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Formulation and evaluation of pulp devitalization paste combination of *Jatropha curcas* L. and *Piper crocatum* Leaves extract

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ABSTRACT

Dental caries requires operative techniques such as pulp devitalization, but pulp devitalization materials that are often used by dentists have serious adverse effects that need to be considered, such as gingival injury and alveolar bone necrosis. Hence, the aim of the present study was to evaluate and formulation of herbal alternatives to pulp devitalization from a combination of Jatropha curcas (*Jatropha curcas* L.) and red betel leaf extract (*Piper crocatum*) in the form of a paste and then conducting physical evaluation tests, Cyclooxygenase-2 (COX-2) tests, and also histopathological picture tests to the sample. The formulation of the pasta sample was carried out by the trituration method. Formulation I (FI) contained 25% of Jatropha resin, 0.25% red betel leaf extract, and 25% Jatropha resin, 0.5% red betel leaf extract for Formulation II (FII). The paste produced was then evaluated for physical properties which consisted of organoleptic, homogeneity, pH, spreadability, adhesion, and in vivo anti-inflammatory effect (animal models). In the COX-2 expression test, FI has a COX-2 expression percentage value of 0.38% and a COX-2 suppression percentage value of 0.62%, while FII has a COX-2 expression percentage value of 0.59% and suppression of COX-2 of 0.41%. The optimal concentration of the paste formulation is the paste with a combination of 25% jatropha latex and 0.25% red betel leaf extract had been shown to have potential as an alternative to pulp devitalization.

1. Introduction

Dental caries is one of the most common chronic diseases in the world (Bansal & Mahajan, 2019). Dental caries causes the pulp chamber to open which will cause pain to inflammation (pulpitis). Treatment for pulpitis teeth can be done with operative techniques such as pulp devitalization, in addition to being able to numb the nerves, the pain that arises can be permanently eliminated through the devitalization material (Tanumihadja et al., 2019).

Pulp devitalization materials that are often used by dentists are paraformaldehyde, cresol, or arsenic trioxide (Chen & Sung, 2014). However, several serious adverse effects have been reported with regard to pulp devitalizing materials. Osteonecrosis can occur due to accidental contact of paraformaldehyde with the surrounding gingiva (Srivastava et al., 2011). Necrosis of the alveolar bone and soft tissue also occurs with the careless use of arsenic trioxide and formaldehyde (Tanumihadja et al., 2019).

The common ingredients for pulp devitalization have numerous serious adverse effects that need to be considered, so there is a need for a safer alternative, especially from natural ingredients. Natural ingredients are currently widely used as treatment, especially in oral problems (Anggraeni et al., 2022) (Wahid & Damarwati, 2021) (Lestari et al., 2021), such as combination of jatropha curcas *(Jatropha curcas L.)* and red betel leaf extract *(Piper crocatum).* Ethnopharmacologically, jatropha latex has benefits as a nerve-killing agent in teeth (Tanumihadja et al., 2019). Phytochemical screening showed that *Jatropha curcas* latex contains tannins and saponins that play a role in numbing the nerves of the teeth. Tannins can cause protein precipitation, while saponins can cause hemolysis in cells (Tanumihadja et al., 2019). Atikaningrum et al. (2013) reported that the flavonoid compounds from red betel leaf extract had an analgesic effect when it was given orally in mice. Flavonoids work by inhibiting the cyclooxygenase enzyme (Atikaningrum et al., 2013).

According to Ribeiro et al. (2015), that flavonoids for the modulation of the inflammatory process, namely the ones presenting a catechol group in B ring, as some flavonoids were able to simultaneously inhibit the production of inflammatory prostaglandin E2 and pro-inflammatory cytokines.

