

Reduction of salivary tumor necrosis factor alpha levels in response to magic mouthwash with *Curcuma xanthorrhiza* in cancer patients undergoing chemotherapy

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ABSTRACT: Tumor necrosis factor-alpha (TNF- α) is pro-inflammatory cytokine that play a key role in initiating and accelerating the development of oral mucositis in cancer patients undergoing chemotherapy. Mixed medication mouthwash called magic mouthwash has been widely used to prevent and treat oral mucositis. Curcuma xanthorrhiza is a traditional herbal medicine, which has shown anti-inflammatory, antibacterial, and antifungal effects. The aim of this study was to evaluate the effect of magic mouthwash with Curcuma xanthorrhiza on salivary TNF- α levels in cancer patients undergoing chemotherapy. The magic mouthwash formulation used in this study contains diphenhydramine, hydrocortisone, nystatin and dry curcuma extract. This study involved 60 cancer patients undergoing 5-Fluorouracil (5-FU)-based chemotherapy who were assigned into two groups, each group consisted of 30 patients. Group 1 instructed for rinsing with magic mouthwash with Curcuma xanthorrhiza and group 2 rinsed with NaCl 0.9% as control group. Unstimulated whole saliva was collected before and after oral rinsing with mouthwashes. Salivary TNF- α levels were measured with enzyme linked immunosorbent assay (ELISA). Data were analyzed statistically with Wilcoxon and Chi square test. The result of this study showed a significant decrease in salivary TNF- α levels on both groups ($p<0.05$). In the study group, more patients were found with salivary TNF- α levels decreased (74.2%) compared to control group (53.5%) and showed significant difference statistically ($p<0.05$). The study concludes that magic mouthwash with Curcuma xanthorrhiza can reduce Salivary TNF- α levels and can be used as an alternative therapy for oral mucositis-induced chemotherapy.

KEYWORDS: Chemotherapy; *Curcuma xanthorrhiza*; magic mouthwash; salivary TNF- α .

1. INTRODUCTION

Oral mucositis is an inflammatory condition of the oral and oropharyngeal mucosa induced by cytotoxic chemotherapy and/or radiotherapy that represent a major clinical problem in oncology. The prevalence of mucositis in patients undergoing standard-dose chemotherapy is approximately 40%, and this ratio exceeds 50% in high-dose chemotherapy protocols [1]. Oral mucositis presents as confluent and deep ulcerations in its severest form. Pain associated with mucositis often impairs a patient's functional status and quality of life. In patients treated with chemotherapy alone or combined chemo-radiation regimens, the whole gastrointestinal tract may be affected. Weight loss is common, and patients may require gastrostomy or parenteral feeding. Severe oral mucositis may lead to dose reductions and unplanned interruptions of cancer therapies [2,3].

Chemotherapy and radiation therapy activate the transcription factor nuclear factor- κ B (NF- κ B) in epithelial, endothelial and mesenchymal cells and macrophages, leading to the upregulation of genes and the production of pro-inflammatory cytokines, such as tumour-necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β). These cytokines amplify the primary signal or may activate NF- κ B in other cells, which results in the transcription of genes encoding mitogen-activated protein kinase (MAPK), cyclooxygenase 2 (COX2) and tyrosine-kinase signalling molecules. TNF- α also activates sphingomyelinase. So, its increased level in the tissue amplifies pro-apoptotic signals that are mediated by the ceramide pathway. In addition, both TNF- α

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and IL-1 β induce matrix metalloproteinase (MMP-1 and MMP-3) activation in cells of the epithelium and lamina propria, which ultimately results in tissue injury [4-6].

