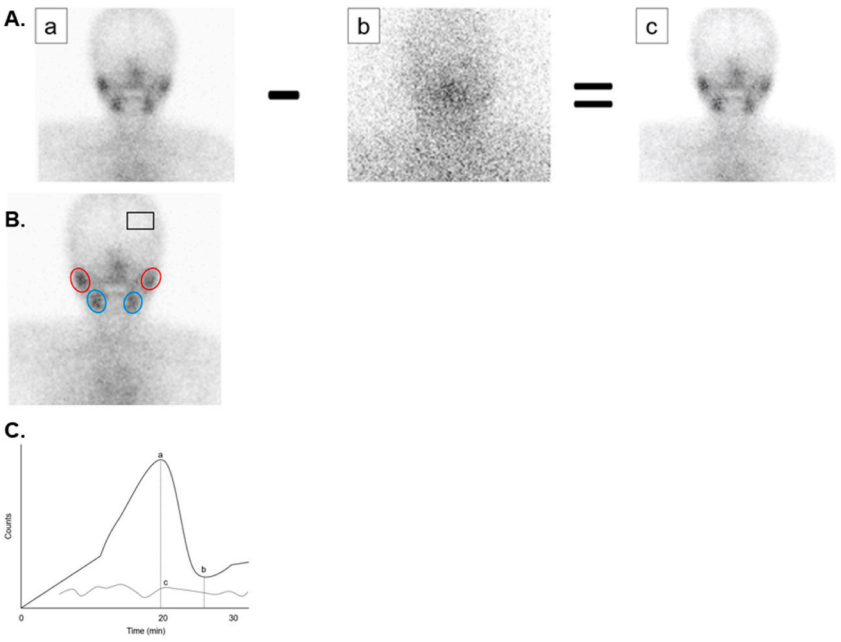



**Fig. 3. A**. The subtraction process for salivary gland scintigraphy in patients after the administration of radioactive iodine. (a) Tc-99 m image and scattered radiation from $^{131}$I (original image). (b) Image of only scattered radiation from $^{131}$I. (c) Image after subtraction (Tc-99 m image). **B**. Regions of interest (ROI) for salivary gland scintigraphy. The red circles near the bottom of the ear indicate ROIs on the parotid glands. The blue circles near the bottom of the chin indicate ROIs on the submandibular glands. The left temporal square shows the background ROI. **C**. Measurement points of salivary gland function on salivary gland scintigraphy. (a) Maximum count before lemon stimulation. (b) Minimum count after lemon stimulation. (c) Background counts at maximum activity. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

### 3.4. Salivary gland scintigraphy

To assess the functional outcome of basil tea administration, participants underwent salivary gland scintigraphy before and five days after RAI administration. After a bolus intravenous injection of 185 MBq (5 mCi) of 99 mTc - pertechnetate, dynamic imaging of the anterior head was performed using a dual-head gamma camera with a parallel-hole, high-energy, medium-sensitivity collimator (Millennium VG, GE Medical Systems, Tokyo, Japan). A sequence of dynamic images was then acquired at 1 min/frame for 30 min with a zoom factor of 1.5 in a 128 × 128 matrix. The photopeak was centered at 140 keV with a 20 % window. After RAIT, salivary gland scintigraphy included $^{131}$I irradiation. The scattered radiation from the 365 keV gamma ray can therefore enter the Tc-99 m window during collection. In this context, the window was set to 180 keV, which is on the high-energy side (140 keV). The examination was performed via dual-energy window collection. Subtraction processing was then performed for image analysis (Fig. 3A). Twenty minutes after the bolus injection, 3 mL of lemon juice (100 % concentrated) was injected into each subject's mouth using a syringe to stimulate salivation. Regions of interest (ROIs) were drawn around the left and right parotid glands and the left and right submandibular glands on the dynamic scintigraphy sum image for quantitative analysis. A background ROI was placed in the temporal region (Fig. 3B). Thus, a time-activity curve was drawn for each salivary gland.