Based on the fourth edition of the Indonesian Pharmacopoeia, a paste is a semi-solid formula containing one or more medicinal ingredients that is intended for topical use. The advantages of paste compared to other topical formulations are that the paste binds to liquid secretions, therefore, paste is better than ointment for acute wounds. The medicinal ingredients in the paste formula are more attached to the skin so that it increases local action. Moreover, the paste does not give a greasy feeling compared to the ointment, the concentration of the paste is thicker than the ointment, the absorption power of paste is greater than ointments, creams, and gels. Besides that, the paste does not melt at body temperature, so it can be used as a covering or protective ointment (Ningsih et al., 2015).

Based on this background, research on alternative pulp devitalization materials from a paste formulation with a combination of jatropha latex *(Jatropha curcas L.)* and red betel leaf extract *(Piper crocatum)* could be conducted. The purpose of this study was to determine the optimal concentration of the paste formulation, to know the physical evaluation test of the paste preparation, and to determine the anti-inflammatory activity of the paste preparation on the dental pulp of rats induced by dental caries in vivo by looking at the expression of COX-2 protein.

2. Materials and Methods

2.1. Instruments

Knife, brown glass bottle, analytical balance (Sartorius®), electric stove (Maspion®, Indonesia), fan, pan, stirrer, filter paper, mortar, stamper, glassware (Pyrex®), porcelain cup, dropper, mica spoon, sample pot, slide (Sail Brand®), microscope (Olympus®), pH meter (Toledo®), adhesive test equipment, weights, glass plate, millimeter block paper, mouse cage, gloves (Sensi®), syringe, micromotor (Strong®), handpiece (NSK®), sonde, tweezers, cotton buds, microtome (Yamato RV-240®), IHK slide glass, label sticker, oven (Memmert®), water bath, and cover glass.

2.2. Materials

Red betel leaf powder, 70% ethanol, jatropha latex, zinc oxide, propylene glycol, methyl paraben, BHT, distilled water, female Wistar rats, AD2 feed, RO drink, ketamine, xylazine, temporary filling (Cevitron®), formaldehyde (DEVIT-S®), sodium chloride 0.9%, 10% neutral buffered formalin,

decalcifier, test animal tissue glass, COX-2 antibody, xylol, absolute alcohol, 96% alcohol, running water, tris EDTA pH 9.0, PBS pH 7.4, peroxidase block, super block, primary antibody, UltraTek Anti-Polyvalent, UltraTek HRP, DAB solution, hematoxylin, and blue reagent.

2.3. Sample processing

Jatropha latex in this study was fresh latex that was obtained from the yard of the house, Bantul, Yogyakarta, Indonesia. Jatropha plants in this study had been determined by Faculty of Science Universitas Ahmad Dahlan Yogyakarta (No 199/Lab.Bio/B/VII/2020) and had stated the authenticity of the Jatropha *(Jatropha curcas L.).* Meanwhile, red betel leaf extract was taken by the maceration extracting method using 70% ethanol solvent. The solution was then concentrated by CV. Herbal Anugrah Alam, Bantul, Yogyakarta, Indonesia using a rotary evaporator method. The red betel plant in this study has a letter of authenticity on the CV. Herbal Anugrah Alam, namely red betel *(Piper crocatum).*

2.4. Formulating paste

The paste preparation was made by trituration method with the following formulation (Table 1).

Table 1. Formulation of pulp devitalization paste

Ingredients	Formulation (F)	
	FI	FII
Jatropha latex	25 %	25 %
Red betel leaf extract	0.25 %	0.5 %
zinc oxide	20 %	20 %
Propylene glycol	10 %	10 %
Methylparaben	0.18 %	0.18 %
BHT	0.1 %	0.1 %
add Aquades	100 %	100 %

Formulation I (FI) contained 25% of Jatropha resin, 0.25% red betel leaf extract, and 25% Jatropha resin, 0.5% red betel leaf extract for Formulation II (FII)

2.5. Paste physical evaluation test

Physical evaluation tests were carried out on both paste formulations, which included organoleptic tests, homogeneity tests, pH tests, adhesion tests, and spreadability tests.

