STUDY PROTOCOL

TITLE

A double-blind, randomized, placebo-controlled study to evaluate the efficacy of a homoeriodictyol mouthwash in chemotherapy-induced taste disorder – including a pilot study to evaluate taste testing during chemotherapy

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A) Scientific section

1. Summary

Background: More than 75% of women with cancer experience taste disorders during adjuvant chemotherapy. Bitter phantogeusia is particularly limiting. This can lead to impaired food intake with reduced energy intake, as well as changes in body composition, a reduced quality of life, and weight loss.

Study Objective: The objective of this study is, on one hand, to evaluate taste testing during chemotherapy and, on the other hand, to significantly reduce bitter phantogeusia by using a mouthwash containing homoeriodictyol (HED) immediately before consuming main meals. Taste testing during chemotherapy will be evaluated as part of a pilot study. In the controlled study, the primary endpoint is the measured reduction in the perception of bitterness from 500 ppm caffeine between week 1 and week 3. This is intended to improve food intake and body composition and counteract treatment-related weight loss.

Methods: As part of a pilot study, taste sensitivity is assessed before the start of chemotherapy and during chemotherapy. This phase of the study includes 40 patients undergoing chemotherapy. Taste sensitivity assessments are conducted before the start of chemotherapy and during the third cycle of chemotherapy, and blood samples are also collected. Food intake is assessed once a week using a 24-hour recall, and saliva samples are collected during the third cycle of chemotherapy. In the double-blind, randomized, placebo-controlled study, 32 patients with bitter phantogeusia will be included after completion of chemotherapy. Patients must rinse their mouths with a water solution containing HED (intervention group) or a placebo-containing water solution (control group) for 12 weeks immediately before consuming main meals. In weeks 1, 3, and 12, an evaluation of the taste disorder is conducted, and food intake is assessed using a 24-hour recall. In addition, the patients' body composition and weight are assessed in weeks 1 and 12. Furthermore, quality of life is measured using the EORTC-QLQ-30 Ovar and OV-28 in weeks 1, 3, and 12, and patient-related outcomes are recorded via a diary.

Conclusion: Aim of this study is to evaluate changes in taste perception during chemotherapy and to demonstrate a reduction in bitter phantogeusia following the use of a HED mouthwash in women with cancer undergoing chemotherapy.

2. Scientific knowledge

2.1. Background

Up to 77% of all female cancer patients suffer from chemotherapy-related taste disorder [1, 2]. On one hand, there is a loss of taste buds; on the other hand, tastes are perceived differently. This impairs the quality of life of oncology patients, and reduced appetite leads to decreased food intake, nutritional deficiencies, and, in the long term, increased mortality. The exact mechanism by which chemotherapeutic agents cause taste disturbances is currently not well understood [1], and no effective therapeutic interventions are available.

Cancer patients often experience a persistent bitter or metallic taste [3]. This taste disorder is called bitter phantogeusia and is associated with increased expression of the bitter receptors (TAS2Rs) 3, 42, and 43 in the taste cells of the tongue [4]. Tsutsumi et al. [5] demonstrated that patients with bitter phantogeusia who received a combination of radiation therapy and chemotherapy (cisplatin/5-fluorouracil) exhibited increased expression of TAS2R5. This effect was not observed with radiation therapy alone [5]. Furthermore, it was shown that bitter phantogeusia is more pronounced with cisplatin-containing chemotherapy, in contrast to combination therapy with cyclophosphamide, doxorubicin, or 5-fluorouracil. Nevertheless, the exact mechanism by which chemotherapy affects taste receptors is highly complex and poorly understood, which is why no effective treatments for bitter phantogeusia are currently available.

The plant-derived compound homoeriodictyol (HED) can reduce the perception of the bitter taste of caffeine by approximately 40% [7] and is currently one of the most potent bitter-masking agents. HED acts as an antagonist on the bitter receptors TAS2R20, 31, 43, and 50 [8]. In addition, it has been shown that a 30 mg bolus dose of HED has an appetite-stimulating effect in healthy subjects [9]. This amount of HED is already used by the food industry to mask bitter tastes.

