The potentiation of Mangifera casturi bark extract on interleukin1β and bone morphogenic protein-2 expressions during bone remodeling after tooth extraction

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Research Report

The potentiation of *Mangifera casturi bark* extract on interleukin-1β and bone morphogenic protein-2 expressions during bone remodeling after tooth extraction

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ABSTRACT

Background: *The main oral health problem in Indonesia is the high number of tooth decay. Tooth extraction is the treatment often received by patients who experience tooth decay and the wound caused by alveolar bone resorption. Bark of Mangifera casturi has been studied and proven to contain secondary metabolite which has the ability to increase osteoblast's activity and suppress osteoclast's activity.* ***Purpose:*** *The purpose of this study was to analyze interleukin-1 beta (IL-1β) and bone morphogenic protein-2 (BMP-2) activities during bone remodeling after Mangifera casturi's bark extract treatment.* ***Method:*** *This study was laboratory experimental research with randomized post-test only control group design. The Mangifera casturi bark was extracted using 96% ethanol maceration and n-hexane fractionation. This study used 40 male Wistar rats which are divided into 4 groups and the tooth extraction was performed on the rats' right mandible incisive tooth. The four groups consisted of 6.35%, 12.7%, 25.4% extract treatment group, and a control group. Wistar's mandibles were decapitated on the 7th and 14th day after extraction. Antibody staining on preparations for the examination of IL-1β and BMP-2 expressions was done using immunohistochemistry.* ***Result:*** *There was a significant difference of IL-1β and BMP-2 expressions in 6,35%, 12,7%, and 25,4% treatment groups compared to control group with* $p<0.05$. ***Conclusion:*** *Mangifera casturi's bark extract was able to suppress the IL-1β expression and increase the BMP-2 expression during bone remodeling after tooth extraction.*

Keywords: *bone morphogenic protein-2; bone remodeling; interleukin-1β; Mangifera casturi (Kosterm.); tooth extraction*

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INTRODUCTION

Bones are the structures built for supporting the body which characteristics are rigid, solid, and have the ability to regenerate and repair themselves.[1] Injury on bones might be caused by both pathological and physiological conditions.[1,2] Injury on jaws, especially mandible, is one of the most common injuries of maxillofacial region, its prevalence ranging from 36% to 59%.[3] Injury on jaw bones can also happen after tooth extraction.[1]

Regeneration and repair of bone tissues are important processes to heal the wounded tissues. Bone tissues repair can be classified into four stages: hematoma formation, soft callus formation, hard callus formation, and bone remodeling.[1,2] In hematoma formation stage, fibroblast and osteoblast migrate to the fracture site and start reconstructing bones. The amount of bone remodeling regulators in the body will affect osteogenic process post tooth extraction.[1,4] These regulators include osteoblasts, osteoclasts, systemic factors such as hormones and vitamins and local factors such as interleukin and bone morphogenic protein (BMP). Interleukin-1 beta (IL-1β) has a role as inflammatory cytokines that regulate immune system. These cytokines are produced by macrophage and other inflammatory cells. IL-1β also gives a chemotactic effect on other inflammatory cells, stimulates extracellular matrix synthesis, angiogenesis, recruits endogen fibrogen cells to the wound site, and in bone resorption stage.

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BMP-2 stimulates osteoconductive activities to regulate differentiation and proliferation of mesenchymal cells into osteoblasts.[5]

Bones are the body's dynamic hard tissues, always undergoing repair when needed. Bone tissues repair is mainly mediated by osteoblasts, the bone-forming cells and osteoclasts, which resorb bones. Alveolar bones repair after tooth extraction molecularly involves receptor activator of NF-kB ligand (RANKL) which stimulates the osteoclast formation, and osteoprotegerin (OPG) which would bind RANKL, thus decreasing osteoclasts and bone resorption.[6]

Bone tissues repair can be accelerated using either natural or synthetic materials. Some of these materials have disadvantaging side effects such as rejection from the recipient's body, faster bone degradation, osteolysis, and ineffective cost.[7] The limitations of these synthetic materials lead many researchers to seek out natural materials which can be easily found around and have fewer side effects.

