Expression of COX-2 on Oral Ulcer Healing with Mangosteen Rind Paste

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Abstract

Patients who visited dental clinic with complaints of oral mucosa injury due to trauma, chemical or infection were around 27%. In the market, topical drug preparation is relatively expensive. It has side effect for hypersensitive patient. Alternative herbal medicine safe, effective and affordable is needed. Some research showed mangosteen rind (MGS) as an anti inflammatory, anti oxidant and anti bacterial. This study aims to determine role of MGS paste on COX (Cyclooxygenase)-2 expression in oral ulcer healing. Type of experimental research, randomly obtained 36 Male Wistar rats divided into 6 groups in which 3 treatment groups (trauma, chemical and infection) and 3 control groups. Treatment groups were smeared with MGS paste while control groups were untreated. Then each group was decapitated on the 3rd, 7th and 10th day. Observations were made macroscopically and microscopically by histopathological examination then the data obtained were carried out by Non-parametric Test. On the 10th day there were significantly different amounts of COX-2 on oral ulcer healing between treatment and control group ($p < 0.010$), except for Infectious Ulcer. The role of MGS paste proved significantly in reducing COX-2 on oral ulcer healing because of trauma and chemical. Usage of MGS paste topically could accelerate and prevent excessive inflammation on oral ulcer healing.

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Introduction

Oral ulcer complained by patients with various causative factors, that was a sign of oral disease involving many causes. Patients who visited the dental clinic with complaints of injury to oral ulcer due to trauma, chemical or infection were 27%.[1] In wound healing process, COX-2 was an enzyme whose existence influenced by stimulation of the tissue, such as cytokine, bacterial lipopolysaccharides, inflammation or other pathological conditions. It was responsible for production of prostaglandin during inflammation.[2]

Now topically medicine preparation used for oral ulcer, was relatively expensive. Sometimes it had side effects for hypersensitive patient, there was needed alternative preparation of herbal medicine that was effective and safe with affordable price. Several studies on mangosteen rind showed therapeutic effects as an anti-inflammatory.[3-4]

Based on research[5] MGS was safe to use. Application of MGS paste reduced number of Polymorphonuclear (PMN) cells in inflammatory phase. Preliminary studies had been carried out by researcher[6] by using MGS paste as a medicine for oral ulcer due to trauma. Researcher had also tried applying mangosteen rind into socket after tooth extraction in male Wistar rats, then monitoring by looking at wound closure and by counting number of PMN cells on the 3rd and 7th day.

Results showed that MGS accelerated wound healing process. However, role of COX-2 in the wound healing process was not known precisely and accurately, so it is necessary to have a supporting examination with histopathological examination.

This study aims to determine role of MGS paste on COX-2 expression in oral ulcer healing.

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Materials and methods

The research was approved by the Health Research Ethics Committee. Sample was 36 Male Wistar rats with weight 250-300 grams and 2-3 months, divided into 6 groups (3 treatment and 3 control groups). Oral Ulcer was made in labial mucosa by scratching using a cutter (Trauma), by exposing H_2O_2 3% for 90 seconds (Chemical) and by injuring with Aggregatibacter actinomycetemcomitans (Aa) bacteria (Infection). The treatment groups were smeared with MGS paste 1x/day for 10 days while the control groups were untreated. MGS paste preparation was a mixture of various size and volume of MGS extract mixed with other ingredients.[7] Each group was decapitated on the 3rd, 7th and 10th day. Examination was carried out macro and microscopically, expression of COX-2 could be seen using immunohistochemical staining and COX-2 marker with an Opticlab microscope. Each preparation was observed in 5 fields of view and recorded quantitatively (Figure 1). Data obtained were analyzed by Non-parametric Test.