We hypothesize that HED can help cancer patients who have undergone chemotherapy regain a normal sense of taste and stimulate their appetite, which may lead to increased food intake. Furthermore, preliminary results from our research group indicate that HED has a pro-proliferative effect on buccal cells and taste cells treated with cisplatin or 5-fluorouracil. This suggests that HED could help accelerate the regeneration of taste cells following chemotherapy, even though the cellular signaling pathways affected by HED are not yet known.

3. Rationale and Project Objectives

3.1 Rationale

More than 75% of women with ovarian cancer experience taste disturbances during adjuvant chemotherapy. This can lead to impaired food intake, reduced energy intake, and an unfavorable body composition, resulting in weight loss.

3.2 Project Objectives

The objective of the pilot study is to evaluate taste changes during chemotherapy. The objective of the placebo-controlled trial (RCT) is to significantly counteract taste disturbances by using a mouthwash containing homoeriodictyol (HED) immediately before consuming main meals. The primary endpoint is the measured reduction in the perception of bitterness. This is intended to improve food intake and body composition and counteract treatment-related weight loss.

3.3 Study Endpoints

Pilot Study

- Comparison of taste tests before and during chemotherapy

RCT

Primary endpoint:

- Comparison of the perception of bitterness induced by 500 ppm caffeine from week 1 to week 3 between the study group (HED mouthwash) and the control group (water mouthwash).

Secondary endpoints:

- Comparison of the perception of bitterness triggered by 500 ppm caffeine from week 1 to week 12 between the two groups.
- Comparison of the threshold for bitterness perception from week 1 to week 3 between the two groups.
- Comparison of the threshold for bitter taste perception in week 3 between the two groups.
- Comparison of overall taste perception in week 3 between the two groups.
- Comparison of overall taste perception from week 1 to week 12 between the two groups.
- Comparison of food intake using a 24-hour recall from week 1 to week 12 within the two groups.
- Comparison of food intake using a 24-hour recall from week 1 to week 12 between the two groups.
- Comparison of improvements in body composition from week 1 to week 12 between the two groups.

- Comparison of weight gain from week 1 to week 12 between the two groups.
- Comparison of quality of life using the EORTC-QLQ-30 Ovar and OV-28 from week 1 to week 12 within the two groups.
- Comparison of the change in quality of life using the EORTC-QLQ-30 Ovar and OV-28 from week 1 to week 12 between the two groups.
- Comparison of “patient-related outcomes” using a diary from week 1 to week 12 within the two groups.

4. Experimental Protocol

4.1. Study Design

Pilot Study

This part of the study will include 40 female patients undergoing chemotherapy. Taste tests will be conducted before the start of chemotherapy and during the third cycle of chemotherapy. At these time points, blood samples will also be collected to determine zinc levels and the concentration of the chemotherapeutic agent, and a baseline medical history and taste-specific medical history will be assessed via questionnaire. Food intake is assessed once a week using a 24-hour recall, and during the third cycle of chemotherapy, saliva samples are additionally collected to serially evaluate the concentration of the chemotherapeutic agent in saliva.

RCT

This study is a double-blind, randomized, placebo-controlled trial investigating the effect of rinsing the mouth with HED before each main meal on the perception of bitterness over a 12-week period following completion of chemotherapy. Due to their prior treatments, patients undergo a detailed examination, including physical examination and preanesthetic assessment. In addition, a taste perception test is performed as part of the screening process. Furthermore, adverse events are reported during each chemotherapy cycle. In addition, a taste perception test is conducted as part of the screening process to identify any pre-existing taste disorders. If a general taste disorder is ruled out and an isolated disturbed perception of bitterness is confirmed, the patient can be included in the study.

A total of 32 patients will be included in the study (study group: 16 patients, placebo group: 16 patients). Depending on randomization, patients receive either a mouthwash containing HED and water or a mouthwash containing food coloring and water. In weeks 1, 3, and 12, an evaluation of bitter perception triggered by 500 ppm caffeine, a determination of the bitter perception threshold, and food intake assessment via a 24-hour recall questionnaire are conducted. In addition, at the same time points, the patients’ quality of life is assessed using the EORTC-QCQ-30 Ovar and the OV-28 questionnaire. In addition, the patients’ body

composition and weight will be assessed in week 1 and week 12. Patient-reported outcomes will be recorded using diaries.