For the time-activity curve, the following points were pre-determined (Fig. 3C): (a) maximum uptake count before stimulation, (b) minimum uptake count after stimulation, (c) background count at peak activity, and (d) injected counts (calculated by counting to 185 MBq and post-injected syringes with the camera, correcting post-injected counts for radioactive decay, and subtracting the post-injected count from pre-injected uptake counts). The washout ratio (WR, a salivary gland function parameter) was calculated using each time-activity curve as follows: washout ratio (WR) = $[1-(b-c)/(a-c)] \times 100$. Higher WR values are associated with better salivary gland function, and a WR of $\geq$50 % is considered normal salivary gland function [33]. Analyses were performed using the rate of change of WR. In the current study, the sum of the WRs of the four salivary glands (WR sum) was calculated as the rate of change before and after RAIT. This rate of change is calculated as follows: (WR sum after RAIT – WR sum before RAIT)/WR sum before RAIT x 100.

### 3.5. Statistical analysis

Data were analyzed using statistical software (XLSTAT version 2021.2.2; Addinsoft, Paris, France). All continuous data were presented as the mean ± standard error. The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Fisher's exact test was used to assess categorical variables. Numeric variables were evaluated using the Wilcoxon rank-sum test or the independent-sample *t*-test. A P-value of $<0.05$ was considered statistically significant.

## 4. Results

### 4.1. Demographic and clinical characteristics

In the current study, 22 patients in Group A and 22 patients in Group B met the selection criteria. In Group A, one patient withdrew from the study due to persistent nausea. In Group B, one patient discontinued RAIT after hospitalization. Finally, the results of 21 patients in each group were used for analyses. Fig. 1 shows the study flow chart, including patient selection for randomization, and Table 1 shows the demographic and clinical characteristics of the participants. Thyroid cancer staging was classified according to version 8 of the tumor-node-metastasis classification (TNM). There was no statistically significant difference in this parameter between the two groups per the independent-sample *t*-test and Fisher's exact test.

### 4.2. STAI

The rates of change of both State Anxiety and Trait Anxiety were significantly lower in Group A than in Group B (Fig. 4, $P < 0.05$). In addition, both rates of change of STAI scores had negative trends in Group A (Table 2), which may indicate a reduction in anxiety. Group B showed a more positive trend in the rate of change of STAI, suggesting an increase in anxiety during RAIT.

**Table 1**
Demographic and clinical characteristics of the participants.

| Characteristics | Group A (n = 21) | Group B (n = 21) | *P*-value |
|---|---|---|---|
| Age at diagnosis (y), mean (range) | 63.2 (29–77) | 67.5 (43–76) | 0.45 |
| Sex (female/male) | 10/11 | 11/10 | 0.39 |
| TNM stage I/II/III | 3/1/1 | 1/0/2 | 0.28 |
| IV A/B/C | 8/2/6 | 6/2/10 | |
| I-131 dose (GBq), average ± SD | 5.42 ± 0.19 | 5.29 ± 0.20 | 0.13 |
| Thyroglobulin (ng/mL), average ± SD | 510.7 ± 111.4 | 425.5 ± 87.5 | 0.42 |

Group A, basil tea intervention group; Group B, control group; TNM, tumor, node, and metastases; SD, standard deviation.