2.6. The test animal preparation

The animal testing used were female white rats of the Wistar strain aged 2-3 months which had a bodyweight range between 150 to 200 g obtained from Integrated Research and Testing Laboratory IV Universitas Gadjah Mada (UGM), Yogyakarta. This research has received approval from the Ethics Committee of Faculty of Medicine and Health Sciences Universitas Muhammadiyah Yogyakarta with Number 053/EP-FKIK-UMY/IX/2020. 15 rats were prepared and grouped into 5 treatment groups, i.e., 1) normal group (without dental caries induced), 2) positive group (caries induced and given 1 mg of formaldehyde pulp devitalization material), 3) negative group (dental caries induced and treated with distilled water, 4) FI group (dental caries induced and given 1 mg of paste formula I), and 5) FII group (dental caries induced and given 1 mg of formula II paste). This study was adopted from research by Enggardipta et al. (2016) and has been modified.

2.7. Handling of test animals

Rats were housed individually and adapted to feed access AD2 10% of body weight and drink RO ad libitum for 7 days before treatment.

2.8. Test animal treatment

The test animals were given general anesthesia by i.m injection of a mixture of ketamine 50 mg/kgBW and xylazine 10 mg/kgBW. This test was adopted from research by The maxillary first molars were prepared using a diamond round bur No. 010 at high speed to perforation. Hypersalivation is overcome by giving a cotton bud. For 60 seconds the teeth are left exposed in the oral environment. The negative control was given distilled water, the positive control was given formaldehyde, the FI group was given the formula I paste preparation, and the FII group was given the formula II paste preparation. Temporary filling was done and leaved to dry. After seven days of treatment, the test animals were euthanized using ketamine 100 mg/kgBW, the neck was dislocated and the jaws were taken from the treated teeth. The tooth tissue was soaked with formalin and decalcified, then processed for the establishment of the microscope slide (Al-Dlaigan, 2015).

2.9. COX-2 Expression test

A review of COX-2 expression was carried out at the Laboratory of Anatomical Pathology, Faculty of Medicine UGM, Yogyakarta. Immunohistochemical (IHK) preparations were stained with ULTRATEK HRP Anti-polyvalent (DAB) Staining Complete System. COX-2 expression was considered as positive if there were brown cells visible under a light microscope at 1000 times magnification. The results were obtained and calculated using the formula for the percentage yield of COX-2 expression and the percentage suppression of COX-2 expression.

2.10. Data analysis

The data obtained were subjected to a statistical analysis by using One Way ANOVA test by using SPSS version 21.0 with a p value set at 0.05. The data from this study were the values obtained from the results of the physical evaluation of the prepared paste and the results of the COX-2 expression test in rat pulp. The results of the COX-2 expression test were the percentage of COX-2 enzyme expression and the suppression percentage of COX-2 enzyme expression which were analyzed statistically with a 95% confidence level.

3. Results and Discussion

3.1 Red betel leaf extraction

Preparation of red betel leaf extract was carried out using the maceration extraction method with 70% ethanol solvent and then concentrated. Yield calculations were carried out with 16.96 g sample weight, and it was found that the percentage yield was 6.78%. In contrast, Ulviani et al. (2016) obtained the red betel leaf extract yield of 6.14%. This is different from several studies which obtained higher extract yields of 13.59% each. The higher the yield value, the more extracts obtained (Waraney et al., 2020).

3.2 Organoleptic test

Organoleptic testing was carried out using the five senses including color, appearance, size, texture, and aroma with visual observations. Based on the research, the paste is brown, smooth, thick and has a minty aroma like toothpaste.

3.3 Homogeneity test

The homogeneity test results obtained a homogeneous paste (Figure 1). The homogeneity of a paste based on SNI 12-3524-1995 is indicated by the absence of air bubbles and separate lumps of particles in the paste preparation. The presence of air bubbles and particle clumps can occur due to the selection and mixing process between the gelling agent and humectant that is not suitable. So that it has an impact on the stability and homogeneity of a paste preparation (Syurgana et al., 2017).