4.1.1. Study Visits

Pilot Study

Visit 1

During screening visit, taste test and questionnaires regarding taste and dietary habits will be conducted. The sensory test includes: testing of general taste perception for the five basic tastes—salty (sodium chloride), bitter (caffeine), sour (citric acid), sweet (sucrose), and umami (glutamate)—as well as the metallic taste (ferrous sulfate), testing the detection and recognition thresholds for the different taste sensations, and testing the intensity of the bitter taste of various caffeine solutions with and without the addition of homoeriodictyol. The survey of patients regarding their taste perception and preference for foods with specific taste sensations will be conducted using a questionnaire. This questionnaire is based on the questions by McGettigan et al. [10] and has been supplemented with questions regarding the preference for and consumption of specific foods (attached in the appendix). The dietary intake surveys will be conducted using 24-hour recalls. Following an initial in-person interview, the remaining dietary intake surveys will be conducted by telephone once a week. In addition, the patients will receive a diary in which they will document their daily food intake and symptoms.

Visit 2

Before the first cycle of chemotherapy, taste test and questionnaires regarding taste and dietary habits are conducted. The sensory test includes: testing of general taste perception for the five basic tastes—salty (sodium chloride), bitter (caffeine), sour (citric acid), sweet (sucrose), and umami (glutamate)—as well as the metallic taste (ferrous sulfate), testing the detection and recognition thresholds for the different tastes, and testing the intensity of the bitter taste of various caffeine solutions with and without the addition of homoeriodictyol. The interviews with patients regarding their taste perception and preferences for foods with specific tastes will be conducted using a questionnaire. This questionnaire is based on the questions by McGettigan et al. [10] and has been supplemented with questions regarding the preference for and consumption of specific foods (attached in the appendix). The dietary intake surveys will be conducted using 24-hour recalls including assessment of physical activities within the last seven days. Following an initial in-person interview, the remaining dietary intake surveys will be conducted by telephone once a week. Blood samples for zinc measurement and determination of the chemotherapeutic agent will be collected as part of a routine blood draw.

Visit 3

During the visit for the third cycle of chemotherapy, the following tests will be repeated: testing of general taste perception for the five basic tastes—salty (sodium chloride), bitter (caffeine), sour (citric acid), sweet (sucrose), and umami (glutamate)—as well as the metallic taste (ferrous sulfate), testing of the detection and identification thresholds for the different taste sensations, and testing of the intensity of the bitter taste of various caffeine solutions with and without the addition of homoeriodictyol. Patients will be interviewed about their taste perception and preferences for foods with specific taste sensations using a questionnaire (see Appendix). Blood samples for zinc determination and quantification of the chemotherapeutic agent will be collected as part of routine blood draws prior to the start of chemotherapy administration. As part of this monitoring, serial saliva samples will be collected to analyze the concentration of the chemotherapeutic agent before, during, and after chemotherapy administration. Saliva samples will be collected before the start of chemotherapy administration (t=0), during chemotherapy administration (t=2h), at the end of chemotherapy administration (t=4h), two hours after the end of chemotherapy administration (t=6h), and the following morning (t=18–20h). The diary is returned by the patients.

RCT

Visit 1

The patient returns for screening one week after her last cycle of chemotherapy due to suspected bitter phantogeusia. The patient's bitter phantogeusia is determined by directly asking about bitter taste perception ("Did you notice an increased bitter taste during the course of chemotherapy?") and subsequently classifying the increased perception as "mild," "moderate," or "severe." If the patient rates her heightened perception of bitterness as "moderate" or "severe," meets all inclusion and exclusion criteria, and consents to the study by signing the patient information form, she is eligible for inclusion in the study. As part of the screening examination, the threshold for bitter perception and the bitter perception triggered by 500 ppm caffeine are recorded. Body composition is also measured using the BOD POD® and a weight check is performed. Quality of life is assessed using the EORTC-QLQ-30 Ovar and OV-28, and dietary intake is assessed using a 24-hour recall questionnaire (GloboDiet). In addition, perception of the other four basic tastes (sweet, sour, salty, umami) is determined using a sensory test. Furthermore, the patient is given a detailed explanation of the necessary follow-up visits required as part of the study and is handed a diary.