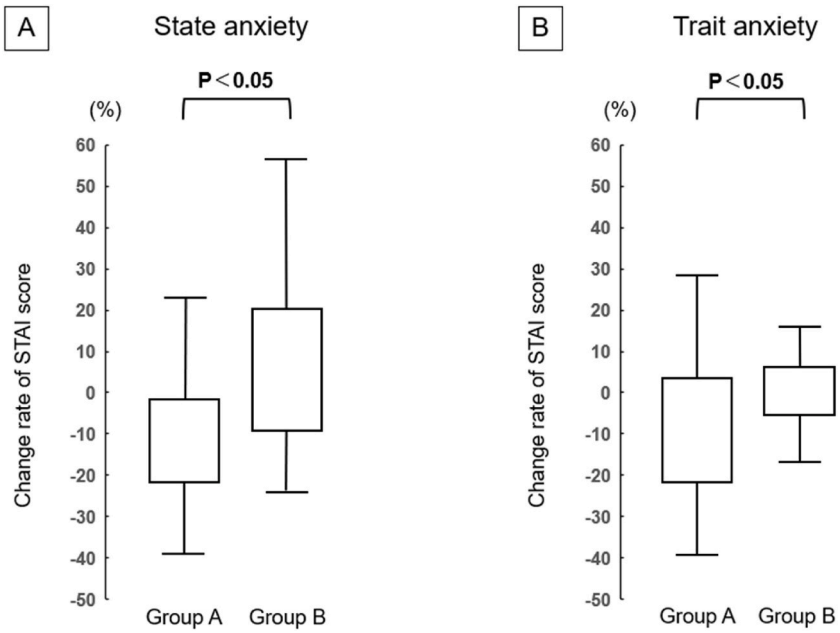



**Fig. 4.** Rates of change in STAI scores (A: State anxiety, B: Trait anxiety) STAI, State-Trait Anxiety Inventory; Group A, basil tea intervention group; Group B, control group.

**Table 2**
Rates of change of STAI scores (State Anxiety and Trait Anxiety).

| Rate of change of the State anxiety score | | | Rate of change of the Trait anxiety score | | |
|---|---|---|---|---|---|
| Group A | Group B | *P*-value | Group A | Group B | *P*-value |
| −3.39 ± 37.48 | 5.38 ± 22.80 | <0.05 | −9.03 ± 15.26 | −0.063 ± 9.36 | <0.05 |

Group A, basil tea intervention group; Group B, control group.

### 4.3. Saliva component test

The rates of change of cariogenic bacteria, ammonia, protein, and occult blood were significantly lower in Group A than in Group B (Fig. 5, P < 0.05). Group A showed negative trends in the rates of change in cariogenic bacteria, proteins, and the amount of occult blood, whereas Group B showed positive trends in these parameters (Table 3). Regarding the rates of change of the amount of ammonia and the number of leukocytes, a stronger negative trend was observed in Group A than in Group B. These results indicate that the

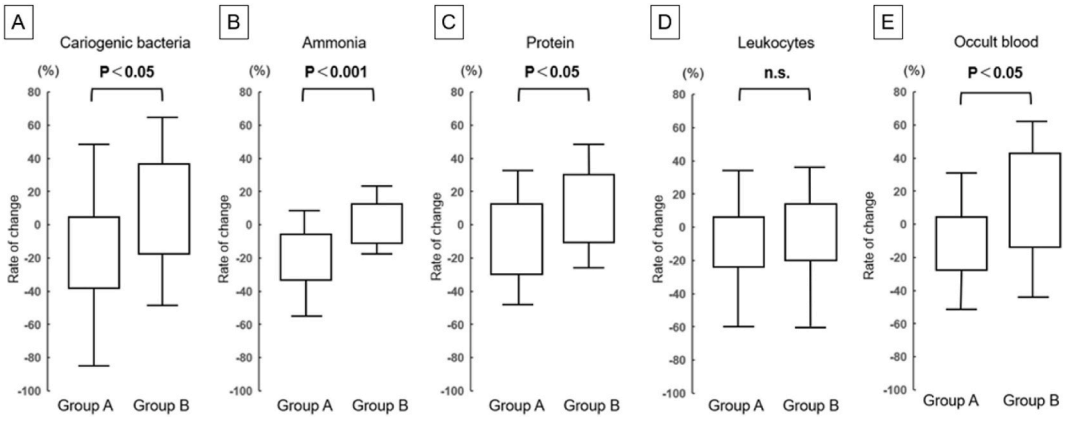



**Fig. 5.** Rate of change of the saliva component test (A: Cariogenic bacteria, B: Ammonia, C: Protein, D: Leukocytes, E: Occult blood) Group A, basil tea intervention group; Group B, control group.