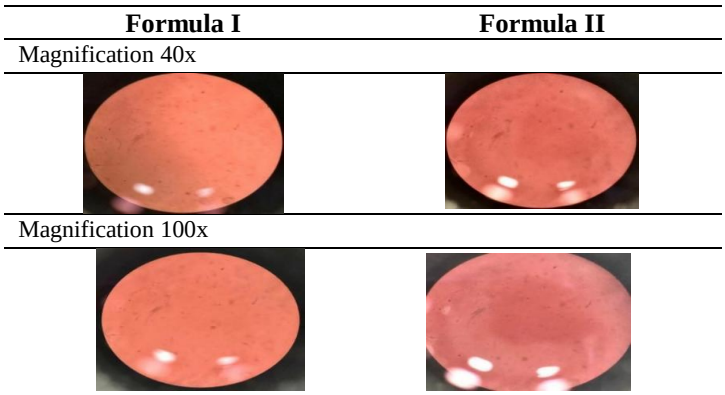

Fig. 1. The homogeneity test results of the prepared paste

3.4 pH test

pH testing was carried out to determine the level of acidity and alkalinity of the prepared paste. Based on SNI 12-3524-1995, the pH value requirements for toothpaste are 4.5 to 10.5 (Syurgana et al., 2017). An acidic pH will cause an increase in the demineralization process of hard tooth tissue which can cause dental caries. Meanwhile, if there is an increase in pH or alkaline, it causes the formation of crystals and the formation of tartar (Oktafriana and Taadi, 2017). Based on the results of the pH test, it showed that the prepared pastes that were tested meet the pH value standards and it is hoped that the prepared paste will not irritate the oral mucosa when applied (Table 2).

3.5 Adhesion test

The adhesion test was carried out to determine the ability of the paste preparation to adhere and coat the skin surface when used so that it is expected that the paste will function optimally and can increase the penetration of the active substance into the skin to provide a therapeutic effect (Ningsih et al., 2015). Based on the results of the adhesion test (Table 3), it was found that the two formulations had met the requirements of the adhesion test, where good adhesion was more than 1 second (Sari et al., 2017).

Table 2. pH test results for pasta preparations

pH test	Formula I	Formula II
Replication-1	6.214	6.187
Replication-2	6.214	6.187
Replication-3	6.214	6.187
Average	6.214 ± 0	6.187 ± 0

Table 3. The results of the adhesive test for paste preparations

Adhesion test	Formula I	Formula II
Replication-1	3.8 seconds	4.3 seconds
Replication-2	4.2 seconds	2.1 seconds
Replication-3	2.7 seconds	3.4 seconds
Average	3.57 ± 0.78 seconds	3.27 ± 1.11 seconds

3.6 Spreadability test

Based on the results of the physical evaluation test to both paste formulas which were the organoleptic test, homogeneity test, pH test, adhesion test, and spreadability test, each has met the specified requirements (Table 4).

The spreadability test shows the ability of the paste preparation to spread and soften so that it can provide comfort during use. The greater the dispersion diameter value, the greater the surface area that can be reached by the paste preparation. The standard of spreadability of semi-solid preparations ranges from 5-7 cm (Syurgana et al., 2017). Based on the results of the spreadability test, it was found that both paste formulations had met the requirements of the spreadability value standard.

Table 4. The results of the spreadability test of prepared paste

Spreadability Test	Formula I	Formula II
Replication-1	5.5 cm	6.1 cm
Replication-2	6 cm	5.9 cm
Replication-3	5.7 cm	6.3 cm
Average	5.7 ± 0.25 cm	6.1 ± 0.20 cm

3.7 COX-2 expression test

The COX-2 expression test was carried out by observing under 1000 times magnification microscope to count the number of brown cells with three different viewpoints. The results of this study can be calculated by the percentage of COX-2 expression and the suppression percentage of COX-2 expression. Based on those observations, the results were obtained as shown on Figure 2.