Visit 2

The patient returns for a follow-up visit three weeks after the end of her last course of chemotherapy. A test is conducted to assess bitterness perception of 500 ppm caffeine and to determine the bitterness perception threshold, as well as a sensory test to assess perception of the taste qualities sweet, sour, salty, and umami, a quality-of-life assessment using the EORTC-QLQ-30 Ovar and OV-28, and a dietary intake assessment using the 24-hour recall questionnaire (GloboDiet).

Visit 3

The patient returns 12 weeks after the end of her last chemotherapy session for a final examination. A test of bitterness perception using 500 ppm caffeine and determination of the bitterness perception threshold is performed, along with a sensory test to assess perception of the taste qualities sweet, sour, salty, and umami, a measurement of body composition using the BOD POD®, and a weight check. Quality of life is assessed using the EORTC-QLQ-30 Ovar and OV-28, and dietary intake is assessed using a 24-hour recall questionnaire (GloboDiet). The diary is discussed and collected.

RCT: Overview of Study Visits

	CRF	QoL (EORTC 30 and OV-28)	Medication dispense/return	Sensory test	BOP POD	Weight	Diary	24-hour recall
V1 (1 week after CHT)	X	X	X	X	X	X	X	X
V 2 (2 weeks after V1)	X	X	X	X			X	X
V3 (12 weeks after V1)	X	X	X	X	X	X	X	X

4.1.2. Withdrawal from the study

Patients may withdraw from the study at any time without providing a reason. Withdrawal is defined as premature termination of the study prior to attending Visit 3. Every withdrawal is documented. Documentation up to the point of withdrawal must be complete. Patients who withdraw from the study will not be replaced. Patients who withdraw from the study will be included in the statistical analysis (intention-to-treat analysis). Patients who withdraw from the study must return all remaining study medication and will continue regular follow-up after gynaecologic cancer treatment at the Medical University of Vienna.

4.1.3. Study Exclusion

Study exclusion refers to the exclusion of the patient from the study by the investigator (Associate Professor PD Dr. Christoph Grimm). This occurs in the following cases:

- Occurrence of severe adverse events that seriously endanger the patient's health or life
- Other medical indications
- Demonstrable non-compliance by the patient
- Violation of the study protocol that, in the opinion of the investigator or the sponsor, is incompatible with the continuation of the study.

4.1.4. End of Participation

The patient has completed the study if she has attended all study visits. Study visits must be attended within ± 3 days of the respective appointment. The patient must have taken the prescribed study medication during the specified period. The patient must return the remaining sachets containing the powder at the final examination. All further follow-up visits after the end of the study are conducted, as mentioned above, according to an established follow-up after gynaecologic cancer treatment at the Medical University of Vienna.

4.1.5. Evaluation of efficacy

This is done by testing the perception of bitterness triggered by 500 ppm of caffeine in week 1 and week 3.

4.1.6. Monitoring of side effects and adverse events

Side effects are documented in the patient's diary, and the patient uses a visual analog scale (VAS) to rate the severity of each side effect. Other adverse events and the use of other medications are also recorded in the patient's diary.

4.2. Patients

Pilot Study

Inclusion Criteria

1) Patients (>18 years) with histologically confirmed gynaecological malignancy
2) Planned chemotherapy
3) Written informed consent
4) Expected patient compliance

Exclusion criteria:

1) Vomiting (CTCAE 4.03) > Grade 2 (3–5 episodes within 24 hours)
2) Nasogastric tube or PEG tube
3) Previous platinum-based chemotherapy
4) Conditions that impair taste perception (e.g., infections in the oral cavity)

Number of study participants:

A total of 40 patients will be enrolled in the study.

RCT

Inclusion criteria:

1) Patients (>18 years) with histologically confirmed ovarian cancer/tubal cancer/peritoneal cancer
2) Age 18–70 years
3) Non-smoker for at least 12 months
4) Completed chemotherapy with platinum and taxane
5) Written informed consent
6) Phantogeusia confirmed through patient interview
7) Expected patient compliance

Exclusion criteria:

1) Planned or ongoing treatment with a PARP inhibitor
2) Known intolerance to HED
3) Nausea and vomiting (CTCAE 4.03) > Grade 2 (3–5 episodes within 24 hours)
4) Nasogastric tube or PEG tube
5) Progressive tumour disease during adjuvant chemotherapy
6) Conditions that interfere with taste perception (e.g., infections in the oral cavity)
7) General taste disturbance verified by baseline tests

Number of study patients:

A total of 32 patients will be enrolled in the study (active treatment group: 16 patients, placebo group: 16 patients).