**Table 3**
Rates of change of the saliva component test results.

| Item of change rate | Group A | Group B |
|---|---|---|
| Cariogenic bacteria * | −15.61 ± 32.90 | 7.52 ± 31.98 |
| Ammonia † | −20.52 ± 18.52 | −0.90 ± 15.51 |
| Leukocytes | −7.35 ± 15.33 | −2.98 ± 18.31 |
| Protein * | −9.42 ± 24.63 | 7.95 ± 23.16 |
| Occult blood * | −9.04 ± 21.25 | 11.52 ± 31.74 |

* Significant ($P < 0.05$) difference between the two groups per the Wilcoxon rank-sum test.
†Significant ($P < 0.001$) difference between the two groups per the Wilcoxon rank-sum test.
Group A, basil tea intervention group; Group B, control group.

administration of basil tea may preserve the oral mucosal condition.

### 4.4. Salivary gland scintigraphy

Salivary gland scintigraphy, as a method of evaluating salivary gland function, suggests that a higher WR sum indicates better preservation of salivary gland function. The rate of change of the WR sum was significantly lower in Group B than in Group A (Fig. 6, $P < 0.05$). The WR sum in Group B tended to decrease after RAIT, while that in Group A tended to increase (Table 4). The outcomes suggest that the participants in Group B may end up suffering acute salivary gland injury, while those in Group A may have been able to prevent it.

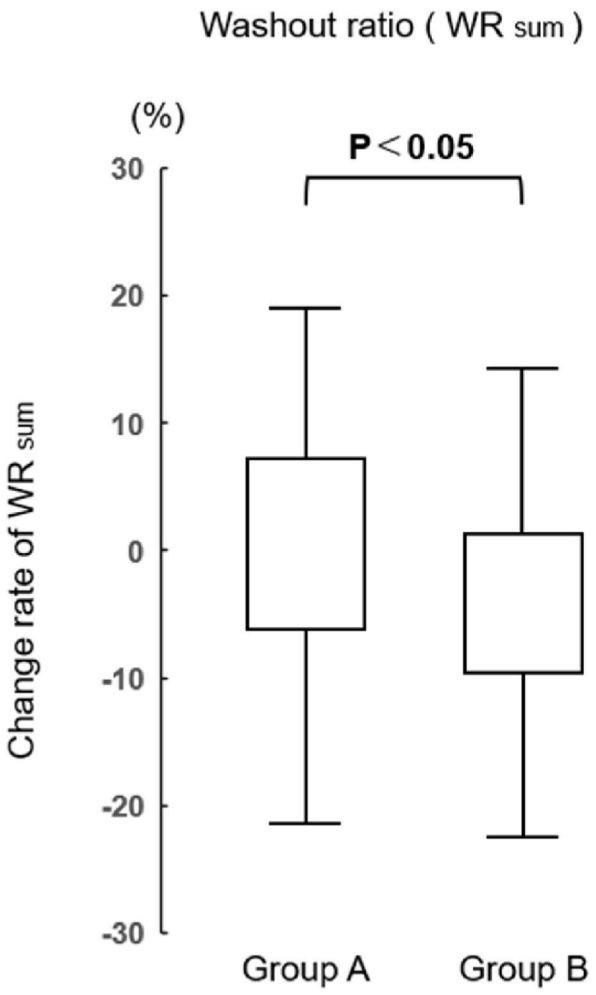



**Fig. 6.** Rate of change of the washout ratio (WR) in salivary gland scintigraphy. WR sum means the sum of the WR in all salivary glands. Group A, basil tea intervention group; Group B, control group.

