Research

Effect of red ginger powder capsule supplementation on laryngopharyngeal reflux

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ABSTRACT

Background: Ginger (Zingiber officinale) is a popular rhizome plant that used as a cooking and medicinal ingredient. Ginger contains many active compounds, such as phenolic and terpenes. Ginger has an anti-inflammatory effect through active ingredients, including diarylheptanoids, oleoresin, gingerol, shogaol and zingerone. Ginger powder is often used as a remedy for gastric acid reflux. In laryngopharyngeal reflux, there is a damage to the laryngopharyngeal mucosa due to irritation of gastric acid and pepsin. **Purpose:** To analyze the effect of red ginger powder capsule supplementation (Zyngiber officinale var. rubrum) on laryngopharyngeal reflux. **Method:** Non-randomized control trial study with a pretest-posttest control group design in laryngopharyngeal reflux. The patients were divided into two groups, where each group was examined for Reflux Symptom Index (RSI) and Reflux Finding Score (RFS). The intervention group was given red ginger powder capsules and lansoprazole, while the control group was given lansoprazole only; then a month later, both groups were examined for RSI and RFS finding score. Data were analyzed statistically with a computer program and were declared significant if $p<0.05$. **Result:** There was a significant difference between RSI and RFS in the intervention group, and there was no significant difference between RSI and RFS in the control group. Meanwhile, there were significant differences in RSI and RFS between the control and intervention groups. **Conclusion:** There was a significant difference between the reflux symptom index and reflux finding score between the intervention group and the control group.

Keywords: red ginger, Zingiber officinale var. rubrum, laryngopharyngeal reflux, reflux symptom index, reflux finding score

ABSTRAK

Latar belakang: *Jahe (*Zingiber officinale*) merupakan tanaman rimpang yang populer digunakan sebagai bahan masakan dan obat. Jahe mengandung banyak senyawa aktif, seperti senyawa fenolik dan terpena. Jahe memiliki efek anti-inflamasi melalui kandungan aktifnya, antara lain* diarylheptanoida, oleoresin, gingerol, shogaol dan zingeron. *Bubuk jahe sering digunakan sebagai pengobatan pada kasus refluks asam lambung. Pada kelainan refluks laringofaring, terjadi kerusakan pada mukosa laringofaring akibat iritasi asam lambung dan pepsin.* ***Tujuan:*** *Menganalisis pengaruh suplementasi kapsul serbuk jahe merah (*Zingiber officinale var. rubrum*) terhadap refluks laringofaring.* ***Metode:*** *Menggunakan metode* non-randomized control trial, *dengan pendekatan* pretest-posttest control group design *pada refluks laringofaring. Pasien dibagi menjadi dua kelompok, dan masing-masing kelompok diperiksa indeks gejala refluks, dan skor temuan refluks. Pada kelompok intervensi diberikan kapsul serbuk jahe merah dan* lansoprazole, *sedangkan pada kelompok kontrol diberikan* lansoprazole *saja; selanjutnya, satu bulan kemudian dilakukan pemeriksaan indeks gejala refluks dan skor temuan refluks. Data dianalisis secara statistik dengan program komputer dan dinyatakan signifikan jika* $p<0,05$.

Hasil: *Terdapat perbedaan yang signifikan antara indeks gejala refluks dan skor temuan refluks pada kelompok intervensi, dan tidak terdapat perbedaan yang signifikan antara indeks gejala refluks dan skor temuan refluks pada kelompok kontrol. Sementara itu, terdapat perbedaan yang signifikan pada indeks gejala refluks dan skor temuan refluks antara kelompok kontrol dan intervensi.* ***Kesimpulan:*** *Terdapat perbedaan yang signifikan antara indeks gejala refluks dan skor temuan refluks antara kelompok intervensi dan kelompok kontrol.*

Kata kunci: *jahe merah,* Zingiber officinale var. rubrum*, refluks laringofaring, indeks gejala refluks, skor temuan refluks*

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INTRODUCTION

The World Health Organization (WHO) stated that up to 65% of the population of developed countries use traditional medicine and medicines from natural ingredients, and half of Indonesia's population still uses traditional medicine in the form of herbs; about 4.5% consume it every day, and the rest only consume it occasionally.[1] One of the most popular medicinal plants used as the main raw material for herbal medicine and traditional medicine is ginger.[2]