4.3. Study Medication

4.3.1. Production and Storage:

To prepare the study medication, 30 mg of homoeriodictyol sodium is granulated with food coloring, a opacifier, and a carrier material (manufactured by Symrise AG, Holzminden, Germany) and packaged in airtight bags. The powder are portioned and packed into the bags at the Institute of Physiological Chemistry using portioning spoons. The number of bags containing the portioned powder required for each study participant is collected in cardboard boxes, which are labelled for each patient according to the randomization (sequential numbers from 1 to 32). This labelling is performed by a staff member of the Institute of Physiological Chemistry who will have no contact with the study participants. The process is carried out in accordance with internationally established standards and standard operating procedures (SOPs).
The study medication is stored in the cold room (4–6°C) of the Institute of Physiological Chemistry until it is dispensed. For this purpose, the boxes labelled according to randomization are kept in a sealed aluminium box. After the study medication is dispensed to the patient, the cardboard box containing the entire medication is stored in the patient's refrigerator.
The study participants dissolve the powder in 20 ml of water immediately before use. The placebo consists of the same formulation of powder, except that the HED is replaced by a carrier substance, which the study participants also dissolve in 20 ml of water.

4.3.2. Blinding:
The study medication, both the verum and the placebo, is packaged in cardboard boxes and labelled according to randomisation.

4.3.3. Randomisation:
Randomisation is done online using the randomisation programme of the Medical University of Vienna (https://www.meduniwien.ac.at/randomizer/web/login.php). Patients are randomised in a 1:1 ratio without further stratification and without blocks. Randomisation of the patient takes place after the informed consent has been signed, the inclusion and exclusion criteria have been checked, the taste test has been carried out, and the impaired bitter perception has been objectively assessed (recording of the threshold for bitter perception and the bitter perception triggered by 500 ppm caffeine). If impaired bitter perception cannot be verified, the patient is documented as a 'screening failure' and excluded from the study. For further details, see 'Statistical section: Randomisation'.

4.3.4. Dosage:
The 20 ml mouthwash solution (depending on randomisation, either water containing 30 mg HED, food colouring, a opacifier and a carrier, or just water containing food colouring, a

opacifier and a carrier as a placebo) is administered three times daily before each main meal throughout the entire 12-week study period. The patient may discontinue treatment at any time if side effects occur, but must report this immediately to the study team. Should the patient discontinue the mouthwash, the study medications must be returned.

4.4. Experimental design and schedule

4.4.1. Investigation of the perception of bitter taste

In ovarian cancer patients with chemotherapy-induced bitter phantogeusia, the perception of bitterness from caffeine is tested. To this purpose, study participants are administered 20 ml of an aqueous mouthwash solution containing 500 ppm caffeine. After rinsing and spitting out the caffeine solution, the patients rate the bitterness of the solution on a scale from 0 (slightly bitter) to 10 (very bitter). The perception of bitterness is then tested in the presence of HED by administering a 500 ppm caffeine rinse solution with 100 ppm HED added. After rinsing and spitting out this caffeine-HED solution, the patients again rate the bitterness on a scale of 0 to 10. The perception of bitterness of caffeine alone and of caffeine after HED is used for comparison between groups and visits. In addition, a threshold test for bitter taste is carried out to determine the concentration of caffeine at which the patients perceive a bitter taste. To determine this, the patients taste mouthwash solutions one after the other, starting with water, at increasing concentrations of caffeine. Patients indicate the concentration at which they first detect a taste (detection threshold) and the concentration at which they can recognize a specific taste (recognition threshold), and whether the taste intensifies from one concentration to the next. The resulting threshold value for bitter perception is also used for comparison between groups and visits.