One Way ANOVA test on the percentage of COX-2 expression obtained a significance level of 0.022, while the percentage of suppression of COX-2 expression obtained a result of 0.027. Therefore, it can be said that the average of the five groups on the percentage of COX-2 expression and the percentage of suppression of COX-2 expression was significantly different (Sig. < 0.05).

The COX-2 enzyme is released when inflammation occurs, this enzyme breaks down arachidonic acid into prostaglandins. Prostaglandin E2 (PGE2) is a major mediator of the inflammatory response and lowers the nociceptive threshold, thereby potentiating the effects of pain-causing agents (eg bradykinin and histamine) (Ribeiro et al., 2015).

The COX-2 expression test is used as an indicator of the level of pain that is directly proportional, if the COX-2 expression that occurs is increasing, the level of pain experienced might also higher (Tanumihadja et al., 2019). Thus, if the level of pain is higher, the inflammatory response that arises will also be higher (Ribeiro et al., 2015). Meanwhile, suppression of COX-2 expression will result in a decrease in prostaglandin production which will lead to reduced pain, edema and vasodilation of blood vessels. Thus the COX-2 expression suppression test is used to determine the reduced level of pain and inflammation (Prasetya et al., 2013). The COX-2 expression test and the COX-2 expression suppression test can be seen in the following graph (Figure 3 and 4).

In the positive control, the percentage of COX-2 expression was 0.40% and the percentage of COX-2 expression suppression was 0.59%. In this control, the dental pulp of rats was induced by dental caries and given a positive control in the form of formaldehyde. In this control, the dental pulp of rats was induced by dental caries and given a positive control in the form of formaldehyde. Formaldehyde has been used for root canal treatment in endodontics. Normal formaldehyde levels in humans are 2-3 g/kg. Formaldehyde has developed as the drug of choice for routine endodontic procedures when adequate anesthesia cannot be obtained (Shetty et al., 2019). The main pharmacological effect of formocresol comes from formaldehyde. Formaldehyde is a product of paraformaldehyde depolymerization. Paraformaldehyde binds to tissues by cross-linking proteins, especially between the essential amino acid residues of lysine.

It is reported that exposure to formaldehyde can irritate the eyes and upper respiratory tract. High concentrations of formaldehyde can cause nasal congestion, pulmonary edema, choking, dyspnea, and chest tightness. In addition, administration of paraformaldehyde can cause pulp necrosis and chronic periapical reactions (Lee et al., 2016). Therefore, an alternative pulp devitalization material that is equivalent to or better than the existing devitalization material is needed with minimal adverse effects.

In the negative control, the percentage of COX-2 expression was 0.48% and the percentage of COX-2 expression suppressed was 0.52%. In this control, the dental pulp of rats was induced by dental caries and given a negative control in the form of aquadest. The results obtained are in accordance with the treatment given, where the COX-2 expression that occurs will be seen a lot.