Ginger cultivation is carried out in almost all regions of Indonesia. Ginger (*Zingiber oficinale*) has been used since ancient times as a traditional medicine, including treating flu, fever, sore throat, and gastric problems such as dyspepsia, gastritis, nausea and vomiting.[3,4] Ginger can reduce the opening pressure on the lower esophageal sphincter (LES), which could reduce intestinal cramps and prevent dyspepsia.[3] In addition, the role of ginger in several studies is also to function as anti-inflammatory, antiemetic, analgesic, improve metabolic function, and other benefits.[5,6]

The inflammation of the upper aerodigestive tract caused by reflux of gastroduodenal contents, either directly or indirectly, is known as laryngopharyngeal reflux (LPR), and it results in morphological abnormalities in the upper aerodigestive tract.[7,8] Worldwide, among head and neck surgery (ENT-HNS) polyclinic patients, the incidence of LPR varies from 10% to 35%.[9] Patients with LPR frequently complain of hoarseness, coughing, frequent clearing of the throat, and a feeling of blockage in their throat.[10,11]

In LPR, there is a damage to the laryngopharyngeal mucosa due to gastric acid and pepsin irritation.[7] Inflammation influenced by LPR causes swelling, mucous hypersecretion, and secretion of inflammatory mediators. Other mechanisms also link to *Helicobacter pylori* infection and mucosal inflammation.[8] Ginger is known to have effects as an anti-inflammatory through its active ingredients including diarylheptanoids, oleoresins,[9] gingerol, shogaol and zingerone.[10] Ginger works by reducing inflammatory factors such as CRP, IL6, TNFα, and shows antagonistic activity against serotonin receptors.[11] In addition, ginger also has the effect of reducing the opening pressure of the LES, and accelerating the process of gastric emptying, so that the risk of reflux decreases.

There has never been any research done on the application of ginger as an LPR treatment. It is believed that the anti-inflammatory, lowering LES opening pressure, antibacterial, and weight-loss properties of ginger, contribute to the improvement of LPR's clinical symptoms. As a result,

scientists were interested in finding out how red ginger powder supplements affected LPR patients.

METHOD

The study used non randomized control trial with a pretest-posttest control group design approach. The population was all patients who had been diagnosed with LPR based on Reflux Symptom Index (RSI) and Reflux Finding Score (RFS), at Dr. M Djamil Hospital Padang. Inclusion criterium was patient acceptance to be a research subject by signing a consent form. Exclusion criteria were: 1) suffering from diabetes mellitus, hepatitis, pregnant, breastfeeding; 2) currently taking red ginger, PPIs, AH2r, Cytoprotectors, NSAIDs in the last 7 days; and 3) allergic to ginger. The research was conducted from September 2021 to October 2022.

The minimum sample size of the study was determined by using the sample size formula based on the hypothesis test formula for the mean of two populations in two independent groups. Type I error was set at 5%, one-way hypothesis, so $Z\alpha = 1.64$; type II error was set at 10%, with $Z\beta = 1.28$. The minimum difference in means, being considered meaningful was 3, and SD = 2.97. Total sample was 34 samples, the number of samples obtained was n = 17 samples in each group. The intervention group was given red ginger powder capsules + lansoprazole, and the control group was given lansoprazole only. All subjects diagnosed with LPR according to the inclusion criteria and exclusion criteria were submitted until the sample size was met.

The independent variable in this research was red ginger powder capsule, and the dependent variable were Reflux Symptom Index (RSI) and Reflux Finding Score (RFS). Red ginger powder capsule was an adjunctive therapy containing standardized red ginger powder capsules at a dose of 1.5 grams per day (3x500mg), given with standard LPR therapy (lansoprazole 2x30 mg) for 1 month. The red ginger powder capsule used was Herbana Relief Red Ginger Juice, with the BPOM registration number TR142378491. Reflux Symptom Index (RSI) is a clinical assessment score consisting of 9 questions, with a score of 0-5 for each question. Reflux Finding Score (RFS) is an assessment score of pathological conditions in larynx performed through fiber-optic laryngoscope examination, includes 8 pathological conditions of the larynx, and assessment score ranges from 0 (no abnormal conditions found) to 26.

The study was conducted on patients with LPR and RFS, performed by the researchers and doctor in charge of the patient (consultant). Patients were given 2x30 mg lansoprazole; then grouped into intervention group (with red ginger powder capsule supplementation), and control group (without red ginger powder capsule supplementation). The research data were processed and analysed. The characteristics of the study sample were presented in tabular forms. The results of RSI and RFS before therapy in both groups were recorded in the research status, then a reassessment of RSI and RFS was carried out on day 30.