Mangifera casturi is the native plant of Kalimantan. Some of this plant's parts have been known to have active substances and can be potentially used with medical purposes. The plant was reported to have alkaloids, flavonoids, saponins, steroids, triterpenoids, and tannins.[8,9] Casturi's bark contains saponins, steroids, and tannins, which have antibacterial properties against *S. mutans*,[10] *S. aureus*, and *E.coli*.[11] The tannins contained in 127.42 grams of *Mangifera casturi bark* extract is 8.5%.[12]

Tannins are polyphenols, belonging to the fenolic acid class. Tannins were reported to have effect in increasing the osteoblast's activities and suppressing the osteoclast's activities.[9] The increase of osteoblast's activities by alkaloids and polyphenols such as tannins is because the induction of IL-1β and BMP-2 expressions on wound site.[13] Secondary substances such as polyphenols in foods and plants, one of them being *Mangifera casturi*, can help bone tissues repair by increasing the osteoblast's activities and suppressing the osteoclast's activities.[9] Terpenoids in casturi bark extract was assumed to play a role in bone regeneration process. Triterpenoids have many prominent physiological activities, thus they are used medically in daily life to help cure diabetes, menstruation problems, venomous snake's bite, skin diseases, liver diseases, and malaria. In plants which contain triterpenoids, there's an ecological value to it because these substances work as antifungal, insecticide, anti-predator, antibacterial, and antiviral substances.[14] The purpose of this study was to examine about the effect of *Mangifera casturi bark* extract on IL-1β and BMP-2 expressions during bone remodeling post tooth extraction.

MATERIALS AND METHODS

This study was true experimental laboratory research, using randomized post test only control group design. Samples used were counted using Lemmeshow equation and each group consisted of 5 samples.

Before the research was carried out on experimental animals, the design has been approved by Ethics Committee of the Faculty of Dental Medicine, Universitas Airlangga. Right mandible incisors from the male wistar rats were extracted using forceps. Outer surface of the forceps were sharpened to improve the internal pressures so they could clasp firmer around the tooth during extraction. Before extraction, rats were sedated intraperitoneally using sodium pentobarbital (50 mg/ kg BB); then they were anesthetized with infiltration technique on lingual fold using 2% lidocaine (1:100.000), to produce the effect of local anesthesia and homeostasis. After extraction, sockets were filled by 6.35%, 12.7% and 25.4% *Mangifera casturi bark* extract. The control group was treated using gel without extract. Post-extraction sites were then sutured using 5.0 monofilament sutures. After this treatment, each animal was administered trimethoprim-sulfa 30 mg/ kg subcutaneously, which worked as antibiotics, per 12 hours for 3 days. Two days post treatment, animals were given soft food to minimize further trauma and prevent delayed healing. After this period, standard foods were given. Foods were given orally using normal saline 5 mL/ kg/ day. After that, rats were sacrificed on day 7 and day 14 through injection of sodium pentobarbital (50 mg/ kg BB). Their mandible parts were decalcified using 10% EDTA. The expressions of IL-1β and BMP-2 were observe on day 7 and 14 using immunohistochemistry methods.

RESULTS

Examinations were done using 400x zoom/ 15625μ^2 in ten fields of view, and the results were calculated to find out the means of each animal. The means were then summed to find out the final means of treatment groups. Statistical tests were carried out to assess the significance of each treatment group.

The observations of IL-1β expression in post mandibular incisor extraction sockets of Wistar rats were done using immunohistochemistry methods (Figure 1 and 2). Cells were counted using Kruskal-Wallis test to assess the differences between groups, and continued by using Mann-Whitney test to assess the significance of the differences.