**Table 4**
Rate of change of the washout ratio (WR) in salivary gland scintigraphy for the sum of all salivary glands (WR sum).

| Rate of change of the washout ratio | | |
|---|---|---|
| Group A | Group B | *P*-value[a] |
| 0.69 ± 8.56 | −5.25 ± 13.54 | <0.003 |

[a] Significant ($P < 0.05$) difference between the two groups per the Wilcoxon rank-sum test.
Group A, basil tea intervention group; Group B, control group.

## 5. Discussion

In the current study, the rate of change of STAI scores, which objectively evaluates the psychological influence of RAIT, was significantly lower in the Basil tea group than in the control group. Basil tea may have reduced patients' RAIT-related anxiety. The saliva component test revealed significant increments in the rate of change of cariogenic bacteria, ammonia, leukocytes, protein, and occult blood only in the control group, suggesting that basil tea may preserve the oral mucosal condition. Furthermore, salivary gland scintigraphy, an objective method of evaluating salivary gland function, revealed a significant decline in the rate of change of the WR sum in the control group, and the WR sum in the control group tended to decrease after RAIT. These results indicated that salivary gland function decreased after treatment in the control group. The administration of basil tea relieves acute salivary gland injury from RAI and may have a protective effect on salivary gland function. These results suggest that the administration of basil tea may protect against both the psychological and physical effects of RAIT. The results of current study indicate that drinking basil tea during RAIT might improve patient's QOL.

RAIT requires the prior cessation of thyroid hormone therapy. Therefore, the only fundamental solution to hypothyroidism-related nausea, loss of appetite, and malaise is to resume taking thyroid hormones after treatment or after RAIT is discontinued. Holy basil contains eugenol, linalool, cineol, α-terpineol, and saponin as biologically effective ingredients [19]. Eugenol, which has digestive and appetite-stimulating properties [20], might effectively alleviate symptoms [21]. Linalool, which has a sweet scent like that of a lily flower, also has stress-reducing and appetite-stimulating effects [22,23]. Eugenol and linalool also have anti-inflammatory and antibacterial properties [24]. α-Terpineol has been reported to have anti-inflammatory properties and gastric lesion-relieving abilities [25], while saponin has been reported to have antioxidant properties and blood flow-promoting activity in peripheral tissues [26]. This study speculates that these substances may have had protective effects on the condition of the oral mucosa and salivary gland function. Furthermore, it has been suggested that the deterioration of the oral condition, which is represented by bad odors, increases stress and anxiety [32]. The protective effect of basil tea on the oral mucosa may also have contributed to the amelioration of RAIT-related anxiety.

In addition to the biochemical benefits of basil, the STAI results might reflect the positive or negative effects associated with the behavior of "drinking basil tea during treatment." In the present study, the STAI scores tended to decline after treatment in the intervention group, suggesting the alleviation of treatment-related anxiety. Although it is difficult to evaluate without biochemical effects of basil, these results suggest that the act of drinking basil tea might not have had a negative impact.

The mechanism of action of RAI is as follows: $^{131}$I is taken up into cells via a sodium iodide symporter (NIS) expressed in thyroid cells [11]. However, a certain amount of RAI is also taken up by salivary glands, as NIS is the second most expressed protein in salivary glands [34]. Thus, sialadenitis and associated salivary gland dysfunction result from the exposure of salivary gland tissue to β-rays from $^{131}$I taken up by NIS. Acute sialadenitis causes swelling and pain in the salivary glands within a few days after $^{131}$I consumption [11]. Acute sialadenitis may resolve spontaneously; however, when the inflammation progresses to the chronic stage, xerostomia develops, which significantly impairs the patient's QOL.

It has been reported that the use of honey for oral mucositis in patients who have undergone chemotherapy or external-beam radiation therapy reduces the incidence of salivary gland disorders [35]. However, since honey contains a certain amount of sugar, it is possible that the treatment is limited to patients without diabetes. Since basil tea contains almost no sugar, it has the advantage that there are no restrictions on its administration, unlike sugar-containing foods. Compared to lemon-containing foods and vitamin C lozenges, basil flavor is considered to be less irritating to the oral mucosa in patients with post-RAIT acute mucositis. Furthermore, holy basil is readily available worldwide, and even in outpatient cases of RAIT, patients can begin taking Holy basil voluntarily or at the recommendation of their physician.