The difference and mean of RSI and RFS (day 0 and 30) in the treatment group and control group were then statistically tested with paired T test and unpaired T test on normally distributed data. All research data were recorded in the research notes that had been made, and the data were processed using the SPSS program. Statistical test results were declared significant if the p value was <0.05. Informed consents were obtained from all subjects. The procedures, objectives and benefits of the study had been approved by the Ethics Committee of Dr. M. Djamil General Hospital, Padang.

RESULT

The baseline characteristics of the study subjects between the intervention group and control group were shown in Table 1. The baseline characteristics shown were gender, age, body mass index (BMI), habitual factors, and diet.

Tabel 2 showed decrease in mean RSI and RFS between pre and post lansoprazole adminstration in the control group, but based on the result of statistical tests using the paired T test for RSI and Wilcoxon test for RFS, there was no significant difference in both RSI and RFS with a p>0.05 value.

Table 1. Characteristics of research subjects

Variable	Group		Total
	Control	Intervention	
1	**2**	**3**	**4**
Gender			
Male	8 (47.05%)	7 (41.17%)	15 (44.11%)
Female	9 (52.94%)	10 (58.82%)	19 (55.88%)
Age			
Mean	42.52	46.94	44.73
Min	19	23	19
Max	68	68	68
±SD	±13.65	±11.64	±12.69
Body Mass Index			
<18.5 *(underweight)*	1 (5.88%)	1 (5.88%)	2 (5.88%)
18.5-22.9 (normal)	6 (35.29%)	7 (41.18%)	13 (38.24%)
23-24.9 *(overweight)*	5 (29.41%)	4 (23.53%)	9 (26.47%)
≥25 *(obese)*	5 (29.41%)	5 (29.41%)	10 (29.41)
1	**2**	**3**	**4**
Habitual and dietary factor			
Alcohol consumption	0 (0 %)	1(5.88%)	1 (2.94%)
Fizzy drinks (sparkling water)	1 (5.88%)	0 (0 %)	1 (2.94%)
Caffeinated drinks (coffee, tea)	9 (52.94%)	10 (58.82%)	19 (55.88%)
Spicy Food	14 (82.35%)	13 (76.47%)	27 (79.41%)
Greasy food	14 (82.35%)	12 (70.59%)	26 (76.47%)
Acidic food	5 (29.41%)	6 (35.29%)	11 (32.35%)
Smoking	4 (23.53%)	2 (11.76%)	6 (17.65%)

Table 2. Effect of Pre and Post RSI and RFS in the control group

	Pre test	Post test	*p*
RSI (mean±SD)	19.94 ±3.71	16.29 ±7.75	0.059[a]
RFS (mean±SD)	9.70 ±2.49	8.00 ±3.69	0.058[b]

Table 3. Effect of pre and post RSI and RFS in the intervention group

	Pre test	Post test	*p*
RSI (mean±SD)	21.52 ±5.11	12.11 ±4.48	0.000[a]
RFS (mean±SD)	11.05 ±4.32	6.58 ±2.62	0.000[b]

Table 3 showed decrease in mean RSI and RFS between pre and post administration of lansoprazole and red ginger powder capsules in the intervention group. Based on the results of statistical tests using the paired T test for RSI and Wilcoxon test for RFS, there was a significant difference in RSI and RFS, with a significance value of $p < 0.05$.

Table 4. Effect of RSI and RFS between control and intervention groups

	Control	Intervention	*p*
RSI (mean±SD)	3.64 ±7.40	9.41 ±3.82	0.029
RFS (mean±SD)	1.70 ±3.67	4.47 ±3.35	0.029

Table 4 showed the difference in the mean difference of RSI and RFS between the control group and the intervention group. In statistical tests using the unpaired T test for RSI and RFS, there were significant differences in RSI and RFS between the control and intervention groups, with a significance value of $p < 0.05$.