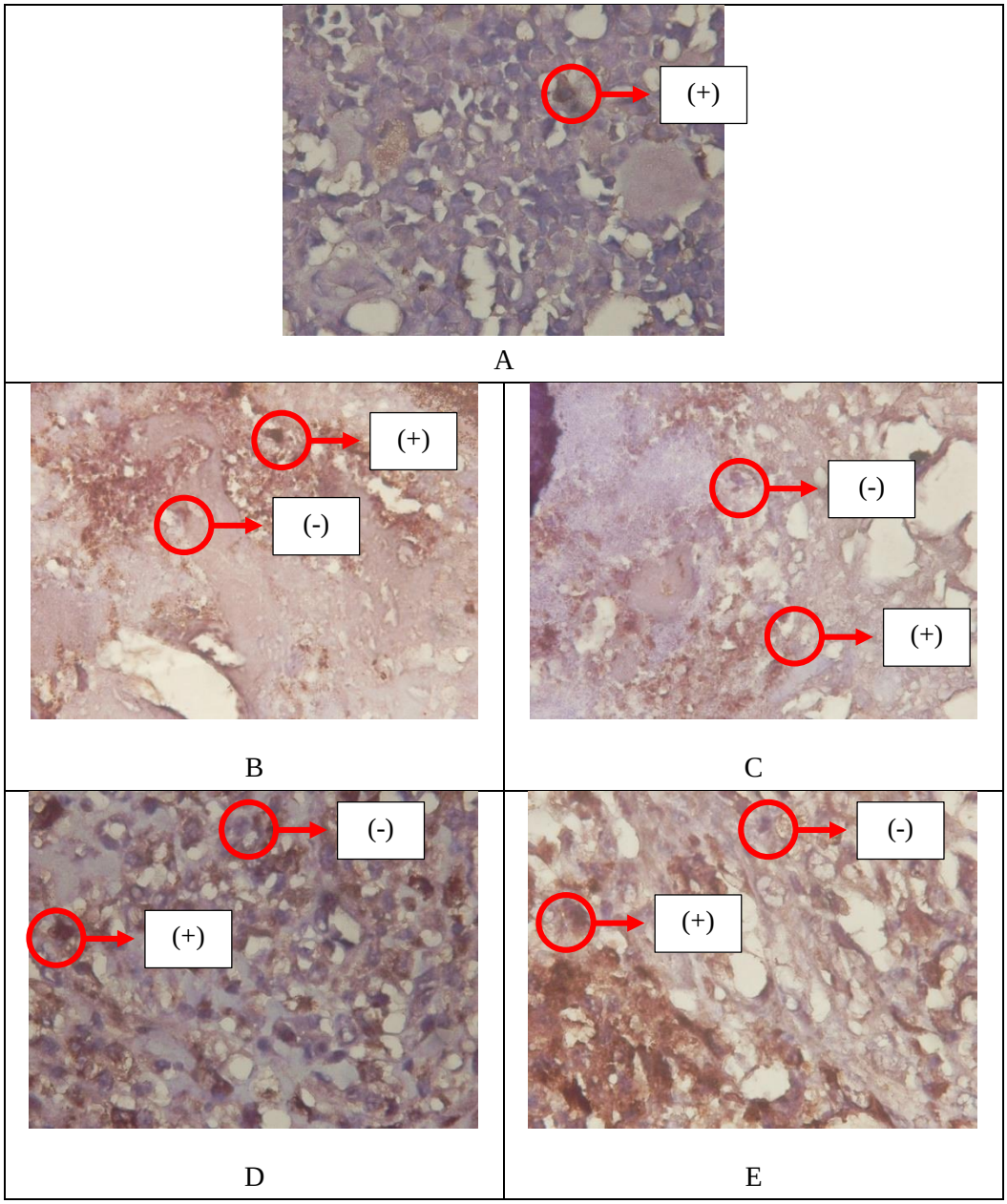

Fig. 2. Dental Pulp of a Rat Induced by Dental Caries observed under a Light Microscope at 1000 times Magnification. (+) cells are brown/dark in color, or express COX-2; (-) cells are purple/blue or do not express COX-2. (A) The test group was normal control; (B) positive control; (C) negative control; (D) formula I; (E) formula II