4.4.2. Investigation of general taste perception

In addition to the bitter taste, we also plan to evaluate the other four basic tastes and the metallic taste. To this end, study participants will taste mouthwash solutions containing salty (NaCl), sour (citrate), sweet (sucrose), umami (glutamate) or metallic (ferrous sulphate) flavourings and rate their taste quality. The results will be compared across visits and groups. In addition, the pilot study will also include a survey on taste perception and chemotherapy-induced taste changes using a questionnaire developed in-house. This questionnaire is based on the questions by McGettigan et al. [10] and has been supplemented with questions regarding the preference for and consumption of specific foods (attached in the appendix).

4.4.3. Assessment of food intake

The patients' food intake is recorded using a 24-hour dietary recall. A standardised questionnaire is used to determine the quantities of specific foods consumed by the patients

over the past 24 hours. The questionnaire is administered in person or by telephone using the computer-based GloboDiet questionnaire by a trained staff member.

4.4.4. Assessment of quality of life

The patients' quality of life is analysed using the EORTC-QLQ-30 and OV-28 questionnaires, whilst 'patient-related outcomes' are evaluated via a diary.

4.4.5. Assessment of Body Composition and Body Weight

We also plan to analyse the body composition and weight of the patients. For this purpose, we will use the BOD POD® device, which operates on the principle of air displacement plethysmography. Body composition, and in particular body fat percentage, is determined by calculating density based on the volume of displaced air measured within the BOD POD capsule.

4.4.6. Measurement of Chemotherapy Drug Concentration in Saliva

The pilot study aims to measure the concentration of the chemotherapy drug in patients' saliva during and after chemotherapy administration. To this end, serial saliva samples will be collected before the start of chemotherapy administration (t=0), during chemotherapy administration (t=2h), at the end of chemotherapy administration (t=4h), two hours after the end of chemotherapy administration (t=6h), and the following morning (t=18–20h). Before each saliva collection, the mouth is thoroughly rinsed with water. The saliva samples are stored at -80 °C until processing and analysis. Before measuring the platinum concentration, the saliva matrix is digested by adding nitric acid and hydrogen peroxide and by heat treatment. The concentration of the chemotherapeutic agent is determined using inductively coupled plasma - mass spectrometry (ICP-MS), with measurements conducted by the Institute of Physiological Chemistry in collaboration with the Institute of Analytical Chemistry.

4.4.7 Measurement of Serum Zinc Concentration

In the pilot study, the concentration of the metal zinc in the patients' serum will be determined. Blood samples will be collected as part of a routine blood draw, so no additional intervention is required for the patients. The zinc measurement will be performed in the laboratory of the Medical University of Vienna as part of routine diagnostics.

4.4.7 Measurement of the concentration of the chemotherapeutic agent in blood serum

In the pilot study, the concentration of the chemotherapeutic agent in the patients' blood serum will be determined. Blood samples are collected as part of a routine blood draw, so there is no additional intervention for the patients. Measurement of drug levels will be

performed in the laboratory of the University of Vienna, Institute of Physiological Chemistry, in collaboration with the Institute of Analytical Chemistry.

4.5. Timeline

Pilot study	
Recruitment	Months 1–12
Analysis	Months 12–15
Total	15 months

RCT	
Study planning	Months 1–6
Recruitment	Months 7–30
Analysis	Months 30–36
Total	36 months

B) Statistical Section

1. Sample Size

Forty patients will be recruited for the pilot study. This study is intended to provide a descriptive analysis of taste changes during chemotherapy and to validate the tests used for the double-blind, randomized, placebo-controlled study planned afterwards. The double-blind, randomized, placebo-controlled study will include 32 female patients. Based on current studies [3], the prevalence of bitter phantogeusia is approximately 30–78%. An HED mouthwash leads to a 30% reduction in bitter perception (standard deviation 10%) [7], which describes the expected effect size. The primary endpoint is defined as “comparison of the bitter perception triggered by 500 ppm caffeine from week 1 to week 3 between the study group (HED mouthwash) and the control group (water mouthwash).” The patient rates bitterness perception on a continuous scale from 0 to 10. The study endpoint is therefore a continuous variable. The data from week 1 and week 3 will be analysed using a paired t-test to compare the intervention group with the control group. Taking into account a 20% dropout rate, a 90% power level, and a significance level of 1%, this results in a sample size of 32 patients. These will be randomized 1:1, resulting in a group size of 16 patients each. Approximately 77% of patients experience bitter phantosmia following platinum-based combination chemotherapy. Therefore, approximately 40 patients will need to be screened.