DISCUSSION

In this study, it was found that patients with LPR were more likely female. There were more women (55.88%) than men (44.11%), with a ratio of 1.26. This result was in accordance with the results obtained by several studies.[12-15] There was an association between the severity of GERD and the development of LPR, so the cause might be hormonal.[16] Estrogen receptors in the gastrointestinal epithelium are involved in the pathophysiology of gastrointestinal disease. This is due to the presence of elevated estrogen hormones in women associated with reflux, which will increase nitric oxide synthesis, causing relaxation of the LES.[17]

This study was conducted on 34 patients with LPR. The mean age of the subjects was 42.5+13.65 years in the control group, and 46.9+11.64 years in the intervention group; and the lowest age was 19 years, and the highest was 68 years. Women, especially those over 35 years of age, will experience perimenopause, which is a period when changes in hormone regulation begin to occur, especially a decrease in estrogen and progesterone hormones. Decreased estrogen and progesterone reduce mucus secretion, which serves to protect the mucosa from reflux.[18]

The most common main complaint that brought the subject to come for treatment was a feeling of blocking in the throat as many as 15 patients (44.12%). The results of this study were in accordance with the research of Hussain et al.[19], Sa'an[20], Massawe et al.[21] and Osman et al.[22], which found the majority of niggling sensations in the throat in the RSI findings. Fiber-optic laryngoscope examination result showed that the highest RFS scoring was in erythema/hyperemic. Kurniawati et al.[23] found erythema/hyperemic results in the majority of RFS findings, which were supported by studies conducted by Afifah et al.[24], and Asyari et al.[25] Although laryngeal erythema/hyperemia is relatively non-specific for the diagnosis of LPR, more than 50% of patients with LPR had erythema/ hyperemia.[30]

Based on the results of the characteristics of habits and dietary factors, the most common dietary habit found was spicy food, as many as 27 patients (79.41%) from both groups. Lechien et al.[16] in his literature review, had divided several categories of food and beverages based on the risk of reflux, namely: very mild reflux risk, mild reflux risk, moderate reflux risk, high reflux risk, and very high reflux risk. Spicy foods fell into the category of foods with a very high risk of reflux.

Proton pump inhibitors (PPI) are commonly used in the clinical empirical treatment of laryngopharyngeal reflux disease. However, the effectiveness of PPIs in laryngopharyngeal reflux therapy has long been debated. The efficacy and safety of PPIs in the treatment of patients with LPR is still controversial, and further research into the efficacy and safety of PPIs in the treatment of LPR is needed and necessary. One meta-analysis study reported that PPI therapy had no significant advantage in reducing LPR symptoms over placebo. Gatta et al.[26] concluded 4 randomized controlled trials in their meta-analysis study, that there was no difference between PPI and placebo therapy in reducing or improving LPR complaints.

Other studies had argued that acid reflux might not be the only mechanism in LPR. The study stated that suppression of acid reflux did not guarantee suppression of laryngeal symptoms.[16] Meanwhile, Cicala et al.[27] in his study on GERD patients found several factors that influence PPI resistance as therapy, including: dose, compliance, timing, reflux pattern, non-acid reflux, mixed reflux, esophageal hypersensitivity, decreased bioavailability, and increased PPI metabolism.

Research on the use of ginger as supplementation, or as the main therapy in LPR had never been done before, so the improvement of complaints and symptoms seen from RSI and RFS in the intervention group was thought to be caused by some of the ingredients possessed by ginger. It was known that the H+/K+ATPase (proton pump) enzyme located in the apical membrane of parietal cells is the enzyme responsible for gastric acid secretion. Ginger has phenolic content (cinnamic, syringic, p-cou- maric acids, gingerol, zingerone) which turns out to be effective in inhibiting H+, K+ -ATPase activity, growth of H. pylori. Meanwhile, the flavonoids contained in ginger can increase prostaglandins that function as protective factors of the stomach.[1]

Ginger has benefits in patients suffering from chronic inflammation, due to its anti-inflammatory and anti-oxidative properties. The anti-inflammatory effect of ginger is due to its inhibitory influence on COX-2, lipoxigenase. NF-κB and TNF-α activity leading to a decrease in inflammatory factors such as IL-1β, IL-6, and IL-2. Laboratory studies had also shown inhibition of serotonin receptors which was associated with decreased TNF-α, IL-1β, IL-6, IL-2 and prostaglandins.[11] The 6-shogaol and 6-gingerol content was shown to significantly inhibit TNF-α.[28]

Research on the effect of ginger supplementation (add on therapy) compared with lansoprazole in LPR patients had never been conducted. The use of red ginger powder capsule supplementation in LPR patients combined with lansoprazole as a definitive therapy is thought to have a synergistic role. Ginger, in addition to having proton pump inhibitory (PPI) effects, also has a role as an anti-inflammatory. Combination therapy with a synergistic approach is a necessary management for the treatment of complex diseases such as inflammatory diseases.[29]

The study conducted by Hussain et al.[19] who used a combination of PPIs and H2Ras, showed improvement in clinical LPR. In addition, because the etiology of LPR is not only acidic factors, it is also necessary to think about non-acidic therapy in LPR

patients. The combination of magaldrate and alginate at bedtime was beneficial in patients with non-acidic or mixed LPR.[30] Ginger not only has an effect as a proton pump inhibitor, but also has a role as an anti-inflammatory, improving gastric motility, and antimicrobial; so it is thought to have a synergistic effect on non-acidic LPR through these mechanisms, which PPIs do not have.