## 6. Limitations

The following are the possible limitations of this study: first, although it is a randomized controlled trial, it is a single-center study. Second, this was a proof-of-concept study with a small sample size due to difficulty in enrolling a large number of patients and the rarity of these cases treated in the hospital. Second, the patients ingested tea extracted from basil leaves, but the chemical composition of the basil tea consumed was not analyzed because we considered that the efficacy of basil tea should be evaluated based not only on its biochemical efficacy, but also on the overall impact of the act of drinking basil tea during treatment. Furthermore, it is unclear whether the dosage, timing, and duration of the basil tea intervention were optimal for the prevailing conditions. In this study, it was administered as a "tea." However, it is also possible to administer it in different forms (for instance, as a powder, and mixed with

meals). In this way, patients may choose how to consume it. Since no similar studies have been conducted yet, it is considered necessary to examine the optimal administration method.

## 7. Conclusions

Basil tea consumption not only protected against salivary gland disorders and adverse oral mucosal conditions but also significantly reduced the patient's RAIT-related anxiety. Therefore, it was suggested that this tea could be useful in maintaining patients' QOL during RAIT.

## Data availability statement

Data will be made available on request.

## Funding sources

The authors received funding from Yamazaki Spice Promotion Foundation for this study on July 31, 2020.

## CRediT authorship contribution statement

**Kenta Nomura:** Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Michihiro Nakayama:** Investigation, Funding acquisition, Formal analysis. **Atsutaka Okizaki:** Supervision, Resources.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

The authors received funding from Yamazaki Spice Promotion Foundation for this study.