The means of IL-1β expression in post mandibular incisor extraction sockets of Wistar rats on day 7 were as following: 20.55 ± 1.761, 20.80 ± 3.222, 14.55 ± 2.911, 13.00 ± 1.806 in control group, 6.35%, 12.7% and 25.4% Mangifera casturi bark extract treatment groups respectively. Kruskal-Wallis test showed $p<0.05$, proving that there was a significant difference between groups. Duncan test was carried out next to find out the significance of differences between each treatment group. There was a significant difference of control group and 6.35% extract treatment group compared to 12.7% and 25.4% extract treatment groups; meanwhile the IL-1β expression in control group

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compared to 6.35% extract treatment group and also in 12.7% extract treatment group compared to 25.4% extract treatment group had no significant differences (Table 1).

The means of IL-1β expression in post mandibular incisor extraction sockets of Wistar rats on day 14 were as following: 19.55 ± 1.605, 22.90 ± 3.007, 14.90 ± 3.401, 14.85 ± 3.731 in control group, 6.35%, 12.7% and 25.4% Mangifera casturi bark extract treatment groups respectively. Kruskal-Wallis test showed $p<0.05$, proving that there was a significant difference between groups. Mann-Whitney test was carried out next to find out the significance of differences between each treatment group. There was a significant difference of control group compared to 6.35%, 12,7% and 25.4% extract treatment groups; the IL-1β expression in 6.35% extract treatment group compared to 12.7%, and 25.4% extract treatment groups had significant difference, but in 12.7% extract treatment group compared to 25.4% extract treatment group, there was no significant difference (Table 1).

The observations of BMP-2 expression in post mandibular incisor extraction sockets of Wistar rats were done using immunohistochemistry methods (Figure 3 and 4). Cells were counted using Kruskal-Wallis test to assess the differences between groups, and continued by using Mann-Whitney test to assess the significance of the differences.

The means of BMP-2 expression in post mandibular incisor extraction sockets of Wistar rats on day 7 were as following: 7.7 ± 2.179, 11.35 ± 2.519, 15.30 ± 2.386, 15.75 ± 2.807 in control group, 6.35%, 12.7% and 25.4% *Mangifera casturi bark* extract treatment groups respectively. Kruskal-Wallis test showed $p<0.05$, proving that there was a significant difference between groups. Mann-Whitney test was carried out next to find out the significance of differences between each treatment group. There was a significant difference of control group compared to 6.35%, 12.7% and 25.4% extract treatment groups; the BMP-2 expression in 6.35% extract treatment

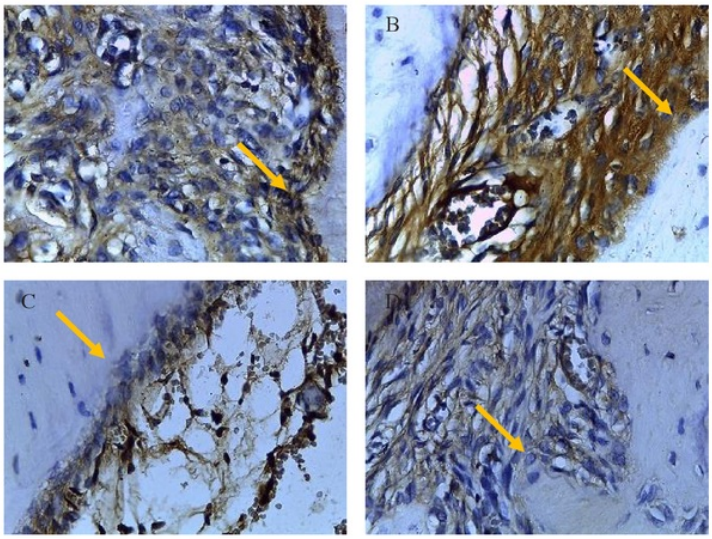

Figure 1. IL-1β expression in the post tooth extraction socket on day 7 using microscope, 400x zoom. (A) control; (B) 6.35% *Mangifera casturi bark extract*; (C) 12.7% *Mangifera casturi bark extract*; (D) 25.4% *Mangifera casturi bark extract*; yellow arrows show IL-1β expression.