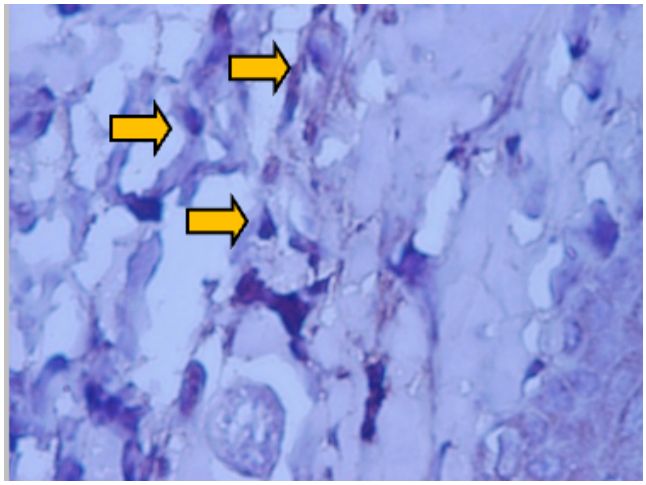

Figure 1. Expression of COX-2.

Results

Based on clinical observation on the 3rd, 7th until 10th day, there was a reduction of wound diameter on ulcer both untreated and treated by MGS, however treatment with MGS paste accelerated ulcer healing process where on the 9th day almost diameter on ulcer < 1 mm even infectious ulcer was healed and faster than untreated infectious ulcer (Table 1). This results were following the expression of COX-2 in Table 2. This table showed that expression of COX-2 gradually decreased in all group on the 3rd, 7th and 10th day. On the 10th day, the most expression of COX-2 on untreated Traumatic Ulcer =6 and the least expression of COX-2 on Infectious Ulcer treated by MGS=1. Based on Kruskal Wallis Test, on the 10th day there was significantly difference expression of COX-2 among group with $p < 0.001$.

Ulcer	Treatment	Rate (mm) Day -					
		0	3	7	8	9	10
Traumatic Ulcer	Untreated	7.80	5.84	3.40	2.23	1.53	0
	Treated by MGS	7.86	5.46	3.32	1.12	0.72	0
Chemical Ulcer	Untreated	7.56	5.38	3.36	2.20	1.20	0
	Treated by MGS	7.60	5.37	3.30	1.10	0.70	0
Infectious Ulcer	Untreated	7.60	5.43	3.49	0.75	0.50	0
	Treated by MGS	7.70	5.40	3.37	0.72	0	0

Table 1. Rate of Diameter Ulcer Healing until the 10th Day. *MGS=Mangosteen Rind

Group	Day-3	Day-7	Day-10
Traumatic Ulcer (Untreated)	14	9	6
Traumatic Ulcer (Treated by MGS)	12	9	3
Chemical Ulcer (Untreated)	11	9	5
Chemical Ulcer (Treated by MGS)	11	9	3
Infectious Ulcer (Untreated)	12	10	2
Infectious Ulcer (Treated by MGS)	11	9	1

Table 2. Expression of COX-2 on Ulcer Healing.

The expression of COX-2 in each group was shown in Figure 2 (Trauma), Figure 3 (Chemical) and Figure 4 (Infection). Figure 2, 3, and 4 showed that expression of COX-2 in Ulcer decreased gradually on the 3rd, 7th and 10thday, based on Mann Whitney test, there was significantly difference expression of COX-2 between groups, for Traumatic Ulcer ($p= 0.008$) and Chemical Ulcer ($p = 0.009$) but there was no difference expression of COX-2 between Infectious Ulcer groups ($p > 0.05$).

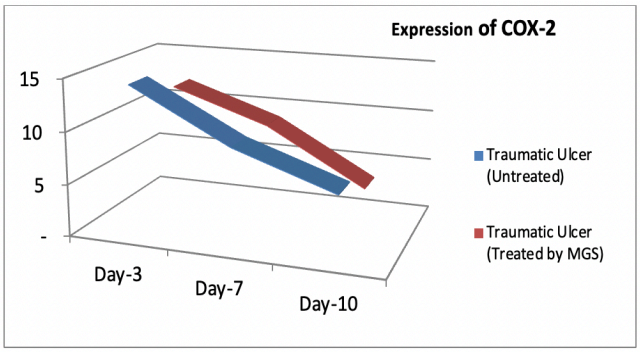

Figure 2. Expression of COX-2 in Traumatic Ulcer on the 3rd, 7th and 10th Day.