## References

[1] F. Pacini, D. Fuhrer, R. Elisei, et al., ETA Consensus Statement: what are the indications for post-surgical radioiodine therapy in differentiated thyroid cancer?, 2022, Eur. Thyroid J. 11 (1) (2022), e210046, https://doi.org/10.1530/ETJ-21-0046.
[2] C. Sparano, S. Moog, J. Hadoux, et al., Strategies for radioiodine treatment: what's new, Cancers 14 (15) (2022) 3800, https://doi.org/10.3390/cancers14153800.
[3] A. Ciarallo, J. Rivera, Radioactive iodine therapy in differentiated thyroid cancer: 2020 update, AJR Am. J. Roentgenol. 215 (2) (2020) 285–291, https://doi.org/10.2214/AJR.19.22626.
[4] A. Charalambous, Seeking optimal management for radioactive iodine therapy-induced adverse effects, Asia Pac J Oncol Nurs 4 (4) (2017) 319–322, https://doi.org/10.4103/apjon.apjon_23_17.
[5] C. Karo, R. Ideguchi, K. Nishi, et al., Radiation monitoring of an isolation room for 131I therapy after the patients were released, Health Phys. 117 (4) (2019) 419–425, https://doi.org/10.1097/HP.0000000000001063.
[6] N. Javaloyes, A. Crespo, M.C. Redal, et al., Psycho-oncological intervention through counseling in patients with differentiated thyroid cancer in treatment with radioiodine (COUNTRY, NCT05054634): a non-randomized controlled study, Front. Psychol. 13 (2022), 767093, https://doi.org/10.3389/fpsyg.2022.767093.
[7] H.X. Wu, H. Zhong, Y.D. Xu, C.P. Xu, Y. Zhang, W. Zhang, Psychological and behavioral intervention improves the quality of life and mental health of patients suffering from differentiated thyroid cancer treated with postoperative radioactive iodine-131, Neuropsychiatric Dis. Treat. 12 (2016) 1055–1060, https://doi.org/10.2147/NDT.S105460.
[8] E. Krčálová, J. Horáček, F. Gabalec, P. Žák, J. Doležal, Scintigraphic evaluation of salivary gland function in thyroid cancer patients after radioiodine remnant ablation, Eur. J. Oral Sci. 128 (3) (2020) 204–210, https://doi.org/10.1111/eos.12689.
[9] G Babu, CT Kainickal, Update on the systemic management of radioactive iodine refractory differentiated thyroid cancer (Review), Mol Clin Oncol 14 (2) (2021), 35, https://doi.org/10.3892/mco.2020.2197.
[10] J. Klubo-Gwiezdzinska, D. Van Nostrand, K.D. Burman, et al., Salivary gland malignancy and radioiodine therapy for thyroid cancer, Thyroid 20 (6) (2010) 647–651, https://doi.org/10.1089/thy.2009.0466.
[11] A. Auttara-Atthakorn, J. Sungmala, T. Anothaisintawee, S. Reutrakul, C. Sriphrapradang, Prevention of salivary gland dysfunction in patients treated with radioiodine for differentiated thyroid cancer: a systematic review of randomized controlled trials, Front. Endocrinol. 13 (2022), 960265, https://doi.org/10.3389/fendo.2022.960265.
[12] K. Nakada, T. Ishibashi, T. Takei, et al., Does lemon candy decrease salivary gland damage after radioiodine therapy for thyroid cancer? J. Nucl. Med. 46 (2) (2005) 261–266.
[13] P.A. Vlaicu, A.E. Untea, R.P. Turcu, M. Saracila, T.D. Panaite, G.M. Cornescu, Nutritional composition and bioactive compounds of basil, thyme and sage plant additives and their functionality on broiler thigh meat quality, Foods 11 (8) (2022) 1105, https://doi.org/10.3390/foods11081105.
[14] A.L. Roe, A. Venkataraman, The safety and efficacy of botanicals with nootropic effects, Curr. Neuropharmacol. 19 (9) (2021) 1442–1467.
[15] M.M. Cohen, Tulsi - ocimum sanctum: a herb for all reasons, J. Ayurveda Integr. Med. 5 (4) (2014) 251–259, https://doi.org/10.4103/0975-9476.146554.
[16] S. Perna, H. Alawadhi, A. Riva, et al., In vitro and in vivo anticancer activity of basil (Ocimum spp.): current insights and future prospects, Cancers 14 (10) (2022) 2375.
[17] Q. Liu, X. Meng, Y. Li, C.N. Zhao, G.Y. Tang, H.B. Li, Antibacterial and antifungal activities of spices, Int. J. Mol. Sci. 18 (6) (2017) 1283, https://doi.org/10.3390/ijms18061283.
[18] A.L. Lopresti, S.J. Smith, A.P. Metse, P.D. Drummond, A randomized, double-blind, placebo-controlled trial investigating the effects of an Ocimum tenuiflorum (Holy Basil) extract (HolixerTM) on stress, mood, and sleep in adults experiencing stress, Front. Nutr. 9 (2022), 965130, https://doi.org/10.3389/fnut.2022.965130.
[19] S. Shiwakoti, O. Saleh, S. Poudyal, A. Barka, Y. Qian, V.D. Zheljazkov, Yield, composition and antioxidant capacity of the essential oil of sweet basil and holy basil as influenced by distillation methods, Chem. Biodivers. 14 (4) (2017), https://doi.org/10.1002/cbdv.201600417.