Magic mouthwash is commonly prescribed for conditions such as chemotherapy/radiation-induced mucositis, cancer sores, mouth pain, etc. The logic behind magic mouthwash is to combine ingredients with different potential mechanisms of action to treat a variety of oral conditions. The current guidelines for the treatment of oral mucositis suggest that compounded magic mouthwashes (with various combinations of viscous lidocaine, benzocaine, milk of magnesia, kaolin-pectin, chlorhexidine, or diphenhydramine) are not better than NaCl 0.9% solution in pain relief [7,8]. *Curcuma xanthorrhiza* is also known as Javanese Turmeric or Temu Lawak. *C. xanthorrhiza* belongs to the family Zingiberaceae. The root contains two classes of characteristic constituents curcuminoids (1-2%) and volatile oil (3-12%). Curcuma (Zingiberaceae) is a large genus of rhizomatous herbs distributed in tropical and subtropical regions especially in India, Thailand, the Malay Archipelago, Indochina, and Northern Australia. Many species have been cultivated, and their powdered rhizomes have been widely used to add flavors in native dishes and as ingredients in many traditional medicines to treat various ailments. The more popular and economically more important species, *C. Domestica* L. and *C. xanthorrhiza* Roxb., are more widely used as condiments than for their medicinal purposes. *Curcuma xanthorrhiza* has anti-inflammation, antimicroba, antifungal effects. Curcuma xanthorrhiza extract is used as natural sanitizer agent for antimicrobial activity against potential pathogenic bacteria [9-12]. In this present study, we investigated the effect of magic mouthwash with *Curcuma xanthorrhiza* on salivary TNF- α levels in cancer patients undergoing chemotherapy in comparison sodium chloride 0.9% solution (NaCl 0.9%).

2. RESULTS

This study enrolled 61 patients under 5-Fluorouracil (5-FU)-based chemotherapy who were divided into magic mouthwash group of 31 patients and control group of 30 patients. Patients characteristic are shown on Table 1. Plot diagram for salivary TNF- α levels before and after rinsing with magic mouthwash and NaCl 0.9% is presented in Figure 1. The result analysis on Table 2 shows that significant differences statistically ($p < 0.05$) on TNF- α salivary level median before rinsing with magic mouthwash (4.761 pg/ml) and after rinsing with magic mouthwash (4.392 pg/ml) and also on TNF- α salivary level median before rinsing with NaCl 0.9% (5.843 pg/ml) and after rinsing with NaCl 0.9% (5.048 pg/ml). The result analysis in Table 3 shows statistically significant differences ($p < 0.05$) on decreased TNF- α salivary level percentage after rinsing with magic mouthwash (74.2%) higher than after rinsing with NaCl 0.9% (53.3%).

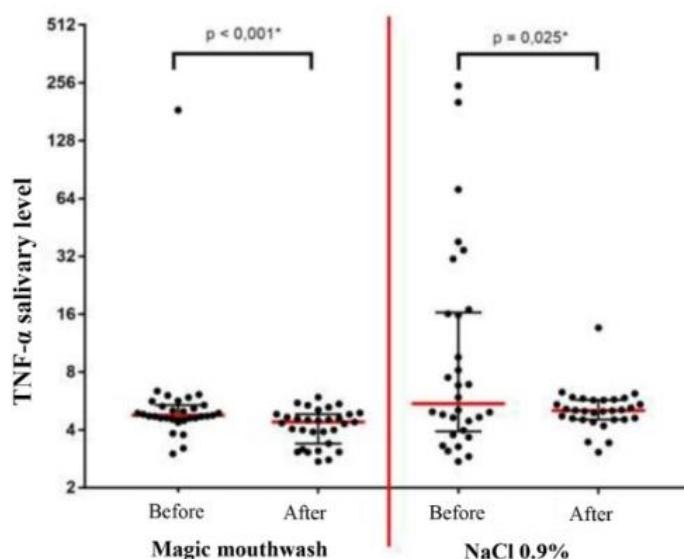


Figure 1. Plot diagram of salivary TNF- α levels before and after rinsing with magic mouthwash and NaCl 0.9%

Table 1. Patient characteristics

Characteristics	MWW group n=30	Normal saline group n=30
Sex, n (%)		
Male	8 (25.8)	2 (6.7)
Female	22 (74.1)	28 (93.3)
Age (year)		
Range 21-71		
Mean \pm SD	48 \pm 11	47 \pm 12
Cancer type, n (%)		
Ca. Mammaria	25 (83.9)	25 (83.3)
Ca. Nasopharynx	3 (9.7)	2 (6.7)
Ca. Cervix st. I	0 (0.0)	2 (6.7)
Ca. Colon	1 (3.2)	1 (3.3)
Ca. Anus	1 (3.2)	0 (0.0)

Table 2. Salivary TNF- α levels before and after rinsing with magic mouthwash compared to NaCl 0.9%