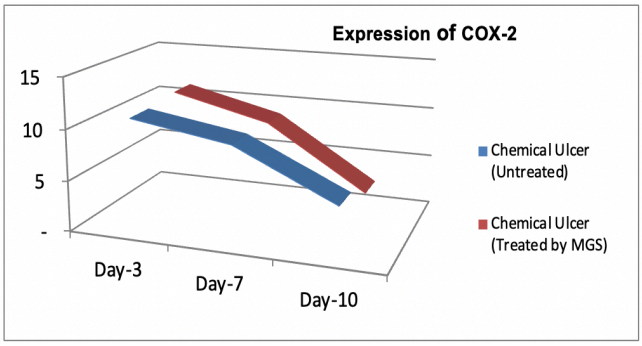

Figure 3. Expression of COX-2 in Chemical Ulcer on the 3rd, 7th and 10th Day.

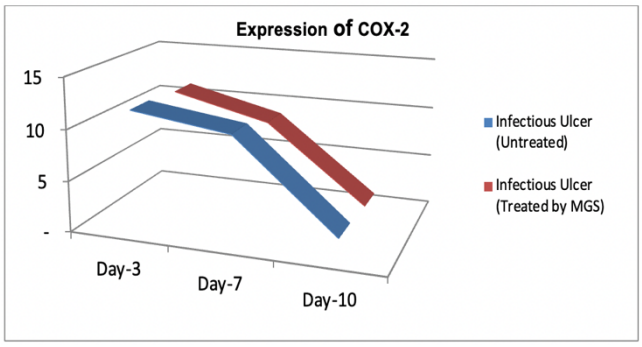

Figure 4. Expression of COX-2 in Infectious Ulcer on the 3rd, 7th and 10th Day.

Discussion

Cyclooxygenase-2 (COX-2) is an enzyme induced and rapidly regulated in response to injury, resulting in the production of prostaglandin E2 (PGE2), a major mediator of inflammation in epithelial tissue.[8] In this study, clinical observation showed that ulcer healing was almost completely healed on the 9 th day of MGS group, this ulcer healing process would be faster in tissues with fewer expression of COX-2. Extract of MGS [3-4] as an antioxidan, anti inflammatory and anti bacterial could inhibit activity of COX-2. Xanthone, the main compound found in MGS, consisted of α-mangostin and ∂-mangostin.[9]. A study [10] found ∂-mangostin potentially inhibited COX-2 activities. The COX-2 and PGE2 played a role in inflammatory response regarded in chronic lessions through iNOS/NO production.

The results showed long-term exposure to ∂-mangostin significantly inhibited the spontaneous release of PGE2 and LPS (Lipopolysaccharide) induced COX-2 protein expression, this role was associated with suppression of NF-kß cells. When ∂-mangostin inhibited NF-kß activity resulting in disrupted synthesis of IL-1 and TNF-α. Inhibition of the synthesis of IL-1 and TNF-α caused no vasodilation of blood vessels, increased capillary permeability so that complement factor C5a was not activated, and inhibited neutrophil adhesion to blood vessel walls. Inhibition of adhesion of neutrophils to blood vessel walls caused neutrophil infiltration into the tissue to decrease so that inflammation would be reduced.[11]. The end result of an excessive inflammatory response could cause local tissue damage, hypoxia and delay wound healing.[12] In this study, mangosteen peel paste was able to reduce the amount of COX-2 to minimize excessive inflammatory response.

Conclusions

Mangosteen Rind paste could inhibit COX-2 expression on oral ulcer healing. The role of mangosteen rind was proved significantly in reducing COX-2 on oral ulcer healing because of trauma and chemical. Usage of mangosteen rind paste topically could accelerate and prevent excessive inflammation on oral ulcer healing.

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Declaration of Interest

No competing interests between authors

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