[20] K. Ogawa, M. Honda, A. Tanigawa, et al., Appetite-enhancing effects of inhaling cinnamon, clove, and fennel essential oils containing phenylpropanoid analogues, J. Nat. Med. 74 (4) (2020) 710–721, https://doi.org/10.1007/s11418-020-01423-8.
[21] T. Huang, X. Chen, D. Chen, et al., Eugenol promotes appetite through TRP channels mediated-CaMKK2/AMPK signaling pathway, Phytother Res. 37 (7) (2023) 2759–2770, https://doi.org/10.1002/ptr.7768.
[22] Q. An, J.N. Ren, X. Li, et al., Recent updates on bioactive properties of linalool, Food Funct. 12 (21) (2021) 10370–10389, https://doi.org/10.1039/d1fo02120f.
[23] P. Du, H. Yuan, Y. Chen, et al., Identification of key aromatic compounds in basil (ocimum L.) using sensory evaluation, metabolomics and volatilomics analysis, Metabolites 13 (1) (2023) 85, https://doi.org/10.3390/metabo13010085.
[24] M.R. Hasan, B.S. Alotaibi, Z.M. Althafar, A.H. Mujamammi, J. Jameela, An update on the therapeutic anticancer potential of ocimum sanctum L.: "elixir of Life", Molecules 28 (3) (2023) 1193, https://doi.org/10.3390/molecules28031193.
[25] S.N. Park, Y.K. Lim, M.O. Freire, E. Cho, D. Jin, J.K. Kook, Antimicrobial effect of linalool and α-terpineol against periodontopathic and cariogenic bacteria, Anaerobe 18 (3) (2012) 369–372, https://doi.org/10.1016/j.anaerobe.2012.04.001.
[26] S. Khan, M. Imran, M. Imran, N. Pindari, Antimicrobial activity of various ethanolic plant extracts against pathogenic multi drug resistant Candida spp, Bioinformation 13 (3) (2017) 67–72, https://doi.org/10.6026/97320630013067.
[27] B.R. Haugen, E.K. Alexander, K.C. Bible, et al., American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer, Thyroid 26 (1) (2015) 1–133, https://doi.org/10.1089/thy.2015.0020, 2016.
[28] C.D. Spielberger, R.L. Gorsuch, R. Lushene, P.R. Vagg, G.A. Jacobs, Manual for the State–Trait Anxiety Inventory (Form Y), Consulting Psychologists Press, Palo Alto, CA, 1983.
[29] Y. Yoshida, K. Horiuchi, T. Okamoto, Patients' view on the management of papillary thyroid microcarcinoma: active surveillance or surgery, Thyroid 30 (5) (2020) 681–687, https://doi.org/10.1089/thy.2019.0420.
[30] L.J. Julian, Measures of anxiety: state–Trait anxiety inventory (STAI), beck anxiety inventory (bai), and hospital anxiety and depression scale-anxiety (HADS-A), Arthritis Care Res. 63 (11) (2011) S467–S472, https://doi.org/10.1002/acr.20561. Suppl 11.
[31] S.S. Adibi, R. Hanson, D.F. Fray, et al., Assessment of oral and overall health parameters using the SillHa oral wellness system, Oral Surg Oral Med Oral Pathol Oral Radiol 133 (6) (2022) 663–674, https://doi.org/10.1016/j.oooo.2022.02.007.
[32] Y. Takaesu, N. Suzuki, M. Naito, et al., Novel oral biomarkers predicting oral malodor, Oral Surg Oral Med Oral Pathol Oral Radiol 130 (6) (2020) 667–674.
[33] J. Booker, D. Howarth, L. Taylor, D. Voutnis, D. Sutherland, Appropriate utilization of semi-quantitative analysis in salivary scintigraphy, Nucl. Med. Commun. 25 (12) (2004) 1203–1210, https://doi.org/10.1097/00006231-200412000-00009.
[34] X. Cai, R. Wang, J. Tan, Z. Meng, N. Li, Mechanisms of regulating NIS transport to the cell membrane and redifferentiation therapy in thyroid cancer, Clin. Transl. Oncol. 23 (12) (2021) 2403–2414, https://doi.org/10.1007/s12094-021-02655-0.
[35] J.L. Xu, R. Xia, Z.H. Sun, et al., Effects of honey use on the management of radio/chemotherapy-induced mucositis: a meta-analysis of randomized controlled trials, Int. J. Oral Maxillofac. Surg. 45 (12) (2016) 1618–1625, https://doi.org/10.1016/j.ijom.2016.04.023.