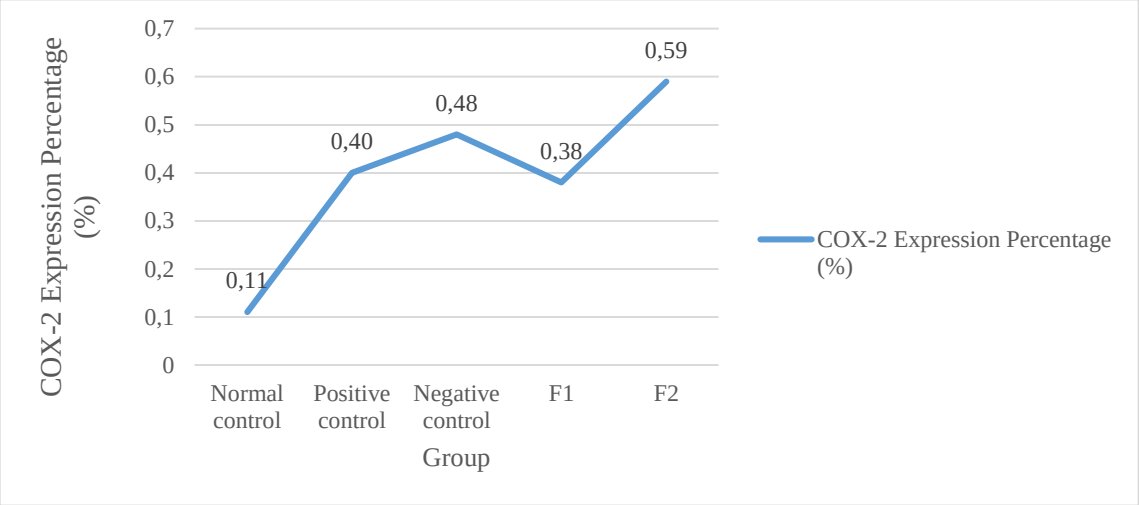

Fig. 3. COX-2 Expression percentage

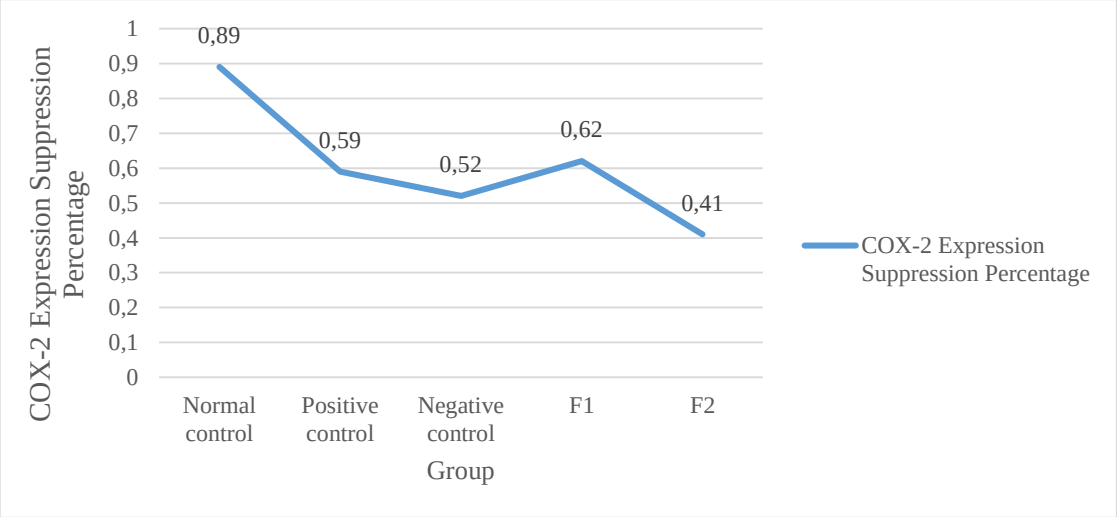

Fig. 4. COX-2 Expression suppression percentage

From these data, it was found that formula I was proven to be used as an alternative pulp devitalization material with a COX-2 expression percentage of 0.38% and a COX-2 expression suppression percentage of 0.62%, where the concentration of jatropha gum used by 25% and the red betel leaf used is 0.25%. Jatropha sap is known to contain tannins and saponins, which have the potential as a nerve agent for teeth, while red betel leaf is known to contain flavonoids which have the potential as anti-inflammatory and analgesic. The devitalizing effect of castor gum has been reported. Mattulada (2008) reported moderate causative inflammation after administration of castor gum for 24 hours and turning to a chronic state afterward, also observed cell lysis indicating rupture of pulp blood vessels, causing pulp necrosis. In contrast, Siregar & Damayanti (2020) reported that inflammation and necrosis were observed on dental pulp, which is in contact with latex, while the tissue underneath is normal.