Table 1. Means and standards deviation of IL-1β and BMP-2 expressions

Group	IL-1β		BMP-2	
	Day 7	Day 14	Day 7	Day 14
Control	20.55 ± 1.761[a]	19.55 ± 1.605[b]	7.7 ± 2.179[a]	8,9 ± 1,804[a]
6.35% extract	20.80 ± 3.222[a]	22.90 ± 3.007[a]	11.35 ± 2.519[b]	10,15 ± 1,387[b]
12.7% extract	14.55 ± 2.911[b]	14.90 ± 3.401[c]	15.30 ± 2.386[c]	17.40 ± 1.759[d]
25.4% extract	13.00 ± 1.806[b]	14.85 ± 3.731[c]	15.75 ± 2.807[c]	15.90 ± 3.110[c]

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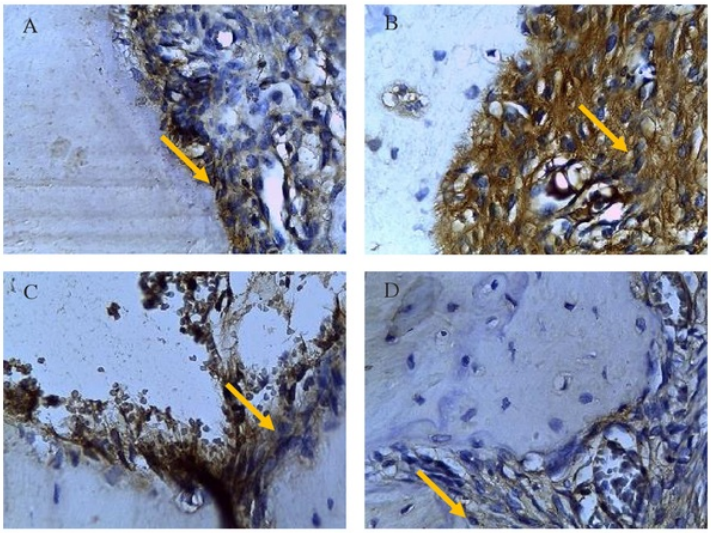

Figure 2. IL-1β expression in the post tooth extraction socket on day 14 using microscope, 400x zoom. (A) control; (B) 6.35% *Mangifera casturi bark extract*; (C) 12.7% *Mangifera casturi bark extract*; (D) 25.4% *Mangifera casturi bark extract*; yellow arrows show IL-1β expression.

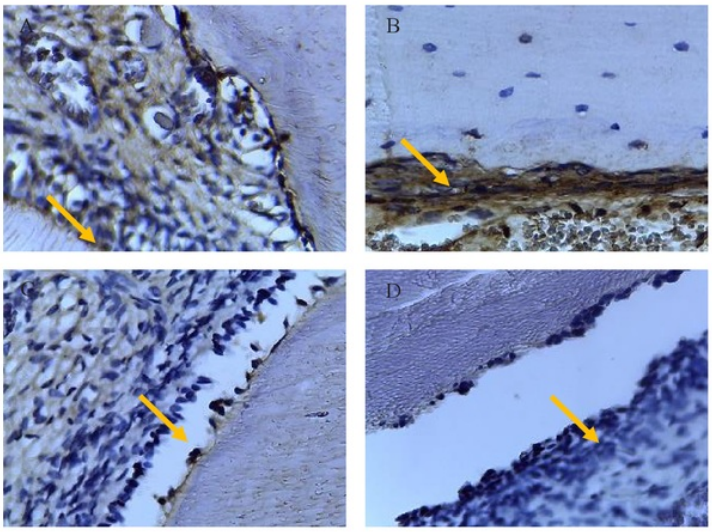

Figure 3. BMP-2 expression in the post tooth extraction socket on day 7 using microscope, 400x zoom. (A) control; (B) 6.35% *Mangifera casturi bark extract*; (C) 12.7% *Mangifera casturi bark extract*; (D) 25.4% *Mangifera casturi bark extract*; yellow arrows show BMP-2 expression.