		Before rinsing Median	After rinsing Median	Median differences (95% CI)	p value
Salivary TNF-α level (pg/ml)	MMW	4,761 (3,005 – 184,700)	4,392 (2,738 – 5,911)	0,715 (0,230 – 1,392)	0,001*
	NaCL 0,9%	5,483 (2,742 – 247,100)	5,048 (3,060 – 13,580)	0,402 (-0,358 – 4,836)	0,025*

Note : wilcoxon test, *p<0,05

Table 3. Differences in salivary TNF- α levels before and after rinsing with magic mouthwash compared to NaCl 0.9%

The changes in salivary TNF- α level	n	MMW n=30	NaCl 0,9% n=30	p value
Decreased salivary TNF- α level	38	23 (74,2)	16 (53,3)	0,045*
Increase salivary TNF- α level	22	7 (25,8)	14 (46,7)	

Note : Chi square test, *p<0,05

3. DISCUSSION

The chemotherapy drugs induce the death of the basal epithelial cells, which may occur by the generation of free radicals. These free radicals activate second messengers that transmit signals from receptors on the cellular surface to the inner cell environment, leading to up-regulation of pro-inflammatory cytokines, tissue injury, and cell death. The pro-inflammatory cytokines produced by macrophages, such as TNF- α , amplify the mucosal injury; the production of these pro-inflammatory cytokines can also be stimulated by a superimposed infection of the ulcerated areas of the mucosa [13-15]. TNF- α is not usually detectable in healthy individuals, but elevated serum and tissue levels are found in inflammatory and infectious conditions and serum levels correlate with the severity of infections. Although the cells of the monocyte/macrophage lineage are the main source of TNF- α in inflammatory disease, a wide range of cells can produce TNF- α , including mast cells, T and B lymphocytes, natural killer (NK) cells, neutrophils, endothelial cells, smooth and cardiac muscle cells, fibroblasts and osteoclasts [16,17].

TNF- α is a key pro-inflammatory cytokine that causes tissue damage, and the release of TNF- α may initiate and accelerate the development of oral mucositis (OM). It has been reported in several human studies that the levels of pro-inflammatory cytokines are increased in the blood and saliva of patients during cancer treatment. Other studies using animal models have shown evidence of changes in the serum level and tissue expression of nuclear factor κ -B and the pro-inflammatory cytokines (TNF- α , interleukin (IL)-1 β and IL-6) following administration of chemotherapeutic drugs [18,19].

This study shows that salivary TNF- α level median before and after rinsing with magic mouthwash with *Curcuma xanthorrhiza* were significantly lower compared to before and after rinsing with NaCl 0.9% ($p<0.05$). The magic mouthwash used in this study contains diphenhydramine as a topical analgesic, hydrocortisone as an anti-inflammation, nystatin as an anti-fungal and dry curcuma extract as a preservative agent. Corticosteroids have an anti-inflammatory effect, which is mainly related to the inhibition of transcription of several pro-inflammatory cytokines/mediators. Other factors contributing to their anti-inflammatory and immunosuppressant properties include the apoptosis of basophils and the inhibition of adhesion molecule expression on the surface of endothelial cells [20].

The naturally occurring and synthetic corticosteroids act by entering the cell by diffusion across the plasma membrane and binds reversibly to glucocorticoid receptors (GR) that is thought to be available in most, if not all, nucleated cells. GR is expressed in almost all tissues although tissue and cell cycle-specific regulation of GR levels have been reported. The expression pattern of GR shows that the receptor is distributed ubiquitously, but is more prevalent in hepatic, nervous system, and muscular tissues. Even though GR is widely distributed, cellular sensitivity to glucocorticoids is complex and dependent on many factors. Consequent to this interaction, the steroid-ligand complex alters its conformation, exposing a DNA-binding domain, and then migrates to the nucleus where it binds to a site on the chromatin. The complex regulates transcription of specific gene sequences into mRNA. This leaves the nucleus to bind to ribosomes where their nucleotide sequences are translated into corresponding amino-acid sequences of proteins and specific enzymes [21-23].