There were several limitations and constraints in this study, including: research subjects were limited to adults, empirically the results of this study did not apply specifically to children, education regarding lifestyle changes and diet, could not be measured for compliance. The research was non-blinded, and definitive diagnosis of LPR using pHmetry could not be made. Nevertheless, the conclusion would still be beneficial in general as a clinical consideration. Some of these limitations could be taken into consideration in future studies.

In conclusion, based on the results of the study, there was a significant difference in RSI and RFS before and after supplementation of red ginger powder capsules and lansoprazole in the intervention group, and significant difference of RSI and RFS between the intervention group and the control group. The use of red ginger powder capsule supplementation in RLF patients, combined with lansoprazole as a definitive therapy was considered to have a synergistic role. Ginger has not only an effect as a proton pump inhibitor, but also has a role as an anti-inflammatory, improving gastric motility, and antimicrobial, so it is thought to have a synergistic effect on non-acidic RLF through these mechanisms, which PPIs do not have. Combination therapy with a synergistic approach is a necessary management for the treatment of complex diseases such as inflammatory disease.

REFERENCE

1. Pairul, Piesta, Prima B, Susianti., Nasution, Syahrul H. Jahe (Zingiber officinale) Sebagai Anti Ulserogenik. Medula. 2017; 7(5):42–6.
2. Salim Z, Munadi E. Info Komoditi Tanaman Obat. Badan Pengkajian dan Pengembangan Perdagangan Kementerian Perdagangan Republik Indonesia. 2017. 1–10 p.
3. Bodagh, Nikkhah M, Maleki I, Hekmatdoost A. Ginger in gastrointestinal disorders: A systematic review of clinical trials. Food Sci Nutr. 2019; 7(1):96–108.
4. Wu, Keng L, Rayner, Christoper K, Chuah, Seng K, Changchien, Chi S, Lu, Sheng N, Chiu, Yi C, et al. Effects of ginger on gastric emptying and motility in healthy humans. Eur J Gastroenterol Hepatol. 2014; 20(5):436–9.
5. Anh NH, Kim SJ, Long NP, Min JE, Yoon YC, Lee EG, et al. Ginger on Human Health: A Comprehensive Controlled Trials. Nutrients. 2020; 12(1):1–28.
6. Najim AJAA. Potential health benefits and scientific review of ginger. J Pharmacogn Phyther. 2017; 9(7):111–6.
7. Pramana C, Muyassaroh M, Antono D. Pengaruh suplementasi zinc terhadap perbaikan klinis penderita laryngopharyngeal reflux disease. ORLI 2015; 44(2):131-6.
8. Liu D, Qian T, Sun S, Jiang JJ. Laryngopharyngeal reflux and inflammatory responses in mucosal barrier dysfunction of the upper aerodigestive tract. J Inflamm Res. 2020; 13:1291–304.
9. Walujo, Eko B, Rostiana O, Wijayahadi N, Elfahmi., Murti, Yosi B, Susilowidodo, Raphael A, et al. Jahe (Zingiber officinale Roscoe). Jakarta: Badan Pengawas Obat dan Makanan; 2016. 1–95 p.
10. Mbaveng, A T, Kuete V. Zingiber officinale. In: Victor K, editor. Medicinal Spices and Vegetables from Africa. 1st ed. Cameroon: Elsevier Inc.; 2017. p. 627–39.
11. Naheed A, Hajar T. Ginger and its Effects on Inflammatory Diseases. Adv Food Technol Nutr Sci. 2015;1(4):97–101.
12. Lee JS, Jung AR, Park JM, Park MJ, Lee YC, Eun YG. Comparison of characteristics according to reflux type in patients with laryngopharyngeal reflux. Clin Exp

Otorhinolaryngol. 2018; 11(2):141–5.