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group compared to 12.7% and 25.4% extract treatment groups had significant difference, meanwhile in 12.7% extract treatment group compared to 25.4% had no significant difference (Table 1).

The means of BMP-2 expression in post mandibular incisor extraction sockets of Wistar rats on day 14 were as following: 8.9 ± 1.804, 10.15 ± 1.387, 17.40 ± 1.759, and 15.90 ± 3.110 in control group, 6.35%, 12.7% and 25.4% *Mangifera casturi bark* extract treatment groups respectively. Kruskal-Wallis test showed $p < 0.05$, proving that there was a significant difference between groups. Mann-Whitney test was carried out next to find out the significance of differences between each treatment group. There was a significant difference of control group and 6.35% extract treatment group compared to 12.7% and 25.4% extract treatment groups; the BMP-2 expression in control group compared to 6.35% extract treatment group had significant difference, and also in 12.7% extract treatment group compared to 25.4% there was a significant difference (Table 1).

DISCUSSION

IL-1β expression in alveolar sockets on day 7 and 14 after casturi bark extract treatment showed a decrease compared to control group, except for 6.35% extract treatment group which showed an increase. IL-1β is involved in osteoclast differentiation. IL-1β synergize with RANKL to induce osteoclast induction and bone resorption and indirectly boost osteoclastogenesis through the excretion of PGE2 and RANKL by osteoblasts.

IL-1β cytokines have important roles on bone destruction by forming osteoclasts and increasing osteoclast's activities. The main role of IL-1β in bone metabolism is to stimulate bone resorption and delay the bone formation. These cytokines work by stimulating T and B lymphocytes to increase inflammatory responses, which is through stimulation of prostaglandin and degradative enzymes, such as colagenase. The bigger the decrease of IL-1β in remodeling process is, the more effective Mangifera casturi extracts help improve post extraction wound site.

Tooth extraction is a treatment to take out tooth from maxilla and mandible because of dental-related disease, such as decay, periodontal diseases, and trauma.[15] This treatment causes wound on alveolar sockets, and this wound will go through healing process, such as hemostasis, inflammation, proliferation, and remodeling.

Inflammation is the body's response to clean out wound sites from foreign objects, bacteria, and dead cells thus the healing process can begin.[16] The inflammatory process started from neutrophils, which is leukocytes, increasing around wound site. Neutrophils work to clear foreign objects and bacteria, and then they would be replaced by macrophages. Macrophages also work to synthesize collagen, form granulation tissues with fibroblasts, produce vascular endothelial growth factor (VEGF)-A which would form new capillary vessels. IL-1β play a role as stimulator of bone resorption before proliferation phase.

TGF-β stimulates the production of VEGF, which play a part in angiogenesis, a new blood vessels formation process. TGF-β also has an important role in immunoregulation through neurophilin-1 (Nrp1, a protein which bind to both active or latent TGF-β).