Topical application of steroids reduces the effect of chemo-attractants on polymorphonuclear neutrophils (PMN) and monocyte aggregation, reduces migration and phagocytosis of PMN, and reverses the dilatation and increased permeability of the small vessels at the site of application. This last property is the basis of the vasoconstriction assay for assessing corticosteroid potency. In addition, corticosteroids have an antimitotic effect on several cell types that could be the basis for at least some of their activity against lichen planus. This activity seems to be non-cell specific; a reduction in RNA synthesis has been demonstrated in both normal and psoriatic skin following exposure to corticosteroids [21]. Aggarwal et al., reported that curcumin has the potential to inhibit NF- κ B. The expression of several genes that are regulated by NF- κ B has also shown to be suppressed by curcumin [24]. These include cell surface adhesion molecules, chemokines, TNF, MMP-9, COX2, and nitric oxide synthase (NOS). Since these genes are critical regulators of inflammation, the suppression of expression of these genes explains the anti-inflammatory effects of curcumin [25,26].

NaCl 0.9% (sodium chloride 0.9% solution) is a harmless bland isotonic oral rinse which has been shown to be beneficial in maintaining appropriate oral hygiene due to its safety, lowest toxicity and physiologic properties [27]. There were several studies on the preventive effect of NaCl 0.9% on oral mucositis in chemotherapy, radiotherapy and/or hematopoietic stem cell transplantation (HSCT) patients [28], however few studies have assessed its effect on prevention of mucositis resulting from chemotherapy [28,29]. NaCl 0.9% showed inferior effect on preventing chemotherapy induced mucositis compared to chlorhexidine and cryotherapy [28]. Another study showed that NaCl 0.9% was less effective in preventing chemotherapy-induced mucositis in comparison to honey plus NaCl 0.9% and placebo groups [29]. The Results and Discussion sections may be combined. The purpose of the discussion is to interpret significance of the results and to relate them to existing knowledge in the field in as clear and brief a fashion as possible. Information given elsewhere in the manuscript should not be repeated in the discussion. Extensive reviews of the literature should be avoided.

4. CONCLUSION

Salivary TNF- α levels were significantly more decreased in cancer patients undergoing chemotherapy after rinsing with magic mouthwash with *Curcuma xanthorrhiza* compared to NaCl 0.9% suggesting that it has the potential as an alternative treatment for chemotherapy-induced oral mucositis.

5. MATERIALS AND METHODS

This research was conducted at Hematology-Oncology Division, Internal Medicine Department, Dr. Hasan Sadikin Hospital Bandung, Indonesia, and the study was approved by The Health Research Ethics Committee, Faculty of Medicine, Padjadjaran University (the number/ID of the approval 366/UN6.C10/PN/2017). Selected sixty participants of the study subjects all received 5-FU based chemotherapy at doses of 600 mg/m² based on patients' body surface area (BSA), once in an interval 21 days, 6 times. They were divided into 2 groups, study and control groups. The study group was given magic mouthwash and the control group was given NaCl 0.9%. Unstimulated whole saliva samples were collected from those patients. These mouthwashes were given after the first collection of saliva samples. Unstimulated whole saliva samples were collected again three weeks (21 days) after the first saliva samples have been collected. salivary TNF- α levels were measured with enzyme linked immunosorbent assay (ELISA). TNF- α ELISA kit were purchased from Elabscience® ELISA Kit. The instruments used for ELISA are a microplate reader (RT-6500; Rayto Life and Analytical Sciences Co., Ltd, Shenzhen, China), and PW-40 microplate washer (Bio-Rad Laboratories, Inc. France).

The magic mouthwash formulation used in this study contains 600 mg Diphenhydramine, 60 mg Hydrocortisone, 1g Nystatin and 16 mg dry curcuma extract, 480 mg Na - CMC (Sodium Carboxymethylcellulose) as suspending agent and 240 ml distilled water given 10 ml swish and spit twice a day.

The dry curcuma extract used in this study were purchased from PT. Konimex Pharmaceutical Laboratories, Jakarta, Indonesia. Hydrocortisone powder were purchased from Sigma-aldrich catalogue number PHR1014. Diphenhydramine powder were purchased from Acros organics catalogue number AC350850000, AC350850250, AC350851000. Nystatin powder were purch from Xabcbiotech. Result data were analyzed statistically with Wilcoxon and Mann-Whitney test ($p < 0.05$).

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