13. Lechien JR, Bobin F, Muls V, Thill MP, Horoi M, Ostermann K, et al. Validity and reliability of the reflux symptom score. Laryngoscope. 2020; 130(3):E98–107.
14. Junaid M, Qadeer Ahmed S, Kazi M, Khan HU, Sohail Halim M. Laryngopharyngeal Reflux Disease: Outcome of Patients After Treatment in Otolaryngology Clinics. Cureus. 2020; 12(12):1–9.
15. Supu RD, Diantini A, Levita J. Red Ginger (Zingiber officinale var. rubrum): It's Chemical Constituents, Pharmacological Activities and Safety. Fitofarmaka J Ilm Farm. 2018; 8(1):25–31.
16. Lechien JR, Saussez S, Muls V, Barillari MR, Chiesa-Estomba CM, Hans S, et al. Laryngopharyngeal Reflux: A State-of-the-Art Algorithm Management for Primary Care Physicians. J Clin Med. 2020; 9(11):1–18.
17. Kang A, Khokale R, Awolumate OJ, Fayyaz H, Cancarevic I. Is Estrogen a Curse or a Blessing in Disguise? Role of Estrogen in Gastroesophageal Reflux Disease. Cureus. 2020; 12(10).
18. Febriyanti R. Korelasi Antara Reflux Symptom Index (RSI) dan Reflux Finding Score (RFS) Pada Penderita Dengan Gejala Refluks Laringofaring di Poliklinik THT-KL RSUP H. Adam Malik Medan. Universitas Sumatera Utara; 2014.
19. Hussain RT, Makhdoomi O, Showkat SA. Combination drug therapy for laryngopharyngeal reflex. Int J Otorhinolaryngol Head Neck Surg. 2020; 6(5):948–54.
20. Sa'an N, Asyari A, Fitri F. Gambaran Pasien Laryngopharyngeal Reflux di Bagian Poliklinik THT-KL. J Ilmu Kesehat Indones. 2020; 1(2):43–9.
21. Massawe WA, Nkya A, Abraham ZS, Babu KM, Moshi N, Kahinga AA, et al. Laryngopharyngeal reflux disease, prevalence and clinical characteristics in ENT department of a tertiary hospital Tanzania. World J Otorhinolaryngol - Head Neck Surg [Internet]. 2021;7(1):28–33. Available from: https://doi.org/10.1016/j.wjorl.2020.04.009
22. Osman HA, Elrhman NHA, Shafy MA. The Efficacy of PPI in the Treatment of Laryngopharyngeal. Gastroenterol Hepatol Res. 2019; 8(1):2800–6.
23. Kurniawati T, Madiadipoera T, Sarbini TB, Saifuddin OM. Perbandingan Efektivitas antara Omeprazol dan Lansoprazol terhadap Perbaikan Kualitas Hidup Penderita Rinosinusitis Kronik Akibat Refluks Laringofaring. Maj Kedokt Bandung. 2012; 44(3):138–46.
24. Afifah F, Fitri F, Amir A. Karakteristik Penderita Laryngopharyngeal Reflux di Bagian THT-KL RSUP Dr. M. Djamil, Padang. Tahun 2019. J Ilmu Kesehat Indones. 2021; 2(1):98–106.
25. Asyari A, Amri D, Novialdi N, Fitri F, Yerizal E, Bachtiar H, et al. Deteksi pepsin pada saliva pasien refluks laringofaring. ORLI. 2018; 48(1):65–73.
26. Gatta L, Vaira D, Sorrenti G, Zucchini S, Sama C, Vakil N. Meta-analysis: The efficacy of proton pump inhibitors for laryngeal symptoms attributed to gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2007; 25(4):385–92.
27. Cicala M, Emerenziani S, Guarino MPL, Ribolsi M. Proton pump inhibitor resistance, the real challenge in gastro-esophageal reflux disease. World J Gastroenterol. 2013; 19(39):6529–35.
28. Morvaridzadeh M, Fazelian S, Agah S, Khazdouz M, Rahimlou M, Agh F, et al. Effect of ginger (Zingiber officinale) on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. Cytokine. 2020; 135(April):1–10.
29. Zhou X, Afzal S, Wohlmuth H, Münch G, Leach D, Low M, et al. Synergistic Anti-Inflammatory Activity of Ginger and Turmeric Extracts in Inhibiting Lipopolysaccharide and Interferon-γ-Induced Proinflammatory Mediators. Molecules. 2022; 27(12):1–17.
30. Lechien JR, Akst LM, Hamdan AL, Schindler A, Karkos PD, Barillari MR, et al. Evaluation and Management of Laryngopharyngeal Reflux Disease: State of the Art Review. Am Acad Otolaryngol Head Neck Surg. 2019; 4(5):1–21.