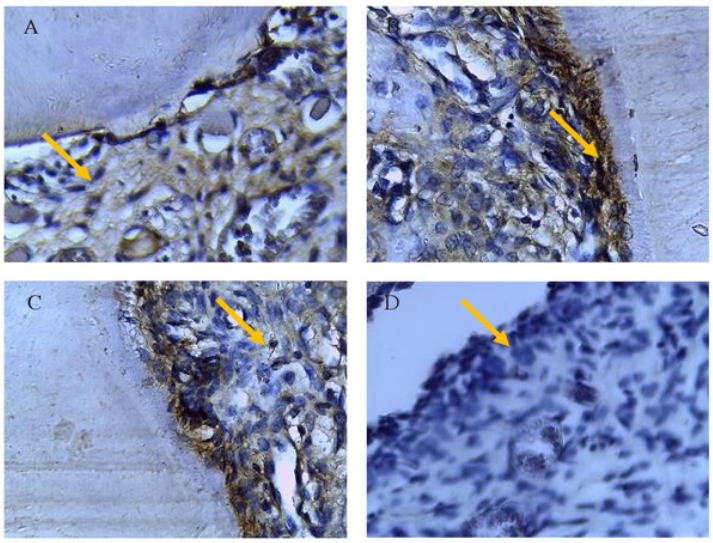

Figure 4. BMP-2 expression in the post tooth extraction socket on day 14 using microscope, 400x zoom. (A) control; (B) 6.35% *Mangifera casturi bark extract*; (C) 12.7% *Mangifera casturi bark extract*; (D) 25.4% *Mangifera casturi bark extract*; yellow arrows show BMP-2 expression

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IL-1β is the cytokine which play a part in inflammatory process, proliferation, tissue remodeling and maturation. TGF-β collaborate with growth factors, such as connective tissue growth factor (CTGF) to stimulate wound healing by forming fibroblast.[17] The higher the expression of IL-1β is, the faster inflammatory process resolves. The decrease of IL-1β shows the end of inflammatory phase and the start of proliferation.

Healing on post extraction wound needs repair on both soft and hard tissues, such as alveolar bones. Bones in mandible and maxilla are tissues with complex mineralization and always undergo remodeling through bone formation and resorption. Repair on alveolar bones after extraction affects growth factors release and one of them plays a part in bone repair, which is BMP-2.

Proliferation phase is marked by granulation tissues formation on wound sites. New capillary vessels formation or angiogenesis is stimulated by VEGF and will also synthesize the endothelial cells formation. New bone tissues formation is heavily influenced by BMP-2. Bone formation in post extraction wound is membranous osteogenesis, started by collage secretions and then mineralization.[16]

BMP-2 is growth factors which is important in new bone formation and can be examined in signaling molecules accelerating bone formation. BMP-2 has in vivo osteoconductive activities compared to other BMP families.[18] BMP-2 expression in alveolar socket day on 7 after 6.35%, 12.7%, and 25.4% extract treatments showed the increase of BMP-2 compared to control group. This increase showed a faster bone formation through cellular mechanism. BMP-2 expression on day 7 was dominated by osteoblasts. Osteoblasts differentiation through BMP ligands bind to receptors, a pair of BMPR-I and BMPR-II form heterotetrameric-activated receptor complex protein Smad, which is a substrate of BMPR-I, and has a function to relay signal from receptors to target gens in nucleus. Dimeric ligand bond to heterometric BMP receptor activates intrinsic serine/threonine kinase and phosphorized R-Smad activities. BMP-2 can phosphorize intracellular transducers, Smad 1 and 5, which will begin the differentiation of osteoblasts.[19]

BMP-2 expression in alveolar socket day on 14 after 6.35%, 12.7%, and 25.4% extract treatments still showed the increase of BMP-2 compared to control group. According to references, BMP-2 on day 14 should decreased which shows the healing responses. This result showed that casturi bark extract hasn't yet optimally help wound healing on day 14.

BMP-2 activates TGF-β and boosts fibroblast formation. Fibroblasts are cellular elements commonly found in gingival connective tissues which proliferate and actively synthesize matrix in wound healing and repair. Fibroblasts are basic substances of scarring and collagens which give the tensile strength in soft tissue wound healing. During inflammation, fibroblasts will migrate to wound site, proliferate and produce collagen matrix to repair tissues.[17] The higher the BMP-2 expression is, the faster proliferation can begin, the decrease of BMP-2 showed the end of proliferation and the start of remodeling. Remodeling is the last phase in wound healing, in this phase, granulation tissues become mature, which is marked by mechanical strength on formed tissues, the decrease of capillary vessels in wound, the decrease of fibroblasts, and the increase of collagen fibers.[15] In conclusion, *Mangifera casturi's* bark extract was able to suppress the IL-1β expression and increase the BMP-2 expression during bone remodeling after tooth extraction

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