This is different from the research by Irmaleny et al. (2011) to evaluate the effect of the latex and extract of J. curcas on the dental pulp expression of COX-2 and Substance P (SP). The results showed that J. curcas latex has lower levels of SP than extract but does not provide precise results in decreased levels of COX-2.

In formula II, the percentage of COX-2 expression was 0.59%. The percentage of COX-2 expression suppression was 0.41%, where the concentration of jatropha sap used was 25% and the red betel leaf used was 0.5%. The red betel leaf concentration at 0.5% is less effective than formula I, with a concentration of 0.25%. The research conducted by Fitriyani *et al.* (2011) suggested that giving the highest dose of red betel leaf does not necessarily provide the greatest anti-inflammatory activity. Also, that several types of drugs in high doses actually cause the release of histamine directly from mast cells, resulting in blood vessels becoming more permeable to plasma fluid and causing an inflammatory process. In the formula II group using 0.5% red betel leaf extract with the possibility that this extract can show the same findings as in previous studies, so that at this concentration it is less effective in reducing inflammation (Fitriyani et al., 2015).

In this study, it was proven that the combination of 25% jatropha latex (Jatropha curcas L.) and 0.25% red betel leaf extract (Piper crocatum) proved to affect the percentage and suppression of COX-2 expression so that it can be used as an alternative material for pulp devitalization. In the in vivo test, Jatropha curcas sap was able to act as an anti-inflammatory in Rattus norvegicus strain wistar rats. The anti-inflammatory activity of flavonoids in Jatropha sap can shorten the inflammatory reaction due to the inhibition of cyclooxygenase and lipoxygenase which causes the number of inflammatory cells to migrate to the wound tissue is limited and does not inhibit the ability of TGF-β to proliferate, thereby making the TGF-β proliferation process take place rapidly (Prastiyanto et al., 2020; Ridha, 2016; Salim et al., 2018). Fitriyani et al. (2015) reported that the administration of P. Crocatum Extract at 50 mg/kg showed the most potent anti-inflammatory activity among the doses used.

The anti-inflammatory mechanism in red betel is caused by inhibiting the release of prostaglandins and anti-inflammatory mediators. This is also related to phytochemical compounds such as saponins, flavonoids, and essential oils in red betel extract. However, the anti-inflammatory mechanism of saponins is not yet known. The possible anti-inflammatory mechanism is that saponins can interact with membrane lipids such as phospholipids as precursors of prostaglandins and other inflammatory mediators. Flavonoids as anti-inflammatory agents are also seen from the side of inhibition of COX and lipoxygenase enzyme activities. Inhibition of COX and lipoxygenase pathways can directly inhibit the biosynthesis of eicosanoids and leukotrienes as end products of the COX and lipoxygenase pathways (Savitri et al., 2020).

4. Conclusion

Based on the results of the study, it was found that the combination of 25% jatropha curcas *(Jatropha curcas L.)* latex and 0.25% red betel leaf extract *(Piper crocatum)* was proven to have potential as an alternative to pulp devitalization.

Author Contributions: Vella Lailli Darmawarti, Rahmat A Hi Wahid, Lana Labibah, and Syahrani, conceived and designed the study. Vella Lailli Darmawarti, Dyani Primasari Sukamdi, Sabtanti Harimurti, Annisa Krisridwany performed all data analyses. Vella Lailli Darmawarti, Lana Labibah, Syahrani, Dyani Primasari Sukamdi, Sabtanti Harimurti, Annisa Krisridwany interpreted the results. Vella Lailli Darmawarti, Rahmat A Hi Wahid, Lana Labibah, Syahrani, Dyani Primasari Sukamdi, Sabtanti Harimurti, and Annisa Krisridwany review, revise and editing. Vella Lailli Darmawarti, Rahmat A Hi Wahid wrote the manuscript. Rahmat A Hi Wahid supervised this manuscript. All authors read and approved the final manuscript.

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Competing Interests

The authors disclose no conflict.

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