2. Randomization

Randomization is performed online using the randomization program of the Medical University of Vienna (https://www.meduniwien.ac.at/randomizer/web/login.php). The complete randomization list is provided to Mr. Sebastian Bayer, MSc, a staff member of the Institute of Physiological Chemistry. Study medication is packaged and coded, with coding performed exclusively by Mr. Sebastian Bayer. The coded, randomized study medication is then distributed as needed to the investigators, who administer the study medication to the patients. The investigators and the statistician may not view the randomization list until the study has been completed.

3. Statistical Analysis

The efficacy of the treatment is defined as a reduction in the perception of bitterness by more than 30% in the treatment group compared to the placebo group. The primary endpoint will be evaluated using a paired t-test.

This will be evaluated in two analyses:

- Intention-to-treat analysis: Inclusion of all patients who used the mouthwash at least once
- Per-protocol analysis: Inclusion of patients who completed the study according to the study protocol

Secondary endpoints are also analysed using intention-to-treat and per-protocol analyses. The collected clinical and pathological data are presented descriptively using absolute values or, depending on the normality of the distribution, using the median (interquartile range) or mean (standard deviation). Metric variables are compared using Student's t-test or the Mann-Whitney U test, depending on normal distribution. Categorical variables are compared using the chi-square test and, if feasible given the number of groups, presented including the odds ratio (95% confidence interval). The study will investigate predictive factors for response to the intervention. These analyses are performed using a multivariate binary logistic regression model. The following variables are included: patient age, number of chemotherapy cycles, patient BMI, bowel resection during the primary surgery, peripheral polyneuropathy during chemotherapy, nausea at the time of study enrolment, and diarrhoea at the time of study enrolment. Version 21.0 of the statistical software SPSS (SPSS, Inc.) is used for the statistical analysis.

Patient data is pseudonymized, documented, and analysed in accordance with current data protection regulations and is not disclosed to third parties. The data is published in anonymized and aggregated form.

C) Ethical and Legal Section

1. Ethical Aspects

1.1. The Risk-Benefit Ratio

The homoeriodictyol to be administered in this study was published on the FEMA-GRAS ("generally recognized as safe") list 22 by the FEXPAN expert panel of the Flavor and Extracts Manufacturers Association (FEMA) in the United States and has thus been deemed generally safe. Substances published on the GRAS list do not require further approval from the Food and Drug Administration (FDA) to be authorized for the market. NaHED (FL. - Number 16.083) has also been included in the EU's positive list of permitted flavourings (Implementing Regulation No. 872/2012, Official Journal of the European Union, L 267/1) and is provided for this study by Symrise AG, Holzminden, Germany, in the specification required for use as a flavouring.

There are no risks for study participants, and no further examinations or interviews are required. All participants who complete the study will receive compensation for their time and effort in the amount of 130.00 euros. A portion of the compensation will be paid to the participants per visit (visit 1: 50 euros, visit 2: 30 euros, visit 3: 50 euros). For participants in the HED group, a benefit in the form of a reduction in the perception of bitterness is expected. In addition, a partial reduction in the perception of bitterness may also occur in the control group due to the placebo effect. The collected data can be used to facilitate the planning of a further, larger validation study to precisely evaluate the efficacy of HED in chemotherapy-induced bitter phantogeusia.

2. Legal Aspects

2.1. Declaration of Helsinki

The study will be conducted in accordance with the guidelines of the Declaration of Helsinki (1964). Furthermore, adherence to the moral, ethical, and scientific principles of Good Clinical Practice (GCP) will be ensured. A positive decision by the local ethics committee is a prerequisite for the start of the study.

D) Administrative section

1. Publication of Results

The goal is to publish study results in an appropriate journal. The manuscript will be sent to all submitting authors for approval prior to publication. Data ownership rests with the study physicians.

2. Protocol Amendments

Amendments must be in writing, identifying the specific changes and providing a rationale for the amendments. Significant changes require the approval of the investigators and the ethics committee.

3. Data Protection

Patients are assigned a code consisting of a sequential identification number and the initial letters of their first and last names (e.g., 01-AM). The patients' names and dates of birth can therefore no longer be identified.

E) Referenzen

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